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Vitamin D Deficiency and Its Association with Disease Activity in Inflammatory Rheumatic Disorders: A Cross-Sectional Experimental Study

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ABSTRACT

Vitamin D has immunomodulatory functions that may influence the pathogenesis and progression of inflammatory rheumatic disorders (IRDs) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS). This study aimed to evaluate the association between serum 25-hydroxyvitamin D [25(OH)D] levels and disease activity in patients with IRDs. In this cross-sectional experimental study conducted at a tertiary rheumatology center, 284 patients diagnosed with RA (n=112), SLE (n=96), or AS (n=76) were enrolled. Serum 25(OH)D levels were measured using chemiluminescent immunoassay and classified as deficient (<20 ng/mL), insufficient (20–29 ng/mL), or sufficient (≥30 ng/mL). Disease activity was assessed using DAS28 for RA, SLEDAI-2K for SLE, and BASDAI for AS. The mean serum vitamin D level was 17.9 ± 6.8 ng/mL, with 59.2% deficient, 27.8% insufficient, and 13.0% sufficient. Patients with vitamin D deficiency had significantly higher disease activity scores across all IRDs (RA-DAS28: 5.8 ± 1.1 vs 4.2 ± 0.9, p<0.001; SLEDAI-2K: 12.6 ± 4.5 vs 7.8 ± 3.1, p<0.001; BASDAI: 5.9 ± 1.3 vs 3.9 ± 1.0, p<0.001). Serum 25(OH)D levels showed a strong inverse correlation with disease activity (r = −0.61, p <0.001). Multivariate regression confirmed vitamin D deficiency as an independent predictor of high disease activity (adjusted OR 3.67; 95% CI 2.05–6.58; p<0.001). These findings suggest that vitamin D deficiency is highly prevalent in IRDs and is significantly associated with increased disease activity, indicating a potential role for vitamin D monitoring and supplementation in disease management.

Keywords: *Vitamin D deficiency; Inflammatory rheumatic disorders; Disease activity; DAS28; SLEDAI; BASDAI*

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INTRODUCTION

Inflammatory rheumatic disorders (IRDs) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS) are chronic autoimmune diseases characterized by persistent inflammation, immune dysregulation, and progressive joint or systemic damage [1]. RA is typified by synovial inflammation, cartilage destruction, and bone erosion, predominantly affecting small joints but often leading to systemic complications [2]. SLE is a multisystem autoimmune disorder manifesting with diverse clinical phenotypes including nephritis, hematologic abnormalities, cutaneous lesions, and central nervous system involvement [3]. AS is an inflammatory spondyloarthropathy affecting axial skeleton joints, causing pain, stiffness, and eventual ankylosis in severe cases [4]. Collectively, these disorders impose significant morbidity, impaired quality of life, and elevated healthcare burden globally, with prevalence rates estimated at 0.5–1% for RA, 0.03–0.1% for SLE, and 0.1–0.3% for AS in most populations [5,6]. In Pakistan and neighboring South Asian countries, the burden is exacerbated by delayed diagnosis, limited access to rheumatology care, and under-recognition of disease-modifying factors [7].

Vitamin D, classically recognized for its role in calcium homeostasis and bone metabolism, has increasingly been implicated in immune regulation [8]. The biologically active form, 1,25-dihydroxyvitamin D3, exerts

immunomodulatory effects by binding to vitamin D receptors (VDRs) expressed in T and B lymphocytes, dendritic cells, and macrophages [9]. Vitamin D inhibits pro-inflammatory T-helper 1 (Th1) and Th17 cell differentiation while promoting regulatory T-cell proliferation, which is crucial in maintaining immune tolerance [10]. In RA, SLE, and AS, aberrant Th1/Th17 activity and diminished regulatory T-cell function contribute to sustained inflammation, tissue damage, and autoantibody production [11]. Thus, vitamin D deficiency may exacerbate disease activity by facilitating immune dysregulation, amplifying inflammatory cytokine cascades, and promoting autoimmunity.

Globally, vitamin D deficiency is highly prevalent, affecting up to one billion individuals across all age groups [12]. Interestingly, vitamin D deficiency is common even in regions with abundant sunlight due to factors such as limited sun exposure, skin pigmentation, cultural clothing practices, urban living, air pollution, and dietary insufficiency [13]. In South Asian populations, studies report prevalence rates of hypovitaminosis D exceeding 70%, with particularly high rates among women and older adults [14]. In Pakistan, small-scale studies suggest that 65–80% of the general population exhibits deficient or insufficient serum 25-hydroxyvitamin D [15]. The high prevalence of deficiency, coupled with the growing burden of autoimmune diseases, underscores the need to evaluate potential associations between vitamin D status and disease activity in IRDs.

Several observational studies have suggested an inverse relationship between vitamin D levels and disease activity in autoimmune disorders. In RA, low serum 25(OH)D has been correlated with elevated Disease Activity Score-28 (DAS28), higher C-reactive protein, and increased radiographic progression [16]. Similarly, in SLE, deficiency has been associated with higher SLE Disease Activity Index (SLEDAI) scores, increased anti-dsDNA titers, and more frequent flares [17]. In AS, patients with lower vitamin D levels tend to have higher Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, more pronounced axial inflammation, and elevated inflammatory markers [18]. Mechanistic studies support these observations, demonstrating that vitamin D modulates cytokine expression, inhibits dendritic cell maturation, reduces B-cell proliferation, and suppresses autoantibody production [19].

Despite these insights, several critical gaps remain in the literature. Many studies have been small, single-center, or cross-sectional, limiting generalizability [20]. Variation in disease assessment tools, heterogeneity in vitamin D measurement methods, and inadequate adjustment for confounding variables such as age, gender, BMI, renal function, medication use, and seasonal variation complicate interpretation [21]. Moreover, studies from South Asia, particularly Pakistan, are sparse, leaving uncertainty about the true prevalence of deficiency among IRD patients and its association with disease activity in this population [22].

Given the chronic inflammatory nature of IRDs, identifying modifiable risk factors that can potentially reduce disease activity is of substantial clinical interest. Vitamin D represents an attractive target because of its immunomodulatory properties, low cost, and feasibility of supplementation [23]. Understanding its relationship with disease activity could guide preventive strategies, supplement therapy, and potentially reduce flares or slow disease progression.

The present study was therefore designed to investigate the prevalence of vitamin D deficiency among patients with RA, SLE, and AS in Pakistan and to evaluate its association with disease activity using standardized and validated scoring systems (DAS28, SLEDAI-2K, and BASDAI). We hypothesized that lower serum 25(OH)D levels would be independently associated with higher disease activity scores across IRDs, after adjusting for relevant demographic, clinical, and laboratory confounders. By addressing regional knowledge gaps and employing rigorous methodology, this study aims to provide meaningful insights into the role of vitamin D as a modifiable determinant of autoimmune disease activity and a potential adjunct in IRD management [24,25].

MATERIAL AND METHODS

Study Design and Setting

This cross-sectional experimental study was conducted at the Bahria University College of Medicine, Islamabad, Islamabad, between January 2024 and December 2024. The study aimed to assess the association between serum vitamin D levels and disease activity in patients with IRDs including RA, SLE, and AS.

Ethical Approval

The study was approved by the Institutional Review Board of Pakistan Institute of Medical Sciences (Approval No: PIMS-RHEUM-ERC-2023-11-039) and conducted according to the principles of the Declaration of Helsinki.

Sample

A total of 284 consecutive patients aged 18–70 years with confirmed diagnosis of RA (n=112), SLE (n=96), or AS (n=76) were enrolled. Sample size was calculated assuming 50% prevalence of vitamin D deficiency among IRD patients, 95% confidence level, 5% margin of error, and 80% study power.

Inclusion Criteria

- Adult patients (≥18 years) with confirmed RA according to 2010 ACR/EULAR criteria, SLE according to 2012 SLICC criteria, or AS according to modified New York criteria.
- Patients under stable medication therapy for at least 3 months.
- Ability to provide informed consent.

Exclusion Criteria

- Chronic kidney disease (eGFR <60 mL/min/1.73m^2)
- Chronic liver disease, malignancy, or infectious disorders
- Recent vitamin D supplementation within 3 months
- Pregnancy or lactation
- Concurrent autoimmune or inflammatory diseases outside RA, SLE, or AS

Data Collection

Baseline demographic and clinical data were recorded including age, gender, BMI, disease duration, medication use (DMARDs, corticosteroids, biologics), smoking status, and comorbidities. Physical examination and routine laboratory evaluation were performed.

Biochemical Assessment

Fasting venous blood samples were collected prior to clinical assessment. Serum 25(OH)D was measured by chemiluminescent immunoassay (CLIA, Abbott Architect i2000SR). Vitamin D status was categorized as:

- Deficient: <20 ng/mL
- Insufficient: 20–29 ng/mL
- Sufficient: ≥30 ng/mL

Additional labs included ESR, CRP, renal and liver function tests, calcium, and phosphate.

Disease Activity Assessment

- **RA:** Disease Activity Score 28 joints (DAS28)
- **SLE:** SLE Disease Activity Index 2000 (SLEDAI-2K)
- **AS:** Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

All assessments were conducted by rheumatologists blinded to serum vitamin D levels.

Statistical Analysis

Data were analyzed using SPSS v26. Continuous variables were expressed as mean ± SD; categorical variables as frequencies and percentages. ANOVA compared mean disease activity scores across vitamin D categories. Pearson correlation assessed associations between serum vitamin D and disease activity. Multivariate logistic regression determined independent predictors of high disease activity, adjusting for age, gender, BMI, disease duration, corticosteroid use, and smoking. $p<0.05$ was considered significant.

RESULTS

Patient Demographics

The study included 284 patients (RA: 112; SLE: 96; AS: 76). Mean age was 42.7 ± 12.3 years; 71% female. Mean disease duration was 6.2 ± 4.5 years. The tables collectively indicate that while baseline characteristics such as age, sex, BMI, disease duration, and corticosteroid use did not significantly differ across vitamin D status groups (Table 1), disease activity was markedly higher in individuals with lower vitamin D levels (Table 2), with RA-DAS28, SLEDAI-2K, and BASDAI scores all showing significant inverse trends from deficient to sufficient vitamin D categories ($p < 0.001$). Correlation analysis (Table 3) confirmed strong negative relationships between serum 25(OH)D levels and disease activity scores ($r = -0.59$ to -0.63, $p < 0.001$), and multivariate logistic regression showed that vitamin D deficiency was independently associated with increased odds of high disease activity (OR 3.67, 95% CI 2.05–6.58, $p < 0.001$), whereas age, sex, BMI, and corticosteroid use were not significant predictors, though longer disease duration modestly increased risk (OR 1.09, $p = 0.008$). Overall, these results suggest that low vitamin D status is strongly linked to higher disease activity across multiple autoimmune conditions, independent of common demographic or clinical confounders.

Vitamin D Status

- Deficient (<20 ng/mL): 59.2% (n=168)
- Insufficient (20–29 ng/mL): 27.8% (n=79)
- Sufficient (≥30 ng/mL): 13.0% (n=37)

Mean serum 25(OH)D: 17.9 ± 6.8 ng/mL.

Table 1: Baseline Characteristics by Vitamin D Status

Variable	Deficient (n=168)	Insufficient (n=79)	Sufficient (n=37)	p-value
Age (years)	43.1 ± 12.6	42.0 ± 11.9	41.8 ± 11.5	0.61
Female (%)	73.2	69.6	64.9	0.45
BMI (kg/m^2)	26.8 ± 4.1	26.1 ± 3.8	25.9 ± 3.6	0.32
Disease duration (years)	6.5 ± 4.7	5.9 ± 4.1	5.7 ± 3.9	0.28
Corticosteroid use (%)	48.8	44.3	41.9	0.58

Table 2: Disease Activity Scores by Vitamin D Category

Disease & Score	Deficient	Insufficient	Sufficient	p-value
RA-DAS28	5.8 ± 1.1	4.8 ± 1.0	4.2 ± 0.9	<0.001
SLEDAI-2K	12.6 ± 4.5	9.2 ± 3.4	7.8 ± 3.1	<0.001
BASDAI	5.9 ± 1.3	4.8 ± 1.2	3.9 ± 1.0	<0.001

Table 3: Correlation and Multivariate Logistic Regression

Parameter	Pearson r / OR (95% CI)	p-value
Serum 25(OH)D vs DAS28	−0.59	<0.001
Serum 25(OH)D vs SLEDAI-2K	−0.61	<0.001
Serum 25(OH)D vs BASDAI	−0.63	<0.001
Vitamin D deficiency OR (high disease activity)	3.67 (2.05–6.58)	<0.001
Age	1.01 (0.98–1.03)	0.46
Female gender	1.12 (0.65–1.94)	0.68
BMI	1.04 (0.99–1.09)	0.10
Disease duration	1.09 (1.02–1.16)	0.008
Corticosteroid use	1.22 (0.71–2.11)	0.46

DISCUSSION

This study demonstrates a strong and clinically significant inverse relationship between serum vitamin D levels and disease activity in patients with inflammatory rheumatic disorders (IRDs), including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS). The prevalence of vitamin D deficiency in this cohort was remarkably high at 59.2%, with only 13% exhibiting sufficient serum 25(OH)D levels. Patients with deficient vitamin D levels had significantly higher disease activity scores across all IRDs: RA-DAS28, SLEDAI-2K, and BASDAI. These findings underscore the potential role of vitamin D as a modifiable determinant of disease activity and provide evidence supporting routine monitoring and potential therapeutic supplementation in IRDs.

The immunopathogenesis of IRDs involves complex interactions between innate and adaptive immune systems. In RA, synovial inflammation is perpetuated by activated T-cells, B-cells, and pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17), resulting in cartilage destruction and bone erosion [11,12]. In SLE, dysregulated B-cell activity leads to autoantibody production, immune complex deposition, and multi-organ damage [13]. In AS, Th17-mediated pathways contribute to enthesitis, osteitis, and progressive spinal ankylosis [14]. Vitamin D, through its active form 1,25-dihydroxyvitamin D3, regulates both innate and adaptive immunity by inhibiting dendritic cell maturation, suppressing Th1 and Th17 differentiation, and promoting regulatory T-cell proliferation [15]. Our findings align with these mechanistic insights, as patients with lower vitamin D levels exhibited higher disease activity, suggesting that vitamin D deficiency may exacerbate autoimmune inflammation.

The results are consistent with prior studies evaluating vitamin D in IRDs. In a cross-sectional study by Cutolo et al., RA patients with vitamin D deficiency had significantly higher DAS28 scores and elevated serum inflammatory markers [16]. Similarly, Abou-Raya et al. observed that SLE patients with low vitamin D levels exhibited higher SLEDAI scores, increased frequency of renal flares, and elevated anti-dsDNA titers [17]. In AS, Zhao et al. demonstrated that BASDAI scores inversely correlated with serum vitamin D, suggesting that deficiency contributes to heightened disease activity [18]. Our study extends these findings to a South Asian population, highlighting the high prevalence of deficiency in Pakistani IRD patients, potentially due to cultural sun exposure limitations, skin pigmentation, and dietary insufficiency.

The multivariate logistic regression analysis in this study confirmed that vitamin D deficiency is an independent predictor of high disease activity (adjusted OR 3.67; 95% CI 2.05–6.58; p<0.001), even after adjusting for age, sex, BMI, disease duration, and corticosteroid use. This indicates that the association is not confounded by demographic or treatment-related variables, supporting the hypothesis that vitamin D deficiency may directly influence autoimmune disease activity. Notably, disease duration also emerged as

a modest but significant predictor, consistent with literature showing that chronic inflammation contributes to cumulative tissue damage and persistent disease activity [19].

Mechanistically, vitamin D may influence disease activity via several pathways. First, it modulates cytokine profiles, reducing TNF-α, IL-6, and IL-17 production, while promoting anti-inflammatory cytokines such as IL-10 [20]. Second, vitamin D regulates B-cell function, decreasing autoantibody production, which is particularly relevant in SLE [21]. Third, it enhances the function of regulatory T-cells, which maintain self-tolerance and suppress excessive autoimmune responses [22]. Fourth, vitamin D deficiency may increase oxidative stress, endothelial dysfunction, and vascular inflammation, indirectly exacerbating systemic manifestations of IRDs [23]. Collectively, these mechanisms plausibly explain the observed inverse correlation between serum 25(OH)D and disease activity.

The high prevalence of vitamin D deficiency in our cohort is noteworthy. Nearly 60% of patients were deficient, with only 13% having sufficient levels. This mirrors findings in other South Asian cohorts, where cultural clothing practices, limited outdoor activity, darker skin pigmentation, and dietary insufficiency contribute to widespread deficiency [24]. Such high prevalence suggests that vitamin D deficiency may act synergistically with genetic and environmental risk factors to exacerbate autoimmune disease expression and activity. Clinically, this underscores the importance of assessing vitamin D status in routine IRD management, particularly in populations with high baseline deficiency.

Therapeutically, several studies suggest that vitamin D supplementation may reduce disease activity. In RA, supplementation with 50,000 IU vitamin D weekly for 12 weeks was associated with a modest but significant reduction in DAS28 scores and inflammatory markers [25]. In SLE, daily supplementation improved SLEDAI scores, fatigue, and complement levels [26]. In AS, supplementation reduced BASDAI scores and improved patient-reported pain and stiffness [27]. These interventional studies, though limited, provide proof-of-concept that correcting deficiency may have tangible clinical benefits. Our study adds further rationale for such trials in Pakistani IRD patients, who are at high risk of deficiency.

While our findings are robust, several limitations merit discussion. First, the cross-sectional design limits causal inference. Although we observed strong associations, prospective or randomized studies are necessary to determine whether vitamin D deficiency actively contributes to increased disease activity or is a consequence of chronic inflammation. Second, we measured serum 25(OH)D at a single time point; seasonal variation, sun exposure, and dietary intake were not accounted for, which may influence levels. Third, genetic factors such as polymorphisms in the vitamin D receptor (VDR) may modulate immune response and disease expression, which were not evaluated. Fourth, medication regimens, including biologics or corticosteroids, can influence both vitamin D metabolism and disease activity; although adjusted for in regression, residual confounding is possible. Lastly, this was a single-center study; generalizability to other Pakistani regions or South Asian populations may be limited.

Despite these limitations, the study has several strengths. It included a relatively large and diverse IRD population encompassing RA, SLE, and AS. Disease activity was rigorously assessed using standardized and validated instruments (DAS28, SLEDAI-2K, BASDAI). Biochemical analyses were performed using chemiluminescent immunoassay, a reliable and reproducible method for serum 25(OH)D measurement. Blinding of clinicians assessing disease activity minimized measurement bias. Finally, multivariate regression controlled for key demographic and clinical confounders, enhancing the robustness of findings.

From a clinical perspective, our results suggest that vitamin D deficiency could be considered both a biomarker and potential therapeutic target in IRDs. Screening for deficiency is inexpensive, widely available, and may guide supplementation strategies to reduce disease activity and improve patient quality of life. Given the high prevalence in South Asian populations, routine monitoring could be integrated into standard rheumatology care. Moreover, vitamin D repletion may complement pharmacologic therapy, potentially allowing lower doses of immunosuppressants, reducing side effects, and improving long-term outcomes.

Future research should focus on longitudinal and interventional studies to assess causal relationships and quantify the clinical impact of vitamin D repletion on disease activity, flare frequency, and long-term organ damage. Additionally, exploring genetic and epigenetic factors that influence vitamin D metabolism and immune modulation could refine personalized supplementation strategies. Multicenter studies encompassing diverse populations will enhance generalizability and inform regional clinical guidelines.

In summary, this study provides compelling evidence that vitamin D deficiency is highly prevalent among patients with IRDs in Pakistan and is independently associated with higher disease activity. These findings highlight vitamin D as a potentially modifiable risk factor and support strategies for routine monitoring and supplementation to improve disease management and patient outcomes.

This study demonstrates that vitamin D deficiency is highly prevalent in patients with IRDs and is strongly associated with higher disease activity across RA, SLE, and AS. The mean serum 25(OH)D level was 17.9 ng/mL, with nearly 60% of patients deficient, consistent with prior reports from South Asia [25–27]. Our

findings reinforce the immunomodulatory role of vitamin D and its relevance in autoimmune disease pathogenesis.

Mechanistically, vitamin D regulates innate and adaptive immune responses by inhibiting Th1 and Th17 differentiation, enhancing regulatory T-cell activity, and suppressing B-cell autoantibody production [28]. These mechanisms align with our observation of higher DAS28, SLEDAI-2K, and BASDAI scores among deficient patients, suggesting that hypovitaminosis D may exacerbate systemic inflammation and autoimmunity.

Previous studies have yielded mixed results. In RA, several reports indicate inverse correlations between 25(OH)D and DAS28 scores ($r \approx -0.45$ to -0.60) [16,29], while others noted weaker associations after adjustment for corticosteroid therapy or seasonal variation [30]. In SLE, vitamin D deficiency has been associated with increased SLEDAI scores, nephritis prevalence, and anti-dsDNA titers [17]. In AS, lower vitamin D correlates with elevated BASDAI, spinal inflammation on MRI, and higher CRP [18]. Our study confirms and extends these findings in a South Asian cohort, providing robust multivariate-adjusted evidence.

Importantly, multivariate regression demonstrated vitamin D deficiency as an independent predictor of high disease activity (OR 3.67, $p<0.001$), even after adjusting for age, sex, BMI, disease duration, and corticosteroid use. This highlights its potential as a modifiable biomarker that could complement conventional disease management.

Potential implications include screening IRD patients for vitamin D deficiency and considering supplementation as adjunctive therapy. Randomized controlled trials have suggested improvements in disease activity, fatigue, and inflammatory markers following vitamin D repletion, though optimal dosing and long-term outcomes remain areas of active investigation [23,28].

Limitations of this study include its cross-sectional design, which precludes causal inference, single-center recruitment, and lack of assessment of seasonal sunlight exposure, dietary intake, or genetic VDR polymorphisms. Nonetheless, the study benefits from a relatively large sample, inclusion of multiple IRDs, standardized disease activity scoring, and blinded assessment of vitamin D status, strengthening internal validity.

Overall, this study provides compelling evidence that vitamin D deficiency is prevalent among IRD patients in Pakistan and is associated with increased disease activity. These findings support further research into interventional strategies and highlight the importance of vitamin D monitoring in routine rheumatology practice.

CONCLUSION

Vitamin D deficiency is highly prevalent in patients with inflammatory rheumatic disorders and is significantly associated with increased disease activity across RA, SLE, and AS. Monitoring and correcting vitamin D status may provide a low-cost, safe adjunctive approach for disease management, with potential benefits in reducing systemic inflammation and improving patient outcomes.

ETHICS STATEMENT

The study protocol was approved by the Institutional Review Board of Pakistan Institute of Medical Sciences (Approval No: PIMS-RHEUM-ERC-2023-11-039). Conducted in accordance with the Declaration of Helsinki.

INFORMED CONSENT

Written informed consent was obtained from all participants prior to enrollment.

COMPETING INTERESTS

The authors declare no competing interests.

FINANCIAL DISCLOSURE

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