RESEARCH PAPER

Influence of Vitamin D3 Supplementation on Serum Interleukin-4 Levels in Pediatric Patients with Nephrotic Syndrome: A Double-Blind Randomized Controlled Trial

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Received: 28th Feb, 2026; Revised: 6th March 2026; Accepted: 7th April, 2026; Available Online: 20th April, 2026

ABSTRACT

Background: In pediatric cases of nephrotic syndrome (NS), there is a link to immune system dysregulation, which includes changes in cytokine profiles like interleukin-4 (IL-4). A deficiency in vitamin D is frequently observed in NS and might affect immune responses, though its impact on IL-4 is not well understood. This research sought to assess how vitamin D3 supplementation affects serum IL-4 levels in children suffering from nephrotic syndrome.

Methods: In a double-blind randomized clinical trial, pediatric NS patients aged between 1 and 18 years were included. The participants were randomly divided to receive a combination of prednisone and either 400 IU/day or 1000 IU/day of vitamin D3 over a period of four weeks. Assessments conducted at the start and end of the intervention measured serum IL-4 and 25(OH)D levels. Statistical analyses utilized suitable parametric and non-parametric tests, maintaining a significance threshold of $p<0.05$.

Results: In the study, 59 individuals participated and completed the research. Initially, the IL-4 and vitamin D levels were similar across the groups. After the supplementation period, both groups experienced a notable rise in vitamin D levels ($p<0.05$), yet there were no significant differences when comparing the groups ($p>0.05$). Although serum IL-4 levels tended to decrease post-intervention, these changes were not statistically significant within any group or between them ($p>0.05$).

Conclusions: Administering Vitamin D3 at doses of 400 IU and 1000 IU notably enhanced vitamin D levels in children suffering from nephrotic syndrome, yet it did not have a significant impact on serum IL-4 concentrations. Additional research involving higher doses and extended treatment periods is necessary to better understand its role in immune modulation.

Keywords: randomized clinical trial, children, interleukin-4, vitamin D3, nephrotic syndrome

How to cite this article: Idrus NA, Jusli, Ridha NR, Rauf S, Angriani H, Astari MM, Influence of Vitamin D3 Supplementation on Serum Interleukin-4 Levels in Pediatric Patients with Nephrotic Syndrome: A Double-Blind Randomized Controlled Trial. Int J Drug Deliv Technol. 2026;16(6): 522-528. DOI: 10.25258/ijddt.16.6.60

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Nephrotic syndrome (NS) continues to pose a significant clinical challenge worldwide, especially in terms of prognosis and treatment response, which are primarily influenced by histopathological characteristics and steroid sensitivity.[1] While minimal change nephrotic syndrome (MCNS) typically responds well to corticosteroid treatment, focal segmental glomerulosclerosis (FSGS) carries a greater risk of acute kidney injury, progression to end-stage kidney disease, and the necessity for renal replacement therapy.[2,3] In children, around 40–60% of steroid-sensitive nephrotic syndrome (SSNS) cases evolve into frequently relapsing or steroid-dependent forms, necessitating extended immunosuppressive treatment. Additionally, 10–20% of pediatric patients develop steroid-resistant nephrotic syndrome (SRNS), which considerably deteriorates long-term kidney outcomes.[4] Therefore, refining therapeutic approaches for NS remains a persistent challenge.[5] The global incidence of pediatric NS varies from 1.15 to 16.9 cases per 100,000 children annually, with differences across regions and ethnic groups.[6] In Indonesia, the incidence is estimated at about 6 cases per 100,000 children under 14 years, with a higher prevalence in males.[7]

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The exact mechanisms behind the pathogenesis of NS are not completely understood, but it is believed to involve immune system dysregulation, factors affecting permeability in circulation, and structural defects in podocytes and the glomerular filtration barrier.[8,9] Interleukin-4 (IL-4) is one immune mediator that has been associated with podocyte damage through processes like membrane ruffling and the retraction of foot processes, which ultimately lead to proteinuria.[10] Research has shown that overexpression of IL-4 can cause podocyte detachment and damage to glomerular capillaries, underscoring its role in disease development.[11] Nevertheless, results are not always consistent, as some research indicates decreased IL-4 expression in NS, possibly due to the effects of immunosuppressive treatments.[12]

Patients with NS often exhibit a deficiency in vitamin D, characterized by notably reduced concentrations of 25(OH)D and 1,25$(OH)_2$D when compared to healthy individuals. Research indicates that vitamin D3 (cholecalciferol) is more effective than vitamin D2 in elevating serum 25(OH)D levels.[13] Apart from its involvement in bone metabolism, vitamin D also plays a role in modulating the immune system, influencing T-helper cell differentiation and cytokine production, including IL-4. Studies examining the relationship between vitamin D and IL-4 have produced inconsistent findings; some suggest a reduction in IL-4 expression after vitamin D supplementation, while others indicate an increase in Th2 cytokine production, such as IL-4, especially in the context of chronic kidney disease.[14] However, there is limited evidence on how vitamin D3 affects IL-4 levels in children with NS. Exploring the interaction between vitamin D3, IL-4, and immune-related podocyte damage could offer valuable insights for enhancing treatment outcomes in pediatric NS. Consequently, this study seeks to assess the impact of vitamin D3 supplementation on serum IL-4 levels in children with nephrotic syndrome.

METHODS

Study Design and Setting

In this experimental research, a double-blind randomized clinical trial was employed to assess how vitamin D3 supplementation influences serum IL-4 levels in children suffering from nephrotic syndrome. Conducted between October 2025 and January 2026, the study took place in both the inpatient and outpatient departments of two tertiary referral hospitals. The laboratory analyses were carried out at a research laboratory affiliated with a university.

Study Population and Sampling

The research involved pediatric patients who had been diagnosed with NS. The intended group was children between the ages of 1 and 18, whereas the accessible group consisted of eligible patients present at the study locations during the research timeframe. Participants were selected through consecutive sampling and then randomly divided into two intervention groups.

Eligibility Criteria

Children between the ages of 1 and 18 years, diagnosed with NS, were eligible to participate, provided their parents or guardians gave written informed consent. Those with cancer, liver issues, previous vitamin D supplementation, or known allergies were not included. Participants who did not adhere to the supplementation, were lost during follow-up, encountered adverse events, or could not finish the study were considered dropouts.

Randomization and Blinding

Participants were divided into two groups through random assignment. Group I was administered standard prednisone treatment along with a daily supplement of 400 IU of vitamin D3. In contrast, Group II received prednisone therapy paired with a daily dose of 1000 IU of vitamin D3 over a period of four weeks. To maintain double blinding, the vitamin D3 supplements were packaged and coded identically, with an independent pharmacy unit overseeing the management to ensure the concealment of group assignments.

Data Collection and Clinical Assessment

Initial data encompassed demographic and clinical features, including age, gender, body measurements, and nutritional condition. The laboratory parameters evaluated included serum 25-hydroxyvitamin D [25(OH)D], IL-4, albumin, total cholesterol, and urinary protein concentrations. Every participant completed both initial and follow-up evaluations after a four-week supplementation period.

Laboratory Procedures

Under aseptic conditions, 3 mL blood samples were obtained through venipuncture and then subjected to centrifugation. Before analysis, the samples were kept at a temperature range of 2–8°C. The levels of serum 25(OH)D were assessed using a chemiluminescence immunoassay. To determine serum IL-4 concentrations, a sandwich enzyme-linked immunosorbent assay (ELISA) was employed, utilizing the BioLegend MAX™ Human IL-4 ELISA Kit according to the manufacturer's guidelines.

Intervention Protocol

In line with institutional clinical guidelines, all participants underwent standard NS treatment. Depending on their group assignment, they received daily Vitamin D3 supplements for a duration of four weeks. Initial measurements of serum vitamin D and IL-4 levels were taken before starting the supplementation and were evaluated again after the intervention period concluded. Any adverse events were tracked, and the supplementation was halted if deemed clinically necessary.

Statistical Analysis

SPSS version 30 was employed for data analysis. Baseline characteristics were summarized through descriptive statistics. The Kolmogorov–Smirnov test was utilized to check normality, while Levene’s test was applied to assess

variance homogeneity. Independent t-tests or Mann–Whitney U tests were used for comparing groups, and paired t-tests or Wilcoxon signed-rank tests were used for within-group analyses. Pearson or Spearman tests were conducted to evaluate correlations as needed, and categorical variables were examined using the chi-square test. Statistical significance was determined at a p-value of less than 0.05.

RESULTS

Baseline Characteristics

Initially, 67 individuals were enrolled in the study, but one was excluded due to a malignancy, leaving 66 participants who were evenly divided into Group I (receiving 400 IU/day of vitamin D3) and Group II (receiving 1000 IU/day of vitamin D3). Throughout the follow-up period, seven participants were removed from the study: one for non-adherence, four due to loss to follow-up, and two because of death, resulting in 59 participants being included in the final analysis.

The groups did not show significant differences in sex distribution (p=0.145) or age categories (p=0.302). However, there was a significant difference in nutritional status between the groups (p=0.003). The remission rates were similar, with Group I at 26.7% and Group II at 37.9% (p=0.355). At the start of the study, there was no significant difference in vitamin D status between the groups (p=0.522), with most participants showing deficiency or severe deficiency. After four weeks of supplementation, both groups experienced an improvement in vitamin D status, yet no significant difference was found between Group I and Group II (p=0.783).

Assessment of Serum Levels of Interleukin-4 and Vitamin D Prior to Vitamin D3 Supplementation (Pretest)

Before supplementation, serum interleukin-4 (IL-4) and vitamin D levels were assessed in Group I (vitamin D3 400 IU) and Group II (vitamin D3 1000 IU), as detailed in Table 2. The Shapiro–Wilk test for normality revealed that pretest IL-4 levels in Group I, as well as the combined groups and delta IL-4, followed a normal distribution. Conversely, pretest IL-4 levels in Group II and vitamin D levels in both groups did not exhibit normal distribution. The initial IL-4 levels were similar across the groups, with Group I having a mean of 0.524 (SD 0.163) pg/mL and Group II showing a mean of 0.550 (SD 0.170) pg/mL. An independent t-test confirmed no statistically significant difference between the groups (p=0.546). Regarding vitamin D, Group I had a median level of 8.295 (0.5–31) ng/mL, while Group II had a median of 10.218 (1.4–32) ng/mL. The Mann–Whitney test showed no significant difference in baseline vitamin D levels between the groups (p=0.200).

Assessment of Serum Interleukin-4 and Vitamin D Concentrations Following Vitamin D3 Supplementation (Posttest)

After a four-week period of standard treatment combined with vitamin D3 supplementation, both groups underwent a reevaluation of their serum interleukin-4 (IL-4) and vitamin D concentrations (refer to Table 3). Following the intervention, IL-4 levels were reduced to 0.524 (SD 0.191) pg/mL in Group I and 0.473 (SD 0.199) pg/mL in Group II. Concurrently, serum vitamin D concentrations rose to 12.959 (2–54.9) ng/mL in Group I and 14.669 (1.2–42.5) ng/mL in Group II. Nonetheless, the differences in IL-4 levels (p=0.326) and vitamin D levels (p=0.347) between the two groups were not statistically significant after the supplementation.

Assessment of Alterations in Serum Interleukin-4 and Vitamin D Concentrations Following Vitamin D3 Supplementation

Table 4 illustrates the comparison of serum interleukin-4 (IL-4) and vitamin D levels before and after vitamin D3 supplementation between Group I (400 IU) and Group II (1000 IU). Both groups showed a decrease in IL-4 levels, with Group I experiencing an average reduction of 0.0003 (SD 0.23) pg/mL and Group II showing a decrease of 0.07 (SD 0.24) pg/mL. Despite these reductions, the independent t-test revealed no statistically significant difference between the groups (p=0.229). Regarding vitamin D levels, Group II exhibited a higher median increase of 5.1 ng/mL compared to 4.7 ng/mL in Group I. However, the Mann–Whitney analysis found no statistically significant difference in vitamin D changes between the groups (p=0.903).

Within-group comparisons of IL-4 levels before and after the intervention are detailed in Table 5. Group I (400 IU) had a mean IL-4 change of 0.0003 (SD 0.235) pg/mL, whereas Group II (1000 IU) experienced a larger reduction of 0.077 (SD 0.249) pg/mL. Nonetheless, these changes were not statistically significant for either group (p=0.995 for Group I and p=0.133 for Group II).

Table 6 outlines the changes in serum vitamin D levels post-supplementation. Group I's median vitamin D levels rose by 4.72 ng/mL, while Group II's increased by 5.17 ng/mL. The mean increase was 10.21 (SD 12.52) ng/mL for Group I and 2.15 (SD 10.65) ng/mL for Group II. Both groups showed statistically significant increases in vitamin D levels (p=0.001 for Group I and p=0.018 for Group II).

DISCUSSION

The demographic profile of participants in this research aligns with the established epidemiology of pediatric nephrotic syndrome (NS), where most cases are found in children aged 5–12 years, with a higher incidence in males. This observation corroborates earlier studies. According to Subandiyah et al. (2018) and Alim et al. (2025), NS predominantly affects children aged 5–10 years, with males being more frequently affected.[12,15] Comparable trends have been noted in other regional studies as reported by Haris et al. (2025) and Shanta et al. (2023).[16,17] Among the baseline variables, nutritional status was the only one that showed a significant

difference between groups, potentially impacting immune responses and cytokine profiles.

During the selection of subjects, a patient diagnosed with nephrotic syndrome and acute lymphoblastic leukemia (ALL L1 HR) as the primary condition was excluded. This decision was made because ALL is linked to a significant rise in pro-inflammatory cytokines, such as IL-4, IL-1β, IL-6, IL-8, GM-CSF, TNF-α, and VEGF, which could complicate the analysis of cytokine profiles in this research.[18] Additionally, studies have shown that IL-6 levels are notably elevated in high-risk ALL (L1 HR) compared to standard-risk ALL (L1 SR), indicating a heightened inflammatory response.[19] Consequently, including such patients might skew the assessment of vitamin D3's immunomodulatory impact on IL-4 levels in children with NS.

Initial serum levels of IL-4 and vitamin D were similar across the groups, suggesting a well-matched baseline. The involvement of IL-4 in NS is still debated. IL-4 levels were found to be higher in active NS, especially in patients with allergies, but this study did not include such cases, which might account for the lower levels observed. Conversely, Deckert et al. (2015) found no notable differences in IL-4 expression among NS subtypes, possibly due to the effects of immunosuppressive treatment.[12] Other research, such as that by Chang and Lee (2016), has also noted increased IL-4 levels in NS compared to controls, emphasizing the variability influenced by study design and participant demographics.[20]

At the start, vitamin D deficiency was widespread, aligning with earlier research. According to Kogon et al. (2022), the majority of pediatric NS patients exhibit inadequate vitamin D levels.[21] This deficiency is mainly due to the urinary loss of vitamin D-binding protein caused by proteinuria.[12,22] After supplementation, both 400 IU and 1000 IU doses of vitamin D3 led to a significant rise in serum vitamin D levels, yet no notable difference was found between the two groups. These results imply that the doses given might not be enough to reach optimal vitamin D levels. Kogon et al. (2022) suggest that higher doses and extended supplementation periods are frequently necessary.[21] Furthermore, ongoing proteinuria and low remission rates could hinder vitamin D recovery, as noted by Yang et al. (2021).[23]

While there was a noted decrease in IL-4 levels following supplementation, the alterations were not statistically significant. This indicates that the doses of vitamin D3 examined may have a limited impact on modulating IL-4 in children with NS. According to Deckert et al. (2015), no significant link was found between vitamin D levels and IL-4 expression in NS patients.[12] Conversely, research outside the NS framework has demonstrated that vitamin D can inhibit Th2 responses and lower IL-4 production. This inconsistency might be due to disease-specific processes, the influence of concurrent immunosuppressive treatments, and the intricate role of vitamin D in modulating the immune system, as it affects various cytokines at once.[24] In summary, this study shows that vitamin D3 supplementation enhances vitamin D levels but does not significantly alter IL-4 levels in children with NS. These results imply that higher doses, extended intervention periods, and more comprehensive immunological evaluations might be necessary to thoroughly understand the immunomodulatory effects of vitamin D in this group.

This research faces several constraints. Initially, participants were divided into just two intervention groups receiving varying doses of vitamin D3, without a healthy control group, which restricts comparative analysis. Additionally, there was no data on baseline serum vitamin D and IL-4 levels before nephrotic syndrome diagnosis, hindering the evaluation of pre-disease conditions. Furthermore, the study did not control or adjust for potential confounders like dietary habits and sunlight exposure. Lastly, the vitamin D3 supplementation lasted only four weeks, a period that might be too brief to reach optimal vitamin D levels or thoroughly assess its effects on IL-4 modulation.

CONCLUSION

According to the results of this study, no statistically significant differences were observed in serum IL-4 and vitamin D levels among children with NS who received vitamin D3 supplementation at doses of 400 IU and 1000 IU, both prior to and following the intervention. Additionally, supplementation with vitamin D3 at either dose did not lead to a notable alteration in serum IL-4 levels. However, there was a statistically significant increase in serum vitamin D levels in both groups associated with vitamin D3 supplementation. These results indicate that while vitamin D3 effectively enhances vitamin D levels, it does not exhibit a significant immunomodulatory impact on IL-4 levels in children with NS under the conditions of this study.

Ethical considerations

This research adhered to the ethical guidelines set forth in the Declaration of Helsinki. Approval for the study was granted by the Health Research Ethics Committee at Hasanuddin University, Makassar, Indonesia (Approval No. 679/UN4.6.4.5.31/PP36/2025; approved on 17 September 2025). The research took place at Universitas Hasanuddin Hospital, Dr. Wahidin Sudirohusodo Hospital, and Jaury Jusuf Putera Academic Hospital, all located in Makassar. Prior to participants being enrolled, written informed consent was secured from their parents or legal guardians.

Data availability

The underlying data supporting the findings of this study are publicly available through the Zenodo repository at https://doi.org/10.5281/zenodo.20530100. The dataset contains de-identified participant-level clinical and laboratory data used for the analyses, including demographic characteristics, nutritional status, proteinuria, albumin, cholesterol, serum vitamin D, IL-4, and

remission outcomes. To protect participant confidentiality, all direct identifiers were removed prior to data sharing. The dataset is openly accessible and may be used for academic and research purposes without additional restrictions.

Reporting guidelines
This study was reported in accordance with the **Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement** for randomized clinical trials.

Competing interests
The authors declare that they have no competing interests.

Grant information
This research received no external funding.

Acknowledgements
The authors would like to thank the Faculty of Medicine, Hasanuddin University, and the participating hospitals for their support in conducting this study.

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Tables

Table 1. Characteristics of Study Subjects

Characteristic	Group I (N=30)	Group II (N=29)	p-value
	n (%)	n (%)	
Sex			
Male	22 (73.3)	16 (55.2)	0.145*
Female	8 (26.7)	13 (44.8)	
Age (years)			
<5 years	2 (6.7)	5 (17.2)	
5–12 years	15 (50)	16 (55.2)	
>12 years	13 (43.3)	8 (27.6)	0.302**
Nutritional Status			
Severe malnutrition	2 (6.7)	0 (0)	
Underweight	1 (3.3)	9 (31)	
Normal	21 (70)	19 (65.5)	
Overweight	6 (20)	1 (3.4)	0.003**
Remission			
Yes	8 (26.7)	11 (37.9)	
No	22 (73.3)	18 (62.1)	0.355*
Vitamin D Status Before Vitamin D3 Supplementation			
Severe deficiency	10 (33.3)	8 (27.6)	
Deficiency	15 (50)	11 (37.9)	
Insufficiency	4 (13.3)	8 (27.6)	
Normal	1 (3.3)	2 (6.9)	0.522**
Vitamin D Status After Vitamin D3			

Supplementation			
Severe deficiency	4 (13.3)	5 (17.2)	
Deficiency	14 (46.7)	10 (34.5)	
Insufficiency	8 (26.7)	8 (27.6)	
Normal	4 (13.3)	6 (20.7)	0.783**

* Chi-Square test; ** Fisher's Exact test

Table 2. Assessment of Serum Interleukin-4 and Vitamin D Concentrations in Pediatric Nephrotic Syndrome Patients Prior to Vitamin D3 Supplementation (Pretest) in Groups I and II

Characteristic	Group I (Vitamin D3 400 IU)	Group II (Vitamin D3 1000 IU)	p-value
Interleukin-4, pg/mL Mean (SD)	0.524 (0.163)	0.550 (0.170)	0.546*
Vitamin D, ng/mL Median (Min–Max)	8.295 (0.5–31)	10.218 (1.4–32)	0.200**

* Independent t-test; ** Mann–Whitney test

Table 3. Serum Interleukin-4 and Vitamin D Levels in Group I and Group II Following Vitamin D3 Supplementation (Posttest)

Characteristic	Group I (Vitamin D3 400 IU)	Group II (Vitamin D3 1000 IU)	p-value
Interleukin-4, pg/mL Mean (SD)	0.524 (0.191)	0.473 (0.199)	0.326*
Vitamin D, ng/mL Median (Min–Max)	12.959 (2–54.9)	14.669 (1.2–42.5)	0.347**

* Independent t-test; ** Mann–Whitney test

Table 4. Evaluation of Alterations in Serum Interleukin-4 and Vitamin D Concentrations in Pediatric Nephrotic Syndrome Patients Following Vitamin D3 Supplementation in Group I and Group II

Characteristic	Group I (Vitamin D3 400 IU)	Group II (Vitamin D3 1000 IU)	p-value
Interleukin-4, pg/mL Mean (SD)	0.0003 (0.235)	0.077 (0.249)	0.229*
Vitamin D, ng/mL Median (Min–Max)	4.7 (−9.2–44.4)	5.1 (−28.1–29.4)	0.903**

* Independent t-test; ** Mann–Whitney test

Table 5. Assessment of Interleukin-4 Level Variations Pre- and Post-Vitamin D3 Supplementation in Groups I and II

Characteristic	Interleukin-4 Pretest	Interleukin-4 Posttest	Deviation*	p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Group I (Vitamin D 400 IU)	0.5243 (0.1631)	0.5241 (0.1919)	0.0003 (0.235)	0.995**
Group II (Vitamin D 1000 IU)	0.5508 (0.1709)	0.4737 (0.1991)	0.077 (0.249)	0.133***

*Pretest IL-4 serum level minus posttest IL-4 serum level; ** Paired t-test; *** Wilcoxon test

Table 6. Evaluation of Serum Vitamin D Level Variations Pre- and Post-Vitamin D3 Supplementation in Group I Versus Group II

Characteristic	Vitamin D Pretest	Vitamin D Posttest	Deviation	p-value
	Median (Min–Max)	Median (Min–Max)	Median (Min–Max) / Mean (SD)	
Group I (Vitamin D 400 IU)	8.29 (0.5–31.0)	12.95 (2.0–54.9)	4.72 (−9.29–44.49) / 10.21 (12.52)	0.001
Group II (Vitamin D 1000 IU)	10.21 (1.4–32.0)	14.66 (1.2–42.5)	5.17 (−28.13–29.47) / 2.15 (10.65)	0.018

Wilcoxon test