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ASSOCIATION BETWEEN VITAMIN D STATUS AND DISEASE ACTIVITY IN CHILDHOOD NEPHROTIC SYNDROME

[*1]Hanin Razaq Al-Hilali, [2]Dr. Shatha Hussain Ali, [3]Khawlah Alwan Salman

[1]F.I.C.M.S (Pediatrics), Al-Imamayn Al-Kadhimein Medical City, Baghdad, Iraq.
[2]Prof. of Pediatrics, C.A.P.D., College of Medicine, Al-Nahrain University, Baghdad, Iraq.
[3]Pediatric Nephrology Unit, Department of Pediatrics, Babil Teaching Hospital for Maternity and Children, Babylon Health Directorate, Babylon, Iraq.

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***Corresponding Author: Hanin Razaq Al-Hilali**

F.I.C.M.S (Pediatrics), Al-Imamayn Al-Kadhimein Medical City, Baghdad, Iraq.

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ABSTRACT

Background: Nephrotic syndrome (NS) is one of the most frequent chronic kidney diseases in children, characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema, with potential complications including infection, thromboembolism, and acute kidney injury. **Aim:** This study aimed to measure serum vitamin D levels in children with NS and assess correlations between vitamin D3 and clinical types of NS, demographic variables (age, sex, age of onset, residence), and laboratory parameters (serum calcium, albumin, urea, creatinine, and cholesterol). **Methods:** A prospective observational study was conducted on 75 pediatric NS patients aged 1–15 years, from April 2022 to August 2022, at Imamian Al-Kadhimain Medical City, Bent Al-Huda Teaching Hospital in Al-Nasiriya, and Karbala Teaching Hospital for Children. Diagnosis and follow-up were performed in pediatric nephrology clinics. **Results:** Males predominated (74.67%), with most patients aged 6–12 years (62.67%). Frequent relapse was the most common NS type (49.33%). Vitamin D deficiency was found in 46.67% of children. Calcium deficiency (69.33%, p=0.044) and hypoalbuminemia (93.33%, p=0.006) were highly prevalent. Vitamin D deficiency was significantly higher among frequent relapse cases (64.86%, p=0.024) than in infrequent relapse (33.33%) or steroid-resistant NS (12.5%). No significant demographic associations were observed. Hypocalcemia (82.86%, p=0.018), hypoalbuminemia (100%, p=0.003), and severe proteinuria (62.86%, p=0.034) were more common with vitamin D deficiency. **Conclusion:** Most children with NS have suboptimal vitamin D levels, especially those with frequent relapses. Vitamin D levels show positive correlations with serum calcium and albumin, emphasizing the need for regular monitoring and supplementation.

KEYWORDS: Frequent relapse was the most common NS type (49.33%). Vitamin D deficiency was found in 46.67% of children.

INTRODUCTION

Nephrotic syndrome (NS) is a clinical entity characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema, resulting from increased glomerular permeability secondary to kidney damage. It commonly manifests in children with periorbital and lower limb edema, progressing to generalized swelling, ascites, pleural effusion, and genital edema. Laboratory findings typically reveal severe proteinuria (>40 mg/m²/h or protein–creatinine ratio >2.0 g/dL), hypoalbuminemia (<2.5 g/dL), and hyperlipidemia.[1] NS is classified as idiopathic (most common), secondary, or congenital. Idiopathic NS encompasses minimal change disease (MCD), mesangial proliferation, and focal segmental glomerulosclerosis (FSGS). MCD accounts for nearly 85% of pediatric cases, with over 95% showing a favorable response to corticosteroids (2). Secondary NS may arise from glomerular disorders (e.g., membranous or lupus nephritis), infections (HBV, HCV, HIV, malaria), medications, or systemic syndromes.[2]

Congenital NS manifests within the first three months of life and may result from genetic defects or congenital infections.[2,3] The annual incidence of idiopathic NS ranges from 2–7 per 100,000 children, with a prevalence of 16 per 100,000.[4] MCD represents 70–90% of cases in children under 10 years.[5] Males are affected nearly twice as often as females, though this difference diminishes in adolescence. The disease is more prevalent among Asian than Caucasian children, while African children more often present with steroid-resistant forms.[6] Edema is the hallmark symptom, often associated with infections, respiratory distress, or abdominal pain. Diagnosis requires confirmation of nephrotic-range proteinuria, hypoalbuminemia, and hyperlipidemia. Further investigations include renal function tests, viral serologies, complement levels, and autoimmune screening.[7,8]

Children with NS are predisposed to infections, thromboembolic events, acute kidney injury, pulmonary edema, hypothyroidism, and growth retardation. Vitamin D deficiency is particularly notable due to urinary loss of vitamin D–binding protein and albumin. This deficiency contributes to hypocalcemia and bone metabolism disturbances.[9,10]

Vitamin D plays crucial roles in calcium and phosphorus homeostasis, bone mineralization, and immune modulation.[11] Corticosteroids, while effective in inducing remission in approximately 80% of idiopathic NS cases, can exacerbate vitamin D loss and impair bone health. Prolonged steroid therapy also contributes to growth impairment, obesity, and behavioral issues.[12] This study aims to measure vitamin D levels in children with NS and to evaluate correlations between vitamin D3 status, NS types, demographic characteristics (age, sex, age of onset, residence), and laboratory findings (serum calcium, albumin, urea, creatinine, cholesterol).

METHOD

A prospective observational study was conducted on seventy-five pediatric patients diagnosed with nephrotic syndrome (NS) between April 1 and August 31, 2022. Participants were aged 1–15 years and were recruited from three tertiary centers: Imamian Al-Kadhimain Medical City in Baghdad, Bent Al-Huda Teaching Hospital in Al-Nasiriya, and Karbala Teaching Hospital for Children. All patients were diagnosed and followed in pediatric nephrology consultation clinics. Diagnosis of NS was based on standard clinical and laboratory criteria, including nephrotic-range proteinuria (protein excretion >40 mg/m²/hr or first-morning urine protein:creatinine ratio >2), hypoalbuminemia (<2.5 g/dL), edema, and hyperlipidemia.[12-14] A structured questionnaire designed by the researchers was used for data collection through direct interviews with patients, their caregivers, and treating physicians. The questionnaire included demographic variables (age, sex, and residence) and clinical characteristics (age at disease onset and NS type). All participants underwent laboratory investigations, including blood urea, serum creatinine, serum albumin, serum cholesterol, serum calcium, and urinary albumin assessment. Serum 25-hydroxyvitamin D [25(OH)D] concentration was measured using an enzyme-linked immunoassay (Mini-Vida Brahms®) performed in hospital laboratories or, when unavailable, in certified private laboratories. Vitamin D3 status was categorized as follows: deficiency (<12 ng/mL), insufficiency (12–20 ng/mL), sufficiency (20–100 ng/mL), and toxicity (>100 ng/mL). Children younger than one year at disease onset and those with secondary NS (resulting from systemic diseases such as systemic lupus erythematosus, infections, diabetes mellitus, malignancy, or drug exposure) were excluded. **Ethical Considerations:** Verbal informed consent was obtained from parents or guardians before enrollment. **Statistical Analysis** Data were analyzed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical data. Associations were assessed using the Chi-square test, and correlations between vitamin D levels and laboratory parameters were evaluated using Pearson's correlation test. A p-value <0.05 was considered statistically significant.

RESULTS

The study included 75 children diagnosed with nephrotic syndrome (NS). Males represented the majority (74.67%) compared to females (25.33%), indicating a clear male predominance consistent with global pediatric NS patterns. The most affected age group was 6–12 years (62.67%), followed by the younger (1–5 years) and older (≥12 years) age groups, each accounting for 18.67%. Similarly, the age of disease onset was most frequently between 1–5 years (56%), suggesting that nephrotic syndrome often begins in early childhood. Regarding residence, the distribution between urban (50.67%) and rural (49.33%) children was nearly equal, showing no significant difference in disease occurrence by location. Analysis of NS subtypes revealed that frequent relapse nephrotic syndrome (FRNS) was the most prevalent type (49.33%), followed by infrequent relapse (40%), while steroid-resistant nephrotic syndrome (SRNS) represented 10.67% of cases. This reflects a predominance of steroid-sensitive and relapsing forms, consistent with findings in other pediatric cohorts. The steroid regimen data showed that 42.67% of patients were on alternate-day therapy, 40% were off steroids, and 17.33% were receiving daily steroids, highlighting the common practice of maintaining alternate-day dosing to minimize steroid-related side effects during remission phases. In terms of vitamin D status, 46.67% of children exhibited vitamin D deficiency, 21.33% had insufficiency, and only 32% maintained sufficient levels. This high prevalence of suboptimal vitamin D status emphasizes the metabolic disturbances associated with nephrotic syndrome, particularly due to urinary loss of vitamin D–binding

protein and corticosteroid-induced bone effects. As in table 1.

Table 1: Demographic, Clinical, and Biochemical Characteristics of the Study Population (n=75).

Variable	Category	No.	%
Sex	Male	56	74.67
	Female	19	25.33
Age (years)	1–5	14	18.67
	6–12	47	62.67
	≥12	14	18.67
Age of onset (years)	1–5	42	56.00
	6–12	28	37.33
	≥12	5	6.67
Residency	Urban	38	50.67
	Rural	37	49.33
Types of nephrotic syndrome	Frequent relapse	37	49.33
	Infrequent relapse	30	40.00
	Steroid resistant	8	10.67
Steroid regimen	No steroid	30	40.00
	Alternate day	32	42.67
	Daily	13	17.33
Vitamin D level (ng/mL)	Deficiency (<12)	35	46.67
	Insufficiency (12–20)	16	21.33
	Sufficiency (20–100)	24	32.00
	Total	75	100

About two-third of children had calcium deficiency, while hypoalbuminemia was reported in the vast majority (93.33%). High serum level of urea and creatinine was found in 10.67% and 6.67% of the children, respectively. Hypercholesterolemia was confirmed in 81.33% of the children. Regarding proteinuria, most children (76%) had 2 pluses (Table 2).

Table 2: Clinic al and Laboratory findings.

Variables		Value	%
Calcium, mg/dl	Mean±SD	7.62±1.0	
	Normal	23	30.67
	Reduced	52	69.33
Albumin, g/dl	Mean±SD	2.12±0.6	
	Normal	5	6.67
	Reduced	70	93.33
Urea, mg/dl	Mean±SD	39.8±26.4	
	Normal	67	89.33
	Elevated	8	10.67
Creatinine , mg/dl	Mean±SD	0.64±0.54	
	Normal	70	93.33
	Elevated	5	6.67
Total cholesterol, mg/dl	Mean±SD	394.08±129.6	
	Normal	14	18.67
	Elevated	61	81.33
Proteinuria	0-2 plus	18	24
	3-4 plus	57	76

High serum level of urea, creatinine and total cholesterol was more common in children with SRNS (50%, 37.5% and 100%, respectively) than either children with frequent relapse (10.81%, 2.7% and 89.19%, respectively) or those with infrequent relapse (0%, 3.33% and 66.67%, respectively) with significant differences (Table 3).

Table 3: Association of clinical and laboratory characteristics with the type of NS.

Variables	Frequent relapse (n=37)	Infrequent relapse (n=30)	SRNS (n=8)	p-value
Calcium, mg/dl				
Normal	11(29.73%)	9(30%)	33(412.50%)	0.906
Reduced	26(70.72%)	21(70%)	5(62.50%)	
Albumin, g/dl				
Normal	4(10.81%)	0(0%)	1(12.50%)	0.165
Reduced	33(89.19%)	30(100%)	7(87.50%)	
Urea, mg/dl				
Normal	33(89.19%)	30(100%)	4(50%)	**<0.001**
Elevated	4(10.81%)	0(0%)	4(50%)	
Cr, mg/dl				
Normal	36(97.30%)	29(96.67%)	5(62.50%)	**0.001**
Elevated	1(2.70%)	1(3.33%)	3(37.50%)	
TC, mg/dl				
Normal	4(10.81%)	10(33.33%)	0(0%)	**0.022**
Elevated	33(89.19%)	20(66.67%	8(100%)	
Proteinuria				
0-2 plus	12(32.43%)	3(10%)	3(37.50%)	0.065
3-4 plus	25(67.57%)	27(90%)	5(62.50%)	

Each of hypocalcemia, hypoalbuminemia and high proteinuria were more common among patients with vitamin D deficiency (82.86%, 100% and 62.86%, respectively) than other status of vitamin D (table 4).

Table 4: Association of vitamin D status with clinical characteristics.

Variables	Deficient (n=35)	Insufficient (n=16)	Sufficient (n=24)	p-value
Calcium, mg/dl				
Normal	6(17.14%)	9(56.25%)	8(33.33%)	**0.018**
Reduced	29(82.86%)	7(43.75%)	16(66.67%)	
Albumin, g/dl				
Normal	0(0%)	0(0%)	19(79.17%)	**0.003**
Reduced	35(100%)	16%(100%)	5(20.83%)	
Urea, mg/dl				
Normal	32(91.43%)	14(87.50%)	21(87.50%)	0.860
Elevated	3(8.57%)	2(12.50%)	3(12.50%)	
Cr, mg/dl				
Normal	33(94.29%)	14(87.50%)	23(95.82%)	0.558
Elevated	2(5.71%)	2(12.50%)	1(4.17%)	
TC, mg/dl				
Normal	5(14.29%)	2(12.50%)	7(29.17%)	0.274
Elevated	30(85.71%)	14(87.50%)	17(70.83%)	
Proteinuria				
0-2 plus	13(37.14%)	1(6.25%)	4(16.67%)	**0.034**
3-4 plus	22(62.86%)	15(93.75%)	20(83.33%)	

Vitamin D deficiency was more frequent in children with frequent relapse NS (64.86%) than either those with infrequent relapse (33.33%) or SRNS (12.5) with significant differences. None of included demographic characteristics had a significant association with vitamin status. As in table 5.

Table 5: Association of vitamin D status with demographic characteristics, type of NS.

Vitamin D	Frequent relapse (n=37)	Infrequent relapse (n=30)	SRNS (n=8)	p-value
Deficiency	24(64.86%)	10(33.33%)	1(12.5%)	
Insufficiency	6(16.22%)	7(23.33%)	3(37.5%)	**0.024**
Sufficiency	7(18.92%)	13(43.33%)	4(50%)	
Variables	**Deficient (n=35)**	**Insufficient (n=16)**	**Sufficient (n=24)**	**p-value**

Age, years				
1-5	6(17.14%)	4(25%)	4(16.67%)	
6-12	21(60%)	11(68.75%)	15(62.50%)	0.684
≥12	8(22.86%)	1(6.25%)	5(20.83%)	
Age at the onset				
1-5	17(48.57%)	9(56.25%)	15(62.50%)	
6-12	16(45.71%)	6(37.50%)	7(29.17%)	0.794
≥12	2(5.71%)	1(6.25%)	2(8.33%)	
Sex				
Male	24(68.57%)	13(81.25%)	19(79.17%)	0.519
Female	11(31.43%)	3(18.75%)	5(20.83%)	
Residence				
Urban	16(45.71%)	9(56.25%)	13(54.17%)	0.719
Rural	19(54.29%)	7(43.75%)	11(45.83%)	

Pearson's correlation was used to explore the possible correlation of vitamin D with other variables. Vitamin D had a significant positive correlation with calcium (r= 0.240, p= 0044) and albumin (r= 0.330, p= 0.006). On the other hand, vitamin D had a significant negative correlation with protein urea (r= -0.305, p= 0.010) as shown in figures 1-3.

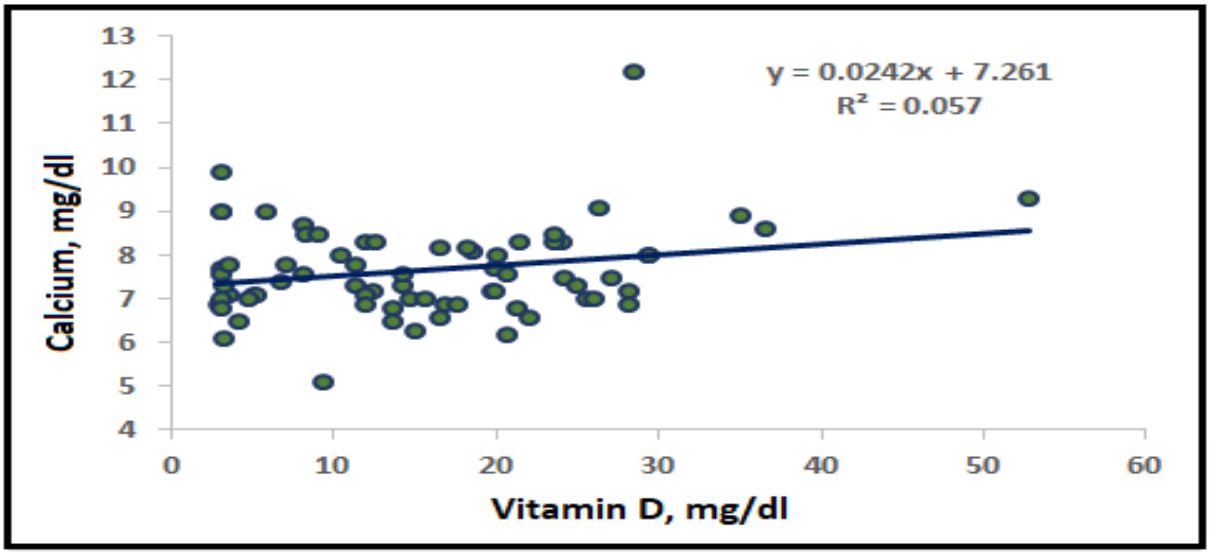

Figure 1: scatter plot and regression line between vitamin D and calcium.

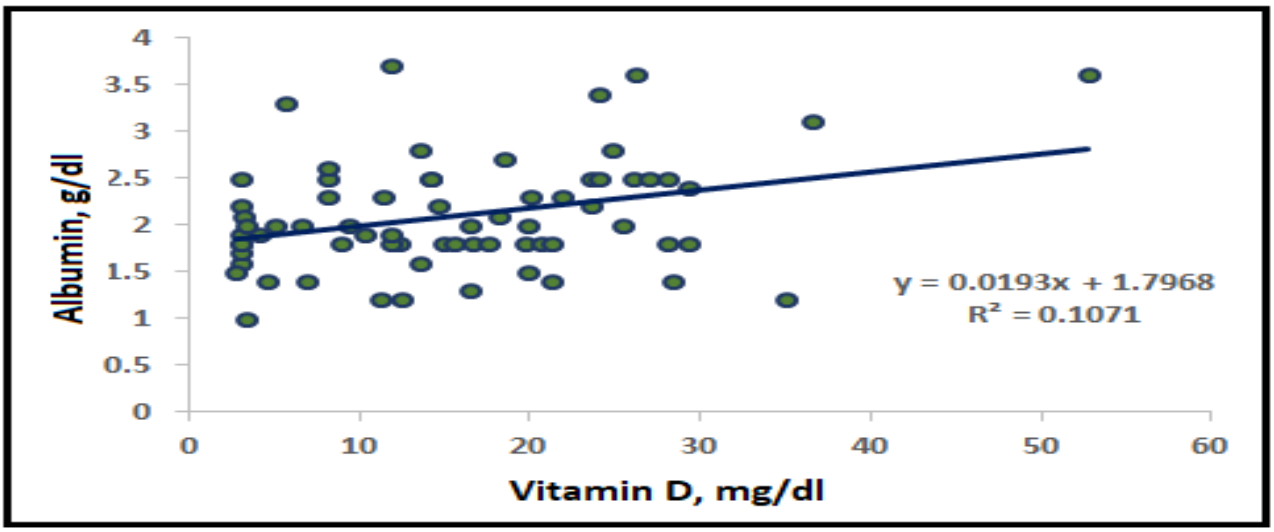

Figure 2: scatter plot and regression line between vitamin D and albumin.

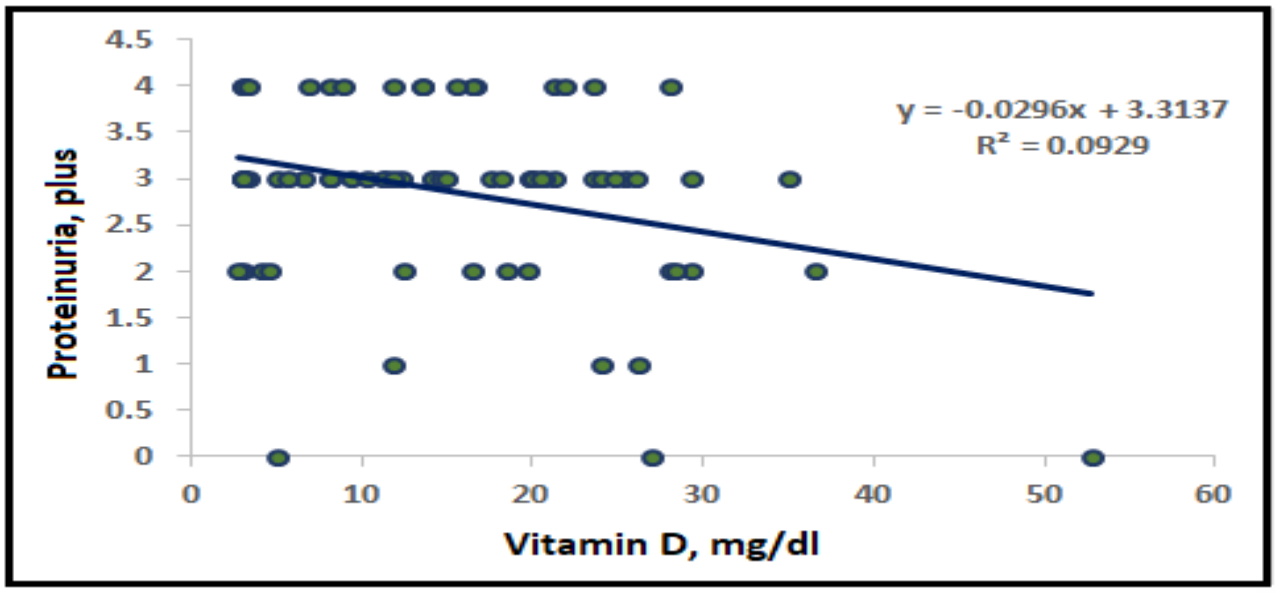

Figure 3: scatter plot and regression line between vitamin D and proteinuria.

DISCUSSION

This study evaluated the burden and correlates of vitamin D deficiency among children with nephrotic syndrome (NS). The cohort's mean age was 8.06 ± 3.65 years (range 1.25–16), with the 6–12-year group predominating (62.67%). Compared with earlier reports—Banerjee et al. (mean 6.25 years)[4], Nielsen et al. (3.4 years)[6], and Solanki et al. (5.7 years)[2]—our slightly older profile likely reflects delayed referral to tertiary care. Male predominance aligned with prior literature: several series reported male proportions of 62–85% across SSNS, SDNS, and SRNS subgroups.[15,16] In our cohort, SSNS was the dominant clinical category with frequent-relapsing (FR) phenotype most common, paralleling global patterns that show SSNS is more prevalent in many regions, with SRNS varying by ethnicity—~20% in Europeans, 27–54% in Asians, and 20–39% in South Asians.[12] Multiethnic data also suggest Asian children exhibit fewer SRNS cases and fewer relapses, with longer relapse-free intervals.[13] Nevertheless, relapse rates remain high worldwide—71.9% overall and 63–80% in country-specific series—driven by practice variation, access, and social determinants.[17,18] Vitamin D deficiency affected 46.67% of our patients, with 21.33% insufficient and 32% sufficient. These figures resemble Illalu et al. (47% deficient; 32% insufficient)[1] but are lower than rates from Gupta et al. (76% <20 ng/mL) and Aggarwal et al. (74% deficient; 26% insufficient)[2], as well as markedly lower than Egyptian and Danish reports (≈93–97%)[4,17] and a Pakistani SSNS cohort with >95% suboptimal status.[6] Such heterogeneity likely reflects differences in age mix, NS subtype, relapse/remission status at sampling, season, medications, and definitional thresholds. Mechanistically, urinary losses of vitamin D–binding protein (DBP) during proteinuric relapses drive transient 25(OH)D depletion, while remission may normalize levels in many children; indeed, Banerjee et al. found no case–control difference during remission.[16-21] Biochemistry in our patients showed reduced calcium and albumin with elevated cholesterol and proteinuria—canonical NS features supported by prior studies and meta-analysis.[9,13] Calcium often rises with remission as albumin improves.[8] Some cohorts report normal calcium/phosphate during remission.[7] Steroid exposure can compound skeletal risk; even low adult doses impair bone health, with pediatric protocols potentially surpassing osteoporosis-risk thresholds during growth[22], providing a biologic link to hypocalcemia and the need for vitamin D/calcium surveillance. Notably, vitamin D deficiency clustered in FRNS (64.86%) more than in IRNS (33.33%) or SRNS (12.5%). Marzouk et al. similarly found lower 25(OH)D in NS vs controls, with pronounced reductions across clinical subgroups.[4] Other series observed the deepest deficits in SRNS, likely due to higher uVDBP losses[14], underscoring that phenotype–vitamin D relationships vary across settings. Correlation analyses in our data reinforce pathophysiology: 25(OH)D correlated positively with calcium ($r = 0.240$, $p = 0.044$) and albumin ($r = 0.330$, $p = 0.006$), and negatively with proteinuria ($r = -0.305$, $p = 0.010$). Prior studies likewise noted inverse associations with 24-hour proteinuria and cholesterol, and positive ties with calcium and HDL.[4,5] While some found no calcium–vitamin D correlation[9], the preponderance supports a link between proteinuric losses, hypoalbuminemia, and lower 25(OH)D.

CONCLUSION

The majority of children with nephrotic syndrome are suffering from suboptimal level of vitamin D, either as deficiency or sufficiency. Calcium and albumin are reduced in NS while total cholesterol is elevated. Vitamin D deficiency is more pronounced in patients frequent relapse nephrotic syndrome. Vitamin D level

positively correlated with serum albumin and calcium and negatively correlated with proteinuria.

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