VITAMIN D'S ROLE IN NEUROPATHIC PAIN – A SYSTEMATIC REVIEW

Shkiryak A.
CEO and chief medical officer "Shkiryak Clinic"
Ukraine
Neurosurgeon
MD, MsSc
ORCID: https://orcid.org/0000-0002-2282-8285
Khanenko S.
"Shkiryak Clinic"
Ukraine
Family doctor
MD, MBA
ORCID: https://orcid.org/0009-0000-4237-1158
https://doi.org/10.5281/zenodo.15220765

Abstract

Chronic neuropathic pain (NP) is a debilitating condition characterized by persistent pain caused by nerve damage. This condition significantly impacts the quality of life, leading to functional limitations, emotional distress, and economic burden. Various underlying conditions, including diabetes, carpal tunnel syndrome, and chronic widespread pain contribute to the NP development. While traditional pharmacological interventions often provide limited relief and have associated side effects, recent research has explored the potential therapeutic benefits of vitamin D. A systematic review was conducted adhering to the PRISMA guidelines to evaluate the efficacy of vitamin D supplementation in managing NP. Seven studies (2016-2024) were included in the analysis, encompassing a total of 561 participants with diverse NP etiologies. The studies investigated the impact of various vitamin D dosages (2000-600,000 IU), administered orally or intramuscularly, for 8 to 20 weeks. Despite the heterogeneity in vitamin D dosage and treatment regimens across the included studies, a consistent trend emerged: a significant reduction in pain scores was observed in all studies following vitamin D supplementation. Moreover, some patients reported improvements in functional mobility and overall quality of life. However, it was difficult to draw a conclusion on the optimal dose of vitamin D for neuropathic pain due to variability on the dose and the route of administration. The findings of this systematic review provide compelling evidence for the potential therapeutic role of vitamin D in the NP management. While further research is warranted to elucidate the optimal dosage, treatment duration, and underlying mechanisms of action, vitamin D supplementation holds promise as a valuable adjunct therapy for individuals suffering from chronic neuropathic pain. Future studies should explore the synergistic effects of vitamin D with other therapeutic interventions and investigate its potential to mitigate the debilitating impact of NP.

Keywords: vitamin D, neuropathic pain.

Introduction

Neuropathic pain (NP), a debilitating condition characterized by lesions or disease in the somatosensory system, significantly impacts both individual productivity and societal function (1). This condition affects an estimated 7-10% of the general population and 30% of individuals with diabetes mellitus. It also often leads to insufficient or incomplete treatment (2, 4). A study involving 70 NP patients found that 65% of patients with diabetic peripheral neuropathy (DPN) missed work or experienced reduced productivity due to pain (5). Several studies also highlight the substantial economic burden of this condition, estimated at $US10 billion annually in the United States alone (6).

NP manifests as a spectrum of unpleasant sensory experiences, including allodynia, hyperalgesia, and paresthesia (7). Allodynia is defined as a painful perception in response to non-noxious stimuli, such as light touch or slight temperature changes. Hyperalgesia, on the other hand, is defined as an excessive response to a noxious stimulus including mechanical, chemical, and thermal induction (8). Paresthesia encompasses a range of abnormal sensations, ranging from tingling and pricking to burning and electrical shocks, further contributing to the debilitating nature of NP (3). These diverse sensory features profoundly impact the quality of life and contribute significantly to the morbidity associated with the condition (9).

Numerous condition associated with neuropathic pain, including trigeminal neuralgia caused by trigeminal nerve dysfunction; painful polyneuropathies, represented by diabetic neuropathy and chronic widespread pain (CWP); postherpetic neuralgia due to previous herpes zoster infection; painful radiculopathy, originating from spinal nerve root compression; central neuropathic pain, caused by lesions within the central nervous system; and mononeuropathies, including carpal tunnel syndrome (CTS), affecting specific nerve distributions. This condition provides valuable insights for diagnosis and treatment (10).

While diagnosing and managing neuropathic pain (NP) remains challenging, due to the lack of standardized biochemical assessment tools (3), clinical symptoms remain as a main clue. To support the diagnosis, validated pain severity scales, including Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), Douleur Neuropathique en 4 Questions (DN4), and Leeds assessment of neuropathic symptoms and signs

(LANSS) can be used. Moreover, quality-of-life questionnaires (NeuroQol) can be performed to see the full picture of how NP affects each patient. By combining these insights with physical examination and imaging results, tailored treatment strategies can be made to alleviate the pain and restore function to those struggling with this often-debilitating condition (11).

Current treatment for neuropathic pain includes a combination of several drugs classes such as weak opioids, non-opioid analgesics, antidepressants, and anticonvulsants like gabapentinoid (1). However, these treatments exhibit variable efficacy, potentially requiring increasing dose, and raising safety concerns, particularly in the elderly population. Several studies demonstrated an increasing risk of mortality, dizziness, cognitive decline, and respiratory depression when using opioid and gabapentinoids combination (12, 13). Pharmacokinetic and pharmacodynamic interactions might be responsible for this condition, where opioids enhance gabapentinoids bioavailability, and further cause respiratory distress, such as in high-dose pregabalin administration (14). Consequently, the need for novel therapeutic agents that potentiate analgesic efficacy while minimizing adverse effects is evident.

The research interest in vitamin D, its properties and recommendations for its intake has not decreased. In fact, it has an increased significantly in recent years, making vitamin D one of the most studied nutrients. This has spurred interest in nutraceuticals, including vitamins, minerals, such as vitamin D, as potential supplementation to the main therapies in combating neuropathic pain (15). These agents might improve pain management with a potentially safer profile. Vitamin D supplementation is a method that has gained interest in the treatment of neuropathic pain because it is recognized to be crucial for nerve health and pain regulation (16). Although several studies have shown an association between low vitamin D levels and increased neuropathic pain sensitization, the exact mechanisms that link the two are still not fully understood.

While clinical research on Vitamin D's efficacy in chronic pain, particularly neuropathic pain, remains in its early stages, compelling evidence suggests its involvement in the pathogenesis of this condition through its anti-inflammatory, analgesic, antioxidant, and neuroprotective properties (9, 11,17). This review (registered in PROSPERO CRD42023433300); therefore, it aims to systematically evaluate the effectiveness of Vitamin D as a potential therapeutic agent for neuropathic pain. In addition, this review also aims to identify and analyse future prospects regarding the use of vitamin D as an additional therapy in neuropathic pain cases with more personalized approach that could lead to more effective clinical management in the future.

Materials and Methods

Literature Search Strategy

The search, screening, and data abstraction were independently conducted by HMS and RR. In June 2023, the search was carried out in the Scopus and PubMed databases. Two medical subject headings (MeSH) phrases were utilized in the search. The keyword combinations used in searches: "((vitamin D*[MeSH Terms]) OR (Calcitriol[MeSH Terms])) OR (cholecalciferol[MeSH Terms] AND (neuropathic*[MeSH Terms]) OR (pain*[MeSH Terms]) OR (burn*[MeSH Terms]) OR (allodynia[MeSH Terms])) OR (hyperalgesia[MeSH Terms]) OR (dysesthesia[MeSH Terms]). An English language and period of study from 2003 to 2024 filter was applied in this search.

Inclusion and Exclusion Criteria

Each paper was reviewed for screening by two reviewers, and a discussion with third reviewer was performed if there was ambiguity or disagreement. Articles had to focus on vitamin D as a therapeutic option for patients suffering from neuropathic pain associated with a variety of conditions, including spinal cord injury, post-stroke, multiple sclerosis, cervical radiculopathy, sciatica, diabetic and non-diabetic neuropathies, HIV/AIDS, post-herpetic neuralgia, osteoarthritis with a neuropathic pain component, and trigeminal neuralgia. Additionally, only studies involving human participants above the age of 18 were included, ensuring the generalizability of findings. Selection criteria did not discriminate based on race, ethnicity, gender, or geographical location. Participants in all included studies were diagnosed with neuropathic pain by a physician based on a combination of symptoms, signs, and/or validated neuropathic pain scoring systems such as DN4. Pain assessment primarily utilized tools like the VAS, NRS, and DN4. Furthermore, functional status outcomes were often evaluated using measures like the Boston Symptoms Severity Scale (SSS), Boston Functional Status Scale (FSS), Pain Disability Index (PDI), and NeuroQol. There were no specific dosages, routes of administration, combinations, durations, or forms of vitamin D. The outcome of the intervention studies was a change in neuropathic pain in terms of pain score and functional outcome. The exclusion criteria were studies with the child population, pregnant women, pain caused by acute trauma, accidents or operations, case reports, case series <20 participants, pre-clinical studies, and studies with multiple publications.

Data Collection Process

To ensure systematic data management and maintain a comprehensive record of collected materials, the authors employed Mendeley Reference Manager software for literature organization. Prior to formal screening against inclusion criteria, researchers conducted a preliminary review of titles and abstracts to identify potentially relevant studies. Articles deemed suitable for inclusion underwent thorough summarization, capturing key details such as research design, pain etiology, participant demographics, sample size, country of origin, intervention and comparator characteristics, study duration, evaluation instruments, data outcomes, and any reported limitations. All included papers underwent a final re-evaluation during the manuscript writing stage.

Synthesis of Results

This study followed the recommended guidelines elements for systematic reviews and meta-analyses (PRISMA) criteria (18). Due to the significant heterogeneity of the included studies, data were synthesized and presented in a narrative format. The analysis focused on examining the effectiveness of vitamin D for

different underlying neuropathic pain conditions, primarily diabetic neuropathy, CTS, and CWP.

Assessment of Bias

Bias assessment was conducted using appropriate tools based on the study design. For randomized controlled trials (RCTs) eligible for risk-of-bias evaluation (n=3), the Cochrane Collaboration's risk-of-bias 2 (RoB 2) tool was utilized. This tool assesses five key domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported outcome. Each domain was categorized as low, high, or of some concern. For non-randomized studies (n=4), the Methodological Index for Non-Randomized Studies (MINORS) was employed for evaluating quality. This index comprises 12 items scored on a 0-2 scale (0=not reported, 1=reported but inadequate, 2=reported and adequate). A perfect score for non-comparative studies is 16. Studies were categorized into quality levels based on their total score (0-5=poor, 6-10=moderate, 11-16=good).

Future Perspective: The Role of Vitamin D

Vitamin D has emerged as a fascinating candidate for many diseases, including neuropathic pain management, recognized as a potent and multifaceted neurosteroid within the brain, exhibits hormonal, paracrine, and autocrine activities (58). Notably, Vitamin D supplementation holds promise even for individuals without overt hypovitaminosis D, suggesting its potential independent of bone metabolism (20). This vitamin D and its receptors participate in numerous metabolic possess and possesses specific neurotrophic properties, demonstrating a crucial role in both regulating the expression of inflammatory cytokines involved in pain processing and restricting neurotrophic deficits to promote nerve healing (16). Furthermore, Vitamin D has been shown to upregulate the expression of genes pivotal for nerve regeneration, such as *Osteopontin (Spp1), Acyl-CoA synthetase 4 (Acls4),* and *Angiotensin II receptor 1a (Agtr1a)* (11, 19). Studies have shown that vitamin D upregulates various antioxidant enzymes that protect cells from oxidative damage (21). Furthermore, vitamin D stabilizes calcium levels by upregulating voltage-gated calcium channels (VGCCs), which regulate calcium influx into neurons and promote nerve growth factor expression (22). In addition, vitamin D enhances the myelination of dorsal root ganglion (DRG) neurons and regulates the expression of genes involved in axon growth. It also influences neurotransmitters such as acetylcholine, serotonin, and GABA, and may modulate opioid peptide genes (POMC, PDYN, and PENK), thereby contributing to pain relief (16). Emerging evidence highlights vitamin D's potential role in managing neuropathic pain, particularly given the consistently low vitamin D levels observed in patients. While the exact reasons for this deficiency remain unclear, vitamin D is thought to influence both peripheral and central nerve function. As a neuroprotective agent, vitamin D may reduce inflammation, oxidative stress, and promote neurotrophic factors, while modulating immune responses (16). Taken together, the combination of conventional treatments like gabapentinoids with vitamin D supplementation could offer a more comprehensive approach by modulating multiple pathways involved in neuropathic pain.

This review points to the potential application of vitamin D therapy as part of a more holistic strategy for the management of neuropathic pain. The potential role of personalized vitamin D supplementation plans also shows promise. This approach could allow for a more tailored treatment plan based on factors such as vitamin D levels in the body, underlying disease type, and individual response to therapy (23). By utilizing genetic, lifestyle, and medical condition data, healthcare providers could develop personalized supplementation plans that may involve specific vitamin D dosage recommendations, frequency, and duration of supplementation tailored to each individual's unique needs, thereby increasing therapeutic efficacy, reducing side effects, and providing long-term benefits in the management of neuropathic pain (23, 24). As the understanding of the role of vitamin D in the regulation of the nervous system and metabolism of the body increases, personalized vitamin D therapy and supplementation have the potential to become an integral part of future medical approaches, bringing new hope to the treatment of neuropathic pain with various disease etiologies.

Conclusion

This systematic review highlights the potential effects of vitamin D in reducing pain symptoms of neuropathic pain, and improving its function in patients with PDN, entrapment CTS, and CWP. However, a critical gap remains in our understanding of optimal dosage and treatment duration for neuropathic pain management. The current evidence base encourages initiating treatment with the standard recommended oral vitamin D dosage while closely monitoring serum levels to ensure adequate repletion and adjusting as needed.

References:

1. Finnerup N.B., Attal N., Haroutounian S., McNicol E., Baron R., Dworkin R.H., Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis, Lancet Neurol, 2015, 14:162-73.

2. Attal N., Lanteri-Minet M., Laurent B., Fermanian J., Bouhassira D., The specific disease burden of neuropathic pain: Results of a French nationwide survey, Pain, 2011, 152:2836-2843.

3. Bouhassira D.J.R.N., Neuropathic pain: definition, assessment and epidemiology, Revue Neurologique, 2019, 175:16-25.

4. Baskozos G., Hébert H.L., Pascal M.M., Themistocleous A.C., Macfarlane G.J., Wynick D., Bennett D.L., Smith B.H., Epidemiology of neuropathic pain: An analysis of prevalence and associated factors in UK Biobank, Pain Reports, 2023, 8:1066.

5. Gore M., Brandenburg N.A., Hoffman D.L., Tai K.S., Stacey B., Burden of illness in painful diabetic peripheral neuropathy: The patients' perspectives, The Journal of Pain, 2006, 7:892-900.

6. Ruiz-Negrón N., Menon J., King J.B., Ma J., Bellows B.K., Cost-effectiveness of treatment options for neuropathic pain: A systematic review, Pharmacoeconomics, 2019, 37:669-688.

7. Colloca L., Ludman T., Bouhassira D., Baron R., Dickenson A.H., Yarnitsky D., Freeman R., Truini A., Attal N., Finnerup N.B., Eccleston C., Neuropathic pain, Nature Reviews Disease Primers, 2017, 3:1-19.

8. IASP, Epidemiology of neuropathic pain: How common is neuropathic pain, and what is its impact?, International Association for the Study of Pain, 2014.

9. Shipton E.A., Shipton E.E., Vitamin D and pain: Vitamin D and its role in the aetiology and maintenance of chronic pain states and associated comorbidities, Pain Research and Treatment, 2015, 2015:904967.

10. Finnerup N.B., Kuner R., Jensen T.S., Neuropathic pain: From mechanisms to treatment, Physiol Rev, 2021, 101:259-301.

11. Chabas J.F., Stephan D., Marqueste T., Garcia S., Lavaut M.N., Nguyen C., Legre R., Khrestchatisky M., Decherchi P., Feron F., Cholecalciferol (vitamin D3) improves myelination and recovery after nerve injury, Plos One, 2013, 8:65034.

12. Fick D.M., Semla T.P., Beizer J., Brandt N., Dombrowski R., DuBeau C.E., Eisenberg W., Epplin J.J., Flanagan N., Giovannetti E., American Geriatrics Society(AGS) 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, Journal of the American Geriatrics Society, 2015, 63:2227-46

13. Hahn J., Jo Y., Yoo S.H., Shin J., Yu Y.M., Ah Y.M., Risk of major adverse events associated with gabapentinoid and opioid combination therapy: A systematic review and meta-analysis, Front Pharmacol, 2022, 13:1009950.

14. Lyndon A., Audrey S., Wells C., Burnell E.S., Ingle S., Hill R., Hickman M., Henderson G., Risk to heroin users of polydrug use of pregabalin or gabapentin, Addiction, 2017, 112:1580-1589.

15. Abdelrahman K.M., Hackshaw K.V., Nutritional supplements for the treatment of neuropathic pain, Biomedicines, 2021, 9:674.

16. Habib A.M., Nagi K., Thillaiappan N.B., Sukumaran V., Akhtar S., Vitamin D and its potential interplay with pain signaling pathways, Frontiers in Immunology, 2020, 11:820.

17. d'Arqom A., Nucleic acid therapy for β-thalassemia, Biologics: Targets and Therapy, 2020, 14:95-105.

18. Page M.J., McKenzie J.E., Bossuyt P.M., Boutron I., Hoffmann T.C., Mulrow C.D., Shamseer L., Tetzlaff J.M., Akl E.A., Brennan S.E., Chou R., The Prisma 2020 statement: An updated guideline for reporting systematic review,.

19. Poisbeau P., Aouad M., Gazzo G., Lacaud A., Kemmel V., Landel V., Lelièvre V., Feron F., Cholecalciferol (vitamin D 3) reduces rat neuropathic pain by modulating opioid signaling, Molecular Neurobiology, 2019, 56:7208-7221.

20. Basit A., Basit K.A., Fawwad A., Shaheen F., Fatima N., Petropoulos I.N., Alam U., Malik R.A., Vitamin D for the treatment of painful diabetic neuropathy, BMJ Open Diabetes Research and Care, 2016, 4:000148

21. Zittermann A., Trummer C., Theiler-Schwetz V., Lerchbaum E., März W., Pilz S., Vitamin D and cardiovascular disease: An updated narrative review, International Journal of Molecular Sciences, 2021, 22:2896.

22. Eyles D.W., Smith S., Kinobe R., Hewison M., McGrath J.J., Distribution of the vitamin D receptor and 1α-hydroxylase in human brain, Journal of Chemical Neuroanatomy, 2005, 29:21-30.

23. Mavar M., Sorić T., Bagarić E., Sarić A., Matek Sarić M., The power of vitamin D: is the future in precision nutrition through personalized supplementation plans?, Nutrients, 2024, 16:1176.

24. Karlic H., Krammer U., Haslberger A., Nutritional supplements for athletes and personalization; A short review, Functional Food Science-Online, 2022, 2:224-241.