Review

Vitamin D in the Prevention and Treatment of Diabetic Neuropathy

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ABSTRACT

Purpose: Neuropathy is one of the most important complications of diabetes. According to recent advances, vitamin D deficiency might play a role in the development and progression of diabetic neuropathy. Moreover, therapeutic vitamin D supplementation has the potential to improve this condition. The aim of the present review was to summarize new data available in this area.

Methods: The PubMed database was searched for articles written in English and published through September 2021, using combinations of the following key words: *vitamin D, diabetes, diabetes mellitus, diabetic neuropathy, polyneuropathy, peripheral neuropathy, cardiac autonomic neuropathy, supplementation,* and *therapy*.

Findings: A number of studies have suggested that vitamin D deficiency can play a significant role in the development of peripheral neuropathy, diabetic foot ulcers, as well as cardiovascular autonomic neuropathy in patients with type 2 diabetes. Vitamin D supplementation might serve as an effective adjuvant therapy for neuropathic pain and may slow or stop the progression of neural damage.

Implications: Vitamin D therapy for diabetic complications could be a reliable option; however, further studies are needed to confirm this notion. (*Clin Ther.* 2022;44:813–823.)

Key words: cardiovascular autonomic neuropathy, sensory neuropathy, vitamin D.

INTRODUCTION

Vitamin D is a secosteroid that differs from most other "vitamins" as it is also synthesized in the body by the skin, kidney, and liver and, in small quantities, is essential for life. There is a wealth of evidence on the various effects of vitamin D other than its known influence on calcium metabolism.[1] Studies have reported that vitamin D deficiency may be associated with cardiovascular disease, tumors, and autoimmune diseases, and might play a role in the development of diabetes and neurodegenerative diseases.[2,3]

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Even during pregnancy, vitamin D deficiency has been reported to be correlated with an increased lifetime risk for type 1 diabetes mellitus (T1DM) in neonates.[4] Additionally and more recently, the immunomodulatory effects of vitamin D have been widely discussed with regard to coronavirus disease 2019.[5,6] There is also growing body of evidence that vitamin D deficiency might have an effect on the development of diabetic sensory motor neuropathy, in particular painful diabetic neuropathy. This review summarizes the data available at present regarding the possible relationship between vitamin D deficiency and diabetic neuropathy.

MATERIALS AND METHODS

The PubMed database was searched for papers published through September 2021. Combinations of the following key words were utilized: *vitamin D, diabetes, diabetes mellitus, diabetic neuropathy, polyneuropathy, peripheral neuropathy, cardiac autonomic neuropathy, supplementation,* and *therapy*. Only articles available in English were considered.

RESULTS

Potential Underlying Mechanisms of the Role of Vitamin D

Several studies have examined the relationship between a low vitamin D level and neuropathy, but the exact underlying mechanisms are still not fully understood.[2,7] Vitamin D receptor (VDR) can be found in the cytoplasm and nuclei of cells throughout the nervous system. VDR is a ligand-activated transcription factor that regulates the expression of a number of genes. VDR has been associated with several diseases in addition to diabetic neuropathy, such as neurodegenerative and autoimmune diseases, suggesting that cholecalciferol has a prominent role in a well-functioning nervous system.[8] Filipovic et al.[8] reported that diabetic rats with a low vitamin D level had high VDR expression in the dorsal root ganglia, which affects every group of neurons, especially small fibers, that correspond to nociception. The investigators suggested that this mechanism might be an important factor of painful neuropathy.

Vitamin D actions have been experimentally linked to a neuroprotective effect.[9] Vitamin D stimulates the production of nerve growth factor (NGF).[10] Treatment of NGF-deficient rats with vitamin D has been associated with increased NGF production, with an apparent preventive effect on neurotrophic deficit.[10] The findings from studies of the relationship between vitamin D, NGF, and cognition have suggested a direct impact of vitamin D on nerve function;[9–12] however, further studies are needed to evaluate this process.

Vitamin D and Diabetic Peripheral Neuropathy

In a case-control study of data from 150 diabetic neuropathy cases and 600 controls, a nonlinear association between serum 25-dihydroxy-vitamin D (25[OH]D) and symptomatic diabetic peripheral neuropathy (DPN) was observed. [13] Compared to individuals with a sufficient (30–40 ng/mL) level of 25(OH)D, patients with a deficient (<20 ng/mL) vitamin D level had greater risk for symptomatic DPN (odds ratio [OR] = 2.04; 95% CI, 0.99–4.02; $P = 0.054$). Nonetheless, patients with a 25(OH)D level of >40 ng/mL had an increased risk for symptomatic DPN compared to individuals with sufficient 25(OH)D (OR = 4.29; 95% CI, 1.59–11.55).[13] These results suggest that vitamin D should be monitored and evaluated carefully.

Abdelsadek et al.[14] reported that vitamin D deficiency had a significant role in the development and severity of DPN in Egyptian patients with type 2 diabetes mellitus (T2DM). Patients with diabetes and with (n = 40) and without (n = 20) DPN, as well as 30 healthy control subjects, were included. DPN was categorized as painful or painless. The mean (SD) serum 25(OH)D level was significantly less in patients with DPN than in those without (21.09 [8.38] vs 31.12 [14.85] ng/mL; $P = 0.001$). The mean serum 25(OH)D level was decreased in patients with painless DPN compared to that in those with painful DPN (10.047 [8.12] vs 18.14 [3.85] ng/mL; $P < 0.05$). On regression analysis, vitamin D deficiency was an independent risk factor for DPN (Odds ratio(OD) = 0.914; $P = 0.007$).

Another study, conducted in France by Skalli et al.,[15] evaluated serum vitamin D concentration in patients with T2DM with and without DPN. Patients with DPN were older and had a longer duration of diabetes, as well as a lesser vitamin D concentration. In addition, the percentage of patients with vitamin D deficiency (<20 ng/mL) was notably greater in the subgroup with DPN.

A cross-sectional study in 136 participants investigated the association between 25(OH)D level and microvascular complications in T2DM.[16] The mean 25(OH)D level was less in patients with DPN

compared to that in those without. Additionally, at a vitamin D deficiency cutoff value of <20 ng/mL, DPN was more frequent in the subgroup with vitamin D deficiency than in those with a 25(OH)D level of >20 ng/mL (63% vs 42%; $P = 0.03$). After adjustment for HbA_{1c}, age, smoking, body mass index, and diabetes duration in a logistic regression model, diabetes duration and 25(OH)D level was a significant predictor of DPN.

Another case-control trial evaluated the association between serum 25(OH)D and DPN in patients with diabetes.[17] Mean 25(OH)D was significantly less in diabetic patients with large-fiber DPN, as diagnosed by electrophysiologic methods (21.2 [11.5] vs 13.5 [5.1] ng/mL; $P = 0.001$). After adjustment for all studied variables, 25(OH)D had an independent and inverse association with both the presence and severity of DPN.

Ozuguz et al.[18] evaluated the relationship between DPN and vitamin D, NGF, and oxidative stress markers in patients with T1DM and with (n = 26) or without (n = 70) DPN. Mean age, duration of diabetes, and retinopathy rate were significantly greater in patients with DPN. The mean level of 25(OH)D was significantly less in the DPN subgroup, while there were no differences in NGF level or in oxidative stress markers. The Michigan Neuropathy Screening Instrument score was positively correlated with age, and diabetes duration was negatively associated with 25(OH)D level. In addition, 25(OH)D was positively correlated with NGF. The most important risk factor for neuropathy in patients with T1DM appeared to be disease duration. Although the mean vitamin D level was significantly less in the DPN subgroup, it was not an independent risk factor for DPN. Nonetheless, the positive correlation between vitamin D level and NGF level, and the negative correlation between vitamin D level and DPN, suggest a need for prospective studies with greater numbers of patients.

In another cross-sectional study in 861 patients with T2DM, vitamin D deficiency was defined as a serum circulating 25(OH)D level of <20 ng/mL.[19] Peripheral neuropathy was evaluated by neurologic symptoms, neurologic signs, neurothesiometry, and electromyography. After adjustment for all potential confounders, vitamin D deficiency was still linked with an increased risk for DPN (OR = 2.59; 95% CI, 1.48–4.53; $P < 0.01$). The investigators concluded that vitamin D deficiency should be considered an independent risk factor for DPN. The correlation between lower levels of vitamin D and microvascular complications was also confirmed in a further report.[20]

In a meta-analysis of data from six studies that involved a total of 1484 patients with T2DM, serum 25(OH)D level was significantly decreased in patients with DPN (weighted mean difference, −6.36 ng/mL; 95% confidence interval(CI), −8.57 to −4.14; $P < 0.00001$).[21] Vitamin D deficiency was also significantly associated with an increased risk for DPN in patients with T2DM (OR = 2.88; 95% CI, 1.84–4.50; $P < 0.00001$).

Intervention Studies With Vitamin D Among Patients With Diabetic Peripheral Neuropathy

Lee et al.[22] observed a relationship between vitamin D deficiency and DPN in 51 patients with T2DM who had a low 25(OH)D serum level and painful DPN. The neuropathic pain score was reduced by 50% after 3 months of vitamin D administration.

In a case report by Bell et al.,[23] a 38-year-old man with a 27-year history of T1DM and a 10-year history of neuropathy symptoms was unable to work and was in need of major analgesics for pain management. His 25(OH)D level was 16.5 ng/dL, and he received vitamin D supplementation. When vitamin D deficiency was corrected, neuropathy symptoms decreased rapidly, and the dosage of analgesics was reduced significantly.

A study in patients with T2DM with (n = 87) and without (n = 123) DPN examined the relationship between DPN and vitamin D deficiency.[24] The serum 25(OH)D level was significantly less in the former group. The symptoms and signs of DPN were also significantly decreased with vitamin D supplementation.[25]

The objective of recent research was to explore the effectiveness and tolerability of vitamin D supplements in painful DPN.[26] Sixty-six patients with T2DM with painful DPN were involved in the study. Patients received 50,000 IU of vitamin D_3 weekly for 12 weeks. Vitamin D supplementation was associated with an improved serum level of 25(OH)D and reduced symptoms and signs of DPN (both, $P < 0.001$).

In a more recent study, the effects of vitamin D supplementation on microcirculation and symptoms of DPN and inflammatory markers in patients with T2DM were assessed.[27] High-dose vitamin D therapy was associated with reduced serum proinflammatory interleukin-6 and increased serum anti-inflammatory interleukin-10 concentrations, and these effects were

related to improvements in severity of DPN and skin microcirculation.[27]

Painful Diabetic Neuropathy and Vitamin D Deficiency

Neurologic deficits, quantitative sensory testing, electrophysiology, skin biopsy, corneal confocal microscopy, and measurement of serum 25(OH)D were performed among 43 patients with T1DM and 14 nondiabetic healthy control subjects in a cross-sectional study.[28] Among the patients with T1DM, 20 had painless DPN, while 23 had painful DPN. The rates of both positive (hyperalgesia and allodynia) and negative (paresthesia and numbness) symptoms of DPN were greater among patients with painful, compared to those with painless, neuropathy ($P = 0.009$ and 0.02, respectively). The serum 25(OH)D level was significantly less in the subgroup with painful DPN compared to those in patients with painless DPN and controls. The results of this study suggest that vitamin D deficiency and insufficiency are associated with painful DPN.[28]

A cross-sectional study by Shillo et al.[29] examined data from 17 patients with painful DPN, 14 with painless DPN, and 14 volunteers with no DPN. All patients and volunteers underwent clinical and neurophysiologic assessments. Vitamin D was the only independent variable to make a statistically significant contribution to the model, with an inverted OR of 1.11. A low 25(OH)D level was also correlated with a lesser cold-detection threshold ($r = 0.39$; $P = 0.02$) and subepidermal nerve fiber density ($r = 0.42$; $P = 0.01$). In summary, a significant difference in 25(OH)D levels has been demonstrated in well-characterized patients with painful DPN.

Vitamin D deficiency was found to be related to painful DPN in Greek but not Bangladeshi patients.[30] The study included 111 Bangladeshi and 101 Greek patients with diabetes. In a subgroup without polyneuropathy, the vitamin D level was significantly less in Bangladeshi than in Greek patients (12.4 [5.9] vs 23 [12.4] ng/mL; $P < 0.01$ [t test]). In the Greek patients, the level of vitamin D was significantly less in the subgroup with small fiber neuropathy compared with that in the subgroup without polyneuropathy ($P < 0.05$), but was not significantly different from that in a subgroup with large fiber neuropathy. In the Bangladeshi patients, the difference in vitamin D levels between the subgroups of patients with and without polyneuropathy was not statistically significant.

Recently, in a prospective pilot study in 40 patients with painful DPN, serum levels of both magnesium and 25(OH)D were significantly elevated at 4 weeks after low-level laser therapy (LLLT) compared with baseline ($P < 0.001$ and <0.002, respectively).[31] At 1 month after LLLT, the mean neuropathy score indicated a significant reduction in pain ($P < 0.001$). A considerable improvement in quality of life after LLLT was observed as well. These results suggest that the improvements in the serum magnesium and vitamin D levels were proportional to quality of life and may be good indicators of the prognosis of patients with DPN after LLLT.

Prospective studies of the effects of vitamin D supplementation in adults with DPN, such as the one being conducted at the Alberta Diabetes Institute,[32] are underway. These studies are expected to provide deeper insight into the potential benefits of vitamin D treatment in DPN.

Intervention Studies With Vitamin D Among Patients With Painful Diabetic Neuropathy

Basit et al.[33] reported that a single intramuscular(IM) dose of 600,000 IU of vitamin D_3 was associated with significant improvement in painful DPN. The study involved 143 patients predominantly with T2DM; mean (SD) Neuropathyique 4 score(DN4) was 3.0 (1.8); total McGill pain score, 21.2 (14.9); and Short Form McGill Pain Questionnaire score, 2.1 (0.9). The mean baseline 25(OH)D level was 31.7 (23.3) ng/mL, and 58 patients (40.5%) had evidence of vitamin D deficiency.

A prospective study in 143 participants, by Alam et al.,[34] assessed the effects of treatment with a single IM injection of high-dose vitamin D_3 (600,000 IU) on quality of life in patients with painful DPN, using the NeuroQoL questionnaire. The neuropathy-specific quality-of-life score was significantly improved following treatment in these patients, particularly in those with vitamin D deficiency. Patient perception of foot problems was significantly reduced, and the percentage of patients reporting an "excellent" quality of life was increased from 1.5% to 7.4% ($P < 0\ 0001$). These data suggest that vitamin D supplementation might be effective in improving quality of life in patients with painful DPN.

Vitamin D Deficiency and Diabetic Foot Ulcer

The relationship between vitamin D deficiency and diabetic foot ulcer was examined in a study in 162 patients without and 162 with diabetic foot ulcer.[35] The median (IQR) 25(OH)D level was less in the patients with foot ulcers compared to that in those without ulcer (6.3 [4.2–11.1] vs 28.0 [21.4–37.0] ng/mL; $P < 0.005$). This finding prompts further inquiry into the role of vitamin D deficiency in the development of diabetic foot ulcer.

Dai et al.[36] evaluated the association between vitamin D deficiency and diabetic foot ulcer in a meta-analysis of data from seven studies (1115 patients). The vitamin D level was significantly reduced in patients with diabetic foot ulcer (mean difference, −13.47 nmol/L; 95% CI, −16.84 to −10.10; $P = 0.34$; $I^2 = 12\%$).

A retrospective study analyzed vitamin D level in relation to Charcot neuroarthropathy, peripheral arterial disease, DPN, and diabetic foot ulcer.[37] Vitamin D levels were compared in 50 patients with Charcot neuroarthropathy and 50 without, with no significant difference found ($P = 0.55$). Among patients with diabetes, the serum vitamin D level was significantly less in those with peripheral arterial disease ($P = 0.03$), diabetic foot infection ($P = 0.0006$), and diabetic foot ulcer ($P = 0.04$) than in those without these complications.

Based on a recent meta-analysis of data from 10 studies,[38] vitamin D deficiency appears to play a significant role in the presence of diabetic foot ulcer. The meta-analysis included data from patients with diabetes and with (n = 817) and without (n = 827) diabetic foot ulcer. The prevalence of severe vitamin D deficiency (<10 ng/mL) was significantly greater in patients with foot ulcer compared to those without (52.5% [95% CI, 0.453–0.596; $I^2 = 56.5\%$] vs 23% [95% CI, 0.155–0.312; $I^2 = 75.3\%$]). Diabetic foot complications seem to be associated with vitamin D deficiency.

In a cross-sectional study, differences in serum vitamin D levels between patients with diabetes and with or without foot ulcer, as well as healthy volunteers, in a southern European country were examined.[39] The healthy volunteers had a greater serum vitamin D level compared with patients with and without diabetic foot ulcer. Serum levels of vitamin D did not differ significantly between patients with and without ulcer ($P = 0.329$). Nonetheless, the prevalences of vitamin D deficiency and insufficiency were high in both diabetic subgroups.

Another work assessed vitamin D status in patients with T2DM and with (n = 73) and without diabetic foot ulcer (n = 169; 106 with DPN, 63 without complications).[40] The mean serum 25(OH)D level was significantly less in the subgroup with ulcer compared to that without ($P = 0.001$). The DPN subgroup presented with a lesser vitamin D level in comparison with that in patients without complications ($P = 0.031$). These data raise the possibility that supplementation of vitamin D might be useful in preventing or improving diabetic foot complications due to the wound-healing effect of vitamin D.

There might be several reasons behind the low vitamin D levels in these patients. They could be less mobile, thus getting less sunlight, but they might eat differently as well. Given that many patients with diabetes-related foot complications have impaired renal function, it is not surprising that such a high percentage of these patients have a reduced level of serum vitamin D. Finally, the effects of vitamin D on wound healing, collagen synthesis, as well as immune functions might contribute to the beneficial effects of vitamin D in patients with diabetic foot ulcer.[41–45]

Vitamin D and Cardiovascular Autonomic Neuropathy

Limited data are available on the relationship between cardiovascular autonomic neuropathy (CAN) and vitamin D deficiency. Some cross-sectional studies have postulated associations between 25(OH)D and the presence and severity of CAN in patients with diabetes.[46,47]

Vitamin D receptors can be found in the vascular smooth muscle cells, endothelium, and cardiomyocytes.[48] Some trials have shown that vitamin D deficiency may be associated with cardiovascular disease, tumor, autoimmune conditions, and overall mortality, and may play a role in the development of diabetes mellitus and neurodegenerative diseases.[49,50] The presence of CAN may increase the risk for cardiovascular-related mortality, as well.[51,52] Vitamin D supplementation has been shown to improve measures of CAN in patients without diabetes.[53]

Low heart-rate variability may be a predictor of cardiovascular disease and should be considered as a risk factor for heart failure and sudden cardiac death.[54] CAN and heart rate variability were examined

Table I. Major studies investigating the relationship between serum vitamin D and diabetic neuropathy.

Study	Design	N	Follow-Up	Primary End Point	Results
Esteghamati et al.[13]	Prospective	750	NA	Diabetic neuropathy symptoms score	Vitamin D should be monitored and evaluated more carefully.
Abdelsadek et al.[14]	Case control	80	6 mo	Neuropathy disability score, McGill visual analog scale score	Vitamin D deficiency is one of the independent risk factors of DPN.
Skalli et al.[15]	Observational	111	NA	Patellar deep tendon reflexes, Achilles sensory loss. 128-Hz tuning fork and Semmes-Weinstein monofilament	Serum 25(OH) vitamin D levels were significantly less in the group with neuropathy than in the group without neuropathy (24.6 [11.98] vs 34.74 [17.26] nmol/L; $P < 0.001$).
Ahmadieh et al.[16]	Cross-sectional	136	NA	UK screening score	Mean 25(OH)D level was less in subjects with diabetic neuropathy compared to those without neuropathy ($P = 0.0004$). Low serum 25(OH)D level was an independent predictor of diabetic neuropathy in patients with diabetes mellitus type 2.
Alamdari et al.[17]	Case control	62	NA	Nerve conduction velocity	Serum vitamin D had an independent and inverse association with both the presence of diabetic neuropathy and its severity.
Ozuguz et al.[18]	Cross-sectional	96	NA	Michigan Neuropathy Screening Instrument, NGF, oxidative stress markers	Positive correlation between vitamin D levels and NGF levels and neuropathy
Shebab et al.[24]	Cross-sectional	210	NA	Neuropathy symptom score, neuropathy disability score, nerve conduction study score	81.5% of patients with diabetic neuropathy had vitamin D deficiency compared with 60.4% of patients with no diabetic neuropathy ($P = 0.005$)
Alam et al.[28]	Cross-sectional	57	NA	Quantitative sensory testing, electrophysiology, skin biopsy, corneal confocal microscopy	Serum 25(OH) vitamin D level was significantly less in painful neuropathy ($P = 0.01$)
Shillo et al.[29]	Cross-sectional	59	NA	Neurophysiologic assessments, lower limb skin biopsy	Significantly decreased 25(OH)D level in patients with painful diabetic peripheral neuropathy

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Table I. (*continued*)

Study	Design	N	Follow-Up	Primary End Point	Results
Zubair et al.[35]	Prospective cohort	324	NA	Clinical evaluation	Subjects with diabetic foot ulcer showed a lower median plasma level of 25(OH)D (6.3 [4.2–11.1] vs 28.0 [21.4–37.0] ng/mL)
Greenhagen et al.[37]	Retrospective	100	NA	Michigan Neuropathy Screening Index, Semmes-Weinstein, 128-Hz tuning fork, Achilles reflex, clinical evaluation, monofilament	Diabetic patients with PAD ($P = 0.03$), DFI ($P = 0.0006$), and DFU ($P = 0.04$) were all found to have significantly lower serum vitamin D levels than diabetic patients without these complications.
Jung et al.[46]	Retrospective	163	NA	Cardiovascular reflex test according to Ewing protocol, heart rate variability	The SDNN and RMSSD were significantly less in patients with the lowest vitamin D levels ($P = 0.048$ and $P = 0.03$, respectively). LF/HF ratio was significantly greater in the group with the lowest vitamin D level ($P = 0.04$).
Hansen et al.[47]	Cross-sectional	113	NA	Three cardiovascular reflex tests, heart rate, heart rate–variability indices	Inverse *U*-shaped association between serum vitamin D level and E/I ratio, 30/15 ratio, and three heart rate variability indices (all, $P < 0.05$).

DFI = diabetic foot infection; DFU = diabetic foot ulcer; DPN = diabetic peripheral neuropathy; E/I = heart rate response to deep breathing; LF/HF = low-frequency/high-frequency ratio; NA = not available; NGF = nerve growth factor; PAD = peripheral arterial disease; RMSSD = square root of the mean of the sum of the squares of the differences between adjacent NN intervals; SDNN = SD of normal-to-normal RR intervals.

in relation to vitamin D status in 163 patients with T2DM.[40] The five cardiovascular reflex tests according to the Ewing protocol, as well as time and frequency domains of heart rate variability, in patients with CAN were assessed. Patients were classified by 25(OH)D level: sufficient (≥20 ng/mL), insufficient (10–<20 ng/mL), or deficient (<10 ng/mL). Vitamin D deficiency was significantly correlated with heart rate–variability parameters. The connection between vitamin D concentration and CAN was of borderline significance. Consequently, further studies are needed to specify the relationship between vitamin D and CAN.

Hansen et al.[47] assessed the associations between serum level of vitamin D and measures of CAN in 113 patients with T1DM or T2DM. Patients underwent vitamin D assessment and three cardiovascular reflex tests: (1) heart rate in response to deep breathing (E/I ratio), standing (30/15 ratio), and the Valsalva maneuver; (2) assessment of 5-minute resting heart rate; and (3) three heart rate–variability indices.[47] An inverse *U*-shaped association between serum vitamin D level and heart-rate response to deep breathing, 30/15 ratio, and the heart rate–variability indices was found. Linear regression models showed that an increase in vitamin D level from 25 to 50 nmol/L was associated

Table II. Major interventional studies investigating the effect of vitamin D on diabetic neuropathy.

Study	Design	N	Follow-Up	Baseline Vitamin D Level	Vitamin D Dose	Follow-Up Vitamin D Level	Primary End Point	Results
Lee and Chen[22]	Observational	55	3 mo	18 ng/mL	2059 IU/d	30 ng/mL	MPQ, 5-cm VAS, monofilament	Significant reductions in pain scores on both the VAS and MPQ, at −48.5% and −39.4%, respectively, with vitamin D repletion.
Bell[23]	Case report	1	4 wk	16.5 ng/mL	50,000 IU/wk	48 ng/mL	Neuropathic symptoms	Symptoms decreased
Ghadiri-Anari et al.[26]	Quasi-experimental	66	12 wk	26.69 (17.26) ng/mL	50,000 IU/wk	55.52 (31.94) ng/mL	Michigan Neuropathy Screening Instrument	Decreased symptoms and signs of diabetic neuropathy with vitamin D supplementation ($P < 0.001$).
Alam et al.[34]	Prospective	143	11 mo	31.7 (23.2) ng/mL	600,000 IU single dose	46.2 (10.2) ng/mL	Neuropathy Specific Quality of Life Questionnaire, DN4 Neuropathic Pain Diagnostic Questionnaire, total McGill pain score, Short Form McGill Pain Questionnaire	600,000 IU of vitamin D in single IM dose appeared to be efficacious treatment for PDN
de Silva et al.[56]	Prospective	23	12 wk	26 (9) ng/mL	<30 ng/mL, >10,000 IU/d; 30–60 ng/mL, >4000 IU/d	54 (25) ng/mL	Data of heart rate variability	Strong association between high-dose vitamin D supplementation and improvement in CAN parameters

CAN = cardiovascular autonomic neuropathy; DN4 = Neuropathyique 4 score; MPQ = McGill pain questionnaire; NA = not available; PDN = painful diabetic neuropathy; VAS = visual analog self-report scale.

with increases in both heart-rate response to deep breathing and 30/15 ratio.[47] On the contrary, an increase from 125 to 150 nmol/L in vitamin D level was associated with decreases in both heart-rate response to deep breathing and 30/15 ratio. These data indicate that both very high, as well as low, levels of vitamin D are related to CAN in patients with T1DM and T2DM.[47]

Vitamin D Deficiency and Mortality

Mortality rate was analyzed in 78,581 patients who had vitamin D measurements, and matched data with the national register of deaths Austrian.[55] Patients were followed for up to 20 years (mean, 10.5 years). Vitamin D deficiency was defined as a level below 50 nmol/L; low and high vitamin D levels were defined as <10 and >90 nmol/L, respectively. During follow-up, 11,877 patients died. Among them, those with a 25(OH)D level of <10 nmol/L were nearly threefold more likely to have died than those with a normal vitamin D level, although mortality risk varied by age.[54] The hazard ratios for mortality were 2.7 (95% CI, 2.1–3.4) in adults younger than 45 years, 2.9 (95% CI, 2.6–3.4) in adults aged 45 to <60 years, and 2 (95% CI, 1.8–2.3) in adults aged 60 to <75 years.[55] Adults with vitamin D deficiency were more likely to have died from complications of diabetes during 10-year follow-up when compared with vitamin D–sufficient patients.[55] The risk for death was not increased in a subgroup with a vitamin D level of >100 nmol/L, diminishing concerns about a possible negative effect of vitamin D in the greater concentration range.

Although genetic and epigenetic factors were not evaluated in the present review, improved parameters of CAN have been observed with high-dose vitamin D supplementation in patients with T1DM.[56] These results are insufficient to clarify the effect of vitamin D on CAN due to the small number of participants, short follow-up, and the absence of a placebo control group.

DISCUSSION

A number of studies have suggested that vitamin D deficiency might play a significant role in the development of DPN, diabetic foot ulcer, as well as CAN in patients with diabetes. Vitamin D supplementation might serve as an effective adjuvant therapy for neuropathic pain and may slow or stop the progression of neuron destruction (Tables I and II). Therefore, vitamin D supplementation should be considered more seriously in the management of patients with neuropathy with or without symptoms. Vitamin D supplementation should be offered in patients with both diabetes and vitamin D deficiency.[57]

Limitations of Available Data

Some recent studies have reported reduced levels of vitamin D in DPN,[29,58] although many of these did not consider major confounding factors, such as sunlight exposure, diet, lifestyle, and regular physical activity.[19,28,46] A majority of the studies did not differentiate between DPN with or without pain.[59] Most of the studies were cross-sectionally designed with relatively small cohort sizes[46] and did not measure inflammatory markers.[7,16,19,24,28,29] Other limitations of most of the works were that they were not population-based studies[16] and that vitamin D deficiency was defined without accounting for differences by ethnicity.[19] In some cases, patients with T1DM and T2DM were not studied separately.[7] In other studies, the sample size was small.[36,38] Further studies, including long-term prospective and interventional trials, are required to confirm the causality between a low vitamin D level and DPN. Moreover, randomized, controlled trials are needed to verify the efficacy and clinical benefits of vitamin D supplementation in this complication of diabetes.

CONCLUSION

Vitamin D therapy could be a reliable option for treating patients with diabetic complications; however, further studies are needed to confirm these notions.

DECLARATION OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

AUTHOR CONTRIBUTIONS

All of the authors participated in the preparation of the manuscript.

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