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Bone Mineral Density in Children with Nephrotic Syndrome Treated under GC for More than 2 Years

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Abstract

Background: Nephrotic Syndrome (NS), common in the pediatric population is typically treated with high-dose glucocorticoid (GC). Long-term GC treatment in refractory cases results in osteoporosis susceptibility. Immunosuppressants adjuvant to GC, used to induce remission in steroid-resistant NS, have shown controversial effects on bone density. This study aims to evaluate and compare bone density in children with NS undergoing GC therapy for ≥2 years with or without immunosuppression using DEXA.

Methods: Twenty-three NS patients were enrolled in the study and underwent DXA scan. Demographic data and years of disease, and electrolytes including calcium, phosphorus, and vitamin D levels, as well as creatinine, Glomerular Filtration Rate (GFR), and albumin were documented.

Results: DEXA scan showed low bone density in 4 out of 23 participants (17.4%), two of whom had scores lower than -2, which is indicative of osteoporosis, 2 of whom received cyclosporine and one received tacrolimus adjuvant therapy. Disease chronicity was significantly higher in children with lower whole-body Z-scores. Lower than normal vitamin D levels were detected in 68% of cases.

Conclusion: Our observations revealed a 2:1 ratio of cyclosporine to tacrolimus use in patients in Z-score <-1. We suggest that pediatric patients undergoing ≥2 years of GC therapy, especially in high doses or adjuvant to immunosuppressants, be screened for bone loss using DEXA scan for timely diagnosis and management. Furthermore, clinicians should be aware of the beneficial effects of vitamin D supplements in long-term GC therapy and evaluate their patients for vitamin D and calcium deficiency.

Key Words: Bone Density, Nephrotic Syndrome, Glucocorticoids, Immunosuppressants.

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1- INTRODUCTION

Nephrotic Syndrome (NS), common in the pediatric population, is characterized by nephrotic range proteinuria, generalized edema, and hypoalbuminemia without renal dysfunction. Children are typically treated with high-dose Gluco-Corticoid (GC), achieving remission in most cases (1). However, after tapering GC, the majority of children experience relapse, requiring treatment with repeated courses of GCs with doses far exceeding the amount believed to make adults susceptible to osteoporosis (2). Osteoporosis is a systemic skeletal disorder characterized by low bone mass and bone microstructural degradation, increasing bone fragility and fracture susceptibility (3) and is often considered as a disease of old age; however, it has been increasingly documented in children and teens, including those receiving GC therapy(4). Loss of bone mass as a result of GC therapy occurs through suppression of osteoblast activity and thus bone formation (5, 6), in addition to osteoclastogenesis promotion leading to bone resorption (7). In fact, long-time GC therapy is a leading cause of osteoporosis in both adults and children (8).

Immunosuppressants adjuvant to GC have long been used to induce remission in steroid-resistant NS (9). The effect of immunosuppressors like cyclosporine and tacrolimus on bone remodeling is controversial. Although cyclosporine is a glucocorticoid-sparing agent and may therefore protect against prednisone-induced osteopenia, combined therapy has been shown to reduce BMD in renal and heart transplant patients (10, 11). Similarly, tacrolimus is associated with rapid bone loss following heart-transplant (12), However as an adjuvant therapy to low-dose steroids it preserves BMD better than cyclosporine concomitant with normal doses of GC in renal transplant patients (13). To our knowledge, the effect of immunosuppressants add-on to GC on bone density has not been documented in pediatric NS. Bone mineral density is usually measured using Dual-Energy X-ray Absorptiometry (DEXA), a 2-dimensional imaging method of the entire human skeleton and of sites known to be most vulnerable to fractures, particularly the lumbar spine (14).

This study aims to evaluate and compare whole body and L1-L4 bone density in children with NS undergoing GC therapy for ≥2 years with or without immunosuppression using DEXA, which considering the notable effect of long-term GC therapy on bone density, can add valuable insights to the field.

2- MATERIALS AND METHODS

This is a cross-sectional study performed at a pediatric tertiary care center in Iran. Children in the age range of 5-18 diagnosed with NS who had been treated with GC for more than 2 years with or without immunosuppressants were entered into the study. After obtaining written informed consent from the parents or legal guardians, all participants underwent DXA scan to determine L1-L4 and whole-body BMD. Demographic data and years of disease were also documented. Electrolytes including calcium, phosphorus, vitamin D, creatinine, glomerular filtration rate (GFR), and albumin were measured.

2-1. Data Analysis

All data was analyzed using SPSS 20.0 (SPSS Inc., USA). While continuous variables were expressed as mean ± standard deviation, categorical data were expressed as n (%). The data was analyzed by Bonferroni post hoc analysis. $P < 0.05$ was considered statistically significant.

3- RESULTS

Twenty-three patients who met the inclusion criteria entered the study, among

whom, 48% were female (n=11), with a mean age of 8.48 ± 3.54. More than half (52%) of the sample pool received daily high dose prednisone (50 mg), and only 16% were treated with 5mg of prednisone every day. Eight children (32%) received adjuvant therapy with immunosuppressors. Mean years of disease was 4.26 years.

Laboratory findings revealed vitamin D deficiency (<20 ng/ml) in 40% of cases and inadequate vitamin D levels in 28% (20-30 ng/ml). DEXA scan showed low bone density in 4 out of 23 participants, two of whom had scores lower than -2, which is indicative of osteoporosis. Measured Z-scores of L1-L4 and whole-body bone density are listed in **Table 1**.

Table-1: L1-L4 and whole-body Z-scores

Z-score	L1-L4		Whole Body	
	Frequency	Percentage	Frequency	Percentage
Z-score> -1	19	82.6	19	82.6
-1>Z-score>-2	2	8.7	3	13.04
Z-score<-2	2	8.7	1	4.34

The correlations investigated between BMD and all study variables were not significant except for vitamin D level. Based on Bonferroni post hoc analysis, mean levels of vitamin D were significantly higher in children with L1-L2 Z-score<-2 (p=0.028), one of whom had a history of long bone fracture and they both had received long-term treatment with vitamin D supplements. Children with whole-body -2<Z scores<-1 had higher Vitamin D levels, but the difference was not statistically significant (p=0.174). Vitamin D levels correlating to patient Z-scores are shown in **Table 2**.

Post-hoc analysis showed significantly higher creatinine levels in children with L1-L4-2<Z-score<-1 (p=0.013). Disease chronicity was significantly higher in children with lower whole-body Z-scores (p=0.021). The study variables were compared in L1-L4 and whole-body Z-scores (**Table 3**).

4- DISCUSSION

In this cross-sectional study we evaluated bone density in 23 children with NS who had undergone GC therapy for more than 2 years, 17.4% (n=4) of whom having lower than normal Z-Scores in both L1-L4 region and the whole-body. Out of these four participants, two received high-dose GC (50 mg prednisolone daily), while one also took tacrolimus. The other two received cyclosporine adjuvant to low-dose GC therapy and one had a history of long bone fracture.

BMD values are influenced by age, height, gender and nutritional status. Thus Z-scores (matched for age) are the best way to evaluate BMD in children (15). Bone density loss caused by GC therapy has long been documented and the earliest changes of GC-induced bone loss are seen in the lumbar spine because of its high BMD (16). Recently, Soliman et al. reported lower than normal lumbar bone density in 40% of their cohort of pediatric NS patients receiving long-term GC therapy (17). Even in GC-responsive NS, higher cumulative dose of GC in children who suffered more frequent relapses, was associated with lower lumbar BMD (18, 19). Corroborating these findings, we observed significantly lower whole-body Z-scores in patients whose disease was more chronic. It can be concluded that bone surveys should focus on the lumbar region for early bone loss detection.

Table-2: Vitamin D levels in relation to patient Z-scores

Bone density status		Vitamin D (Mean ± SD)	P value
L1-L4	Z-score> -1	22.36 ± 9.62	P > 0.05
	-1>Z-score>-2	32.24 ± 4.73	0.024
	Z-score<-2	48.11 ± 34.92	0.028
Whole-body	Z-score> -1	22.44 ± 9.71	P > 0.05
	-1>Z-score>-2	29.83 ± 8.43	0.174
	Z-score<-2	23.42 ± 0	P > 0.05

Table-3: Study variables in relation to L1-L4 and whole-body Z-scores

Variable	L1-L4 Z-score (mean ± SD)		P	whole-body Z-scores (mean ± SD)		P
Z score	-1 to -2	>-2	value	-1 to -2	>-2	value
age	11.9±1.31	10.1 ± 7.17	0.333	8.23±3.31	9.29±3.48	0.560
Calcium	9.15±1.04	9.45±0.26	0.238	9.95±0.79	9.54±0.82	0.358
Phosphorous	4.73± 0.66	5.18±0.48	0.807	5.18± 0.79	4.77±0.81	0.357
Albumin	3.35±1.62	4.80±0.26	0.271	3.88± 0.88	4.58±0.25	0.138
Cr	1.35±0.77	0.92±0.6	0.012	0.72±0.32	0.78±0.24	0.717
GFR	52.61±38.74	64.53±22.04	0.0161	76.17±18.38	69.8±12.37	0.518
Years of disease	8±2.82	4 ± 1.41	0.127	3.17±2.14	7.0±.55	0.021

Treatment with tacrolimus and cyclosporine in transplant patients is associated with rapid bone loss which is exacerbated in the cases of high-dose adjuvant GC (20). The effect of these immunosuppressants on bone mineral density in pediatric NS has not been studied, but we observed lower Z-scores in both the lumbar region and in the whole body in the 3 patients receiving tacrolimus/cyclosporine plus GC. It has been shown that immunosuppression protocols with lower doses of prednisone administration over shorter time intervals may help prevent post-transplantation bone loss (21). This approach may also be useful in preserving bone density in NS patients; as Shimizu et al. reported, cyclosporine adjuvant to GC therapy decreased BMD loss in GC-dependent NS (22). However, tacrolimus in combination with low-dose GC seems more favorable than cyclosporine, considering the lower risk of relapses (23) and better BMD preservation (13). Our observations confirmed this finding, with a 2:1 ratio of cyclosporine to tacrolimus use in patients in the Z-score <-1.

Although it has been shown that calcium and vitamin D supplementations are associated with preventing GC therapy-induced BMD loss (24, 25), inadequate or deficient vitamin D levels were present in 68% of our cases, highlighting the need for better recognition and management of bone disease in pediatric NS. Notably, their vitamin D status has been shown to be worse than that in healthy children, even in patients with steroid-sensitive nephrotic syndrome (26).

4-1. Limitations of the study

Our findings should be interpreted in the light of our limitations. Our sample pool is relatively small; however, it is mostly a consequence of enrolling patients with ≥2 years of GC therapy, which is what sets our study apart. We also did not have baseline Z-scores for our patients, which is a given for cross-sectional studies. Although DEXA scan can only yield 2-dimensional imaging, it is readily

accessible and affordable, making it a great choice for screening. The effect of immunosuppressants on bone density has rarely, if ever, been studied in pediatric NS. Our study provides preliminary evidence of these effects, which should be confirmed by further research.

5- CONCLUSION

The disease mechanisms and the treatment side-effects in pediatric patients with NS turns them into a vulnerable population who need special considerations. We suggest that pediatric patients undergoing ≥2 years of GC therapy, especially in high doses or adjuvant to immunosuppressants, be screened for bone loss using DEXA scan for timely diagnosis and management. Furthermore, clinicians should be aware of the beneficial effects of vitamin D supplements in long-term GC therapy and evaluate their patients for vitamin D and calcium deficiency, so as to be able to early manage these insufficiencies.

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