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Benefits of vitamin D as an additional therapy in painful diabetic neuropathy: Case report and recent literature review

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ABSTRACT

The common chronic complication from diabetes mellitus (DM) is painful diabetic neuropathy. The available symptomatic treatment with standard therapy is not sufficient for pain reduction. Previous studies showed that vitamin D deficiency was common in type 2 diabetes. Some studies report the benefit of vitamin D supplementation. We report a case of a type 2 diabetic 54-year-old obese female with painful diabetic neuropathy. The combination of lifestyle modifications and 2000 IU vitamin D supplementation improved neuropathy eight weeks of therapy symptoms. The literature search found a valid article that supports the use of combined exercise and vitamin D supplementation. Further research with a larger sample and better design is warranted.

Keywords: vitamin D, diabetes, painful diabetic neuropathy, pain, therapy

INTRODUCTION

Diabetes mellitus is one of the most common non-communicable diseases. Data from the International Diabetes Federation (IDF) Diabetes Atlas in 2019 shows that there are 460 million diabetics and is predicted to increase by 51% by 2045. Sixty percent of people with diabetes will experience complications in diabetic peripheral neuropathy, with 54,000 people with diabetes experiencing amputation every year [1]. Diabetic peripheral neuropathy is one of the most common chronic complications of diabetes mellitus. Painful diabetic neuropathy is characterized by tingling, burning, shooting, numbness or even electric shock sensations that can decrease the patient's quality of life [2].

Symptomatic first-line treatment for diabetic neuropathic pain is adjuvant analgesics consisting of tricyclic antidepressants such as amitriptyline and imipramine, SNRIs (Serotonin Norepinephrine Reuptake Inhibitors) such as duloxetine and anticonvulsants such as pregabalin and gabapentin. However, the available study data indicate that the current symptomatic therapy is not optimal in reducing pain and is only beneficial in one in three patients [3]. In addition, the use of this standard therapy is also limited due to the emergence of unwanted side effects so that the treatment of painful diabetic neuropathy patients is not limited to a single treatment [3,4].

Vitamin D deficiency is common in diabetic patients. Low vitamin D concentrations are associated with painful diabetic neuropathy through microvascular injury or direct neuronal metabolic injury [5,6]. Vitamin D deficiency is an independent predictor of painful diabetic neuropathy [7–9]. Vitamin D has a neuroprotective effect by regulating the VDR (vitamin D receptor) and L-type calcium channels [4]. Diabetic peripheral neuropathy is associated with decreased expression of the Nerve Growth Factor (NGF), while vitamin D is known to increase NGF synthesis in human nerve cells [10,11]. Moreover, at recommended doses, vitamin D tends to have low

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side effects, so vitamin D therapy is considered a promising intervention for treating painful diabetic neuropathy [12]. However, current evidence from randomized controlled trials on vitamin D in treating painful diabetic neuropathy is currently lacking, and relevant systematic reviews and meta-analyses are also minimal [4].

Symptomatic treatment of diabetes with existing therapies is still not optimal in reducing symptoms. An additional treatment that improves symptoms and plays a role in the pathomechanism of neuropathy in diabetes is urgently needed [11,13].

CLINICAL QUESTION

A 54-year-old woman came to the neurological department in early March 2021 with complaints of tingling, burning pain and electric shock accompanied by numbness in the tips of her feet and hands since five months ago. The complaint has worsened in the last one month. Pain interferes with the patient's sleep and daily activities. Since six years ago, the patient is a type 2 diabetes mellitus patient with poor blood sugar control (last HbA1c was 7.2%). Patients take metformin two to three times daily and acarbose twice daily. The patient's lipid profile was as follows: LDL cholesterol 130 mg/dL, HDL 40 mg/dL, and triglycerides 242 mg/dL. Blood pressure was controlled with candesartan 8 mg per day. The patient has a body mass index (BMI) value of 24.8 kg/m^2. Neurological physical examination leads to painful diabetic neuropathy. Examination of latency and nerve conduction velocity (electroneuromiograph) confirmed demyelinating type polyneuropathy.

Symptomatic therapy with gabapentin at a dose of 2 times 300 mg per day reduces pain by less than 30%. Additional therapy with mecobalamin three times daily did not significantly reduce pain. Adjunctive therapy with amitriptyline 10 mg at night improved sleep but did not significantly reduce pain. The daily pain intensity in patients with a numeric pain scale is 5-7 out of 10.

Examination of vitamin D levels in the patient showed a deficiency of 8 ng/ml (normal > 30 ng/ml). Non-pharmaceutical and pharmacological treatments are more intensive in patients to achieve the HbA1c and LDL targets. Non-pharmaceutical therapy with regular exercise and diet is carried out. Pharmacological management is added with vitamin D 1000 IU twice a day. In the evaluation of the first month, the complaints are much reduced. The daily pain intensity value is 4-5 from a 10 numeric pain scale. There was an improvement in the LDL value to 88 mg/dL. Patients claim to be more regular in exercising every day between 20-30 minutes with a morning walk around the housing complex.

On the second visit, the complaints got better. Sleep and daily activities improve. Measurement of vitamin D levels improved to 31 ng/ml (normal). The daily pain intensity value is 2-3 from a 10 numeric pain scale. Blood sugar levels ranged from 100-112 mg/dL, and current blood sugar levels ranged from 150-180 mg/dL. The patient's BMI value improved to 22.6 kg/m^2.

The clinical question arises: "Can additional vitamin D therapy reduce pain in painful diabetic neuropathy?". The PICO (population-intervention-comparison-outcome) components of the clinical question were as follows: population: patients with painful diabetic neuropathy, intervention: supplementary vitamin D therapy, comparison: symptomatic therapy alone, and outcome: painful diabetic neuropathy.

METHODS

The literature search was performed in four databases, including PubMed, CENTRAL, EbscoHost, and ProQuest. Keywords included are vitamin D, neuropathy, painful diabetic neuropathy, therapy, pain, diabetes, type 2 diabetes.

After checking for duplication and elimination with endnote, the first screening stage was carried out by limiting the search to articles by design: in English, in humans, published in the last five years. Stage 1 screening received 11 articles. Based on the best and most current scientific evidence, only further research will be carried out with randomized controlled trial designs.

The second screening stage was carried out by entering the criteria for a randomized controlled trial and accessible full text, seven articles were obtained. By excluding the administration of high-dose vitamin therapy intramuscularly, three articles were found that fit the clinical question and matched the patient's characteristics [14–16].

RESULTS

Critical review

The first step after an article is selected is to determine the degree of scientific evidence and validity of the therapeutic article. The validity was based on the Canter of Evidence-Based Medicine Criteria at the University of Oxford [11,12]. There are several requirements for the validity of a therapeutic article: [1] randomization, [2] blinding, [3] the same characteristics at the beginning of the study, [4] there is no difference in treatment between groups except in terms of the drug/tool being tested, [5] reasonably complete follow-up, and [6] an intention-to-treat analysis was performed.

TABLE 1. Summary of articles on vitamin D therapy for diabetic neuropathy

Author (year)	Method	Subject	Measurement	Result
Nadi et al. (2017)	Randomized Clinical Trial	81 female patients with diabetic neuropathy, divided into two groups	Outcome measurement after 12 weeks of combination therapy of vitamin D and aerobic exercise. Measurements with the Michigan Neuropathy Screening Instrument (MNSI), examination of the patellar reflex on the knee, Achilles reflex on foot, and assessment of the tuning fork between the two groups.	There was a significant improvement in numbness, pain, tingling, and weakness in the experimental group. There was no difference in the improvement of patellar and Achilles reflexes between the two groups.
Karonova, T, et al. (2020)	Randomized Clinical Trial	Sixty-seven patients with type II diabetes mellitus and peripheral neuropathy (34 females) were divided into two groups with different doses of vitamin D administration.	Outcome measurement after 24 weeks. Neuropathy severity measure using NSS, NDS score, and Visual Analogue Scale	There was a significant improvement in clinical symptoms, cutaneous microcirculation, and markers of inflammation in the group given vitamin D3 40,000 IU per week orally. There was no difference in the group given vitamin D3 5000 IU per week orally
Davoudi, M, et al. (2021)	Randomized Clinical Trial	225 diabetic neuropathic pain patients were divided into five groups	Outcome measurement after 12 weeks. Measuring neuropathic pain using the Pain Disability Index (PDI), Specific QOL questionnaire, and neuropathic pain severity scale	There was an improvement in all groups except the placebo-only group. The vitamin D + mindfulness group had a more significant improvement than the other groups ($p<0.05$)

TABLE 2. Assessment of article validity

Author (year)	Validity question	Rated articles	Description
Nadi et al., 2017	Has the placement of each patient for treatment been randomized?	Yes, in the method section	Not explained how to randomize
	Were each group similar when the study began?	Yes, in the results section, table 1	There was no difference in terms of age, height, weight, and BMI values. There is no other information regarding HbA1c, duration of DM, and other drugs
	Were all patients enrolled in the study recorded? And were they analyzed for intention to treat?	Unclear	There is no information about loss of follow-up and no information on the intention to treat analysis
	Are measurements still "blind"?	Unclear	No blinding information
Karonova, T, et al., 2020	Has the placement of each patient for treatment been randomized?	Yes, in the method section	Randomization of patients using the even/odd method into two groups of cholecalciferol treatment
	Were each group similar when the study began?	Yes, in the results section, table 1	There were no significant differences in the distribution of gender, age, BMI, duration of the history of type 2 diabetes mellitus, HbA1c, and other drugs.
	Were all patients enrolled in the study recorded? And were they analyzed for intention to treat?	Unclear	After randomization, three patients refused to participate in the study, and two patients with upper respiratory tract infections were excluded from the study. There is no information on the intention to treat analysis
	Are measurements still "blind"?	Unclear	No blinding information
Davoudi, M, et al., 2021	Has the placement of each patient for treatment been randomized?	Yes, in the method section	Participants were randomized into five groups using a random table
	Were each group similar when the study began?	Yes, in the results section, table 1	There is no difference in terms of age and gender. There is no other information regarding HbA1c, duration of DM, BMI, and other drugs
	Were all patients enrolled in the study recorded? And were they analyzed for intention to treat?	Unclear	There is no information on loss of follow-up and no info on intention-to-treat analysis
	Are measurements still "blind"?	Yes, in the method section	Patients receiving vitamin D or placebo were blinded

DISCUSSION

Based on the journal search results, three articles matched the clinical questions posed, and then a critical study was conducted. After confirming that the article is valid and the results are essential, it is determined whether it can be applied. The questions that should be asked before using the study results to patients are: [1] Are our patients so different from the article reviewed that the results are not applicable? [2] Is the treatment feasible in the current situation? And [3] Will the potential benefits of the treatment outweigh the potential harm of the treatment to the patient?

The three studies found were randomized clinical trials to determine the effect of vitamin D administration on reducing the pain intensity of diabetic neuropathy. Nadi et al., 2017 combine training, and vitamin D administration for 12 weeks to improve sensory-motor neuropathy in 81 diabetic neuropathy patients. The subjects of this clinical trial were females aged 20-55 years who had a history of type II diabetes mellitus for more than five years and had no other comorbidities. Karonova et al., 2020 compared two doses of vitamin D for 24 weeks to improve microcirculation, decrease inflammation, and reduce pain in diabetic neuropathy patients. The subjects used were 67 patients (female predominance) aged 18-65 years and had a history of diabetes for five years. Research by Davoudi et al., 2021 combines vitamin D supplementation and mindfulness training on pain severity, pain-related disability, and neuropathy-specific quality of life dimensions in painful diabetic neuropathy. The subjects were 225 patients aged 20-70 years, had vitamin D insufficiency or deficiency, and had no severe comorbidities. The subjects used in the three articles reviewed were according to the basic characteristics of the patients in this study, namely a female patient aged 54 years and has a history of type II diabetes for six years.

The results of a clinical trial by Nadi et al., 2020 showed that after three months of combined training with vitamin D supplementation, there was a significant reduction in numbness (p=0.001), pain (p=0.002), tingling (p=0.001), and weakness (p=0.002) in the lower limbs. There was also an increase in the sense of touch intervention (p=0.005), detects the position of the fingers (p=0.001), and vibration perception (p=0.001). However, there was no significant change in the patellar reflex in the knee (p=0.77) and the Achilles tendon reflex in the ankle (p=0.47) after the intervention [14].

These results are similar to those experienced by patients reported in this study, is after patients were given additional vitamin D therapy, there was a decrease in daily intensity values from the baseline numeric pain scale of 5-7 to a scale of 4-5 in the first-month evaluation and a scale of 2-3 at the second-month evaluation.

The study by Karonova et al., 2020 after 24 weeks of intervention, found that the group was given high-dose vitamin D supplementation of 40,000 IU/week showed a significant reduction in neurological deficits based on NDS points (p=0.001), decrease in pain severity as assessed by VAS (p=0.001), and a significant decrease in the neuropathic symptom score (NSS) (p=0.001). Meanwhile, no difference was found in the group given vitamin D 5000 IU/week [15].

Davoudi et al., 2021 showed that compared to the placebo group, giving an oral dose of vitamin D 4000 IU/day could significantly improve the total Quality of Life (QOL) score, especially on the pain, interpersonal, and emotional burden subscale. In addition, it can also significantly improve pain-related disability and reduce the severity of pain in diabetic neuropathy. However, the most significant improvement was in the combination group of vitamin D + Mindfulness training [16].

Between the three studies reviewed with our patients, differences were in the dose used. However, a search for articles had excluded high-dose vitamin D therapy administration intramuscularly according to our patient's clinical inquiry. Our patients received a higher dose of vitamin D, which is 2 x 1000 IU daily, compared to the clinical trial by Nadi et al., 2017 which used vitamin D in tablet form consisting of 500 mg calcium carbonate + 200 units of vitamin D every 12 hours. However, it is lower than the dose used in clinical trials by Karonova, et al., 2020 and Davoudi et al., 2021. Karonova, et al., 2020 compared the effectiveness of 2 doses of vitamin D, 5000 IU, and 40,000 IU once a week peroral for 24 weeks. While Davoudi et al., 2021 used vitamin D 4000 IU per day orally for 12 weeks. The results of the three clinical trials reviewed showed no severe side effects were reported. Likewise, in our case, no side effects were reported by the subjects. Thus, the ratio of benefit to risk in the administration of vitamin D is good.

Several previous studies showed similar results [11,17–21]. Basit et al. 2016 with a prospective open-label method, included 143 patients with predominant type 2 diabetes mellitus aged 52.31 ± 11.48. Assessment using Douleur Neuropathique 4 score (DN 4) (3.0±1.8), McGill total pain score (21.2±14.9), and Short Form McGill Pain Questionnare (SFMPQ) score (2.1 ± 0 ,9). It showed that treatment with a single dose of 600,000 IU of vitamin D intramuscularly affected reducing painful diabetic neuropathy, which was assessed for 20 weeks [18].

A prospective, placebo-controlled trial by Alam et al., 2017 included 112 diabetic patients with peripheral diabetic neuropathy and vitamin D deficiency [25(OH)D]. Subjects were divided into two groups: the intervention group with 57 people and

the placebo group with 55 people. The intervention group was given 600,000 IU of vitamin D intramuscularly once a week, assessed using neuropathy specific quality of life (NeuroQoL) questionnaire for both groups. The results of this study were that there was a significant increase in 25(OH)D ($p<0.0001$), calcium ($p=0.009$), HDL ($p=0.03$), and a reduction in HbA1c ($p=0.02$). There was a significant improvement in the NeuroQoL score in the stress section. Still, there was no significant change in the NeuroQoL score in the paresthesias, temperature, and touch sensation [19].

A quasi-experimental trial (before-after) by Ghadiri-Anari et al., 2019 with subjects of 58 diabetic neuropathic pain patients, the results showed that after administration of vitamin D3 5000 IU/week orally for 12 weeks, there was a significant increase in HbA1c, vitamin D levels, and Michigan Neuropathy Screening Instrument (MNSI) assessment ($p<0.001$) (17). A recent randomized placebo-controlled study by Sari et al., 2020, with 258 patients also showed similar results. The intervention group was given 300,000 IU intramuscular vitamin D supplementation showed a significant reduction in total DN4 score after 12 weeks. ($p=0.008$). Similarly, the Pinzon and Christi, 2020 study, also conducted at the same hospital as this study, showed that vitamin D supplement therapy was beneficial in reducing the painful symptoms of diabetic neuropathy compared to symptomatic therapy alone [20].

The results of a review of the available scientific evidence for vitamin D therapy show that there is a very promising potential benefit as an adjunct therapy for patients with diabetic neuropathic pain. Further research on a larger scale and more extended observations are needed. Research to assess the most optimum dose is also required. The administration of vitamin D therapy is following recent studies that state that pathognomonic treatment is required in painful diabetic neuropathy, not only focusing on symptom reduction [5,13].

CONCLUSION

A case of diabetic neuropathic pain has been reported in a 54-year-old woman that showed improvement after giving 2000 units of vitamin D per day. These results are supported by research with valid scientific evidence.

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