IJCNP : (Indonesian Journal of Clinical Nutrition Physician)

Open Access Full Text Article

# EFFECTS OF VITAMIN D ADMINISTRATION FOR WOUND HEALING IN PATIENTS WITH DIABETIC FOOT ULCERS: EVIDENCE BASED CASE REPORT

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## Abstract

**Background:** Diabetes mellitus can cause microvascular and macrovascular complications. Diabetic foot ulcer is the complications that often occur in DM patients, which is as much as 10%-25%. In Indonesia, the incidence of diabetic foot ulcers is 12% and DM patients can be at risk of diabetic foot ulcers as much as 55.4%. The mortality rate that occurs because of diabetic foot ulcers can reach around 15-30%. Patients who have diabetic foot ulcers significantly decreased vitamin D levels. This study aims to determine the effectiveness of vitamin D supplementation for wound healing in diabetic foot ulcers.

**Objective:** This study aims to evaluate the effect of high-dose vitamin D for wound healing in diabetic foot ulcers.

**Methods:**

Literature search was carried out by advanced searching on Pubmed, Cochrane Library, Scopus, and Science Direct using a combination of MeSH Terms and Title/Abstract. After screening for duplications, the literature obtained then screened according to predetermined eligibility criteria. The appropriate literatures were critically reviewed, and the level of evidence determined based on the Oxford Center for Evidence Based Medicine.

**Result:**

From 305 articles screened, 3 suitable literatures were obtained to answer clinical questions, 1 Systematic Review / Meta-Analysis (SR / MA) literature and 2 Randomized Controlled Trial (RCT) literature. All three literatures concluded that improvement of healing process ulcer area is statistically and clinically significant after vitamin D supplementation dose 50.000 – 300.000 IU / week for 12 weeks. Therefore, it can be applied to clinical scenarios.

**Conclusion:**

Vitamin D administration can improve wound healing in patients with diabetic foot ulcers.

**Keywords:**

"Vitamin D", "vitamin D3", "wound healing", "diabetic foot", "diabetic feet", "diabetic foot ulcer", "diabetic feet ulcer").

## Introduction

Diabetes mellitus (DM) can cause microvascular and macrovascular complications, consisting of diabetic retinopathy, diabetic kidney disease and diabetic foot ulcers. Diabetic foot ulcers are combination of neuropathy and ischemia in the lower limbs that occur in patients with DM and one of the complications that often occur in DM patients, which is as much as

Received : May 11, 2023
Accepted : 30 June 2024
Publish : 04 July 2024

10%-25%.[1–3] In Indonesia, the incidence of diabetic foot ulcers is 12% and DM patients are at risk of diabetic foot ulcers as much as 55.4%.[4]

Diabetic foot ulcers are also the main cause of increased numbers morbidity and mortality doubled compared to those without diabetic foot ulcers.[1,5,6] The mortality rate that occurs as the result of diabetic ulcers tic foot reach 15-30%.[4] In DM patients who have diabetic foot ulcers, there is a significant decrease in vitamin D levels. Low vitamin D levels can increase proinflammatory cytokines and delay wound healing in patients with diabetic foot ulcers.[7]

Giving vitamin D is thought to improve wound healing in patients with diabetic foot ulcers. Research conducted by Dai J, et al.,[7] stated that vitamin D deficiency can increase the risk of diabetic foot ulcers.[7] This is reinforced by another study by Kinesya E, et al,.[1] mentioned that vitamin D supplementation may play an indirect role in wound healing due to the corrective effect of blood glucose.[1]

**Case Illustration**

A 54-year-old woman was treated and diagnosed with diabetic foot ulcer with complaints of a wound on her left leg that was difficult to heal and worsen 1 week before admission to the hospital. Patients often experience tingling and numbness that arising mainly in the feet and hands. One month prior to hospital admission, the patient's left leg was injured by wood chips while she was cleaning the yard. At that time the patient did not use footwear. The wound is washed only with clean water and not been bandaged. Initially, the wound on the foot was only small about the size of a mung bean seed and without realizing it, the wound was getting bigger, producing fester and smelly. The patient has a 5-year history of diabetes and has been treated with metformin, although not taken routinely. There is no history of hypertension, heart disease, lung disease, kidney disease, liver disease, or malignancy. The patient's mother has a history of diabetes mellitus. There is no family history of hypertension, lung disease, heart disease, or malignancy. The patient has a habit of eating sweet and fried foods. There is no history of alcohol consumption or smoking. On physical examination, hemodynamically within normal limits. The patient's body weight is 68 kg, height is 165 cm with a body mass index (BMI) of 24.9 kg/m$^2$ (overweight). General status from head, neck,

thorax, abdomen within normal limits. Complete blood laboratory examination shows leukocytosis (leukocytes 21,040/µL), current blood glucose 268 mg/dL, fasting blood glucose 162 mg/dl, 2-hour PP blood glucose 314 mg/dl and HbA1c 9%. Patients are planned for debridement and consulted to the Nutrition Clinic for meal arrangements for better blood glucose control. In addition to controlling blood glucose, vitamin D supplementation is also planned to improve wound healing, but vitamin D is rarely given to patients with diabetic foot ulcers. The patient asked the clinical nutritionist whether vitamin D supplementation has beneficial effect to improve wound healing on her feet. Because as far as patients know, vitamin D is beneficial for bone health.

**Clinical questions**

**I**n this case scenario, in diabetic foot ulcers, may vitamin D supplementation support wound healing?

**Methods**

The literature search was conducted on March 5, 2023, with advanced searching on Pubmed, Cochrane Library, Scopus, and Science Direct and using a combination of MeSH Terms and Title/Abstract from each PICO component and using boolean operators "OR" to increase sensitivity and "AND" to increase specificity (Table 1). Keywords used are "vitamin D", "vitamin D3", "wound healing", "diabetic foot", "diabetic feet", "diabetic foot ulcer", "diabetic feet ulcer". Critical appraisal tools and determination of levels of evidence are based on the Oxford Centre for Evidence Based Medicine.

**Research Results**

This study obtained 25 literatures derived from PubMed, 7 literatures derived from Cochrane Library, 140 literatures derived from Scopus and 133 literatures derived from Science Direct. The further screening test was conducted by comparing the titles and abstracts to the suitability of the inclusion criteria. Eligibility criteria were articles published in full text, written in English, subjects over 18 years of age with a diagnosis of diabetic foot ulcer, the study used randomized controlled trial (RCT) design and systematic review/meta-analysis from RCT. Subjects in the intervention group was given vitamin D, while the control group was given placebo or no medication or vitamin D low dose (800 IU / day). Outcomes in the form

of wound healing and published from 2017 to 2023. After screening duplication and selecting articles according to eligibility criteria, three literatures from Kinesya E, et al.[1] and Kamble A, et al.[10] and Halschou-Jensen PM, et al.[8] were found to be relevant and could be analyzed to answer clinical question.

**Discussion**

Based on the results of critical review, all SR/MA and RCT articles show that administration of vitamin D significantly improve wound healing in patients with diabetic foot ulcers. Patients with diabetic foot ulcers had vitamin D deficiency compared to patients who do not have diabetes mellitus or DM without ulcers.[8,9] Vitamin D deficiency is associated with increased insulin resistance, disruption of pancreatic beta cells and progression to DM. Hyperglycemia in patients with diabetes mellitus causes disruption of normal cytokine production, causing disruption in wound healing process if patients have ulcers or wounds.

Vitamin D supplementation provides a beneficial effect for diabetic foot ulcers healing process, improve insulin resistance, biomarkers of inflammation, oxidative stress so that they can kill bacteria contained in ulcers, besides vitamin D and its active metabolite 1,25-(OH)2 vitamin D3 plays a role in the growth and differentiation of keratinocyte cells and fibroblasts especially modulates growth factors (i.e., TGF β, EGF, PDGF) and cytokines such as IL-1α, Il-6, and IL-8. Keratinocytes and fibroblasts are implicated in patients with diabetic foot ulcers and adequate intake of 25-hydroxyvitamin D3 is an important condition for normal wound healing.[5,8]

Systemic review/meta-analysis (SR / MA) by Kinesya E, et al.[1] consisted of 3 studies comparing vitamin D administration in patients with diabetic foot ulcers with placebo, 1 other study comparing vitamin D administration with low doses of vitamin D. This SR / MA stated that vitamin D administration can significantly help diabetic foot ulcer healing faster by decreasing ulcer area from 2.8 ± 1.0 cm to 2.3 ± 0.6 cm with a mean difference of [-2.70(-2.90, -2.50) $p<0.00001$] and a confidence interval of 95%.[1]

The RCT study conducted by Kamble A, et al.[10] conducted a study on 60 diabetic patients with grade II/III diabetic foot ulcers between 2019-2020 who were then observed for 12 weeks. The study found that vitamin D supplementation (60,000 IU) in patients with grade II/III diabetic foot ulcers improved ulcer area (29.83-15.02 vs. 21.76-11.30, $p = 0.02$). Another RCT study was conducted by Halschou-Jensen PM, et al.[8] also given similar results. In the

study with high-dose vitamin D administration (6800 IU / day) for 48 weeks found an increase in ulcer healing (adjusted OR=4.11, 95% CI=1.11-17.29) with a value of p = 0.018. The results of both RCTs are statistically and clinically significant. [8,10]

Study from Kinesya E, et al.[1] and Kamble A, et al.[10] show there is a shrinking area of wounds in the group given vitamin D. Vitamin D plays a very important role in diabetic foot ulcers healing process, through several mechanisms, such as increase glycemic control and promote wound healing. Patients with DM occur disturbances in the wound healing process, characterized by the presence of chronic inflammatory phases, disruption of angiogenic processes, and imbalances in the regulation of the extracellular matrix. Chronic inflammatory processes are caused by a non-ideal environment in DM patients. Pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF)- α are elevated only during the initial phase of inflammation, but the presence of pro-inflammatory cytokine levels remain elevated, causing delayed wound healing. Therefore, the administration of vitamin D may reduce levels of pro-inflammatory cytokines so that wound healing occurs in diabetic foot ulcer patients.[1,10] Study from Halschou-Jensen PM, et al.[8] showed that administration of high doses of vitamin D (6800 IU/day) was better than low doses (800 IU/day), because administration of high doses of vitamin D can reach vitamin 25 (OH) D content of 50-160 nmol/L, therefore the 25(OH)D level is optimal in the blood and do not cause deficiency. Wound healing was also better in the high-dose group than in the low-dose group.[9] All three studies conducted by this critical review; the selection of subjects was based on DM sufferers who had ulcers regardless of the vitamin D status of the subject. However, the study from Halschou-Jensen PM, et al.[8] excluded patients receiving vitamin D supplementation (>20 µg/day).[8]

Vitamin D contributes to wound healing. In addition to improve wound healing in diabetic foot ulcers. A case report stated that vitamin D supplementation showed effectiveness in the healing process of wounds in the oral mucosa. The patient in this case report had complaints oral thrush that is difficult to heal and after checking vitamin D levels there was insufficiency (28.7 ng / mL), then the patient was given vitamin D supplementation as much as 400 IU for 3 months, normal vitamin D levels were obtained and oral thrust also improved significantly.[11] Another study conducted that vitamin D can improve wound healing in adult patients with burns had a synergistic effect of vitamin D and TGF-β1, resulting in an increase

in TGF-1 gene expression, β connective tissue and fibronectin growth factors, increased fibroblast migration, myofibroblast formation, and collagen production.[12]

Food sources containing vitamin D are found in fatty fish (trout, salmon, tuna, and mackerel), fish liver oil which is the best source of vitamin D. Beef liver, egg yolks, and cheese contain little vitamin D, especially in the form of vitamin D3 and its metabolite 25(OH)D3. In addition, vitamin D is also found in low-fat or fat-free milk, and egg yolks.[13] Most people in the world get a portion of their vitamin D needs through sun exposure. Type B ultraviolet (UVB) radiation with a wavelength of about 290–320 nanometers penetrate uncovered skin and converts 7-dehydrocholesterol into provitamin D3, which in turn becomes vitamin D3. Some experts and researchers recommend about 5–30 minutes of sun exposure, especially between 10 a.m. and 4 p.m., either daily or twice a week to the face, arms, hands, and feet without sunscreen to get enough vitamin D synthesis.[14]

Based on the critical studies above and several studies related to the effectiveness of vitamin D in wound healing, it is better to check vitamin D levels first before high-dose vitamin D supplementation to help wound healing. If there is insufficiency or deficiency, vitamin D supplementation can be given until vitamin D levels are optimal and normal. Vitamin D supplementation can be given in doses according to recommended dietary allowance (RDA) of 15 mcg / day or 600 IU / day.

## Conclusions and Recommendation

Based on the review of relevant journals, the administration of vitamin D for 12 weeks at dosages ranging from 50,000 to 300,000 IU per week in patients with diabetic foot ulcers has been found to be statistically and clinically significant in promoting and accelerating ulcer healing. Vitamin D supplementation should be particularly considered for patients who exhibit vitamin D deficiency. However, there is currently no data on the appropriate dosage of vitamin D for aiding and accelerating ulcer healing in patients with normal vitamin D levels. Therefore, it is essential to assess vitamin D levels prior to supplementation and to monitor them regularly. This approach ensures that optimal vitamin D levels are maintained to facilitate wound healing in patients with diabetic foot ulcers while avoiding potential toxic side effects.

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**Acknowledgement**

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**Competing Interest**

The authors declare that there are no competing interests related to the study

**List Of Abbreviations**

BMI : body mass index

DM : Diabetes mellitus
EGF : Epidermal Growth Factor
HbA1C : glycated hemoglobin
IL-1α : interleukin-1
Il-6 : interleukin-6
IL-8 : interleukin-8
PDG : Platelet-derived growth factor

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TGF β1: Transforming growth factor beta
TNF- α : tumor necrosis factor alfa
UVB : Type B ultraviolet

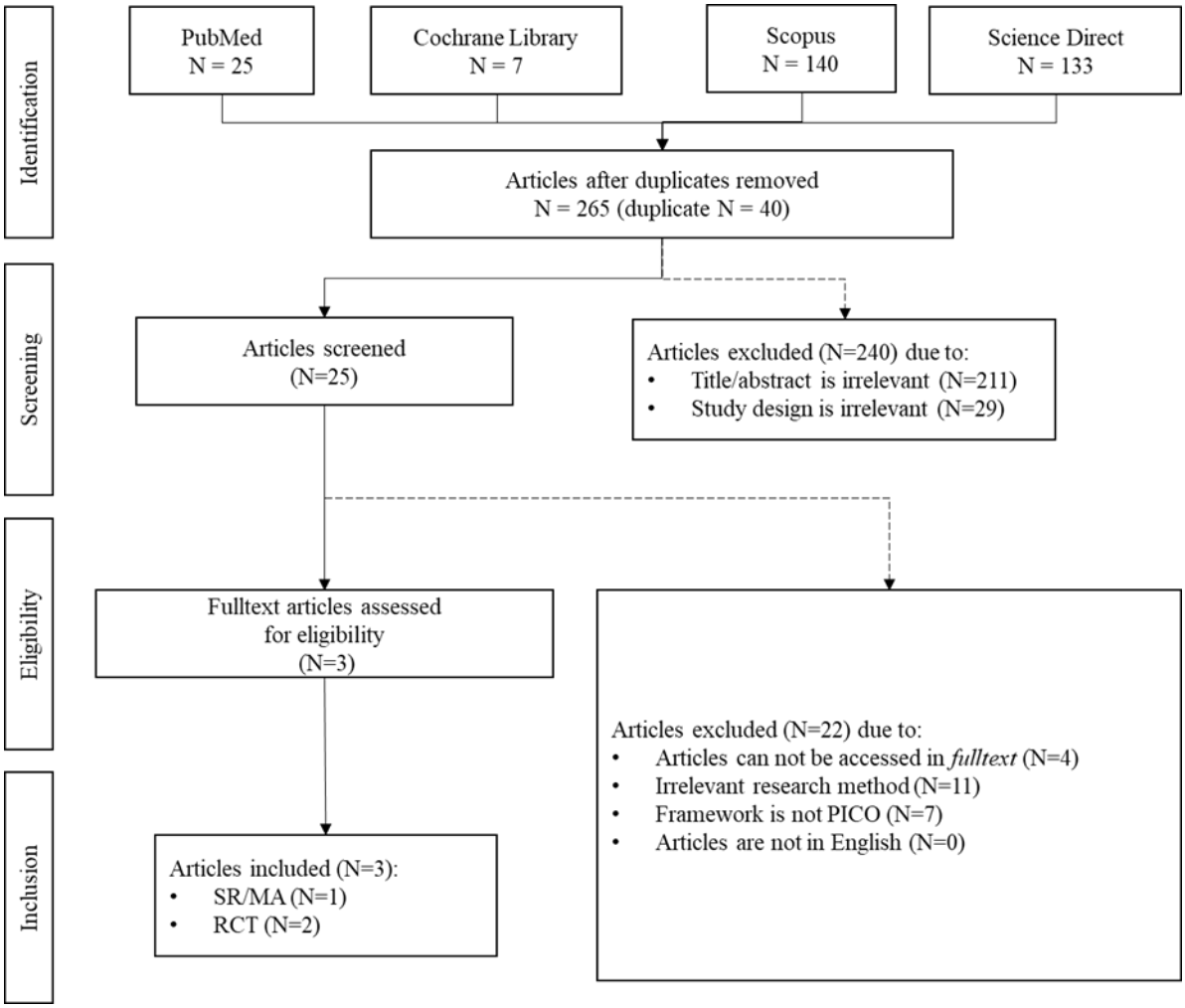


Figure 1. Prisma's Flowchart

**Table 1. Assessment of Literature Characteristics**

| Writer | Desain Studi | Characteristics of Populasi | Intervension | Outcomes |
|---|---|---|---|---|
| Kinesya E, et al. (20 23)[1] | *Systematic review* and Meta-analysis of RCT | The subjects are: 197 Patients with *diabetic foot* ulcers. | Patients with diabetic foot ulcers were given vitamin D dose 50000-300000 IU/week supplementation compared to placebo who were not given vitamin D supplementation. | Area of diabetic foot ulcer and laboratory results (HbA1c, total choles, terol, erythrocyte sedimentation rate (ESR), C-reactive protein |

| | | | | |
|---|---|---|---|---|
| | | | | (CRP), Triglycerides (TAG) and fasting blood glucose. |
| Kamble A, et al. (2020) [8] | *Randomized Controlled Trial* | The subjects are: 60 diabetic patients with grade II/III *diabetic foot* ulcers between 2019-2020. Patients were randomly divided into 2 groups, into group A (vitamin D supplements) and group B (controls) | Patients received vitamin D supplements weekly given for 12 weeks. Group A was given cholecalciferol 60000 IU in the form of *sachets* and group B (control group) was not given any drugs. | Levels of vitamin D, HbA1c. Triglycerides, total cholesterol, HDL and changes of wound area after 2 weeks. |
| Halschou-Jensen PM, et al. (2021) [9] | *Randomized Controlled Trial* | 48 diabetic patients who had 1 or more *non-healing diabetic foot* ulcers for more than 6 weeks were outpatient. Then randomization was divided into 2 groups, namely the high-dose group and the placebo group (low-dose) | high-dose group (vitamin 6800 IU/day) and placebo group (vitamin D 800 IU/day) | Healing in chronic *diabetic foot* ulcers |

**Table 2 Critical Review of Validity, Importance, Applicability and Level of Evidence Criteria**

| | Study design | Number of patients | Randomization | Similarity treatment and control | Blinding comparable treatment | Domain | Determinant | Measurement of outcomes | Quality of evidence | Level of evidence |
|---|---|---|---|---|---|---|---|---|---|---|
| Kinesya E, et al.[1] | + | + | + | + | + | + | + | + | Moderate | 1A |
| Kamble A, et al.[8] | + | + | + | + | + | + | + | + | Moderate | 1B |
| Halschou-Jensen PM, et al.[9] | + | + | + | + | + | + | + | + | Moderate | 1B |

**Table 3. Validity criteria for Kinesya E, et al.**

| Article | Study Design | Question | Find | Appraise | Inclusion | Total Up | Heterogeneity | Result | Applicability |
|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Kinesya E, et al.[1] | Systematic Review / Meta-Analysis of Randomized Controlled Trials | + | + | + | + | + | - | A | + |

Vitamin D administration can significantly help diabetic foot ulcer healing faster by decreasing ulcer area from 2.8 ± 1.0 cm to 2.3 ± 0.6 cm with a mean difference of [-2.70(-2.90, -2.50) p<0.00001] and a confidence interval of 95%.

**Table 4. Critical research assessments of randomized control trial**

| Parameters | Question | Kamble A, et al.[8] | Halschou-Jensen PM, et al.[9] |
|---|---|---|---|
| Validity | Is the distribution of patients for treatment random? | Yes | Yes |
| | Were the two groups similar at the start of the study? | No | No |
| | Apart from the allocation of therapy, are the two groups treated equally? | Yes | Yes |
| | Are all subjects included in the study properly accounted for until the end of the study? And were the subjects analyzed according to the group to which they were randomized? | Yes | No |
| | Is the measurement objective or does the patient and clinician remain "blind" when therapy is administered? | No | Yes |
| Importance | How large is the therapeutic effect? | The data is displayed in the form of wound surface area changes. Vitamin D supplementation per day for 12 weeks improved WSA compared to control group, result was p = 0.0014 | The data is displayed in the form of an ulcer area measurement at the end, the result is p = 0.0 18, or p <0.05 which means significant |
| | How precise is the estimation for therapeutic effects? | There was a change in WSA (8.06±6.82 3.76±1.73. p= 0.0014) in the intervention group with CI 95% | The intervention group, namely high doses of vitamin D (6800 IU / day) obtained a significant increase in wound healing with *adjusted* OR=4.11, 95% IK= 1.11-17.29). |
| | Do the possible benefits of treatment outweigh the harm and cost? | Based on the calculations in the table below | Based on the calculations in the table below |

| | Intervention | Control |
|---|---|---|
| After | 18.5 | 20.1 |
| Before | 31 | 20.5 |

| | Intervention | Control |
|---|---|---|
| After | 20 | 11 |
| Before | 28 | 29 |

| | | | |
|---|---|---|---|
| | | Total 49.5 40.6<br>EER= 18.5/49.5 = 0.37<br>CER= 20.1/40.6 =0.49<br>RR= EER/CER=0.37/0.49 = 0.755<br>ARR= CER-EER=0.49-0.37 = 0.12<br>NNT= 1/ARR= 1/0.12 = 8.3<br><br>Based on the results of NNT calculation, it takes 8 subject to get an additional 1 person who has improved healing of diabetic foot ulcers. | Total 48 40<br>EER= 20/48 = 0.42<br>CER=11/40 = 0.27<br>RR= EER/CER= 0.42/0.27 = 1.56<br>ARR=CER-EER = 0.27-0.42= -0.15<br>NNT= 1/ARR= 1/-0.15 = 6.7<br><br>Based on the results of NNT calculation, it takes 6-7 subject to get an additional 1 person who has improved healing of diabetic foot ulcers |
| Applicability | Do the characteristics of the patients that we faced are like the characteristics of the study patients? | Yes | Yes |
| | Can the exposure in the study be given in the condition of our patients? | Yes | Yes |
| | Are the potential benefits of therapy higher than the disadvantages of therapy for our patients? | Yes | Yes |