



Effect of Vitamin D Supplementation on Hemoglobin Level in Hemodialysis Patients: Evidence-Based Case Report

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ABSTRACT

Introduction: Anemia is a common complication of end-stage chronic kidney disease (CKD), particularly in patients undergoing hemodialysis. Vitamin D, a micronutrient with receptors in various cell types, plays a role in enhancing erythropoiesis by promoting the proliferation of erythroid progenitor cells, reducing proinflammatory cytokines and hepcidin, thereby increasing iron bioavailability for hemoglobin (Hb) synthesis. This study aims to investigate the effect of vitamin D supplementation on Hb levels in chronic hemodialysis patients. **Methods:** A systematic literature search was conducted across 4 databases: PubMed, ProQuest, Cochrane, and Scopus. Inclusion criteria were studies on adult patients undergoing chronic hemodialysis with anemia and with any vitamin D status, published within the last 5 years, and consisting of systematic reviews and meta-analyses (SR-MA) of randomized controlled trials (RCTs) or RCTs. Critical appraisal was performed using the validity, importance, and applicability (VIA) framework from the Oxford Centre for Evidence-Based Medicine (OCEBM). **Results:** Two RCTs and one SR-MA were critically appraised. Vitamin D supplementation was found to improve Hb levels in chronic hemodialysis patients, with statistically significant effects observed in longer supplementation durations. **Conclusion:** Vitamin D supplementation in chronic hemodialysis patients has shown promising results in improving Hb levels. Further research is required to determine the optimal type, dosage, and duration of vitamin D supplementation.

Kata Kunci: Anemia, hemodialysis, hemoglobin, vitamin D.

ABSTRAK

Latar belakang: Anemia merupakan salah satu komplikasi umum penyakit ginjal kronik (PGK) stadium akhir, terutama pasien yang menjalani hemodialisis. Vitamin D, mikronutrien dengan reseptor pada banyak sel, juga memiliki peran meningkatkan eritropoiesis dengan meningkatkan proliferasi sel progenitor eritrosit, serta menurunkan ekspresi sitokin proinflamasi dan hepsidin, sehingga meningkatkan bioavailabilitas besi untuk sintesis Hb. Studi ini bertujuan menelaah pengaruh suplementasi vitamin D terhadap kadar Hb pasien hemodialisis kronik. **Metode:** Pencarian literatur dilakukan pada 4 basis data: PubMed, ProQuest, Cochrane, Scopus. Kriteria inklusi berupa studi dengan subjek dewasa yang menjalani hemodialisis rutin dan mengalami anemia dengan status vitamin D apapun yang dipublikasi dalam 5 tahun terakhir, merupakan *systematic reviews* dan *meta-analyses* (SR-MA) dari *randomized controlled trial* (RCT) atau RCT. Pengkajian kritis dilakukan dengan perangkat yang mencakup komponen VIA dari OCEBM. **Hasil:** Dua artikel RCT dan satu SR-MA dikaji secara kritis. Suplementasi vitamin D dapat meningkatkan kadar Hb pada pasien hemodialisis kronik, efek signifikan dicapai pada durasi suplementasi lebih panjang. **Simpulan:** Suplementasi vitamin D pada pasien hemodialisis kronik menunjukkan hasil menjanjikan terhadap perbaikan kadar Hb. Diperlukan penelitian lebih lanjut mengenai jenis, dosis, dan durasi suplementasi vitamin D yang optimal. **Jessica Winarsa, Diana Sunardi. Efek Suplementasi Vitamin D pada Kadar Hemoglobin Pasien Hemodialisis: Laporan Kasus Berbasis Bukti.**

Keywords: Anemia, hemodialisis, hemoglobin, vitamin D.

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INTRODUCTION

Anemia is a common complication in end-stage CKD patients, particularly in those undergoing hemodialysis.¹ The decline in glomerular filtration rate (GFR) correlates with the severity of anemia; its prevalence is

up to 90% in patients with a GFR less than 30 mL/min.² A study by Weinhandl, *et al.*,³ in 2019, on dialysis patients in the United States showed that 35.8% patients had hemoglobin (Hb) levels of 10.0–10.9 g/dL and 27.7% had levels of 11.0–11.9 g/dL. A similar study by

Al-Jabi, *et al.*,¹ at 3 dialysis centers, reported that anemia prevalence (Hb < 11 g/dL) was 59%. A study by Ginting, *et al.*,⁴ at Fatmawati Hospital, Jakarta, showed that the prevalence of anemia in hemodialysis patients was 53.7%.

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Erythropoietin is a hormone produced by the kidneys to stimulate the bone marrow to produce red blood cells and increase Hb levels.⁵ The process of erythropoiesis is also influenced by the availability and accessibility of iron in the body. Patients with CKD experience decreased production of endogenous erythropoietin, reduced iron absorption, and ineffective iron storage due to increased hepcidin and systemic inflammation.⁶ These physiological changes occur chronically and can manifest as severe anemia in the end stage. Although dialysis is one of the treatments for end-stage CKD, it can lead to blood loss and exacerbate anemia.⁶ Anemia in dialysis patients increases morbidity and mortality rates, worsens clinical outcomes, and reduces quality of life.¹

According to KDIGO guidelines,⁷ the treatment strategy for anemia in CKD starts with correcting iron deficiency and administering erythropoiesis-stimulating agents (ESAs). Blood transfusions may be considered for patients who do not respond to or are contraindicated from receiving ESA therapy. Additionally, there are acute conditions that require rapid Hb correction, such as in cases of bleeding or myocardial ischemia. However, ESA therapy is expensive and not always available in all healthcare facilities. Repeated blood transfusions also increase the risk of infection, transfusion reactions, and iron overload.⁷

Vitamin D is a fat-soluble vitamin with various roles, especially in the regulation of the immune and inflammatory systems.⁸ Vitamin D can be obtained from food (in the form of vitamin D2 or D3) or synthesized from cholesterol and converted to vitamin D3 in the skin with the help of ultraviolet light. After that, vitamin D undergoes metabolism in the liver to become 25(OH)-vitamin D and in the kidneys to become calcitriol.^{8,9} Calcitriol is the biologically active form of vitamin D, allowing it to bind to vitamin D receptors and exert various effects on cells, such as increasing the absorption of calcium and phosphate in the digestive tract.¹⁰ Vitamin D also enhances erythropoiesis by promoting the proliferation of erythrocyte progenitor cells and reducing pro-inflammatory cytokines. The reduction in pro-inflammatory cytokine production and direct regulation of the hepcidin antimicrobial

peptide (HAMP) gene transcription by vitamin D decreases hepcidin expression. This increases the bioavailability of iron needed for erythropoiesis and hemoglobin synthesis, prevents iron sequestration in macrophages, and reduces iron absorption disturbances in the digestive tract; vitamin D is reported to improve anemia.^{5,11}

Vitamin D deficiency and insufficiency are quite common in end-stage CKD patients, especially those on dialysis.¹² This is not only due to dietary restrictions but also to low sun exposure. A study by Nazzal, *et al.*,¹³ on hemodialysis patients showed that 65% patients had vitamin D insufficiency and 22.1% had deficiency. Uremia in hemodialysis patients is also reported to inhibit the plasma vitamin D activation response to ultraviolet B radiation exposure.²

Despite the high prevalence of insufficiency and deficiency, and numerous vitamin D benefits, vitamin D supplementation is not routinely provided to hemodialysis patients. This evidence-based critical review aims to determine the effect of vitamin D supplementation on Hb levels in hemodialysis patients.

CASE

A 52-year-old woman came for routine hemodialysis. The patient has a history of hypertension for 15 years, but has not been consistently taking her medication, leading to kidney complications. For the past 5 years, the patient has been undergoing routine hemodialysis twice a week. The patient also regularly receives blood transfusions and erythropoietin every 2–3 months due to frequent low Hb levels. The doctor wants to investigate whether there is a supplement that can improve the Hb profile of hemodialysis patients. He wants to find out whether vitamin D supplementation can improve Hb levels in hemodialysis patients.

CLINICAL QUESTIONS

The clinical question is: "In adult patients undergoing routine hemodialysis, what is the effect of vitamin D supplementation on hemoglobin levels?" Based on the clinical question, the PICO is as follows:

- P: Patients undergoing routine hemodialysis

- I: Vitamin D supplementation
- C: Placebo or without vitamin D supplementation
- O: Hemoglobin levels

Inclusion criteria:

1. Subjects undergoing routine hemodialysis for ≥ 3 months
2. Subjects have a hemoglobin level of < 12 g/dL prior to intervention
3. Study published in the last 5 years
4. Study providing vitamin D supplementation as an intervention
5. Study outcome is blood hemoglobin levels
6. Study design is a systematic review/meta-analysis of randomized controlled trials or a randomized controlled trial

Exclusion criteria:

1. Full-text article is not available
2. The article written in languages other than English and Indonesian.

METHODS

The article search was conducted using advanced searching by combining MeSH Terms, Textwords, or Title/Abstract/Keywords in databases such as PubMed, ProQuest, Cochrane, and Scopus with eligibility criteria on September 3rd, 2024. The keywords used were "vitamin D" OR "vitamin D3", "supplementation" OR "supplementations", "hemoglobin" OR "haemoglobin" OR "hemoglobins", "hemodialysis" OR "haemodialysis". The search results were then screened for duplicates using the Covidence tool, followed by title and abstract screening based on relevance to PICO, full-text article retrieval, and selection based on the predetermined eligibility criteria. After these processes, if a primary study was included in the systematic review/meta-analysis, the study was excluded. The selected studies were then critically appraised using the Oxford Centre for Evidence-Based Medicine (OCEBM) tools according to the study design. The level of evidence of the selected studies was determined based on the OCEBM Level of Evidence guidelines.¹⁴

RESULTS

After conducting a literature search based on the searching strategy in the PubMed, ProQuest, Cochrane, and Scopus databases, a total of 20, 8, 18, and 72 studies were found, respectively (**Table 1**). The search

EVIDENCE-BASED CASE REPORT



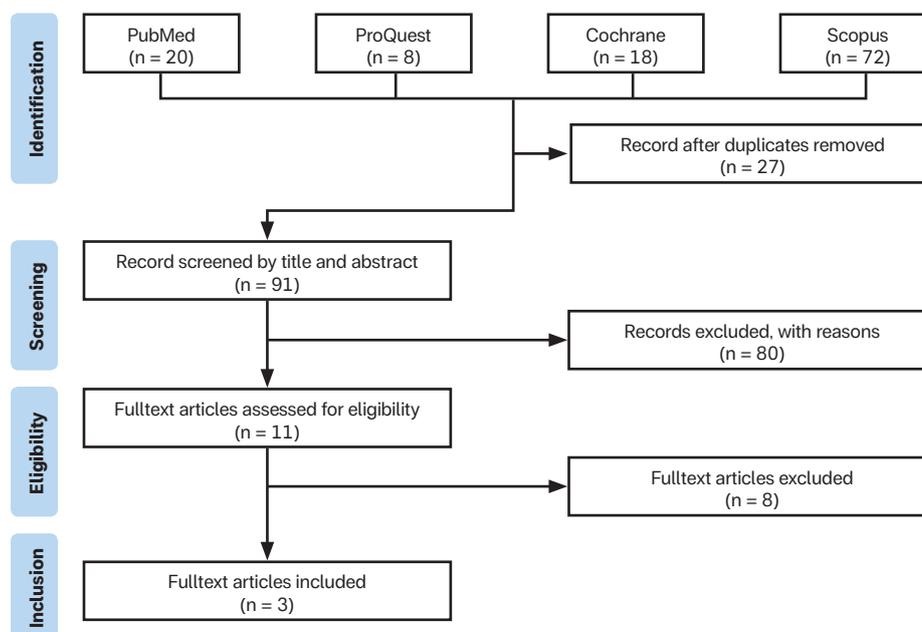
results were then screened for duplicates, and 27 studies were excluded. Additionally, 80 studies were excluded due to title and abstract discrepancies. Subsequently, a full-text search and eligibility assessment

were conducted based on inclusion and exclusion criteria, resulting in 3 relevant studies, consisting of 1 systematic review-meta-analysis (SR-MA) and 2 randomized controlled trials (RCT) (**Scheme, Table 2**).

A critical appraisal was then performed on these 3 studies using the techniques of validity, importance, and applicability (VIA) (**Table 3–5**).

Table 1. Literature searching strategy.

Database	Searching Strategy	Hits (N)	Selected Articles (N)
PubMed	#1 ((vitamin D[MeSH Terms]) OR (vitamin D[Title/Abstract])) OR (vitamin D3[Title/Abstract]) #2 ((supplementation[Title/Abstract]) OR (supplementations[Title/Abstract])) #3 (((hemoglobins[MeSH Terms]) OR (hemoglobin[Title/Abstract])) OR (haemoglobin[Title/Abstract])) OR (hemoglobins[Title/Abstract]) #4 ((hemodialysis[MeSH Terms]) OR (hemodialysis[Title/Abstract])) OR (haemodialysis[Title/Abstract]) #1 AND #2 AND #3 AND #4	20	2
ProQuest	(abstract(vitamin D) OR abstract(vitamin D3)) AND (abstract(supplementation) OR abstract(supplementations)) AND (abstract(hemoglobin) OR abstract(haemoglobin) OR abstract(hemoglobins)) AND (abstract(hemodialysis) OR abstract(haemodialysis))	8	1
Cochrane	"vitamin D" OR "vitamin D3" in Title Abstract Keyword AND "supplementation" OR "supplementations" in Title Abstract Keyword AND "hemoglobin" OR "haemoglobins" in Title Abstract Keyword AND "hemodialysis" OR "haemodialysis" in Title Abstract Keyword - (Word variations have been searched)	18	1
Scopus	TITLE-ABS-KEY ("vitamin D" OR "vitamin D3") AND TITLE-ABS-KEY ("supplementation" OR "supplementations") AND TITLE-ABS-KEY ("hemoglobin" OR "haemoglobin") AND TITLE-ABS-KEY ("haemodialysis" OR "hemodialysis")	72	1



Scheme. PRISMA flowchart.



Table 2. Characteristics of included studies.

Author	Year	Country	Study Design	N	Population	Intervention	Comparison	Outcome
Ayub, et al. ¹⁵	2022	Pakistan	Double-blind, randomized controlled trial	70	Hemodialysis patients	Vitamin D3 (dose varies) for 2 months	Placebo	Hb levels
Ahmad, et al. ⁵	2023	Pakistan	Systematic review and meta-analysis	878	Hemodialysis patients	Vitamin D3 (dose varies)	None	Hb levels
Emarah, et al. ²	2024	Egypt	Double-blind, randomized controlled trial	100	Hemodialysis patients with vitamin D deficiency	Vitamin D3 50,000 IU monthly for 6 months	Placebo	Hb levels

Table 3. Internal validity of included RCT studies.

Author	Year	Randomized Treatment	Similar Characteristic between Groups	Equally Treatment on Both Groups	All Patients Accounted	Double-blinded Objective Measurement
Ayub, et al. ¹⁵	2022	+	+	+	+	+
Emarah, et al. ²	2024	+	+	+	+	+

Table 4. Internal validity of included SR-MA study.

Author	Year	PICO Question Addressed Clearly	No Relevant Studies Missed	Eligibility Criteria Appropriate	Included Studies Valid	Similar Results from Study to Study
Ahmad, et al. ⁵	2023	+	+	+	+	-

Table 5. Importance and applicability of included studies.

Author	Year	Importance			Applicability		Level of Evidence
		Large Treatment Effect, Not a Coincidence	Precise Estimated Treatment Effect, Clinically Significant	Patients' Similarities to My Patients So That Results Can Apply	Treatment Feasibility in My Setting	Potential Benefits will Outweigh the Harm of Treatment for My Patient	
Ayub, et al. ¹⁵	2022	+	-	+	+	+	2
Ahmad, et al. ⁵	2023	+	+	+	+	+	1
Emarah, et al. ²	2024	+	+	+	+	+	2

DISCUSSION

The RCT conducted by Ayub, et al.¹⁵ involved chronic hemodialysis patients with anemia and vitamin D deficiency. Vitamin D supplementation was administered at a dose of 50,000 IU per week for patients with serum 25(OH)-vitamin D levels below 15 ng/mL, and 10,000 IU per week for those with levels between 16 and 30 ng/mL. All participants in both intervention and placebo groups received the same dose of erythropoietin over a 2-month follow-up period. The study found a nonsignificant increase in Hb levels

in the intervention group (from 10.14 ± 1.4 to 10.43 ± 1.42 g/dL, $p = 0.172$) as compared with the placebo group (from 10.2 ± 1.58 to 10.23 ± 1.55 g/dL, $p = 0.821$). This outcome may be attributed to the relatively short duration of the intervention or variability in the supplementation dosages.

Another RCT by Emarah, et al.² was also conducted on chronic hemodialysis patients with anemia and vitamin D deficiency, using vitamin D supplementation at a dose of 50,000 IU monthly for up to 6 months. All

participants in both the intervention and placebo groups received the same type of short-acting intravenous erythropoietin. Baseline Hb levels were 10 (9.2–10.5) g/dL in the intervention group and 9.8 (8.9–10.4) g/dL in the placebo group ($p = 0.231$). Hemoglobin levels were monitored monthly through the sixth month. The results showed a significant increase in Hb levels in the intervention group, reaching approximately 11.5 g/dL by the sixth month. The study also demonstrated that the intervention group required lower doses of erythropoietin



during the monitoring period compared to the placebo group.

A SR-MA by Ahmad, *et al.*⁵ included 10 studies comprising a total of 878 chronic hemodialysis patients. The cumulative data revealed a baseline mean Hb level of 11.18 g/dL and an average patient age of 57.5 years. Among the studies, 3 had an intervention duration of 3 months, 3 lasted 6 months, 3 lasted 12 months, and 1 extended to 18 months. The overall effect across all studies showed a statistically significant improvement in Hb levels, with a mean difference of -0.61 (95% CI: -0.96 to -0.26). However, subgroup analysis indicated that significant Hb improvement was only observed in interventions lasting 12 months (mean difference -0.98; 95% CI: -1.88 to -0.08) and 18 months (mean difference -1.80; 95% CI: -2.56 to -1.04). These differences in subgroup results may be attributed to heterogeneity among the studies, such as variations in the agent and dosage of vitamin D supplementation used.

Although the 3 studies yielded varying results, the majority demonstrated a positive effect of vitamin D supplementation in improving Hb levels. This may be attributed to the fact that most hemodialysis patients experience vitamin D deficiency due to reduced sunlight exposure, decreased and restricted dietary intake, poor absorption, and proteinuria. However, the duration of supplementation may also influence the therapeutic outcome. In a study by Jetty, *et al.*¹⁶ administering 50,000 IU of vitamin D weekly to 282 patients for 6 months significantly increased the average vitamin D levels from 20.1 ± 6.9 to 48.4 ± 19.4 ng/mL ($p < 0.001$). In contrast, the study by Ayub, *et al.*¹⁵ involved a supplementation period of only 2 months, which was likely insufficient to raise serum vitamin D levels to an optimal range and produce a more significant improvement in Hb.

Nevertheless, this EBCR has several limitations. First, only three studies met the inclusion and exclusion criteria, which may limit the strength and generalizability of the

conclusions. In addition, the sample sizes in the individual RCTs were relatively small, potentially reducing the statistical power to detect significant differences in hemoglobin levels. Considerable heterogeneity was also observed among the studies in terms of vitamin D formulation, dosage, frequency of administration, and duration of supplementation, which may have contributed to the variability in outcomes.

CONCLUSION

Vitamin D supplementation in chronic hemodialysis patients may increase serum Hb levels; adjunct therapy to erythropoietin administration may be considered to achieve a higher increase in Hb levels and reduce the frequency of blood transfusions. Further research is required to determine the optimal preparation, dosage, and duration of vitamin D supplementation that can significantly enhance Hb concentration.

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