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HIGH DOSE VITAMIN D SUPPLEMENTATION AS ADJUVANT THERAPY IN THE MANAGEMENT OF DIABETIC FOOT ULCERS

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Abstract
Objective: This study aimed to assess the impact of high-dose vitamin D supplementation as an adjunctive treatment in diabetic foot ulcer (DFU) management. Methods: Relevant literature was searched in PubMed, ScienceDirect, ClinicalTrial, and Google Scholar databases from inception until May 2025. Eligible studies included randomized controlled trials (RCTs), interventional research, or studies with a comparator group. The primary outcomes considered were ulcer reduction and healing. Results: Five RCTs involving 245 participants were included. Most of the trials demonstrated greater ulcer reduction in the intervention groups compared with controls. Furthermore, high-dose vitamin D supplementation was associated with significantly higher healing rates than low-dose regimens. No significant adverse events were reported. Conclusions: High-dose vitamin D supplementation significantly enhances wound healing in DFU patients by reducing ulcer area. Greater doses produced more favorable healing outcomes compared with lower doses.
Keywords: Diabetic foot ulcer, vitamin D, diabetes mellitus, systematic review.

INTRODUCTION

Diabetic foot ulcer (DFU) is among the most frequent complications of diabetes mellitus, affecting approximately 10%–25% of individuals with the condition. The annual incidence of ulcer formation ranges from 2.5% to 10.7%, while amputation rates are reported between 0.25% and 1.8%.[1] Mortality in DFU patients is nearly twice as high compared to diabetic patients without ulcers, making DFU a major contributor to morbidity and premature death in this population. The main underlying causes of DFU include peripheral vascular disease and diabetic neuropathy. In addition, oxidative stress, inflammation, insulin resistance, and dyslipidemia play central roles in its pathophysiology.[2]

Vitamin D supplementation has been suggested to aid wound healing and improve metabolic dysfunctions by enhancing macrophage phagocytosis and bacterial clearance, suppressing interferon-γ–mediated macrophage activation, promoting insulin receptor expression, and downregulating cytokine release.[3] Previous clinical trials indicate that vitamin D administration can mitigate oxidative stress, insulin resistance, osteoporosis, and inflammatory markers. A randomized trial has also shown improved wound healing in DFU patients receiving vitamin D.[4] Furthermore, several studies report that vitamin D deficiency contributes to β-cell destruction, immune dysregulation, and impaired insulin secretion. Beyond hyperglycemia, deficiency in vitamin D may further weaken the immune system of diabetic patients, increasing their susceptibility to foot infections and worsening outcomes.[5-8]

This review therefore aims to examine the role of vitamin D supplementation as an adjunctive therapy in the management of DFU.

METHODS

A systematic review was conducted on all relevant publications in English and Indonesian up to May 2025. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO). Three reviewers (KMD, I, and KM) independently searched PubMed, ScienceDirect, ClinicalTrials.gov, and Google Scholar databases using the keywords *"high doses of vitamin D," "vitamin D,"* and *"diabetic foot ulcer."*

Study eligibility criteria

Studies were included if they: (1) involved patients diagnosed with diabetic foot ulcer; (2) reported relevant clinical outcomes; (3) applied a randomized controlled trial (RCT) design or included at least two comparison groups; and (4) were published in English or Indonesian. Exclusion criteria were opinion papers, case reports, studies on incidence or prevalence, and articles without full-text availability.

Data extraction

Two reviewers (KMD and KM) independently extracted eligible study data into a structured table. Extracted information included first author, year of publication, study location, design, sample size for intervention and control groups, treatment details, and outcomes. This review also examined the significance of vitamin D supplementation effects.

Endpoints

The primary outcome was wound healing. Secondary outcomes included inflammatory markers, laboratory parameters, and reported adverse events.

Quality assessment

Risk of bias was independently assessed by three reviewers (KMD, I, and KM). Tools used were the Cochrane Risk of Bias (RoB 2) for RCTs, the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) for non-RCTs, and the Newcastle–Ottawa Scale (NOS) for observational studies (cohort, cross-sectional, and case-control designs). Any disagreements were resolved through consensus.

RESULTS

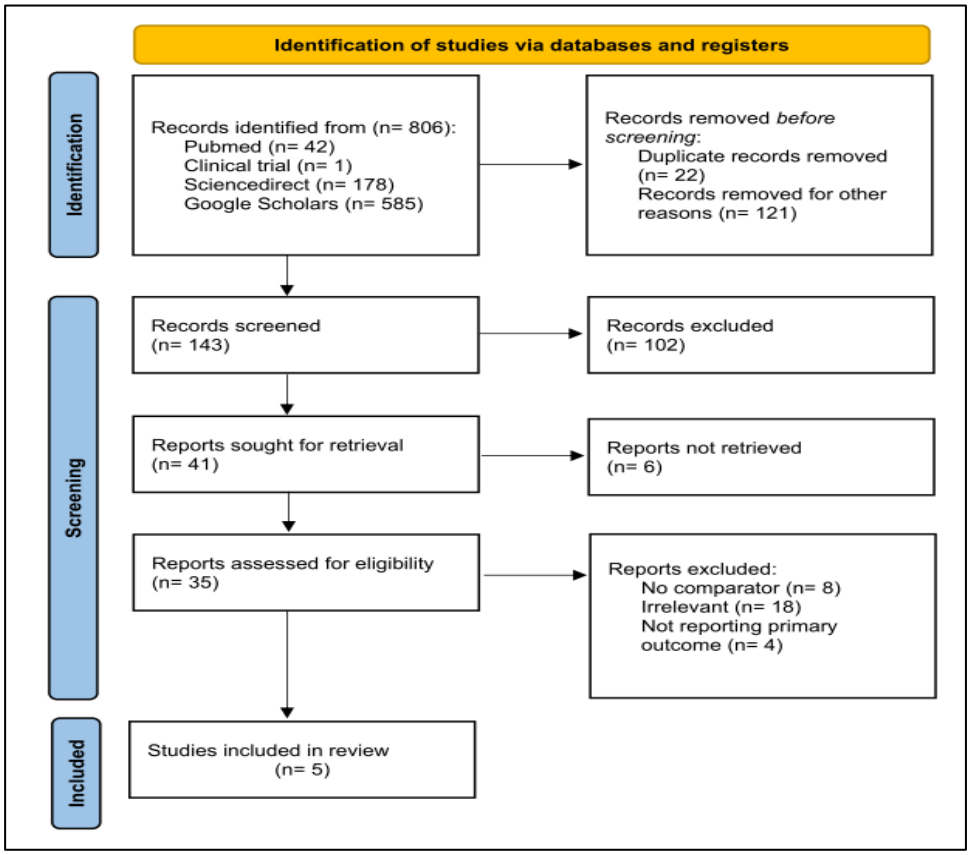

Figure 1. PRISMA flowchart

A total of five studies were retrieved and included in this review (Figure 1) from 806 identified studies in the first step. All included studies are RCT studies, as shown in Table 1. In this review, two RCTs used a single-blind method, two performed double-blind, and one performed an open-label design. As shown in Table 1, a total of 245 participants were enrolled in this review. All studies reported the effect of vitamin D on wound ulcers, though the parameters varied. The dose of vitamin D and duration of administration were various. Meanwhile, the secondary outcomes were HbA1c, WBC, ESR, FBS, CRP, Cholesterol, BMI, triglyceride, HDL, and LDL. (Table 1)

Table 1. Characteristics of included studies

First author, year	Study Design	Country	Sample size		Intervention		Duration of Administration	Outcomes
			Exp	Control	Exp	Control		
Jensen 2021[9]	RCT	Denmark	24	24	High-dose oral of Vit. D (170 ug/day)	Low-dose oral of Vit D (20 ug/day)	48 weeks	Ulcer healing, HbA1c
Khosravi 2016 [10]	RCT	Iran	24	23	High dose oral of Vit D (300,000 IU)	Low dose oral of Vit D (150,000 IU)	4 weeks	Ulcer area, WBC, ESR, FBS, and CRP
Kamble 2020 [11]	RCT	India	30	30	Oral vit D (60,000 IU)	Placebo	12 weeks	Change in Wound surface area, cholesterol, BMI, HbA1c, TG,
Razzagi 2016 [12]	RCT	Iran	30	30	Oral Vit D (50,000 IU)	Placebo	Every 2 weeks for 12 weeks	Ulcer healing, cholesterol, HbA1c, ESR, HDL, LDL
Rahman 2013 [13]	RCT	Iraq	15	15	Oral vit D (1,000 IU)	Placebo	Twice daily for 4 weeks	Ulcer healing HDL, LDL,

The effect on wound ulcers

All included studies demonstrated improvements in diabetic foot ulcers. Khosravi et al. reported that after four weeks of intervention, serum vitamin D levels reached sufficiency, with both groups showing significant increases from baseline ($P < 0.01$).[10] Correspondingly, ulcer surface area significantly decreased in both groups compared with baseline values ($P < 0.01$). Similarly, Kambel et al. found that vitamin D levels rose markedly after 12 weeks of supplementation (12.5 ± 10.1 vs. 0.4 ± 0.3, $P = 0.0001$). The intervention group also experienced a notable reduction in wound surface area compared with controls (8.06 ± 6.82 vs. 5.1 ± 1.3, $P = 0.0001$).[11] Rahman et al. further observed a significant difference in ulcer reduction percentage after four weeks of treatment compared with placebo ($P < 0.01$).[13] In another trial, Razzaghi et al. demonstrated that vitamin D supplementation significantly reduced ulcer length (-2.1 ± 1.1 vs. -1.1 ± 1.1 cm, $P = 0.001$), width (-2.0 ± 1.2 vs. -1.1 ± 1.0 cm, $P = 0.02$), and depth (-1.0 ± 0.5 vs. -0.5 ± 0.5 cm, $P < 0.001$) after 12 weeks compared with placebo.[12] Intention-to-treat analysis showed that ulcer healing was significantly higher in the high-dose group, with 21 of 30 patients (70%) achieving complete healing versus 12 of 34 (35%) in the low-dose group ($P = 0.012$). Per-protocol analysis confirmed these findings, with 20 of 28 patients (71%) in the high-dose group achieving healing compared to 11 of 29 (37%) in the low-dose group ($P = 0.023$).[9]

DISCUSSION

High-dose vitamin D demonstrated a more pronounced effect compared to low-dose supplementation. Beyond wound healing, vitamin D in DFU patients also showed favorable impacts on metabolic and inflammatory parameters, including glucose regulation, LDL and HDL cholesterol, ESR, hs-CRP, and MDA levels.[14] Burkiewicz et al. reported an association between vitamin D and skin health improvement. In their trial, participants received 50,000 IU of vitamin D for two weeks. Following the intervention, mean ulcer area decreased from 25 cm^2 to 18 cm^2 in the treatment group and from 27 cm^2 to 24.5 cm^2 in the placebo group ($P = 0.78$ and 0.70, respectively), indicating no significant difference between vitamin D–deficient and non-deficient groups.[15] Interestingly, another study revealed that higher doses ranging from 150,000 to 300,000 IU of vitamin D produced a significant reduction in ulcer size. These findings suggest that megadoses of vitamin D may offer superior benefits in managing DFU.[10,16]

Previous studies showed that the severity of vitamin D deficiency was high in patients with DFU.[17-19] Chronic wounds

formed when diabetic individuals experience hyperglycemia, which interferes with the body's natural cytokine production process. Furthermore, defects in wound healing in diabetics are caused by a number of physiological reasons, including reduced growth factor production, altered cytokine production, and macrophage activity. According to the previous research, a vitamin D shortage may enhance an individual's vulnerability to illness.[20]

The mechanisms underlying the role of vitamin D in wound healing are multifaceted. Vitamin D interacts with its receptors in the skin, enhancing the secretion of cathelicidin, an antimicrobial peptide that promotes cell proliferation and migration, thereby accelerating wound repair. In addition to its direct role in wound healing, vitamin D also influences other factors relevant to diabetic patients. Deficiency in vitamin D triggers calcium release from bones, contributing to osteopenia, a hallmark of diabetic osteoarthropathy (Charcot's foot). Moreover, patients with diabetic foot ulcers often experience reduced mobility and require offloading to minimize pressure, which decreases sun exposure and further exacerbates vitamin D deficiency. This deficiency is linked to elevated levels of pro-inflammatory cytokines, such as IL-1β and IL-6, which impair and delay wound healing—creating a vicious cycle between vitamin D deficiency and worsening ulcer progression.[21-23]

Vitamin D also modulates cellular activity in the proliferation and remodeling phases of wound repair by enhancing antimicrobial peptide expression while suppressing pro-inflammatory responses. In vitro studies demonstrated that calcitriol upregulates proangiogenic factors, including vascular endothelial growth factor A (VEGFA), hypoxia-inducible factor 1-alpha (HIF-1α), and angiogenin, thereby stimulating cell migration and promoting antimicrobial peptide expression in keratinocytes derived from DFU patients.[24] Another in vitro study showed that vitamin D increases the expression of *DEFB4* and *CAMP* genes, resulting in elevated production of human beta-defensin-2 (HBD-2) and LL-37, peptides with antimicrobial activity against *Escherichia coli* that also enhance keratinocyte migration. [25]

This review, however, has limitations. Considerable variability existed across the included studies in terms of vitamin D dosage, participant numbers, and outcome measurements. Combined with the relatively small sample size, these factors limit the robustness of the conclusions. Therefore, future research with larger sample sizes and greater methodological consistency is needed to validate these findings.

CONCLUSION

High-dose oral vitamin D supplementation administered either weekly or daily would significantly improve wound healing in DFU patients by reducing the wound ulcer area. Higher doses of vitamin D resulted in better wound healing outcomes. Vitamin D affects wound healing by improving factors that interfere with diabetic wound repair and by stimulating the body's immunity. Oral vitamin D can be an additional therapy for DFU patients to help wound healing.

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