Vitamin D in the prevention and treatment of diabetic neuropathy

Zsuzsanna Putz,[1] Dóra Tordai,[1] Noémi Hajdú,[1] Orsolya Erzsébet Vági,[1] Miklós Kempler,[2] Magdolna Békeffy,[1] Anna Erzsébet Körei,[1] Ildikó Istenes,[1] Viktor Horváth,[1] Anca Pantea Stoian,[3] Manfredi Rizzo,[3,4,5] , Nikolaos Papanas[6], Péter Kempler[1]

[1]Semmelweis University, Department of Internal Medicine and Oncology

[2]Semmelweis University, Department of Internal Medicine and Hematology

[3]Diabetes, Nutrition and Metabolic Diseases Department, Carol Davila University, Bucharest, Romania;

[4]Biomedical Department of Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy;

[5]Division of Endocrinology, Diabetes and Metabolism, University of South Carolina School of Medicine, Columbia, South Carolina, USA;

[6]Second Department of Internal Medicine, Democritus University of Thrace, Greece

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/Search strategy

An electronic search was performed in the PubMed database until 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. Only articles written in English were considered.

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 type 2 diabetes. Vitamin D supplementation might serve as an effective adjuvant therapy for neuropathic pain and may be able to slow down or stop the progression of neural damage.

Keywords: vitamin D, sensory neuropathy, cardiovascular autonomic neuropathy

Introduction

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

Even during pregnancy Vitamin D deficiency correlates with an increased lifetime risk of type 1 diabetes mellitus (T1DM) in the new born [4].Additionally and more recently the immunomodulatory effect of vitamin D have been widely discussed COVID infection [5, 6]. There is also growing body of evidence that vitamin D might have an effect on the development of diabetic sensory motor neuropathy, in particular painful diabetic neuropathy. The aim of this review is to summarize the data available at present regarding the possible relationship between vitamin D and diabetic neuropathy.

Search strategy

An electronic search was performed among papers published before September 2021 using the PubMed database. The combinations of the following key words were utilized: vitamin D, diabetes, diabetes mellitus, diabetic neuropathy, polyneuropathy, peripheral neuropathy, cardiac autonomic neuropathy, supplementation, therapy. Only articles written in English were considered.

Potential underlying mechanisms of the role of Vitamin D

Several studies have examined the relationship between low vitamin D levels and neuropathy, but the exact underlying mechanisms are still not fully understood [2, 7]. Vitamin D receptors (VDR) can be found in the cytoplasm and nuclei of cells widespread in the whole 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, which suggests that cholecalciferol has a prominent role in a well-functioning nervous system [8]. Filipovic et al. [8] found that diabetic rats with low vitamin D levels have high VDR expression in the dorsal root ganglia which affects every group of neurons, especially small fibres, that corresponds to

nociception. The authors 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 increased NGF production and prevented neurotrophic deficit [10] Studies investigating the relationship among vitamin D, NGF and cognition [9-12] suggest a direct impact of vitamin D on nerve function, however, further studies are needed to evaluate this process.

Vitamin D and diabetic peripheral neuropathy (DPN)

In a case-control study examining 150 cases with and 600 controls without diabetic neuropathy, a non-linear association was detected between serum 25-dihydroxy-vitamin D (25OHD) and symptomatic DPN was observed. When compared to individuals with 25OHD between 30–40 ng/mL, patients with deficient (<20 ng/mL) vitamin D levels had higher risk of having symptomatic DPN (OR: 2.04, 95%CI: 0.99–4.02, P = 0.054). Nevertheless, patients with 25OHD greater than 40 ng/mL had increased odds of having symptomatic DPN compared to individuals with sufficient levels of 25OHD (30–40 ng/mL), (OR: 4.29, 95%CI: 1.59–11.55). These results suggest that vitamin D should be monitored and evaluated more carefully [13].

Abdelsadek et al. [14] reported that vitamin D deficiency has a significant role in the development and severity of DPN in Egyptian patients with T2DM. In this study, 40 diabetic patients with DPN, 20 without, as well as 30 healthy control subjects were included. Patients with DPN were categorized as painful and painless DPN patients. Serum level of 25OHD in patients with DPN (21.09 ± 8.38) was significantly lower than that in patients without DPN (31.12 ± 14.85) ($p = 0.001$). Mean serum level of 25OHD in patients with painless DPN (10.047 ± 8.12) was decreased compared to that of patients with painful DPN (18.14 ± 3.85), ($p < 0.05$).

Regression analysis revealed that vitamin D deficiency is one of the independent risk factors of DPN, (OD, 0.914), ($p = 0.007$).

Another study, conducted in France by Skalli et al. [15] found the evaluated serum vitamin D concentration in T2DM subjects with and without neuropathy. Patients with DPN were older and had longer diabetes duration, as well as lower vitamin D concentration. In addition, the number of patients with vitamin D deficiency, i.e. 25OHD<20 ng/ml, was notably higher among patients with neuropathy.

In a cross-sectional study of 136 participants [16] investigated the association between 25OHD levels and microvascular complications in T2DM. Mean 25OHD levels were lower in subjects with diabetic neuropathy compared to those without. Additionally, using a cut-off value of 20 ng/ml, diabetic neuropathy was more frequent in subjects with vitamin D deficiency than in those with 25OHD levels above 20 ng/ml (63 vs. 42 %, $p=0.03$). After adjustment for HbA_{1c}, age, smoking, BMI and diabetes duration in a logistic regression model, diabetes duration and 25OHD level proved to be a significant predictor of diabetic neuropathy.

Another case control trial [17] evaluated the association between serum 25OHD and DPN in diabetic subjects. 25OHD was significantly lower in diabetic patients with large-fibre neuropathy (21.2 ± 11.5 vs. 13.5 ± 5.1 ng/mL, $p=0.001$) diagnosed by electrophysiological methods. After adjustment for all studied variables, 25OHD had an independent and inverse association with both the presence and severity of diabetic neuropathy.

Ozuguz et al [18] evaluated the relationship between DPN and vitamin D, nerve growth factor (NGF) and oxidative stress markers in 26 T1DM patients with DPN and 70 T1DM patients without DPN. Mean age, duration of diabetes and retinopathy were found significantly higher in patients who had neuropathy. Levels of 25OHD were significantly lower in the neuropathy group, while there were no differences in NGF levels or in oxidative stress markers. The Michigan neuropathy screening instrument score was positively correlated with age, and

diabetes duration was negatively associated with 25OHD levels. In addition, 25OHD was positively correlated with NGF. The most important risk factor for the development of neuropathy in T1DM patients appeared to be disease duration. Although vitamin D levels were significantly lower in neuropathic patients, it was not an independent risk factor for neuropathy development. Nevertheless, the positive correlation between vitamin D levels and NGF levels, and the negative correlation between vitamin D levels and neuropathy suggest that there is a need for prospective studies with higher number of patients.

In another cross-sectional study [19] in 861 type 2 diabetic (T2DM) patients, vitamin D deficiency was defined as serum circulating 25OHD level < 20 ng/mL. Peripheral neuropathy was evaluated by neurological symptoms, neurological signs, neurothesiometer and electromyogram. After adjusting for all potential confounders, vitamin D deficiency was still linked with increased risk of DPN [odds ratio2.59 (1.48–4.53)] ($p<0.01$). The authors concluded that vitamin D deficiency should be considered an independent risk factor for diabetic peripheral neuropathy. The correlation between lower levels of vitamin D and microvascular complications was also confirmed in a further report [20].

Six studies that involved a total of 1,484 T2DM patients were included in a meta-analysis [21]. The results showed that there were obviously decreased serum 25OHD levels in patients with DPN [weighted mean difference (WMD) = −6.36 ng/ml, 95 % confidence interval (95 % CI) −8.57 to −4.14, $P < 0.00001$]. Vitamin D deficiency was also significantly associated with increased risk of DPN in patients with T2DM [odds ratio (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. They examined 51 subjects with T2DM who had low 25OHD serum levels and painful diabetic

neuropathy. The neuropathic pain score was reduced by 50% after 3 months of vitamin D administration.

The case report conducted by Bell et al. [23] included a 38-year-old male subject with a history of T1DM for 27 years and neuropathic symptoms for 10 years, unable to work and in need of major analgesics for pain management. His 25OHD level was 16.5 ng/dl, and he received vitamin D supplementation. When vitamin D deficiency was corrected, neuropathic symptoms decreased rapidly and the dosage of major analgesics was reduced significantly.

A study including 87 T2DM subjects with neuropathy and 123 without was to examine the relationship between neuropathy and vitamin D deficiency [24]. Serum 25OHD level was significantly lower in the former group. Vitamin D supplementation also significantly decreased the symptoms and the signs of peripheral neuropathy [25].

The objective of a recent research was to explore the effectiveness and safety of vitamin D supplements in painful diabetic neuropathy [26]. Sixty-six T2DM with painful DPN were involved in the study. Patients received 50,000 IU vitamin D3 weekly for 12 weeks. Vitamin D supplementation improved serum levels of 25OHD and reduced symptoms and signs of diabetic neuropathy ($p<0.001$).

In a more recent study, the effect of vitamin D supplementation on microcirculation and symptoms of peripheral neuropathy and inflammatory markers was assessed in T2DM [27]. High-dose vitamin D therapy reduced serum pro-inflammatory interleukin-6 (IL-6) and increased serum anti-inflammatory interleukin 10 (IL-10) concentrations, and these effects were related to improvements in severity of neuropathy and skin microcirculation [27].

Painful diabetic neuropathy and vitamin D deficiency

Neurologic deficits, quantitative sensory testing (QST), electrophysiology, skin biopsy, corneal confocal microscopy (CCM) and measurement of serum 25OHD were performed

among 43 patients with T1DM and 14 non-diabetic healthy control subjects in the cross-sectional study [28]. Among the T1DM patients, 20 had painless, while 23 had painful neuropathy. Both positive (hyperalgesia and allodynia) and negative symptoms (paresthesia and numbness) of diabetic neuropathy were greater among patients with painful, compared to those with painless neuropathy ($p = 0.009$ and $p = 0.02$, respectively). Serum 25OHD levels were significantly lower in painful compared to painless DPN and controls. The results of this study suggests that vitamin D deficiency and insufficiency are associated with painful diabetic neuropathy [28].

Seventeen patients with painful diabetic peripheral neuropathy was examined in cross-sectional study by Shillo et al [29], 14 with painless diabetic peripheral neuropathy and 14 with no diabetic peripheral neuropathy. All patients and volunteers underwent clinical and neurophysiological assessments. Vitamin D was the only independent variable to make a statistically significant contribution to the model with an inverted odds ratio of 1.11. Lower 25OHD levels also correlated with lower cold detection thresholds ($r = 0.39$, $P = 0.02$) and subepidermal nerve fibre densities ($r = 0.42$, $P = 0.01$). In summary, a significant difference in 25OHD levels has been demonstrated in well-characterized people with painful diabetic peripheral neuropathy,

Vitamin D deficiency was found [30] to be related to diabetic painful neuropathy in Greek but not Bangladeshi patients. The study included 111 Bangladeshi immigrants and 101 Greek diabetic patients. Vitamin D levels were significantly lower in Bangladeshi than in Greek patients with diabetes without polyneuropathy (12.4 ± 5.9 *vs.* 23 ± 12.4 ng/ml, *t*-test: $p<0.01$). In Greek patients, the levels of vitamin D were significantly lower in those with small fiber neuropathy compared with those in the group without polyneuropathy ($p<0.05$), but not in those with large fiber neuropathy. In Bangladeshi patients, there was no statistically significant difference in the subgroup of patients with or without polyneuropathy.

Recently, a prospective pilot study [31] using low-level laser therapy (LLLT) in 40 patients with painful DPN demonstrated a significant baseline elevation of both serum magnesium ($p < 0.001$) and 25OHD ($p < 0.002$) in all patients at four weeks after therapy. At one month after LLLT, neuropathy scores indicated a significant improvement. This was associated with a marked reduction in pain ($p > 0.001$). They observed a considerable improvement in the quality of life after LLLT, as well. These results suggest that the progress in the serum magnesium and vitamin D levels were proportional to the quality of life and may be a good indicator of the prognosis of DPN after LLLT.

Prospective future studies investigating the effect of vitamin D supplementation in adults with diabetic neuropathy, such as the one being conducted in the Alberta Diabetes Institute [32] are under way. These studies are expected to give a 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] has shown that a single intramuscular dose of 600.000 IU vitamin D3 provides significant improvement in painful DPN. They involved 143, predominantly T2DM patients with a DN4 score (3.0±1.8), total McGill pain score (21.2±14.9), and SFMPQ score (2.1±0.9). The mean baseline 25OHD level was 31.7±23.3 ng/mL and 58 (40.5%) patients had evidence of vitamin D deficiency.

In a prospective study of 143 participants by Alam et al [34] also assessed the effect of treatment with a single intramuscular injection of high dose vitamin D (600.00 IU) on quality of life in patients with painful DPN using the NeuroQoL questionnaire. A significantly improved neuropathy-specific quality of life was observed following a single high-dose intramuscular treatment with vitamin D3 in these patients, particularly in those with vitamin D deficiency. A significant reduction in patient perception on foot problems was demonstrated,

as well as an increase in the response of an "excellent QoL" 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 ulcers

The relationship between diabetic foot ulcers and vitamin D deficiency were examined in a study of 162 patients without and 162 with diabetic foot ulcers [35]. Patients with foot ulcers had lower median 25OHD levels compared to those without ulcers [6.3 (4.2-11.1) vs. 28.0 (21.4-37.0 ng/ml), p<0.005]. This finding prompts further enquiry into the role of vitamin D deficiency in the development of diabetic foot ulcers.

Dai et al. [36] evaluated the association between vitamin D deficiency and diabetic foot ulcers in a meta-analysis. This evaluation including 7 studies (1115 patients) demonstrated significantly reduced vitamin D levels 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 [37] analyzed vitamin D levels in relation to Charcot neuroarthropathy, peripheral arterial disease, peripheral neuropathy and diabetic foot ulcers. Vitamin D levels were compared in 50 patients with Charcot neuroarthropathy and 50 without, and no significant difference was found (p=0.55). Among subjects with diabetes, those with peripheral arterial disease (p=0.03), diabetic foot infection (p=0.0006), and diabetic foot ulcers (p=0.04) exhibited significantly lower serum vitamin D levels than those without these complications.

Based on the data of a recent meta-analysis of 10 studies [38], vitamin D deficiency appears to play a significant role in the presence of diabetic foot ulcers. The meta-analysis included 817 diabetic patients with foot ulcers and 827 patients without. Prevalence of severe vitamin D deficiency (< 10 ng/mL) was significantly higher in diabetic patients with foot ulcers

compared to those without /52.5% (95% CI = 0.453 to 0.596, $I^2 = 56.5\%$) vs 23% (95% CI = 0.155 to 0.312, $I^2 = 75.3\%$)/. Diabetic foot complications seem to be associated with significantly lower levels of vitamin D.

In a cross-sectional study [39], differences in serum vitamin D levels between diabetic patients with foot ulcer and without, as well as healthy volunteers in a Southern European country were examined. They found that healthy volunteers had higher serum vitamin D levels compared with patients with and without diabetic foot ulcer. Serum levels of vitamin D did not differ between patients with and without ulcer (p= 0.329). Nevertheless, the prevalence of vitamin D deficiency and insufficiency was high in both diabetic groups.

Another work [40] including 73 diabetic patients with diabetic foot ulcer and 169 without (106 with DPN, 63 without complications) was conducted to assess vitamin D status in these patients with T2DM. Serum 25OHD levels were significantly lower in subjects with ulcer compared to those without (p=0.001). Furthermore, the diabetic peripheral neuropathy subgroup was presented with lower vitamin D levels in comparison with patients without complications (p=0,031). These data raise the possibility that supplementation of vitamin D might help to prevent or improve diabetic foot complications due to wound healing effect of vitamin D.

There might be several reasons behind the the low vitamin D levels of these patients. They could be less mobile, thus getting less sun light but they might eat differently as well. Since many patients with diabetes-related foot complications have impaired renal function, it is not surprising that such a high percentage of these patients have reduced levels 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 effect of vitamin D in diabetic foot ulcer patients [41-45].

Vitamin D and cardiovascular autonomic neuropathy

Limited data is available on the relationship between cardiovascular autonomic neuropathy (CAN) and vitamin D deficiency. Some cross-sectional studies [46, 47] postulated that there is an association between 25OHD and the presence and severity of CAN in subjects with diabetes.

Vitamin D receptors can be found in the vascular smooth cells, endothelium and cardiomyocytes [48]. Some trials have shown that vitamin D deficiency can be associated with cardiovascular disease, tumors, 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 can increase cardiovascular mortality, as well [51, 52]. Vitamin D supplementation has been shown to improve measures of CAN in subjects without diabetes [53].

Low heart rate variability may predict 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 in relation to vitamin D status in 163 T2DM subjects [40]. The five cardiovascular reflex tests according to Ewing's protocol and time as well as frequency domains of heart rate variability in autonomic cardiac neuropathy were assessed. Patients were divided into three groups according to their 25OHD levels: sufficient [25OHD $\geqslant$ 20 ng/ml], insufficient [10 $\leqslant$ 25OHD <20] and deficient [25OHD <10] groups. The study results indicated that vitamin D deficiency significantly correlated with heart rate variability parameters. The connection between vitamin D concentration and cardiac autonomic neuropathy was of borderline significance. Consequently, further studies are needed to identify the specific relationship between vitamin D and cardiovascular autonomic neuropathy.

Hansen et al. [47] assessed the association between serum levels of vitamin D and measures of CAN in 113 subjects with T1DM or T2DM. They underwent vitamin D assessment and three cardiovascular reflex tests [heart rate response to deep breathing (E/I ratio), standing (30/15 ratio) and the Valsalva maneuver], as well as assessment of 5-min resting heart rate and heart rate variability indices [47]. An inverse U-shaped association between serum vitamin D levels and heart rate response to deep breathing, 30/15 ratio and three heart rate variability indices was found. Linear regression models showed that an increase in vitamin D levels from 25 to 50 nmol/l was associated with an increase in heart rate response to deep breathing and an increase in the 30/15 ratio [47]. On the contrary, an increase from 125 to 150 nmol/l in vitamin D level was associated with a decrease in heart rate response to deep breathing and in the 30/15 ratio. Their data indicate that both very high, as well as low levels of vitamin D are related to CAN in subjects with T1DM and T2DM [47].

Vitamin D deficiency and mortality

Mortality rate was analyzed [55] in 78.581 patients who had vitamin D measurements, and matched data with the national register of deaths. Patients were followed for up to 20 years (mean follow-up 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 nmol/L and 90 nmol/L, respectively. During follow-up, 11,877 subjects died. Among them, those with a 25OHD level of less than 10 nmol/L were nearly 3 times more likely to die than those with a normal vitamin D level, although mortality risk varied by age [54]. The hazard ratio (HR) for mortality was 2.7 (95% CI: 2.1-3.4) for adults younger than 45 years, 2.9 (95% CI: 2.6-3.4) for adults aged 45 to 60 years, and 2 (95% CI: 1.8-2.3) for adults aged 60 to 75 years [55]. Adults with vitamin D deficiency were more likely to die of complications from diabetes during 10 years of follow-up when compared with vitamin D sufficient subjects [55]. The risk for death according to vitamin D level in

various subgroups did not demonstrate increased mortality risk at vitamin D levels above 100 nmol/L, diminishing concerns about a possible negative effect of vitamin D in the higher concentration range.

Although genetic and epigenetic factors were not evaluated, improved parameters of CAN in T1DM was observed with high dose vitamin D supplementations [56]. These results are insufficient to clarify the effect of vitamin D on CAN due to the small number of participants, short period of time and the absence of a placebo control group.

Limitations of available data

Some of the recent studies have reported reduced levels of vitamin D in DPN [29, 57] although many of these did not consider major confounding factors, such as sunlight exposure, diet, lifestyle and regular physical activity- [19, 28, 46]. Moreover, majority of the studies did not differentiate between DPN with or without pain [58]. Most of the studies were cross-sectionally designed with relatively small cohort size [46] and did not measure inflammatory markers.[7, 16, 19, 24, 28, 29]. Another limitation of most of the works is that they are not population-based studies [16] and vitamin D deficiency was defined without accounting for different ethnicities [19]. In some cases, T1DM and T2DM patients 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 low vitamin D levels and diabetic neuropathy. Moreover, randomized, controlled trials are needed to verify the efficacy and clinical benefits of vitamin D supplementation in this complication of diabetes.

Conclusions

A number of studies have suggested that vitamin D deficiency might play a significant role in the development of peripheral neuropathy in diabetes, diabetic foot ulcers as well as

cardiovascular autonomic neuropathy. Vitamin D supplementation might serve as an effective adjuvant therapy to neuropathic pain and may be able to slow down or stop the progression of neuronal destruction **(Table 1, Table 2).** Therefore, vitamin D supplementation should be considered more seriously in the management of neuropathy with or without symptoms. Vitamin D supplementation should be offered to patients with both diabetes who are vitamin D deficient [59]. Overall, vitamin D therapy could be a reliable option for treating diabetic complications, however, further studies are needed to confirm these notions.

References

1. Alam, U., et al., *Marked vitamin D deficiency in patients with diabetes in the UK: ethnic and seasonal differences and an association with dyslipidaemia.* Diabet Med, 2012. **29**(10): p. 1343-5.
2. Putz, Z., et al., *Is there an association between diabetic neuropathy and low vitamin D levels?* Curr Diab Rep, 2014. **14**(10): p. 537.
3. Bivona, G., et al., *Serum Vitamin D as a Biomarker in Autoimmune, Psychiatric and Neurodegenerative Diseases.* Diagnostics (Basel), 2022. **12**(1).
4. Hypponen, E., et al., *Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study.* Lancet, 2001. **358**(9292): p. 1500-3.
5. Hadizadeh, F., *Supplementation with vitamin D in the COVID-19 pandemic?* Nutr Rev, 2021. **79**(2): p. 200-208.
6. Bilezikian, J.P., et al., *MECHANISMS IN ENDOCRINOLOGY: Vitamin D and COVID-19.* Eur J Endocrinol, 2020. **183**(5): p. R133-R147.
7. Soderstrom, L.H., et al., *Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001-2004 NHANES.* Diabet Med, 2012. **29**(1): p. 50-5.
8. Filipovic, N., et al., *Increased vitamin D receptor expression in dorsal root ganglia neurons of diabetic rats.* Neurosci Lett, 2013. **549**: p. 140-5.
9. Garcion E, W.-B.N., Montero-Menei CN, Berger F, Wion D, *New clues about vitamin D functions in the nervous system.* Trends Endocrinol Metab, 2002.
10. Riaz, S., et al., *A vitamin D(3) derivative (CB1093) induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats.* Diabetologia, 1999. **42**(11): p. 1308-13.
11. Annweiler, C., et al., *Dietary intake of vitamin D and cognition in older women: a large population-based study.* Neurology, 2010. **75**(20): p. 1810-6.
12. Llewellyn, D.J., et al., *Vitamin D and risk of cognitive decline in elderly persons.* Arch Intern Med, 2010. **170**(13): p. 1135-41.
13. Esteghamati, A., et al., *Non-linear contribution of serum vitamin D to symptomatic diabetic neuropathy: A case-control study.* Diabetes Res Clin Pract, 2016. **111**: p. 44-50.
14. Abdelsadek, S.E., E.O. El Saghier, and S.I. Abdel Raheem, *Serum 25(OH) vitamin D level and its relation to diabetic peripheral neuropathy in Egyptian patients with type 2 diabetes mellitus.* Egypt J Neurol Psychiatr Neurosurg, 2018. **54**(1): p. 36.
15. Skalli, S., et al., *Vitamin D deficiency and peripheral diabetic neuropathy.* Eur J Intern Med, 2012. **23**(2): p. e67-8.
16. Ahmadieh, H., et al., *Hypovitaminosis d in patients with type 2 diabetes mellitus: a relation to disease control and complications.* ISRN Endocrinol, 2013. **2013**: p. 641098.
17. Alamdari, A., et al., *An inverse association between serum vitamin D levels with the presence and severity of impaired nerve conduction velocity and large fiber peripheral neuropathy in diabetic subjects.* Neurol Sci, 2015. **36**(7): p. 1121-6.
18. Ozuguz, U., et al., *Does vitamin D have any role in the improvement of diabetic peripheral neuropathy in type 1 diabetic patients?* J Endocrinol Invest, 2016. **39**(12): p. 1411-1417.
19. He, R., et al., *Vitamin D deficiency increases the risk of peripheral neuropathy in Chinese patients with type 2 diabetes.* Diabetes Metab Res Rev, 2017. **33**(2).
20. Bajaj, S., et al., *Vitamin D levels and microvascular complications in type 2 diabetes.* Indian J Endocrinol Metab, 2014. **18**(4): p. 537-41.

21. Lv, W.S., et al., *Serum 25-hydroxyvitamin D levels and peripheral neuropathy in patients with type 2 diabetes: a systematic review and meta-analysis.* J Endocrinol Invest, 2015. **38**(5): p. 513-8.
22. Lee, P. and R. Chen, *Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain.* Arch Intern Med, 2008. **168**(7): p. 771-2.
23. Bell, D.S., *Reversal of the Symptoms of Diabetic Neuropathy through Correction of Vitamin D Deficiency in a Type 1 Diabetic Patient.* Case Rep Endocrinol, 2012. **2012**: p. 165056.
24. Shehab, D., et al., *Does Vitamin D deficiency play a role in peripheral neuropathy in Type 2 diabetes?* Diabet Med, 2012. **29**(1): p. 43-9.
25. Wei, W., et al., *The efficacy of vitamin D supplementation on painful diabetic neuropathy: Protocol for a systematic review and meta-analysis.* Medicine (Baltimore), 2020. **99**(31): p. e20871.
26. Ghadiri-Anari, A., et al., *Dose vitamin D supplementations improve peripheral diabetic neuropathy? A before-after clinical trial.* Diabetes Metab Syndr, 2019. **13**(1): p. 890-893.
27. Karonova, T., et al., *High-Dose Vitamin D Supplementation Improves Microcirculation and Reduces Inflammation in Diabetic Neuropathy Patients.* Nutrients, 2020. **12**(9).
28. Alam, U., et al., *Vitamin D deficiency is associated with painful diabetic neuropathy.* Diabetes Metab Res Rev, 2021. **37**(1): p. e3361.
29. Shillo, P., et al., *Reduced vitamin D levels in painful diabetic peripheral neuropathy.* Diabet Med, 2019. **36**(1): p. 44-51.
30. Zambelis, T., et al., *Lack of Definite Association of Vitamin D Deficiency with Diabetic Neuropathy. Investigation in Greek and in Bangladeshi Patients.* In Vivo, 2017. **31**(2): p. 259-261.
31. Anju, M., et al., *Effect of Low Level Laser Therapy on serum vitamin D and magnesium levels in patients with diabetic peripheral neuropathy - A pilot study.* Diabetes Metab Syndr, 2019. **13**(2): p. 1087-1091.
32. Institute, U.o.A.D. *Future trials of vitamin D supplementation in painful diabetic neuropathy* https://www.ualberta.ca/alberta-diabetes/clinical-research/clinical-research studies/index.html?details=11].
33. Basit, A., et al., *Vitamin D for the treatment of painful diabetic neuropathy.* BMJ Open Diabetes Res Care, 2016. **4**(1): p. e000148.
34. Alam, U., et al., *Improvement in Neuropathy Specific Quality of Life in Patients with Diabetes after Vitamin D Supplementation.* J Diabetes Res, 2017. **2017**: p. 7928083.
35. Zubair, M., et al., *25-Hydroxyvitamin D [25(OH)D] levels and diabetic foot ulcer: is there any relationship?* Diabetes Metab Syndr, 2013. **7**(3): p. 148-53.
36. Dai, J., et al., *Vitamin D and diabetic foot ulcer: a systematic review and meta-analysis.* Nutr Diabetes, 2019. **9**(1): p. 8.
37. Greenhagen, R.M., R.G. Frykberg, and D.K. Wukich, *Serum vitamin D and diabetic foot complications.* Diabet Foot Ankle, 2019. **10**(1): p. 1579631.
38. Yammine, K., F. Hayek, and C. Assi, *Is there an association between vitamin D and diabetic foot disease? A meta-analysis.* Wound Repair Regen, 2020. **28**(1): p. 90-96.
39. Tsitsou, S., et al., *Evaluation of Vitamin D Levels in Patients With Diabetic Foot Ulcers.* Int J Low Extrem Wounds, 2021: p. 1534734620984584.
40. Todorova, A.S., et al., *Vitamin D Status in a Bulgarian Population With Type 2 Diabetes and Diabetic Foot Ulcers.* Int J Low Extrem Wounds, 2020: p. 1534734620965820.
41. Hewison, M., *Vitamin D and the immune system: new perspectives on an old theme.* Endocrinol Metab Clin North Am, 2010. **39**(2): p. 365-79, table of contents.

42. Trujillo, V., et al., *Calcitriol promotes proangiogenic molecules in keratinocytes in a diabetic foot ulcer model.* J Steroid Biochem Mol Biol, 2017. **174**: p. 303-311.
43. Costa, P.L.F., et al., *Transcriptomic Response to 1,25-Dihydroxyvitamin D in Human Fibroblasts with or without a Functional Vitamin D Receptor (VDR): Novel Target Genes and Insights into VDR Basal Transcriptional Activity.* Cells, 2019. **8**(4).
44. Ding, J., et al., *Synergistic effect of vitamin D and low concentration of transforming growth factor beta 1, a potential role in dermal wound healing.* Burns, 2016. **42**(6): p. 1277-86.
45. Dobak, J., et al., *1,25-Dihydroxyvitamin D3 increases collagen production in dermal fibroblasts.* J Dermatol Sci, 1994. **8**(1): p. 18-24.
46. Jung, C.H., et al., *The relationship between vitamin D status and cardiac autonomic neuropathy in patients with type 2 diabetes mellitus.* Diab Vasc Dis Res, 2015. **12**(5): p. 342-51.
47. Hansen, C.S., et al., *High and low vitamin D level is associated with cardiovascular autonomic neuropathy in people with Type 1 and Type 2 diabetes.* Diabet Med, 2017. **34**(3): p. 364-371.
48. Holick, M.F., *Vitamin D deficiency.* N Engl J Med, 2007. **357**(3): p. 266-81.
49. Dobnig, H., et al., *Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality.* Arch Intern Med, 2008. **168**(12): p. 1340-9.
50. Cigolini, M., et al., *Serum 25-hydroxyvitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients.* Diabetes Care, 2006. **29**(3): p. 722-4.
51. Ziegler, D., *Diabetic cardiovascular autonomic neuropathy: prognosis, diagnosis and treatment.* Diabetes Metab Rev, 1994. **10**(4): p. 339-83.
52. Ziegler, D., . *Cardiovascular autonomic neuropathy: clinical manifestations and measurement.* Diabetes Reviews 1999.
53. Mann, M.C., et al., *Vitamin D supplementation is associated with improved modulation of cardiac autonomic tone in healthy humans.* Int J Cardiol, 2014. **172**(2): p. 506-8.
54. Pilz, S., et al., *Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography.* J Clin Endocrinol Metab, 2008. **93**(10): p. 3927-35.
55. Marculescu R, E.G., Yang L, Haidinger G, Wagner O, Waldhör T., *Vitamin D deficiency, overall and cause specific mortality: the impact of age and diabetes.* European Diabetes Association for the Study of Diabetes Annual Meeting, 16-20 Sept, Barcelona, Spain, 2019.
56. Silva, L.S.D., et al., *Improvement in Cardiovascular Autonomic Neuropathy After High-Dose Vitamin D Supplementation in Patients With Type 1 Diabetes.* Front Endocrinol (Lausanne), 2020. **11**: p. 605681.
57. Qu, G.B., et al., *The association between vitamin D level and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus: An update systematic review and meta-analysis.* J Clin Transl Endocrinol, 2017. **9**: p. 25-31.
58. Straube, S., et al., *Vitamin D for the treatment of chronic painful conditions in adults.* Cochrane Database Syst Rev, 2010(1): p. CD007771.
59. Papandreou, D. and Z.T. Hamid, *The Role of Vitamin D in Diabetes and Cardiovascular Disease: An Updated Review of the Literature.* Dis Markers, 2015. **2015**: p. 580474.

Authors	Type of study	Number of subjects	Follow-up periods	Main outcome	Results
Esteghamati et al.[13]	Prospective	750	NA	Diabetic neuropathy sypmtoms score (DNS)	Vitamin D should be monitored and evaluated more carefully.
Abdelsadek et al. [14]	Case Control	80	6 months	Neuropathy disability score, McGill visual analog scale (VAS)	Vitamin D deficiency is one of the independent risk factots 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 lower in the group with neuropathy, 24.6±11.98 vs. 34.74±17.26 nmol/l in the group without neuropathy (p<0.001)
Ahmadieh K et al. [16]	Cross-sectional	136	NA	UK screening score	Mean 25OHD levels were lower in subjects with diabetic neuropathy compared to those without neuropathy p=0.0004. Low serum 25OHD level was an independent predictor of diabetic neuropathy in patients with DM2T.
Alamdari et al. [17]	Case-control study	62	NA	NCV (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 (MNSI), nerve growth factor (NGF), oxidative stress markers	Positive correlation between vitamin D levels and NGF levels and neuropathy.
Shebab D et al. [24]	Cross-sectional	210	NA	Neuropathy symptom score (NSS), neuropathy disability score (NDS), nerve conduction study (NCS) 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 U et al. [28]	Cross-sectional	57	NA	Quantitative sensory testing, electrophysiology, skin biopsy, corneal confocal microscopy	Serum 25-OH-vitamin D levels were significantly lower in painful neuropathy (p=0,01).
Shilo P et al. [29]	Cross-sectional	59	NA	Neurophysiological assessments, lower limb skin biopsy	Significantly decreased 25OHD levels in subjects with painful diabetic peripheral neuropathy
Zubair M et al.[35]	Prospective cohort	324	NA	Clinical evaulation	Subjects with diabetic foot ulcer showed lower median plasma level of 25(OH)D [6.3(4.2–11.1) vs 28.0(21.4–37.0)] ng/ml.
Greenhagen MR .[37]	Retrospective	100	NA	Michigan Neuropathy Screening Index, Semmes–Weinstein, 128-Hz tuning fork, Achilles reflex, clinical evaulation, 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 CH et al. [46]	Retrospective	163	NA	Cardiovascular reflex test according Ewing's protocol, heart rate variability	The SDNN and RMSSD were significantly lower in patients with the lowest vitamin D levels (p=0.048 and p=0.03, respectively). LF/HF ratio was significantly higher in the group with the lowest vitamin D level (p=0.04).
Hansen CS et al. [47]	Cross-sectional	113	NA	Three cardiovascular reflex tests, heart rate, heart rate variability indices	They found an inverse U-shaped association between serum vitamin D level and E/I ratio, 30/15 ratio and threeheart rate variability indices (P <0.05).

Table 1. Major studies investigating the relationship between serum vitamin D and diabetic neuropathy

DFI diabetic foot infection, **DFU** diabetic foot ulcers, **DNS** diabetic neuropathy symptom score, **DPN** diabetic peripheral neuropathy, **E/I** heart rate response to deep breathing, **LF/HF** low frequency/high frequency ratio, **NA** not available, **MNSI** Michigan Neuorpathy Screening Instrument, **NCS** nerve conduction study, **NCV** nerve conduction velocity, **NDS** neuropathy disability score, **NGF** nerve growth factor, **PAD** peripheral arterial disease, **RMSSD** square root of the average of the sum of the squares of the differences between adjacent NN intervals, , **SDNN** standard deviation of normal to-normal RR intervals, **VAS** visual analogue self-report scale,

Authors	Type of study	Number of subjects	Follow-up periods	Baseline vitaminD level	Doses of vitamin D supplementation	Follow-up vitamin D level	Main outcome	Results
Lee P et al. [22]	Observational	55	3 months	18 ng/ml	2059 IU (per day)	30 ng/ml	MPQ, 5-cm VAS, monofilament	Vitamin D repletion resulted in a significant reduction in pain scores on both the VAS and MPQ at −48.5 and −39.4 %, respectively.
Bell et al.[23]	Case Report	1	4 weeks	16,5 ng/ml	50 0000 IU (weekly)	48 ng/ml	Neuropathic symptoms	symptoms decreased
Ghadiri-Anari A et al. [26]	Quasi-experimental	66	12 weeks	26,69± 17,26 ng/ml	50 000 IU (weekly)	55,52±31,94 ng/ml	Michigan Neuropathy Screening Instrument (MNSI)	Vitamin D supplementation decreased in the symptoms and sign of diabetic neuropathy ($p<0.001$).
Alam U et al. [34]	Prospective	143	11 months	31,7±23,2 ng/ml	600,000 IU single dose	46,2±10,2 ng/ml	Neuropathy Specific Quality of Life Questionnaire (NeuroQoL), DN4 Neuropathic Pain Diagnostic Questionnaire, total McGill pain score, Short Form McGill Pain Questionnaire (SFMPQ)	600 000 IU of vitamin D in single intramuscular dose, appears to be efficacious treatment for PDN
de Silva DD et al. [56]	Prospective	23	12 weeks	26±9 ng/ml	‹30 ng/ml--›10000 IU (per day) 30-60 ng/ml--›4000 IU (per day)	54±25 ng/ml	Data of heart rate variability	They found a strong association between high-dose vitamin D supplementation and improvement in CAN parameters

Table 2. Major interventional studies investigating the effect of vitamin D on diabetic neuropathy

CAN cardiovascular autonomic neuropathy, **DN4** Neuropathyique 4 score, **MNSI** Michigan Neuropathy Screening Instrument, **MPQ** McGill pain questionnaire, **NA** not available, **PDN** painful diabetic neuropathy, **SFMPQ** Short Form McGill Pain Questionnaire **VAS** visual analogue self-report scale,