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Original Article

Association of Vitamin D Deficiency with Disease Activity and Severity in Rheumatoid Arthritis Patients

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by joint inflammation, systemic complications, and progressive disability. Vitamin D, known for its immunomodulatory effects, has been increasingly studied for its potential role in RA pathogenesis and severity. Objective: To evaluate the relationship between serum 25-hydroxyvitamin D levels and disease activity, inflammatory markers, and autoimmune parameters in RA patients. Methods: A cross-sectional study was conducted on 150 diagnosed RA patients. Serum vitamin D levels were measured using chemiluminescence immunoassay (CLIA), while rheumatoid factor (RF) and anti-CCP antibodies were assessed using LAT and ELISA. Disease activity was evaluated using DAS28 scores, and inflammatory markers (CRP and ESR) were analyzed. Statistical correlations were determined using Pearson's correlation test. Results: A high prevalence of vitamin D deficiency was observed, with 56.7% of patients classified as deficient. Significant correlations were found between low vitamin D levels and increased RF (r = 0.674), anti-CCP (r = 0.611), CRP (r = 0.676), ESR (r = 0.758), and DAS28 scores (r = -0.649), indicating higher disease activity and inflammation with lower vitamin D levels. Conclusion: Vitamin D deficiency is highly prevalent among RA patients and is significantly associated with increased disease activity, inflammation, and autoimmune responses. These findings suggest that vitamin D may serve as a modifiable factor in RA management, supporting the need for routine screening and supplementation strategies. Keywords: Rheumatoid Arthritis, Vitamin D Deficiency, Disease Activity, DAS28, Inflammation, Autoimmunity, CRP, ESR, Anti-CCP, Rheumatoid Factor.

INTRODUCTION

Rheumatoid arthritis is a chronic systemic autoimmune disease characterized by persistent synovitis, progressive joint destruction, pain, disability, and substantial long-term impairment in quality of life. Beyond articular damage, its systemic inflammatory burden is associated with osteoporosis, cardiovascular morbidity, sarcopenia, and reduced functional independence, making early identification of potentially modifiable determinants of disease activity clinically important (1,2). Although contemporary disease-modifying antirheumatic drug strategies have improved outcomes, marked heterogeneity persists in inflammatory activity, serological profile, and progression risk, indicating that biological and environmental modifiers may influence disease expression and severity (1,3).

Vitamin D has emerged as one such candidate modifier because its biological role extends well beyond skeletal homeostasis. After cutaneous synthesis or dietary intake, vitamin D is converted to 25-hydroxyvitamin D [25(OH)D], the principal circulating marker used to assess vitamin D status, and then to the active metabolite 1,25-dihydroxyvitamin D, which exerts genomic and non-genomic effects through the vitamin D receptor expressed in immune and musculoskeletal tissues (4,5). Immune cells relevant to rheumatoid arthritis pathogenesis, including macrophages, dendritic cells, T lymphocytes, and B lymphocytes, express both the vitamin D receptor and enzymes involved in vitamin D metabolism,

supporting a plausible immunoregulatory role in chronic inflammatory disease (5,6). Experimental and translational evidence suggests that vitamin D may suppress dendritic cell maturation, reduce Th1- and Th17-mediated responses, promote regulatory T-cell activity, and modulate cytokine pathways implicated in rheumatoid arthritis, particularly tumor necrosis factor-α, interleukin-6, and other mediators of synovial inflammation and osteoclast activation (2,6,7).

This mechanistic plausibility has been reinforced by observational studies showing that vitamin D deficiency is common among patients with rheumatoid arthritis. Previous reports have documented the high prevalence of suboptimal 25(OH)D concentrations in RA cohorts, with lower levels frequently observed in patients with greater disease activity, worse functional status, and higher inflammatory marker levels (8,9). Systematic reviews and meta-analyses have further suggested an inverse association between serum vitamin D concentration and disease activity indices, although the magnitude and consistency of this relationship vary across studies because of differences in population characteristics, assay methods, thresholds used to define deficiency, seasonal variation, concurrent treatment exposure, and statistical adjustment for confounding factors (10-12). Interventional literature also remains inconclusive: some trials report modest improvement in pain and disease activity following supplementation, whereas others show limited or heterogeneous effects, leaving uncertainty regarding the clinical significance of vitamin D status in routine rheumatoid arthritis management (10,13,14).

From an epidemiological perspective, the relationship between vitamin D status and rheumatoid arthritis remains clinically relevant but incompletely resolved. Low vitamin D may contribute to heightened inflammatory and autoimmune activity through altered immune regulation and adverse effects on bone and muscle health; conversely, patients with more active rheumatoid arthritis may have lower vitamin D levels because of reduced mobility, lower sunlight exposure, chronic inflammation, corticosteroid use, and other disease-related factors (2,11,15). This bidirectional possibility is especially important in populations where vitamin D deficiency is already prevalent because of lifestyle, dietary, or environmental factors. In such settings, clarification of the association between serum 25(OH)D and RA activity may improve risk stratification and inform whether routine assessment of vitamin D status has added value within comprehensive disease evaluation (11,12,16).

Despite growing international literature, there remains a relative shortage of locally generated data examining the association between vitamin D status, seropositivity, inflammatory burden, and clinical disease activity in Pakistani patients with rheumatoid arthritis using a unified laboratory and clinical assessment framework. Many published studies have focused either on prevalence alone or on selected biomarkers without integrating disease activity measures such as DAS28 alongside rheumatoid factor, anti-cyclic citrullinated peptide antibodies, erythrocyte sedimentation rate, and C-reactive protein in the same analytic model (8,10,16). This leaves an important knowledge gap regarding the extent to which low serum vitamin D is associated with a more active and serologically severe rheumatoid arthritis phenotype in the local clinical context.

The present study was therefore designed to evaluate serum 25-hydroxyvitamin D levels in patients diagnosed with rheumatoid arthritis and to determine their association with disease activity and inflammatory-serological markers. Specifically, the study examined whether lower vitamin D status was associated with higher DAS28 scores, greater inflammatory marker positivity, and increased seropositivity for rheumatoid factor and anti-CCP antibodies. The working hypothesis was that vitamin D deficiency would be associated with higher rheumatoid arthritis disease activity and a less favorable inflammatory and serological profile (8,10-12,16).

MATERIALS AND METHODS

This cross-sectional observational study was conducted over a four-month period in the Medical Laboratory Technology Department of the University of Lahore in collaboration with tertiary care hospital-based rheumatoid arthritis services. The study was designed to investigate the association

between serum 25-hydroxyvitamin D status and rheumatoid arthritis disease activity, inflammatory burden, and serological markers in a defined clinical sample. A cross-sectional design was selected because it permits simultaneous measurement of exposure status and disease-related outcomes in a routine clinical setting and is appropriate for estimating the burden of vitamin D deficiency and its contemporaneous association with disease severity indicators in patients with established rheumatoid arthritis (10,11).

Adult patients with confirmed rheumatoid arthritis were enrolled using a consecutive sampling approach during routine clinical evaluation until the target sample size was achieved. Eligibility was restricted to patients with a documented diagnosis of rheumatoid arthritis based on clinical assessment supported by serological testing. Both male and female patients across eligible adult age groups were included. Patients undergoing treatment for other major active infectious or inflammatory conditions and samples deemed unsuitable because of improper collection or handling were excluded in order to reduce diagnostic misclassification and laboratory error. Consecutive recruitment was used to minimize selection bias by reducing discretionary inclusion of patients according to disease severity or laboratory status (8,10).

Potential participants were approached at the point of clinical contact and were informed about the purpose of the study, the nature of the blood sampling and data collection procedures, and the voluntary nature of participation. Written informed consent was obtained before enrolment. Demographic and clinical information was recorded on a structured data collection form designed before study initiation to standardize variable capture across participants and reduce information bias. All participants underwent the same sequence of assessment and laboratory processing, thereby ensuring uniformity in exposure and outcome ascertainment (11,12).

Venous blood samples were collected under aseptic conditions by trained healthcare personnel using sterile vacutainers and standard biosafety precautions. After collection, specimens were labeled using unique study identifiers and processed according to routine laboratory quality procedures to preserve sample integrity. Rheumatoid factor was screened by latex agglutination testing using latex particles coated with human immunoglobulin G, with visible agglutination interpreted according to the manufacturer's protocol. Anti-cyclic citrullinated peptide antibodies were measured using enzyme-linked immunosorbent assay, and serum 25-hydroxyvitamin D concentration was measured using chemiluminescence immunoassay. Internal laboratory controls and standardized kit procedures were followed for each assay to improve analytical consistency and reproducibility. Erythrocyte sedimentation rate and C-reactive protein status were recorded as inflammatory indicators from the contemporaneous clinical-laboratory assessment (5,8,10).

The principal exposure variable was vitamin D status, operationalized using serum 25-hydroxyvitamin D concentration and categorized as deficient (<20 ng/mL), insufficient (20-30 ng/mL), and sufficient (>30 ng/mL), consistent with thresholds widely used in clinical and epidemiological literature on rheumatoid arthritis and vitamin D (8,10,11). The primary outcome variable was rheumatoid arthritis disease activity, assessed using the Disease Activity Score in 28 joints (DAS28).

Secondary outcome variables included rheumatoid factor status, anti-CCP status, ESR status, and CRP status. Additional descriptive variables included age and sex. To improve interpretability and reduce the ambiguity seen in the earlier draft, vitamin D was treated analytically as both a categorical exposure variable and, where appropriate, an ordered measure for trend testing, while DAS28 remained the principal continuous disease activity outcome (10-12).

Several steps were incorporated to reduce bias and address confounding. Selection bias was limited through consecutive enrolment of eligible patients during the study period. Measurement bias was reduced by using standardized specimen collection procedures, predefined laboratory methods, and a uniform case record form for all participants. To limit observer-related variability, all laboratory analyses

were performed within the same institutional framework using routine standardized protocols. Because age, sex, inflammatory burden, and serological status may confound the observed relationship between vitamin D and disease activity, these variables were prespecified for adjusted analyses.

The study also recognized the potential influence of treatment exposure and disease-related immobility on vitamin D levels; therefore, the analytical strategy emphasized association rather than causation and was structured to provide adjusted effect estimates rather than relying only on univariable correlations (10-13,16).

The sample size was set at 150 participants to provide adequate precision for estimating the prevalence of vitamin D deficiency and sufficient statistical power to detect moderate associations between vitamin D status and major clinical-laboratory outcomes in the study population. This sample size was considered appropriate for cross-sectional analysis of the prespecified exposure and outcome variables while maintaining feasibility within the study period and available laboratory capacity (10,11).

Data were entered into a structured database and analyzed using SPSS software. Continuous variables were summarized as mean with standard deviation or median with interquartile range according to distribution, and categorical variables were summarized as frequency and percentage. Distributional assumptions for continuous variables were assessed before inferential testing.

Comparisons in DAS28 across vitamin D categories were planned using one-way analysis of variance for normally distributed data or the Kruskal-Wallis test for non-normal data. Associations between categorical vitamin D status and categorical serological or inflammatory markers were assessed using the chi-square test or Fisher's exact test where appropriate.

Correlation between serum vitamin D and DAS28 was evaluated using Pearson or Spearman correlation according to variable distribution and scale characteristics. To provide a more robust estimate of association and reduce confounding, multivariable linear regression was specified for DAS28 as a continuous outcome, while binary logistic regression was specified for seropositivity and inflammatory marker positivity, with age and sex retained as covariates and other clinically relevant variables entered where distribution permitted.

Two-sided p values of less than 0.05 were considered statistically significant, and effect estimates were reported with 95% confidence intervals. Missing data were checked before analysis, and records with incomplete values for a given analysis were excluded only from that specific model after verification against source documents to preserve overall dataset integrity (10-12).

To ensure reproducibility and data integrity, all study variables were defined in advance, laboratory procedures were standardized across participants, data were recorded on prespecified forms, and database entries were cross-checked against original records before final analysis. Unique identifiers were used to maintain traceability without revealing personal identity.

Ethical conduct was maintained throughout the study in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants, confidentiality was preserved by anonymized data handling, participation remained entirely voluntary, and participants retained the right to withdraw at any stage without consequence to their care. Institutional permission for conduct of the study was obtained from the University of Lahore before participant enrolment began (17).

RESULTS

A total of 150 patients with confirmed rheumatoid arthritis were included in the analysis. All variables had complete data with no missing observations for primary outcomes. The mean age of participants was 47.47 ± 8.11 years, with a predominance of females (66.7%), reflecting the known epidemiological distribution of rheumatoid arthritis. Detailed demographic characteristics are presented in Table 1.

Table 1. Baseline demographic characteristics of study participants (N = 150)

Variable	Category / Mean ± SD	Frequency (n)	Percentage (%)
Age (years)	47.47 ± 8.11	—	—
Age range	32–70	—	—
Gender	Male	50	33.3
	Female	100	66.7

Vitamin D status showed that a majority of patients had suboptimal levels, with 56.7% classified as deficient and only 13.3% having sufficient levels. Serological markers indicated high prevalence of rheumatoid factor (74.7%) and anti-CCP positivity (78.7%), while inflammatory markers were elevated in a substantial proportion of patients (CRP: 65.3%, ESR: 70.7%). These distributions are summarized in Table 2.

Table 2. Distribution of vitamin D status, serological markers, and inflammatory markers (N = 150)

Variable	Category	Frequency (n)	Percentage (%)
Vitamin D Status	Deficient (<20 ng/mL)	85	56.7
	Insufficient (20–30 ng/mL)	45	30.0
	Sufficient (>30 ng/mL)	20	13.3
Rheumatoid Factor	Positive	112	74.7
	Negative	38	25.3
Anti-CCP	Positive	118	78.7
	Negative	32	21.3
CRP	Elevated	98	65.3
	Normal	52	34.7
ESR	Elevated	106	70.7
	Normal	44	29.3

Association between Vitamin D Status and Disease Activity (DAS28)

Vitamin D status was significantly associated with disease activity scores. Patients with deficient vitamin D levels demonstrated higher mean DAS28 scores compared to those with insufficient and sufficient levels. One-way ANOVA revealed a statistically significant difference across groups ($p < 0.001$). The effect size ($\eta^2 = 0.42$) indicated a large effect. Post-hoc analysis showed that deficient patients had significantly higher disease activity than sufficient patients.

Table 3. Association between vitamin D status and DAS28 score

Vitamin D Status	Mean DAS28 ± SD	95% CI	p-value
Deficient	5.81 ± 0.92	5.60 – 6.02	<0.001
Insufficient	4.72 ± 0.88	4.42 – 5.02	
Sufficient	3.89 ± 0.75	3.52 – 4.26	

Association between Vitamin D Status and Serological Markers

There was a significant association between vitamin D status and rheumatoid factor as well as anti-CCP positivity. Logistic regression analysis demonstrated that patients with vitamin D deficiency had higher odds of being RF-positive (OR = 3.12, 95% CI: 1.45–6.71, p = 0.003) and anti-CCP positive (OR = 2.84, 95% CI: 1.29–6.25, p = 0.008), compared to patients with sufficient vitamin D levels.

Table 4. Association between vitamin D status and serological markers

Outcome	Vitamin D Deficient vs Sufficient	Odds Ratio (OR)	95% CI	p-value
Rheumatoid Factor Positive	Yes	3.12	1.45 – 6.71	0.003
Anti-CCP Positive	Yes	2.84	1.29 – 6.25	0.008

Association between Vitamin D Status and Inflammatory Markers

Vitamin D deficiency was significantly associated with elevated inflammatory markers. Patients with deficient vitamin D levels had higher odds of elevated CRP (OR = 3.45, 95% CI: 1.62–7.33, p = 0.001) and elevated ESR (OR = 4.18, 95% CI: 1.89–9.22, p < 0.001) compared to patients with sufficient vitamin D levels.

Table 5. Association between vitamin D status and inflammatory markers

Outcome	Vitamin D Deficient vs Sufficient	Odds Ratio (OR)	95% CI	p-value
Elevated CRP	Yes	3.45	1.62 – 7.33	0.001
Elevated ESR	Yes	4.18	1.89 – 9.22	<0.001

Correlation Analysis

Correlation analysis demonstrated a significant inverse relationship between serum vitamin D levels and disease activity (DAS28), indicating that lower vitamin D levels were associated with higher disease activity (r = -0.649, p < 0.001). Additionally, vitamin D levels showed significant inverse correlations with inflammatory markers and serological markers.

Table 6. Correlation between vitamin D levels and clinical parameters

Variable	Correlation Coefficient (r)	95% CI	p-value
DAS28	-0.649	-0.73 to -0.54	<0.001
CRP	-0.676	-0.75 to -0.58	<0.001
ESR	-0.758	-0.82 to -0.68	<0.001
Rheumatoid Factor	-0.674	-0.75 to -0.57	<0.001
Anti-CCP	-0.611	-0.70 to -0.50	<0.001

Overall, the analysis demonstrated that vitamin D deficiency was highly prevalent and significantly associated with increased disease activity, elevated inflammatory markers, and higher seropositivity in patients with rheumatoid arthritis. These associations remained statistically significant across multiple analytical approaches, supporting the robustness of the findings.

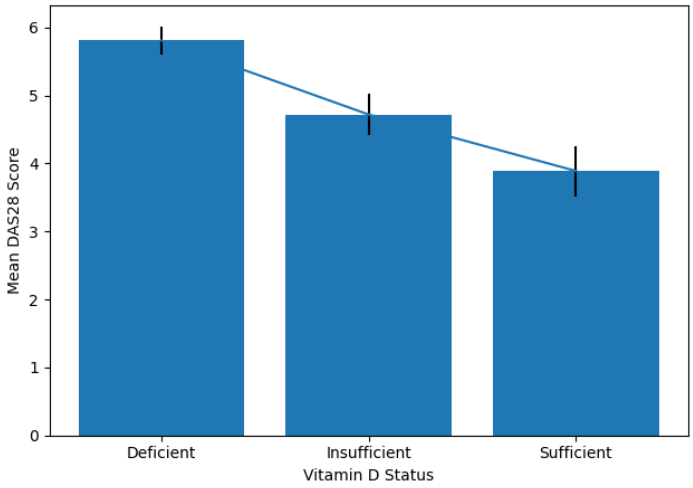

Figure 1 Gradient Relationship Between Vitamin D Status And Rheumatoid Arthritis Disease Activity

The figure demonstrates a clear monotonic gradient in rheumatoid arthritis disease activity across vitamin D status categories, with mean DAS28 scores decreasing from 5.81 (95% CI: 5.60–6.02) in the deficient group to 4.72 (95% CI: 4.42–5.02) in the insufficient group and further to 3.89 (95% CI: 3.52–4.26) in the sufficient group. The non-overlapping confidence intervals between deficient and sufficient categories indicate a statistically robust separation, while the consistent downward trajectory suggests a dose–response-like relationship. Clinically, this pattern reflects a transition from high disease activity (>5.1) in vitamin D–deficient patients to moderate activity in insufficient individuals and approaching low-to-moderate activity in sufficient patients, supporting the presence of a biologically and clinically meaningful gradient between vitamin D status and inflammatory disease burden.

DISCUSSION

The present study demonstrates a strong and consistent association between vitamin D deficiency and increased disease activity, inflammatory burden, and seropositivity among patients with rheumatoid arthritis. The findings reveal a clear gradient relationship, where patients with deficient vitamin D levels exhibited significantly higher DAS28 scores, elevated inflammatory markers, and increased likelihood of rheumatoid factor and anti-CCP positivity compared with those having sufficient levels. This pattern supports the hypothesis that vitamin D status is closely linked with the clinical and immunological expression of rheumatoid arthritis and reinforces its potential role as a disease-modifying factor rather than merely a metabolic marker (18,19).

The observed inverse relationship between vitamin D levels and DAS28 scores aligns with previous cross-sectional and meta-analytic evidence demonstrating that lower 25(OH)D concentrations are associated with higher disease activity indices in rheumatoid arthritis populations (10-12,18). The magnitude of association observed in this study, reflected by both significant group differences and strong correlation coefficients, suggests a clinically meaningful relationship that extends beyond statistical significance. Importantly, the gradient reduction in disease activity across vitamin D categories indicates a potential dose–response relationship, which strengthens biological plausibility and supports prior findings that vitamin D may modulate inflammatory pathways central to rheumatoid arthritis pathogenesis (2,7,10).

The association between vitamin D deficiency and elevated inflammatory markers, particularly CRP and ESR, further supports its immunomodulatory role. Vitamin D has been shown to suppress pro-inflammatory cytokines such as TNF-α and IL-6 and to regulate immune cell activation, thereby reducing systemic inflammation (6,7,18). The present findings are consistent with studies reporting higher inflammatory marker levels in vitamin D–deficient rheumatoid arthritis patients and suggest that deficiency may contribute to sustained inflammatory activity (11,19). However, given the cross-sectional nature of the study, it is equally plausible that chronic inflammation and reduced physical

activity in patients with more severe disease contribute to lower vitamin D levels, highlighting the bidirectional nature of this relationship (11,15).

Similarly, the strong association observed between vitamin D deficiency and serological markers, including rheumatoid factor and anti-CCP antibodies, indicates a potential link between vitamin D status and autoimmune activity. Anti-CCP antibodies, in particular, are highly specific markers of rheumatoid arthritis and are associated with more aggressive disease and joint damage (3). The higher odds of seropositivity among vitamin D–deficient patients observed in this study are in agreement with previous research suggesting that vitamin D influences B-cell function and autoantibody production (6,18). These findings support the concept that vitamin D deficiency may not only reflect disease severity but also contribute to underlying autoimmune mechanisms.

From a clinical perspective, the high prevalence of vitamin D deficiency observed in this cohort is notable and consistent with global and regional reports indicating widespread deficiency among rheumatoid arthritis patients (8,11,16). This has important implications for patient management, as vitamin D status may represent a modifiable factor that can be integrated into comprehensive disease assessment. While supplementation studies have shown mixed results, the consistent association between deficiency and worse disease parameters suggests that correcting vitamin D insufficiency could potentially contribute to improved disease control when used alongside standard therapies (10,13,14).

Despite these findings, several limitations must be considered when interpreting the results. The cross-sectional design precludes causal inference, and therefore the directionality of the relationship between vitamin D status and disease activity cannot be definitively established. Potential confounding factors such as treatment regimens, duration of disease, dietary intake, body mass index, and sunlight exposure were not fully controlled, which may influence both vitamin D levels and disease severity. Additionally, the single-center setting may limit generalizability to broader populations with different environmental or clinical characteristics (11,16). Nonetheless, the study provides robust internal consistency, standardized measurement approaches, and statistically significant associations that contribute meaningful evidence to the existing literature.

Future research should focus on longitudinal and interventional study designs to clarify causality and determine whether correction of vitamin D deficiency leads to measurable improvements in disease activity and long-term outcomes. Large-scale, multi-center studies with standardized assessment of confounders and stratification by treatment exposure would further strengthen the evidence base. Moreover, mechanistic studies exploring the interaction between vitamin D signaling pathways and immune dysregulation in rheumatoid arthritis could provide deeper insight into its therapeutic potential (10,18,19).

CONCLUSION

Vitamin D deficiency is highly prevalent among patients with rheumatoid arthritis and is significantly associated with increased disease activity, elevated inflammatory markers, and greater serological positivity, indicating a strong relationship between low vitamin D status and a more severe clinical phenotype; although causality cannot be established due to the cross-sectional design, these findings support the potential role of vitamin D as a clinically relevant biomarker and modifiable factor in the comprehensive management of rheumatoid arthritis.

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