Narrative Review

Vitamin D Supplementation in the Management of Painful Diabetic Peripheral Neuropathy: A Narrative Review

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Background: Painful diabetic peripheral neuropathy (DPN), a debilitating complication of diabetes mellitus (DM), significantly reduces quality of life. Vitamin D deficiency is common in patients with DM and has been associated with both the presence and severity of DPN.

Objectives: This systematic review aims to investigate whether vitamin D supplementation improves neuropathic symptoms in patients with painful DPN.

Study Design: A narrative review.

Methods: A systematic literature search was conducted in MEDLINE (PubMed), the Cochrane Library, Embase, Scopus, and the Web of Science for English-language articles published through August 7, 2025. Studies were included if they evaluated the effects of vitamin D supplementation in patients with painful DPN.

Results: Overall, 50 articles were identified through the database search. After screening titles and abstracts, 39 articles were excluded for not meeting the inclusion criteria. The remaining 11 articles were assessed for full-text eligibility. Finally, 7 studies were included in this review. Most of those studies reported improvements in pain scores, quality of life, and serum 25(OH)D levels following vitamin D supplementation. The findings suggest that vitamin D alleviates neuropathic pain by modulating inflammatory responses, promoting nerve regeneration, and enhancing the expression of neurotrophic factors.

Limitations: Further randomized controlled trials are needed to confirm the therapeutic efficacy of vitamin D supplementation and to establish the optimal dosage, frequency, and treatment duration associated with it.

Conclusion: The findings support the consideration of vitamin D supplementation as a potential adjunctive strategy for managing painful DPN.

Key words: Vitamin D, diabetes mellitus, diabetic neuropathy, neuropathic pain, quality of life

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Neuropathic pain, a chronic and debilitating condition, is caused by injury or dysfunction of the somatosensory nervous system. Many factors contribute to the development of neuropathic pain, including spinal cord injury, metabolic disorders, organ dysfunction, postherpetic neuralgia, fibromyalgia, autoimmune diseases, chronic alcohol use, chemotherapy, and diabetic neuropathy (1). Neuropathic pain causes significant suffering and impairs patients' functional capacity and quality of life, posing a significant societal burden (2). Despite the availability of various therapeutic approaches for neuropathic pain, the effective management thereof remains a clinical challenge.

Diabetic peripheral neuropathy (DPN), one of the most common complications of diabetes mellitus

(DM), affects approximately 50% of individuals with DM (3). Patients who have DPN present with various symptoms, including muscle weakness in the hands and feet, impaired balance, and neuropathic pain (4,5). Approximately 15-25% of individuals with DM experience neuropathic pain, a condition known as painful DPN (6). Painful DPN refers to pain directly caused by damage or dysfunction within the somatosensory system in individuals with DM (7). This condition is commonly associated with abnormal sensory symptoms, such as allodynia, hyperalgesia, and paresthesia—manifesting as cramps, numbness, burning, tingling, and a pins-and-needles sensation. These symptoms can significantly disrupt sleep and diminish overall quality of life (8). The U.S. Food and Drug Administration has approved pregabalin, duloxetine, and tapentadol for managing painful PDN; however, many patients continue to experience persistent symptoms despite treatment with these agents (6).

Vitamin D deficiency is commonly observed in individuals with DM and has been identified as an independent risk factor for DPN (9,10). Low serum levels of vitamin D are associated with both the presence and severity of DPN (9). Vitamin D, specifically 25-hydroxyvitamin D [25(OH)D], is a fat-soluble vitamin that acts as a key regulator of bone metabolism and calcium homeostasis (11). The biologically active form of vitamin D is vitamin D_3, known as calcitriol. Vitamin D can be synthesized in the skin via sun exposure or obtained from dietary sources, including fatty fish, egg yolks, and fortified dairy products. Emerging evidence suggests that vitamin D supplementation may prevent the onset of painful DPN and alleviate neuropathic pain in individuals with existing DPN (12).

This systematic review aims to evaluate the effects of vitamin D supplementation on neuropathic pain in individuals with painful DPN.

Methods

A systematic review of existing studies was conducted to investigate the effects of vitamin D supplementation on individuals with painful DPN.

Search Strategy

MEDLINE (PubMed), the Cochrane Library, Embase, Scopus, and Web of Science were searched for English-language articles on painful DPN and vitamin D published through August 7, 2025. The following search terms were used in combination to identify relevant studies: ("vitamin D" OR "cholecalciferol" OR "ergocalciferol" OR "25-hydroxyvitamin D" OR "vitamin D deficiency") AND ("diabetic neuropathy" OR "diabetic peripheral neuropathy" OR "painful diabetic neuropathy" OR "neuropathic pain") (Supplementary 1). Studies were included if they (1) involved patients with painful DPN and (2) evaluated the use of vitamin D supplementation for the treatment of DPN-related symptoms.

Results

Overall, 912 potentially relevant articles were identified via the initial search. Titles and abstracts were screened, followed by a full-text review to assess eligibility. Ultimately, 7 studies were included in this review (Fig. 1). Table 1 presents details of the included articles. All 7 studies involved patients with type 2 DM, although one study included both type 1 and type 2 DM (13), with most patients having the latter. The included studies comprised 2 randomized controlled trials (RCTs) (14,15), one open-label RCT (16), one quasi-experimental study (3), 2 prospective observational studies (17,18), and one open-label clinical trial (13).

In 2008, Lee et al conducted a prospective observational study to evaluate the effects of vitamin supplementation on neuropathic pain in patients with type 2 DM and vitamin D insufficiency (18). Fifty-one patients with symptoms of neuropathy (e.g., burning, tingling, numbness, and throbbing sensations) were enrolled. All patients had vitamin D insufficiency (serum 25(OH) D concentration $\leq$ 24 ng/mL) and received oral supplements of vitamin D_3 (mean dose: 2059 IU/day) for 3 months. Following supplementation, significant reductions in pain scores were observed, including a 48.5% decrease in visual analog scale (VAS) scores and a 39.4% decrease in McGill Pain Questionnaire (MPQ) scores. Pain reduction correlated with increased vitamin D levels, suggesting an association between adequate serum 25(OH)D levels and relief from neuropathic pain. The findings imply the potential role of vitamin D supplementation as a safe and effective adjunct therapy for managing neuropathic pain in patients with DPN.

The study by Basit et al (13) evaluated the effects of high-dose vitamin D on painful PDN in 143 patients with type 2 DM. Every patient in the study received a single intramuscular dose of 600,000 IU of vitamin D_3, followed by assessments over 5 visits across 20 weeks, with evaluations conducted every 4 to 6 weeks. Serum 25(OH)D levels increased significantly ($P < 0.0001$), accompanied by a reduction in pain scores on the MPQ, Douleur Neuropathique 4 Questions (DN4) question-

naire, and short-form MPQ. Analgesic effects peaked at approximately 10 weeks and lasted through week 20. These findings indicate that a single high-dose intramuscular vitamin D_3 injection is effective for managing painful PDN.

Alam et al (17) conducted a prospective study involving 143 patients with symptomatic painful DPN. Each patient received a single intramuscular injection of 600,000 IU cholecalciferol and was followed up every 4 weeks over a 20-week period. The Neuropathy-Specific Quality of Life (NeuroQoL) questionnaire was used to assess domains such as pain, emotional distress, sensory symptoms, and daily functioning. The study shows that vitamin D supplementation improved scores on the emotional distress subscale significantly, particularly among patients with vitamin D deficiency. However, no significant improvements were observed in pain- and paresthesia-related domains. The findings suggest that while vitamin D alleviates emotional distress, the vitamin does not reduce neuropathic pain in patients with painful DPN.

In contrast, Ghadiri-Anari et al (3) reported that vitamin D supplementation effectively alleviated pain in patients with DPN. The study included 58 patients with type 2 DM, all of whom received a weekly dose of 50,000 IU of oral vitamin D_3 for 12 weeks. Neuropathy symptoms and signs were assessed before and after the treatment, using the Michigan Neuropathy Screening Instrument (MNSI), which included a 15-item self-administered questionnaire and a physical examination. The MNSI questionnaire assessed DPN symptoms, such as numbness, tingling, pain, and other sensory disturbances in the feet. Following the 12-week intervention, scores on both the MNSI questionnaire and physical examination improved significantly ($P < 0.001$), indicating reductions in the severity of neuropathy. Weekly oral vitamin D_3 supplementation also improved serum 25(OH)D levels and alleviated DPN symptoms. Although this study did not quantify the extent of pain reduction in relation to the increase in serum vitamin D levels, it suggests that vitamin D supplementation has beneficial effects in painful DPN treatment.

In 2020, Sari et al (14) conducted an RCT to evaluate the effects of vitamin D supplementation on neuropathic pain and balance in patients with painful DPN. This study included 57 patients with type 2 DM, all presenting with neuropathic pain symptoms for > 3 months and serum 25(OH)D levels below < 30 ng/mL. Patients were assigned randomly to a treatment group (n = 32) or the control group (n = 25). The treatment group received a single intramuscular injection of 300,000 IU of vitamin D, while the control group received an intramuscular saline injection. After 12 weeks, the treatment group showed a significant decrease in neuropathic pain, as measured on the DN4 questionnaire. The patients in the treatment group also showed greater improvements in balance, assessed using the Berg Balance scale, than did those in the control group. Additionally, symptoms such as burning and electric-shock sensations improved significantly in the treatment group exclusively. These findings suggest that vitamin D supplementation may help in reducing neuropathic pain and enhancing balance in patients with painful DPN and vitamin D deficiency.

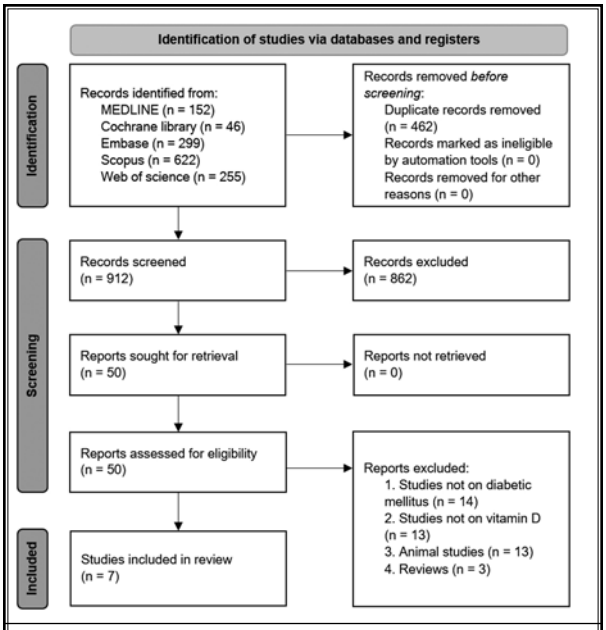

Fig. 1. *Flowchart depicting the article search results.*

The effects of combining vitamin D with other treatments, such as mindfulness training, in addition to vitamin D alone, have also been examined. A 2021 study by Davoudi et al (15) investigated the combined effects of vitamin D supplementation and mindfulness training on pain, disability, and quality of life in patients with painful DPN. Overall, 225 patients with vitamin D insufficiency (serum vitamin D between 10 ng/ML to 30 ng/mL) were randomized into 5 groups: (1) vitamin D plus mindfulness, (2) vitamin D alone, (3) mindfulness alone, (4) mindfulness plus placebo, and (5) placebo. Vitamin D was administered orally at a dose of 4,000 IU daily (28,000 IU weekly) for 12 weeks. Mindfulness training comprised 90-minute sessions incorporating pain management techniques—breathing exercises, meditation,

Table 1. *Characteristics of the included studies.*

No.	Author	Year	Study design	Number of participants	Intervention group	Control group	Treatment duration	Follow-up period	Evaluation measures	Results
1	Lee et al (18)	2008	POS	51	Daily oral cholecalciferol (mean 2,059 IU/day)	No control	3 months	3 months	VAS, MPQ, and serum 25(OH)D	VAS pain score was decreased by 48.5%; MPQ reduced by 39.4%, with a significant increase in serum 25(OH) D levels.
2	Basit et al (13)	2016	OLCT	143	Single intramuscular injection of 600,000 IU vitamin D_3	No control	One-time injection	20 weeks, assessments every 4–5 weeks	DN4 questionnaire, MPQ, SF-MPQ, serum 25(OH)D	Significant improvements in pain scores and serum 25(OH)D; modest but significant improvements in HbA1c and HDL cholesterol.
3	Alam et al (17)	2017	POS	143	Single intramuscular injection of 600,000 IU vitamin D3	No control	Single injection	Five visits at 4-week intervals (20 weeks)	NeuroQoL questionnaire (QOL, emotional distress, pain)	Significant improvement in emotional distress (P = 0.04), especially in patients with baseline vitamin D <30 ng/mL; no significant changes in pain or other QoL domains.
4	Ghadiri-Anari et al (3)	2019	QES	60 (58 completed)	50,000 IU/week oral vitamin D_3 for 12 weeks	None	12 weeks	End of treatment (12 weeks)	MNSI, HbA1c, serum 25(OH)D	Significant improvements in MNSI and serum 25(OH)D; HbA1c improved (all $P < 0.001$).
5	Sari et al (14)	2020	RCT	57 (28 intervention vs. placebo 29)	Single intramuscular injection of 300,000 IU vitamin D_3	Placebo (saline injection)	One-time injection	12 weeks	DN4 questionnaire, Berg Balance Test, serum 25(OH)D	The vitamin D group showed significant improvements in neuropathic pain scores (DN4) and balance (Berg Balance Scale) compared to the placebo group.
6	Davoudi et al (15)	2021	RCT	225 (45 per group: vitamin D + mindfulness, vitamin D only, mindfulness only, placebo + mindfulness, placebo only)	28,000 IU/week oral vitamin D	Mindfulness, vitamin D, placebo	12 weeks	Not reported	PDI, NPS, NeuroQoL	The combination group (vitamin D + mindfulness) showed the greatest improvements in pain severity, disability, and quality of life compared to other groups.
7	Pinzon et al (16)	2021	OLRCT	68 (34 intervention vs. 34 control)	Oral vitamin D 5,000 IU/day + standard medication	Standard medication only	8 weeks	8 weeks	VAS, NRS, BPI, serum 25(OH)D, mood and sleep assessments	The treatment group showed significantly reduced VAS and burning pain scores and improved mood compared to standard treatment alone; vitamin D levels negatively correlated with pain intensity.

Abbreviations: DPN, diabetic peripheral neuropathy; OLCT, open-label clinical trial; OLRCT, open-label randomized controlled trial; POS, prospective observational study; QES, quasi-experimental study; RCT, randomized controlled trial; VAS, Visual Analog Scale; MPQ, McGill Pain Questionnaire; SF-MPQ, Short-Form McGill Pain Questionnaire; DN4, Douleur Neuropathique 4; MNSI, Michigan Neuropathy Screening Instrument; BPI, Brief Pain Inventory; PDI, Pain Disability Index; NRS, Numeric Rating Scale; NPS, Neuropathic Pain Scale; NeuroQoL, Neuropathy-Specific Quality of Life; 25(OH)D: 25-Hydroxyvitamin D; HbA1c, Hemoglobin A1c; QOL: Quality of Life.

progressive muscle relaxation, and cognitive strategies. These interventions aimed to enhance patients' awareness of bodily sensations and emotions, reduce pain catastrophizing, and improve coping mechanisms. The placebo group received only placebo capsules with no active treatment. Pain severity was assessed using the Neuropathic Pain Scale, pain-related disability was measured on the Pain Disability Index, and quality of life was evaluated using the NeuroQoL. After 12 weeks, both vitamin D supplementation and mindfulness training led independently to a significant reduction in pain and disability, alongside improvement in quality of life. However, the combination therapy resulted in significantly greater improvements. No improvement was observed in the placebo-only group. The study concluded that combining vitamin D supplementation and mindfulness training could be considered a therapeutic strategy for treating painful DPN symptoms.

In 2021, Pinzon et al (16) conducted an RCT to evaluate the efficacy of adjunctive oral vitamin D in patients who had painful DPN and received standard pharmacological treatment. Sixty-eight patients who had type 2 DM as well as serum vitamin D levels below 30 ng/mL and reported neuropathic symptoms, such as burning or tingling, were enrolled. The treatment group (n = 34) received 5,000 IU of oral vitamin D daily alongside standard medications—pregabalin, gabapentin, or amitriptyline, with dosages adjusted according to symptom severity for 8 weeks. The control group (n = 34) received standard medication alone. Compared to the control group, the vitamin D group showed significantly greater improvements in pain severity (measured by VAS and burning pain scores), mood, and serum vitamin D levels. While some improvements were observed in tingling and numbness, the most significant effects were reductions in burning pain and mood enhancement. No adverse events were reported, supporting the safety and potential efficacy of vitamin D as an adjunctive therapy for DPN management.

Seven studies investigated the therapeutic potential of vitamin D supplementation in patients with painful PDN, focusing on its effect on neuropathic pain (3,13-18). Most reported positive outcomes include pain reduction and improvements in quality of life and functioning (3,13-16,18). Most studies included patients with type 2 DM and low serum vitamin D levels who were administered therapeutic doses of vitamin D either intramuscularly or orally (3,14-18). Study design, outcomes, and inclusion of adjunctive therapies varied. While most studies showed significant pain reduction, Alam et al (17) reported improvement only in emotional distress, possibly because the NeuroQoL scale focused on symptom frequency rather than pain intensity. Two of the most recent studies (15,16) examined the additive or synergistic effects of combining vitamin D with other treatments, offering broader insights into integrative treatment approaches. Overall, vitamin D supplementation appears to be a promising intervention for managing painful DPN.

Discussion

Vitamin D is a secosteroid hormone, essential for calcium homeostasis and skeletal health as well as regulating immune and inflammatory pathways (19). Upon binding to the vitamin D receptor in muscle and immune cells, the vitamin enhances the production of anti-inflammatory cytokines, such as IL-10, while suppressing pro-inflammatory mediators, including TNFα and IL-1 (20). Vitamin D deficiency is associated with various musculoskeletal pain disorders, including osteoarthritis, fibromyalgia, and low back pain (21-23). Additionally, low serum vitamin D levels are associated with reduced pain relief after interventional procedures such as transforaminal epidural steroid injections (24). Vitamin D deficiency is also associated with various acute and chronic conditions, including DM, cardiovascular disease, autoimmune disease, and frailty (25,26). Serum vitamin D levels are inversely associated with all-cause mortality, with moderate evidence also indicating inverse associations with cancer- and respiratory-related mortality (27). These associations are biologically plausible, given the anti-inflammatory, antiproliferative, antioxidative, and immunomodulatory properties of vitamin D, which may collectively enhance overall health and survival (28).

Vitamin D deficiency is common in individuals with DM and is associated with the presence and severity of painful DPN. This association supports the hypothesis that vitamin D supplementation may mitigate neuropathic DPN symptoms. Evaluating vitamin D status in a patient is therefore essential to determine whether that patient is suitable for supplementation. Most studies define vitamin D deficiency as a serum 25-hydroxyvitamin D concentration < 20 ng/mL and insufficiency as 20–30 ng/mL (19). While optimal vitamin D intake depends on factors such as age, baseline serum levels, and geographic location, daily supplementation of 2,000-4,000 IU is generally recommended to correct deficiency and maintain skeletal health (19,29). Of the 7 studies on painful DPN included in this review, 6 report

improvements in pain scores, quality of life, and serum 25(OH)D levels following vitamin D supplementation, whereas one study (17) shows benefits limited to reducing emotional distress. High-dose regimens—such as 3,000–5,000 IU/day orally or a single intramuscular injection of 300,000–600,000 IU administered over 8–20 weeks—are effective in correcting deficiency and enhancing pain and functional outcomes. After the deficiency is corrected, a maintenance dose of 800–2,000 IU/day is generally recommended, with dosage adjustments based on serum levels and individual risk factors. In summary, measuring baseline serum 25-hydroxyvitamin D levels and re-evaluating them after 8–12 weeks is advised to ensure a target concentration of ≥ 30 ng/mL is achieved and to guide subsequent dose modifications.

Previous studies show that vitamin D supplementation exerts analgesic effects in various pain conditions, including musculoskeletal pain and fibromyalgia (30,31). These benefits are thought to result from upregulating neurotrophic factor expression, modulating inflammatory pathways, and promoting nerve regeneration. Low serum vitamin D levels are associated with increased pain sensitivity and a higher risk of developing chronic pain syndromes (31). The beneficial effects of vitamin D supplementation in painful DPN observed in this review are consistent with those of previous studies on their role in pain management (19,30,32,33). Therefore, correcting vitamin D deficiency should be considered in patients with acute and chronic musculoskeletal pain, as well as in those with painful DPN, as part of strategies to reduce pain intensity and enhance patient outcomes.

To further clarify the therapeutic potential of vitamin D for painful DPN, the underlying pathophysiological mechanisms contributing to its development should be considered. Painful DPN in patients with DM is linked to the neurotoxic effects of chronic hyperglycemia (34). The accumulation of advanced glycation end products and reactive oxygen radicals can damage the microvascular system, impairing blood flow to peripheral nerves (35). Nerve injury can cause neuropathic symptoms such as altered sensations, burning, numbness, tingling, and pain. Studies report that low vitamin D levels increase the risk of hyperglycemia and its complications, while adequate vitamin D intake may help improve glycemic control (36). Therefore, maintaining sufficient serum vitamin D levels may help mitigate or delay the onset of diabetes-related complications, including painful DPN.

Beyond its role in general pain management, vitamin D has demonstrated efficacy in reducing neuropathic pain, particularly in patients with painful DPN. Vitamin D's therapeutic potential for alleviating neuropathic symptoms is attributed to its ability to promote axonal regeneration, reducing nerve damage, including demyelination (17). Additionally, vitamin D contributes to the synthesis of neurotransmitters and neurotrophins, which are crucial for the development, maintenance, and survival of sympathetic and sensory neurons. The vitamin also regulates neuronal differentiation, growth, and function (37). Patients with vitamin D deficiency often exhibit lower pain tolerance, impaired nociceptor function, and increased susceptibility to nerve damage (37,38). Moreover, nociceptive calcitonin gene-related peptide (CGRP)-positive neurons, which mediate pain transmission and inflammatory responses, exhibit vitamin D-responsive phenotypes (39). Low vitamin D levels increase the number of axons expressing CGRP, potentially exacerbating neuropathic pain. Therefore, vitamin D supplementation may mitigate pain by modulating CGRP-related activity (40) and upregulating nerve growth factor (NGF), a key protein involved in the development and maintenance of peripheral nerves (16).

Most of the included studies were conducted in Asian and Middle Eastern countries, including Korea (18), Pakistan (13,17), Iran (3,15), Turkey (14), and Indonesia (16). In these nations, vitamin D deficiency is common. Previous research reports a high prevalence of vitamin D deficiency in Asia and the Middle East (41,42), which is potentially attributable to darker skin pigmentation, cultural clothing habits that limit skin exposure to sunlight, hot climates that discourage outdoor activities, geographic location, season, and low dietary intake of vitamin D-rich foods. While vitamin D deficiency is also relatively common in Europe (41), no studies involving European populations are included in this review. Therefore, further research involving Western populations is needed to determine whether these results can be generalized globally. Expanding the evidence base beyond Asia and the Middle East to include diverse geographic regions would strengthen the conclusion that identifying and correcting vitamin D deficiency to optimal levels is a beneficial therapeutic strategy for alleviating patients' DPN symptoms.

While the findings of the included studies suggest that vitamin D supplementation can help alleviate neuropathic pain in patients with painful DPN, this review has some limitations. First, some studies were observational and lacked control groups, increasing

the risk of bias. Second, most studies had small sample sizes, limiting the generalizability of their findings. Third, outcome measures were primarily based on subjective, self-reported pain scales, which are potentially prone to reporting bias. Fourth, variations in study duration, dosage, and formulation of vitamin D supplementation might have resulted in heterogeneity in the results. Additionally, potential confounding factors, such as comorbidities, concurrent medications, and lifestyle variables—sun exposure and dietary intake—were not controlled consistently across studies. Notably, the included studies did not address the role of lifestyle modification or patient education as either related to the risks of excessive vitamin D supplementation. While vitamin D supplementation is generally safe and rarely raises serum levels to the toxic range, prolonged excessive intake can cause hypercalcemia, hyperphosphatemia, and hypercalciuria, which are early signs of vitamin D toxicity (43). Such disturbances in calcium and phosphorus homeostasis can cause tissue and organ damage, including vascular calcification. Patients should be counseled on the risks of vitamin D toxicity and the importance of adhering to prescribed regimens (44). Despite these limitations, vitamin D supplementation appears to be a safe, cost-effective, and potentially beneficial adjunctive therapy for painful DPN management. Assessing serum vitamin D levels in affected individuals and initiating supplementation in those with vitamin D deficiency can alleviate DPN symptoms and enhance quality of life. However, further RCTs are needed to confirm the therapeutic efficacy of vitamin D supplementation and to establish the optimal dosage, frequency, and duration of this treatment.

Conclusion

Painful DPN is a debilitating complication of DM that impairs patients' quality of life. Correcting vitamin D deficiency helps mitigate neuropathic pain, enhance quality of life, and restore serum vitamin D levels. Evaluating serum 25(OH)D status and providing supplementation for patients with vitamin D deficiency represents a potential adjunctive strategy for managing painful DPN.

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