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Original article

Effect of Vitamin D Supplementation on Serum Hepcidin Levels and Anemia of Hemodialysis Patient

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Abstract:

Background: Anaemia is a frequent complication among end-stage renal disease (ESRD) patients, affecting almost all hemodialysis (HD) patients. Hepcidin is the key regulator of iron haemostasis. Anaemia is a common consequence of vitamin D deficiency in HD participants, which can affect hepcidin levels and inflammatory processes. This study aims to detect Vitamin D supplementation effect on serum Hepcidin levels and anaemia of haemodialysis patients. **Methods:** This randomized prospective study was performed on 50 HD cases at nephrology Department (Hemodialysis Unit), Shibin El Qanater University Hospital. All laboratory investigations were assessed at 8 weeks and at 16 weeks. **Results:** There were significant increases or decreases ($P \leq 0.05$) were observed for Hb, MCV, MCH, PTH, ALP, total and ionized calcium, inorganic phosphorus, total cholesterol, LDL, HDL, triglycerides, serum ferritin, serum iron, and hepcidin (P1, P2, P3 < 0.05). Non-significant parameters included TLC, platelets, serum creatinine, blood urea, and serum uric acid (P1, P2, P3 > 0.05) **Conclusions:** Vitamin D supplementation in maintenance hemodialysis patients significantly improved anemia, enhanced iron mobilization through hepcidin suppression, and normalized calcium–phosphate balance without adversely affecting residual renal function. These results underscore the safety and efficacy of vitamin D as an adjunct therapy in the treatment of ESRD.

Keywords: Vitamin D, Serum Hepcidin Levels, Hemodialysis, Anemia, End-Stage Renal Disease

Introduction

The life-sustaining therapy and backbone for end-stage renal disease (ESRD) participants who are undergo haemodialysis (HD) as they are unable to undergo renal transplantation. Anaemia is a prevalent adverse event among ESRD cases, afflicting nearly all HD cases [1].

Anaemia is related to impaired quality of life (HRQOL), adverse cardiovascular outcomes, and mortality and morbidity. The leadership of anaemia in individuals who are receiving renal replacement therapy is a topic of debate, notwithstanding the presence of erythropoietin-stimulating agents (ESAs) [2].

Vitamin D (Vt. D) is a steroid hormone that is vital and has properties that extend beyond its traditional function in bone-mineral disorder. Vt. D deficiency is described as 25(OH) D levels below 20 ng/ml, while adequacy is defined as levels of 30 ng/ml or higher [3, 4].

A prevalent complication in HD patients is CKD–mineral bone disorder (CKD-MBD), which is related to cardiovascular disease and skeletal fragility. The complex pathologies of CKD-MBD are characterised by secondary hyperparathyroidism, which typically results in fibrous osteitis and a high-turnover bone condition. Conversely, relative hypoparathyroidism or parathyroid hormone (PTH) resistance to bone is associated with a dynamic bone disease (ABD). ABD is diagnosed as a secondary osteoporosis due to bone fragility and limited bone turnover, which are associated with arterial calcification [5].

Through its binding to ferroportin, an iron transport protein that is situated on the surface of iron-exporting cells, hepcidin regulates plasma iron availability. Iron exporting cells are prevented from releasing iron by binding to ferroportin [6].

Hepcidin levels decreased as a consequence of high-dose VD supplementation, probably as a consequence of a decline in iron status [7].

The inhibitory impact of nutritional VD on serum levels of HEP-25 in non-dialysis CKD participants has been evaluated in a limited number of interventional studies. With the exception of a trial in paediatric CKD participants (stage 2-5) that was unable to confirm a suppressive impact on serum HEP-25 values after 12 weeks of VD supplementation [8].

The aim of this work was to review the effect of Vitamin D supplementation on serum Hepcidin levels and anaemia of HD participants.

Patients and Methods:

This prospective interventional before-and-after study was conducted at the Hemodialysis Unit of Benha University Hospital from January 2024 to January 2025.

The patient provided written consent that was informed. The research was performed with the sanction of the Research Ethical Committee at the Benha Faculty of Medicine.

Inclusion criteria included cases of age ≥18 years, undergo to hemodialysis, and who indicated for vit. D treatment and wasn't on treatment. Exclusion criteria included patients not indicated for vit D treatment and patient on vit d treatment, all types of malignancy, kidney transplantation, <18 years, and exclude inflammatory or hepatic disease interfering with hepcidin All cases were subjected to full history taking, general examination, systemic examination, laboratory investigations, and special investigations included ECG and ECHO.

All laboratory investigations (CBC, PTH, serum creatinine, blood urea, electrolytes blood, lipid profiles, serum ferritin, serum iron, alkaline phosphatase, and level of hepcidin) were assessed at 8 weeks and at 16 weeks.

Approval code: MS 17-1-2024

Statistical analysis

Statistical analysis was performed by SPSS v26 (IBM Inc., Armonk, NY, USA). Shapiro-Wilks test and histograms were

utilized to assess the normality of the distribution of data. Quantitative data were expressed as mean and standard deviation (SD) and were assessed by mixed-effects model Qualitative variables were expressed as frequency and percentage (%). A two tailed P value ≤ 0.05 was regarded as statistically significant.

Results:

The table showed the baseline demographic, clinical, and vital sign parameters of the participants, including age, sex distribution, BMI, comorbidities, and key vital parameters **Table 1.**

There were significant increases or decreases (P ≤ 0.05) were observed for Hb, MCV, MCH, PTH, ALP, total and ionized calcium, inorganic phosphorus, total cholesterol, LDL, HDL, triglycerides, serum ferritin, serum iron, and hepcidin (P1, P2, P3 < 0.05). Non-significant parameters included TLC, platelets, serum creatinine, blood urea, and serum uric acid (P1, P2, P3 > 0.05) **Table 2**.

Table 1: Baseline characteristics of the studied cases

		(n=50)
Age (years)		45.8 ± 9.1
Sex	**Male**	35 (70%)
	Female	15 (30%)
BMI (kg/m^2)		33.66 ± 3.32
Medical history		
Hypertension		42 (84%)
DM		22 (44%)
Anemia		31 (62%)
Liver cirrhosis		6 (12%)
Lower limb edema		18 (36%)
Pulmonary congestion		12 (24%)
Vital signs		
Pluse rate (beats/min)		73.1 ± 8.24
Systolic blood pressure (mmHg)		146.2 ± 15.8
Diastolic blood pressure (mmHg)		88.6 ± 9.7
Respiratory rate (breaths/min)		15.9 ± 2.39
Temperature (°C)		37.1 ± 0.29
Capillary filling time (Sec)		2.7 ± 1.15

Data expressed as mean ± SD or number (%), DM: Diabetes mellitus, BMI: Body mass index.

Table 2: Complete blood count and PTH, Kidney function, Electrolytes blood, Lipid profiles, Serum ferritin, serum iron and level of hepcidin tests of the studied patients

	Baseline	8 weeks	16 weeks	P1	P2	P3
Complete blood count test and PTH						
Hb (g/dL)	9.85 ± 1.05	10.3 ± 1	10.7 ± 0.85	<0.001*	<0.001*	<0.001*
MCV (fL)	84.8 ± 7.64	85.26 ± 7.68	87.4 ± 7.74	<0.001*	<0.001*	<0.001*
MCH (pg)	27.02 ± 3.01	28.5 ± 3.16	30.52 ± 3.25	<0.001*	<0.001*	<0.001*
TLC (×10³/µL)	6.95 ± 1.58	6.93 ± 1.61	6.8 ± 1.67	0.792	0.232	0.108
Platelets (×10³/µL)	232.38 ± 72.03	231.38 ± 76.26	230.56 ± 76.33	0.511	0.254	0.233
PTH (pg/mL)	356.82 ± 88.14	312.46 ± 86.92	274.38 ± 85.67	<0.001*	<0.001*	<0.001*
ALP (U/L)	210.5 ± 45.3	185.2 ± 40.1	160.8 ± 38.6	<0.001*	<0.001*	<0.001*
Kidney function test						
Serum creatinine (mg/dL)	8.92 ± 1.78	8.89 ± 1.81	8.87 ± 1.79	0.318	0.214	0.487
Blood urea (mg/dL)	132.45 ± 21.36	132.88 ± 21.12	133.21 ± 20.94	0.742	0.366	0.529
Serum uric acid (mg/dL)	6.81 ± 1.09	6.79 ± 1.11	6.83 ± 1.13	0.651	0.588	0.704
Electrolytes blood test						
Total serum calcium (mg/dL)	8.14 ± 0.78	8.63 ± 0.79	8.94 ± 0.81	<0.001*	<0.001*	<0.001*
Ionized serum calcium (mmol/L)	1.34 ± 0.17	1.38 ± 0.17	1.43 ± 0.18	<0.001*	<0.001*	<0.001*
Inorganic phosphorous (mg/dL)	6.38 ± 0.94	5.86 ± 0.92	5.32 ± 0.90	<0.001*	<0.001*	<0.001*
Lipid profiles test						
Total cholesterol (mg/dL)	192.9 ± 34.92	192.1 ± 34.62	179.54 ± 35.26	0.086	<0.001*	<0.001*
LDL (mg/dL)	129.36 ± 31.22	128.68 ± 31.17	115.28 ± 31.92	0.119	<0.001*	<0.001*
HDL (mg/dL)	36.8 ± 8.07	36.54 ± 8.46	42.18 ± 8.18	0.319	<0.001*	<0.001*
Triglycerides (mg/dL)	152.12 ± 36.28	152.2 ± 36.74	139.6 ± 36.79	0.851	<0.001*	<0.001*
Serum ferritin, serum iron and level of hepcidin test						
Serum ferritin (ng/mL)	449.16 ± 42.89	426.66 ± 27.99	381.6 ± 124.48	<0.001*	<0.001*	<0.001*
Serum iron (µg/dL)	56.26 ± 16.32	63.68 ± 16.36	68.38 ± 16.49	<0.001*	<0.001*	<0.001*
Serum hepcidin (ng/mL)	10.19 ± 3.08	8.62 ± 2.58	6.72 ± 2.07	<0.001*	<0.001*	<0.001*

Data are expressed as mean ± SD or number (%). P1: P value between baseline and 8 weeks, P2: P value among baseline and 16 weeks, P3: P value between 8 weeks and 16 weeks, *: significant as $P \leq 0.05$, Hb, Hemoglobin; MCV, mean corpuscular volume; MCH, Mean corpuscular hemoglobin; TLC, Total leukocyte count; PTH, Parathyroid hormone; ALP: Alkaline phosphatase; LDL, Low-density lipoprotein; HDL, High-density lipoprotein.

Discussion:

Anemia and disturbances in mineral metabolism remain among the most prevalent and clinically significant complications in patients with ESRD undergoing maintenance hemodialysis. Despite advances in dialysis techniques and ESA therapy, anemia continues to affect a substantial proportion of this population, contributing to an elevation in cardiovascular disease and death, a reduction in HRQOL, and fatigue [9].

The present study evaluated supplementation impacts on hematological, biochemical, and mineral metabolism parameters among patients undergoing maintenance hemodialysis. The mean age was 45.8 ± 9.1 years, representing a relatively young to middle-aged dialysis population. Males predominated (70%), consistent with prior

epidemiologic data reporting higher hemodialysis prevalence among men, possibly due to differences in the progression of chronic kidney disease (CKD) regarding sex [10]. The mean BMI of 33.66 ± 3.32 kg/m² highlights a predominantly obese cohort, a clinically important finding given the growing recognition of obesity as a modulator of inflammation, vitamin D metabolism, and hepcidin regulation factors that may collectively influence anemia severity and responsiveness to therapy [11].

Anemia was presented in 62% of the studied patients, in line with the established high burden of anemia in ESRD populations [12]. Hypertension (84%) and diabetes mellitus (44%) were the leading etiologies of ESRD, mirroring global patterns of renal disease causation [13]. Liver cirrhosis was present in 6 (12%) patients, lower limb edema was found in 18 (36%) cases, and pulmonary congestion was detected in 12 (24%) patients reflecting heterogeneity in volume overload and cardiovascular adaptation among these patients. Overall, vital signs remained within normal physiological limits, suggesting adequate hemodynamic stability and absence of acute intercurrent illness during the study period.

Similarly, a multifactorial cross-sectional analysis by Yin et al. [14] reported that the prevalence of anemia reached 89.29 percent (1,475/1,652), while the hemoglobin compliance rate was only 46.25 percent (764/1,652). Notably, Hb compliance varied significantly across MHD cases with different primary etiologies ($P < 0.05$).

A major outcome of our work is the significant development in hematological indices after VD supplementation. Hemoglobin, MCV, and MCH levels elevated progressively throughout the 16-week follow-up ($p < 0.001$), denoting enhanced erythropoiesis and amelioration of anemia. These results align with emerging evidence that vitamin D exerts hematopoietic benefits, possibly through modulation of erythropoietin sensitivity, suppression of pro-inflammatory cytokines, and reduction of hepcidin levels mechanisms that collectively enhance iron availability for red cell production. The stability of leukocyte and platelet counts suggests that the intervention selectively influenced erythroid parameters without broadly altering hematopoietic cell lines.

Consistent with our results, Ahmad et al. [15], found significant rise in haemoglobin concentration was documented at 12 and 18 months (MD = −0.98, −1.80; 95% CI: −1.88 to −0.08 and −2.56 to −1.04; p = 0.03, < 0.00001; $I^2 = 91\%$). Conversely, no statistically significant effect was observed at 12 weeks, 3 months, 6 months, or 15 months. In general, the aggregated analysis demonstrated that VD supplementation was related to substantial elevation in haemoglobin across the studies (MD = −0.61; 95% CI: −0.96 to −0.26; p = 0.03; $I^2 = 60.7\%$), underscoring a time-dependent improvement in erythropoietic response among hemodialysis patients

Serum parathyroid hormone (PTH) levels demonstrated a robust decline following supplementation ($p < 0.001$), corroborating the established vitamin D role in mitigating secondary hyperparathyroidism in ESRD. This reduction was accompanied by significant increases in total and ionized calcium levels and a concomitant decrease in serum phosphate concentrations, signifying restoration of mineral homeostasis. Such findings are clinically relevant, as improved calcium–phosphate balance reduces vascular calcification risk and contributes to better bone mineral metabolism critical outcomes in long-term dialysis management.

Ergocalciferol 50,000 IU was administered on a weekly or monthly basis in a larger trial, which also exhibited an elevation in 25(OH)D values. No variations were documented in the levels of PTH, haemoglobin, 1,25(OH)2D, or blood pressure. It is important to note that the levels of FGF-23 elevated in all

populations, including the placebo population [16].

We can infer that nutritional VD (cholecalciferol and ergocalciferol) are efficient in enhancing 25(OH)D values without elevating the risk of hypercalcemia or hyperphosphatemia; however, the impacts on cases findings are not presently understood.

Renal function indices, comprising blood urea, serum creatinine, and uric acid, remained stable throughout the study, indicating that vitamin D supplementation did not adversely affect residual renal function. This observation is consistent with previous reports suggesting the renal safety of vitamin D analogues in dialysis populations.

Vitamin D effects on lipid metabolism were particularly notable after 16 weeks of therapy, with significant reductions in LDL, total cholesterol, and triglyceride levels alongside a rise in HDL ($p < 0.001$ for all). These findings highlight vitamin D's potential cardiometabolic benefits, potentially mediated via anti-inflammatory, insulin-sensitizing, and endothelial-stabilizing pathways. Such lipid profile improvements may translate into reduced cardiovascular morbidity a paramount concern in hemodialysis patients who remain at exceptionally high cardiovascular risk.

In the interim, Milajerdi et al. [17] demonstrated that VD supplementation or treatment in CKD participants with could reduce triglycerides and total cholesterol, while it did not affect LDL and HDL. In an additional meta-analysis, VD administration led to a substantial elevation in LDL, but it did not have any impact on triglycerides, total, or HDL cholesterol levels [18].

Importantly, vitamin D supplementation was related with significant modulation of iron metabolism markers. Serum iron increased, whereas ferritin and hepcidin levels declined substantially ($p < 0.001$ for all comparisons). The reduction in hepcidin, a key regulator of iron sequestration, suggests a mechanistic link through which vitamin D enhances iron mobilization and erythropoiesis. These observations are consistent with prior studies indicating that vitamin D downregulates hepatic hepcidin transcription and mitigates functional iron deficiency in CKD.

Zughaier et al. [19] found that 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), the hormonally active form of VD, is related to diminished hepcidin and elevated expression of ferroportin in THP-1 cells stimulated with lipopolysaccharide (LPS), which is consistent with our findings. In vitro, 1,25(OH)2D3 also led to a dose-dependent reduction in the secretion of pro-hepcidin cytokines, IL-6 and IL-1β. Furthermore, we demonstrate that systemic hepcidin values in individuals with early-stage CKD are affected by high-dose VD therapy.

Taken together, the present findings underscore the multifaceted benefits of VD in hemodialysis patients, extending beyond mineral metabolism to encompass hematologic, metabolic, and inflammatory domains. The results support the hypothesis that treatment of vitamin D deficiency may improve anemia management and overall metabolic stability in ESRD.

Limitations:

This study is limited by a limited sample size, single-center design, and short follow-up (16 weeks). Inflammatory markers (e.g., IL-6, CRP) were not routinely measured, and baseline variations in vitamin D status, erythropoietin dosing, and iron supplementation were not fully standardized, potentially influencing outcomes.

This study has several limitations that should be acknowledged. First, the study is limited by a relatively small sample size, single-center design, and short follow-up duration (16 weeks), which may affect the generalizability of the findings. In addition, inflammatory markers such as

IL-6 and C-reactive protein (CRP) were not routinely measured, which limits the ability to fully explore inflammatory pathways.

Importantly, this study lacked a control group; therefore, causality between vitamin D supplementation and the observed improvements cannot be definitively established, and the results should be interpreted with caution. Potential confounding factors, including variability in erythropoiesis-stimulating agent (ESA) dosing, iron supplementation, and baseline differences in vitamin D status, were not fully standardized and may have influenced the outcomes.

Despite these limitations, the study provides clinically relevant insights into the potential beneficial role of vitamin D in improving anemia and mineral metabolism in patients undergoing maintenance hemodialysis.

Conclusions:

Vitamin D supplementation in maintenance hemodialysis patients significantly improved anemia, enhanced iron mobilization through hepcidin suppression, and normalized calcium–phosphate balance without adversely affecting residual renal function. These results underscore the safety and efficacy of vt. D as an adjunct therapy in the treatment of ESRD.

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Conflict of Interest: Nil

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