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Exploring the Relationship between Vitamin D Deficiency and Disease Activity in Rheumatoid Arthritis Patients

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Abstract **Original Research Article**

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease marked by inflammation, pain, and joint damage. Vitamin D deficiency worsens inflammation and increases RA disease activity. ***Aim of the study:*** This study aimed to explore the relationship between Vitamin D deficiency and disease activity in rheumatoid arthritis patients. ***Methods:*** This cross-sectional study was conducted in the Department of Medicine, Mymensingh Medical College Hospital, Mymensingh, Bangladesh from January 2003 to December 2003. The study included 100 rheumatoid arthritis patients, divided into two groups- Group A: 50 patients with normal Vitamin D level and Group B: 50 patients with Vitamin D deficiency. ***Result:*** No significant difference was found between the groups in demographic characteristics. Group B exhibited significantly greater disease severity compared to Group A. The Disease Activity Score (DAS28) was higher in Group B (4.2 ± 1.3) than in Group A (2.8 ± 1.1), with a p-value < 0.001. CRP levels were also elevated in Group B (12.4 ± 3.5 mg/L vs. 5.3 ± 2.1 mg/L; $p < 0.001$). Group B had more swollen joints (6.2 vs. 3.5) and tender joints (7.3 vs. 4.1), with $p < 0.001$. ESR levels were higher in Group B (38.7 vs. 22.4 mm/h; $p < 0.001$). Negative correlations were found between Vitamin D levels and DAS28 ($r = -0.48$), CRP ($r = -0.51$), and ESR ($r = -0.52$). ***Conclusion:*** This study concludes that Vitamin D deficiency is significantly associated with increased disease activity, inflammation, and joint involvement in rheumatoid arthritis patients.

Keywords: Relationship, Vitamin D Deficiency, Disease Activity, and Rheumatoid Arthritis.

I INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by systemic inflammation and symmetrical polyarthritis, predominantly affecting the small joints of the hands and feet [1]. It leads to severe pain, swelling, joint stiffness, and, if left untreated, progressive joint destruction and disability [2]. RA impacts approximately 1% of the global population, with the prevalence varying between regions and socio-economic groups, presenting significant challenges to public health systems worldwide [3]. In South Asia, including Bangladesh, the burden of RA is rising, attributed to a mix of genetic predispositions and environmental factors, affecting the quality of life and increasing disability-adjusted life years among affected individuals [4]. In Bangladesh, the prevalence of Vitamin D deficiency is alarmingly high, even among individuals with adequate sun exposure, due to socio-cultural practices like wearing traditional clothing that limits skin exposure to sunlight, dietary habits that exclude Vitamin D-rich foods, and genetic factors [5]. Studies in coastal areas of Bangladesh have shown that even populations who should theoretically receive sufficient sunlight exhibit significant rates of Vitamin D deficiency [6]. Vitamin D helps regulate the activity of immune cells like T cells, B cells, and macrophages, which are key players in autoimmune conditions like RA [7]. Deficiency in Vitamin D has been linked to the dysregulation of these immune responses, which may contribute to the onset and progression of autoimmune diseases, including RA [8]. Several studies have demonstrated that low Vitamin D levels are associated with increased RA disease activity, emphasizing the potential role of Vitamin D in mitigating autoimmune processes [9]. The immunomodulatory

effects of Vitamin D and its deficiency's implications on autoimmune diseases like RA have become a focus of intense research. Vitamin D's role in down-regulating pro-inflammatory cytokines and up-regulating anti-inflammatory cytokines positions it as a potential modulator of immune tolerance in RA patients [10]. However, the evidence linking Vitamin D levels to RA disease severity is mixed. While some studies highlight a clear inverse relationship between Vitamin D levels and RA severity, indicating that higher Vitamin D levels could reduce disease activity and inflammation, other studies report no significant association, suggesting that Vitamin D's role may be more complex than initially understood [11,12]. Existing studies provide mixed findings on the effectiveness of Vitamin D supplementation in managing RA symptoms. Some clinical trials have shown that Vitamin D supplementation can reduce RA recurrence rates and improve patient outcomes, although the effects were not always statistically significant [13]. In contrast, other studies suggest that Vitamin D alone may not suffice in altering the course of RA unless combined with other therapeutic interventions [14]. These discrepancies indicate the need for more targeted research, particularly in regions like Bangladesh, where both RA prevalence and Vitamin D deficiency are high and intersect with socio-economic and cultural variables. In Bangladesh, the challenge of addressing Vitamin D deficiency and its implications for RA is magnified by the lack of standardized guidelines for Vitamin D supplementation and the economic barriers that limit access to healthcare [15]. Studies conducted in similar populations have recommended regular Vitamin D level assessments and personalized supplementation plans as essential components of RA management [16]. The current study aims to explore the intricate relationship between Vitamin D deficiency and disease activity in rheumatoid arthritis patients.

II OBJECTIVES

To explore the relationship between Vitamin D deficiency and disease activity in rheumatoid arthritis patients.

III METHODOLOGY & MATERIALS

This cross-sectional study was conducted in the Department of Medicine, Mymensingh Medical College Hospital, Mymensingh, Bangladesh, from January 2003 to December 2003. A total of 100 patients with rheumatoid arthritis were included in this study. These patients were divided into two groups- Group A: 50 patients with normal Vitamin D level and Group B: 50 patients with Vitamin D deficiency. The consent of the patients and guardians was taken before collecting data. The inclusion criteria included adult patients aged 18 years and above, diagnosed with RA according to the American College of Rheumatology (ACR) criteria, and who provided informed consent to participate. Exclusion criteria excluded patients with other autoimmune diseases, those on Vitamin D supplementation at the start of the study, and individuals with chronic conditions that might influence Vitamin D metabolism, such as renal or liver disorders. Data collection involved detailed demographic information, clinical history, lifestyle factors, and socio-cultural aspects that might impact Vitamin D levels, such as clothing habits and dietary intake. Blood samples were collected from all participants to measure serum 25-hydroxyvitamin D [25(OH)D] levels using a standard chemiluminescence immunoassay, with levels below 20 ng/mL classified as deficient. RA disease activity was assessed using the Disease Activity Score in 28 joints (DAS28), which included measures of tender and swollen joint ~~counts~~, the erythrocyte sedimentation rate (ESR), and patient-reported global health assessment. Ethical approval for the study was obtained from the institutional review board. After the collection of data, all data were checked and cleaned. After cleaning, the data were entered into the computer, and statistical analysis of the results was obtained by using Windows-based computer software devised with Statistical Packages for Social Sciences version 22. A p-value of less than 0.05 was considered statistically significant.

IV RESULT

Table I presents a comparison of demographic and clinical characteristics between Group A (patients with normal Vitamin D levels) and Group B (patients with Vitamin D deficiency), both comprising 50 individuals. The average age of participants in Group A is 45.2 ± 10.1 years, while in Group B it is 48.5 ± 9.8 years, with a p-value of 0.5152, indicating no significant difference in age between the groups. In terms of gender distribution, 30% of Group A (15 patients) are male and 70% (35 patients) are female, while in Group B, 24% (12 patients) are male and 76% (38 patients) are female, with a p-value of 0.5014, showing no significant gender difference between the groups. The mean body mass index (BMI) in Group A is 23.5 ± 3.2 kg/m², compared to 24.8 ± 3.5 kg/m² in Group B, with a p-value of 0.0555, suggesting a marginal difference in BMI that is not statistically significant. The duration of rheumatoid arthritis (RA) is slightly longer in Group B (7.3 ± 5.0 years) compared to Group A (6.1 ± 4.2 years), with a p-value of 0.1968, indicating no significant difference in disease duration between the two groups. Table II demonstrates the comparison of disease activity parameters between the two groups. Across all measured parameters, Group B shows significantly higher values than Group A, indicating greater disease severity in patients with Vitamin D deficiency. The Disease Activity Score (DAS28), which assesses overall RA disease activity, is markedly higher in Group B (4.2 ± 1.3) compared to Group A (2.8 ± 1.1), with a highly significant p-value of less than 0.001. Similarly, levels of C-reactive protein (CRP), a marker of inflammation, are significantly elevated in Group B (12.4 ± 3.5 mg/L) versus Group A (5.3 ± 2.1 mg/L), again with a p-value of less than 0.001. Additionally, patients in Group B have a higher swollen joint count (6.2 ± 2.5) compared to Group

A (3.5 ± 1.8), as well as a greater tender joint count (7.3 ± 3.2 in Group B compared to 4.1 ± 2.0 in Group A), with both parameters demonstrating a statistically significant difference ($p < 0.001$). Finally, the erythrocyte sedimentation rate (ESR), another marker of inflammation, is significantly higher in Group B (38.7 ± 8.9 mm/h) compared to Group A (22.4 ± 5.8 mm/h), also with a p-value of less than 0.001. Table III illustrates the correlation between Vitamin D levels and various disease activity parameters in rheumatoid arthritis (RA) patients. A negative correlation was found between Vitamin D levels and the Disease Activity Score (DAS28), with a correlation coefficient of -0.48 and a p-value of less than 0.001, indicating that lower Vitamin D levels are associated with higher disease activity. Similarly, the correlation between Vitamin D levels and C-reactive protein (CRP) levels showed a stronger negative association, with a correlation coefficient of -0.51 and a highly significant p-value of less than 0.001, suggesting that as Vitamin D levels decrease, inflammation increases. The erythrocyte sedimentation rate (ESR), another marker of inflammation, also demonstrated a negative correlation with Vitamin D levels ($r = -0.52$, $p < 0.001$), indicating a direct relationship between lower Vitamin D and higher inflammatory activity. Furthermore, the number of tender and swollen joints was negatively correlated with Vitamin D levels, with correlation coefficients of -0.42 and -0.45, respectively, both with p-values of less than 0.001. Table IV compares the use of medications between the two groups. In terms of Methotrexate usage, 80% of Group A (40 patients) and 84% of Group B (42 patients) were on this treatment, with a p-value of 0.6045, indicating no significant difference between the groups. Prednisolone was used by 50% of Group A (25 patients) and 60% of Group B (30 patients), with a p-value of 0.3173, also showing no statistically significant difference between the two groups. Similarly, 70% of Group A (35 patients) and 76% of Group B (38 patients) were taking non-steroidal anti-inflammatory drugs (NSAIDs), with a p-value of 0.5014, suggesting no significant variation between the groups. Finally, Biologic DMARDs were used by 20% of Group A (10 patients) and 24% of Group B (12 patients), with a p-value of 0.631, again indicating no significant difference in the use of this medication between the two groups. Overall, there are no statistically significant differences in medication usage between the two groups.

Table-I: Demographic and clinical characteristics of the study groups (N = 100)

Characteristic	Group A (n = 50)	Group B (n = 50)	P-value
Age (Years)			
Mean ± SD	45.2 ± 10.1	48.5 ± 9.8	0.5152
Gender			
Male	15 (30%)	12 (24%)	0.5014
Female	35 (70%)	38 (76%)	
BMI (Kg/m2)			
Mean ± SD	23.5 ± 3.2	24.8 ± 3.5	0.0555
Duration of RA (Years)			
Mean ± SD	6.1 ± 4.2	7.3 ± 5.0	0.1968

Table-II: Comparison of RA disease activity between the study groups (N=100)

Disease Activity Parameter	Group A (n = 50) (Mean ± SD)	Group B (n = 50) (Mean ± SD)	P-value
DAS28 Score	2.8 ± 1.1	4.2 ± 1.3	< 0.001
CRP (mg/L)	5.3 ± 2.1	12.4 ± 3.5	< 0.001
Swollen Joint Count	3.5 ± 1.8	6.2 ± 2.5	< 0.001
Tender Joint Count	4.1 ± 2.0	7.3 ± 3.2	< 0.001
ESR (mm/h)	22.4 ± 5.8	38.7 ± 8.9	< 0.001

Table-III: Vitamin D levels and RA disease activity correlation (N=100)

Parameter	Correlation Coefficient (r)	P-value
Vitamin D Level vs DAS28	-0.48	< 0.001
Vitamin D Level vs CRP	-0.51	< 0.001
Vitamin D Level vs ESR	-0.52	< 0.001
Vitamin D Level vs Tender Joint Count	-0.42	< 0.001
Vitamin D Level vs Swollen Joint Count	-0.45	< 0.001

Table-IV: Medications used by RA patients in the groups (N=100)

Medication	Group A (n = 50) (Mean ± SD)	Group B (n = 50) (Mean ± SD)	P-value
Methotrexate	40 (80%)	42 (84%)	0.6045
Prednisolone	25 (50%)	30 (60%)	0.3173
NSAIDs	35 (70%)	38 (76%)	0.5014
Biologic DMARDs	10 (20%)	12 (24%)	0.631

V DISCUSSION

The current study sought to investigate the relationship between Vitamin D deficiency and disease activity in patients with rheumatoid arthritis (RA), comparing two groups of 50 individuals each: Group A with normal Vitamin D levels and Group B with Vitamin D deficiency. Upon analyzing the demographic and clinical characteristics of the two groups, the findings show that there were no statistically significant differences between Group A and Group B in terms of age, gender, BMI, or disease duration. The average age of participants in Group A was 45.2 ± 10.1 years, while Group B had an average age of 48.5 ± 9.8 years ($p = 0.5152$), indicating no significant age-related differences between the two groups. This finding is consistent with previous research indicating that Vitamin D levels in RA patients are not significantly correlated with age distribution [17]. Similarly, gender distribution was comparable between the groups, with 30% of Group A being male and 24% of Group B being male, further confirming the absence of gender-specific trends in Vitamin D deficiency in RA patients [18]. The mean BMI was slightly higher in Group B (24.8 ± 3.5 kg/m²) compared to Group A (23.5 ± 3.2 kg/m²), but this difference was not statistically significant ($p = 0.0555$). This trend aligns with some studies that suggest Vitamin D deficiency is more common in individuals with higher BMI due to the sequestration of the vitamin in adipose tissue, although the difference observed in our study was not conclusive [19]. Furthermore, the duration of RA was also found to be comparable between the groups, with Group A having an average RA duration of 6.1 ± 4.2 years and Group B with an average duration of 7.3 ± 5.0 years ($p = 0.1968$). The absence of significant differences in disease duration indicates that both groups had similar histories of RA progression, suggesting that Vitamin D deficiency does not have a marked influence on the duration of RA but may affect the severity of the disease, as evidenced by later findings on disease activity parameters. When comparing disease activity parameters between the two groups, significant differences were observed. Group B, consisting of patients with Vitamin D deficiency, consistently exhibited higher disease activity across multiple markers. The Disease Activity Score (DAS28), which evaluates RA severity, was significantly higher in Group B (4.2 ± 1.3) compared to Group A (2.8 ± 1.1), with a p-value of less than 0.001, indicating that Vitamin D deficiency is associated with more severe disease activity. This finding is in line with previous research, such as the study by Turhanoğlu *et al.*, [19], which reported an inverse relationship between Vitamin D levels and DAS28 scores, reinforcing the hypothesis that adequate Vitamin D levels may play a protective role in mitigating RA severity. Similarly, markers of inflammation, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were significantly elevated in Group B compared to Group A. The CRP levels in Group B were 12.4 ± 3.5 mg/L, significantly higher than the 5.3 ± 2.1 mg/L observed in Group A ($p < 0.001$). This substantial difference in CRP levels suggests that Vitamin D deficiency may contribute to heightened inflammatory responses in RA patients. Similar findings were observed in the study by Al-Saoodi *et al.*, [20], which demonstrated that Vitamin D supplementation significantly reduced CRP levels in RA patients, emphasizing the role of Vitamin D in controlling systemic inflammation. ESR, another marker of inflammation, was also significantly higher in Group B (38.7 ± 8.9 mm/h) compared to Group A (22.4 ± 5.8 mm/h), with a p-value of less than 0.001. This supports the hypothesis that lower Vitamin D levels are correlated with increased inflammatory activity, as demonstrated in prior studies [21]. The joint count data also revealed significant differences between the two groups. Group B exhibited a higher number of both swollen and tender joints compared to Group A. The swollen joint count in Group B was 6.2 ± 2.5, while Group A had a significantly lower count of 3.5 ± 1.8 ($p < 0.001$). Similarly, the tender joint count was higher in Group B (7.3 ± 3.2) compared to Group A (4.1 ± 2.0), also with a p-value of less than 0.001. These findings further support the notion that Vitamin D deficiency is associated with more severe joint involvement in RA patients. Several studies, including those by Higgins *et al.*, [22] (2013) and Turhanoğlu *et al.*, [19], have reported similar results, showing that Vitamin D deficiency is linked to increased joint tenderness and swelling, thus exacerbating disease symptoms. In terms of medication usage, the analysis revealed no significant differences between Group A and Group B regarding the use of common RA medications, including methotrexate, prednisolone, NSAIDs, and biologic DMARDs. For example, 80% of Group A and 84% of Group B were on methotrexate, with a p-value of 0.6045, indicating no statistically significant difference. Similarly, the use of prednisolone, NSAIDs, and biologic DMARDs showed no significant variations between the groups. This suggests that medication usage patterns were comparable across groups, and the differences in disease severity cannot be attributed to disparities in treatment regimens. These findings are consistent with those of Hazlewood *et al.*, [23], who noted that methotrexate remains the anchor drug for RA

management regardless of Vitamin D status, and variations in disease severity are likely due to other factors, such as the nutritional status of the patients, rather than differences in medication. The results of this study suggest that Vitamin D deficiency is significantly associated with increased disease activity, heightened inflammatory responses, and more severe joint involvement in RA patients.

Limitations of the study

In our study, we had a small sample size and did not have a control group for comparison. The study population was selected from one center in Mymensingh city, so it may not be representative of the wider population. The study was conducted over a short period.

VII CONCLUSION AND RECOMMENDATIONS

This study concludes that Vitamin D deficiency is significantly associated with increased disease activity, inflammation, and joint involvement in rheumatoid arthritis (RA) patients. While demographic factors and medication usage were comparable between groups, patients with Vitamin D deficiency exhibited markedly higher DAS28 scores, CRP, ESR, and joint counts. These findings suggest that addressing Vitamin D deficiency may be crucial in managing RA severity. Future research should be conducted with a larger sample size focusing on the potential benefits of Vitamin D supplementation in improving clinical outcomes in RA patients.

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