

# Diabetic Foot Ulcers and Vitamin D Status: A Literature Review

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## Abstract

Approximately 15% of patients with diabetes mellitus (DM) are prone to developing diabetic foot ulcers (DFU) in their lifetime. The term vitamin D status or 25-hydroxyvitamin D (25(OH)D) levels is used interchangeably to represent the status of vitamin D in individuals throughout this article. Evidence suggests a relationship between 25(OH)D levels and DFU. However, very minimal data are available on the association between DFU and vitamin D deficiency. After a careful review of the literature, it was inferred that vitamin D could be associated with DFU and diabetic foot infections. Available evidence on vitamin D and DFU suggests a negative correlation between 25(OH)D levels and the presence of DFU. Evidence also supports a negative relationship between 25(OH)D levels and diabetic foot infections. Further large-scale randomized controlled studies need to be done to confirm the relationship between 25(OH)D levels and DFU including the use of vitamin D in the management of DFU and diabetic foot infections.

## Keywords

vitamin D status, 1, 25-dihydroxyvitamin D, diabetic foot ulcers, diabetic foot infections

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According to Armstrong, Boulton, and Bus (2017), diabetic foot ulcer (DFU) is the most frequent complication of the lower extremity associated with diabetes mellitus (DM). According to the Centers for Disease Control and Prevention (2014), DFU accounted for about 113,000 hospitalizations in the United States in 2007. Infected DFU is one of the common causes of hospitalization related to DM, and it accounts for 20% of hospital admissions (Frykberg, Wittmayer, & Zgonis, 2007). Every half a minute, someone in the world loses a lower extremity secondary to DM (Khatib & Tabatabaei-Malazy, 2007). The most common cause of lower extremity amputation in developed countries is DM (Leone, Pascale, Vitale, & Esposito, 2012).

The risk of mortality in 5 years in a patient with DM who also has DFU is 2.5 times higher than the 5-year mortality risk in a patient with DM and no DFU (Armstrong et al., 2017). The most common cause of lower extremity amputation in patients with DM is DFU, and DFU often contributes to disability (Ghanassia et al., 2008). Evidence shows poor quality of life related to health in patients with DFU when compared with non-DM patients and DM patients

without DFU (Ribu, Hanestad, Moum, Birkeland, & Rustoen, 2007).

## Risk Factors for Developing DFU

Peripheral vascular disease and diabetic neuropathy are the important risk factors associated with the development of DFU (Sinwar, 2015). In addition to diabetic neuropathy and peripheral vascular disease, foot deformities and prior history DFU are risk factors associated with the development of DFU (Monteiro-Soares, Boyko, Ribeiro, Ribeiro, & Dinis-Ribeiro, 2012). Furthermore, oxidative stress and inflammation have an important role in the pathogenesis of DFU (Sytze Van Dam, Cotter, Bravenboer, & Cameron, 2013). The role of 25-hydroxyvitamin D (25(OH)D) levels in oxidative stress and inflammation has been studied recently (Asemi,

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Hashemi, Karamali, Samimi, & Esmailzadeh, 2013; Zubair, Malik, Meerza, & Ahmad, 2013). Treatment with vitamin D in type 2 DM has been associated with improved glycemic control (Lee et al., 2017). Can vitamin D be used as a game changer in the treatment and prevention of DFU and diabetic foot infections?

## Vitamin D Metabolism

A review of vitamin D metabolism is essential to understand how vitamin D is utilized in the body and the role of vitamin D in the pathophysiology and potential management of DFU and diabetic foot infections. Vitamin D is obtained from foods that contain vitamin D and is also produced in the skin with exposure to sunlight. Sunlight causes conversion of 7-dehydrocholesterol in the skin to produce previtamin D<sub>3</sub>. Previtamin D<sub>3</sub> in the skin can undergo membrane-enhanced isomerization into vitamin D<sub>3</sub> aided by heat versus photoconversion to tachysterol, lumisterol, and 7-dehydrocholesterol. Vitamin D<sub>3</sub> also referred to as cholecalciferol is expelled from the keratinocyte plasma membrane, which is absorbed into the dermal capillary bed with the help of vitamin D-binding protein (DBP). Vitamin D<sub>2</sub> also known as ergocalciferol is obtained from yeast and mushrooms exposed to sunlight (Norris, 2018). Ingested vitamin D is absorbed into chylomicrons that are dispersed into the lymphatic system and goes to the venous blood. In the venous blood, vitamin D binds with lipoproteins and DBP and is transported to the liver (Hosseini-Nezhad & Holick, 2013).

Vitamin D<sub>3</sub> and vitamin D<sub>2</sub> are hydroxylated by vitamin-25-hydroxylase (CYP2R1) in the liver to produce 25(OH)D, the major vitamin D metabolite found in circulation that is used to determine vitamin D status in individuals. The 25(OH)D encounters further hydroxylation in the kidneys aided by 25(OH)D-1 $\alpha$ -hydroxylase (CYP27B1) to form 1,25-dihydroxy vitamin D [1,25-(OH)<sub>2</sub>D]. The DBP bound 25(OH)D undergoes renal filtration followed by reabsorption in the renal tubules by receptors called megalin-cubilin receptors. The 1 $\alpha$ -hydroxylation of 25(OH)D is increased by hypocalcemia, hypophosphatemia, and parathyroid hormone while inhibited by fibroblast growth factor-23, hyperphosphatemia, and 1,25-(OH)<sub>2</sub>D (Hosseini-Nezhad & Holick, 2013).

The active metabolite of vitamin D is 1,25-(OH)<sub>2</sub>D that exerts its effects by binding to nuclear vitamin D receptor (VDR) found in a variety of cells in the body. The 1,25-(OH)<sub>2</sub>D binds to nuclear VDR that in turn binds retinoic acid X receptor producing a heterodimeric complex, which binds to specific sequences of nucleotides in the DNA referred to as vitamin D response elements. Vitamin D plays an important role in maintaining serum phosphorus and calcium levels within normal ranges. The 1,25-(OH)<sub>2</sub>D binds with VDR located in the small

intestine to increase calcium and phosphorus absorption. The 1,25-(OH)<sub>2</sub>D also binds with osteoblasts (bone-forming cells) that stimulate a receptor activator for nuclear factor- $\kappa$ B ligand that further relates with receptor activator of the nuclear factor- $\kappa$ B on preosteoclasts that are immature while stimulating them to change to mature osteoclasts (bone-resorbing cells). The mature osteoclasts aid in removing phosphorus and calcium from the bone to maintain appropriate serum calcium and phosphorus levels. Meanwhile, renal reabsorption of calcium is stimulated by 1,25-(OH)<sub>2</sub>D. There are almost 2,000 genes that are regulated by 1,25-(OH)<sub>2</sub>D and has a myriad of functions including inducing terminal cell differentiation, stimulating insulin production, inhibiting angiogenesis, stimulating macrophage cathelicidin production, inducing apoptosis, and inhibiting renin production (Hosseini-Nezhad & Holick, 2013).

## Literature Search Strategies

The objective of the literature search was to identify all the available original research studies that involved topics including vitamin D deficiency in DM and DFU; the use of vitamin D in DFU; the prevalence of DFU, glycemic control, and vitamin D status; and so on. Most of the literature search was done using the major electronic databases including Cumulative Index to Nursing and Allied Health Literature, Medical Literature On-Line, Cochrane Library, and ProQuest. The search criteria were refined to full-text and peer-reviewed articles. The Boolean operators such as "AND," and the truncation symbol asterisk was also employed for searching the articles.

## Synthesis of Evidence

### *Vitamin D Status and DFUs*

Vitamin D is a pleiotropic micronutrient that is fat soluble. The active form of vitamin D, 1,25-(OH)<sub>2</sub>D functions as a ligand for an intracellular receptor and transcription factor VDR (Rosen et al., 2012; Vanchinathan & Lim, 2012). Most of the effects of vitamin D as 1,25-(OH)<sub>2</sub>D are mediated by VDR (Rosen et al., 2012). Vitamin D has nonskeletal effects that include effects on the skin. The skin contains all the units of the regulatory system of vitamin D, and vitamin D plays a key role in maintaining hair follicles and the skin barrier (Rosen et al., 2012). Vitamin D as 1,25-(OH)<sub>2</sub>D exerts prodifferentiative and antiproliferative effects on the keratinocytes on the skin (Bikle et al., 2004) that in turn provides defense against toxins and pathogens while preventing water loss from the skin (Rosen et al., 2012).

Studies have shown low levels of circulating 25(OH)D in patients with DFU (Asemi et al., 2013; Tiwari et al., 2013;

Zubair et al., 2013). Low levels of circulating 25(OH)D can cause increased concentrations of inflammatory cytokines in patients with DFU and delay wound healing (Tiwari, Pratyush, Gupta, & Singh, 2014). Evidence from prior studies has concluded favorable effects of vitamin D in the healing of DFU (Gonzalez-Curiel et al., 2014; Razzaghi et al., 2017). Keratinocytes around a wound produce increased expression of the genes responsible for microbial pattern recognition receptors such as toll-like receptors that in turn results in increased expression of the antimicrobial peptide cathelicidin. The genes responsible for increased cathelicidin production are induced by 1,25-(OH)<sub>2</sub>D (Schauber et al., 2007). Cathelicidin is an antimicrobial peptide that promotes wound healing (Gonzalez-Curiel et al., 2014; Zhang, Wu, & Sun, 2013). Based on the literature available on vitamin D and DFU, three themes are identified below.

*Vitamin D Status and DFU.* Two studies reported a relationship between vitamin D deficiency and the presence of DFU. A prospective cohort hospital-based study by Zubair et al. (2013) revealed that the patients with DFU had a lower median serum level of 25(OH)D when compared with the patients without DFU (6.3 [4.2–11.1] vs. 28.0 [21.4–37.0] ng/ml). The study compared 162 diabetic patients with foot ulcers and 162 diabetic patients with no foot ulcers. The study also highlighted possible outcomes including a possible relationship between deficiency of vitamin D and DFU (Zubair et al., 2013). The study by Tiwari et al. (2013) also showed relatively lower 25(OH)D levels in patients with DFU as compared with those without DFU.

*Vitamin D deficiency and diabetic foot infections.* Evidence suggests a relationship between low 25(OH)D levels and the presence of diabetic foot infections. Although the prevalence of hypovitaminosis D is more in patients with DM, the magnitude of vitamin D deficiency was noticed to be more in patients with infected DFU (Kota, Meher, Jammula, & Modi, 2013; Tiwari et al., 2013; Tiwari, Pratyush, Gupta, & Singh, 2014). The study by Tiwari et al. (2013) identified a cutoff value for 25(OH)D levels in patients with DM that put them at risk for developing diabetic foot infections. The study objective was to evaluate the severity and presence of vitamin D deficiency in diabetic foot infections. The study showed that the cases had significantly low levels of 25(OH)D than the controls (40.25 [*SD* 38.35] vs. 50.75 [*SD* 33.00];  $p < .001$ ; Tiwari et al., 2013). The “study has 99% power to define 25(OH)D < 10 ng/ml as the risk point for diabetic foot infection” (Tiwari et al., 2013, p. 101). The authors convey that severe deficiency of vitamin D can be a contributing factor toward diabetic foot infections, and supplementation of vitamin D

may provide better clinical outcomes (Tiwari et al., 2013).

Tiwari, Pratyush, Gupta, and Singh (2014) showed increased concentrations of inflammatory cytokines with severe deficiency of vitamin D. Deficiency of vitamin D increases the risk of diabetic foot infections possibly because of dysregulation of the immune system (Tiwari, Pratyush, Gupta, & Singh, 2014). The decreased defense against pathogens with low 25(OH)D levels (Bikle et al., 2004) could be another reason for the increased incidence of diabetic foot infections with vitamin D deficiency.

*Vitamin D in the Management of DFU.* The potential for using vitamin D for the clinical management of DFU has been discussed in the literature. A prospective, randomized, double-blind, placebo-controlled clinical trial by Razzaghi et al. (2017) suggested that vitamin D supplementation may have an indirect role in the healing of DFU because of its beneficial effect on improving glycemic control. The authors mention significant reduction in ulcer length ( $-2.1 \pm 1.1$  vs.  $-1.1 \pm 1.1$  cm,  $p = .001$ ), width ( $-2.0 \pm 1.2$  vs.  $-1.1 \pm 1.0$  cm,  $p = .02$ ), and depth ( $-1.0 \pm 0.5$  vs.  $-0.5 \pm 0.5$  cm,  $p < .001$ ) with vitamin D supplementation when compared with placebo therapy (Razzaghi et al., 2017). Vitamin D supplements can also help reduce inflammatory cytokines in patients with DFU, and vitamin D supplements can be considered as a treatment strategy for infection control and faster healing of DFU (Gupta, Dwivedi, & Singh, 2017).

A study by Gonzalez-Curiel et al. (2014) demonstrated the possible therapeutic use of keratinocyte-conditioned medium from stimulated DFU cells with 1,25-(OH)<sub>2</sub>D<sub>3</sub> in the treatment of DFU. The results revealed that primary culture from DFU managed with 1,25-(OH)<sub>2</sub>D<sub>3</sub> showed increased human cathelicidin antimicrobial peptide and defensin, beta 4 genes. Treatment with 1,25-(OH)<sub>2</sub>D<sub>3</sub> also increased the formation of cathelicidin (LL-37) and human  $\beta$ -defensin-2 in the culture supernatant. Stimulation of culture media with 1,25-(OH)<sub>2</sub>D<sub>3</sub> produced up to 100 ng/ml of LL-37, reaching close to the detected values of healthy controls (Gonzalez-Curiel et al., 2014). The healing process that involves migration, proliferation, as well as differentiation of epidermal keratinocytes and dermal fibroblasts is stimulated by human  $\beta$ -defensin-2 (Niyonsaba et al., 2007). Keratinocyte migration and angiogenesis are stimulated by LL-37 (Koczulla et al., 2003). Although the study sample by Gonzalez-Curiel et al. (2014) was small, the findings of the study promise the potential use of keratinocyte-conditioned medium from stimulated DFU cells with 1,25-(OH)<sub>2</sub>D<sub>3</sub> in the management of DFU. A study done decades ago on the topical use of 1,25-(OH)<sub>2</sub>D<sub>3</sub> concluded that 1,25-(OH)<sub>2</sub>D<sub>3</sub> analogs may

arise as a new category of compounds that could be used in the healing of wounds in the future (Tian, Chen, & Holick, 1995).

### Critique of the Evidence

Based on the review of the literature on vitamin D and DFU, it was concluded that there is only minimal literature available on the subject. Three relevant articles on the proposed subject are reviewed here.

#### Razzaghi et al.'s Study

The essence of this study is the potential use of vitamin D supplements in the clinical management of DFU. The study is a prospective, randomized, double-blind, placebo-controlled clinical trial. The intervention group received 50,000 international units (IU) of vitamin D biweekly for 12 weeks. Vitamin D supplementation resulted in a significant improvement in the serum 25(OH)D levels of the intervention group ( $+12.9 \pm 10.0$  vs.  $-1.8 \pm 15.7$  ng/ml,  $p < .001$ ). The authors suggest that vitamin D supplementation may have an indirect role in the healing of DFU because of its beneficial effect on improving glycemic control (Razzaghi et al., 2017). Please see Appendix A for the detailed matrix.

**Method.** The trial was done by following the Declaration of Helsinki after getting informed consent from the subjects, and it was favored by the ethics committee at the research facility (Razzaghi et al., 2017). The study population and the sample are clearly defined in this study. Although the sample size was adequate ( $N = 60$ , 30 controls and 30 intervention) based on a power analysis, the authors suggest that the sample size is relatively small. The authors measured the key variables using appropriate methods. The researchers describe specific instruments used in the study and the use of stringent methods for data collection by trained staff. The authors described the interventions adequately and did not mention any biases involved in data collection.

**Results.** The researchers employed appropriate statistical analyses based on the levels of measurement involved and the number of groups compared. The authors did not clearly mention the measures taken to avoid Type I and Type II errors. The authors reported statistical significance of all the findings and summarized the findings using tables. However, the authors do not mention the precision of the estimates or the effect size.

The findings were presented in a way that can facilitate a meta-analysis.

#### Zubair et al.'s Study

The objective of the study was to identify the potential relationship between vitamin D deficiency and DFU. The study was a prospective cohort hospital-based study that compared 162 diabetic patients with foot ulcers and 162 diabetic patients with no foot ulcers. Individuals with DFU had a median lower level of plasma 25(OH)D when compared with the control group (6.3 [4.2–11.1] vs. 28.0 [21.4–37.0] ng/ml) after adjusting the basic metabolic index and age (Zubair et al., 2013). Please see Appendix A for the detailed matrix.

**Method.** The trial was done by following the Declaration of Helsinki after getting informed consent from the subjects (Zubair et al., 2013). The authors clearly identify the population and the sample. The sampling was not randomized, and the sample was regarded as relatively large (Zubair et al., 2013). The authors do not mention any power analysis involved in determining the sample size. The authors measured the key variables using appropriate methods and did not mention any bias involved in data collection.

**Results.** The researchers employed appropriate statistical analyses based on the levels of measurement involved and the number of groups compared. The authors did not clearly mention the measures taken to avoid Type I and Type II errors. The authors reported statistical significance of all the findings and summarized the findings using tables. The authors did mention the precision of the estimates and the effect size with odds ratios and relative risks with confidence intervals. The findings were presented in a way that can facilitate a meta-analysis.

#### Tiwari et al.'s Study

The study identified a cutoff value for 25(OH)D levels in patients with DM that put them at risk for developing diabetic foot infections. The study is a prospective cohort research study that involved a sample of 289 subjects that compared 125 diabetic subjects with diabetic foot infection to 164 diabetic patients without diabetic foot infection at two hospital-based clinics in India (Tiwari et al., 2013). Please see Appendix A for the detailed matrix.

**Method.** The trial was done by following the Declaration of Helsinki after getting informed consent from the subjects, and the study was approved by the Banaras Hindu University Institute Ethics Committee (Tiwari et al., 2013). The authors had clearly identified the population and the sample, and the sampling was not randomized (Tiwari et al., 2013). The authors did not mention any power analysis involved in the study. The key variables are measured using appropriate methods, and the interventions are described adequately.

**Results.** The researchers employed appropriate statistical analyses based on the levels of measurement involved and the number of groups compared. The authors did not mention any measures taken to avoid Type I and Type II errors. The authors reported statistical significance of all the findings and summarized the findings using tables. The authors did mention the precision of the estimates and the effect size with odds ratio and with confidence interval. The findings were presented in a way that can facilitate a meta-analysis.

## Gaps in Evidence

Based on the review of the literature, it is obvious that adequate evidence is not available to support the relationship between hypovitaminosis D and DFU. However, after a careful review of the literature, it can be inferred that vitamin D deficiency has been associated with DFU and diabetic foot infections. Available evidence on vitamin D and DFU suggests a negative correlation between 25(OH)D levels and the presence of DFU. Evidence also supports a negative relationship between 25(OH)D levels and diabetic foot infections. Interestingly, a study by Afarideh et al. (2016) showed an increase in circulating 25(OH)D levels in patients with active chronic DFU. As stated by the authors, this is the only study that showed increased 25(OH)D levels with DFU (Afarideh et al., 2016). The conflicting finding by Afarideh et al. (2016) suggests further clarification of the results. Further large-scale randomized controlled studies are necessary to confirm the relationship between 25(OH)D levels and DFU.

The literature available on vitamin D and DFU suggests vitamin D supplements to have the potential to accelerate the healing of DFU. Nevertheless, the literature does not recommend any specific dosage for vitamin D supplements for use in DFU. Literature supports an

increased risk of diabetic foot infections with hypovitaminosis D. However, it is hard to find any literature that addresses the prophylactic use of vitamin D supplements in DM to prevent DFU or in DFU to prevent diabetic foot infections. The literature on vitamin D supplementation to improve wound healing is not sufficient to suggest that vitamin D supplementation alone improves wound healing. For example, Razzaghi et al. (2017) highlight that vitamin D may have an indirect effect on the healing of DFU because of its effects on improving serum glucose levels.

The Endocrine Society defines vitamin D deficiency as a serum 25(OH)D less than 20 ng/ml. Measuring serum 25(OH)D is the recommended assay for diagnosing vitamin D deficiency. The recommended treatment for vitamin D deficiency can be done with either vitamin D3 or vitamin D2 (Holick et al., 2011). The treatment for vitamin D deficiency is guided by the age-group, the presence of comorbidities, and so on. There are no current recommendations on vitamin D dosage for individuals with DFU who also have vitamin D deficiency. Adults who are vitamin D deficient should be treated with 6,000 IU of vitamin D2 or D3 daily for 8 weeks to achieve a serum 25(OH)D level of more than 30 ng/ml, and thereafter to be continued on 1,500 to 2,000 IU daily for maintenance therapy (Holick et al., 2011).

## Conclusion

In conclusion, very minimal data are available on the association between DFU and vitamin D deficiency (Zubair et al., 2013). There are insufficient data available on the presence of any standardized measures or guidelines about the correlation of low 25(OH)D levels with DFU and the significance of vitamin D in DFU. Data available on DM and DFU do not comment on the recommendations on vitamin D use in the prevention and treatment of DFU. Literature does not support the routine use of vitamin D in the treatment and prevention of diabetic foot infections. The literature available on the different types of DM and the role of vitamin D in the development of DFU is scarce. Further research is needed to confirm the relationship between DFU and vitamin D including the use of vitamin D in the management of DFU and diabetic foot infections. Despite the lack of strong evidence to recommending vitamin D in DM and DFU, it is not a bad idea to provide routine vitamin D supplements to patients with DM and DFU for its other benefits.

## Appendix A

Table A1. Literature Review Matrix.

Author (year)	Purpose	Sample	Design	Data analysis	Findings	Strengths and weaknesses
Razzaghi et al. (2017)	The study focused on the clinical question of the effects of vitamin D in aiding the healing of DFU and optimizing metabolic status in patients with DFU	The study included a sample of 60 subjects (30 intervention and 30 placebo) between ages 40 and 85 years with grade three DFU who visited the Shahid Beheshti Clinic in Iran. The study excluded those who were taking vitamin supplements previously, pregnant and breastfeeding, and other conditions that predispose to DFU. The sampling was randomized. The intervention group received 50,000 international units of vitamin D biweekly for 12 weeks	The study was a prospective randomized, double-blind placebo-controlled clinical trial	The authors used Kolmogorov–Smirnov test to confirm the normal distribution of variables. The intention-to-treat principle was employed in the analyses. The researchers used the Last-Observation-Carried-Forward method to address missing values. The authors used one-way repeated measures ANOVA to determine the effects of vitamin D on the dependent variables (Razzaghi et al., 2017). A repeated measures ANOVA is apt when variables are to be measured repeatedly over a period (Kim & Mallory, 2017). The researchers used Student's <i>t</i> test to detect differences in anthropometric measures and nutrient intake between the study group and the control group. Paired samples <i>t</i> tests were employed to identify differences in variables within the group. Differences in nominal variables within the group were done with McNemar's test. The <i>p</i> value was set < .05 for all the calculations (Razzaghi et al., 2017).	Vitamin D supplementation resulted in a significant improvement in the serum 25(OH)D levels of the intervention group ( $+12.9 \pm 10.0$ vs. $-1.8 \pm 15.7$ ng/ml, $p < .001$ ). The authors mention significant reduction in ulcer length ( $-2.1 \pm 1.1$ vs. $-1.1 \pm 1.1$ cm, $p = .001$ ), width ( $-2.0 \pm 1.2$ vs. $-1.1 \pm 1.0$ cm, $p = .02$ ) and depth ( $-1.0 \pm 0.5$ vs. $-0.5 \pm 0.5$ cm, $p < .001$ ) with vitamin D supplementation when compared with placebo therapy. The authors also mention a significant reduction in biomarkers of insulin resistance including the homeostasis model of assessment-insulin resistance ( $-1.5 \pm 4.1$ vs. $+1.7 \pm 5.1$ , $p = .01$ ) in the treatment group	The authors indicate the strength of their recommendations by mentioning that this is the first randomized, double-blind, placebo-controlled trial that evaluated the effects of vitamin D supplementation on patients with DFU. The study design is rigorous, provided the goals of the study. Nevertheless, the authors convey the need for further similar studies including larger samples to confirm the results of the study

(continued)

Table A1. Continued.

Author (year)	Purpose	Sample	Design	Data analysis	Findings	Strengths and weaknesses
Zubair et al. (2013)	The study addressed a focused clinical question of comparing blood levels of 25(OH)D in participants with DFU and those without DFU	The study compared 162 diabetic patients with foot ulcers and 162 diabetic patients with no foot ulcers in a hospital in India. The sampling was not randomized	The study was a prospective cohort study based in a hospital	The authors used the Shapiro–Wilk test to confirm the normal distribution of variables. The authors calculated group differences with Student <i>t</i> test and non-parametric Mann–Whitney tests as appropriate. The researchers used multiple linear regression, logistic forward regression, and $\chi^2$ to analyze the relationship between the inflammatory parameters and the variables that predicted the development of DFU. The researchers also estimated the risk of DFU development with risk ratios and ORs with a confidence interval of 95%. The <i>p</i> value was set < .05 for all the calculations (Zubair et al., 2013)	The study revealed that the patients with DFU had a lower median serum level of 25 (OH)D when compared with the patients without DFU (6.3 [4.2–11.1] vs. 28.0 [21.4–37.0] ng/ml) (Zubair et al., 2013)	The authors indicate the strength of their recommendations including analysis of a relatively large study population and the availability of data on potential confounders to run multiple regression analyses to assess the impact of confounders on the results of the study (Zubair et al., 2013). The study design is not rigorous, provided the goals of the study. The sampling was not randomized. Although, the authors claim the sample to be relatively large (Zubair et al., 2013), they did not mention any power analysis involved in determining the sample size
Tiwari et al. (2013)	The study was focused on the clinical question of evaluating the presence and magnitude of deficiency of vitamin D in patients with diabetic foot infections	The study involved a sample of 289 subjects that compared 125 diabetic subjects with diabetic foot infection to 164 diabetic patients without diabetic foot infection at two hospital-based clinics in India. The sampling was not randomized	The study was a prospective cohort study	The authors used the Shapiro–Wilk test to confirm the normal distribution of variables. The authors calculated group differences with independent <i>t</i> tests. The researchers calculated OR for three cutoffs of deficiency in vitamin D to predict the risk point for infection of a diabetic foot. The <i>p</i> value was set < .05 for all the calculations (Tiwari et al., 2013)	The study showed that the cases had significantly low levels of vitamin D than the controls (40.25 [SD 38.35] vs. 50.75 [SD 33.00]; <i>p</i> < .001; Tiwari et al., 2013)	The authors indicate the strength in their recommendations by stating that the “study has 99 % power to define 25(OH)D < 10 ng/ml as the risk point for diabetic foot infection” (Tiwari et al., 2013, p. 101). The authors also mention that the strength of their study is reflected in identifying the vitamin D cutoff value of less than 10 ng/ml for immune dysfunction and compromised defense

(continued)

Table A1. Continued.

Author (year)	Purpose	Sample	Design	Data analysis	Findings	Strengths and weaknesses
						against bacterial invasions (Tiwari et al., 2013). The sampling was not randomized (Tiwari et al., 2013). The authors do not mention any power analysis involved in determining the sample size

Note. ANOVA = analysis of variance; DFU = diabetic foot ulcer; 25(OH)D = 25-hydroxyvitamin D; OR = odds ratio; SD = standard deviation.

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### References

- Afarideh, M., Ghanbari, P., Noshad, S., Ghajar, A., Nakhjavani, M., & Esteghamati, A. (2016). Raised serum 25-hydroxyvitamin D levels in patients with active diabetic foot ulcers. *The British Journal of Nutrition*, *115*(11), 1938–1946. doi:10.1017/S0007114516001094.
- Armstrong, D. G., Boulton, A. M., & Bus, S. A. (2017). Diabetic foot ulcers and their recurrence. *New England Journal of Medicine*, *376*(24), 2367–2375. doi:10.1056/NEJMr1615439.
- Asemi, Z., Hashemi, T., Karamali, M., Samimi, M., & Esmailzadeh, A. (2013). Effects of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation, and oxidative stress in gestational diabetes: A double-blind randomized controlled clinical trial. *American Journal of Clinical Nutrition*, *98*(6), 1425–1432. doi:10.3945/ajcn.113.072785.
- Bikle, D., Chang, S., Crumrine, D., Elalieh, H., Man, M., Choi, E., . . . , Elias, P. (2004). 25 Hydroxyvitamin D 1  $\alpha$ -hydroxylase is required for optimal epidermal differentiation and permeability barrier homeostasis. *Journal of Investigative Dermatology*, *122*(4), 984–992. doi:10.1111/j.0022-202X.2004.22424.x.
- Centers for Disease Control and Prevention. (2014). *Diabetes public health resource*. Retrieved from [https://www.cdc.gov/diabetes/statistics/hosp/plea/diabetes\\_complications/fig1\\_number.htm](https://www.cdc.gov/diabetes/statistics/hosp/plea/diabetes_complications/fig1_number.htm).
- Frykberg, R. G., Wittmayer, B., & Zgonis, T. (2007). Surgical management of diabetic foot infections and osteomyelitis. *Clinics in Podiatric Medicine and Surgery*, *24*(3), 469–482. doi:10.1016/j.cpm.2007.04.001.
- Ghanassia, E., Villon, L., Dit Dieudonne, J. T., Boegner, C., Avignon, A., & Sultan, A. (2008). Long-term outcome and disability of diabetic patients hospitalized for diabetic foot ulcers: A 6.5-year follow-up study. *Diabetes Care*, *31*(7), 1288–1292. doi:10.2337/dc07-2145.
- Gonzalez-Curiel, I., Trujillo, V., Montoya-Rosales, A., Rincon, K., Rivas-Calderon, B., deHaro-Acosta, J., . . . , Rivas-Santiago, B. (2014). 1,25-Dihydroxyvitamin D3 induces LL-37 and HBD-2 production in keratinocytes from diabetic foot ulcers promoting wound healing: An in vitro model. *PLoS One*, *9*(10), e111355. doi:10.1371/journal.pone.0111355.
- Gupta, B., Dwivedi, A., & Singh, S. K. (2017). Effect of vitamin D supplementation on cytokines expression in patients with diabetic foot infection. *Indian Journal of Endocrinology & Metabolism*, *21*, 49–49. Retrieved from <http://eds.b.ebs-cohost.com.proxy.library.maryville.edu/ehost/pdfviewer/pdfviewer?vid=6&sid=a2e631c7-6081-46df-a132-43ca4d3047ec%40sessionmgr102>.
- Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., . . . , Weaver, C. M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, *96*(7), 1911–1930. doi:10.1210/jc.2011-0385.
- Hossein-Nezhad, A., & Holick, M. F. (2013). Vitamin D for health: A global perspective. *Mayo Clinic Proceedings*, *88*(7), 720–755. doi:10.1016/j.mayocp.2013.05.011.
- Khatib, O., & Tabatabaei-Malazy, O. (2007). Prevention and public approach to diabetic foot. *Iranian Journal of Diabetes and Metabolism*, *7*(2), 123–133. Retrieved from [http://ijddl.tums.ac.ir/browse.php?a\\_id=276&sid=1&slc\\_lang=en](http://ijddl.tums.ac.ir/browse.php?a_id=276&sid=1&slc_lang=en).
- Kim, M., & Mallory, C. (2017). *Statistics for evidence-based practice in nursing* (2nd ed.). Burlington, MA: Jones & Bartlett.
- Kocuzulla, R., von Degenfeld, G., Kupatt, C., Krötz, F., Zahler, S., Gloe, T., . . . , Bals, R. (2003). An angiogenic role for the

- human peptide antibiotic LL-37/hCAP-18. *The Journal of Clinical Investigation*, 111(11), 1665–1672. doi:10.1172/JCI200317545.
- Kota, S. K., Meher, L. K., Jammula, S., & Modi, K. D. (2013). Inflammatory markers in diabetic foot and impact of vitamin D deficiency. *Endocrine Abstracts*, 31, 198. doi:10.1530/endoabs.31.P198.
- Lee, C. J., Iyer, G., Liu, Y., Kalyani, R. R., Bamba, N., Ligon, C. B., . . . , Mathioudakis, N. (2017). The effect of vitamin D supplementation on glucose metabolism in type 2 diabetes mellitus: A systematic review and meta-analysis of intervention studies. *Journal of Diabetes and Its Complications*, 31(7), 1115–1126. doi:10.1016/j.jdiacomp.2017.04.019.
- Leone, S., Pascale, R., & Esposito, S. (2012). Epidemiology of diabetic foot. *Infezioni in Medicina*, 20(Suppl. 1): 8–13.
- Monteiro-Soares, M., Boyko, E., Ribeiro, J., Ribeiro, I., & Dinis-Ribeiro, M. (2012). Predictive factors for diabetic foot ulceration: A systematic review. *Diabetes/Metabolism Research & Reviews*, 28(7), 574–600. doi:10.1002/dmrr.2319.
- Niyonsaba, F., Ushio, H., Nakano, N., Ng, W., Sayama, K., Hashimoto, K., . . . , Ogawa, H. (2007). Antimicrobial peptides human beta-defensins stimulate epidermal keratinocyte migration, proliferation and production of proinflammatory cytokines and chemokines. *The Journal of Investigative Dermatology*, 127(3), 594–604. doi:10.1038/sj.jid.5700599.
- Norris, J. (2018). *Vitamin D part 2: Research*. Retrieved from <https://veganhealth.org/vitamin-d-part-2-the-research/#d2d3>.
- Razzaghi, R., Pourbagheri, H., Momen-Heravi, M., Bahmani, F., Shadi, J., Soleimani, Z., & Asemi, Z. (2017). The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. *Journal of Diabetes and its Complications*, 31(4), 766–772. doi:10.1016/j.jdiacomp.2016.06.017.
- Ribu, L., Hanestad, B. R., Moum, T., Birkeland, K., & Rustoen, T. (2007). A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population. *Quality of Life Research*, 16(2), 179–189. doi:10.1007/s11136-006-0031-y.
- Rosen, C. J., Adams, J. S., Bikle, D. D., Black, D. M., Demay, M. B., Manson, J. E., . . . , Kovacs, C. S. (2012). The non-skeletal effects of vitamin D: An Endocrine Society scientific statement. *Endocrine Reviews*, 33(3), 456–492. doi:10.1210/er.2012-1000.
- Schauber, J., Dorschner, R. A., Coda, A. B., Büchau, A. S., Liu, P. T., Kiken, D., . . . , Gallo, R. L. (2007). Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. *The Journal of Clinical Investigation*, 117(3), 803–811. doi:10.1172/JCI30142.
- Sinwar, P. D. (2015). The diabetic foot management: Recent advance. *International Journal of Surgery*, 15, 27–30. doi:10.1016/j.ijssu.2015.01.023.
- Sytze Van Dam, P., Cotter, M. A., Bravenboer, B., & Cameron, N. E. (2013). Review: Pathogenesis of diabetic neuropathy: Focus on neurovascular mechanisms. *European Journal of Pharmacology*, 719(1–3), 180–186. doi:10.1016/j.ejphar.2013.07.017.
- Tian, X. Q., Chen, T. C., & Holick, M. F. (1995). 1,25-Dihydroxyvitamin D<sub>3</sub>: A novel agent for enhancing wound healing. *Journal of Cellular Biochemistry*, 59(1), 53–56. doi:10.1002/jcb.240590107.
- Tiwari, S., Pratyush, D. D., Gupta, B., Dwivedi, A., Chaudhary, S., Rayicherla, R. K., . . . , Singh, S. K. (2013). Prevalence and severity of vitamin D deficiency in patients with diabetic foot infection. *British Journal of Nutrition*, 109(1), 99–102. doi:10.1017/S0007114512000578.
- Tiwari, S., Pratyush, D. D., Gupta, S. K., & Singh, S. K. (2014). Vitamin D deficiency is associated with inflammatory cytokine concentrations in patients with diabetic foot infection. *The British Journal of Nutrition*, 112(12), 1938–1943. doi:10.1017/S0007114514003018.
- Vanchinathan, V., & Lim, H. W. (2012). A dermatologist's perspective on vitamin D. *Mayo Clinic Proceedings*, 87(4), 372–380. doi:10.1016/j.mayocp.2011.12.010.
- Zhang, Y., Wu, S., & Sun, J. (2013). Vitamin D, vitamin D receptor, and tissue barriers. *Tissue Barriers*, 1(1), e23118. doi:10.4161/tisb.23118.
- Zubair, M., Malik, A., Meerza, D., & Ahmad, J. (2013). 25-Hydroxyvitamin D [25(OH)D] levels and diabetic foot ulcer: Is there any relationship? *Diabetes & Metabolic Syndrome*, 7(3), 148–153. doi:10.1016/j.dsx.2013.06.008.