

Assessment of Biochemical measurements with vitamin D deficiency in nephrotic syndrome patient

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Abstract

OBJECTIVE: To determine the frequency of vitamin D deficiency and bone mineral metabolism abnormalities in patients with nephrotic syndrome.

PATIENTS AND METHODS: Between June to December 2019, all patients who fulfilled the inclusion criteria and visited to SIUT, Karachi were included in the study, which is a descriptive cross sectional study. Informed consent was taken after explaining the procedure, risks and benefits of the study. Blood samples of all the patients were taken for measurement of vitamin D and bone mineral metabolism abnormalities.

RESULTS: Out of 92 patients, 51(55.4%) were male while 41 (44.6%) were female Mean $\pm$ SD of age was 32.76 ± 10.16 years. Vitamin D deficiency was found in 49 (53.3%) patients. Hypocalcemia occurred in 48 (52.2%) patients. Raised Alkaline phosphate was found in 42 (45.7%) patients.

CONCLUSION: It is to be concluded that vitamin D deficiency and bone mineral metabolism abnormalities were documented in considerable number of patients presenting with nephrotic syndrome.

Key Words: Vitamin D Deficiency, Bone Mineral Metabolism, Nephrotic Syndrome, Calcium

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DOI: 10.53778/pjkd81247

Received March 14,2024 and accepted March 31,2024

PJKD 2024;8(1):27-33

Introduction

Patients with nephrotic syndrome (NS) frequently exhibit abnormalities of calcium and vitamin D homeostasis, mainly hypocalcemia and reduced circulating vitamin D levels. Vitamin D-binding globulin (DBG), which binds up to 98% of the 25-hydroxy-vitamin D (25(OH)D) and has a molecular weight lower than that of albumin, may be lost in the urine causing a low globulin bound (25(OH)D) in blood.¹⁻⁴ However, the free fraction vitamin D (calcidiol) remains normal.⁵⁻⁷

A study conducted by Nielsen et al. have reported vitamin D deficiency in 93% of the patients, out of which 86% had severe deficiency, presenting with nephrotic syndrome.⁶ Selewski et al. found vitamin D deficiency in 100% of their studied patients presenting with nephrotic syndrome.⁷ A study conducted by Sheikh A et al reported vitamin D deficiency (48.6%) in nephrotic patients.⁸ The consequences of low vitamin D on bone metabolism in nephrotic syndrome remains debatable.⁹⁻¹⁰ A study conducted in India by Yadav et al. concluded that vitamin D deficiency is associated with lower levels of calcium

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and phosphorus and recommended calcium and phosphate supplementation should be given to patients with NS.¹¹

Two studies in which bone biopsies were performed in a small number of nephrotic patients with normal renal functions, showed that about 50% patient of study subject had osteomalacia.¹²⁻¹³ In contrast a study by A. Korkor did not find any evidence of osteomalacia in bone biopsy specimen of nephrotic syndrome patient despite low level of vitamin D.¹⁴ Vitamin D deficiency is quite prevalent among general population of our country, so it is likely that patient with nephrotic syndrome may have severe vitamin D deficiency compared to other regions.¹⁵

Vitamin D deficiency was found in 74% nephrotic patients in a study conducted by Aggarwal A et al in the year 2016.¹⁶ We set out to analyze the frequency of vitamin D deficiency and bone mineral metabolism abnormalities in patients with nephrotic syndrome.

In Pakistan, the incidence of vitamin D deficiency and bone mineral metabolism abnormalities is on the rise and to the best of our knowledge based on literature search very scanty studies are available in national and international level focusing on adult nephrotic patients in terms of vitamin D deficiency and bone mineral metabolism abnormalities. As these patients are usually treated with high dose steroid for prolong period and relatively in high risk of developing bone disease. So, this was the need of hour to carry out this analysis in our population in order to find out the current magnitude of vitamin D deficiency and bone mineral metabolism abnormalities. By doing this study, we developed guidelines for early diagnosis, prevention and treatment of such patients. Furthermore, the findings of this study guided the clinicians to treat the patients effectively on time and to make the strategies for further research in this respect to improve the quality of care we provide to these patients.

PATIENTS & METHODS

This was a descriptive Cross-Sectional Study, carried out at Department of Nephrology, Sindh Institute of Urology & Transplantation (SIUT), Karachi, between June to December 2019. Based on previous study which revealed vitamin D deficiency (74%) in nephrotic patients [16]. 92 patients were included, calculated by using W.H. O sample size calculator with margin error (d)=9% and 95% confidence level. Non-Probability, Consecutive Sampling was done.

INCLUSION CRITERIA: All adult patients (>18 years of age) and both gender with e-GFR more than > 60% ml/min, presenting with nephrotic syndrome were included in study. Nephrotic Syndrome was defined as edema, hypoalbuminemia, proteinuria and hypercholesterolemia. Vitamin D levels < 12 ng/mL on 25-hydroxy vitamin D blood test was labelled as vitamin D deficiency.

EXCLUSION CRITERIA: Patients with history of vitamin D supplement during last three months, who received steroid during past 3 months' period, history of calcium supplements, Diabetic patients fasting (BSR > 126 mg/dl or taking antibiotic drugs for more than 6 months, patients with history of carotid surgery, ischemic heart disease or stroke and smokers (smoke > 10 pack-year either currently smoking for > 1 year or quit smoking since < 6 months were excluded.

DATA COLLECTION: A total number of 92 patients with diagnosis of nephrotic syndrome (NS) fulfilling the inclusion criteria of the study were registered. A written informed consent was taken from all patients after explaining the objectives of the study, ensuring them confidentiality of the information provided and fact that there was no risk involved to the patient while taking

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part in this study. Blood samples were taken to all the patients for measurement of vitamin D and bone mineral metabolism abnormalities in accordance with operational definition. Confounding variables and biasness were controlled by strictly following inclusion and exclusion criteria.

DATA ANALYSIS: Data analysis was carried out by using SPSS version 23 software. Mean and standard deviation were used to present age, weight, height and BMI. Frequency and percentage were calculated for gender and outcome variable i.e. vitamin D deficiency and bone mineral metabolism abnormalities i.e. (raised alkaline phosphatase and hypocalcaemia). Effect modifiers such as age, gender and BMI were controlled by stratification. Post-stratification, chi-square test was applied to assess the effect of these on outcome variables. Considered $P < 0.05$ was taken as significant.

RESULTS:

In this study 92 patients were included to assess the frequency of vitamin D deficiency and bone mineral metabolism abnormalities in patients with nephrotic syndrome. Among the studied population 51 were male and 41 were female with mean age of 32.76 ± 10.16 years, mean Body mass index (BMI) in studied population was 26.71 ± 3.68 .

Vitamin D deficiency was found to be in 49 (53.3%) patients, Hypocalcemia was noted in 48 (52.2%) patients, Raised Alkaline phosphate was found abnormal in 42 (45.7%) patients.

Stratification of age group, gender and body mass index were done with respect to vitamin D deficiency and bone mineral metabolism abnormalities (hypocalcemia & raised alkaline phosphate) in patients in order to found significant difference from Table 1.

Table 1: Stratification of different parameters and their significance in 72 patients with nephrotic syndrome.

Parameter	Age (years) 18-40	Age (years) >40	P value*	BMI 18-24	BMI >24	P value*	Gender Male	Gender female	P value*
Vit. D deficiency			0.495			0.001			0.275
Yes									
No	37 35	12 8		4 16	45 27		28 23	21 20	
Hypocalcemia			0.019			0.006			0.273
Yes									
No	33 39	15 5		5 15	43 29		24 27	24 17	
Raised Alk Phos			0.280			0.343			0.252
Yes									
No	35 37	7 13		11 9	31 41		25 26	24 16	

*Chi Square test applied

Discussion:

Chronic kidney disease (CKD) is a modern-day global epidemic and it is now recognized as a public health issue.¹⁷ Disturbance in mineral and bone metabolism accompanied by soft tissue and vascular calcification is one of the most common and important consequences of CKD development and progression. This systemic disorder is now referred to as CKD – mineral and bone disorder (CKD – MBD).¹⁸ Renal osteodystrophy is a bone disease characterized by deranged bone morphology in patients with CKD. It is now considered as a component of CKD – MBD. Although renal osteodystrophy is

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typically seen in advanced kidney failure, other features of CKD – MBD begin to develop at earlier stages of CKD and contribute to the pathogenesis of renal osteodystrophy.¹⁹ Alteration in vitamin D metabolism is one of the key features of CKD – MBD that has major clinical and research implications.

Vitamin D is important for normal development and maintenance of the skeleton. It is well known that Vit. D deficiency is related to rickets and osteomalacia. The relationship between Vit. D and bone mineral density and osteoporosis are still controversial while new evidence suggest that Vit. D may play a role in other bone conditions such as osteoarthritis and stress fractures. Vitamin D is not in the strict sense a vitamin, but a hormone. Vitamin D is synthesized in the skin by the action of sunlight. Once vitamin D is formed in the skin or ingested in the diet, it journeys to the liver and kidney, where it is hydroxylated sequentially on carbons 25 and 1, respectively, to form its biologically active form 1,25-dihydroxyvitamin D (1,25[OH]₂D). The major physiologic function of vitamin D is to maintain the extra-cellular and blood concentrations of calcium within the physiologic range in order to maintain cellular activities and neuromuscular function. Vitamin D is not only important for the skeletal health in healthy growing children, but this hormone is also essential for maintaining a healthy skeleton throughout our lives.

Vitamin D is also important in the regulation of calcium. It is synthesized in the skin or can be obtained through dietary sources; it is carried in the bloodstream to the liver, where it is converted into calcidiol. Calcidiol can then be metabolized by the kidney, via 1α-hydroxylase, to the biologically active form of vitamin D, calcitriol, which then acts throughout the body and essentially functions as a hormone. The most important function is exerted on the small intestine, where calcitriol regulates the intestinal reabsorption of calcium and, to a lesser degree, phosphorus. Calcitriol inhibits PTH secretion. In summary, the integrated actions of PTH and vitamin D on target tissues gives precise control of serum concentrations of calcium and phosphorus.²⁰

Vitamin D has a variety of actions on calcium, phosphate, and bone metabolism. Its most important biological action is to promote enterocyte differentiation and the intestinal absorption of calcium and phosphorus, thereby promoting bone mineralization. At high vitamin D concentrations, under conditions of calcium and phosphate deficiency, it also stimulates bone resorption, thereby helping to maintain the supply of these ions to other tissues. Vitamin D deficiency or resistance interferes with these processes, sometimes causing hypocalcemia and hypophosphatemia. Since hypocalcemia stimulates the release of parathyroid hormone (PTH), however, the development of hypocalcemia is often masked. The secondary hyperparathyroidism, via its actions on bone and the kidney, partially corrects the hypocalcemia but enhances urinary phosphate excretion, thereby contributing to the development of hypophosphatemia and osteomalacia.

Patients who have nephrotic syndrome and normal renal function frequently have abnormalities in calcium metabolism that manifest as hypocalcemia, hypocalciuria and reduced intestinal absorption of calcium.^{21,22} Although hypocalcemia was initially attributed to hypoalbuminemia, many patients with nephrotic syndrome have low levels of ionized calcium.²³⁻²⁵

Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia associated with peripheral edema [94]. Patients with Nephrotic syndrome (NS) lose 25-hydroxyvitamin

D in the urine and can have low blood levels of this metabolite. These patients may also have secondary hyperparathyroidism with normal renal function and display evidence of defective mineralization of bone and enhanced bone resorption.²⁶ 25-Hydroxyvitamin D (25-OHD) circulates in blood, bound to Vitamin D binding protein. Of the possibility is that patient with Nephrotic syndrome lose 25-Hydroxyvitamin D with protein in the urine. If the magnitude of such losses of 25-Hydroxyvitamin D is marked and its duration is prolonged, a state of vitamin-D deficiency may ensue and be responsible for the abnormalities of calcium homeostasis.²⁷⁻³⁰

Decreased BMD has been described in a wide spectrum of paediatric disorders ranging from juvenile rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus therapy, leukaemia and asthma, as well as after bone marrow transplant, cardiac transplant, liver transplant and kidney transplant.³¹⁻³³

In our study, the mean age was 32.76 ± 10.16 years. The study of Joshi U, et al reported the mean age as 44.4 ± 15.1 years. Chauhan R, et al noted mean age in his study as 56.02 ± 9.89 years.^{34,35} In this study, the mean weight and height were 75.09 ± 9.47 kg and 1.68 ± 0.78 meters, respectively. In current study, the mean body mass index was 26.71 ± 3.68 kg/m². Cetin N, et al noted BMI as 21.5 ± 3.89 kg/m² while Bhan I, et al reported the mean body mass index as 32.0 ± 9.5 kg/m².^{36,37} In present study, out of 92 patients, 51 (55.4%) were male while 41 (44.6%) were female. There were 56.25% males and 43.75% females in the study of Cetin N, et al [36]. In the study of Erdem E, et al, there were 40 (53%) males and 35 (47%) females.³⁸

In a recent study, Vitamin D deficiency was found in 49 (53.3%) patients. Bhan I, et al reported the vitamin D deficiency in 34% patients. However, Bansal B, et al noted a high prevalence of 88.0% patients who were vitamin D deficient. Marquardt P, et al. noted the deficiency in 32.7% patients.^{37,39,40} Another study conducted by Agarwal A, et al on pediatrics population who were taken steroid reported the vitamin D deficiency 74% in nephrotic patients.¹⁶ While in our study was included on other patients who never taken steroid or any other drugs. In this study, hypocalcemia was noted in 48 (52.2%) patients. In our study, raised alkaline phosphate was found abnormal in 42 (45.7%) patients. In present study, stratification of confounders / effect modifiers with respect to vitamin D deficiency, insignificant difference was noted in age group ($P=0.495$), body mass index ($P=0.001$) and gender ($P=0.725$). In current study, stratification of confounders / effect modifiers with respect to hypocalcemia, insignificant difference was documented in age group ($P=0.019$), body mass index ($P=0.006$) and gender ($P=0.273$). In the current study, stratification of confounders / effect modifiers with respect to alkaline phosphatase insignificant difference was reported in age group ($P=0.280$), body mass index ($P=0.343$) and gender ($P=0.252$).

Conclusion

It is to be concluded that vitamin D deficiency and bone mineral metabolism abnormalities were documented in considerable number of patients presenting with nephrotic syndrome. As it is associated with increased risk of complications therefore, it is imperative to identify the underlying risk factors to address the burden of diseases and to optimize the management strategies for this already compromised cohort of patient.

References

1. Geme JW, Schor NF, Behrman RE. Nelson textbook of pediatrics. Elsevier Health Sciences; 2016.
2. Esmaeili M, Azarfar A, Hoseinalizadeh S. Calcium and vitamin D metabolism in pediatric nephrotic syndrome; an update on the existing literature. *Int J Pediatr*. 2015;3(2):103-9.
3. Banerjee S, Basu S, Sengupta J. Vitamin D in nephrotic syndrome remission: a case control study. *Pediatr, Nephrol*. 2013;28(10):1983-9.
4. Subandiyah K, Khanifa H, Kardani AK. Effect of corticosteroid and vitamin D3 as combined therapy on 25 (OH) vitamin D serum level and regulatory T (TReg) cells population in children with idiopathic nephrotic syndrome. *Bali Med J*. 2018;7(3):639-44.
5. Powe CE, Ricciardi C, Berg AH. Vitamin D-binding protein modifies the vitamin D-bone mineral density relationship. *J Bone Min Res*. 2011;26(7):1609-16.
6. Nielsen CA, Jensen JE, Cortes D. Vitamin D status is insufficient in the majority of children at diagnosis of nephrotic syndrome. *Dan Med J*. 2015;62(2):A5017.
7. Selewski DT, Chen A, Shatat IF, Pais P, Greenbaum LA, Geier P, et al. Vitamin D in incident nephrotic syndrome: a Midwest Pediatric Nephrology Consortium study. *Pediatr Nephrol*. 2016;31(3):465-72.
8. Sheikh A, Saeed Z, Jafri SA, Yazdani I, Hussain SA. Vitamin D levels in asymptomatic adults-a population survey in Karachi, Pakistan. *Plos One*. 2012;7(3):e33452.
9. Solanki JR, Sudhakaran S, Shringarpure KS. Prevalence of Vitamin D3 deficiency among pediatric patients with idiopathic nephrotic syndrome in remission: a cross-sectional observational study from Vadodara, Gujarat. *Indian Child Health*. 2018;5(7):481-3.
10. Yadav VK, Sharma S, Debata PK, Patel S, Kabi BC, Aggrawal KC. Change in bone mineral density and role of Vitamin D and calcium supplementation during treatment of first episode nephrotic syndrome. *J Clin Diagn Res*. 2017;11(9):SC18.
11. Khan AH, Iqbal R, Naureen G, Dar FJ, Ahmed FN. Prevalence of vitamin D deficiency and its correlates: results of a community-based study conducted in Karachi, Pakistan. *Arch Osteoporos*. 2012;7(1 – 2):275 – 82.
12. Iqbal R, Jafri L, Haroon A, Habib A. Illuminating the dark side-vitamin D status in different localities of Karachi. *J Coll Physicians Surg Pak*. 2013;23(8):604-6.
13. Korkor A, Schwartz J, Bergfeld M, Teitelbaum S, Teitelbaum L, Klahr S, et al. Absence of metabolic bone disease in adult patients with the nephrotic syndrome and normal renal function. *J Clin Endocrinol Metab*. 1983;56(3):496-500.
14. Goldstein DA, Oda Y, Kurokawa K, Massry SG. Blood levels of 25-hydroxy vitamin D in nephrotic syndrome. Studies in 26 patients. *Ann Intern Med*. 1977;87(6):664 – 7.
15. Shivanand I, Velagala SV, Sudhindrashayana RF. Study of prevalence of vitamin D deficiency in nephrotic syndrome. *Int J Contemp Pediatr*. 2019;6(2).
16. Aggarwal A, Yadav AK, Ramachandran R, Kumar V, Kumar V, Sachdeva N, et al. Bioavailable vitamin D levels are reduced and correlate with bone mineral density and markers of mineral metabolism in adults with nephrotic syndrome. *Nephrol*. 2016;21(6):483-9.
17. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. *Lancet* 2005;365:331 – 40.
18. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;69:1945 – 53.
19. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 2007;71: 31 – 8.
20. Al Zahrani A, Levine MA. Primary hyperparathyroidism. *Lancet*. 1997;349:1233-8.
21. Malluche HH, Goldstein DA, Massry SG. Osteomalacia and hyperparathyroid bone disease in patients with nephrotic syndrome. *J Clin Invest* 1979;63:494-500
22. Goldstein DA, Oda Y, Kurokawa K, Massry SO. Blood level of 25-hydroxyvitamin-D in nephrotic syndrome. *Ann Intern Med* 1977;87:664-7.
23. Tessitore N, BoNucci E, D'Angelo A, Lund B, Corgnati A, Lund B, et al. Bone histology and calcium metabolism in patients with nephrotic syndrome and normal or reduced renal function. *Nephron* 1984;37:153-9.
24. Freundlich M, Bourgoignie JJ, Zilleruelo G, Jacob AI, Canterbury JM, Strauss J. Bone modulating factors in nephrotic children with normal glomerular filtration rate. *Pediatrics* 1985;76:280-5.

25. Alon U, Chan JCM. Calcium and vitamin-D metabolism in nephrotic syndrome. *J Pediatr Nephrol* 1983;4:115-8.
26. Nelson W, Kliegman R. *Nelson Textbook of Pediatrics*. Philadelphia, PA: Elsevier; 2016.
27. Goldstein DA, Haldimann B, Sherman D, Norman AW, Massry SG. Vitamin D metabolites and calcium metabolism in patients with nephrotic syndrome and normal renal function. *J Clin Endocrinol Metabol*. 1981;52(1):116-21.
28. Bak M, Serdaroglu E, Guclu R. Prophylactic calcium and vitamin D treatments in steroid treated children with Nephrotic syndrome. *Pediatr Nephrol*. 2006;21:350-4.
29. Kinra S, Rath B, kabi B. Indirect quantification of lipid peroxidation in steroid responsive nephrotic syndrome. *Arch Dis Child*. 2000;82:76-8.
30. Elsevier Clinical Advisory Board, Clinical Update: Nephrotic Syndrome. 2012.
31. Cunnane G, Lane NE. Steroid induced osteoporosis in SLE. *Rheum Dis North Am* 2000;26:311-29.
32. Pitt P, Todd P, Webber D, Pack S, Moniz C. A double blind placebo controlled study to determine the effects of intermittent cyclical etidronate on bone mineral density in patients on long term oral corticosteroid treatment. *Thorax* 1998;53:351-6.
33. Sambrook PN. Inhaled corticosteroids, bone density and risk of fracture. *Lancet* 2000;355:9213.
34. Joshi U, Subedi R, Poudel P, Ghimire PR, Panta S, Sigdel MR. Assessment of quality of life in patients undergoing hemodialysis using WHOQOL BREF questionnaire: a multicenter study. *Int J Nephrol Renovasc Dis*. 2017;10:195-203.
35. Chauhan R, Mendonca S. Adequacy of twice weekly hemodialysis in end stage renal disease patients at a tertiary care dialysis centre. *Indian J Nephrol*. 2015;25(6):329.
36. Cetin N, Gencler A, Sivrikoz IA. Bone mineral density and vitamin D status in children with remission phase of steroid-sensitive nephrotic syndrome. *Saudi J Kidney Dis Transpl*. 2019;30(4):853.
37. Bhan I, Dobens D, Tamez H, Deferio JJ, Li YC, Warren HS, et al. Nutritional vitamin D supplementation in dialysis: a randomized trial. *Clin J Am Soc Nephrol*. 2015;10(4):611-9.
38. Erdem E. Proton pump inhibitors use in hemodialysis patients and serum magnesium levels. *Int J Clin Exp Med*. 2015;8(11):21689.
39. Bansal B, Bansal S, Mithal A, Kher V, Marwaha R. Vitamin D deficiency in hemodialysis patients. *Indian J Endocrinol Metab*. 2012;16(2):270.
40. Marquardt P, Krause R, Schaller M, Bach D, von Gersdorff G. Vitamin D status and cancer prevalence of hemodialysis patients in germany *Anticancer Res*. 2015;35(2):1181-87.
41. Frost M, Abrahamsen B, Nielsen TL, Hagen C, Andersen M, Brixen K. Vitamin D status and PTH in young men: A cross-sectional study on associations with bone mineral density, body composition and glucose metabolism. *Clin Endocrinol (Oxf)* 2010;73:573- 80.