**Original research article**

# Requirement of Vitamin D in Patients with Nephrotic Syndrome on Long Term Steroid

**Pankaj Bhansali[1], Apurva Deshmukh[2], Lalit Une[3], Aisha Siddiqui[4]**

[1]Assistant Professor, Dept. of Paediatrics, IIMSR, Medical College, Jalna

[2]Registar, Dept. of Paediatrics, Shankarrao Chavhan Government Medical College, Nanded

[3]Professor and HOD, Dept. of Paediatrics, IIMSR, Medical College, Jalna

[4]Junior Resident, Dept. of Paediatrics, IIMSR, Medical College, Jalna

**Corresponding Author: Dr. Aisha Siddiqui**

**E-mail: aishasiddiqui000@gmail.com**

## ABSTRACT

**Introduction:** Nephrotic Syndrome is characterised by nephrotic range proteinuria and the triad of clinical findings i.e., hypoalbuminemia, edema and hyperlipidemia. Glucocorticoid-sensitive nephrotic syndrome remits completely and quickly in response to glucocorticoids. Steroids are known to cause osteoporosis and loss of bone mineral density in NS patients. So, we decided to study requirement of vitamin D in nephrotic syndrome in patients who are on remission during steroid therapy and Comparison of normal and high dose of vitamin D supplementation to achieve normal vitamin D level in nephrotic syndrome patient, in remission on prednisolone therapy.

**Material And Methods:** The present descriptive observational study, was conducted amongst 31 patients from August 2014 to August 2016 in the pediatric department of tertiary care centre on both indoor (IPD) and outdoor (OPD) patients of Nephrotic syndrome those who are in remission on steroid. Patients having normal 25 OH Vitamin D level were included in study. These patients were randomly divided in two groups using random sampling by lottery method. a. First group was given vitamin D therapy as 20, 000 IU/month (600IU/day) for three months b. Second group was given 60,000 IU /month (2000IU/day) for three month.

**Results:** Out of 31 patients in this study, mean age at inclusion in group A was 5.4 years whereas, it was 7.2 years in group B. Majority 12 of the patients were having SDNS as diagnosis. Both the groups showed elevated levels of 25(OH) after supplementation. The levels of serum ionic calcium levels were not affected in both the groups, but the mean values of serum Ionic Calcium was found to be on higher side after Calcium supplementation especially in group B. The serum values were not affected in both groups.

**Conclusion:** The results concludes that there is no need for vitamin D supplementation in higher doses in steroid-sensitive nephrotic syndrome in patients those who are in remission and on minimal dose of steroids. So, dosage of vitamin D should be according to Recommended Dietary Allowances (RDA) when patient is on minimal dose of steroids.

**Keywords:** Vitamin D, Nephrotic Syndrome, Steroids, Supplementation, hypoalbuminemia

## Introduction

Nephrotic Syndrome is characterised by nephrotic range proteinuria and the triad of clinical findings i.e. hypoalbuminemia, edema and hyperlipidemia associated with large urinary losses of protein. Nephrotic range proteinuria is defined as protein excretion of > 40mg/m2/hr or a

first morning protein: creatinine ratio of > 2-3:1.[1] First published series of nephrotic syndrome dates back to 1484 by Cornelius Roleans (or Roleants) of Mecheln in Belgium (1450 -1525). He described 52 diseases of children of which 51st is "Swelling of whole body in child", in his book 'Liber de aegritudinibusinfantium' published in 1484.[2] It is Richard Bright (1789 – 1858) who described Nephrotic Syndrome in all its detail in his classic "Report of Medical Cases of 1827". John Bostock quantified urine and serum protein by methods depending on specific gravity.

Glucocorticoid-sensitive nephrotic syndrome remits completely and quickly in response to glucocorticoids.[3] Unfortunately, the nephrotic syndrome relapses at intervals in the majority of the children after the dose of glucocorticoids is reduced or discontinued, resulting in protracted, repeated courses of glucocorticoids. Although relapses of the nephrotic syndrome are associated with transient increases in cytokines and urinary losses of vitamin D, these abnormalities promptly resolve with glucocorticoid therapy and disease remission. Steroids are known to cause osteoporosis and loss of bone mineral density in NS patients.[4] During relapse, the condition is thought to worsen due to frequent loss of vitamin D via vitamin D binding protein (DBP) and metabolites and calcium in the urine. The diminished mineralization reported in children's with nephrotic syndrome has been tested by bone densiometry methods.[5] Glucocorticoid therapy appears to increase expression of 24- hydroxylase and decrease expression of renal 1-alpha hydroxylase, decreasing levels of 1,25 (OH)2 D3.[6]

Randomized controlled trials by Bak et al [7] studied role of vitamin D supplementation in patients with nephrotic syndrome and concluded that there is positive effect of calcium and vitamin D supplementation and decrease in incidence of low bone mineral density.

Michael F. Holick et al [8] published his work in Endocrine Society Clinical Practice Guideline regarding vitamin dosage in paediatric age group. They suggested that infants and children aged 0–1 yr require at least 400 IU/d (IU = 25 ng) of vitamin D, and children 1 yr and older require at least 600 IU/d to maximize bone health. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1000 IU/d of vitamin D. he also suggest that patients on glucocorticoids should receive two to three times more vitamin d for their age group to satisfy their body's vitamin D requirement. Though, there are no clear guidelines of effect of steroids on vitamin D.

Etiopathogenesis of Idiopathic Nephrotic Syndrome: [1]
Glomerular filtration barrier is main part which is mostly affected in nephritic syndrome. It selectively allows the ultrafiltration of water and solutes while preventing the passage of large molecular weight molecules (>40,000 Daltons) like albumin and clotting factors. This is called Selective Glomerular Permeability. The Glomerular Filtration Barrier consists of 3 components – epithelial cells (podocytes), Glomerular basement membrane and fenestrated endothelial cells. Podocytes cover the outer surface of thin glomerular basement membrane which measures about 0.3μ and is resting on fenestrated glomerular capillary endothelial cells which lie on the other side. For the last 3-4 decades, glomerular basement membrane was thought to play a main role in pathogenesis of proteinuria. However, in last 5-7 years, studies of familial Nephrotic Syndrome/ FSGS have led to the discovery of several genes that are expressed in podocytes and are associated with proteinuria. These discoveries have shifted the focus from glomerular basement membrane to podocytes in pathogenesis of nephrotic syndrome. Podocytes are specialised epithelia having a cell body and several foot processes which are in contact with each other with the help of inter podocyte connection called Slit diaphragm (SD).

Slit diaphragm is now being recognised as a well differentiated structure with its own unique functions and has an electron dense zipper like structure composed of several components. The extracellular components, including nephrin, are
connected through other specialised structures within the cell (i.e. podocin, CD2AP) to the main cell body as described in figure.1

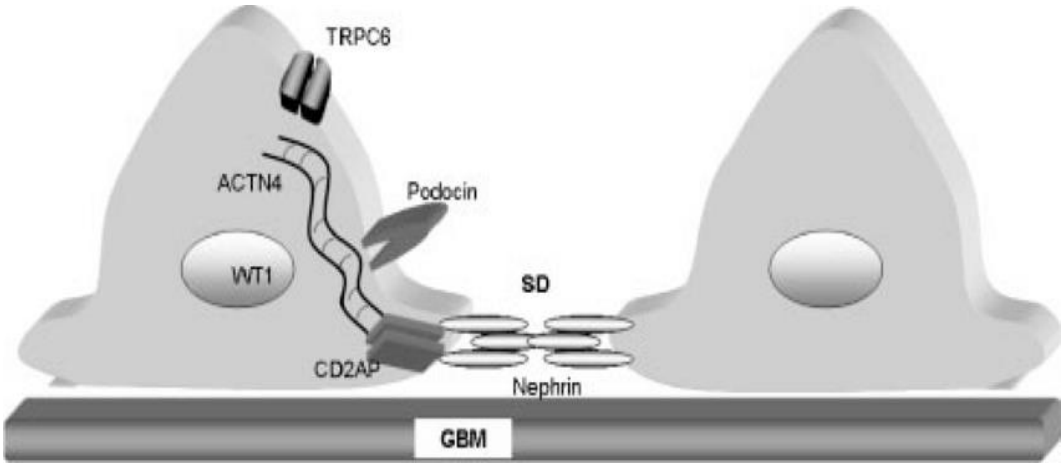



**Figure no.1: Podocyte components associated with Nephrotic Syndrome**

**Table no.1: Causes of Childhood Nephrotic Syndrome [1]**

| Genetic Disorders | Idiopathic Nephrotic Syndrome | Secondary Causes |
|---|---|---|
| Nephrotic Syndrome (Typical) | Minimal Change disease | Infections |
| Finnish – type congenital nephrotic syndrome | FSGS | Hepatitis B,C |
| FSGS | Membranous Nephropathy | HIV |
| Diffuse mesangial sclerosis | | Malaria |
| Denys – Drash Syndrome | | Syphilis |
| Proteinuria with or without Nephrotic syndrome | | Toxoplasmosis |
| Nail – patella syndrome | | Drugs |
| Alport Syndrome | | Penicillamine |
| Multisystem Disorders with or without Nephrotic Syndrome | | Gold |
| Galloway Mowat syndrome | | Nonsteroidal anti-inflammatory drugs |
| Charcot-Marie-Tooth disease | | Pamidronate |
| Jeune syndrome | | Interferon |
| Cockayne syndrome | | Mercury |
| Laurence-Moon-Biel-Bardet Syndrome | | Heroin |
| Metabolic Disorders with or without Nephrotic Syndrome | | Lithium |

| | | |
|---|---|---|
| Alagille syndrome | | Immunologic or allergic reactions |
| α1 Antitrypsin deficiency | | Castleman disease |
| Fabry disease | | Kimura disease |
| Glutaric Acidemia | | Bee sting |
| Glycogen Storage Disease | | Food allergens |
| Hurler Syndrome | | Associated with Malignant disease |
| Lipoprotein disorders | | Lymphoma |
| Mitochondrial cytopathies | | Leukemia |
| Sickle cell disease | | Glomerular Hyperfiltration |
| | | Oligomeganephronia |
| | | Morbid Obesity |
| | | Adaption to nephr. Red. |

So, we decided to study requirement of vitamin D in nephrotic syndrome in patients who are on remission during steroid therapy and Comparison of normal and high dose of vitamin D supplementation to achieve normal vitamin D level in nephrotic syndrome patient, in remission on prednisolone therapy.

**Material And Methods:**
The present descriptive observational study, was conducted amongst 31 patients from August 2014 to August 2016 in the pediatric department of tertiary care centre on both indoor (IPD) and outdoor (OPD) patients of Nephrotic syndrome those who are in remission on steroid. All the patients of Nephrotic syndrome fulfilling the following inclusion criteria were included in the study, Idiopathic nephrotic syndrome, patients who are receiving steroids on alternate day, age group of 1-18 years, patients having normal e-GFR and normal vitamin D level.

Exclusion Criteria:
Following patients were excluded from the study, whose parents did not give consent to participate in this study, congenital or infantile onset nephrotic syndrome, steroid resistant nephrotic syndrome and nephrotic syndrome due to secondary causes.

Study Methods:
All patients of Nephrotic Syndrome diagnosed according to International Study of Kidney Disease in children (ISKDC) criteria, who were in remission with steroids since last 3 months came to follow up were examined in detail and their detailed clinical history was taken. Patients having normal 25 OH Vitamin D level were included in study.

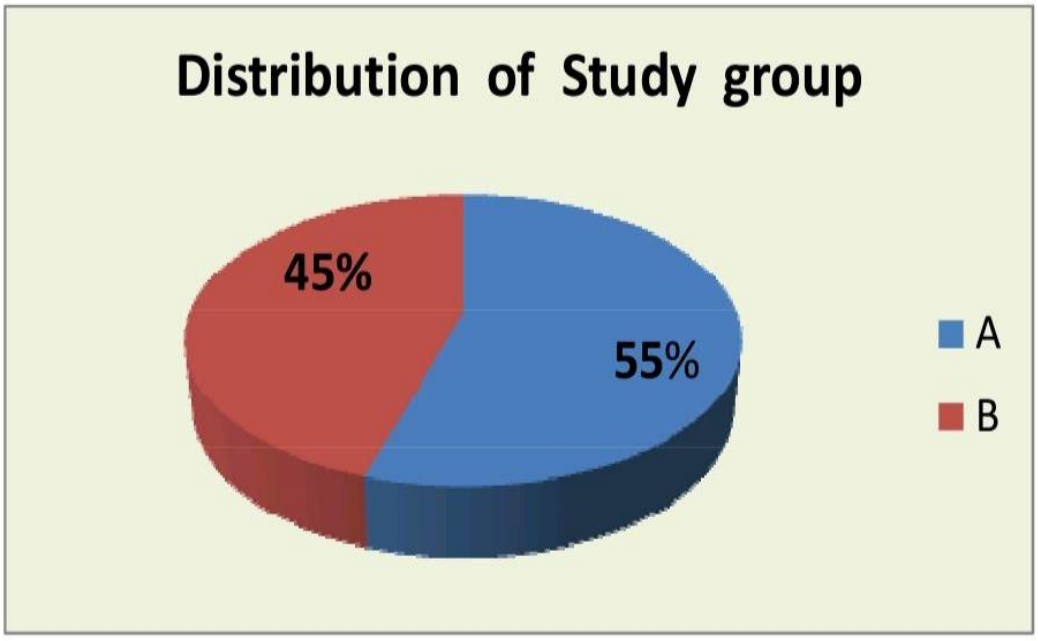
These patients were randomly divided in two groups using random sampling by lottery method.
a. First group was given vitamin D therapy as 20, 000 IU/month (600IU/day) for three month
b. Second group was given 60,000 IU /month (2000IU/day) for three month.
Appropriate laboratory investigation were done like Ionised Calcium, Phosphorous, alkaline phosphatase urinary calcium to creatinine ratio before and after vit D supplementation.

**Clinical Evaluation:**
Detailed records were maintained on proforma including symptoms, signs and various investigations, previous attacks, hospitalisation and relapses, steroid therapy, its dosage and compliance were noted. Patients were examined in detail with special attention to oedema,

blood pressure, abdominal tenderness and any sign suggestive of rickets. Patients were investigated for routine blood and urine examination along with Serum Vitamin D3 level, Serum Ionic calcium, Serum Ionic Phosphorus, Serum Alkaline phosphatase, Urinary Calcium / Creatinine and Urinary Protein / Creatinine. Low levels of 25(OH) D were defined as "insufficient" if <20 ng/ml and "deficient" if <10 ng/ml, as in previous studies. All patients on follow up were advised to watch edema, urine output and urine dip stick test for protein at home. If any of the warning sings noted, parents were advised to follow up in OPD. At 3 months follow up, patients were again examined and investigated in the similar manner.

**Results:**

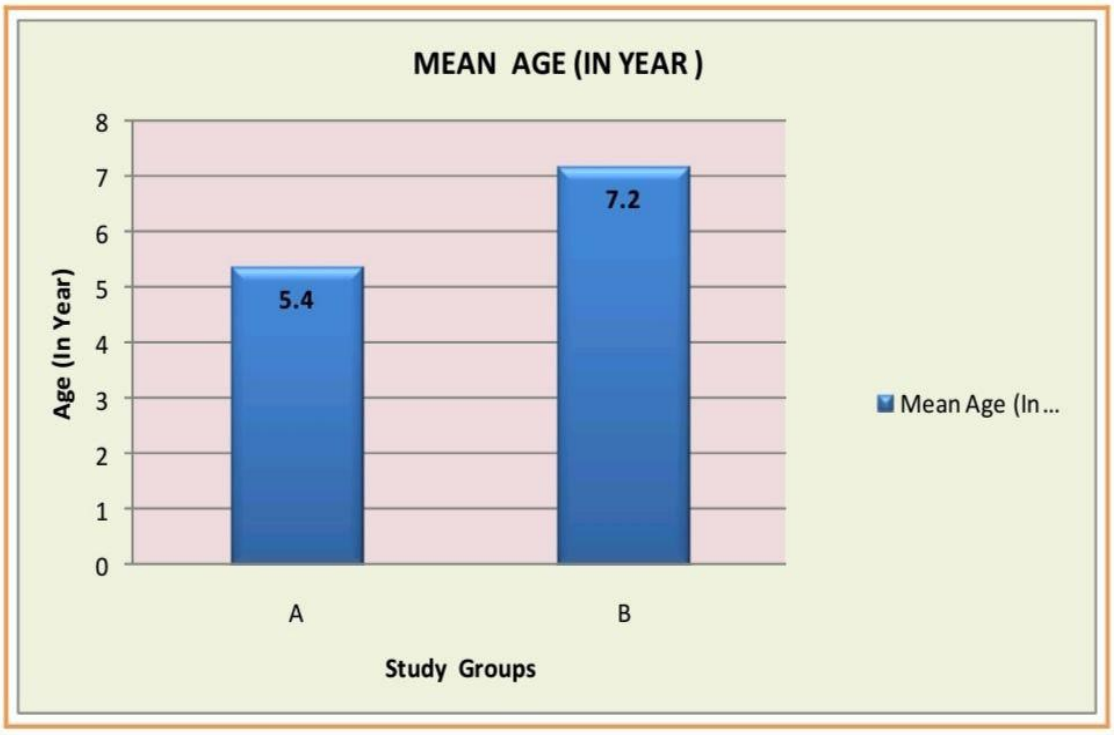
In this study, total 31 patients were studied. Patients were classified in to group A & B according to dosage of supplementation of vitamin D 3 in patients with nephrotic syndrome those on steroid remission. Group wise distribution of the patients was done on lottery basis.




**Graph – 1 :** Group wise distribution

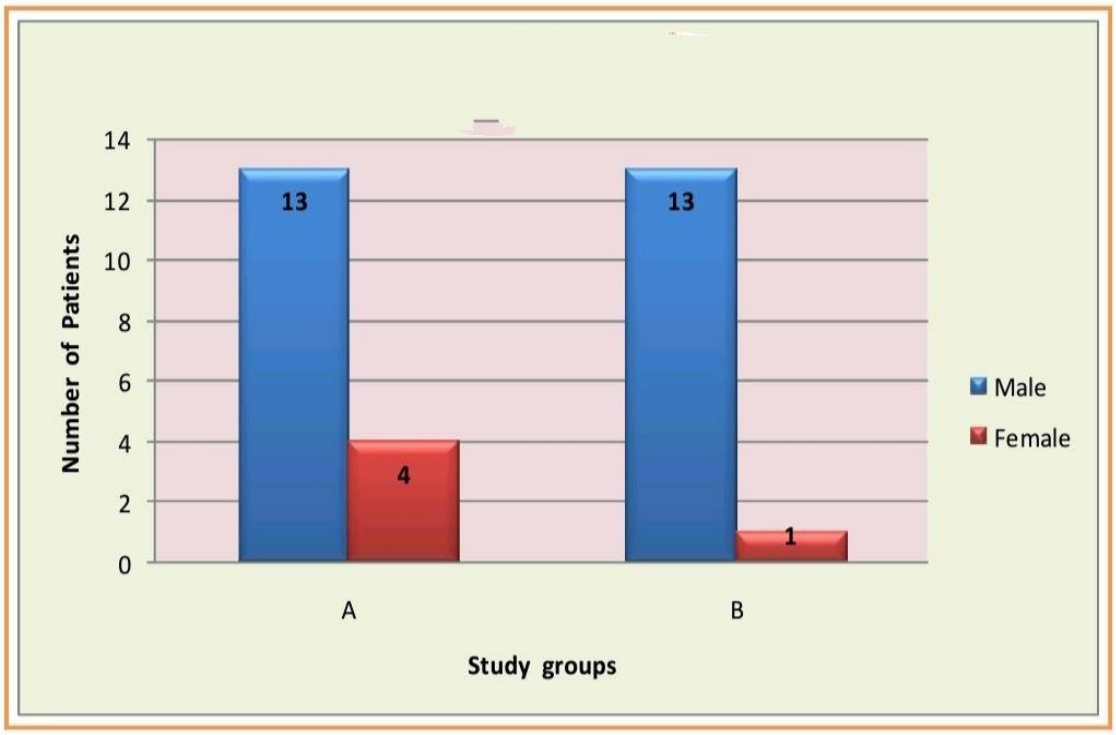
Out of 31 patients, group-A patients were 17 and group-B were 14.

Group A received vitamin D therapy as 20, 000 IU/month (600IU/day) for three month.
Group B received 60,000 IU per month (2000IU/day) for three months.




**Graph no.2: Age wise distribution of patients.**

Out of 31 patients in this study, youngest was of age 1 year and the eldest child was of 12 year old. Most of the patients were from school age group of 6-11 years. There were no infants and neonates in this study. Mean age at inclusion in group A was 5.4 years whereas, it was 7.2 years in group B.




**Graph no.3: Gender wise distribution of patients.**

This graph shows that there was a male preponderance among the patients. 84% cases were males while as 16% cases were females.

**Table no.2: Distribution of patients according to the Diagnosis.**

| Groups | Diagnosis | | | |
|---|---|---|---|---|
| | 1st episode of NS | FRNS | SDNS | Total |
| A | 7 | 5 | 5 | 17 |
| B | 3 | 4 | 7 | 14 |
| Total | 10 | 9 | 12 | 31 |

Table no.2 shows the distribution of nephrotic syndrome and its subtypes in group A & B. Majority 12 of the patients were having SDNS as diagnosis.

**Table no.3: Distribution of patients according to mean level of Serum vitamin 25(OH) D levels in group A &B before and after supplementation.**

| Groups | | Min | Max | Mean ± SD | t value | p value |
|---|---|---|---|---|---|---|
| A | Before | 24.50 | 47.40 | 34.8 ± 7.1 | 2.053 | 0.0568** |
| | After | 24.29 | 55.90 | 38.1 ± 9.1 | | |
| B | Before | 28.00 | 48.00 | 37.9 ± 6.1 | 0.1046 | 0.9183** |
| | After | 25.90 | 57.00 | 38.2 ± 10.9 | | |

Table no.3 shows that the serum 25-hydroxyvitamin D [25(OH)D] concentrations are the best indicator of vitamin D nutritional status5. This is significance test between study group A and study group B for levels of serum vitamin D, before and after Vitamin D supplement. According to paired-t test, p value was less than 0.05, so the correlation was non-significant but both groups showed elevated levels of25(OH) after supplementation. So, the levels of serum vitamin 25(OH) levels were not affected in both the groups.
**Non-Significant (p>0.05), (Test: Paired t -Test), Normal Value: 20-100 (ng/ml)

**Table no.4: Distribution of patients according to mean level of Serum Ionic calcium levels in group A & B before and after supplementation.**

| Groups | | Min | Max | Mean ± SD | t value | p value |
|---|---|---|---|---|---|---|
| A | Before | 1.030 | 1.600 | 1.154 ± 0.15 | NA | 0.8683** |
| | After | 1.010 | 1.270 | 1.144 ± 0.08 | | |
| B | Before | 1.040 | 1.300 | 1.157 ± 0.09 | 1.006 | 0.3326** |
| | After | 1.010 | 4.700 | 1.417 ± 0.95 | | |

Table no.4 shows that there is significance test between Study group A and Study group B for levels of Ionic calcium, before and after supplementation of oral vitamin in case of given Vitamin D supplement. According to paired-t test, p value was less than 0.05, so this was non-significant. So, the levels of serum ionic calcium levels were not affected in both the groups, but the mean values of serum Ionic Calcium was found to be on higher side after Calcium supplementation especially in group B.

**Table no.5: Distribution of patients according to mean level of Serum phosphorus levels in group A & B before and after supplementation.**

| Groups | | Min | Max | Mean ± SD | t value | p value |
|---|---|---|---|---|---|---|
| A | Before | 3.2 | 5.6 | 4.4 ± 0.7 | 0.3350 | 0.7420 |
| | After | 3.2 | 5.6 | 4.3 ± 0.7 | | |
| B | Before | 3.2 | 6.1 | 4.2 ± 0.9 | 0.5048 | 0.6222 |
| | After | 3.3 | 6.1 | 4.2 ± 0.8 | | |

Table no.5 shows that there is no significant difference between mean level of Serum phosphorus levels in group A & B before and after supplementation.

**Table no.6: Distribution of patients according to mean level of Serum Alkaline phosphatase levels in group A & B before and after supplementation.**

| Groups | | Min | Max | Mean ± SD | t value | p value |
|---|---|---|---|---|---|---|
| A | Before | 117 | 210 | 165.8 ± 27.05 | 0.3350 | 0.7420** |
| | After | 119 | 214 | 165.1 ± 25.3 | | |
| B | Before | 103 | 210 | 156.5 ± 29.9 | 0.9494 | 0.3597** |
| | After | 101 | 208 | 155.4 ± 29.6 | | |

Table no.6 shows that the Paired-T test for serum ionic phosphorus and serum Alkaline phosphatase between group A and B before and after vitamin D supplementation. Here, p value was more than 0.5, so the test was not significant and the serum values were not affected in both groups.

**Discussion:**

This is the first study that correlates comparison of normal and high dose of vitamin D supplementation to achieve normal vitamin D level in nephrotic syndrome patient, those who are on remission on prednisolone therapy. To our knowledge, this is also the first report of vitamin D stores in NS patients from Maharashtra region. As such, the results are relevant since the main source of vitamin D is sunlight and exposure, both of which vary from region to region.

In our study, mean age at inclusion in group A was 5.4 years where, it was 7.2 years in group B. In a study by Banerjee et al [9] age at inclusion 6.25 years (4–10). Out of 31 patients in our study 26 (84%) were male and 5 (16%) were female. In an Indian study by Arif et al[10], 45 (60%) children were male, and 30 (40%) were female.

Mean age of onset in group A patients was 4.2 (± 2.7) years and in group B was 3.9 (± 1.3) years whereas mean age of onset in study by Banarjee et al [9] was 2.5 years.

In our study, majority of patients had steroid dependant NS (12 cases), 9 children had frequent relapse NS, 10 children had 1st episode NS. While in study by Banarjee et al [9], Two children had had their first episode of NS, 19 had infrequent relapses, eight had frequent relapses, 12 were steroid dependent, and three were initially steroid resistant but maintained remission.

There are many studies of NS which describes variable effect on vitamin D, ionic calcium, urinary calcium, serum phosphorus level and alkaline phosphatase level during relapse as well as during remission. Some of these studies also explain the role of vitamin D supplementation. But no study had compared the result of normal dose vitamin D against the 2-3 times higher

dose of vitamin D on these parameters (as recommended by Endocrine society). Majority of Pediatric NS patients are in relapse for a very short duration of time, in our study we measured the steady state of 25(OH)D body stores during remission, after resolution of proteinuria for >3 month.

In our study, the mean levels of serum vitamin 25(OH) D in group A was 34.8±7.1 ng/ml and it was 37.9 ± 6.1 ng/ml in group B which was normal before supplementation while after supplementation, it was 38.1 ± 7.1 ng/ml in group A and 38.2 ± 10.9 ng/ml (within normal range) in group B despite giving high dose. Ayi Dilla Septarini et al [11] studied the patients on nephrotic syndrome in remission. He compared the serum 25 (OH) D levels before and after 8 weeks of 400 IU/day of Vitamin D, which were 20 ±7.7 ng/ml and 25.5 ±7.7 ng/ml. So, there was no significant change.

In a study by Banerjee et al [9] had similar results after 3 months Vitamin D Supplementation. 25(OH)D levels did not differ in 15 patients on calcium and vitamin D supplementation compared to those not on supplements [median 20 (IQR 12.9–24.25) vs. 16 (IQR 12.8–19) ng/ml, respectively; p=0.3].

Huang Jian et al [12] studied the effect of Vitamin D therapy in patients with active disease. They found the mean serum 25 (OH) D levels increased from 5.70 ±1.9 ng/ml to 15.7 ± 4.86. But initial 25OH D levels i.e., during relapse were too low to begin with.
Previous studies estimating 25(OH) D levels in NS remission have reported mixed results. Early studies by Freundlich et al [13] and Huang et al[12] showed that low levels of 25(OH) D during relapse normalized quickly post remission, after the resolution of proteinuria and loss of DBP by urinary

leakage. In contrast, Bykilli et al [14] showed that although 25(OH) D levels rise after remission has been achieved with steroid therapy, they are still lower than in controls at 3 months. The study by Weng et al [15] also revealed significantly low levels of 25(OH) D in NS remission compared to controls after a median of 3.5 months from last relapse, but there was no correlation with time interval since last relapse. Hypocalcemia frequently occurred during active stage of NS as described by Freundlich M et al [13] Earlier it was thought that hypocalcemia in nephrotic syndrome is due to the reduction in the protein bound calcium. Fraction secondary to heavy proteinuria and serum ionized fraction was not thought to be affected. However, subsequent studies showed that the reduction in serum calcium concentration was not only in the protein bound fraction but also in ionized calcium. These changes cannot be attributed to renal insufficiency because most nephrotic patients with this alteration showed normal or slightly reduced GFR. Serum ionic calcium levels were found to be lower in patients during active disease than patients in remission which can be explained by frequent urinary losses of vitamin D metabolites and calcium during relapse.

In our study, the mean levels of serum ionic calcium in our study was group A was 1.154 mmol/lt and 1.157 mmol/lt before and after supplementation, while in group B it was 1.144 mmol/lt and 1.147 mmol/lt before and after supplementation which was normal even after high dose of vitamin D. These values are not statistically significant and not altered after supplementing with higher doses of Vitamin D. Study by Ayi Dilla Septarini et al [11] which shows ionised calcium levels before vitamin D supplementation were 1.15 mmol/lit, while after 8 weeks of Vitamin D supplementation it was 1.18mmol/lit. But Lim et al [16] noticed ionized

calcium were declined remarkably in active phase of disease (1.08 ± 0.10 (SD)) which increased to 1.21 ± 0.10 (SD) during remission.

The mean Serum phosphorus levels in group A and B before supplementation were 4.4 ± 0.7 and 4.3 ± 0.7 while it was 4.2 ±0.9 in group A and 4.2±0.8 in group B after supplementation. In group B level of phosphorus is not increased even after receiving high dose of vitamin D. Study by Banarjee et al [9] reported levels of serum phosphorus were not statistically different between the NS group and the control group. As per our study, there was no evidence hypercalcemia despite giving high dose of vitamin D in group B. Low Alkaline Phosphatase levels in NS have been documented in various other studies and one of the probable reasons for this is negative action of steroids on the osteoblastic cells. In our study the mean Serum Alkaline Phosphatase levels were 165.8 ± 27.05 and 165.1 ± 25.3 groups A and B before supplementation and it was 156.5 ± 29.9 and 155.4 ± 29.6 in group A and B respectively after supplementation.

There is no statistical difference with high dose and low dose supplementation of vitamin D, and there are no side effects high dose vitamin D supplementations at the end of our study.

**Conclusion:**

All results discussed above concludes that there is no need for vitamin D supplementation in higher doses in steroid-sensitive nephrotic syndrome in patients those who are in remission and on minimal dose of steroids. Higher doses of Vitamin D don't have additional benefits have in terms of Serum 25(OH) D levels, Serum Ionised Calcium levels, Serum Phosphorus Levels and Serum Alkaline Phosphatase levels. So, dosage of vitamin D should be according to Recommended Dietary Allowances (RDA) when patient is on minimal dose of steroids.

**Limitations of the Study:**

1. It is cross-sectional study with very small sample size.
2. The data need to be confirmed with multi-centric, comprehensive studies.
3. We did not include measurements of BMD, and it is possible that low 25(OH) D levels lasting for even a few months post-relapse may contribute to the osteoporosis that has been shown to occur early in steroid-treated NS and respond at least partially to vitamin D therapy.
4. Parathyroid hormone assay was not measured due financial restraint of the studies.
5. This study was carried for short duration we need to follow up these patients to see effect on bone mineralization.

**APPENDICES:**

IPD- Indoor Patient department
OPD - Outdoor Patient department
IU – International Units
SDNS – steroid-dependent nephrotic syndrome
FRDS – Frequently relapsing nephrotic syndrome
RDA – Recommended dietary allowances
DBP – Vitamin D binding protein
GFR - Glomerular filtration rate
NS - Nephrotic Syndrome

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