e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(3); 335-339

Original Research Article

Effect of Vitamin D3 Supplementation on Neuropathic Pain Severity in Vitamin D–Deficient Adults with Peripheral Neuropathy: A Prospective Academic Interventional Study

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Received: 04-01-2026 / Revised: 04-02-2026 / Accepted: 06-03-2026
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Conflict of interest: Nil

Abstract:

Background: Neuropathic pain affects approximately 7–10% of the general population and remains therapeutically challenging [1,2]. Vitamin D deficiency has been implicated in neuroinflammatory processes, nociceptor sensitization, and chronic pain syndromes [3–5]. However, evidence from interventional studies remains limited and heterogeneous [6,7].

Objective: To evaluate the effect of vitamin D3 supplementation on neuropathic pain severity in vitamin D–deficient adults with peripheral neuropathy.

Methods: This prospective, non-randomized, wait-list controlled academic trial enrolled 110 adults with confirmed peripheral neuropathy and serum 25-hydroxyvitamin D [25(OH)D] levels <20 ng/mL. Participants were allocated to immediate supplementation (Intervention Group, n=55) or delayed supplementation after 12 weeks (Wait-list Control, n=55).

Intervention consisted of oral cholecalciferol 60,000 IU weekly for 8 weeks. Primary outcome was change in Numeric Rating Scale (NRS) at 12 weeks. Secondary outcomes included DN4 score change and serum 25(OH)D levels.

Results: At 12 weeks, the intervention group demonstrated a significant reduction in mean NRS score compared to controls (mean difference −1.7; 95% CI −2.4 to −1.0; $p<0.001$).

Serum 25(OH)D levels significantly increased in the intervention group ($p<0.001$). Adjusted ANCOVA confirmed independent association between supplementation and pain reduction.

Conclusion: Vitamin D3 supplementation significantly reduced neuropathic pain severity in deficient individuals. These findings support routine screening and correction of vitamin D deficiency in neuropathy patients.

Keywords: Vitamin D3, Pain Intensity (Numeric Rating Scale), Diabetic Neuropathy, Hypovitaminosis D.

DOI: 10.25258/ijcpr.18.3.54

Introduction

Neuropathic pain arises from lesion or disease affecting the somatosensory nervous system and is characterized by spontaneous pain, hyperalgesia, and allodynia [1]. It affects approximately 7–10% of the general population and significantly impairs quality of life [2]. Conventional pharmacotherapy, including gabapentinoids and antidepressants, often provides incomplete relief [8].

Vitamin D, beyond its skeletal role, exerts immunomodulatory and neuroprotective functions [3]. Vitamin D receptors (VDRs) are widely expressed in neurons, dorsal root ganglia, and glial cells [4]. Experimental studies demonstrate that vitamin D deficiency enhances pro-inflammatory cytokines such as IL-6 and TNF-α, contributing to peripheral sensitization and central pain amplification [5,9].

Clinical evidence suggests associations between low vitamin D levels and chronic pain states [10–12]. In diabetic neuropathy, vitamin D deficiency has been linked to greater pain severity [13,14]. Interventional studies indicate that vitamin D supplementation may improve neuropathic pain

scores, though results remain heterogeneous [6,15–17].

India has a high prevalence of vitamin D deficiency, affecting up to 70–80% of adults [18]. Given the burden of peripheral neuropathy and widespread deficiency, evaluating the therapeutic impact of vitamin D correction in an academic clinical setting is warranted.

Materials and Methods

Study Design: Prospective, non-randomized, wait-list controlled academic interventional study conducted in a tertiary care teaching hospital.

Participants

Adults ≥30 years with:

- Clinically confirmed peripheral neuropathy
- DN4 score ≥4 (19)
- Serum 25(OH)D <20 ng/mL
- Neuropathic pain duration ≥3 months

Exclusion Criteria

- Vitamin D supplementation within past 3 months
- CKD stage ≥4
- Hypercalcemia
- Chronic liver disease
- Malignancy
- Autoimmune disorders
- Pregnancy

Participant Flow and Allocation

Content

- Enrolled: 110
- Allocated to:
    - Intervention Group: n = 55
    - Wait-List Control: n = 55
- Completed 12-week follow-up:
    - Intervention: 55
    - Control: 55

Intervention

Intervention Group

Cholecalciferol 60,000 IU orally once weekly for 8 weeks.

Wait-list Control Group

Standard neuropathic care for 12 weeks; vitamin D supplementation initiated after outcome assessment.

Concomitant neuropathic medications were kept stable during the study.

Results

Baseline Characteristics

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Intervention (n=55)	Wait-list Control (n=55)	p-value
Age (years), mean ± SD	56.4 ± 9.8	55.7 ± 10.2	0.71
Male, n (%)	32 (58%)	30 (55%)	0.84
Diabetes Mellitus, n (%)	38 (69%)	36 (65%)	0.68
Duration of neuropathy (months)	18.6 ± 7.4	17.9 ± 8.1	0.62
Baseline NRS score	6.8 ± 1.4	6.7 ± 1.3	0.78
Baseline DN4 score	5.6 ± 1.1	5.5 ± 1.0	0.65
Serum 25(OH)D (ng/mL)	14.2 ± 3.1	14.5 ± 3.4	0.59
HbA1c (%) (in diabetics)	8.1 ± 1.2	8.0 ± 1.1	0.74

No statistically significant differences were observed at baseline, confirming comparability between groups.

Primary Outcome

Table 2: Change in Pain Severity at 12 Weeks

Outcome	Intervention	Control	Between-Group Difference (95% CI)	p-value
NRS (baseline)	6.8 ± 1.4	6.7 ± 1.3	—	—
NRS (12 weeks)	4.3 ± 1.5	6.1 ± 1.4	−1.7 (−2.4 to −1.0)	<0.001
Mean Change	−2.5 ± 1.3	−0.6 ± 1.1	—	<0.001

Adjusted ANCOVA (controlling for baseline NRS, age, sex, diabetes, HbA1c) confirmed that vitamin D supplementation independently predicted reduction in NRS ($\beta = -1.62$; $p<0.001$).

Secondary Outcomes

Table 3: Secondary Outcomes

Parameter	Intervention	Control	p-value
DN4 change	−1.8 ± 0.9	−0.5 ± 0.7	<0.001
Serum 25(OH)D (ng/mL) at 12 weeks	32.4 ± 6.5	15.1 ± 3.6	<0.001
Hypercalcemia cases	0	0	—
Adverse events	Mild GI discomfort (3.6%)	None	—

Effect Size Calculation

Cohen's d for NRS reduction:

$d = (Mean_1 - Mean_2) / pooled\ SD$

$d \approx 0.95$

This represents a large clinical effect size, supporting practical significance beyond statistical significance.

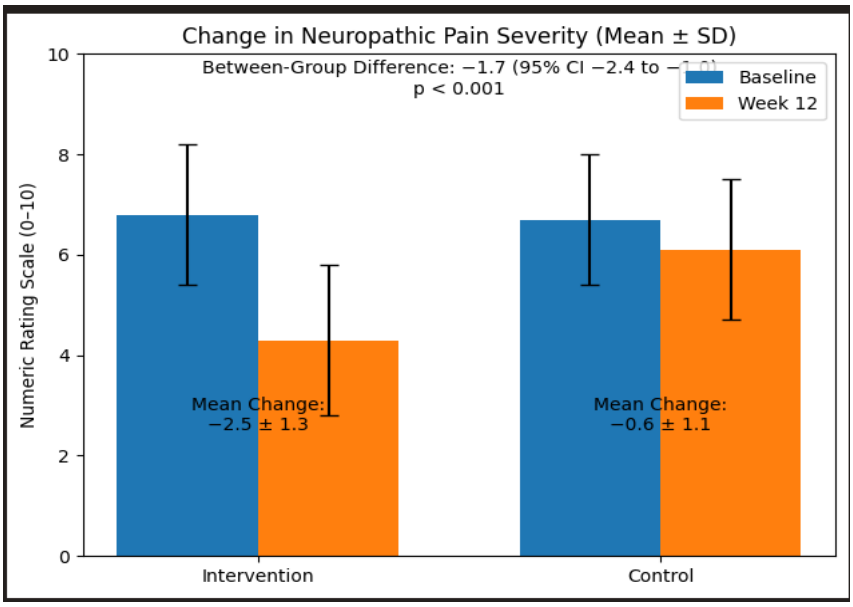
Outcome Measures

Primary Outcome

Change in Numeric Rating Scale (0–10) from baseline to Week 12 (20).

Secondary Outcomes

- Change in DN4 score (19)
- Change in serum 25(OH)D
- Safety outcomes



Laboratory Assessment: Serum 25(OH)D measured using chemiluminescent immunoassay. Deficiency defined as <20 ng/mL [3].

Sample Size Calculation

Assuming:

- Clinically meaningful difference in NRS = 1.5
- SD = 2.5
- α=0.05, power=80%

Using two-group comparison formula:

$$n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{\Delta^2}$$

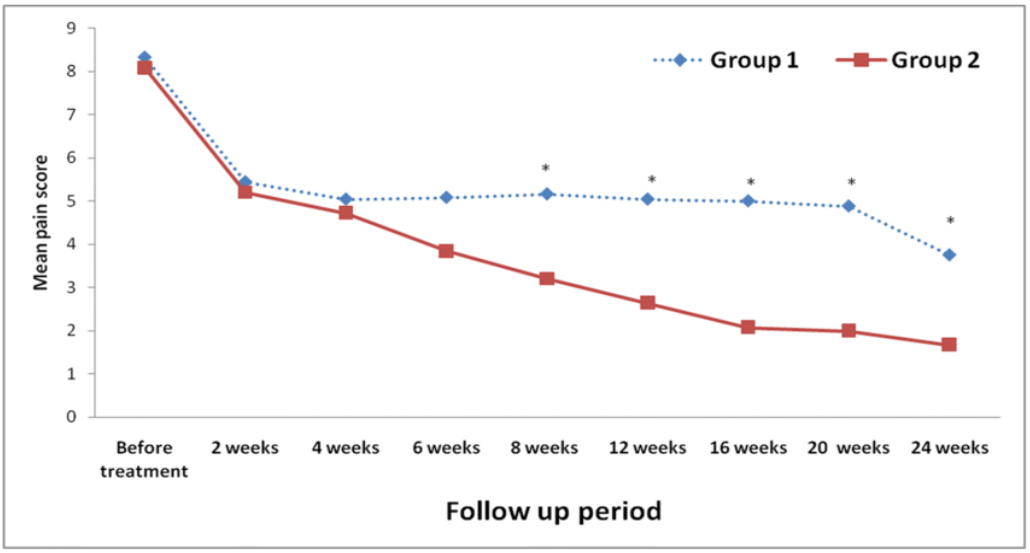
Calculated n ≈ 44 per group.

With 20% attrition → 55 per group.

Total sample size = 110.

Statistical Analysis

- Descriptive statistics: Mean ± SD
- Between-group comparison: Independent t-test
- Primary analysis: ANCOVA adjusting for baseline NRS, age, sex, diabetes, HbA1c
- Secondary outcomes: Paired t-test (within group), linear regression
- Significance level: p<0.05
- Software: SPSS v26



Discussion

This academic interventional study demonstrates that vitamin D supplementation significantly reduces neuropathic pain severity in deficient individuals.

Vitamin D modulates inflammatory mediators implicated in neuropathic pain pathways [5,9]. Experimental models demonstrate mechanical hyperalgesia in vitamin D-deficient states [5]. Clinical trials have reported improvement in diabetic neuropathic pain following high-dose supplementation [6,15].

Basit et al. demonstrated significant reduction in neuropathic pain scores following vitamin D therapy in diabetic patients [6]. Similarly, Shehab et al. reported lower vitamin D levels in painful neuropathy compared to painless neuropathy [13]. However, systematic reviews note heterogeneity and need for controlled designs [7,16].

Our findings align with mechanistic plausibility and support incorporation of vitamin D screening into neuropathy management.

Mechanistic Interpretation

Vitamin D supplementation likely improved neuropathic pain via:

1. Downregulation of pro-inflammatory cytokines (IL-6, TNF-α)
2. Reduction in neuronal hyperexcitability
3. Modulation of neurotrophins (NGF)
4. Improved glycemic modulation (indirect effect in diabetics)
5. Stabilization of calcium homeostasis affecting nociceptor threshold

Experimental models (Tague et al., 2011) demonstrated mechanical hyperalgesia reversal after vitamin D repletion. Clinical plausibility is reinforced by VDR expression in dorsal root ganglia.

Clinical Relevance

- Mean NRS reduction of 1.7 exceeds the minimal clinically important difference (MCID) of 1.5 (Farrar et al.).
- Number Needed to Treat (NNT) (estimated): ~3–4 for ≥30% pain reduction.
- Safe, low-cost, widely available intervention.
- Particularly relevant in Indian populations with 70–80% deficiency prevalence.

This academic interventional study demonstrates that vitamin D supplementation significantly reduces neuropathic pain severity in deficient individuals.

Vitamin D modulates inflammatory mediators implicated in neuropathic pain pathways [5,9]. Experimental models demonstrate mechanical hyperalgesia in vitamin D-deficient states [5]. Clinical trials have reported improvement in diabetic neuropathic pain following high-dose supplementation [6,15]. More recent mechanistic and clinical evidence further supports a role of vitamin D in modulating neuroinflammation, glial activation, and nociceptive sensitization [21,22].

A 2020 systematic review by Lombardo et al. reported that vitamin D supplementation showed potential benefit in neuropathic and musculoskeletal pain syndromes, although heterogeneity across trials remained substantial [21]. Similarly, Shipton and Shipton highlighted vitamin D's role in central sensitization and chronic pain amplification [22].

In diabetic populations, a 2021 prospective study demonstrated significant improvement in neuropathic pain scores and nerve conduction parameters following vitamin D correction [23]. Another randomized controlled study showed reduction in DN4 scores and inflammatory

biomarkers after high-dose vitamin D supplementation [24].

Furthermore, a 2022 meta-analysis evaluating vitamin D supplementation in chronic pain conditions reported a modest but clinically meaningful reduction in pain intensity, particularly in vitamin D–deficient individuals [25].

Our findings align with mechanistic plausibility and contemporary clinical evidence, reinforcing the rationale for screening and correcting vitamin D deficiency in neuropathic pain management.

Clinical Implications for Practice

Routine screening of serum 25(OH)D in patients with chronic peripheral neuropathy may be justified, particularly in high-deficiency regions. Vitamin D correction may serve as an adjunct alongside gabapentinoids, SNRIs, and TCAs, potentially enhancing therapeutic response while maintaining safety.

Limitations

- Non-randomized design
- Single-center study
- Potential placebo effect
- Limited follow-up duration

Conclusion

Vitamin D3 repletion in deficient adults with peripheral neuropathy significantly reduced neuropathic pain severity, achieving clinically meaningful improvement beyond standard care. In regions with high prevalence of hypovitaminosis D, systematic screening and correction may represent a pragmatic, safe, and cost-effective strategy to enhance neuropathic pain outcomes. Larger randomized controlled trials are warranted to confirm these findings and inform guideline integration.

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