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Vitamin D and Diabetic Foot

Antony Macido

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 are used interchangeably to represent the status of vitamin D in individuals throughout this paper. Evidence suggests a relationship between 25(OH)D levels and DFU. However, very minimal data is 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, 1,25-dihydroxyvitamin D, diabetic foot ulcers, diabetic foot infections

1. Introduction

The role of serum vitamin D in diabetes mellitus (DM) and in the complications related to DM is an area of interest among researchers in the recent past [1, 2]. Diabetic foot complications including diabetic foot ulcers (DFU) and diabetic foot infections are often common with vitamin D deficiency [3]. The global prevalence of diabetic foot complication is 6.3% [4]. Almost 15% of patients with DM can develop DFU in their lives [1]. Infection of DFU is one of the common causes of hospitalization related to DM and accounts for 20% of admissions to hospitals [5]. Recurrence rates are very high with DFU although the recurrence rates have decreased recently [6].

DFU accounts for growing economic burden, while increasing the morbidity and mortality globally. It is estimated that the global economic burden of caring for DFU is more than \$1.5 billion per year [7]. Every 30 seconds someone loses a lower extremity from DM in the world [8]. The five-year mortality in patients with DFU is 2.5 times higher than patients with DM but has no DFU [9].

There is growing evidence on the relationship between DFU and vitamin D levels. Nevertheless, data is scarce on the association between vitamin D deficiency and DFU [2]. Evidence suggests a negative correlation between DFU and vitamin D levels. There is growing evidence on a negative relationship between diabetic foot infections and vitamin D levels. Further large-scale randomized controlled studies are needed to solidify the evidence of the correlation between DFU and

vitamin D levels. Before evaluating the significance of vitamin D in diabetic foot complications it is essential to review the effects of vitamin D in diabetic foot complications including the non-skeletal effects of vitamin D.

2. Non-skeletal effects of vitamin D

Vitamin D is a fat-soluble vitamin that has effects that are not confined to the skeleton. Vitamin D aids in glucose metabolism, angiogenesis, and migration of inflammatory cells [10]. 1,25-(OH)₂D is the active form of vitamin D and it acts as a ligand for an intracellular receptor and transcription factor VDR [11, 12]. Vitamin D in the form of 1,25-(OH)₂D exerts prodifferentiative and antiproliferative effects on the cutaneous keratinocytes [13], which in turn helps in defense against toxins and pathogens while helping to prevent water loss from the skin [11]. Vitamin D receptor is essential for differentiation, migration, and self-renewal of epidermal stem cells in wound healing [14].

3. Diabetic foot ulcers

International Working Group on the Diabetic Foot (IWGDF) defines DFU as a foot ulcer in persons with previously diagnosed or currently diagnosed DM and is usually accompanied by peripheral artery disease (PAD) and/or neuropathy in the lower extremity. Diabetic foot is defined as an ulceration, infection, or destruction of tissues of the foot of an individual with previously or currently diagnosed DM, usually accompanied by PAD and/or neuropathy in the lower extremity. A foot ulcer involves a break of the skin of the foot involving the entire epidermis and the dermis in part [15]. Diabetic foot ulcers can be located in different areas of the foot. Almost 25% of DFU are plantar ulcers that are localized to the forefoot [16].

4. Risk factors for developing DFU

Peripheral vascular disease and diabetic neuropathy are the important risk factors associated with the development of DFU [17]. Foot deformities and prior history of DFU are also risk factors associated with the development of DFU [18]. Inflammation along with oxidative stress have been postulated in the development of DFU [19]. Vitamin D deficiency is labeled as an independent risk factor in the development of diabetic neuropathy [20].

5. Vitamin D deficiency as a risk factor for diabetic foot ulcers/infections

Significantly low levels of vitamin D can be seen with diabetic foot complications [3]. Although vitamin D deficiency is common in DM, the magnitude of hypovitaminosis D is noticed to be more significant with infected DFU [21–23]. Vitamin D deficiency can in turn increase inflammatory cytokines and delay wound healing in patients with DFU [23]. An antimicrobial peptide called cathelicidin has an important role in wound healing process [24, 25]. In fact, 1,25-(OH)₂D can increase the genes capable of inducing cathelicidin production [26]. The literature on vitamin D deficiency and diabetic foot can be synthesized as follows.

6. Literature review

Although there is literature available on the association between vitamin D and diabetic foot, only a few randomized controlled studies and metaanalyses are available. A metaanalysis by Iannuzzo et al. [27] reported that vitamin D deficiency was associated with PAD and may be an independent risk factor for developing PAD. Adults with diabetes and severe vitamin D deficiency are three times more likely to develop a diabetic foot ulcer than similar patients with sufficient vitamin D levels [28]. The Dai et al. [28] study is the first meta-analysis demonstrating the association between serum vitamin D levels and DFU.

A double-blind, randomized controlled clinical trial by Razzaghi et al. [29] showed that vitamin D supplementation can aid in the healing of DFU possibly from its effect of improved glycemic control. The study revealed reasonable decrease in ulcer depth, width, and length in the experiment group with vitamin D therapy [29]. The Tiwari et al. [22] study identified a cutoff value for vitamin D levels ($25(\text{OH})\text{D} < 25 \text{ nmol/l}$) in diabetic patients that put them at risk to develop diabetic foot infections. The study was a prospective cohort research but not randomized. Another non-randomized prospective cohort hospital-based study by Zubair et al. [2] revealed that patients with DFU had a median lower plasma level of $25(\text{OH})\text{D}$ than the control group.

There is more than a dozen of other non-randomized studies that evaluated the prevalence of vitamin D deficiency and the potential use of vitamin D in diabetic foot complications. Majority of these studies reported low vitamin D levels in patients with DFU when compared to their counterparts with no DFU [3]. This strong association between vitamin D deficiency and DFU may not imply causation or correlation. However, this relationship of vitamin D deficiency and the presence of DFU may have implications in the clinical management of DFU [3]. Surprisingly, a study by Afarideh et al. [30] revealed increased levels of circulating $25(\text{OH})\text{D}$ with active chronic DFU. The authors claim that this is the only study that showed the conflicting finding of increased vitamin D levels in patients with DFU [30].

7. Vitamin D deficiency and supplementation

According to The Endocrine Society, vitamin D deficiency implies a serum $25(\text{OH})\text{D}$ of less than 20 nanograms per milliliter (ng/ml). The recommended assay for diagnosing vitamin D deficiency is the measurement of serum $25(\text{OH})\text{D}$. Vitamin D deficiency can be treated with either vitamin D3 or vitamin D2 [31]. Vitamin D supplementation needs to be tailored according to the age, sex, presence of comorbidities, etc. Vitamin D deficiency in adults need to be treated with 50,000 IU of vitamin D2 or D3 once a week for a duration of eight weeks or its equivalent vitamin D2 or vitamin D3 as daily doses to achieve a serum $25(\text{OH})\text{D}$ level of more than 30 ng/ml, followed by 1500–2000 IU daily for maintenance therapy [31]. There are no current recommendations on vitamin D dosage for individuals with DM or individuals with DFU who also have vitamin D deficiency.

8. Conclusion

There is insufficient data on the significance of vitamin D in DFU. There are no guidelines or standardized measures available on routine evaluation of vitamin D levels and vitamin D supplementation in DFU or infected 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. Provided the beneficial effects on wound healing, identification and treatment of vitamin D deficiency could improve or prevent diabetic foot complication outcomes [3]. Despite the lack of strong evidence to recommending vitamin D in DM and DFU, routine vitamin D supplements in patients with DM and DFU should be considered for its other benefits.

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