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Literature Review: Role of Vitamin D in Diabetic Foot Ulcer Wound Healing

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Abstract: DFU is a common consequence of DM. Vitamin D has multiple positive effects on DFU. Search data from; Google Scholar, Science Direct, Scopus, EBSCO, Medline and PubMed. Publication at least ten years (2013 until 2022). Inclusion criteria; full paper in English, Study about vitamin D and DFU in human, exclusion criteria; animal model and invitro study. Results; 27 journals; Seven Randomized Controlled Trial. Vitamin D phase on DFU which one substantially smaller. Severe vitamin D insufficiency is known with significance linked for an elevated risk of DFU. Vitamin D supplementation can prevent or improve diabetic foot complications.

Keywords: Diabetic Foot Ulcer; Diabetes Mellitus; Vitamin D; Wound Healing

Introduction

DM are metabolic state in which marked through a uncontrolled rise in blood glucose levels (Alexiadou & Doupis, 2012; Khan et al., 2020; Mariadoss et al., 2022; Urbanovych & Shykula, 2022; Zhang et al., 2017). DFU has characteristics of sensory, motor, autonomic neuropathy disorders as well as macrovascular and microvascular disorders. The prevalence of DFU in diabetics is around 5 to 9% globally. Diabetics with DFU have an 85% chance of having an amputation and have a 23-fold risk of experiencing a lower extremity amputation compared to people without diabetes. The mortality rate of a diabetic patient who has DFU for 5 years is 2.5 times greater than that of a diabetic patient without DFU. DFU recovery takes 3 months to 6 months, or even a year, depending on severity, because it corresponds with high blood sugar levels, infection level, vitamin D levels, and onset, all of which impact the length of the healing process (Kinesya et al., 2023; Macido, 2018).

Vitamin D is a steroid vitamin that is taken from food and is made in the dermis, kidneys, and liver. It is required for survival. Sunlight can stimulate the skin to

convert 7-dehydrocholesterol to provitamin D₃. (OH)₂D are the active type vitamin D₃ (calcitriol). Vitamin D are acknowledged for its vital function in regulating proper levels of serum phosphorus and calcium, which includes its capability to improve absorption of calcium also phosphorus at small intestine. In its active form, Vitamin D possesses the capacity to trigger insulin producer, impede angiogenesis, imitate macrophage cathelicidin synthesis, initiate apoptosis, and restrain renin producer (Gombart et al., 2005). There are facts that prove this vitamin D has impact beyond its main function in calcium metabolism. Research indicates that insufficient vitamin D level may linked to heart attack, various cancers, autoimmune disorders, and also contribute to the onset of diabetes and neurological conditions. Research have demonstrated that vitamin D can exert a neuroprotective influence. Neural Growth Factor (NGF) production can be stimulated by vitamin D (Alam et al., 2017; Bartley, 2010; Greenhagen et al., 2019; Ismailova & White, 2022; L Bishop et al., 2021; Martens et al., 2020; Putz et al., 2022).

Vitamin D has an immunomodulatory effect that could potentially be used as a therapy for the prevention of worsening wounds in people with DF that has the

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capability to act being anti-inflammatory stimulus by increasing the product of anti-inflammatory cytokines while reducing the levels of pro-inflammatory cytokines. These pro-inflammatory cytokines are very closely related to the increased tissue damage in DFU thereby reducing the wound healing process. Therefore, vitamin D has the opportunity to molecularly improve the wound healing process in DFU. Moreover, it is widely acknowledged that individuals with diabetes mellitus (DM) who have severe vitamin D insufficiency are at a substantial risk of developing DFU. The ability of vitamin D can also affect the wound healing process because it is associated with its ability to increase the proliferation and remodeling of wound tissue (Arafat et al., 2020; Lennarz & Lane, 2013; Marcinowska-Suchowierska et al., 2018; Ramasamy, 2020; Y. Wang et al., 2012; Yamada et al., 2003).

Method

This literature review used the keywords "Diabetic Foot Ulcer", "Vitamin D", "1,25-(OH)2D", "Diabetes Mellitus", and "Calcitriol". The sources for this literature review study were gathered from universal article sites eg Elsevier, EBSCO, also Wiley. The literacy search including Randomized Clinical Trial research, meta-analysis, case control, cohort study, literature and systematic review publication requirements with at least the last ten years. The exclusion criteria were journals that were not in English language.

The evaluation of inclusion and exclusion criteria starts with a literature search. Initially, the title and

abstract of each study are assessed. Subsequently, the full text is examined if there is a connection or correlation between the keywords used in the paper. This process helps in crafting a comprehensive description and analysis of the literature under review. To determine article eligibility, a priori established PICOS framework was applied (Mousa et al., 2018). A literature search based on inclusion and exclusion criteria yielded 27 journals, which were used to write this literature review.

Result and Discussion

Based on the search results, There were 27 journals; Seven randomized controlled trial (El Hajj et al., 2020; Halschou-Jensen et al., 2023; Karonova et al., 2020; Lin et al., 2023; Mozaffari-Khosravi et al., 2016; Razzaghi et al., 2017; Wu et al., 2017) seven meta-analysis (Dai et al., 2019; Dashti et al., 2021; Kinesya et al., 2023; Lin et al., 2023; Mousa et al., 2018; Wu et al., 2017; Yasmine et al., 2020), two clinical trials (Al-Ahmady, 2013; Mozaffari-Khosravi et al., 2016), one cross-sectional study (Tang et al., 2023), four case control studies (Arafat et al., 2020; Çağlar et al., 2018; Feldkamp et al., 2018; F. Wang et al., 2022), one study using cohort design (Greenhagen et al., 2019), four study systematic literature review (Kurian et al., 2021; Macido, 2018; Smith & Hewlings, 2021; Urbanovych & Shykula, 2022), one Observational Study (Kamble & Swarnkar, 2019). All the result of these reviews are shown in Tabel 1.

Table 1. There were 27 journals studied about Vitamin D and Diabetic Foot Ulcer

Author	Year, Country and Design	Aim of Study	Number of Sample, Dose and Duration of Study	Result	Conclusion
Halschou-Jensen, P. M., Sauer, J., Bouchelouche, P., Fabrin, J., Brorson, S., & Ohrt-Nissen, S	2021 <i>Randomized Controlled Trial</i>	Improving Diabetic Foot Ulcer Treatment Following Height-Doses Vitamin D: A Randomi Double-Blind Clinicals Testing	48 patients (24 in each group), total 64 ulcers, routine oral requirements height-doses (170 µg) or lowly-doses (20 µg) vitamin D3. Follow up; 4, 12, 24, 36, and 48 weeks	Observation of intention to heal revealed that the height-doses group has a significantly relatively high ulcer healing rates, with 21 of 30 (70%) treat boils through comparison against 12 of 34 (35%) at the lowly-doses group. The conclusion is, median ulcer reduction has 100% at the height-doses parties also 57% at the lowly-doses parties. Thus, on observing the re-weighing type, we discovered significant impact on high vitamin D levels in ulcer dosing.	Height-doses vitamin D3 was found going more effective than lowly-doses vitamin D3 at encouraging healing.
Karonova, T., Stepanova, A.,	2020, Russia,	The researchers	67 patients	There was a substantial reduction at NSS also skin	In individuals with T2DM with peripheral

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Bystrova, A., & Jude, E. B.	Randomized Controlled Trial	looked at how different vitamin D supplementations on levels affected microcirculation, peripheral neuropathy symptoms, also inflammatory symbol at type 2 diabetic sufferer.	5000 IU also 40,000 IU once/week oral towards 24 weeks	healing MC are analyzed (p < 0.05). And also discovered decrease at IL-6 level also a rise in IL-10 levels	neuropathy, height-doses cholecalciferol supplement has related with improvements at clinic presentation, dermal microcirculation, also inflammatory symbols.
El Hajj C, Walrand S, Helou M, Yammine K	2020, Lebanon, Randomized Controlled Trial	Examine impacts vitamin D supplement at inflammatory symbol at non-obese Lebanon individuals T2DM sufferer.	N=88 30.000 IU cholecalciferol / week for a half year period	The vitamin D parties has greater blood levels of also a substantial dose hs-CRP also TNF-α concentrations. The apparent reduction in IL-6 concentration isn't statistically significantly. FBG also HbA1c level did not alter significantly.	Vitamin D supplement reduced several inflammatory symbols at T2DM sufferer.
Gupta, B., Dwivedi, A., Singh, S. K.	2017, India, Randomized Controlled Trial	Examine impact of vitamin D supplements in cytokine expression in diabetic foot infection patients.	120 patients, 30.0000 IU per oral are 5 dividing doses when registering	The mean blood concentration 25-OH vitamin D3 in the basic line as well after 4 weeks were substantially not the same in the two settings also patients. The unequal mean serum inflammatory cytokine levels that carry out exchange TNF-α also IL-6 in the first and after the action is not significant in category 1 but the significance in the category II.	Vitamin D supplement lowered inflammatory cytokines at diabetes foot sufferer with a rising reactivity to that cytokines.
Razzaghi R, Pourbagheri H, Momen-Heravi M, Bahmani F, Shadi J, Soleimani Z	2017, Iran Randomized Controlled Trial	Effect of vitamin D supplements in the treatment of diseases as well as metabolism condition at diabetic foot ulcer sufferer.	60 samples; 50.000 IU vitamin D for 2 weeks and 12 weeks; 12 weeks	Serum insulin concentrations, Insulin resistance, HbA1c, Cholesterol level, LDL, HDL cholesterol, ESR	vitamin D supplemented improved disease treatment as well metabolic state at DFU.
Alam U, Asher Fawwad, Fariha Shaheen, Bilal Tahir, Abdul Basit, Rayaz A, Malik	2017, Pakistan, Randomized Controlled Trial	Assess Impact of individual intramuscular injections of large doses of vitamin D on quality of life in people with	143 samples; 600.000 IU IM; 10 months	41.3% participants were deficient in vitamin D. Healing through vitamin Gives an increase in significance 25 also a significantly increase at the Neuro QoL subscale number for emotional suppression, without significantly changes	High vitamin D levels of 600.000 IU give result at substantial rise at 25(OH)D (P < 0.0001) also were effective at enhancing grade life of DN

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		diabetic neuropathy who are ill with use NeuroQoL questionnaire.		at the another Neuro QoL domain of pain and paresthesia symptoms; loss of temperature as well as the feeling of touch, instability, limitations on routine activities, as well as interpersonal constraints.	patients with DFU (n=143).
Hassan Mozaffari-Khosravi	2016, Iran, <i>Randomized Controlled Trial</i>	Two Comparative Effects The current study compared the effects of 150,000 also 300,000 IU of vitamin D in a state of treatment diabetes foot ulcers in diabetic sufferer.	47 patients 150.000 IU 300.000 IU, intra muscular injection, 4 weeks follow up	Both groups' serum vitamin D levels were considerably higher than outline (P<0.01). Meaning blood vitamin D decreases in G150 and G300 which is 12.6 ± 5.0 also 18.4 ± 6.4 ng/ml, respectively. When compared to the baseline, the ulcer area was considerably decreased in two types (P<0.01). In both types, WBC, ESR, FBS, also CRP levels are significant lower than at the start. The mean increases in serum FBS and CRP levels, on the other hand, were shown to be substantially different between groups. Regular impact capital or irregular impact were used to predict refrigerator area collected, also fasting plasma glucose which is 95% trust interval. We considered four publications with a total sample size of 197 participants that reported on vitamin D capability as a healing for DFU sufferer.	In diabetic foot ulcer patients, 150,000 also 300,000 IU of vitamin D treat ulcers as well vitamin D circumstances while decreasing ESR, CRP, WBC, and FBS. Furthermore, 300,000 IU of vitamin D was far better beside 150,000 IU.
Kinesya, Edwin, et al.	2023; <i>Mechanical Analysis and Meta-observation</i>	Analyze role of vitamin D administering at DFU	4 papers with 197 people.	DFU with less significance vitamin D levels through great heterogeneity due to I2 = 95%, prevalence of vitamin deficiency heterogeneity is symbolized as moment (I2 = 68%), also number of vitamin D weakness higher weight through moderate heterogeneity are I2 = 69% compared to non-ulcerated diabetes subjects.	As a healing adjunct for diabetic foot ulcers, vitamin D supplementation is effective. It has the potential to accelerate disease treatment as well reduce the dependent imposed for diabetes foot ulcers.
Lin J, Xinxin Mo, Yejun Yang, Chao Tang, Jia Chen ^a	2022, China <i>Meta-observation</i>	Examine the connection between vitamin D insufficiency and DFU.	7586 samples	Based on the data, it was finding that vitamin D greatly get reduce serum CRP concentrations (mean weight difference also TNF-α	When compared to non-DFU diabetics, diabetic patients with DFU had considerably lowers vitamin D level also a highest predominancy of vitamin D insufficiency.
Dashti F, Seyed Mohammad Mousavi, Bagher Larijani, Ahmad Esmailzadeh.	2021, Iran, <i>Meta-analysis study</i>	Summarize past research on the impact vitamin D supplement at inflammation for people	4568 studies (38included)		In persons with AGH, circulating levels inflammatory cytokines like CRP, TNF-α, also IL-6 may decrease which is

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Dai J, Jiang C, Chai Y.	2019, China, Meta-observation	Examine the relationship among vitamin D weakness too DFU at diabetes patients.	7 studies that involved 1115 patients	DFU had significantly lower vitamin D level. Complex vitamin D these weaknesses linked to an elevated risk of DFU.	Severe vitamin D weakness has been linked to growth risk DFU.
Yammine K, Fady Hayek, Chahine Assi.	2019, Lebanon, Meta-observation	Examine the unity among vitamin D insufficiency also DFU complications.	1644 samples, 4 months	Pooled serum vitamin D level which is 13.7 3.7 and 19.8 4.7 ng/mL for the legs also control groups, severally. The differences in the weighted means are -0. and -0.93 with fixed-effect also random-effect models severally. That findings imply reduced vitamin D levels in the legs. Funnel and Egger statistics on 7.8 (95% CI = 25.84 to 10.22, p = 0.3397) imply that publication bias is unlikely. The sensitivity analysis produced comparable results when one study was excluded at a time.	Vitamin D Supplements can provide prevention or improve diabetic foot complications
Mousa A, Naderpoor N, Teede H, Scragg R, de Courten B. ¹²	2018, mechanical analysis as well as meta-observations	Analysis of the impact of vitamin D supplement at inflammatory symbols at category 2 diabetes sufferer and identify related information gaps.	20 Sources RCT Study, 1270 sample player	vitamin D- the type given the supplement has a relatively small level C-reactive protein also tumor necrosis cause α , a lowest erythrocyte sediment level, also highest-level leptin comparasion by control category. There were no dissimilarities were found that were analyzed for use adiponectin, interleukin 6, or E-selectin.	This meta-analysis shows preliminary evidence thats vitamin D administration may reduce chronic lowly-quality inflammation at type 2 diabetic sufferer.
Wu C, Shanhu Qiu, Xiangyun Zhu, Ling Li.	2016, China, Meta-Analysis	Summarize the data from RCTs for determined the goodness vitamin D supplement at lowering glycosylated hemoglobin A1c also FBG level.	637 samples; 10 years	Supplementation with vitamin D was related wich is lower HbA1c level but has no effect at FBG level. Significantly lower HbA1c levels were also shown to be linked by vitamin D supplement in a subset of category 2 diabetic sufferer by BMI of <30 kg m-.	Vitamin D supplement will improve glycemic arrangement at category 2 diabetes sufferer who are vitamin D deficient but not obese.

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Rahman NMA, et.	2013, Iraq, Clinical Trial	Comparing the effects zinc also vitamin D3 at fructosamine levels, number of cures, as well lipid profiles at diabetic individuals with DFU.	30 DFU patients Participants irregularly ordered to one of the two parties: vitamin D or placebo. Vitamin D tablets 1000 IU orally after food daily for 4 weeks	The difference in ulcer place decrease among the vitamin D also control groups was $(71.86 \pm 4.79\%$ vs $32.06 \pm 4.28\%$; $p < 0.01$). After 4 weeks healing, fructosamine levels at the treatment parties decreased significantly. Hieight densitys lipoprotein also lowly densitys lipoprotein level did not alter significantly.	There was a decrease in ulcer area in the vitamin D group
Khosravi, et. al	2016, Iran, Clinical Trial	In order to make a comparison of the impact on 150,000 also 300,000 IU dosages of Vitamin D at the threatement circumstances of DFU in people with diabete ²⁵ .	Single dose intramuscular injection, patients (47 DFU) which is divides at two parties; 150,000 IU of vitamin D and 300,000 IU	Serum vitamin D levels were considerably higher in both groups comparing to outline ($P < 0.01$). Serum vitamin D levels decreased by both groups' ulcer place has significantly reduce ($P < 0.01$). At both partoes, leukocytes, ESR, FBS, and CRP levels dropped dramatically.	Vitamin D, particularly 300,000 IU, accelerates ulcer repair. As a result, vitamin D level must be assessed at the clinic management diabetic foot sufferer.
Eman S. Arafat, Inass M. Taha, Shahad W. Kattan, Nouf Abubakr Babteen ⁴ , Iman Fawzy. ¹⁷	2022, Egypt, Case-control study	Examine the relationship between blood 25-hydroxy Vitamin D, VDR, and VDBP levels in category 2 diabetes sufferer versus controls.	110 female patients	The levels of 25(OH)3D were considerably lower at the diabetes parties comparing to control, also they were strongly adversely linked by lowly density lipoprotein cholesterol at category 2 DM. Vitamin D deficiency has found to be significan related to VDR deficiency. There was no significantly relationship detected among vitamin D also VDBP level.	Vitamin D insufficiency are common at diabetics also is linked to poor management also outcome. That shows that Vitamin D plays a role at the etiology also management of T2DM. Serum VDBP levels at diabetic may be unrelated to 25(OH)3D levels.
Wang F, Luyao Zhou, Di Zhu, Caizhe Yang.	2022, China, Case-control study.	Prediction ²⁶ link among 25-OH-vitamin D levels also DFU at diabetic mellitus sufferer, also establish a theoretic foundation for DFU preventing also therapy.	429 samples; 10 months	The effect of 25-OH-vitamin D has statistic significantly ($p < 0.05$). Analysis of multivariation logistic regression DFU is protected by 25-OH-vitamin D on its own [OR 95%, CI 0.984 (0.969, 0.92)], $p < 0.05$]. The distribution of 25-OH-vitamin D nutrition circumstances differed between the non-DFU also DFU groups. Vitamin D insufficiency was found in 86.78% of DFU sufferer but	DFU and 25-OH-vitamin D are highly associated, and 25-OH-vitamin D are an individualistic preventive cause towards DFU.

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Caglar S, Aysel Caglar, Saadet Pilten, Cem Albay, Ozay Beytemur, Hakan Sari.	2018, Turkey, Case-control	Determine deficiencies and degrees of ugliness 25(OH)D deficiency in DFU sufferer with comparing OPG also 25-hydroxy vitamin D levels.	105 samples; 1 year	just 74.33% of non-DFU sufferer. The 25-OH-vitamin D level DFU sufferer from Wagner Quality 1 into 5 decreases ($p < 0.01$). OPG level which is substantially highest at the diabetic foot parties ($p < 0.05$). The DFU group has significantly reduced 25(OH)D levels ($p < 0.05$). There are positively connections among OPG level also CRP also creatinine level at diabetic foot sufferer.	DFU may require vitamin D supplementation.
Feldkam J, Karsten Jungheim, Matthias Schott, Beatrix Jacob, Michael Roden.	2018, United States, Case-control	Compare level 25-hydroxy-vitamin at in DM sufferer by UKD and without UKD	104 samples	Sufferer who has DFU had lowers level 25-hydroxyvitamin D3 than the controls parties (27.2 ± 12.2 ng/ml). There was no dissimilarity among in- also outsufferer. Fifty-eight DFU patients showed severe 25-hydroxyvitamin D3 insufficiency, with values under 10 ng/ml. Just 12% sufferer had levels of 25-hydroxyvitamin D3 exceeding 20 ng/ml. Secondary hyperparathyroidism has discovered at 27.9% of sufferer, while 11.5% which is hypocalcemic. Arm-strong category also 25-hydroxyvitamin D3 the state of having a negative network. DFU (77.51%) had greater levels of insufficiency and vitamin D deficiency than Non-DFU (59.2%). DFU has lower levels 25-OH-vitamin D more than the non DFU. Sufferer by small glycemic acces has decreased 25-OH-vitamin D levels. In the winter and spring, 25-OH-vitamin D levels are lowest. DF sufferer 25-OH-vitamin D level are still decreased throughout the same season ($P < 0.001$). Sufferer has Wagner quality 0 into 5 had a decreasing trend in 25-OH-vitamin D levels.	Patients with DFU are in height risk vitamin D3 laxity, hence we propose evaluating vitamin D3 levels and considering vitamin D3 therapy in this group of patients.
Tang W, Lihong Chen, Wanxia Ma, Dawei Chen, Chun Wang, Yun Gao, Xingwu Ran. ⁴⁴	2022, China, Cross-sectional	Measure relationship among vitamin D also DFU in sufferer with category 2 DM	1721 samples; 7 years	DFU (77.51%) had greater levels of insufficiency and vitamin D deficiency than Non-DFU (59.2%). DFU has lower levels 25-OH-vitamin D more than the non DFU. Sufferer by small glycemic acces has decreased 25-OH-vitamin D levels. In the winter and spring, 25-OH-vitamin D levels are lowest. DF sufferer 25-OH-vitamin D level are still decreased throughout the same season ($P < 0.001$). Sufferer has Wagner quality 0 into 5 had a decreasing trend in 25-OH-vitamin D levels.	Low serum vitamin D levels which found to be substantially related by a highest prevalence diabetic foot in Chinese individuals which category 2 diabetic.

Author	Year, Country and Design	Aim of Study	Number of Sample, Dose and Duration of Study	Result	Conclusion
Greenhagena, Robert G. Frykberg and Dane K. Wukich,	2019, USA, Cohort Study	Comparison serum vitamin D level at DM with also without CN, PAD, DFI, DFU, also DPN.	50 samples; 13 months	The amount of 25-OH-vitamin D was found to be independently related to diabetic foot. 78% of we sufferer were vitamin D deficient. After operation serum vitamin D level did not differ substantially among CN also Non-CN (p = 0.55), however sufferer have PAD, also DFU had considerably lowest serum vitamin D level than these uncomplicated diabetes sufferer. Subjects DFU had lowest serum albumin level and highest serums creatinine level.	Vitamin D serum levels lower significantly in DM accompanied by PAD, DFI, and DFU.
Karen Smith, et al.	2022, USA, Systematic Review	Examines recent discussion related to the correlation among low vitamin D level also wound healing.	10 studies, involving 2359 participants	There was a considerable association between low 25-hydroxyvitamin D levels also the occurrence of every three categories of difficult-to-treatment lesions.	According to discussion, there is a link among lowly vitamin D level also difficult-to- treat disease. However, it is valid unclear whether the association are factitive or merely correlative. Thats is now the evidence that emerges that vitamin D supplementation can help repair difficult- to treat disease. Relatively much discussion are needed fully understand relationship among vitamin D also difficult-to-treatment disease.
Urbanovych, A., & Shykula, S.	2022, Ukraine, Literature Review	The impacts vitamin D on diabetes mellitus also associated consequences, like diabetes retinopathy.		Function vitamin D in enhancing glycemic management also wound healing is underlined.	It is advised that people with diabetes mellitus be tested for vitamin D insufficiency and that this supplement be used to cure diabetes microvascular and its meaning problems.
Kurian S et al.	2021, Literatur Review	Examine function vitamin D at the treatment DFU.		Vitamin D promotes many stages of disease treatment as well hence speeds up the phases, according to preclinical and clinical research. It influences numerous cells during the	According to this study, vitamin D plays a protection effect at the immunological also circulatory systems, as well as improving glycemic outcomes also

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				proliferation also remodeling process. Vitamin D can increase the expressiveness antimicrobial peptides, which aid in the elimination of germs, and it suppresses proinflammatory short reactions promoting anti-inflammatory reactions.	wound treatment. The results, vitamin D may a favored helper at the treatment of DFU.
Macido, et al.	2018, USA, Literature Review	Diabetic Foot Ulcers and Vitamin D Status: A Literature Review	10 study	According to the available information at vitamin D also DFU, there is a negatively relationship among 25(OH)D level also the presentage of DFU. Even proof suggests a link among 25(OH)D level also diabetes foot infection.	DFU also diabetic foot infection have been link to vitamin D insufficiency.
Kamble A, Manish Swarnkar.	2019, India, Observatio nal Study	Vitamin D deficit and its impact on treatment at diabetes foot patients with also without vitamin D lack.	50 patients	Vitamin D found insufficient substantially associated by vascular calcification. A substantial difference at wound treatment was detected among sufferer with also without vitamin D lack.	This research raises the possibility of vitamin D insufficiency being a risk cause towards diabetes foot infection also recommends the necessity into vitamin D supplement.

Discussion

Randomized controlled trial (RCT) study conducted by (Alam et al., 2017; El Hajj et al., 2020; Gupta et al., 2017; Halschou-Jensen et al., 2023; Karonova et al., 2020; Mozaffari-Khosravi et al., 2016; Razzaghi et al., 2017), the dosage of vitamin D used range from 50.000 IU to 600.000 IU. Duration of study for supplementation of vitamin D from 4 weeks to 10 months. Patients involved in the studies range from 40 to 167 patients. The result of the study done by Halschou-Jensen et al. (2023) said that in stimulating medical treatment in acute diabetic foot ulcers, big dose vitamin D3 was found being more beneficial than small dose vitamin D31, Karonova et al. (2020) irregular arrangements are made study involving individuals diagnosed through typtthrough category 2 diabetic mellitus also peripheral neuropathye 2 diabetes mellitus and peripheral neuropathy, high-dose cholecalciferol supplementation was related with improvements in clinical manifestations of cutaneous microcirculation and inflammatory markers (Karonova et al., 2020). Int the RCT done by El Hajj et al. (2020) conclude that some inflammatory indicators were reduced by vitamin D treatment (CRP and TNF-Alfa) in patients with T2DM3. In the RCT done by Gupta et al. (2017) said that vitamin D therapy reduced the levels based on inflammatory

cytokines at diabetes foot patients who had a heightened reactivity to these cytokines. Razzaghi et al. (2017) conclude that administering 50.000 IU vitamin D improved wound healing and metabolic conditions in DFU, resulting in a significant increase in wound healing parameters in comparison to the placebo group (Alam et al., 2017) implemented irregularly controlled testing in which high vitamin D 600.000 IU cause substantial rise in 25(OH)D (P < 0.0001) also was effective at enhancing the standard of living in diabetic neuropathy (DN) with DFU (n=143) patients. Mozaffari-Khosravi et al. (2016) conclude in their s⁴dy if individuals with diabetic foot ulcers were given 150,000 or 300,000 IU of vitamin D, it provides ulcer repair as well vitamin D circumstances as well lowered ESR, CRP, WBC, and FBS.

5ven meta-analysis studies were conducted by (Dai et al., 2019; Dashti et al., 2021; Kinesya et al., 2023; Lin et al., 2023; Mousa et al., 2018; Wu et al., 2017; Yammine et al., 2020), when compared to DM participants without DFU, diabetics with DFU had substantially less vitamin D concentrations and a greater incidence of vitamin D insufficiency than non-ulcerated diabetic patients. Inadequate vitamin D concentrations are linked to a higher vulnerability to infections. Vitamin D can enhance macrophage phagocytosis and destroy intestinal germs, and it is a powerful inhibitor of

interferon- mediation macrophage activations. Vitamin D also emphasized T lockup proliferation also reduces the secretion of T helper category 1 cytokines, moment simultaneously increasing the productions of type 2 T cytokines help, both of which can improve wound healing characteristics (Putz et al., 2022).

In a meta-observation research, Yammine et al. (2020) discovered that DFU problems were related with considerably lower vitamin D levels. People with DFU are more prone to have significant vitamin D deficiency. The calculated average difference has 0.93 risk ratio for severe vitamin D insufficiency. Vitamin D improved treatment of streptozotocin-induced diabetes rats through inhibition of the endoplasmic reticulum as well factor B- features of gene-mediated inflammation, according to in vitro research. Individual skins fibroblasts exposed by vitamin D boosted wound healing dermal fibroblasts, indicating that the use of vitamin D could be a crucial step in enhancing wound rejuvenation and healing in vitamin D lacking patients. Vitamin D therapy may reduce the elevated levels of inflammatory cytokines found in infectious DFU (Yammine et al., 2020).

Dashti et al. (2021) in their study showed that vitamin D have close correlation to proinflammatory markers, such as TNF- α . Vitamin D ifound be able to give emphasis monocyte and T-cell proliferation. Consequently, this could result in a reduced level in inflammatory cytokine release like CRP, IL-6, also TNF- α , while increasing the production through the anti-inflammatory symbol such as IL-10. A number of researches have suggested that vitamin D may affect IL-6 production. Furthermore, vitamin D reduces TNF- α synthesis, which increases IL-6 synthesis in cells via the P38 signaling pathway.

TNF- α is a pro-inflammatory cytokine primarily synthesized by monocytes and macrophages, contributing to various physiological processes and playing a critical part in the growth of conditions such as septic shock, cancer, rheumatoid arthritis, multiple sclerosis, and other autoimmune disorders or inflammatory diseases. TNF- α is also associated with insulin resistance and obesity. Chronic hyperglycemia can stimulate monocytes and macrophages as well as pancreatic beta cells to release proinflammatory cytokines, namely TNF- α . In diabetic foot ulcers, increased TNF- α levels cause enhanced fibroblast apoptosis and reduced fibroblast proliferation, resulting in poorer ulcer processes of recovery. TNF- α also stimulates MMP (Metalloproteinase Matrix) production and activity, notably MMP-9, which promotes matrix protein and growth factor breakdown, both of which are critical elements in wound healing. As a result, the healing process becomes fragmented and disjointed. Furthermore, TNF- α suppresses TGF- β , which

encourages myofibroblasts to proliferate and generate proteins critical in extracellular matrix remodeling, for example α -SMA, category 1A collagen, also fibronectin, impairing wound healing (Dashti et al., 2021).

Cross-sectional study by Lin et al. (2023) involving 1,721 DM patients in 2022, through comparison vitamin D level at two DM patient category (DFU and non-DFU). Then, compare the ulcer healing process. The study discovered that the DFU group had a greater percentage of insufficiency and vitamin D deficiency than the non-DFU group of Wagner grade 0 to 5 patients, the study also prove that the sufferer went through vitamin D who have normal level are smaller likely to develop DFU than patients who are insufficient vitamin D (Ramasamy, 2020). Vitamin D appears to participate to cure disease process in the accompany manner: it controls inflammation while curing the disease by communication against TGF- β signal path, supporting a balanced inflammatory response while inhibiting expression of inflammatory genes to cure inflammation. Additionally, it influences vascular regeneration by enhancing the VEGF signaling induced by hypoxia, thereby increasing proangiogenic factors like VEGF-A, HIF-1 α , also angiogenin gene expressions. Moreover, vitamin D may play a role on the repair, transfer, and differentiation of the main cells of the epidermis as well their offspring, promoting reepithelialization of ulcers (Yammine et al., 2020). Moreover, vitamin D able to use enhance the based picture antimicrobial peptide genes while also preventing endoplasmic reticulum and oxidative stress. These actions have an indirect influence on disease treatment, attributed use it impacts in glycemic regulation (Wu et al., 2017).

Case control studies conducted by (Arafat et al., 2020; Çağlar et al., 2018; Feldkamp et al., 2018; F. Wang et al., 2022). F. Wang et al. (2022) conducted a case-control research on 429 DM patients with DFU and non-DFU for 10 months. The study discovered that vitamin D was strongly linked to DFU and vitamin D. According to multivariate logistic regression analysis, 25-OH-vitamin D is a self-sufficient DFU safeguarding factor [OR 95%, CI 0.984 (0.969, 0.998), $p < 0.05$]. The non-DFU and DFU groups had different distributions of 25-OH-vitamin D nutritional statuses. Vitamin D insufficiency was found in 86.78% of DFU patients but just 74.33% of non-DFU sufferer. The 25-OH-vitamin D level of DFU sufferer from Wagner's figure 1 into 5 decreased ($p < 0.01$), indicating that vitamin D are essential preventive because of use DFU. Vitamin D deficit or inadequacy can exacerbate islet cell dimension through humoral immunological mechanisms and cellular cell death, triggering unstable blood glucose control. Vitamin D insufficiency reduces NGF and impairs nutrition, promotes an inflammatory reaction in the neurological system, and accelerates the onset and progression of

neuropathy. DFU patients are less active and have a shorter duration in the sun, resulting in a vitamin D shortage or deficiency. Vitamin D can suppress T helper type 1 cytokine release while enhancing cytokine synthesis, which can speed up wound healing.

There are four systematic literature review conducted by (Kurian et al., 2021; Macido, 2018; Smith & Hewlings, 2021; Urbanovych & Shykula, 2022). Kurian et al. (2021) discovered that vitamin D has an impact on many phases of wound healing. Vitamin D affects cells engaged in the inflammatory, proliferative, and transformation procedures. Vitamin D also boosts the development of antimicrobial peptides (AMP), which aid in the elimination of microorganisms, as well as the anti-inflammatory response (Kurian et al., 2021; Macido, 2018; Smith & Hewlings, 2021; Urbanovych & Shykula, 2022). Çağlar et al. (2018) discovered who have some diabetic foots higher level of osteo-protegerin also lower levels of vitamin D compared control group, suggesting that vitamin D administration may help the DFU healing process. In addition, another study conducted by Feldkam et al.20 discovered that vitamin D level at DFU patients are smaller comparing in the DM patient group that did not have DFU. hen, according to Alam U et al.,6 vitamin D therapy can increase the wound healing process in DFU patients.

Conclusion

In diabetics, DFU has a substantial connection with reduced serum vitamin D levels. DM Patients with DFU relatively able vitamin D deficient than DM without DFU. Vitamin D works on diabetic foot wound inflammation, immunity, phagocytosis, granulation, and remodeling (Azizieh et al., 2016; Hewison, 2011; Schauber & Gallo, 2008; Tiwari et al., 2014).^{24,14,36,45-48} Vitamin D can be an opportunity in increasing DFU healing because vitamin D helps to prevent and accelerate wound healing in DFU patients by regulating AMP expression, reducing the imbalance in MMP-9/TIMP-1 levels in the ECM proteolysis process, decreases inflammatory cytokine levels such as TNF- α and IL-6 thereby reducing tissue inflammation, and increases VEGF thereby increasing nutrient intake for repair of damaged tissue. More research at the function of Vitamin D as extra healing on DM sufferer for avoid DFU and promote wound healing is required.

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Conflicts of Interest

The authors declare no conflict of interest.

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