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The Effect of High-Dose Vitamin D3 on Hemoglobin Levels in Dialysis Patients

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ABSTRACT

Background and Objective: Hemoglobin levels are crucial for infection control in dialysis units. Given the role of vitamin D in reducing anemia in dialysis patients, this study was conducted to investigate the effect of high doses of vitamin D3 on hemoglobin levels in dialysis patients.

Methods: This cross-sectional study was conducted on 33 dialysis patients hospitalized at Shohada Gomnam Hospital in Tehran. After initial assessment of demographic information, hemoglobin concentration, vitamin D3 levels, and other clinical indicators, the patients were divided into two groups: control (n=18) and intervention (n=15). The intervention group received intramuscular injection of 5 µg of vitamin D3 every week for four weeks, while the control group was given placebo. One month after the final dose, changes in vitamin D3 levels, hemoglobin, and other blood factors were measured and compared in the two groups.

Findings: The mean age of patients in the intervention group was 51.53±18.52 years and the control group was 50.83±13.30 years. The mean hemoglobin level in the intervention group increased from 9.22±0.94 mg/dL to 11.37±0.70 mg/dL (p=0.011). Other variables including Kt/v, MCV, creatinine, BUN, calcium, phosphorus, albumin, serum iron, TIBC, ferritin and CRP did not differ significantly between the two groups. Ferritin level increased from 268.13±170.34 to 385.07±159.52, while PTH level decreased.

Conclusion: The results of the study showed that high-dose vitamin D3 administration can improve hemoglobin levels and other blood factors in dialysis patients. Therefore, vitamin D3 can be used as an effective supplement for managing anemia in dialysis patients.

Keywords: *Vitamin D3, Hemoglobin, Anemia, Dialysis, Vitamin D Deficiency*.

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Introduction

Anemia is a common complication in dialysis patients, especially those with chronic kidney disease (CKD), affected by reduced erythropoiesis, iron deficiency, and chronic inflammation. Effective management of this condition is critical to achieve better clinical outcomes, such as reduced mortality and hospitalization (1). Approaches such as the use of erythropoiesis-stimulating agents (ESAs) and iron supplementation are common, but international studies have shown much diversity in anemia management (2). Also, algorithm-based protocols and nursing management have been as effective as individual dosing in achieving hemoglobin-related goals (3). Recent advances, including personalized ESA dosing, artificial intelligence-based tools such as the anemia control model (ACM), and telemedicine platforms, have improved hemoglobin stability and reduced cases of severe anemia (4-6). Early management of anemia in children on dialysis has also shown significant benefits in preventing complications and improving long-term outcomes (7). These innovations underscore the importance of using technology in anemia management to improve clinical outcomes and enhance patients' quality of life (8).

Hemoglobin levels play an important role in the outcomes of dialysis patients because of their direct association with morbidity, mortality, and quality of life. Maintaining hemoglobin levels within the target range (11-12 g/dL) has been associated with improved post-dialysis outcomes, including lower major adverse cardiovascular events (MACE) and mortality (9). In addition, one study found that a mean hemoglobin level of less than 100 g/L significantly increased the risk of mortality and cardiovascular complications in peritoneal dialysis patients (10). In addition, studies conducted in Canada have shown that better anemia management has resulted in reduced mortality, even in the presence of low hemoglobin levels at the start of dialysis (11). Some studies have shown that vitamin D plays a key role in vascular protection and repair, and normalizing its levels can significantly improve vascular function indices (12, 13).

Vitamin D plays a critical role in bone health, regulating calcium and phosphorus, and supporting immune function. Its deficiency is associated with osteoporosis and fractures, as well as an increased risk of autoimmune diseases and infections (14-16). Recent studies have shown that vitamin D deficiency, which is common in CKD and dialysis patients, leads to reduced erythropoiesis and exacerbated anemia (17). Similarly, studies have shown that higher vitamin D levels are associated with improved hemoglobin in dialysis patients, independent of iron status (18, 19). Given the growing evidence for the role of vitamin D in erythropoiesis and the management of anemia, it is important to investigate the effect of high doses of vitamin D3 on hemoglobin levels in dialysis patients. Although ESAs are widely used, their efficacy may vary and are associated with side effects. Since the effect of vitamin D3 as an adjunctive therapy, and especially its direct effect on hemoglobin levels, has not yet been well studied, this study was conducted to investigate the effect of high doses of vitamin D3 on increasing hemoglobin levels in dialysis patients hospitalized at Shohada Gomnam Hospital in Tehran.

Methods

After approval by the Ethics Committee of Shahid Beheshti University of Medical Sciences with the code IR.SBMU.RETECH.REC.1399.472 and registration at the Clinical Trials Center with the code IRCT20190202042588N2, this randomized, double-blind clinical trial was conducted in the dialysis department of Shohada Gomnam Hospital in Tehran over a period of six months on 33 dialysis patients who were randomly divided into intervention (15 patients) and control (18 patients) groups. Patients aged 18 years of age and older who had been on dialysis for at least six months were included in the study after obtaining written informed consent, and patients with conditions such as anemia or chronic liver disease

that may affect hemoglobin and vitamin D3 levels were excluded from the study. Also, those with abnormally high or low vitamin D3 levels, inability to attend one-month follow-ups, and dissatisfaction with the study were excluded. Demographic information including age and gender was collected using a checklist.

First, a baseline assessment of hemoglobin and vitamin D3 levels was performed. The randomization process was performed using a computerized list to ensure that patient allocation was unbiased and concealed. Study blinding was maintained by keeping participants and the research team unaware of group allocation.

Patients in the intervention group received 5 micrograms of vitamin D3 via intramuscular injection every week for four weeks, while the control group was given placebo. Then, one month after the final dose, a final assessment was performed to examine changes in hemoglobin levels, vitamin D3, Kt/v, cell volume (MCV), creatinine (Cr), blood urea nitrogen (BUN), calcium (Ca), phosphorus (P), albumin (Alb), parathyroid hormone (PTH), serum iron (SI), total iron binding capacity (TIBC), ferritin and C-reactive protein (CRP), and hemoglobin (Hb) levels.

Data were analyzed using SPSS version 22 and paired t-tests, Fisher, Wilcoxon Signed-Sum and Covariance (ANCOVA) tests, and Kolmogorov-Smirnov test, and $p<0.05$ was considered significant.

Results

The mean age of the patients was 51.15±15.64 years, while the mean age in the intervention group was 51.53±18.52 years and in the control group it was 50.83±13.30 years. There were 13 males in the intervention group and 14 males in the control group. The mean hemoglobin level in the intervention group increased from 9.22±0.94 mg/dL to 11.37±0.70 mg/dL ($p=0.011$).

No significant statistical difference was observed between the two groups in terms of age and gender. The duration of dialysis treatment varied between 6 and 96 months and the mean duration of treatment was 23.67±20.94 months. The predominant routes of access to dialysis included Permacath (45.5%), AVF (48.5%), and AVG (6.1%), and no significant difference was observed between the two groups in terms of the type of access to dialysis (Table 1).

Hemoglobin (Hb) levels in the intervention group were significantly lower than those in the control group (9.22±0.94 mg/dL vs. 11.17±0.91 mg/dL) ($p<0.001$). There was no significant difference in 25(OH) vitamin D levels between the two groups. However, parathyroid hormone (PTH) levels were significantly higher in the intervention group (335.00 vs. 306.50 pg/mL) ($p=0.002$). Total iron binding capacity (TIBC) was significantly lower in the intervention group (250.07±33.10 vs. 250.07±16.60 mcg/dL) ($p=0.019$). Other variables including Kt/v, MCV, creatinine (Cr), blood urea nitrogen (BUN), calcium (Ca), phosphorus (P), albumin (Alb), serum iron (SI), ferritin, and C-reactive protein (CRP) did not show statistically significant differences between the two groups (Table 1).

After the intervention, the hemoglobin level in the intervention group was significantly lower than the control group ($p=0.011$) and the serum PTH level was also significantly higher ($p=0.034$) (Table 2).

However, after adjusting for the variables of pre-intervention hemoglobin, Kv/t, serum PTH, TIBC, and ferritin, the post-intervention hemoglobin level in the intervention group was significantly higher than the control group ($p=0.008$) (Table 3).

Table 1. Comparison of laboratory findings between the two groups before intervention

Basic information	Group		p-value
	Control Mean±SD	Intervention Mean±SD	
Age (years)	50.83±13.30	51.53±18.52	0.901
Gender, Number(%)			
Male	14(77.8)	13(86.7)	0.665
Hb, mg/dL	11.17±0.91	9.22±0.94	<0.001
25(OH) Vitamin D, IU	22.83±11.55	19.93±8.22	0.422
Kt/v	1.17 (1.15-1.19)	1.14 (1.09-1.18)	0.155
MCV, fL	91±6.03	92.38±6.79	0.541
Chrome, mg/dL	8.02±0.71	8.08±0.79	0.824
BUN, mg/dL	134.06±8.63	133.53±11.27	0.881
Calcium, mg/dL	8.51±0.48	8.46±0.44	0.755
Phosphorus, mg/dL	5.52±0.67	5.78±0.43	0.207
Alb, g/dL	3.78±0.34	3.84±0.28	0.606
PTH, pg/ml	306.50 (297.50-311.50)	335 (310-345)	0.002
SI, mcg/dL	34.78±8.37	36.53±16.61	0.714
TIBC, mcg/dL	274.06±16.60	250.07±33.10	0.019
Ferritin, mg/dL	342.72±130.86	268.13±170.34	0.165
CRP, mg/dL	8 (6.80-10.25)	6.90 (6-12)	0.381

Hb: Hemoglobin, MCV: Mean Corpuscular Volume, BUN: Blood Urea Nitrogen, PTH: Parathyroid Hormone, SI: Serum Iron, TIBC: Total Iron Binding Capacity, CRP: C-Reactive Protein

Table 2. Comparison of laboratory findings between the two groups after intervention

Variable	Group		p-value
	Control Mean±SD	Intervention Mean±SD	
Hb, mg/dL	11.37±0.70	10.62±0.90	0.011
25(OH)vitamin D, IU	40.06±17.22	43.80±12.83	0.492
Kt/v	1.20±0.03	1.20±0.02	0.552
MCV, fL	91.61±5.39	92.04±5.50	0.823
Chrome, mg/dL	7.97±0.69	7.70±1.02	0.371
BUN, mg/dL	133.44±8	132.53±8.88	0.759
Calcium, mg/dL	8.51±0.35	8.71±0.25	0.077
Phosphorus, mg/dL	5.43±0.44	5.39±0.41	0.794
Alb, g/dL	3.78±0.28	3.92±0.23	0.164
PTH, pg/ml	269.17±27.89	288.27±20.03	0.034
SI, mcg/dL	43 (38.25-51.75)	45 (27-52)	0.817
TIBC, mcg/dL	271.33±25.47	261.33±23.27	0.252
Ferritin, mg/dL	439.89±123.43	385.07±159.52	0.274
CRP, mg/dL	8.33±4.16	6.80±3.96	0.290

Hb: Hemoglobin, MCV: Mean Corpuscular Volume, Cr: Creatinine, BUN: Blood Urea Nitrogen, Alb: Albumin, PTH: Parathyroid Hormone, SI: Serum Iron, TIBC: Total Iron Binding Capacity, CRP: C-Reactive Protein

Table 3. Comparison of hemoglobin levels after intervention with and without adjustment for pre-intervention differences

Variable	Group		p-value	
	Control Mean±SD	Intervention Mean±SD	Unadjusted	Adjusted
Hemoglobin level after intervention, mg/dL				
Observed	11.37±0.70	10.62±0.90	0.001	0.008
Adjusted estimates	10.75±0.23	11.36±0.26		

Hemoglobin levels in the intervention group improved significantly (p<0.001), while no significant change was observed in the hemoglobin levels of the control group. Furthermore, the increase in hemoglobin levels was significantly greater in the intervention group (p<0.001). Kv/t, 25(OH) vitamin D, and ferritin levels improved significantly in both groups, while PTH levels decreased. In addition, statistically significant changes were observed in creatinine, calcium, phosphorus, and CRP levels in the intervention group, while serum iron levels increased significantly in the control group (Table 4).

Table 4. Comparison of pre- and post-test findings in each group

Variable	Group					
	Intervention			Control		
	Before Mean±SD	After Mean±SD	p-value	Before Mean±SD	After Mean±SD	p-value
Hemoglobin, mg/dL	9.22±0.94	10.62±0.90	<0.001	11.17±0.91	11.37±0.70	0.073
25(OH) vitamin D, IU	19.93±8.22	43.80±12.83	<0.001	22.83±11.55	40.06±17.22	<0.001
Kt/v	1.14 (1.09-1.18)	1.21 (1.18-1.23)	0.001	1.17 (1.15-1.19)	1.20 (1.18-1.23)	<0.001
MCV, fL	92.38±6.79	92.04±5.50	0.559	91±6.03	91.61±5.39	0.395
Creatinine, mg/dL	8.08±0.79	7.70±1.02	0.033	8.02±0.71	7.97±0.69	0.688
BUN, mg/dL	133.53±11.27	132.53±8.88	0.610	134.06±8.63	133.44±8	0.619
Calcium, mg/dL	8.46±0.44	8.71±0.25	0.021	8.51±0.48	8.51±0.35	1.00
Phosphorus, mg/dL	5.78±0.43	5.39±0.41	0.023	5.52±0.67	5.43±0.44	0.536
Albumin, g/dL	3.84±0.28	3.92±0.23	0.234	3.78±0.34	3.78±0.28	1.00
PTH, pg/ml	335 (310-345)	286 (275-300)	<0.001	306.50 (297.50-311.50)	273.50 (254.25-287.50)	0.004
SI, mcg/dL	36 (20-50)	45 (27-52)	0.094	32.50 (28.50-42.25)	43.00 (38.25-51.75)	0.010
TIBC, mcg/dL	250.07±33.10	261.33±23.27	0.169	274.06±16.60	271.33±25.47	0.632
Ferritin, mg/dL	268.13±170.34	385.07±159.52	0.004	342.72±130.86	439.89±123.43	0.001
CRP, mg/dL	6.90 (6-12)	6.70 (3.70-9.80)	0.027	8.00 (6.80-10.25)	8.00 (5.00-12.00)	0.162

MCV: Mean Corpuscular Volume, BUN: Blood Urea Nitrogen, PTH: Parathyroid Hormone, SI: Serum Iron, TIBC: Total Iron Binding Capacity, CRP: C-Reactive Protein

Discussion

In this study, after the intervention, hemoglobin levels in the intervention group improved significantly after adjusting for pre-intervention variables. Clinical variables such as vitamin D, Kt/v, and total iron binding capacity (TIBC) did not show significant differences between the groups, except for TIBC, which was lower in the intervention group. Subsequent evaluations showed that hemoglobin, vitamin D, and ferritin levels improved significantly in both groups, and PTH levels decreased. In addition, improvements in creatinine, calcium, phosphorus, and CRP levels were observed in the intervention group, indicating the effectiveness of high-dose vitamin D3 in improving clinical outcomes in dialysis patients. Our results showed a complex relationship between vitamin D3 dose and improvement in blood parameters. However, a systematic study by Arabi et al. reported no significant effect of vitamin D3 on hemoglobin levels in various medical conditions (20). Differences in the types of vitamin D used in different studies, such as consumption of vitamin D-rich foods, oral supplements, and different forms of vitamin D such as cholecalciferol, ergocalciferol, and calcitriol, may contribute to the conflicting results of these studies. The improvement in hemoglobin may be due to the effects of vitamin D3 on red blood cell synthesis and regulation of erythropoietin (EPO) through vitamin D receptors in hematopoietic tissues. Vitamin D may also affect inflammatory pathways associated with anemia through changes in iron metabolism and immunomodulatory effects. Other contributing factors include impaired calcium homeostasis, genetic variations, and excessive vitamin D intake leading to hypercalcemia. Interactions of vitamin D with other micronutrients such as vitamin K and magnesium may also be involved (21-32).

Serum ferritin and iron levels did not show significant differences between the control and intervention groups at both pre- and post-intervention periods. It is well established in the literature that serum ferritin and iron levels can act as confounding variables and introduce potential biases when assessing the effect of vitamin D on hemoglobin levels. By carefully controlling for these variables, we aimed to isolate the true effect of vitamin D supplementation on hemoglobin concentrations. The systematic review by Arabi et al provides valuable insights into the broader context of vitamin D supplementation and its effects on serum ferritin and iron levels. Their comprehensive analysis, including 11 studies with a total of 1363 participants, showed that vitamin D supplementation did not result in a significant improvement in total ferritin concentrations. Subgroup analysis in anemic patients, which included a combined effect, further emphasized the limited impact of vitamin D interventions on ferritin levels in this specific population. Additionally, results from four studies involving 736 participants showed significant improvements in serum iron levels with vitamin D supplements compared to the placebo group (20). The association between vitamin D3 and serum iron has also been demonstrated in other studies (33-39). However, the study by Greenwood et al. did not show an association between vitamin D3 and serum iron and ferritin (40). The contradictions in findings regarding the association between vitamin D3 and serum iron levels across studies can be attributed to several factors. First, differences in the study populations, including variations in age, sex, and health status, may contribute to the different results. Second, variations in the dose and duration of vitamin D3 supplementation, as well as the method of administration, could influence the observed effects. In addition, differences in baseline vitamin D3 and serum iron levels among participants in different studies may show conflicting results. In addition, the presence of confounding variables, such as dietary habits, genetics, and general health conditions, may complicate the interpretation of the association between vitamin D3 and serum iron. Methodological differences, including variations in study design, could also contribute to the observed discrepancies. These collective findings emphasize the importance of considering and controlling serum iron levels when examining the effects of vitamin D on hemoglobin, ensuring a more accurate and reliable interpretation of study results.

Our study highlights the significant effect of high doses of vitamin D3 on hemoglobin levels in dialysis patients, showing a significant reduction in the intervention group compared with the control group. Despite the relatively small sample size and the focus of the study on a specific hospital setting, the findings demonstrate the potential of vitamin D3 supplementation to modulate hemoglobin dynamics, even after adjusting for confounding factors such as ferritin and serum iron levels. However, the differences in results between different studies emphasizes the complexity of this relationship, which is potentially influenced by factors such as erythropoiesis, iron metabolism, and inflammatory pathways. Future research with larger and more diverse populations and longer intervention periods is necessary to fully understand the mechanisms and broader applicability of the effects of vitamin D3 on hemoglobin levels in dialysis patients.

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