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THE SKELETAL STATUS OF CHILDREN WITH STEROID SENSITIVE NEPHROTIC SYNDROME BY DUAL-ENERGY X RAY ABSORPTIOMETRY DXA SCAN

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ABSTRACT

Objective: The study performed for evaluation of BMD in idiopathic nephrotic syndrome in children using Dual –energy X ray absorptiometry (DXA). **Methods:** Cross sectional study performed on 70 patients with aged 4-18years old, 36 patients with infrequent relapse (group A) and 34 patients with frequent relapsing and steroid dependent NS (group B) followed up in pediatric nephrology clinic in Ibn sina teaching hospital in mosul city. Complete evaluation of patients including thorough history, physical examination and laboratory investigation including vitamin D level and PTH. DXA Scan used to assess LSS BMD and Total Hip BMD Z Scores. **Results:** The study show prevalence of vitamin D deficiency with male predominance, greater steroid dose and longer duration associated with negative effect on BMD. Increase PTH and total alkaline phosphatase level significantly especially in group B. Predominance of average LSS BMD 54.28% then osteopenia in 27.14% and osteoporosis in 18.57%. **Conclusion:** The use of steroid in nephrotic syndrome in children have negative impact on the bone mineral density. **Abbreviation:** SSNS = steroid sensitive nephrotic syndrome, NS =nephrotic syndrome, BMD =bone mineral density, PTH = parathyroid hormone.

KEYWORD: Nephrotic syndrome, Bone mineral density, Dual –energy X ray absorptiometry.

INTRODUCTION

Childhood Nephrotic syndrome (NS) is characterized by nephrotic-range proteinuria, widespread edema, hypoalbuminemia, and hyperlipidemia in the presence of normal renal function.[1]

Children who experience their initial episode of idiopathic nephrotic syndrome (NS) are typically treated with high-dose glucocorticoid (GC) treatment regimen lasting for a duration of 4 to 6 weeks following their initial episode.[2]

However, episodic relapses occur in two-thirds of the cases, necessitating subsequent courses of GC.[3]

Generally, a renal biopsy is not recommended for children aged 1–10 years who exhibit typical symptoms and achieve complete remission with corticosteroids.[4]

Three morphological patterns are seen under light microscopy: minimal change disease, FSGS and diffused mesangial proliferation. While FSGS is present in 5-7 percent of children, most other children have minimal change disease.[5]

Children with NS are predisposed to MBD even before glucocorticoid treatment due to a loss of calcium, phosphate, and vitamin D binding proteins in the urine, which is exacerbated by long-term glucocorticoid use.[6,7]

Glucocorticoid therapy induces the earliest changes in bone mineral density (BMD) in the lumbar spine, which contains the highest trabecular bone.[8]

Corticosteroids limit bone growth by suppressing osteoblast activity and the production of bone matrix. Furthermore, they stimulate bone resorption both directly and indirectly by lowering calcium absorption via Vitamin D inhibition, with a subsequent rise in parathyroid hormone release.[9,10] Children with steroid-dependent SSNS had low bone area and trabecular thickness, as well as focal osteoid accumulation associated with osteopenia and aberrant mineralization.[10]

Osteoporosis is a skeletal disorder that is characterized by a reduction in bone mass and deterioration of the microstructure of bone tissue throughout the body. This leads to an increased vulnerability of bones to fractures and a heightened risk of bone fragility.[11]

The most frequent type of secondary osteoporosis is glucocorticoid-induced osteoporosis.[12]

Loss of bone density, changes in bone structure, and increased fracture risk have all been linked to the use of glucocorticoids.[12,13]

The growing skeletal structure may exhibit heightened vulnerability to these impacts, possibly leading to compromised processes of bone formation and remodeling[14] resulting in microarchitectural degradation and increased fracture risk.[15]

Fractures caused by osteoporosis are more likely to occur in skeletal areas with a rich trabecular bone, such as the wrist, spine, and hip.

The International Society for Clinical Densitometry (ISCD) recommends dual-energy X-ray absorptiometry (DXA) as the recognised reference standard for determining bone mineral density (BMD) in both adults and children.[17,18]

The evaluation of paediatric bone health has been greatly enhanced by the widespread availability, affordability, ease of use, and low radiation dosage (1–6 μSv) of this technique, making it very beneficial in clinical settings.[19,20]

Exposure to the very low doses of ionizing radiation with DXA poses no known health risk.[21]

Pregnancy, recent oral contrast agent administration, and recent (<2 days) isotopic study administration are among the conditions that preclude the use of DXA.[22]

The aim of this study were to detect the patients who has bone diseases among steroid sensitive nephrotic syndrome and to evaluate the correlation between the dose of prednisolone and severity of bone disease.

PATIENTS AND METHODS

Prospective observational cross sectional study of 70 children with steroid sensitive nephrotic syndrome who were evaluated and followed up in nephrology clinic in Ibn sena teaching hospital/Mosul city / Iraq.

The study started in the first of June 2021 till 30 of December 2022 include patients who were steroid sensitive nephrotic syndrome, aged between 1-18years old who were treated with prednisolone for a duration between 6months to 9years.

The consent were taken from the patients and parents for doing DXA scan.

The study was approved by local ethical committees of Nineveh health department.

Inclusion criteria includes steroid dependant, frequent relapsers and infrequent relapsers nephrotic syndrome.

Patients with steroid resistant, nephrotic syndrome secondary to systemic diseases and patients with bone diseases were excluded from the study.

The informations that collected includes name, age, gender, body weight(kg), height(cm), tanner stage, age at presentation (year), duration of illness, dose of prednisolone (mg), cumulative dose of prednisolone, cumulative dose of prednisolone (mg)/year.

Pubertal status was determined by a physical examination and classified according to the method of Tanner.[23]

Laboratory investigations done include S. Albumin, S. Calcium, S. Phosphate, S. vitamin D and parathyroid hormone (Which was measured using Cobus e411 analyzer that is fully automated and uses Electrochemiluinescence technology for immunoassay analysis) kidney biopsy was available only for 14 patients.

The patients were divided into 2 groups
Group A: Includes infrequent relapsers and their number were 36 patients.
Group B: Includes steroid dependant and frequent relapsers, their number were 34 patients.

Definisions[24]

Nephrotic range proteinuria: Urine dipstick protein 3+ (300 mg/dL) or more; first-morning spot urine protein to creatinine ratio (UPCR) >2 mg/mg; 24-h protein >1000 mg/m^2

Steroid dependant NS: Two consecutive relapses when on alternate day steroids or within 14 days of cessation of therapy.

Frequent relapser NS: Two or more relapses in the first 6 months after stopping initial therapy, or ≥3 relapses in 1 year.

Infrequent relapser NS: less than four times relapses in 12 months period.
Dual X ray Absorptiometry DXA scan done using Primus, narrow fan beam bone densitometer system Doc. Version: 2.0(2018), OsteoSys co., Seoul, Republic of Korea.

DXA scan measure bone mineral density BMD of the lumber spine (L1-L4) and total hip on the bases of BMD Z score.
The Z-score is preferred for paediatric patients as it standardizes BMD relative to an age- and gender-matched population.[25]
Z Scores were calculated using the following equation
Z score =[BMD (gr /cm3)-BMD predicted for age and gender /SD for BMD]
A patient considered to have osteopenia if the Z score is <-1.0, when Z score ≤ -2.5 the patient considered to have osteoporosis.[26]

Statistical analysis
Statistical analysis was performed using IBM SPSS for Windows version 22(SPSS Inc, Chicago, IL). For all statistical tests P value < 0.05 was considered as significant. Continuous variables were presented using Mean ± SD and compared by using student's t-test and Chi-square test for categorical variables. The correlation of BMD with other data were studied using Pearson correlation coefficient method.

RESULTS
The total number of 70 patients were enrolled in this study, 48 (68.6%) patients were male and 22(31.4%) were female, age between 4-18 years old.

Mean duration of nephrotic syndrome 3.08± 2.01(p=0.000), prednisolone dose were range between 27-60mg/day, longer duration of nephrotic syndrome associated with higher glucocorticoid dose and frequent courses were highly statistically significant.

The patients divided into 2 groups: group A include infrequent relapser SSNS 36(51.45%) patients and group B include steroid dependent and frequent relapser SSNS 34 (48.57%) patients.

Pubertal stage
Stage 1 (no., %) (49, 70)
Stage 2-5 (no.,%) (21, 30)

The most common clinical manifestation were bone pain in 55(78.6%), backache in 32(45.7%), cushing syndrome 24(34.28%), dental caries in 8 (11.4%), tremor in 7(10%), carpal tunnel syndrome in 6 (8.57%), twitching and fracture (femor) in 2(2.9%).

The number of patients who used immunosuppressive drug were 40 (57.14%), among those who used IS drugs; 11patients (27.5%) used more than one IS drug. Most of these patients received cyclophosphamide in 28 patients (40%), cyclosporine in 19 patients (27%), tacrolimus in 3 patients (4.3%) and myfortic in 2 patients (2.9%).

The PTH level was statistically significant increased in group B while serum vitamin D was decrease in group B and statistically significant as compared to group A.

Table 1: Comparison of the demographic, laboratory and pathological characteristics between two groups of SSNS.

Variables		Infrequent relapse (n=36)	Frequent relapse + steroid dependent NS (n-34)	Total (n=70)	P* value
		Mean ± SD	Mean ± SD	Mean ± SD	
Age (year)		8.8.57 ± 3.42	9.58 ± 2.91	9.06 ± 3.20	0.189
Gender	Male No. (%)	23 (63.9)	25 (73.5)	48 (68.6)	0.385
	Female No.(%)	13 (36.1)	9 (26.5)	22 (31.4)	
Body weight(kg)		30.69 ± 11.76	35..12 ± 12.71	32.84 ± 12.34	0.135
Height(cm)		126.39 ± 18.21	130.79 ± 13.76	128.53 ± 16.24	0.260
Tanner stage		1.50 ± 1.02	1.53 ± 0.93	1.51 ± 0.97	0.901
Duration of NS		2.23 ± 1.59	4.01 ± 2.03	3.09 ± 2.01	0.000
Cumulative dose of prednisolone/year		2667.83±1506.10	6122.65±1659.73	4345.89 ± 2343.67	0.000
Cumulative dose of prednisolone		7337.25±8301.97	24352.12±14993.04	15601.61±14691.33	0.000
S.Ca(mmol/l)		1.88±0.12	1.90 ± 0.14	1.89 ± 0.13	0.384
S.Phosphorous(mmol/l)		1.97 ± 0.26	2.05 ± 0.29	2.01 ± 0.27	0.231
S.Alkaline phosphatase		205.03 ± 76.55	206.62 ± 82.45	205.80 ± 78.89	0.934
S.PTH		35.99 ± 18.92	50.06 ± 37.20	42..83 ± 29.89	0.048
S.Vitamine D		19.53 ± 9.30	14.71 ± 8.07	17..19 ± 8.99	0.024
Kidney biopsy	MCD	3 (8.3)	8 (23.5)	11 (15.7)	0.158
	FSGS	1 (2.8)	2 (5.9)	3 (4.3)	
	Not done	32 (88.9)	24 (70.6)	56 (80.0)	

* independent t - test has been used. & Chi-square test has been used

Table 2: The correlation of radiological characteristics with the types of SSNS.

Radiological variables		Infrequent relapse (n=36)	Frequent relapse + steroid dependent NS (n-34)	Total (n=70)	P value
		Mean ± SD	Mean ± SD	Mean ± SD	
DXA LSS		-0.81 ± 1.02	-1.22 ± 0.87	-1.01 ± 0.96	0.080
DXA total Hip		0.61 ± 1.11	0.38 ± 1.22	0.50 ± 1.16	0.403
Spine	BMD (g/cm^2)	0.62 ± 0.16	0.61 ± 0.08	0.62 ± 0.12	0.770
	BMC (g)	24.02 ± 12.10	24.02 ± 6.50	24.02 ± 9.72	1.000
Total hip	BMD (g/cm^2)	0.68 ± 0.15	0.67 ± 0.09	0.67 ± 0.12	0.965
	BMC (g)	15.04 ± 6.21	15.17 ± 4.04	15.10 ± 5.23	0.922

* independent t – test has been used.

Regarding the the correlation of radiological characteristics with the types of SSNS show no statistical difference between group A and B

Total calcium daily supplementation (DRI %) were
<50% in 38 patients (54.28%)
50-<100% in 24 patients (34.28%)
≥100% in 8 patients (11.42%)

Total Vitamine D supplementation (DRI%)
<50% in 45 patients (64.28%)
50-<100% in 8 patients (11.42%)
≥100% in 17 patients (24.28%)

LSS BMD Z score
≥ -1 (no., %) (38, 54.28)
< -1 (no., %) (19, 27.14)
≤ -2.5 (no.,%) (13, 18.57)

Total hip BMD Z score
≥ -1 (no., %) (61, 87.14)
< -1 (no., %) (9, 12.85)
≤ -2.5 (no.,%) (0, 0)

Table 3: Correlation of the Clinical and Biochemical data to the Spine DXA.

Variables	Spine DXA Z score r (p-value)	p-value
Age (year)	-0.293	(0.014) *
Body weight(kg)	0.050	(0.680)
Tanner stage	0.012	(0.923)
Duration of NS	0.012	(0.922)
Cumulative dose of prednisolone/year	-0.066	(0.589)
Cumulative dose of prednisolone	-0.054	(0.655)
s.Ca(mmol/l)	-0.128	(0.290)
s.phosphorous(mmol/l)	-0.163	(0.178)
s.alkaline phosphatase	0.034	(0.783)
s.PTH	-0.037	(0.761)
s.Vitamine D	-0.041	(0.735)

Pearson correlation coefficient & t-test for correlation

Table 4: Correlation of the Clinical and Biochemical data to the Total Hip DXA.

Variables	Total hip DXA Z score r (p-value)	p-value
Age (year)	-0.420	(0.000) *
Body weight(kg)	0.086	(0.481)
Tanner stage	-0.049	(0.690)
Duration of NS	-0.007	(0.951)
Cumulative dose of prednisolone/year	0.026	(0.831)
Cumulative dose of prednisolone	-0.001	(0.997)
s.Ca(mmol/l)	-0.148	(0.222)
s.phosphorous(mmol/l)	-0.251	(0.036) *
s.alkaline phosphatase	-0.029	(0.813)
s.PTH	0.155	(0.200)
s.Vitamine D	-0.212	(0.078)

Correlation of the clinical and biochemical data to the DXA Z score were non significant except for age which were weakly negative and significant for both LSS and total hip DXA Z score (LSS r = -0.293, P= 0.014) (total hip r =-0.420, P=0.000).

S. phosphorous to total hip DXA Z score show weakly negative and significant correlation (r = - 0.251, P=0.036).

DISCUSSION

Idiopathic nephrotic syndrome is one of common renal diseases that occur in children. glucocorticoids are the main treatment of this disease which have many adverse effects.

In this study we evaluate the undesirable effect of glucocorticoid on the bone of children with steroid sensitive nephrotic syndrome, as these children at high risk of bone loss from frequent and long term use.

In this study we compare the demographic, laboratory and radiological characteristics between group A (which include 36 patients with infrequent relapsing NS) and group B (which include 34 patients with frequent relapsing and steroid dependent NS)

The ages of children with idiopathic nephrotic syndrome in this study ranged from 4-18years old, mean 9.06 ± 3.20 years, a study of soliman et al of the bone geometry in children with INS show mean age 9.06± 3.9years.[27]

The study show male predominance (68.6%), this agrees with the study done by Rhuma et al for children with INS on prolonged steroid therapy.[28]

The increasing body weight is one of the adverse effect of glucocorticoid which will be more with higher dose and frequent prolonged use.

The anabolic effect of glucocorticoid on body weight occur due to increase appetite and low energy expenditure through stimulation of neuropeptide Y and down regulation of corticotrophine hormone.[24]

In this study comparable difference in mean weight between group A and B similar to a study by sharawat k indar et al in which group 2(FRNS, SD, SRNS) have comparable difference but not significant than group 1 (initial episode and IFNS).[29] the same result with a study by Ribeiro et al.[30]

Mean s.Ca below normal in both groups as the glucocorticoids decrease the intestinal absorption of calcium with increase tubular calcium excretion, this similar to El-Mashad GM, Who found lower level of ionized Calcium than control but no statistical difference In the mean s.Ca level between the two groups.[31] also this is similar to a study by Sinha N et al Who found no difference in s.Ca level between patients and control this may be explained by geographical variation or due to the use of calcium supplement.[32]

Alkaline phosphatase represent a marker of osteoblast activity and reflect bone formation. In children, bone specific alkaline phosphatase form 80-90% of total alkaline phosphatase in the absence of liver disease.[33]

There are an increase in the mean s.phosphate and total alkaline phosphatase specially in group B, this results similar to a study of Soliman et al.[27]

GCs impair the function and lifetime of osteoblasts and osteocytes while increasing the survival of osteoclasts, altering the balance of bone resorption and formation.[15]

Mean PTH value increase among children in group B in comparison with group A and statistically significant, this is similar to a study Kuroki Y et al.[34]

Increase PTH release could be caused by low calcium level as a consequence of glucocorticoid use that result in decrease intestinal absorption of calcium and increase renal tubular loss of calcium.[35]

Vitamin D deficiency prevalent in children with INS,[36] due to lose 25-hydroxyvitamin D [25(OH)D] in their urine and have low amounts of this metabolite in their blood.[37]

other factors contribute to vitamin D deficiency as whole body clothing, lack of outdoor activities, enviromintal pollution and restricted diary product.(38) Similar to a study selewski T et al (36)

The study of canalis show that glucocorticoids can lead to decrease bone formation and consequently bone loss by means of suppression of osteoblast differentiation and increasing of apoptosis of mature osteoblast, as a result osteoporosis and pathological fracture can occur in these patients.[39]

The GH/IGF1 axis has anabolic effect on bone development and density. High amounts of glucocorticoids inhibit these hormones.[40]

There is a predominance of the average LSS BMD Z score among patients (54.28%) while osteopenia (27.14%) and osteoporosis (18.57%) which is similar to a study of Soliman et al in which the average LSS BMD Z Score was 63%, osteopenia 26.7% and osteoporosis 13.3%[27] and a study of Phan V et al.[1]

The mean LSS BMD Z Score (-1.01 ±0.96) and LSS BMD value (0.62±0.12) were low similar to a study of El-Mashad et al[31] in which the mean LSS BMD Z Score was -1.11±1.08 and LSS BMD value 0.61±0.10 Mean LSS BMD Z Score and mean total hip BMD Z Score were lower in group B than group A but not statistically significant, this similar to a study by Nurmalia et al who

observed lower LSS BMD Z Score in SD and FRNS than in IFRNS.[41]

Higher cumulative dose of steroid and cumulative dose per year were associated with significant effect on LSS BMD and increase bone loss which is similar to a study Sharawat I et al[29] and of Aceto et al[35]

The study of Basiratnia et al elucidated that steroid dependent nephrotic patients prone to bone loss caused by higher cumulative dose of steroid.[42]

More bone loss associated with increase cumulative dose of steroid was also found in the studies of sabyasachi som et al[43] and Leonard MB et al.[44]

Older age of onset was correlated negatively and significant to LSS BMD Z Score (-0.293, p-value 0.014) and total Hip BMD Z Score (-0.420, p-value 0.000), similar to a study by Soliman S.A.[27] and Sharawat et al.[29]

However duration of NS not statistically significant with LSS and total Hip BMD Z Score similar to a study by Gulati et al.[45]

The correlation of body weight, tanner stage and duration of NS have a weak positive effect to the LSS BMD Z score despite the effect of GC on the bone. in healthy children increase in body weight and tanner stage associated with increase in BMD Nakavachara P et al[46] may be due to use of calcium and vitamin D supplement similar to a study by Gulati et al.[45]

Other data like cumulative dose of GC, cumulative dose of GC per year, S.Ca, S. phosphorous S.PTH and S.Vitamin D weak negative non significant correlation with LSS BMD Z score. Sharawat I[29] and Soliman S. A.[27]

Total hip BMD Z score negative correlation but not significant with other clinical and biochemical data, similar to a study by Arabi A et al.[47]

A population-based research heightened susceptibility to fractures in children who had more than four courses of glucocorticoid treatment.[31]

In our study no evidence of fracture among children even those who show osteoporosis with DXA Scan.

Limitation

The limitation of this study is the short duration of the study, absence of vitamin D level before starting glucocorticoid treatment, in addition to the assessment of BMD using spine and total hip DXA only instead of total body not including the head.

CONCLUSION

In children with nephrotic syndrome, more frequent and higher doses of glucocorticoid associated with bone loss as assessed by DXA scan, older age at onset more prone to bone mass loss, reflect the importance of assessment of bone mineral density in these patients with the use of DXA scan regularly, in addition to prophylactic use of vitamine D and calcium supplement during steroid treatment.

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