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Diabetic Foot Ulcers and Vitamin D: 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 (Leone, Pascale, Vitale, & Esposito, 2012). According to Armstrong, Boulton, and Bus (2017), DFU is the most frequent complication of the lower extremity associated with DM. The most common cause of lower extremity amputation in patients with DM is DFU (Ghanassia et al., 2008). Every half a minute someone in the world loses a lower extremity secondary to DM (Khatib & Tabatabaei-Malazy, 2007). Infected DFU is one of the common causes of hospitalization related to DM (Frykberg, Wittmayer, & Zgonis, 2007). The risk of mortality in five years in a patient with DM who also has DFU is 2.5 times higher than the five-year mortality risk in a patient with DM and no DFU (Armstrong et al., 2017). Evidence shows poor quality of life related to health in patients with DFU when compared to non-DM patients and DM patients without DFU (Ribu, Hanestad, Moum, Birkeland, & Rustoen, 2007).

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 (Dai et al., 2019). 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 abstract. In addition to peripheral vascular diseases and diabetic neuropathy (Sinwar, 2015), oxidative stress and inflammation have an important role in the pathogenesis of DFU (Sytze Van Dam, Cotter, Bravenboer, & Cameron, 2013). Serum 25(OH)D has an important role in oxidative stress and inflammation (Asemi, Hashemi, Karamali, Samimi, & Esmaillzadeh, 2013; Zubair, Malik, Meerza, & Ahmad, 2013). Data indicates a relationship between levels 25(OH)D and DFU. Nonetheless, very limited details are available on the relationship between DFU and vitamin D deficiency.

Vitamin D has non-skeletal 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). There are almost 2000 genes that are regulated by 1,25(OH)2D and has a myriad of functions including inducing terminal cell differentiation, stimulating insulin production, inhibiting angiogenesis, simulating macrophage cathelicidin production, inducing apoptosis, and inhibiting renin production (Hossein-Nezhad & Holick, 2013).

Vitamin D as 1,25-(OH)2D exerts pro-differentiative 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). Keratinocytes around a wound produce increased expression of the genes responsible for microbial pattern recognition receptors such as toll-like receptors (TLR) 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)2D (Schauber et al., 2007). Cathelicidin is an antimicrobial peptide that promotes wound healing (Gonzalez-Curiel et al., 2014; Zhang, Wu, & Sun, 2013).

Upon close analysis of the literature, it was concluded that DFU and diabetic foot infections may be linked with vitamin D. 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). 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). There is evidence available on vitamin D and DFU that suggests a negative correlation between 25(OH)D levels and DFU presence. 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). The literature available on vitamin D and DFU suggest 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. Data also suggests a detrimental association between rates of 25(OH)D and infections of diabetic foot. 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. 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 theincreased incidence of diabetic foot infections with vitamin D deficiency.

Most recently a study by Dai and his colleagues concluded that severe vitamin D deficiency is significantly associated with an increased risk of DFU. This is the first meta-analysis

demonstrating the association between serum vitamin D levels and DFU (Dai et al., 2019). 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. 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.

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