

Research Article

Association of Serum Vitamin D and Ferritin Levels with Disease Activity in Patients with Rheumatoid Arthritis

Aniqa Ashfaq¹, Dr Zainab Akhtar², Dr Sarah Arif³, Dr Sahrish Jabeen⁴, Dr Awais Latif⁵, Dr Arzoo Fatima⁶

¹Medical specialist, Fcps medicine, CMH LMC and IOD, Senior registrar.

²Medical Officer, Ziauddin University.

³Demonstrator Community Medicine Department, King Edward Medical University, Lahore.

⁴Medical Officer.

⁵Civil Medical Officer.

⁶CMH Lahore medical college and Institute of dentistry.

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ABSTRACT

Objective: This study aims to study association of serum vitamin d and ferritin levels with disease activity in patients with rheumatoid arthritis.

Methodology: 89 adult patients with rheumatoid arthritis fulfilling the 2010 ACR/EULAR classification criteria were included. Demographic and clinical data, including disease duration, medication history, tender and swollen joint counts, ESR, and CRP, were recorded. Disease activity was assessed using the Disease Activity Score-28 (DAS28). Fasting venous blood samples were obtained for measurement of serum 25-hydroxyvitamin D and ferritin using standardized immunoassay methods. Patients were categorized according to DAS28 disease-activity levels. Statistical analysis included descriptive statistics, correlation analysis, and multivariable regression. Pearson's or Spearman's correlation was used to assess associations between vitamin D, ferritin, and DAS28. A p-value <0.05 was considered statistically significant.

Study Design Duration: 06 months from March 2026 to August 2026.

Results: Among 89 patients, mean age was 45.8 ± 10.7 years and 75.3% were female. Mean vitamin D and ferritin levels were 19.6 ± 7.8 ng/mL and 286.4 ± 174.7 ng/mL, respectively. Vitamin D deficiency was present in 61.8% patients. Moderate-to-high disease activity was observed in 73.0%. Vitamin D demonstrated a significant inverse correlation with DAS28 ($r = -0.46$, $p < 0.001$), whereas ferritin showed a significant positive correlation ($r = 0.52$, $p < 0.001$). Vitamin D and ferritin remained significantly associated with DAS28 after adjustment for age, sex, and disease duration.

Conclusion: Lower vitamin D and higher ferritin levels were significantly associated with greater rheumatoid arthritis disease activity.

Keywords: Vitamin D, Ferritin Levels, Rheumatoid Arthritis, RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory condition associated with persistent inflammatory synovial involvement, progressive joint destruction, pain, functional disability and marked deterioration in quality of life. It is not fully understood what causes RA but genetic susceptibility, environmental, immune system and inflammatory factors play a role in its development and progression. Evaluation of disease activity is fundamental in determining the prognosis and the management of the disease. Therapeutic response and the inflammatory activity of the disease are typically evaluated by clinical and laboratory parameters such as the Disease Activity Score-

28 (DAS28), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).[1]

Besides its well-known role in calcium and bone metabolism, vitamin D plays important immunomodulatory effects. Vitamin D receptors are present in various immune cells, and vitamin D can affect the differentiation of T cells, their production of cytokines, and their immune responses. There have been numerous reports of vitamin D deficiency in patients with RA and some studies suggest that vitamin D deficiency levels correlate with disease activity, though the strength and consistency of this association is unclear. It is possible that clarifying this association may be useful in determining possible factors that can be modified to reduce disease burden.[2]

Serum ferritin is mainly identified as a sign of body iron stores and also serves as an acute-phase reactant in systemic inflammation. Ferritin has been reported as elevated in other inflammatory and autoimmune diseases, and may be a marker of the severity of RA inflammation. But the ferritin level–RA disease activity link remains not fully understood especially when combined with vitamin D levels.[3]

Hence, the aim of this study is to identify the relationship of serum vitamin D and ferritin level with the activity of the disease in patients suffering from rheumatoid arthritis. The understanding of these relationships could give us another clue as to the inflammatory profile of RA and the possible clinical value of vitamin D and ferritin in the assessment of the disease.

METHODOLOGY

To investigate the relationship between serum vitamin D and ferritin with disease activity in rheumatoid arthritis (RA) patients, a hospital-based analytical cross-sectional study was performed. The study was conducted in Medicine department of a tertiary-care hospital of CMH Lahore Medical College and IOD for a period of 6 months from March 2026 to August 2026. Informed written consent was obtained and patients who met the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatism (ACR/EULAR) classification criteria for RA were consecutively recruited. The study received the institutional ethical review committee approval.

Inclusion criteria were a confirmed diagnosis of RA for ≥ 6 months and attending the rheumatology/medicine outpatient department (OPD) ≥ 18 years of age. Disease duration, sex or ongoing disease-modifying antirheumatic drug (DMARD) treatment were not exclusionary criteria. Other systemic autoimmune and connective tissue diseases, chronic kidney disease, chronic liver disease, active infection, malignancy, hematological disorders, and those that can significantly affect ferritin levels were excluded. Other exclusions included pregnant women, women who were lactating, high dose vitamin D supplement over the last 3 months, blood transfusion and acute inflammatory illness.

Demographic and clinical data such as age, sex, disease duration, drugs used, morning stiffness, number of tender/swollen joints and related comorbidities were collected with a structured questionnaire. DAS28 was used to evaluate the disease activity on the basis of

tender joint count, swollen joint count, ESR or CRP and patient's global assessment scores. Patients were classified based on the usual thresholds for disease activity (DA) according to DAS28.

Venous blood samples were taken after an overnight fast in aseptic conditions. Vitamin D was determined to be serum vitamin D [25-hydroxyvitamin D, 25(OH)D] by a standardized chemiluminescent immunoassay with the automated immunoassay method for serum ferritin. Other routine biochemical investigations such as ESR, CRP, complete blood count etc. were also done. Vitamin D status was defined by standard laboratory/reference values.

Descriptive statistics were used to analyse the data with suitable software. Data for continuous variables are presented as mean $\pm$ SD or median (IQR), and for categorical variables as frequencies and percentages. Vitamin D, ferritin and DAS28 score relationships were evaluated by Pearson's, or Spearman's, correlation. Where applicable, independent associations were assessed using multivariable regression analysis, adjusting for potentially confounding factors. P value < 0.05 was set as statistically significant.

RESULTS

A total of 89 patients with rheumatoid arthritis (RA) were included in the study. The mean age of the study population was 45.8 ± 10.7 years, with an age range of 22–68 years. There was a female predominance, with 67 (75.3%) patients being female and 22 (24.7%) male. The mean duration of RA was 6.4 ± 3.9 years. Most patients were receiving disease-modifying antirheumatic drugs, while a smaller proportion were receiving corticosteroids or combination therapy.

The mean serum 25-hydroxyvitamin D level was 19.6 ± 7.8 ng/mL, indicating a high frequency of vitamin D insufficiency/deficiency in the study population. Vitamin D deficiency (< 20 ng/mL) was observed in 55 (61.8%) patients, while 23 (25.8%) had insufficient levels (20–29 ng/mL) and only 11 (12.4%) had sufficient vitamin D levels (≥ 30 ng/mL). The mean serum ferritin concentration was 286.4 ± 174.7 ng/mL. Elevated ferritin levels according to the laboratory reference range were observed in 38 (42.7%) patients.

The mean DAS28 score was 4.9 ± 1.2 . Based on DAS28 classification, 8 (9.0%) patients were in remission, 16 (18.0%) had low disease activity, 32 (36.0%) had moderate disease

activity, and 33 (37.1%) had high disease activity. Thus, moderate-to-high disease activity was present in 65 (73.0%) patients. Patients with higher disease activity demonstrated lower mean serum vitamin D levels and higher mean ferritin concentrations. Patients with high disease activity had a mean vitamin D level of 14.8 ± 5.7 ng/mL compared with 25.1 ± 7.1 ng/mL among patients with low disease activity. Conversely, mean ferritin increased from 181.5 ± 94.6 ng/mL in patients with low disease activity to 371.2 ± 190.5 ng/mL among those with high disease activity. These differences were statistically significant.

Correlation analysis demonstrated a significant inverse correlation between serum vitamin D and DAS28 score ($r = -0.46$, $p < 0.001$), indicating that lower vitamin D concentrations were associated with greater RA disease activity. Serum ferritin showed a significant positive correlation with DAS28 score ($r = 0.52$, $p < 0.001$). Vitamin D and ferritin also demonstrated a modest inverse correlation ($r = -0.31$, $p = 0.003$). On multivariable analysis, both lower vitamin D and higher ferritin levels remained significantly associated with increased DAS28 scores after adjustment for age, sex, and disease duration.

Table 1. Baseline Demographic and Clinical Characteristics of Participants

Variable	Finding
Age, mean $\pm$ SD (years)	45.8 $\pm$ 10.7
Age range (years)	22–68
Female sex, n (%)	67 (75.3)
Male sex, n (%)	22 (24.7)
Disease duration, mean $\pm$ SD (years)	6.4 $\pm$ 3.9
DAS28 score, mean $\pm$ SD	4.9 $\pm$ 1.2
ESR, mean $\pm$ SD (mm/hr)	43.6 $\pm$ 21.8
CRP, mean $\pm$ SD (mg/L)	18.7 $\pm$ 12.4
Vitamin D, mean $\pm$ SD (ng/mL)	19.6 $\pm$ 7.8
Ferritin, mean $\pm$ SD (ng/mL)	286.4 $\pm$ 174.7
Vitamin D deficiency, n (%)	55 (61.8)
Vitamin D insufficiency, n (%)	23 (25.8)
Vitamin D sufficiency, n (%)	11 (12.4)
Elevated ferritin, n (%)	38 (42.7)

Table 2. Vitamin D and Ferritin Levels According to Rheumatoid Arthritis Disease Activity

DAS28 category	n (%)	Vitamin D (ng/mL), mean $\pm$ SD	Ferritin (ng/mL), mean $\pm$ SD
Remission	8 (9.0)	28.7 $\pm$ 6.4	142.6 $\pm$ 71.5
Low activity	16 (18.0)	25.1 $\pm$ 7.1	181.5 $\pm$ 94.6
Moderate activity	32 (36.0)	19.2 $\pm$ 6.3	286.7 $\pm$ 131.4
High activity	33 (37.1)	14.8 $\pm$ 5.7	371.2 $\pm$ 190.5
High activity	33 (37.1)	14.8 $\pm$ 5.7	371.2 $\pm$ 190.5
Overall	89 (100)	19.6 $\pm$ 7.8	286.4 $\pm$ 174.7
p-value	—	<0.001	<0.001

Table 3. Correlation of Vitamin D and Ferritin with Disease Activity

Parameter	DAS28 correlation (r)	p-value
Serum vitamin D	-0.46	<0.001
Serum ferritin	+0.52	<0.001
Vitamin D vs ferritin	-0.31	0.003
ESR vs DAS28	+0.58	<0.001
CRP vs DAS28	+0.55	<0.001

Multivariable linear regression demonstrated that both serum vitamin D and ferritin remained independently associated with DAS28 score after adjustment for age, sex, and duration of RA. Lower vitamin D levels were associated

with higher disease activity, whereas higher ferritin concentrations were associated with greater disease activity. These findings suggest that vitamin D deficiency and increased ferritin levels may be associated with increased

inflammatory disease activity in patients with RA.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease in which the synovial inflammation persists, leading to progressive joint damage, functional limitation and significant morbidity. Evaluation of disease activity plays a key role in RA since steady inflammatory activity is linked with structural disease progression and poor functional outcomes. The current study (n = 89) revealed a high prevalence of vitamin D deficiency and the serum ferritin was significantly increased in a large percentage of patients with RA. Serum vitamin D significantly negatively correlated with DAS28 score; ferritin significantly positively correlated with DAS28 score was important. These data indicate that vitamin D levels are inversely related to inflammatory activity in patients with RA, and that higher levels of ferritin are associated with higher inflammatory activity.

The mean vitamin D serum level in the current study was 19.6 ± 7.8 ng/mL with 61.8% of patients having vitamin D deficiency. This is a relatively common occurrence, similar to what was seen in some of the other studies which reported a high prevalence of vitamin D deficiency in the people suffering from RA. These patients may have lower levels of vitamin D due to decreased exposure to sunlight, decreased physical activity, decreased outdoor mobility due to joint pain, nutritional factors, corticosteroid use, and chronic inflammation. Moreover, vitamin D metabolism has a close relationship with the immune system, suggesting a potential biological mechanism for the observed relationship between vitamin D status and inflammatory disease activity.[4]

In the present study, there was a significant inverse correlation between vitamin D and DAS28 ($r = -0.46$, $p < 0.001$). Disease activity was significantly associated with vitamin D level, with patients with high disease activity having significantly lower mean vitamin D levels than those with low disease activity and/or remission. The same has been reported in other observational studies, in which lower levels of 25(OH)D were correlated with higher DAS28 scores, elevated inflammatory markers and higher clinical disease activity. Vitamin D exhibits immunomodulatory properties and could affect both innate and adaptive immune responses. It can have effects on antigen-presenting cells, T lymphocytes, B lymphocytes

and cytokine production, its active metabolite does. Vitamin D could induce a more regulatory immune profile and inhibit overproduction of pro-inflammatory mediators. Thus, vitamin D deficiency may potentially play a role in the persistence of the inflammatory activity.[5]

The cross-sectional study design used in the present study, however, did not allow for determining whether vitamin D deficiency itself is directly associated with increased levels of RA activity or whether high levels of RA activity are associated with lower vitamin D levels. This distinction is significant, as a more active disease may mean that patients are less mobile and there may be less exposure to the outdoors, which can both negatively affect vitamin D levels. In addition, vitamin D levels could be affected by nutritional status or medication intake. However, the relationship that was observed is plausible, but it is not considered to be causal.[6]

The other significant finding was a positive correlation between serum ferritin with RA disease activity. The mean ferritin level was 286.4 ± 174.7 ng/mL and 42.7% had high ferritin levels. Ferritin is the traditional marker of body iron stores, but is also an acute-phase reactant and may rise with systemic inflammation. In RA, inflammatory cytokines have a potential to trigger hepatic acute-phase response and iron metabolism changes. Thus, high ferritin levels may be a measure of inflammatory activity, rather than just greater iron stores.[7]

There was a significantly positive correlation between serum ferritin and DAS28 score ($r = 0.52$, $p < 0.001$) in current study. The ferritin levels were significantly higher in patients with high disease activity compared to those with low disease activity and remission. This discovery suggests that ferritin could also be used as a laboratory marker for inflammation. Similar observations have been made in inflammatory and autoimmune conditions where ferritin levels rise in proportion to the inflammatory load in the system. The association could be, in part, due to cytokine-driven alteration of iron homeostasis, such as through the action of IL-6 and hepcidin.[8]

Another interesting finding of this study was the negative correlation between vitamin D and ferritin levels ($r = -0.31$, $p = 0.003$). This association suggests that vitamin D deficiency and enhanced inflammatory activity can be concurrent in a subset of RA patients. Experimental studies have indicated that vitamin D may be able to modulate

inflammatory signalling pathways and cytokine production, and chronic inflammation may have a negative effect on nutritional and metabolic parameters. This moderate correlation, however, suggests that vitamin D and ferritin are probably not the same process and should not be used interchangeably as markers.[9]

The distribution of disease activity in this study also highlights the inflammatory burden among the subjects. 73% of patients had moderate to high disease activity and 9% were considered in remission. This could be a reflection of the characteristics of a hospital based population with patients who have persistent symptoms or poorly controlled disease more likely to attend specialist care. The high prevalence of active disease also offers a good clinical context to investigate relationships between laboratory markers and DAS28.[10]

Lower vitamin D and higher ferritin were still independently associated with increased DAS28 scores after adjusting for the other factors mentioned above. The observed associations were not accounted for by these basic demographic and disease-duration characteristics, as suggested by this finding. However, other potential factors which could affect the observed relationships, such as body mass index, sun exposure, diet, corticosteroid therapy, DMARD therapy, disease severity at diagnosis, physical activity and socioeconomic factors should be considered.[11]

Results have clinical implications. Vitamin D may be of particular interest in vitamin D-deficient RA patients, but routine supplementation should be performed based on clinical indications and not on the assumption that correcting vitamin D deficiency will diminish the activity of RA disease. Likewise, high ferritin levels require consideration along with other inflammatory markers and clinical data as ferritin is not specific and could be influenced by infection, liver disease, malignancy, metabolic status, and iron status. Thus, ferritin should be used alongside existing parameters like DAS28, ESR and CRP rather than being used in place of them.

The present study indicates that there is a significant relationship between decreased serum vitamin D levels and increased disease activity in RA patients, however, there is no significant relationship between the serum ferritin level and disease activity in RA patients. Vitamin D was inversely related with DAS28 and Ferritin was positively related with DAS28. The results indicate the need for additional studies of both biomarkers as potential complementary

markers of the inflammatory profile of RA. Future multicenter trials with larger cohorts and longer follow-up are needed to assess the relationship between vitamin D correction or ferritin levels with subsequent disease activity improvement. [12]

The findings of the present study also highlight the potential interaction between nutritional status and systemic inflammation in rheumatoid arthritis (RA). Vitamin D deficiency is particularly relevant in RA because chronic inflammation may coexist with reduced physical activity, limited sunlight exposure, and dietary inadequacy. Patients experiencing pain, stiffness, and functional limitation may spend less time outdoors, potentially reducing cutaneous vitamin D synthesis. Conversely, insufficient vitamin D may contribute to an unfavorable immunological environment. Therefore, the relationship between vitamin D and RA disease activity is likely multifactorial rather than attributable to a single mechanism. [13]

The association between ferritin and disease activity deserves additional consideration. Ferritin can increase substantially during inflammatory states independent of total body iron stores. In RA, chronic cytokine activation can promote hepatic synthesis of acute-phase proteins and alter iron sequestration within macrophages. This process may explain why patients with higher DAS28 scores in the current study also demonstrated higher ferritin concentrations. Ferritin may therefore serve as an indirect marker of systemic inflammatory burden. However, interpretation should remain cautious because ferritin can also increase in hepatic disease, infection, malignancy, metabolic disorders, and iron overload.[14]

The simultaneous assessment of vitamin D and ferritin may provide a broader understanding of disease-associated biological changes. In the current study, patients with greater disease activity generally had lower vitamin D and higher ferritin levels. Although this pattern supports an association between these biomarkers and inflammatory activity, neither biomarker should currently be regarded as a substitute for validated disease-activity measures. DAS28 remains clinically important because it incorporates objective joint findings together with inflammatory markers and patient assessment.[15]

An additional consideration is the possible influence of treatment. Corticosteroids, conventional synthetic DMARDs, and biologic therapies can modify inflammatory activity and

potentially influence laboratory parameters. Patients with more severe disease may also receive more intensive treatment, creating potential confounding in cross-sectional analyses. Future studies should therefore incorporate detailed treatment histories, cumulative corticosteroid exposure, nutritional status, body mass index, sunlight exposure, and disease duration into multivariable models. Longitudinal research would be particularly valuable. Serial measurements of 25-hydroxyvitamin D, ferritin, DAS28, ESR, and CRP before and after treatment could determine whether changes in these biomarkers parallel changes in disease activity. Such studies could also clarify whether correction of vitamin D deficiency is associated with improved clinical outcomes or merely accompanies changes in disease status. Larger multicenter studies would further improve the generalizability of these findings across different populations and treatment settings.

Limitation

A few caveats are warranted. First, because the cross-sectional design does not allow the temporal or causal relationship to be determined. Second, the study was performed at a single hospital, and included a relatively small number of 89 patients, which is not representative. Third, there was not a sufficient assessment of seasonal variation in vitamin D level, dietary intake, and sun exposure, or of body mass index, or of duration and type of RA treatment. Finally, there is the possibility that RA-related inflammation is not the only factor that can affect ferritin. Lastly, no longitudinal assessment was conducted to see if the changes in vitamin D and ferritin levels were linked to changes in disease activity after treatment.

CONCLUSION

A significant relationship between serum 25OHD and ferritin level with the disease activity in patients with RA. Vitamin D deficiency was prevalent among the study subjects and the DAS28 score was inversely correlated, suggesting that patients with low vitamin D levels had more disease activity. Serum ferritin was however, shown to have a significant positive association with DAS28 where the highest levels of ferritin were observed in patients with moderate and high disease activity. The results indicate that vitamin D and ferritin may have different inflammatory burden components in RA.

Vitamin D levels could be useful in detecting vitamin D deficiency in patients who need vitamin D supplementation, and high ferritin levels should be viewed in conjunction with other markers of inflammation and clinical history.

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