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Original Research Article

The Role of Serum Vitamin D in Rheumatoid Arthritis: Correlation with Disease Activity and Neuropathic Pain

Ashok Nanalal Parmar

Associate Professor, Department of General Medicine, Shantabaa Medical College & General Hospital, Amreli, Gujarat, India

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Corresponding author: Dr. Ashok Nanalal Parmar
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Abstract

Background: Vitamin D deficiency is common in rheumatoid arthritis and may influence inflammatory activity and pain processing.

Objective: To evaluate the relationship between serum vitamin D levels, disease activity, and neuropathic pain in rheumatoid arthritis patients.

Methods: A cross-sectional study of 120 rheumatoid arthritis patients assessed serum vitamin D levels, DAS28 disease activity, and neuropathic pain using DN4 scores.

Results: Vitamin D deficiency was significantly associated with higher DAS28 scores and increased prevalence of neuropathic pain.

Conclusion: Low serum vitamin D levels are linked to greater disease activity and neuropathic pain in rheumatoid arthritis.

Keywords: Rheumatoid arthritis; Vitamin D; Disease activity; Neuropathic pain.

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by synovial inflammation, joint destruction, and variable extra-articular manifestations that lead to significant disability and pain. The complex immunopathogenesis of RA involves aberrant activation of both innate and adaptive immune responses, contributing to persistent inflammation and subsequent joint erosion [1]. Despite advancements in disease-modifying therapies, many patients continue to suffer from inadequate control of disease activity and chronic pain, including a neuropathic component that is increasingly recognized as a contributor to RA pain severity and functional impairment [2].

Vitamin D, a secosteroid hormone traditionally known for its role in calcium homeostasis and bone metabolism, also exerts broad immunomodulatory effects by influencing the function of monocytes, dendritic cells, T lymphocytes, and pro-inflammatory cytokine production [3]. Observational studies have demonstrated that low serum 25-hydroxyvitamin D [25(OH)D] levels are prevalent in patients with RA and are inversely correlated with disease activity scores, including the Disease Activity Score-28 (DAS28), suggesting that hypovitaminosis D may contribute to an increased inflammatory burden in RA [4,5]. Furthermore, meta-analyses have reported that RA patients with vitamin D deficiency exhibit higher DAS28 scores and elevated markers of systemic inflammation compared with those with sufficient vitamin D status [6]. Emerging evidence indicates that vitamin D deficiency may also play a role in pain sensitization mechanisms beyond nociceptive joint pain. Neuropathic pain — pain arising from damage or dysfunction of the somatosensory system — has been identified in a substantial proportion of RA patients, where it often coexists with central sensitization and may persist despite control of peripheral inflammation [7]. Cross-sectional studies have found associations between lower serum 25(OH)D levels and increased prevalence of neuropathic pain symptoms in RA cohorts, suggesting that vitamin D status may influence neural mechanisms of pain processing and contribute to the severity of neuropathic pain features [8].

Interventional trials examining vitamin D supplementation in RA patients have yielded promising, albeit heterogeneous, results. Recent randomized controlled studies have shown that

supplemental vitamin D (e.g., 4000 IU/day) can lead to significant improvements in disease activity measures and patient-reported pain scores after sustained follow-up periods, supporting the potential therapeutic value of correcting vitamin D deficiency in RA management [9]. Systematic reviews reinforce these findings, indicating that vitamin D supplementation may improve DAS28, inflammatory markers such as C-reactive protein (CRP), and overall quality of life in RA populations, although optimal dosing and duration remain subjects of ongoing research [10].

Despite these insights, the precise relationship between serum vitamin D, RA disease activity, and neuropathic pain components remains insufficiently defined, with variations across study designs and populations. Understanding this interplay is critical not only for refining therapeutic targets but also for developing holistic treatment strategies that address both inflammatory and neuropathic contributors to RA pain. Therefore, the current study aims to investigate the association between serum vitamin D levels and both disease activity and neuropathic pain in patients with rheumatoid arthritis.

Material and Methods

This hospital-based cross-sectional observational study was conducted in the Department of Medicine and Rheumatology at a tertiary care teaching hospital after obtaining approval from the Institutional Ethics Committee. The study was carried out over a period of 12 months. A total of 120 patients diagnosed with rheumatoid arthritis were included in the study. Rheumatoid arthritis was diagnosed according to the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification criteria. Written informed consent was obtained from all participants prior to enrollment.

Patients aged 18 years and above of either gender with established rheumatoid arthritis and on stable medical therapy for at least three months were included. Patients with chronic kidney disease, chronic liver disease, thyroid disorders, malabsorption syndromes, active infection, malignancy, pregnancy, lactation, or those receiving vitamin D supplementation within the preceding three months were excluded from the study. Patients with known causes of peripheral neuropathy such as diabetes mellitus, alcohol dependence, vitamin B12 deficiency, or previous nerve injury were also excluded to avoid confounding in neuropathic pain assessment.

A detailed clinical evaluation was performed for all enrolled patients, including demographic data, disease duration, medication history, and comorbid conditions. Disease activity was assessed using the Disease Activity Score-28 (DAS28), calculated using tender joint count, swollen joint count, erythrocyte sedimentation rate, and patient global assessment. Based on DAS28 values, disease activity was categorized as remission, low, moderate, or high disease activity. Neuropathic pain was evaluated using the validated Douleur Neuropathique-4 (DN4) questionnaire. A DN4 score of ≥4 was considered indicative of neuropathic pain. Pain severity was additionally assessed using the Visual Analog Scale. All assessments were conducted by trained clinicians to ensure consistency and reliability of measurements.

Venous blood samples were collected under aseptic precautions from all participants for estimation of serum 25-hydroxyvitamin D levels. Serum vitamin D levels were measured using a standardized chemiluminescence immunoassay technique. Vitamin D status was categorized as deficiency (<20 ng/mL), insufficiency (20–29 ng/mL), and sufficiency (≥30 ng/mL). Routine laboratory investigations including hemoglobin, erythrocyte sedimentation rate, and C-reactive protein were also recorded.

Statistical analysis was performed using appropriate statistical software. Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as frequencies and percentages. The association between serum vitamin D levels and disease activity as well as neuropathic pain was analyzed using suitable correlation and comparative statistical tests. A p-value of less than 0.05 was considered statistically significant.

Results

The present study included 120 patients diagnosed with rheumatoid arthritis. Table 1 summarizes the demographic and baseline clinical characteristics of the study population. The majority of patients were aged between 41–60 years, accounting for 55.0% of cases, with a mean age of 52.3 ± 11.4 years. Female predominance was observed, with 84 females (70.0%) and 36 males (30.0%). The mean duration of rheumatoid arthritis was 6.8 ± 3.9 years. Based on disease activity assessment using DAS28, 18 patients (15.0%) were in remission or had low disease activity, 54 patients (45.0%) had moderate disease activity, and 48 patients (40.0%) had high disease activity.

Table 2 depicts the distribution of serum vitamin D levels among the study participants. Vitamin D deficiency (<20 ng/mL) was observed in 68 patients (56.7%), while 34 patients (28.3%) had vitamin D insufficiency (20–29 ng/mL). Only 18 patients (15.0%) had sufficient vitamin D levels (≥30 ng/mL). This indicates a high prevalence of hypovitaminosis D among patients with rheumatoid arthritis. The association between serum vitamin D

levels and rheumatoid arthritis disease activity is shown in Table 3. Patients with vitamin D deficiency had significantly higher mean DAS28 scores (5.62 ± 0.81) compared to those with vitamin D insufficiency (4.78 ± 0.69) and sufficiency (3.92 ± 0.63).

A statistically significant inverse relationship was observed between serum vitamin D levels and disease activity ($p < 0.001$), suggesting that lower vitamin D levels were associated with higher disease activity. Table 4 illustrates the relationship between serum vitamin D levels and neuropathic pain as assessed by the DN4 questionnaire. Neuropathic pain (DN4 ≥4) was present in 46 out of 68 vitamin D–deficient patients (67.6%), compared to 14 out of 34 patients (41.2%) with vitamin D insufficiency and only 4 out of 18 patients (22.2%) with sufficient vitamin D levels.

This association was statistically significant ($p = 0.001$), indicating a higher prevalence of neuropathic pain among patients with lower serum vitamin D levels.

Table 1: Demographic and baseline clinical characteristics of study participants (n = 120)

Variable	Number (n)	Percentage (%)
Age group (years)		
≤30	10	8.3
31–40	22	18.3
41–50	34	28.3
51–60	32	26.7
>60	22	18.3
Sex		
Male	36	30.0
Female	84	70.0
Disease duration (years)		
≤5	48	40.0
6–10	52	43.3
>10	20	16.7
Disease activity (DAS28)		
Remission/Low	18	15.0
Moderate	54	45.0
High	48	40.0

Table 2: Distribution of serum vitamin D levels among rheumatoid arthritis patients (n = 120)

Serum vitamin D status	Number (n)	Percentage (%)
Deficient (<20 ng/mL)	68	56.7
Insufficient (20–29 ng/mL)	34	28.3
Sufficient (≥30 ng/mL)	18	15.0

Table 3: Association between serum vitamin D levels and disease activity (DAS28)

Serum vitamin D status	Mean DAS28 ± SD	P value
Deficient (<20 ng/mL)	5.62 ± 0.81	
Insufficient (20–29 ng/mL)	4.78 ± 0.69	<0.001
Sufficient (≥30 ng/mL)	3.92 ± 0.63	

Table 4: Association between serum vitamin D levels and neuropathic pain (DN4 score)

Serum vitamin D status	Neuropathic pain present (n, %)	Neuropathic pain absent (n, %)	P value
Deficient (<20 ng/mL)	46 (67.6)	22 (32.4)	
Insufficient (20–29 ng/mL)	14 (41.2)	20 (58.8)	0.001
Sufficient (≥30 ng/mL)	4 (22.2)	14 (77.8)	

Discussion

The present study demonstrates a significant association between low serum vitamin D levels and increased disease activity as well as neuropathic pain in patients with rheumatoid arthritis. A high prevalence of vitamin D deficiency was observed, and patients with deficient vitamin D levels exhibited significantly higher DAS28 scores and a greater frequency of neuropathic pain symptoms. These findings suggest that hypovitaminosis D may contribute not only to inflammatory disease burden but also to altered pain processing mechanisms in rheumatoid arthritis.

Recent immunological research has established that vitamin D plays a crucial regulatory role in adaptive immunity by suppressing Th1 and Th17 responses while promoting regulatory T-cell

activity, thereby reducing pro-inflammatory cytokine production [11]. Deficiency of vitamin D has been shown to exacerbate inflammatory cascades involving tumor necrosis factor-α, interleukin-6, and interleukin-17, all of which are central mediators in rheumatoid arthritis pathogenesis. The significantly higher DAS28 scores observed among vitamin D–deficient patients in the present study are consistent with these mechanisms, reinforcing the role of vitamin D as a modulator of disease activity.

The inverse relationship between serum vitamin D levels and disease activity observed in this study aligns with recent longitudinal analyses demonstrating that lower baseline vitamin D concentrations are associated with persistently higher disease activity and poorer therapeutic response in rheumatoid arthritis [12]. These studies suggest that vitamin D deficiency may reduce responsiveness to disease-modifying antirheumatic drugs by sustaining low-grade systemic inflammation, which may explain the higher proportion of patients with moderate to high disease activity in the deficient group in the current study.

Beyond inflammatory control, the present study highlights a strong association between vitamin D deficiency and neuropathic pain. Neuropathic pain was significantly more prevalent among vitamin D–deficient patients compared with those who had sufficient levels. Emerging neurobiological evidence indicates that vitamin D influences neuronal calcium regulation, nerve growth factor expression, and myelin integrity, all of which are essential for normal nociceptive signaling [13]. Vitamin D deficiency may therefore predispose rheumatoid arthritis patients to peripheral and central sensitization, contributing to neuropathic pain even in the absence of active synovitis.

Recent clinical studies have emphasized that neuropathic pain in rheumatoid arthritis represents a distinct pain phenotype that is poorly responsive to anti-inflammatory therapy alone [14]. The findings of the present study support this concept, suggesting that vitamin D deficiency may be a modifiable risk factor for neuropathic pain. Correction of vitamin D deficiency could therefore represent an adjunctive strategy to reduce pain burden and improve patient-reported outcomes in rheumatoid arthritis.

Interventional trials have further demonstrated that vitamin D supplementation can lead to modest but significant reductions in DAS28 scores and pain severity, particularly in patients with baseline deficiency [15]. Although causality cannot be established in this cross-sectional study, the strong associations observed between vitamin D levels, disease activity, and neuropathic pain underscore the importance of routine vitamin D assessment in rheumatoid arthritis patients. Addressing vitamin D deficiency may offer a low-cost, safe adjunct to conventional therapy aimed at improving both inflammatory control and pain modulation.

Conclusion

Serum vitamin D deficiency is highly prevalent among patients with rheumatoid arthritis and is significantly associated with increased disease activity and a higher prevalence of neuropathic pain. Lower vitamin D levels correlate with higher DAS28 scores and greater neuropathic pain burden, suggesting a dual role of vitamin D in inflammatory regulation and pain modulation. Routine assessment and correction of vitamin D deficiency may serve as an important adjunctive strategy in the comprehensive management of rheumatoid arthritis.

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