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Vitamin D deficiency among outpatients and hospitalized patients with diabetic foot ulcers: A systematic review and meta-analysis

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Abstract

BACKGROUND

Diabetic foot syndrome definition varied depending on location and resources. Few classifications are available according to the indication. Diabetic foot ulcers and vitamin D deficiency are common diseases among patients with diabetes. Although previous literature showed an association between diabetic foot ulcer and vitamin D deficiency. However, the available meta-0analysis was limited by substantial bias.

AIM

The current meta-analysis aimed to investigate the association between diabetic foot ulcers and vitamin D levels.

METHODS

We searched PubMed, MEDLINE, and Cochrane Library. EBSCO, and Google Scholar for studies comparing vitamin D levels and diabetic foot. The keyword, diabetic foot ulcer, diabetic foot syndrome, diabetic septic foot, vitamin D level, 25-hydroxy vitamin D, vitamin D status, and vitamin D deficiency were used. The search engine was set for articles published during the period from inception to October 2022. A pre-determined table was used to collect study information.

RESULTS

Vitamin D level was lower among patients with diabetic foot ulcer compared to their counterparts, odd ratio, -5.77, 95% *CI*, -7.87, -3.66. The chi-square was 84.62, mean difference, 9, I^2 for heterogeneity, 89%, P <0.001, and the P-value for overall effect <0.001. The results remain robust for hospitalized patients (odd ratio, -6.32, 95% *CI*, -11.66, -0.97, chi-square was 19.39, mean difference, 2, I^2 for heterogeneity, 90%, P, value, 0.02).

CONCLUSION

Vitamin D was lower among outpatients and hospitalized patients with diabetic foot ulcers. Further larger randomized controlled trials are needed.

INTRODUCTION

Diabetes mellitus (DM) is an epidemic globally. DM is a morbid disease with many complications including microvascular and microvascular disease. Diabetic foot syndrome (DFS) is defined as peripheral neuropathy, limited joint mobility, peripheral arterial disease, immunopathy, ulceration, and Charcot arthropathy [1]. The combination of foot syndrome elements provides an environment for unrecognized injury, foot infection, and possible amputation [2]. Diabetes foot syndrome is characterized by peripheral arterial disease, but the symptoms are masked by the accompanied peripheral neuropathy. The pathology varied from pre-ulcerative callouses, ulceration, and necrosis developing at the site of high pressure (deformities of the toes and feet). Patient education and feet inspection is mandatory because repetitive trauma might be passed unnoticed due to loss of pain sensation [3]. Diabetic foot syndrome is a common complication of diabetes with a great economic burden; DTS substantially affects the patient's quality of life and leads to premature death. In addition, patients with DFS are prone to psychiatric disease [4].

There are nearly forty classifications for DFS, with wide variation depending on the availability of resources and geographical variations. It is recommended to use classification in the light of specific indications. Few classifications were validated for use; the site, ischaemia, neuropathy, bacterial infection, area, and depth (SINBAD) is a six-questions with yes or no answers with a maximum of six points. SINBAD score is better for communication between clinicians [5]. While, Infectious Diseases Society of America/International Working Group on Diabetic Foot (IDSA/IWGDF), and wound depth, ischaemia, and foot infection (WIfI) scoring are better for infection and perfusion respectively [6, 7]. The spectrum of DFS varied from minor erythema to tissue necrosis and lower limb deformity and amputation [8]. The mortality of DFS is comparable to breast and lung cancer, Five year mortality for minor and major amputations, Charcot, and diabetic foot ulcer, were 56.6%, 46.2%, 30.5%, 29% respectively. The pooled mortality from breast, all cancer, and lung cancer were 9%, 30%, and 80% respectively [9] The lifetime of developing foot ulcers among patients with diabetes varies between 19-34% with nearly two-thirds of recurrence in five years and one in five patients with moderate to severe foot ulcers resulting in amputation. The majority of lower extremities amputations are preceded by foot ulcers and three amputations occur every minute due to diabetes. Patients with foot ulcers had a 2.5 times mortality rate compared to their counterparts [10, 11].

25-Hydroxyvitamin D (25(OH) D) is present in almost all immune cells and is a major immunomodulatory hormone. In addition, the vitamin is a potent endothelial membrane stabilizer [12]. Due to its anti-inflammatory effects, the active form of vitamin D plays an important role in inflammatory diseases including rheumatic disorders, and a growing piece of evidence is present regarding its effects on infectious diseases [13]. Vitamin D deficiency is common, larger studies suggested that in Europe, 40% and 13% of the population are vitamin D deficient and severely deficient respectively [14]. Vitamin D deficiency was found to be associated with vascular diseases including diabetes mellitus, hypertension, and dyslipidemias [15].

The small number of included studies, including studies published by the same authors, and including poster presentations [16, 17], limits the previous meta-analysis on vitamin D deficiency and diabetic septic foot. Therefore, this meta-analysis aimed to investigate vitamin D levels among patients with the diabetic septic foot.

MATERIALS AND METHODS

Eligibility Criteria:

The studies were eligible if they compare the level of vitamin D among patients with diabetic foot ulcer and their counterparts without diabetic foot ulcers and they are randomized controlled trials or case-control studies, prospective and retrospective cohorts, and cross-sectional studies. Case reports, case series, and animal and experimental studies were excluded.

Outcomes measures:

The primary outcome was the level of vitamin D among patients with a diabetic foot ulcers.

Vitamin D assessment methods:

Vitamin D measurement varied between the included studies, references 18, 19, 21, and 23 used ELIZA, references 20, 22, and 25 used radioimmunoassays, references 24, 26, and 28 used electro-chemiluminescence immunoassay, reference 27 used liquid chromatography-tandem mass spectrometry, while, reference 29 used chemiluminescence assay. The Newcastle Ottawa Scale was used to assess the quality of the included studies [30].

The setting and diabetic foot ulcer definition:

All the studies approached outpatient except 18, 24, 28, and 29 in which hospitalized patients were included.

Information sources and search:

The researcher searched PubMed, MEDLINE, and Cochrane Library. EBSCO and Google Scholar use the keyword, diabetic foot ulcer, diabetic foot syndrome, diabetic septic foot, vitamin D level, 25-hydroxy vitamin D, vitamin D status, and vitamin D

deficiency. The search engine was set for articles published during the period from inception to October 2022. A pre-determined table was used to collect study information including author name, year of publication, country, age, sex, patient's number in control and interventional group, duration of diabetes, HbA1c in intervention and control groups, vitamin D level among patients with foot ulcers and control groups. Figure 1 & tables 1-3.

Data analysis: The RevMan (version 5.4) system for meta-analysis was used, and the data were all continuous. We pooled data from twelve studies to compare vitamin D levels among patients with and without diabetic septic foot; a sub-analysis was done to compare vitamin D among hospitalized patients. The random effect was used because significant heterogeneity was observed. Funnel plots were used to assess lateralization. A P-value of <0.05 was considered significant.

RESULTS

The current meta-analysis included twelve studies including 7619 patients. The included studies were seven cross-sectional, three prospective, and two retrospective, nine were published in Asia, and three were from Europe [18-29]. Vitamin D was lower among patients with diabetic foot ulcers, odd ratio, -5.77, 95% *CI*, -7.87, -3.66. The chi-square was 84.62, mean difference, 9, I^2 for heterogeneity, 89%, P <0.001, and the P-value for overall effect <0.001. Figure 2. Vitamin D level was low when a sub-analysis was conducted including only hospitalized patients with diabetes septic foot, odd ratio, -6.32, 95% *CI*, -11.66, -0.97, chi-square was 19.39, mean difference, 2, I^2 for heterogeneity, 90%, P, value, 0.02. Figure 3. Vitamin D level was lower among patients with diabetic foot ulcers after including studies that controlled for age, sex, duration of diabetes, and HbA1c (, odd ratio, -6.32, 95% *CI*, -923, -3.42, chi-square was 18.72, mean difference, 4, I^2 for heterogeneity, 79%, P, value < 0.001. Figure 4.)

DISCUSSION

In the present meta-analysis, vitamin D levels were lower among patients with diabetic foot ulcers compared to their counterparts without foot ulcers odd ratio, -5.77, 95%CI, -7.87, -3.66, and respectively. No differences between hospitalized and outpatients. The results stand robust when including studies that controlled for age, sex, duration of diabetes, and HbA1c. The current findings were in line with a narrative review including three studies [31]. The present findings were similar to the first meta-analysis published by Dai and colleagues in the year 2019. Dai *et al* [32] found an association between vitamin D levels and diabetic foot ulcers. However, Dai *et al* included studies published by the same authors and some were poster presentations [33]. Yammine *et al* [34] found similar results. Importantly, Yammine and colleagues included poster presentations, studies published by the same authors, and studies that assessed Charcot's joints [35]. In addition, the previous meta-analysis included Zubair *et al* study [36] in which vitamin D median was reported and not mean± SD. A recently published meta-analysis reported similar findings to our results. However, the substantial heterogeneity, including posters, research by the same authors, and different primary outcomes limited their results [37]. The main strength of this meta-analysis is the sub-analysis on vitamin D among hospitalized patients. Although a single measurement is not enough during stress, the results remain robust even among admitted patients [38].

Although vitamin D has been looked for as a magic bullet and cures many chronic disorders. However, the results were obtained from observational studies. The findings of lower foot ulcers among patients with higher vitamin D may not prove causality. Other confounders might explain the lower vitamin D levels among patients with diabetic foot ulcers including a healthier diet, good exposure to sunlight, and physical activity [39, 40]. In addition, vitamin D was found to improve glycemic control among patients with diabetes [41. 42]. Thus, high vitamin D may indirectly protect against diabetic foot ulcers by improving glycemic control.

Osteoblasts (bone formation) and osteoclasts (bone resorption) orchestrate bone remodeling. Osteoclasts genesis activation is through receptor activator of tumor necrosis factor (RANK-Osteoprotegerin) ultimately leading to osteolysis and

destruction of bone tissue. This pathway is of great therapeutic and clinical implications. Medications that influence different levels of RANK-Osteoprotegerin are bisphosphonates, calcitonin, and Denosumab. Denosumab is encouraging in the treatment of Charcot Diabetic Foot. However, bisphosphonates have been under evaluated recently due to the adverse events. Calcitonin efficacy is limited [43, 44].

In this review, some of the included studies were not matched for age, duration of diabetes, duration of diabetes, and HbA1c. The young age of control subjects, their good glycemic control, and the short duration of diabetes might increase their risk of diabetic foot ulcers.

Vitamin D supplementation and diabetic septic foot:

Although, the association between low vitamin D levels and diabetic septic foot was documented. However, the role of vitamin D therapy effects on diabetic foot ulcers is scarce. In addition, it is not clear if the relationship is correlated or causal [45]. A double-blinded randomized controlled trial showed that high-dose vitamin D supplementation (170 micrograms/day) was superior to low doses (20 micrograms/day) on diabetic ulcer healing [46]. A recent review showed that Vitamin D improved diabetic septic foot healing; an effect mediated by remodeling and proliferation of cells involved.in addition, vitamin D suppresses proinflammatory responses, enhances antimicrobial peptides, and enhances anti-inflammatory effects [47]. Papaioannou and colleagues' review, which included 34 studies [48], supported the above findings. A randomized controlled trial published in Asia showed that vitamin D supplementation reduced ulcer length, width, and depth [49]. A recent review of the literature concluded that vitamin D supplementations might slow the progression of neural damage. In addition to the adjuvant role in neuropathic pain and cardiovascular autonomic neuropathy among patients with type 2 diabetes [50].

The current meta-analysis strength is that we included observational studies excluding poster presentations, studies published by the same authors, and studies that used the median of vitamin D. The study limitations were the substantial heterogeneity

CONCLUSION

Vitamin D levels were lower among patients with diabetic foot ulcers compared to their counterparts without ulcers. A low level was observed among hospitalized patients. Randomized control trials investigating the association of vitamin D and diabetic foot ulcers and assessing the role of vitamin D supplementation are needed.

ARTICLE HIGHLIGHTS

Research background

Vitamin D deficiency is associated with various disorders ranging from glycemic control to cancer and suicide. Diabetic foot syndrome is a common disorder with high morbidity and mortality. The association of diabetic foot ulcers with vitamin D deficiency was documented. However, the available meta-analyses were limited by bias and few included studies.

Research motivation

+ADw-html+AD4APA-p+AD4-Diabetes mellitus is approaching an epidemic, the disease is associated with vascular and neuropathic complications. Most people with diabetes are not approaching the recommended targets for cardiovascular risk factors with increasing foot ulcers. Diabetic foot ulcers are a preventable disease and vitamin D deficiency is promising. Despite the association of vitamin D deficiency and diabetes mellitus and its complications. However, a cause and effect were not confirmed. In addition, vitamin D supplementation is not without complications and vitamin D is readily synthesized by sun exposure. We included vitamin D supplementation to address this issue.+ADw-/p+AD4APA-/html+AD4-

Research objectives

To assess vitamin D levels among patients with diabetic septic foot and the role of vitamin D supplementation in the treatment of Diabetic foot syndrome.

Research methods

We searched four databases and included studies other than case reports, perspectives, opinions, and editorials. The studies were included if they assessed the relationship between diabetic foot ulcers and vitamin D levels. The most recent RevMan system was used for data analysis.

Research results

Evidence from observational studies confirmed the association between vitamin D deficiency and diabetic foot ulcers, both among outpatients and Hospitalized patients, the associations remained robot after controlling for demographic factors, the duration since the diagnosis of type 2 diabetes, and the glycated hemoglobin (odd ratio, -6.32, 95% *CI*, -923, -3.42).

Research conclusions

Vitamin D deficiency was associated with diabetic foot ulcers, and vitamin D supplementation was effective in slowing the progress. Various therapies along the RANK-Osteoprotegerin pathway are promising.

Research perspectives

The question of vitamin D and the optimal effective dose is elucidated. in addition, future therapies along the RANK-Osteoprotegerin might address this dangerous diabetes complication.

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