International Journal of Clinical Biochemistry and Research 2022;9(4):315–321

Content available at: https://www.ipinnovative.com/open-access-journals

International Journal of Clinical Biochemistry and Research

Journal homepage: https://www.ijcbr.in/

Original Research Article

Four hundred IU vs One thousand IU of vitamin D supplementation in first episode of nephrotic syndrome

Seema Lekhwani[1,*], **Narain Das Vaswani**[2], **Sudeep Kumar**[2], **Pradeep Kamboj**[3]

[1]*Dept. of Biochemistry, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India*
[2]*Dept. of Pediatrics, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India*
[3]*Dept. of Orthopedics, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India*

ARTICLE INFO

Article history:
Received 04-07-2022
Accepted 31-08-2022
Available online 31-12-2022

Keywords:
BMC: Bone mineral content
BMD: Bone mineral density
DXA: Dual energy x-ray absorptiometry
NS: Nephrotic syndrome
Vitamin D
Calcium
Prednisolone
ALP: Alkaline phosphatase

ABSTRACT

Use of steroids in nephrotic children may lead to changes in bone mineral density and osteoporosis eventually affecting growth on a long term basis. We compared the proportionate changes in bone mineral content (BMC) and density(BMD), Vitamin D levels, Serum Calcium, phosphate and alkaline phosphatase levels in nephrotic children with the aim of giving high Vs low vitamin D doses (1000 IU Vs 400 IU) to two groups; group 1 (n=20) vs group 2 (n=20) respectively. The median BMC in group 1 increased from 11.53±3.48 g to 11.61±3.54 g after 1000 IU Vitamin D supplement and was statistically significant. However group 2 showed insignificant increases in BMC from 11.24±2.71 g to 11.25±2.67 g following 400IU Vitamin D. The change in BMD observed in group 1 from a mean of 0.426 to 0.429g/cm2 whereas in group 2 with 400 IU of vitamin D it didn't show any significant change. The median vitamin D increased significantly in both groups; from 16.62±7.20 ng/ml to 27.45±6.47 ng/ml in group 1 while in group 2 from 18.72±8.07 ng/ml to 26.18±7.61 ng/ml which was statistically significant. The serum calcium levels normalized irrespective of 1000 IU or 400 IU of vitamin D supplementation. Changes in serum phosphate levels (decline from initial) were statistically significant however the changes in serum ALP were insignificant. We concluded that children supplemented with 1000 IU /day of vitamin D had better osteoprotection as compared to the other group.

1. Introduction

Infancy and childhood are crucial phases for bone growth. Any risk during this time is fatal to the overall bone mass, which decides the stability and strength of the bone. Glucocorticoids are needed at some point in life by an estimated 10% of children[1] and have long been known to have adverse effects on bone growth. Nephrotic syndrome provides a clinical model for the effect of chronic glucocorticoid therapy on the skeletal system. Nephrotic syndrome in children is classically defined by KDIGO (Kidney Disease Improving Global Outcomes) as proteinuria in the nephrotic range (≥40 mg/m2/hour or urinary protein/creatinine ratio ≥200 mg/ml or 3+ protein on urine strip), hypoalbuminemia (<25g/l) and edema.[2] Proteinuria usually results from the loss of charge and size selectivity in the filter membrane, but hemodynamic changes in the glomeruli are induced by the renin-angiotensin system.[3] Nephrotic syndrome is one of the most common renal disorders in children with an annual incidence approximately 2–7 per 1,000,000 children in Western countries.[4] with an even higher incidence in South Asia.[5] In India, the pattern of glomerular pathology varies by demographic location, with mesangioproliferative glomerulonephritis being the most common cause of

* *Corresponding author*.
E-mail address: s_lekhwani@yahoo.co.in (S. Lekhwani).

https://doi.org/10.18231/j.ijcbr.2022.062

nephrotic syndrome from South India, while primary IgA nephropathy is more common in young adults in second to third decade of life from western India, and the minimal-change disease dominates northern India.[6]

The treatment of choice for nephrotic syndrome has been glucocorticoids, which act to suppress T-cell function and also stabilize the podocyte cytoskeleton. However, with long-term treatment with corticosteroids, the side effects are growth disorders, cataract, hypertension and also substantial weight gain. Studies have shown a correlation between cumulative steroid dose and bone density; therefore, treatment with the lowest possible dose of steroids is important.[7] Glucocorticoids have important effects on the skeleton because they improve bone resorption and reduce bone formation, which leads to a decrease in bone mass[8] and by affecting the replication of growth plate chondrocyte cells, steroids can profoundly affect longitudinal growth. Damage to bone formation is a consequence of the direct effect of glucocorticoids on osteoblastic activity and the inhibitory effect on bone matrix formation.[9] Also, reduced intestinal and renal absorption of calcium and phosphate leads to secondary hyperparathyroidism.[10] Steroids thus have a negative effect on bone mineral content by promoting osteoblast apoptosis, stimulating osteoclasts and reducing growth hormone secretion, resulting in reduced bone mineralization and osteoporosis as an additive effect.[11]

Patients with nephrotic syndrome have an associated vitamin D deficiency, attributed in large part to the loss of its carrier protein, vitamin D-binding protein (VDBP). Studies have shown that urinary excretion of VDBP is greater in children with nephrotic syndrome than in general.[12] Urinary vitamin D is unconjugated and is likely to be excreted with VDBP, which has a molecular weight and isoelectric point similar to albumin.[13] Therefore, low 25-hydroxycholecalciferol would also contribute to poor bone health. The current study was aimed at comparing the proportional change in bone mineral content and density in children with a first episode of nephrotic syndrome on steroid therapy and evaluating the therapeutic amount for vitamin D supplementation to slow the osteoporotic changes associated with steroid therapy.

2. Materials and Methods

Randomized controlled study design was used to remove bias. Children with a first episode of nephrotic syndrome without previous use of glucocorticoids were included. Children with clinical or biochemical evidence of metabolic bone disease were excluded. Chronic liver or kidney disease. Steroid dependence, steroid resistance, frequently relapsing nephrotic syndrome, children receiving vitamin D or calcium supplementation within the past 6 months, or drugs that affect vitamin D or calcium metabolism (phenytoin, methotrexate), or children with secondary nephrotic syndrome. However, 49 patients with a first episode of nephrotic syndrome were enrolled, 3 patients had steroid-dependent disease and 2 patients had pre-existing bone disease. Finally, 44 recruited subjects were randomized into two groups using a computer- assisted block randomization technique, although 4 patients were lost to follow-up. Informed written parental consent was taken. Ethical approval of the study was obtained from the Institutional Ethical Committee (IEC). According to the study protocol, 20 children in group 1 and 2 received 1000 IU and 400 IU vitamin D respectively with 500 mg elemental calcium each per day. Serum Vitamin D levels were measured by using Radioimmunoassay (Machine name**:** SR 300 Stratec made in Germany).

3 ml of blood sample was drawn for analysis and 30- 100 ng/ml was accepted as a normal reference range for vitamin D levels. (Kit name: Bekman Coulter). BMD of the lumbar spine (L2-4) was determined by DEXA scans. Abnormal BMD was defined as low or low normal BMD. A DEXA scan was a quick, painless procedure on lower back and spine. Each scan took 10-20 minutes. Radiation exposure was low. Patients were asked to lie down on an open X-ray table, and the machine measured the number of X-rays passing through the bone from each radiation, which varied with bone thickness. Based on the difference between the two beams, the patient's bone density was measured.

2.1. Data collection and statistical analysis

Children tested in two groups on the day of presentation and after randomization were tested 12 weeks apart. Vitamin D levels, serum calcium, and DEXA scans were all repeated. The collected data was converted into variables, coded and entered into Microsoft Excel. Data were analyzed and statistically evaluated using SPSS-PC-17 version.

Quantitative data were expressed as mean ± standard deviation (SD) or median with interquartile range(IQR) whereas qualitative data as percentages. Means and SD were compared using student t test; Median and IQR were compared using Mann Whitney U-Test. Statistical differences between proportions were tested by the chi-square test. A "P"value of less than 0.05 was considered statistically significant.

3. Results

Demographic profile tables:

Table 1: Age wise distribution of study subjects

Age Group	Group 1 (n=20)		Group 2 (n=20)	
	No.	%	No.	%
Up to 4 years	8	40.0	8	40.0
5-8 years	12	60.0	12	60.0

The study population initially included 49 children presenting with first episode of nephrotic syndrome, 9

children could not be followed up and the remaining 40 were randomly divided into 2 groups.(Table 1)

Table 2: Gender distribution of study subjects

Gender	Group 1 (n=20)		Group 2 (n=20)	
	No.	%	No.	%
Male	11	55.0	14	70.0
Female	9	45.0	6	30.0

In group 1, there were 11 (55%) males when compared to 14 (70%) males in group 2.(Table 2)

Group 1 included 9 (45%) girls and 6 (30%) in group 2. In either group male gender dominated.

Table 3: Comparison of demographic and anthropometric parameters between two groups

Parameter	Group 1 (n=20)	Group 2 (n=20)
Age in years	5.35±1.87	4.85±1.59
Weight (kgs)	20.25±4.96	17.40±3.88
Height (cm)	107.80±12.44	105.10±10.34
BMI (kg/m^2)	17.26±1.87	15.57±0.95

Table 3 shows that median age in group 1 was 5.35±1.87 years when compared to 4.85±1.59 years in group 2. The mean weight and height in group 1 were 20.25±4.96 kg and 107.80±12.44 cm respectively. The median BMI in this group was 17.26±1.87 kg/m^2. In the second group, the median weight was 17.40±3.88 kg and the median height was 105.10±10.34 cm with a mean BMI of 15.57±0.95 kg/m^2.

Comparison of various other parameters before and after intervention

Table 4: Systolic and Diastolic BP in both groups

BP	Group 1 (n=20)	Group 2 (n=20)
Pre intervention SBP	95.70±5.92	97.30±4.78
Post intervention SBP	96.60±5.69	96.70±4.69
Pre intervention DBP	57.30±6.37	58.40±6.73
Post intervention DBP	61.0±6.37	62.30±5.67

Table 4 represents the systolic and diastolic blood pressure between the two groups before and after vitamin D supplementation was given. It shows that the mean SBP in group 1 was 95.70±5.92 mmHg which increased to 96.60±5.69 mmHg post intervention. In group 2 the post interventional SBP was 96.70±4.69 mmHg which was not significantly different from pre interventional value of 97.30±4.78 mmHg.

The mean DBP in group 1 was 57.30±6.37 mmHg in study subject and it increased to 61.0±6.37 mmHg after 1000 IU/day of vitamin D supplementation. A similar trend was observed in group 2 where the initial mean DBP of 58.40±6.73 mmHg increased to 62.30±5.67 mmHg.

Table 5: Serum Calcium levels

Serum calcium level	Group 1 (n=20)	Group 2 (n=20)	p-value between groups
Pre intervention	8.70±1.27	8.66±1.01	0.77
Post intervention	9.91±0.54	9.50±0.61	0.02
p-value between pre and post within group	<0.001	<0.001	

From Table 5 we can observe the serum calcium in group 1 8.70±1.27 mg/dl increased to 9.91±0.54 mg/dl after supplementation (statistically significant). In group 2 who were supplemented with 400 IU of vitamin D, the calcium increased to 9.50 0.61 mg/dl from an initial value of 8.66 1.01 mg/dl. It also proved to be statistically significant.

Table 6: Serum Phosphate levels

Serum phosphate level	Group 1 (n=20)	Group 2 (n=20)	p-value between groups
Pre intervention	5.86±1.11	5.69±1.27	0.51
Post intervention	3.94±0.60	3.77±0.45	0.42
p-value between pre and post within group	<0.001	<0.001	

On comparing the serum phosphate levels between the two groups it was observed that group 1 showed a decline on serum phosphate from 5.86±1.11 mg/dl to 3.94±0.60 mg/dl and the decrease was statistically significant. In the second group with supplementation of 400 IU of vitamin D, the change in serum phosphate was also significant with a p-value of <0.001. The serum phosphate decreased from 5.69±1.27 mg/dl to 3.77±0.45 mg/dl.(Table 6)

Table 7: Serum Alkaline Phosphatase levels

Serum ALP level	Group 1 (n=20)	Group 2 (n=20)
Pre intervention	172.25±45.49	173.50±18.21
Post intervention	161.50±23.19	165.25±14.73
p-value between pre and post within group	0.21	0.06

Table 7 shows that serum ALP in group 1 was 172.25±45.49 mg/dl and it decreased to 161.50±23.19 mg/dl after intervention. On comparing this with group 2 there was a similar decrease in serum phosphate from 173.50 18.2 mg/dl to 165.25 14.7 mg/dl in children supplemented with 400 IU of vitamin D. In both groups the change was insignificant statistically.

When serum cholesterol was compared in the two groups Table 8 showed that group 1 had a mean value of

Table 8: Serum Cholesterol levels

Serum cholesterol level	Group 1 (n=20)	Group 2 (n=20)
Pre intervention	385.10±64.51	424.05±47.01
Post intervention	175.65±10.02	176.65±10.66
p-value between pre and post within group	<0.001	<0.001

385.10±64.51 mg/dl during presentation and it significantly decreased to 175.65±10.02 mg/dl after intervention. Similar trend was seen in group 2 where serum cholesterol decreased to 176.65±10.66 mg/dl from pre-interventional value of 424.05±47.01 mg/dl. The p-value was statistically significant <0.001 in both the groups.

Table 9: S.Creatinine levels

Serum creatinine level	Group 1 (n=20)	Group 2 (n=20)
Pre intervention	0.47±0.14	0.48±0.10
Post intervention	0.47±0.11	0.44±0.10
p-value between pre and post within group	0.91	0.31

When serum creatinine was compared between the two groups there was no significant difference between both pre and post intervention value. Serum creatinine was 0.47±0.14 mg/dl and 0.48±0.10 mg/dl in group 1 and group 2 respectively.(Table 9) After supplementation with vitamin D the change was 0.47±0.11 mg/dl in group 1 and 0.44±0.10 mg/dl in group 2.

Table 10: Serum Albumin levels

Serum albumin level	Group 1 (n=20)	Group 2 (n=20)
Pre intervention	2.03±0.36	1.89±0.18
Post intervention	3.71±0.39	3.90±0.45
p-value between pre and post within group	<0.001	<0.001

Table 10 shows that group 1 has significant increase from 2.03±0.36 mg/dl to 3.71±0.39 mg/dl post supplementation in albumin levels. Similar trend was observed in group 2 where initial serum albumin with a median of 1.89±0.18 mg/dl increased to 3.90±0.45 mg/dl after intervention with 400 IU of vitamin D.

The median vitamin D in group 1 was 16.62±7.20 ng/ml when children were initially recruited. It significantly increased to 27.45±6.47 ng/ml after 1000 IU of vitamin D supplementation. In children allotted group 2 similar trend was observed as an initial vitamin D of 18.72±8.07 ng/ml increased to 26.18±7.61 ng/ml and difference was also statistically significant with a p-value of <0.001.(Table 11)

The median BMC in group 1 was 11.53±3.48 g which rose to a median of 11.61±3.54 g post supplementation statistically significant (p-value was <0.01). However, children supplemented with 400 IU of vitamin D the increase in BMC from 11.24±2.71 g to 11.25±2.67 g was not significant statistically with a p-value of 0.86.(Table 12)

Similar trend of BMD for group 1 occurred as it increased from a median of 0.426 to 0.429 g/cm2 (p value< 0.01). However, in children supplemented with 400 IU BMD showed no significant change.(Table 13)

From Table 15 it was evident that the mean BMD and BMC in the pre intervention group were 0.421±0.038 g/cm^2 and 11.385±3.09 g which increased to 0.422±0.038 and 11.43±3.10 (p value .04 & .01 respectively). Vitamin D levels significantly increased from 17.67±7.63 ng/ml to 26.82±7.01 ng/ml as the p value was <0.001. Similar trends were seen with serum calcium, phosphate, serum cholesterol & albumin. The change was insignificant for ALP & Creatinine.

4. Discussion

Steroid therapy affects bone mineral status in every measurement(length, breadth & depth). BMC is considered to be an acute and precise indicator of bone mass in the pediatric population because it takes into account all three parameters as compared to BMD which is calculated by dividing BMC by bone area (depth excluded).[14]

The present study is an attempt to look into BMC(mainly) and changes in BMD after treating with daily dosage of vitamin D as compared to bolus regimens used in the previous studies. Although the prevalence of adherence to bolus regimens have been high, bolus dosing is associated with a greater production of 24, $25(OH)_2$ D_3 owing to the induction of 24- hydroxylase enzyme (CYP24A1) and thus was inversely associated with $24,25(OH)_2D_3/25(OH)D_3$ ratio. Therefore, daily dosing of vitamin D have a more lasting effect in increasing $25(OH)D_3$ with lesser diversion of the same to $24,25(OH)_2D_3$ as compared to bolus regimens.[15] When compared to the daily dosing in our study, Singh et al.[16] compared supplementation of 1000 IU/day of vitamin D as a bolus dose and observed 13.36% change in BMC and a 5.6% change in BMD in contrast to 11.59% and 5.35% change in BMC and BMD respectively when 400 IU/day of vitamin D was given.

Muske et al.[17] concluded similar results to the present study with a greater median proportionate change in BMC in the children who received 1000 IU/ day vitamin D [3.25% (−1.2 to 12.4)] than in those who received 400 IU/day vitamin D [1.2% (−2.5 to 3.8)] (p-value <0.048) given as bolus dose. The present study showed that BMC decreased in 11 children out of 40 wherein 5 received 1000 IU and 6 received 400 IU of vitamin D daily, similar to the findings of Muske et al. where 32 children (of 92 subjects enrolled), despite treatment with vitamin D had decrease in BMC (15 received 1000 IU/day vitamin D and 17 received 400 IU/day vitamin D) suggesting that even relatively short-term steroids (up to 3 months of prednisolone therapy) could

Table 11: Vitamin D levels

Serum vitamin D level (ng/ml)	Group 1 (n=20)	Group 2 (n=20)	p-value between groups
Pre intervention	16.62±7.20	18.72±8.07	0.41
Post intervention	27.45±6.47	26.18±7.61	0.41
p-value between pre and post within group	<0.001	<0.001	

Table 12: BMC levels

BMC (gm)	Group 1 (n=20)	Group 2 (n=20)	p-value between groups
Pre intervention	11.53±3.48	11.24±2.71	0.74
Post intervention	11.61±3.54	11.25±2.67	0.83
p-value between pre and post within group	<0.01	0.86	

Table 13: BMD levels

BMD	Group 1 (n=20)	Group 2 (n=20)	p-value between groups
Pre intervention	0.426±0.037	0.415±0.038	0.35
Post intervention	0.429±0.038	0.415±0.037	0.19
p-value between pre and post within group	<0.01	0.66	

Table 14: Outcome variables between the two groups (a minus sign indicates the proportionate fall in the respective parameter)

Characteristics (%change)	Group 1 (n=20)	Group 2 (n=20)	p-value
BMD	-0.70 (-1.06 to -0.41)	-0.23 (-0.46 to +0.95)	<0.01
BMC	-0.73 (-1.23 to +0.11)	-0.41 (-0.68 to +0.69)	0.01
Vitamin D	68.05 (44.11-116.74)	41.71 (24.05-72.28)	0.01
Calcium	-11.17 (-29.8 to -4.64)	-5.05 (-18.91 to -2.84)	0.18
Phosphate	34.83 (20.73-44.08)	27.74 (16.03-44.14)	0.58
ALP	13.10 (-8.32 to 27.86)	4.92 (-5.80 to 10.25)	0.31
S. Cholesterol	54.44 (45.97-58.02)	58.44 (54.03-61.82)	0.07

Table 15: Comparison of BMC, BMD and other laboratory parameters in the study groups before and after vitamin D supplementation

Parameters	Pre intervention (n=20)	Post-intervention (n=20)	p-value
BMD	0.421±0.038	0.422±0.038	0.04
BMC	11.385±3.09	11.43±3.10	0.01
Vitamin D	17.67±7.63	26.82±7.01	<0.001
Calcium	8.68±1.13	9.70±0.61	<0.001
Phosphate	5.78±1.18	3.86±0.53	<0.001
ALP	172.88±34.21	163.38±19.27	0.02
S. Cholesterol	404.58±59.10	176.16±10.23	<0.001
S. Creatinine	0.48±0.13	0.46±0.11	0.56
Albumin	1.97±0.29	3.81±0.43	<0.001

have significant detrimental effects on BMC.

Unlike our study a few studies have shown decrease in BMC in children with nephrotic syndrome despite supplementation with vitamin D. Yadav et al.[18] observed significant decrease in vitamin D levels in control and interventional groups but the decrease in mean value of BMD score was significantly different between the 2 groups (p-value <0.001) as the decrease in BMD in interventional group concluded that the supplement (vitamin D 400 IU and elemental Ca 200 mg) was not adequate to prevent bone deficit. A non-randomized study in Poland[19] showed a significant decrease in the BMD Z-score and 25-hydroxy vitamin D_3 serum levels despite the administration of vitamin D (800 IU/day), thus supplementation with vitamin D at a dose higher than 800 IU/day was recommended to prevent osteopenia. Banerjee et al.[20] observed contrasting results when supplemented the interventional group with vitamin D as 60,000 IU orally per week along with calcium and concluded significant improvements in the treatment group compared with controls (p-value < 0.001) but not associated with differences in bone mineral content (BMC) (p-value =0.44) or bone mineral density

(BMD) (p =0.64) between the groups. The present study evaluated proportionate change in BMC as the primary outcome. It showed statistically significant increase in vitamin D in group 1 (68.05%) as compared to group 2 (41.71%). Multiple cross-sectional studies of children with NS demonstrate a prevalence of 25-hydroxy vitamin D deficiency of 20–100% owing to the excretion of vitamin D binding protein in urine.[21] However, it has also been observed that serum 25-hydroxy vitamin D levels do not accurately represent vitamin D stores in nephrotic children because, loss of protein bound 25-hydroxy vitamin D causes low serum 25-hydroxy vitamin D despite normal 1,25-dihydroxy vitamin D levels which makes it difficult to estimate serum 25- hydroxy vitamin D in nephrotic children. A study by Ketha et al[22] concluded that a daily dose of vitamin D may have more lasting effectiveness in increasing $25(OH)D_3$ with lesser diversion of $25(OH)D_3$ to $24,25(OH)_2D_3$ ratio than does larger bolus dosing in maternal Vitamin D3 supplementation. American Academy of Pediatrics recommends 600 IU/day of Vitamin D between 1 and 18 years age.[23] The Endocrine Society recommends for children at risk of deficiency an intake of 600 IU/day–1000 IU/day of Vitamin D. Conclusively children who were supplemented with 1000 IU of vitamin D had better outcome when compared to children given 400 IU/day of vitamin D in terms of bone safeguarding and this higher dose was not associated with any side effects like hypercalcemia or Vitamin D toxicity.

The current study has few limitations like Serum 1, 25 dihydroxycholecalciferol levels were not measured which could have been a better predictor of vitamin D status. BMC was decreased in one- fourth of cases when compared before and after vitamin D supplementation. Had DEXA scans been performed at follow-ups, data regarding the trend of BMC (rise or fall) could have had obtained. Also, parathyroid hormone levels were not estimated which has key role in regulating Calcium, phosphorus and Vitamin D. Future research should be based on large number of subjects and even higher doses of Vitamin D to establish its therapeutic supermacy in bone protection.

5. Conclusion

In summary, vitamin D supplementation with 1000 IU/day in prednisolone-treated children with a first episode of nephrotic syndrome was associated with a lower rate of bone loss (20% in group 1 vs. 31% in group 2). As shown, bone protection was improved, but further studies with larger samples are needed to demonstrate its superiority in the future.

6. Author's Contribution

SL, NDV: Concept and design of the study; SY, NDV: drafting the manuscript and review of literature; SL, NDV, SY: Critical review of manuscript and final approval of the version to be published; PK: analysis of BMC and BMD. All authors approve of the final version.

7. Funding Support

Nil.

8. Conflicts of Interest

None.

9. Ethical Approval

An institutional ethical approval was obtained before the commencement of study.

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Author biography

Seema Lekhwani, Assistant Professor https://orcid.org/0000-0002-0025-9448

Narain Das Vaswani, Professor and Unit Head https://orcid.org/0000-0002-7773-3478

Sudeep Kumar, Junior Resident https://orcid.org/0000-0002-6188-2794

Pradeep Kamboj, Senior Professor https://orcid.org/0000-0002-6526-9823

Cite this article: Lekhwani S, Vaswani ND, Kumar S, Kamboj P. Four hundred IU vs One thousand IU of vitamin D supplementation in first episode of nephrotic syndrome. *Int J Clin Biochem Res* 2022;9(4):315-321.