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# Vitamin Therapy and its Role in Repletion of Neurological Deficits

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## ABSTRACT

The article discusses the features of the role of vitamin therapy in the repletion of neurological deficits. The authors point out that the studied literature indicates that vitamin D deficiency in certain cases is a negative factor that directly affects the development of diabetes and related diseases. The conducted studies of various types and volumes allow us to conclude that the attention paid to vitamin therapy in medicine today is not enough, since achieving a balance of certain vitamins in the body can reduce the risk of certain diseases, as well as improve the quality of life of patients.

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## INTRODUCTION

Deficiency of certain vitamins in the human body can lead to various malfunctions of organs or their groups, for this reason, the study of vitamin balance is one of the important areas of scientific research. One of the vitamins that have a significant impact on a number of metabolic processes is vitamin D. This vitamin is synthesized in the body by the skin, kidneys and liver and is necessary for life in small quantities.[1]

There is a lot of data on the various effects of vitamin D, in addition to its known effect on calcium metabolism. Studies have shown that vitamin D deficiency may be associated with cardiovascular diseases, tumors and autoimmune diseases, and may also play a role in the development of diabetes and neurodegenerative diseases.

It is known that even during pregnancy, vitamin D deficiency correlates with an increased lifetime risk of developing type 1 diabetes mellitus (DM1) in newborns. Also, due to the development of coronavirus infection, the immunomodulatory effects of vitamin D have received wide coverage.[2]

There is evidence in the literature that vitamin D deficiency can affect the development of diabetic sensory-motor neuropathy, in particular painful diabetic neuropathy. It is particularly interesting to study the possible relationship between vitamin D deficiency and diabetic neuropathy.

## MATERIALS AND METHODS

Articles and publications within the framework of this research topic were studied, the information obtained was processed through analytical and comparative research methods.

## RESULTS

One of the areas of study in this context was the study of the relationship between low vitamin D levels and neuropathy, but the exact mechanisms underlying this phenomenon have not yet been fully studied.[3] The vitamin D receptor (VDR) can be found in the cytoplasm and cell nuclei throughout the nervous system. VDR is a ligand-activated transcription factor that regulates the expression of a number of genes. In addition to diabetic neuropathy, VDR has been associated with several diseases such as neurodegenerative and autoimmune diseases, suggesting that cholecalciferol plays an important role in the normal functioning of the nervous system.[4]

The researchers noted that rats who were diagnosed with diabetes and who had low vitamin D levels had high VDR expression in the ganglia of the posterior roots, which affected each group of neurons, especially the small fibers that correspond to nociception. The authors suggested that this mechanism may be an important factor in pain neuropathy.

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The effect of vitamin D, as the researchers point out, is associated with a neuroprotective effect. Vitamin D stimulates the production of nerve growth factor (NGF). Treatment of rats with NGF deficiency with vitamin D was associated with an increase in NGF production with a clear preventive effect against neurotrophic deficiency. The results of studies of the relationship between vitamin D, NGF and cognitive functions suggest a direct effect of vitamin D on nervous function.[5]

Also, various authors have conducted practical studies of the relationship between vitamin D and diabetic peripheral neuropathy.

In a case-control study of data from 150 patients with diabetic neuropathy and 600 control patients, a nonlinear relationship was observed between serum 25-dihydroxyvitamin D (25[OH] D) and symptomatic diabetic peripheral neuropathy (DPN). Compared to individuals with sufficient (30-40 ng/ml) level of 25(OH)D in patients with insufficient (<20 ng/ml) vitamin D levels, the risk of developing symptomatic DPN was higher (odds ratio [OR] = 2.04; 95% CI, 0.99–4.02; P = 0.054). However, patients with level 25(OH)D >40 ng/ml had an increased risk of symptomatic DPN compared to individuals with a sufficient level of 25(OH)D (OR = 4.29; 95% CI, 1.59–11.55). These results suggest that vitamin D levels should be carefully monitored and evaluated.[6]

Another group of authors concluded that vitamin D deficiency plays a significant role in the development and severity of DPN in Egyptian patients with type 2 diabetes mellitus (DM2). The study included patients with DM and with (n = 40) and without (n = 20) DPN, as well as 30 healthy individuals of the control group. DPN was classified as painful or painless.[7]

Medium (SD) level 25(OH)Serum D was significantly lower in patients with DPN than in patients without DPN (21.09 vs. 31.12 ng/ml; P = 0.001). Average level 25(OH)Serum D was reduced in patients with painless DPN compared to that in patients with painful DPN (10.047 vs. 18.14 ng/ml; P< 0.05). In regression analysis, vitamin D deficiency was an independent risk factor for DPN (odds ratio (OD) = 0.914; P = 0.007).

Another study evaluated the concentration of vitamin D in serum in patients with DM2 with and without DPN. Patients with DPN were older and had a longer duration of diabetes, as well as a lower concentration of vitamin D. In addition, the percentage of patients with vitamin D deficiency (<20 ng/ml) was noticeably higher in the DPN subgroup.[8]

A cross-sectional study involving 136 participants examined the relationship between level 25(OH)D and microvascular complications in DM2. Average level 25(OH)D was lower in patients with DPN compared to that in patients without DPN. In addition, with a threshold value of vitamin D deficiency <20 ng/ml, DPN was more common in the subgroup with vitamin D deficiency than in the group with a level of 25(OH)D >20 ng/ml (63% vs. 42%); p = 0.03). After adjusting for HbA 1c, age, smoking, body mass index and duration of diabetes in the logistic regression model, duration of diabetes and level 25(OH)D were significant predictors of DPN.[9]

Another case-control study assessed the relationship between level 25(OH)D in blood serum and DPN in diabetic patients. Average value 25(OH)D was significantly lower in patients with diabetes mellitus with DPN of large fibers, which was diagnosed by electrophysiological methods (21.2 vs. 13.5 ng/ml; P = 0.001). After adjusting all studied variables 25(OH)D had an independent and feedback relationship with both the presence and severity of DPN.[10]

Another group of researchers evaluated the relationship between DPN and markers of vitamin D, NGF and oxidative stress in patients with DM1 and with (n = 26) or without (n = 70) DPN. The average age, duration of diabetes and retinopathy were significantly higher in patients with DPN. Average level 25(OH)D was significantly lower in the DPN subgroup, while there were no differences in NGF levels or markers of oxidative stress. The score of the Michigan Neuropathy Screening Tool was positively correlated with age, and the duration of diabetes was negatively associated with the level of 25(OH) D. Also, 25(OH)D was positively correlated with NGF. The most important risk factor for neuropathy in patients with DM1 was the duration of the disease.[11]

Although the average vitamin D level was significantly lower in the DPN subgroup, it was not an independent risk factor for DPN. Nevertheless, the positive correlation between vitamin D levels and PHR levels and the negative correlation between vitamin D levels and DPN indicate the need for prospective studies with a large number of patients.

In another cross-sectional study involving 861 patients with DM2, vitamin D deficiency was defined as the level of circulating 25(OH)D in serum <20 ng/ml. Peripheral neuropathy was assessed by neurological symptoms, neurological signs, neurotesometry and electromyography. After adjusting for all potential distorting factors, vitamin D deficiency was still associated with an increased risk of DPN (OR = 2.59; 95% CI, 1.48-4.53; P <0.01). The researchers came to conclusion that vitamin D deficiency should be considered as an independent risk factor for DPN. The correlation between lower vitamin D levels and microvascular complications was also confirmed in the following report.[12]

In a meta-analysis of data from six studies involving a total of 1,484 patients with DM2, level 25(OH)Serum D was significantly reduced in patients with DPN (weighted mean difference, -6.36 ng/ml; 95% confidence interval (95%). CI), from -8.57 to -4.14; P <0.00001). Vitamin D deficiency was also significantly associated with an increased risk of DPN in patients with DM2 (OR = 2.88; 95% CI, 1.84–4.50; P <0.00001).[13]

The researchers also observed a relationship between vitamin D deficiency and DPN in 51 patients with DM2 who had a low level of 25(OH)D in the blood serum and painful DPN. The assessment of neuropathic pain decreased by 50% after 3 months of taking vitamin D.

In one report, a 38-year-old man with a 27-year history of DM1 and a 10-year history of neuropathy symptoms was unable to work and needed strong analgesics for pain relief. His level is 25(OH)D was 16.5 ng/dl, and he was receiving vitamin D supplements. With the correction of vitamin D deficiency, the symptoms of neuropathy decreased rapidly, and the dosage of analgesics decreased significantly.[14]

In a study in patients with DM2 with (n = 87) and without (n = 123) DPN, the relationship between DPN and vitamin D

deficiency was studied. Level 25(OH)Serum D was significantly lower in the first group. The symptoms and signs of DPN also decreased significantly when taking vitamin D supplements.

Also, the purpose of one study was to study the efficacy and tolerability of vitamin D supplements in painful DPN. 26 66 patients with DM2 with painful DPN were included in the study. Patients received 50,000 IU of vitamin D3 weekly for 12 weeks. Vitamin D supplementation has been linked to an improvement in 25(OH) levelsD in serum and a decrease in symptoms and signs of DPN (both values of P <0.001).[15]

A later study evaluated the effect of vitamin D supplementation on microcirculation and DPN symptoms and markers of inflammation in patients with DM2. Therapy with high doses of vitamin D was associated with a decrease in the concentration of pro-inflammatory interleukin-6 in serum and an increase in the concentration of anti-inflammatory interleukin-10 in serum, and these effects were associated with an improvement in the severity of DPN and microcirculation of the skin.[16]

Neurological deficits, quantitative sensory testing were performed among 43 patients with DM1 and 14 healthy people without diabetes in the control group in a cross-sectional study. Among patients with DM1, 20 had painless DPN, and 23 had painful DPN. The frequency of both positive (hyperalgesia and allodynia) and negative (paresthesia and numbness) symptoms of DPN was higher among patients with pain neuropathy compared with patients with pain-free neuropathy (*P* = 0.009 and 0.02, respectively). Level 25(OH)Serum D was significantly lower in the subgroup with painful DPN compared to that in patients with pain-free DPN and the control group. The results of this study suggest that vitamin D deficiency and insufficiency are associated with painful DPN. The relationship between vitamin D deficiency and diabetic foot ulcer was studied in a study involving 162 patients without diabetic foot ulcer and 162 patients with diabetic foot ulcer. Median (IQR) level 25(OH) D was lower in patients with foot ulcers compared to patients without ulcers (6.3 vs. 28.0 ng/ml; *P* <0.005). This discovery encourages further study of the role of vitamin D deficiency in the development of diabetic foot ulcers.

Researchers evaluated the association between vitamin D deficiency and diabetic foot ulcer in a meta-analysis of data from seven studies (1,115 patients). Vitamin D levels were significantly reduced in patients with diabetic foot ulcer (mean difference -13.47 nmol/L; 95% CI from -16.84 to -10.10; *P* = 0.34; *I2* = 12%).[17]

In a retrospective study, vitamin D levels were analyzed in connection with Charcot's neuroarthropathy, peripheral artery disease, DPN and diabetic foot ulcer. Vitamin D levels were compared in 50 patients with Charcot's neuroarthropathy and in 50 patients without neuroarthropathy, while no significant differences were found (P = 0.55). Among patients with diabetes mellitus, the level of vitamin D in serum was significantly lower in patients with peripheral artery disease (P = 0.03), diabetic foot infection (P = 0.0006) and diabetic foot ulcer (P = 0.04) than in those without these complications.[18]

It can be concluded that vitamin D deficiency seems to play a significant role in the presence of diabetic foot ulcers. 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 higher in patients with foot ulcer compared to patients without it (52.5% [95% CI, 0.453–0.596; *I2* = 56.5%] vs. 23% [95% *CI* 0.155–0.312; *I2* = 75.3%]). Complications of diabetic foot appear to be associated with vitamin D deficiency.

In a cross-sectional study, differences in serum vitamin D levels were studied between patients with diabetes and with or without foot ulcers, as well as in healthy volunteers in a southern European country. Healthy volunteers had higher serum vitamin D levels compared to patients with and without diabetic foot ulcer. Serum vitamin D levels did not differ significantly between patients with and without ulcers (*P* = 0.329). Nevertheless, the prevalence of vitamin D deficiency and insufficiency was high in both subgroups of diabetics.[19]

There is limited data on the relationship between cardiovascular autonomic neuropathy (CAN) and vitamin D deficiency. Some cross-sectional studies have postulated a relationship between 25(OH)D and the presence and severity of CAN in diabetic patients. Vitamin D receptors can be found in vascular smooth muscle cells, endothelium and cardiomyocytes. Some studies have shown that vitamin D deficiency may be associated with cardiovascular diseases, tumors, autoimmune conditions and overall mortality, and may also play a role in the development of diabetes mellitus and neurodegenerative diseases. The presence of CAN can also increase the risk of cardiovascular mortality. Vitamin D supplements have been shown to improve CAN scores in patients without diabetes.

Low heart rate variability can be a predictor of cardiovascular disease and should be considered as a risk factor for heart failure and sudden cardiac death. CAN and heart rate variability were investigated depending on vitamin D status in 163 patients with DM2. Five cardiovascular reflexes were evaluated by Ewing protocol tests, as well as the temporal and frequency regions of heart rate variability in patients with CAN. Patients were classified according to level 25(OH)D: sufficient (≥20 ng/ml), insufficient (10–<20 ng/ml) or insufficient (<10 ng/ml).

Vitamin D deficiency was significantly correlated with heart rate variability parameters. The relationship between vitamin D concentration and CAH was of borderline significance.

**Discussion.** In some studies, it was indicated that vitamin D deficiency can play a significant role in the development of DPN, diabetic foot ulcers, etc. Vitamin D supplementation can serve as an effective adjunctive therapy for neuropathic pain and can slow down or stop the progression of neuronal destruction. Therefore, vitamin D supplements should be considered more seriously when treating patients with or without neuropathy symptoms. Vitamin D supplements should be included in the diet of patients with both diabetes and vitamin D deficiency.

Some recent studies have reported a decrease in vitamin D levels in DPN, although many of them did not take into account the main distorting factors such as exposure to sunlight, diet, lifestyle and regular physical activity. Most studies did not distinguish between DPN with or without pain. Most of the studies were planned using a cross-section with relatively small cohort sizes and did not measure markers of inflammation. Other disadvantages of most of the studies were that they were not population studies and that vitamin D deficiency was determined without taking into account differences by ethnicity.

Further studies, including long-term prospective and interventional studies, are needed to confirm the causal relationship between low vitamin D levels and DPN. In addition, randomized controlled trials are needed to test the efficacy and clinical benefit of vitamin D supplementation in this complication of diabetes.

## CONCLUSION

Thus, the studied literature indicates that vitamin D deficiency in certain cases is a negative factor that directly affects the development of diabetes and related diseases. The conducted studies of various types and volumes allow us to conclude that the attention paid to vitamin therapy in medicine today is not enough, since achieving a balance of certain vitamins in the body can reduce the risk of certain diseases, as well as improve the quality of life of patients.

### Author Contributions

All authors contributed in reviewing the final version of this paper.

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