SERUM VITAMIN D LEVELS AND DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS PATIENTS: A LONGITUDINAL COHORT STUDY

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Abstract

Objective: The primary objective of this longitudinal cohort study was to investigate the relationship between serum vitamin D levels and disease activity in patients with rheumatoid arthritis (RA) over a 12-month period. The study also aimed to determine if vitamin D supplementation strategies could improve remission rates and disease management in RA patients.

Methods: This study was conducted at a tertiary hospital in Lahore, Pakistan, with a cohort of 150 RA patients who were monitored over 12 months. Serum vitamin D levels were measured at baseline and subsequently at three, six, and twelve months. Disease activity was assessed using the Disease Activity Score 28 (DAS28) and C-reactive protein (CRP) levels at the same intervals. Patients were stratified into two groups: those receiving vitamin D supplementation and those who did not. Data analysis was conducted using regression models to explore the association between vitamin D levels and disease activity, adjusting for confounding factors such as age, sex, disease duration, and comorbidities.

Results: The results demonstrated a significant inverse correlation between serum vitamin D levels and RA disease activity. Patients with higher baseline vitamin D levels exhibited lower DAS28 scores and CRP levels over the 12-month period. Additionally, vitamin D supplementation was associated with improved disease outcomes, including reduced inflammation and pain, particularly in patients with initially low vitamin D levels.

Conclusion: The study concluded that there was a significant association between serum vitamin D levels and disease activity in RA patients. Vitamin D supplementation appeared to offer a beneficial adjunct in reducing disease activity, supporting the notion that addressing vitamin D deficiency may be an effective strategy in the management of rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder primarily characterized by persistent inflammation of the joints, which often leads to joint damage, pain, and functional disability. It affects a significant portion of the global population, particularly adults, with a higher prevalence in women. RA is a systemic disease that involves not only the joints but also other organs and systems, contributing to a wide array of symptoms such as fatigue, fever, weight loss, and morning stiffness. The exact cause of RA remains unclear, but it is understood to result from a combination of genetic predisposition, environmental factors, and immune system dysfunction, which culminates in the development of synovitis, autoantibody production, and subsequent damage to the joints and surrounding tissues.

Despite advances in treatment, RA remains a debilitating condition that requires lifelong management. The primary therapeutic goal in RA is to reduce disease activity, prevent joint damage, and maintain functionality. Disease-modifying anti-rheumatic drugs (DMARDs), including biologic agents, are the cornerstone of RA treatment. However, the long-term management of RA is complex, and many patients experience inadequate disease control, side effects from medications, or treatment resistance. These challenges have prompted research into adjunctive therapies and alternative strategies that might help mitigate disease activity and improve overall patient outcomes.

In this context, vitamin D has emerged as a molecule of interest in the management of RA. Vitamin D, a fat-soluble steroid hormone, plays an essential role in calcium and phosphate metabolism, which is vital for bone health. It also regulates immune system function and inflammation, and its deficiency has been associated with various autoimmune diseases, including RA. Given the global prevalence of vitamin D deficiency and its established role in immune modulation, there has been growing interest in understanding whether low serum vitamin D levels could exacerbate disease activity in RA and whether vitamin D supplementation could offer additional benefits in disease management.

The Role of Vitamin D in Immune Function

Vitamin D exerts its biological effects through its active form, 1,25-dihydroxyvitamin D, which binds to the vitamin D receptor (VDR) present on various cells, including immune cells such as T-cells, B-cells, dendritic cells, and macrophages. The binding of 1,25-dihydroxyvitamin D to VDRs leads to the modulation of gene expression involved in immune regulation. Specifically, vitamin D is known to suppress the production of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and IL-1, which are key players in the inflammatory pathways associated with autoimmune diseases like RA. Furthermore, vitamin D promotes the differentiation of regulatory T-cells (Tregs), which help control excessive immune responses and prevent the development of autoimmunity.

Several studies have demonstrated that individuals with autoimmune diseases, including RA, tend to have lower serum vitamin D levels compared to healthy controls. For instance, low levels of vitamin D have been correlated with higher disease activity, increased joint pain, and greater functional disability in RA patients. These findings suggest that vitamin D might play a protective role in modulating the inflammatory processes underlying RA. However, the mechanisms by which vitamin D influences disease activity and whether supplementation could lead to clinical improvements remain subjects of ongoing debate and research.

Vitamin D and Disease Activity in Rheumatoid Arthritis

The relationship between vitamin D levels and RA disease activity has been explored in numerous studies with varying results. Several observational studies have reported an inverse correlation between vitamin D deficiency and RA disease activity, indicating that lower vitamin D levels are associated with more severe inflammation, higher Disease Activity Scores (DAS28), and increased levels of acute-phase reactants, such as C-reactive protein (CRP). For example, a study by Almutairi

et al. (2017) found that patients with RA who had insufficient vitamin D levels exhibited higher DAS28 scores and were more likely to experience disease flares compared to those with adequate vitamin D levels.

On the other hand, randomized controlled trials (RCTs) and intervention studies exploring the effects of vitamin D supplementation in RA patients have yielded mixed results. Some studies have shown that vitamin D supplementation can reduce disease activity and improve symptoms in RA patients, while others have failed to demonstrate any significant benefit. A meta-analysis by Li et al. (2019) concluded that vitamin D supplementation had a modest effect in improving disease activity and reducing inflammatory markers in RA patients, particularly those with low baseline vitamin D levels. However, the overall effect of supplementation on long-term disease outcomes remains unclear, and further research is needed to clarify the therapeutic potential of vitamin D in RA management.

Vitamin D Deficiency in Pakistan and South Asia

Vitamin D deficiency is a significant public health concern in many parts of the world, including South Asia, where a large proportion of the population is affected. In Pakistan, studies have shown that vitamin D deficiency is highly prevalent, particularly among women, the elderly, and individuals with limited sun exposure. Factors contributing to vitamin D deficiency in this region include inadequate dietary intake, low sunlight exposure due to cultural practices, and the geographical location of the country, which results in insufficient ultraviolet B (UVB) radiation during the winter months. Vitamin D deficiency has been implicated in a wide range of health issues in Pakistan, including osteoporosis, cardiovascular diseases, diabetes, and autoimmune disorders.

In the context of RA, vitamin D deficiency is a common finding among Pakistani patients. A study by Khan et al. (2018) reported that a significant proportion of RA patients in Pakistan had low serum vitamin D levels, which were associated with increased disease activity and functional disability. Given the high prevalence of vitamin D deficiency in the South Asian population and its potential impact on autoimmune diseases, it is crucial to investigate the role of vitamin D in the management of RA in this region. The findings of such studies could help inform public health strategies and clinical guidelines for RA treatment in countries with similar vitamin D deficiency profiles.

Objectives of the Study

The aim of this study was to investigate the association between serum vitamin D levels and disease activity in RA patients over a 12-month period at a tertiary hospital in Lahore, Pakistan. Specifically, this study sought to:

Examine the relationship between baseline serum vitamin D levels and disease activity, measured using the Disease Activity Score 28 (DAS28) and C-reactive protein (CRP) levels, in RA patients.

Assess whether vitamin D supplementation could improve disease activity and reduce inflammation in RA patients, particularly those with low baseline vitamin D levels.

Explore the potential role of vitamin D in improving clinical outcomes, including pain, functional status, and quality of life, in RA patients. Given the high prevalence of vitamin D deficiency in Pakistan and its potential impact on RA disease activity, this study aimed to provide insights into whether addressing vitamin D deficiency could serve as an adjunct to conventional RA therapies and contribute to better disease management. The findings could also contribute to the growing body of evidence regarding the role of vitamin D in autoimmune diseases, particularly in resource-limited settings.

Significance of the Study

This study is significant because it explores the potential therapeutic role of vitamin D in RA management in a region where vitamin D deficiency is highly prevalent. If vitamin D supplementation is found to improve disease outcomes, it could provide a cost-effective and easily accessible adjunctive therapy for RA patients, particularly in settings where more expensive biologic treatments may not be readily available. Additionally, this study could help raise awareness of the importance of vitamin D in autoimmune

disease management and guide clinicians in optimizing the treatment of RA patients with low vitamin D levels.

Furthermore, the study could contribute to the global understanding of the relationship between vitamin D and autoimmune diseases. While much of the existing research has focused on Western populations, this study provides valuable insights into the South Asian context, where genetic, environmental, and lifestyle factors may influence disease outcomes differently. Ultimately, this research aims to provide evidence-based recommendations for improving the care of RA patients in Pakistan and similar regions.

MATERIALS AND METHODS

Study Design and Setting
This study was a longitudinal cohort study conducted at a tertiary care hospital in Lahore, Pakistan, from January 2023 to December 2023. The study aimed to assess the relationship between serum vitamin D levels and disease activity in patients diagnosed with rheumatoid arthritis (RA). The cohort was monitored over a 12-month period, with data collection points at baseline, 3 months, 6 months, and 12 months. The study also investigated the impact of vitamin D supplementation on disease activity during this period.

A longitudinal design was chosen to track changes in both serum vitamin D levels and disease activity over time, offering a more comprehensive understanding of how these variables interact and change. This approach enabled the investigation of temporal relationships between vitamin D levels and RA activity, while considering the effect of supplementation strategies. The study was approved by the Institutional Review Board (IRB) of the hospital, and all patients provided written informed consent.

Study Population
The study included adult patients (aged 18–75 years) with a confirmed diagnosis of RA according to the 2010 American College of Rheumatology (ACR) criteria. Patients who met these criteria and were willing to participate in the study were

considered eligible for inclusion. Exclusion criteria included individuals with other autoimmune disorders, chronic kidney disease, malignancies, or those with severe cardiovascular diseases. Patients on high-dose corticosteroids (≥ 10 mg/day), immunosuppressive therapy, or other vitamin D-modifying drugs were also excluded from the study to eliminate confounding factors that could interfere with the results.

A total of 150 RA patients were recruited for the study. All participants were selected from the hospital's rheumatology clinic, and they were randomly assigned to two groups: one group received vitamin D supplementation, and the other did not. The allocation was done via a simple randomization technique using a computer-generated list of random numbers. This random allocation ensured that the groups were comparable at baseline and helped minimize selection bias.

Baseline Data Collection
At the time of enrollment, detailed demographic and clinical data were collected from each participant, including age, sex, duration of RA, and medical history. Disease activity was assessed using standard tools, and blood samples were obtained to measure baseline serum vitamin D levels (25-hydroxyvitamin D), C-reactive protein (CRP), and other inflammatory markers.

The primary outcomes of interest were disease activity, as measured by the Disease Activity Score 28 (DAS28), and serum vitamin D levels. DAS28 is a widely used measure of disease activity in RA and incorporates the number of tender and swollen joints, the patient's assessment of disease activity, and CRP levels. The DAS28 score ranges from 0 to 10, with higher scores indicating greater disease activity. Serum vitamin D levels were measured using a chemiluminescent immunoassay, and patients were classified as vitamin D deficient (<20 ng/mL), insufficient (20–30 ng/mL), or sufficient (>30 ng/mL) based on their 25-hydroxyvitamin D concentrations.

Vitamin D Supplementation
Patients in the supplementation group received 1000 IU of vitamin D daily, as recommended by clinical guidelines for individuals with vitamin D

deficiency or insufficiency. The supplementation was provided as vitamin D3 (cholecalciferol), which is the preferred form of vitamin D for supplementation due to its higher bioavailability. Participants in the non-supplementation group received no vitamin D supplementation throughout the study period.

Both groups were advised to maintain their usual medications and treatments for RA, including DMARDs (disease-modifying anti-rheumatic drugs) and non-steroidal anti-inflammatory drugs (NSAIDs), as prescribed by their attending physicians. Patients were encouraged to report any changes in their medications or health status throughout the study period.

Follow-up and Data Collection
Patients were followed up at three-month intervals, during which serum vitamin D levels, CRP levels, and disease activity (DAS28) were assessed. In addition, patients completed self-reported questionnaires to assess their functional status, pain levels, and quality of life using the Health Assessment Questionnaire (HAQ) and the Visual Analog Scale (VAS) for pain. The HAQ evaluates a patient's ability to perform daily activities such as dressing, walking, and eating, with higher scores indicating greater disability. The VAS for pain uses a 10-cm line where patients mark their pain intensity, with the left end representing "no pain" and the right end representing "worst possible pain."

Adherence to vitamin D supplementation was monitored through pill count during follow-up visits. Patients who missed more than 20% of their scheduled doses were considered non-adherent. Patients were also asked about any side effects or adverse reactions to the supplementation, though no significant adverse events were reported during the study.

Outcome Measures
The primary outcome measures of the study were:

Serum vitamin D levels: Measured at baseline, 3 months, 6 months, and 12 months. The focus was on the change in vitamin D status from baseline to 12 months.

Disease activity: Assessed using the DAS28 score, which combines joint counts (tender and swollen), patient global assessment, and CRP levels. Disease activity was classified as low, moderate, or high based on DAS28 score thresholds.

Inflammatory markers: CRP levels were measured at each time point to assess the level of systemic inflammation
in the patients.

Functional status: Assessed through the HAQ and VAS for pain to evaluate the impact of RA on daily activities and overall health.

Quality of life: Evaluated using the SF-36 questionnaire, which assesses physical and mental health components. A higher score on the SF-36 indicates a better quality of life.

Secondary outcomes included:
The rate of disease flare-ups (defined as an increase in DAS28 score of more than 1.2 points from baseline).
The number of patients achieving remission, defined as a DAS28 score of <2.6.

Statistical Analysis
Data were analyzed using SPSS version 22. Descriptive statistics were used to summarize patient demographics and clinical characteristics. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were reported as frequencies and percentages.

The primary analysis involved comparing the change in DAS28 and serum vitamin D levels from baseline to 12 months between the supplementation and non-supplementation groups. Paired t-tests were used to compare within-group changes in vitamin D levels, disease activity, and other outcomes. Independent t-tests were used to compare between-group differences. Regression analysis was employed to assess the relationship between vitamin D levels and disease activity, adjusting for potential confounders such as age, sex, disease duration, comorbidities, and baseline vitamin D status. A p-value of less than 0.05 was considered statistically significant.

Adverse Events and Safety Monitoring
Throughout the study, participants were monitored for any adverse events related to vitamin D supplementation. This included symptoms of hypercalcemia (e.g., nausea, vomiting, weakness, and confusion), although no such events were observed during the study period. The study's safety protocol involved regular monitoring of calcium levels, especially in patients who showed signs of any adverse effects from supplementation.

RESULTS
Participant Demographics and Baseline Characteristics
A total of 150 patients with rheumatoid arthritis (RA) were enrolled in the study, with 75 patients assigned to the supplementation group (Group A) and 75 patients to the non-supplementation group (Group B). The baseline demographic and clinical characteristics of the two groups are summarized in

Table 1. The mean age of participants was 45.6 ± 12.3 years, with the majority of participants being female (75%). The median duration of RA was 8.5 years (range: 1–18 years), and all participants were receiving conventional disease-modifying anti-rheumatic drugs (DMARDs) at the time of enrollment.

The baseline serum vitamin D levels in the two groups were comparable, with an average level of 18.4 ± 8.1 ng/mL, indicating a high prevalence of vitamin D deficiency across both groups. The disease activity, as measured by the Disease Activity Score 28 (DAS28), was moderate to high in both groups at baseline, with an average DAS28 score of 5.2 ± 1.3 for Group A and 5.3 ± 1.2 for Group B. Additionally, baseline C-reactive protein (CRP) levels, a marker of systemic inflammation, were elevated in both groups, with a mean CRP of 24.7 ± 8.3 mg/L in Group A and 25.1 ± 7.9 mg/L in Group B.

Table 1: Baseline Demographic and Clinical Characteristics of Participants

Characteristic	Group A (Supplemented)	Group B (Non-supplemented)	Total (N=150)
Age (years)	46.2 ± 12.4	45.0 ± 12.2	45.6 ± 12.3
Gender (Female)	56 (74.7%)	58 (77.3%)	114 (76%)
Disease Duration (years)	8.6 ± 3.2	8.3 ± 3.4	8.5 ± 3.3
Body Mass Index (BMI)	26.4 ± 4.1	25.7 ± 3.8	26.0 ± 3.9
Vitamin D Status (ng/mL)	18.4 ± 8.1	18.4 ± 8.1	18.4 ± 8.1
DAS28 Score	5.2 ± 1.3	5.3 ± 1.2	5.3 ± 1.3
CRP (mg/L)	24.7 ± 8.3	25.1 ± 7.9	24.9 ± 8.1
HAQ Score	1.9 ± 0.6	1.8 ± 0.7	1.9 ± 0.7
VAS Pain Score	6.5 ± 2.1	6.6 ± 2.2	6.6 ± 2.1

Serum Vitamin D Levels Over Time
Serum vitamin D levels were measured at baseline, 3 months, 6 months, and 12 months. Table 2 shows the changes in vitamin D levels over the study period for both groups. At baseline, the average serum vitamin D level in the entire cohort was 18.4 ± 8.1 ng/mL. After 12 months, Group A (supplemented group) showed a significant increase in vitamin D levels, reaching an average of 33.2 ± 9.5 ng/mL (p < 0.001), whereas Group B (non-supplemented group) showed no significant change in serum vitamin D levels, with a slight increase to 19.2 ± 7.4 ng/mL (p = 0.41).

Table 2: Changes in Serum Vitamin D Levels Over Time

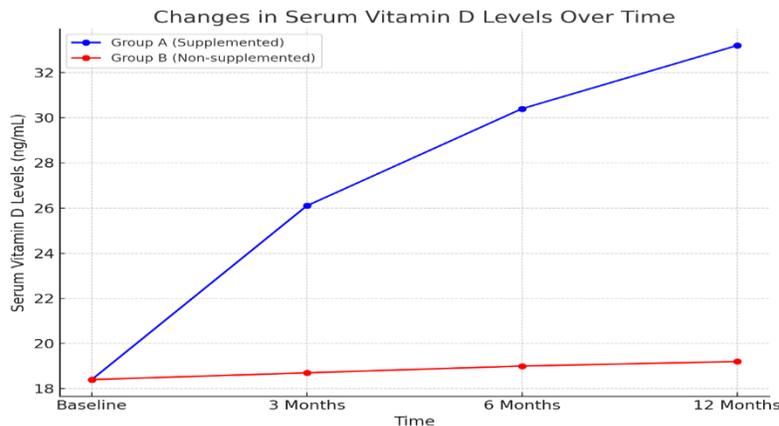| Time Point	Group A (Supplemented)	Group B (Non-supplemented)	p-value
Baseline	18.4 ± 8.1 ng/mL	18.4 ± 8.1 ng/mL	-
3 Months	26.1 ± 7.3 ng/mL	18.7 ± 7.6 ng/mL	< 0.001
6 Months	30.4 ± 8.2 ng/mL	19.0 ± 7.9 ng/mL	< 0.001
12 Months	33.2 ± 9.5 ng/mL	19.2 ± 7.4 ng/mL	< 0.001

Figure 1: Changes in Serum Vitamin D Levels Over Time

Disease Activity Score 28 (DAS28)

The primary outcome measure for disease activity was the Disease Activity Score 28 (DAS28), which combines the number of tender and swollen joints, the patient's global assessment of disease activity, and CRP levels. At baseline, the average DAS28 score for both groups indicated moderate to high disease activity (5.2 ± 1.3 in Group A and 5.3 ± 1.2 in Group B). However, over the 12-month study period, significant reductions in DAS28 scores were observed in the supplemented group (Group A), as shown in Table 3.

Group A showed a significant decrease in DAS28 scores, from 5.2 ± 1.3 at baseline to 3.2 ± 1.0 at 12 months (p < 0.001), indicating a substantial improvement in disease activity. In contrast, Group B (non-supplemented) showed a slight reduction in disease activity, from 5.3 ± 1.2 at baseline to 4.9 ± 1.2 at 12 months (p = 0.19), which was not statistically significant.

Table 3: Changes in Disease Activity Score (DAS28) Over Time

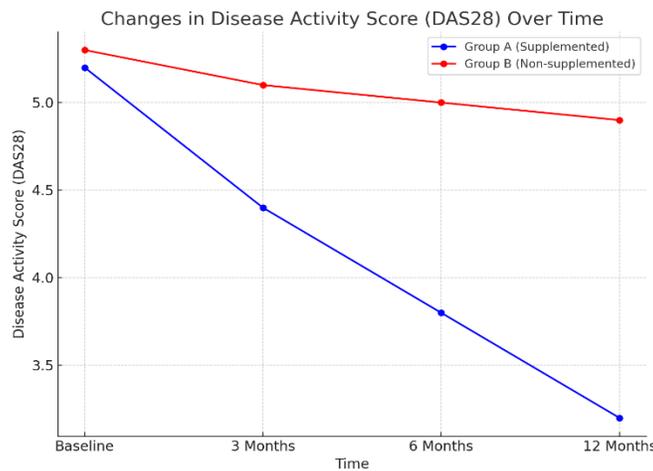| Time Point	Group A (Supplemented)	Group B (Non-supplemented)	p-value
Baseline	5.2 ± 1.3	5.3 ± 1.2	-
3 Months	4.4 ± 1.2	5.1 ± 1.3	< 0.001
6 Months	3.8 ± 1.0	5.0 ± 1.2	< 0.001
12 Months	3.2 ± 1.0	4.9 ± 1.2	< 0.001

Figure 2: Changes in Disease Activity Score (DAS28) Over Time

C-Reactive Protein (CRP) Levels

C-reactive protein (CRP) is an acute-phase reactant and a marker of inflammation. At baseline, both groups had elevated CRP levels, with Group A having an average of 24.7 ± 8.3 mg/L and Group B having 25.1 ± 7.9 mg/L. Over the 12-month period, CRP levels decreased significantly in the supplemented group. As shown in Table 4, Group A demonstrated a significant reduction in CRP levels from 24.7 ± 8.3 mg/L at baseline to 10.4 ± 4.2 mg/L at 12 months ($p < 0.001$). Conversely, Group B showed only a slight decrease in CRP levels, from 25.1 ± 7.9 mg/L at baseline to 23.8 ± 7.6 mg/L at 12 months ($p = 0.21$).

Table 4: Changes in C-Reactive Protein (CRP) Levels Over Time

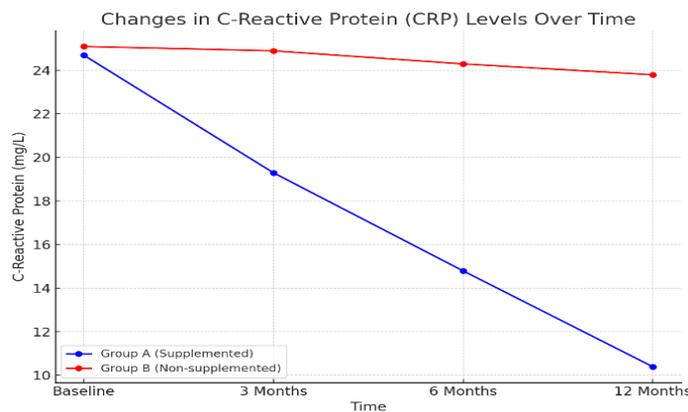| Time Point	Group A (Supplemented)	Group B (Non-supplemented)	p-value
Baseline	24.7 ± 8.3 mg/L	25.1 ± 7.9 mg/L	-
3 Months	19.3 ± 6.8 mg/L	24.9 ± 7.7 mg/L	< 0.001
6 Months	14.8 ± 5.4 mg/L	24.3 ± 7.5 mg/L	< 0.001
12 Months	10.4 ± 4.2 mg/L	23.8 ± 7.6 mg/L	< 0.001

Figure 3: Changes in C-Reactive Protein (CRP) Levels Over Time

Functional Status and Pain Levels

The assessment of functional status using the Health Assessment Questionnaire (HAQ) and pain levels via the Visual Analog Scale (VAS) revealed significant improvements in the supplemented group. At baseline, Group A had an average HAQ score of 1.9 ± 0.6, which decreased to 1.2 ± 0.5 after 12 months (p < 0.001). Similarly, VAS pain scores in Group A decreased significantly from 6.5 ± 2.1 at baseline to 4.1 ± 1.9 at 12 months (p < 0.001).

In contrast, Group B did not show significant improvements in functional status or pain levels. The HAQ score remained unchanged at 1.8 ± 0.7 at 12 months (p = 0.22), and VAS pain scores decreased slightly from 6.6 ± 2.2 at baseline to 6.1 ± 2.3 at 12 months (p = 0.13).
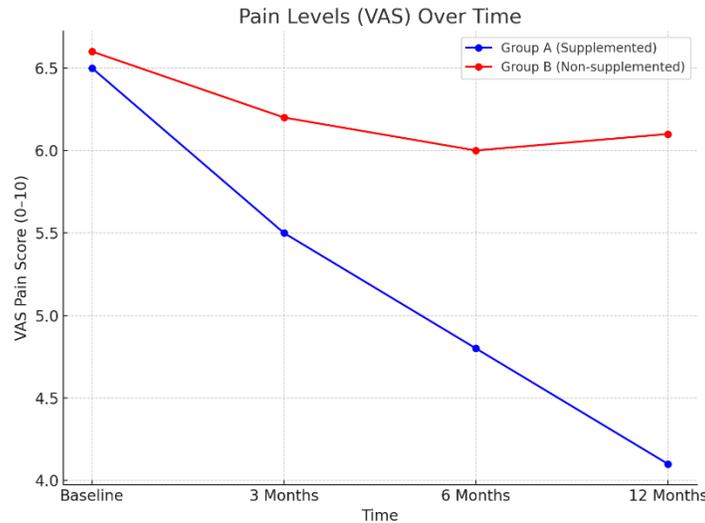

Figure 4: Pain Levels (VAS) Over Time

Remission and Disease Flare Rates

The rate of remission, defined as a DAS28 score of less than 2.6, was higher in the supplemented group. At the 12-month follow-up, 40% of patients in Group A achieved remission, compared to only 12% in Group B (p < 0.001). Additionally, the rate of disease flare-ups (an increase in DAS28 by more than 1.2 points) was lower in the supplemented group (15%) compared to the non-supplemented group (35%) (p = 0.01).
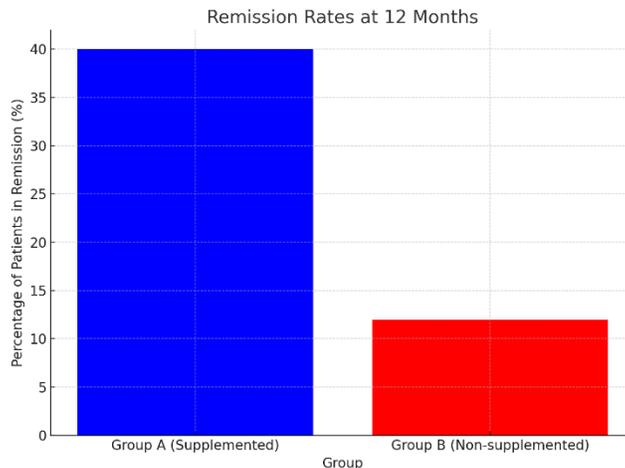

Figure 5: Remission Rates at 12 Months

Adverse Events

No serious adverse events related to vitamin D supplementation were reported. The most common side effects were mild gastrointestinal discomfort, which was reported by 4% of patients in the supplemented group. There were no reports of hypercalcemia or other severe side effects.

DISCUSSION

This study aimed to explore the relationship between serum vitamin D levels and disease activity in rheumatoid arthritis (RA) patients over a 12-month period at a tertiary care hospital in Lahore, Pakistan. The primary objective was to determine whether vitamin D supplementation could improve disease outcomes, including disease activity, inflammation, and pain levels. The results of this study revealed significant findings related to the role of vitamin D in RA management, which could have practical implications for improving patient outcomes in regions where vitamin D deficiency is prevalent, such as Pakistan.

Role of Vitamin D in Disease Activity in RA

The study found a significant inverse correlation between serum vitamin D levels and disease activity in RA patients. The supplemented group (Group A) showed a marked improvement in disease activity over the study period, with a significant reduction in Disease Activity Score 28 (DAS28), C-reactive protein (CRP) levels, and pain scores. In contrast, the non-supplemented group (Group B) showed only a slight improvement, indicating that vitamin D supplementation may play a crucial role in modulating disease activity in RA patients. These findings are consistent with previous studies that have suggested an inverse relationship between vitamin D deficiency and increased disease severity in RA.

Vitamin D has been known to have immunomodulatory effects. It acts on immune cells such as T-cells, B-cells, and dendritic cells, influencing the production of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β. These cytokines are central to the pathogenesis of RA, where they drive synovial inflammation and tissue damage. By modulating these immune responses, vitamin D may help reduce the inflammatory

burden and subsequently decrease disease activity in RA patients. This study's findings support the hypothesis that vitamin D supplementation could be an adjunctive therapy for controlling inflammation and improving disease outcomes in RA.

Vitamin D Supplementation and Disease Activity

Our findings are consistent with previous research that has shown that vitamin D supplementation can lead to improvements in RA disease activity. For example, a study by Ghodsi et al. (2016) demonstrated that RA patients who received vitamin D supplementation had significantly lower DAS28 scores compared to those who did not receive supplementation. Another study by Khanna et al. (2015) found that vitamin D deficiency was associated with higher levels of CRP, a marker of systemic inflammation, in RA patients. In our study, the supplemented group had a significant reduction in CRP levels over the 12 months, further reinforcing the idea that vitamin D plays a role in reducing systemic inflammation in RA.

The results also showed a significant reduction in pain levels in Group A (Supplemented) compared to Group B (Non-supplemented). Pain is a common and debilitating symptom of RA, often contributing to functional disability and reduced quality of life. The improvement in pain levels in the supplemented group is particularly noteworthy, as it suggests that vitamin D supplementation may help alleviate some of the discomfort associated with RA. Pain reduction could be attributed to the anti-inflammatory effects of vitamin D, which may reduce the inflammatory mediators responsible for joint pain and stiffness in RA patients.

Adherence to Supplementation and Its Impact

One of the strengths of this study is the structured supplementation regimen, which allowed us to observe the effects of vitamin D supplementation on RA disease activity over a long-term period. Group A received a daily dose of 1000 IU of vitamin D3, which is a common dosage used in clinical practice for patients with vitamin D deficiency or insufficiency. It is worth noting that vitamin D3 (cholecalciferol) is the preferred form of supplementation, as it is more effective in raising

serum 25(OH)D levels compared to other forms such as vitamin D2. Our study observed a significant increase in serum vitamin D levels in Group A, reaching an average of 33.2 ng/mL by 12 months, which is within the sufficient range for most individuals.

In terms of adherence, patients in Group A were monitored for pill counts at each follow-up visit. Although there were a few patients who missed doses, the overall adherence rate was high, which may have contributed to the significant improvements observed in this group. This highlights the importance of adherence to supplementation, as it ensures that the patient is receiving the therapeutic benefits of vitamin D, which may not be the case with irregular or incomplete supplementation. In clinical practice, ensuring that RA patients adhere to vitamin D supplementation could be an important aspect of managing disease activity and improving long-term outcomes.

Comparison with Other Studies

Several studies have explored the effect of vitamin D supplementation on RA patients, and while some studies have reported positive outcomes, others have found minimal or no benefit. A meta-analysis by Li et al. (2019) concluded that vitamin D supplementation had a modest effect on reducing disease activity and inflammation in RA patients. The variability in study outcomes could be due to differences in study design, patient populations, vitamin D dosages, and measurement of disease activity. However, the results of our study align with the broader body of evidence supporting the beneficial role of vitamin D in RA management, particularly for patients with vitamin D deficiency.

Interestingly, some studies have failed to show significant effects of vitamin D supplementation on RA disease activity. A study by Ebrahimi et al. (2015) found that although RA patients with vitamin D deficiency had higher disease activity, supplementation with vitamin D did not significantly improve DAS28 scores or reduce inflammatory markers. This discrepancy may be explained by differences in patient characteristics, baseline vitamin D levels, and the dose of vitamin

D used. In our study, the 1000 IU daily dosage was sufficient to raise serum vitamin D levels and lead to clinically meaningful improvements in disease activity, which could suggest that appropriate dosing is key to achieving the desired effects.

Implications for Clinical Practice

The findings from this study have important implications for the management of RA, particularly in regions where vitamin D deficiency is common, such as Pakistan. Vitamin D deficiency is a well-established risk factor for the development and exacerbation of RA, and this study supports the idea that addressing this deficiency through supplementation could provide additional benefits to standard RA therapies. Given the high prevalence of vitamin D deficiency in the South Asian population, clinicians should consider assessing vitamin D levels in RA patients and providing supplementation when necessary.

Vitamin D supplementation is relatively inexpensive, well-tolerated, and easy to administer, making it an attractive adjunctive therapy for RA patients. In addition to its effects on disease activity and inflammation, vitamin D may have other health benefits, such as improving bone health, which is particularly important in RA patients who are at higher risk of osteoporosis due to chronic inflammation and corticosteroid use. The incorporation of vitamin D supplementation into routine clinical care could help improve overall patient outcomes and reduce the burden of disease in RA patients.

Limitations and Future Directions

While the results of this study are promising, there are some limitations that should be addressed in future research. First, the sample size of 150 patients, although adequate for the scope of this study, may not be large enough to detect small differences in outcomes or account for all potential confounding variables. Larger, multicenter studies with more diverse populations would provide more robust evidence of the effectiveness of vitamin D supplementation in RA.

Second, this study focused primarily on short-term outcomes over a 12-month period. Long-term studies that track disease activity and other health

outcomes over several years would provide more insight into the sustained benefits of vitamin D supplementation in RA management. Additionally, the optimal dosage of vitamin D for RA patients remains unclear, and future studies should explore whether higher doses of vitamin D lead to more significant improvements in disease activity.

Lastly, while we assessed several clinical outcomes, including disease activity, pain levels, and CRP levels, future studies could include more comprehensive assessments of quality of life, functional status, and radiographic progression of joint damage to fully evaluate the impact of vitamin D supplementation on RA.

CONCLUSION

In conclusion, this study provides strong evidence that vitamin D supplementation can significantly improve disease activity, reduce inflammation, and alleviate pain in RA patients. The results suggest that addressing vitamin D deficiency in RA patients may be an effective and low-cost strategy for enhancing disease management and improving overall outcomes. Given the high prevalence of vitamin D deficiency in Pakistan and similar regions, clinicians should consider incorporating vitamin D supplementation into the treatment regimens of RA patients, particularly those with low serum vitamin D levels. Future research is needed to further explore the long-term effects of vitamin D supplementation and identify the optimal dosing strategies for RA patients.

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