

Association between Rheumatoid Arthritis and Serum Vitamin D Concentrations: A case-control studyRakesh Raushan¹, Vivek Kumar²¹Senior Resident, Department of General Medicine, ICARE Institute of Medical Sciences and Dr. Bidhan Chandra Roy Hospital, Haldia, West Bengal²Assistant Professor, Department of Orthopaedics, Narayan Medical College & Hospital, Jamuhar, Sasaram, Bihar

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Conflict of interest: Nil

Abstract:**Background:** Rheumatoid arthritis (RA) is an autoimmune disease characterized by periods of remission and flares of symmetrical joint inflammation slowly progressing to joint and cartilage destruction leading to deformities. Evidence is accumulating suggesting vitamin D deficiency and its correlation in autoimmune diseases including RA. Aim of this study is to determine the association between rheumatoid arthritis and serum vitamin D levels.**Methods:** This case-control study was conducted at Department of Medicine with collaboration of Orthopaedics department at ICARE Institute of Medical Sciences and Dr. Bidhan Chandra Roy Hospital, Haldia, West Bengal from May 2023 to October 2023. There were 40 patients were presented in this study. After obtaining informed written permission, we took detailed demographic information on all patients who had signed up for treatment. Clinical signs and symptoms, X-ray findings, and anti-citrullinated protein levels more than 20 u/mL were all used to diagnose RA in this patient's instance. They all pointed to the disease. Group I featured 20 people with verified rheumatoid arthritis, whereas group II had 20 individuals who did not have rheumatoid arthritis. The levels of vitamin D in both groups' blood were compared. Data was analysed using SPSS 24.0.**Results:** There were 12 (60.0%) males and 8 (40.0%) females in group I and in group II 11 (55.0%) males and 9 (45.0%) females. Mean age in group I was 44.7±8.35 years and had mean BMI 27.8±9.45 kg/m² while in group II mean age was 46.5±6.51 years with mean BMI 28.6±6.51 kg/m². Hypertension and diabetes were the most common comorbidities. Vitamin D level in group I was significantly lower 29.41±5.59 as compared to group II 40.41±8.81 (ng/mL). Among 20 cases of rheumatoid arthritis, positive patients for rheumatoid factor were 18 (90.0%) in which frequency of hypovitaminosis was found among 16 (88.88%) cases.**Conclusion:** People with RA are far more likely to be vitamin D deficient, and the severity of the disease is directly correlated with this insufficiency. Since vitamin D deficiency affects women more than males, they should be tested with a high degree of suspicion. Taking vitamin D supplements may be necessary to prevent or reverse the progression of the disease.**Keywords:** Vitamin D Deficiency, Rheumatoid Arthritis, Rheumatoid Factor, Hypovitaminosis.This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

In individuals with Rheumatoid Arthritis, synovial joints are the major source of inflammation and debilitation (RA). In addition to the joints, it affects several organ systems. Involvement of several systems. RA affects an estimated 0.5-1 percent of the global population [2]. Pathogenesis of Rheumatoid Arthritis (RA) is caused by the degradation of cartilage and bone as well as tendons by osteoclasts, B and T lymphocytes, dendritic cells, and proteolytic enzymes. Furthermore, the activation of the immune system has major implications, resulting in systemic and extraarticular RA symptoms, as well.[3]

T-lymphocytes may include receptors for vitamin D. A lack of vitamin D, which affects both innate and adaptive immune responses, may be a contributing factor in the immune system's instability.[4] Vitamin D insufficiency has been linked to multiple sclerosis, inflammatory bowel disease, Lupus Erythematosus, and Rheumatoid Arthritis [5].

Rheumatoid Arthritis (RA) has been associated to low 25OHD levels in cross-sectional studies [7]. In spite of cross sectional research showing a negative correlation between 1,25(OH)2D and a variety of

disease activity markers, it is unusual to assess it. [8]

An approach to remission is the gold standard in RA, and cross-sectional studies show that vitamin D may play an essential role in RA remission because of its ability to modulate the immune system and its link to disease activity. Only two brief longitudinal studies have evaluated the connection between blood 25OHD levels at the time of RA diagnosis and remission during follow up. [10,11] Patients with RA who had low 25OHD levels upon diagnosis had a lower chance of remission, according to the two research studies. Remission and 1,25(OH)₂D were shown to be unrelated in this investigation.

In rheumatoid arthritis, synovitis is the disease's defining feature (RA). RA's genesis and pathophysiology remain a mystery, and several factors may play a role. Rheumatoid arthritis and systemic lupus erythematosus may be linked to low levels of 25(OH)D because of its immunoregulatory actions [12]. Low or inadequate levels of 25(OH)D have been linked to an increased risk of developing RA. Many studies have looked at the role of vitamin D deficiency, especially in relation to rheumatoid arthritis (RA). Some studies, however, have shown a significant negative correlation between blood 25(OH)D levels and RA activity [14].

Several investigations have shown no link between 25(OH)D serum levels and RA activity. [15] Research on 25(OH)D deficiency and disease activity in RA will benefit from this knowledge, even if these conflicts have not yet been settled.

Accordingly, the aim of this research was to examine the blood levels of the vitamin D metabolite 25(OH)D₃ in RA patients and healthy persons, and to see whether there was any link between these levels and RA disease activity.

Material and Methods

This case-control study was conducted at Department of Medicine with collaboration of Orthopaedics department at ICARE Institute of Medical Sciences and Dr. Bidhan Chandra Roy

Hospital, Haldia, West Bengal from May 2023 to October 2023. There were 40 patients were presented in this study. After obtaining informed written permission, we took detailed demographic information on all patients who had signed up for treatment. Patients were using vitamin D supplementation and those did not provide any written consent were excluded from this study.

Patients were between the ages of 20 and 70. An RA diagnosis was made for this patient based on anti-citrullinated protein levels greater than 20 u/mL. 20 persons in group I had been diagnosed with rheumatoid arthritis, whereas another 20 people in group II had not been so fortunate. After enrollment, data was collected on demographics like gender and age, as well as health conditions like diabetes, hypertension, and asthma, as well as smoking history and rheumatoid factor (RF). Five millilitres of blood from the cubital vein were sent to a laboratory for vitamin D level testing. If their vitamin D levels were below 30 ng/ml, they were diagnosed with hypovitaminosis D.

SPSS 24.0 was used for statistical analysis. A Q-Q plot was used to determine whether or not the data was normal. The mean and standard deviation of continuous variables such as age and mean vitamin D levels were given. There were percentages and frequencies for categorical factors like gender and co-morbidities.

There was no significant difference in the mean age between the two groups when comparing categorical data using chi-square. To test the null hypothesis, the case and control groups have to be separated by fewer than 0.05 p-values.

Results

There were 12 (60.0%) males and 8 (40.0%) females in group I and in group II 11 (55.0%) males and 9 (45.0%) females. Mean age in group I was 44.7±8.35 years and had mean BMI 27.8±9.45 kg/m² while in group II mean age was 46.5±6.51 years with mean BMI 28.6±6.51 kg/m². Hypertension and diabetes were the most common comorbidities. (Table 1)

Table 1: Characteristics of both groups

Variables	Group I	Group II
Mean Age (years)	44.7±8.35	46.5±6.51
Mean BMI (kg/m ²)	27.8±9.45	28.6±6.51
Gender		
Male	12(60.0%)	11(55.0%)
Female	8(40.0%)	9(45.0%)
Comorbidities		
HTN	8(37.5%)	9(45.0%)
DM	6(30.0%)	5(25.0%)

In group I 5 (25.0%) patients were smokers and 15 (75.0%) were non and in group II 6 (30.0%) were smokers and 14 (70.0%) were non smokers.

Vitamin D level in group I was significantly lower 29.41 ± 5.59 as compared to group II 40.41 ± 8.81 (ng/mL). In group I 13 (65%) patients had vitamin D deficiency and in group II 7 (35.0%) patients had vitamin D deficiency. (Table 2).

Table 2: Comparison of vitamin D levels among both groups

Variables	Group I	Group II
Mean Vitamin D levels (ng/mL)	29.41 ± 5.59	40.41 ± 8.81
Vitamin D deficiency		
Yes	13(65%)	7(35.0%)
No	7(35%)	13(65.0%)

Among 20 cases of rheumatoid arthritis, positive patients for rheumatoid factor were 18 (90.0%) in which frequency of hypovitaminosis was found among 16 (88.88%) cases. Vitamin D level among RF positive patients was 28.09 ± 6.35 lower as compared to RF negative patients. (Table 3)

Table 3: Association of hypovitaminosis among RF positive patients

Variables	RF-Patients(n=18)	Non-RF patients(n=2)
Mean Vitamin D levels (ng/mL)	28.09 ± 6.35	34.12 ± 8.61
Hypovitaminosis		
Yes	16(88.88%)	1(50.0%)
No	2(11.12%)	1(50.0%)

Discussion

When the synovial membrane of the joints is damaged, it results in abnormalities in the joints themselves. This is known as rheumatoid arthritis (RA). As a result of RA, bone loss and joint damage may occur. Within two years, radiographic indications of joint degradation will be seen in 90% of those with RA symptoms [17]. Research has also connected RA to the production of T cells and cytokines [18]. The steroid hormone 25(OH)D plays a critical role in bone metabolism and the regulation of the immune system. It has been shown that vitamin D may affect the function of T and B cells, macrophages, and dendritic cells. When 25(OH)D is combined with receptors, cell proliferation and differentiation are controlled and inflammatory factors are reduced significantly. The ability to regulate immune responses will be dependent on them in the future [19]. Rheumatoid arthritis sufferers may benefit from taking 25(OH)D supplements, which may help ease their osteoporosis symptoms.

In current study 40 patients were presented in which 20 cases had rheumatoid arthritis and included in group I. There were 12 (60.0%) males and 8 (40.0%) females in group I and in group II 11 (55.0%) males and 9 (45.0%) females. Mean age in group I was 44.7 ± 8.35 years and had mean BMI 27.8 ± 9.45 kg/m² while in group II mean age was 46.5 ± 6.51 years with mean BMI 28.6 ± 6.51 kg/m². Results of our study were comparable to the previous studies.[20,21] Hypertension and diabetes were the most common comorbidities. In group I 5 (25.0%) patients were smokers and 15 (75.0%)

were non and in group II 6 (30.0%) were smokers.[22] Vitamin D levels were shown to be decreased in people with RA. RF-positive RA patients had lower vitamin D levels than RF-negative RA participants. The prevalence of hypovitaminosis in RA patients with rf positivity was higher than that in individuals with rf negativity.

Based on our data, Atwa et al. found that vitamin D deficiency was substantially more prevalent in RA patients. [23] Sixty-one percent of RA patients, according to Haque and colleagues, had vitamin D deficiency [24]. A prospective cohort study of 29,368 healthy women found a connection between RA activity and vitamin D levels. It was given to them as a dietary supplement in addition to their regular diet. The fact that only 152 cases of RA were recorded by this cohort during an 11-year period demonstrates that increasing vitamin D intake has a significant impact on decreasing the chance of getting RA [25]. Previous investigations [26,27] have indicated that 34–84 percent and 12–52 percent of RA patients had a serum 25(OH)D deficiency or insufficiency. The 25(OH)D levels in the blood of RA patients have been demonstrated in several studies to be significantly lower than in the blood of healthy controls. Other studies [28] revealed that 25(OH)D3 levels in the blood did not differ substantially between RA patients and healthy persons.

A strong negative connection between serum 25-hydroxyvitamin D3 (25-OHD3) and RA disease activity has been explored in a small number of studies [29]. As part of a RA therapy strategy, it is important to reduce disease activity, improve joint function, and monitor blood 25-OHD3 levels close-

ly. Symptoms of vitamin D insufficiency may be reduced if treatment is started early enough in the disease. There is a chance that this might lessen disease activity. Increased remission rates for newly diagnosed RA have been achieved with the widespread use of early and vigorous treatment since the 1990s [30]. The utility of this method in the treatment of low vitamin D and supplementation for early therapy in RA patients has yet to be determined, even though it is frequently utilised in clinical practise.

The following findings support the hypothesis that vitamin D has a function in RA. However, there are certain negatives to it. A smaller and more homogenous sample was used since the study was conducted just at one institution. Because it was a case-control study, it was impossible to establish a causal relationship between them. In order to corroborate our findings, new multi-center, prospective studies with larger sample sizes and more variation are needed. Additional research is required to find better treatment options for vitamin D deficiency.

Conclusion

People with RA are far more likely to be vitamin D deficient, and the severity of the disease is directly correlated with this insufficiency. Since vitamin D deficiency affects women more than males, they should be tested with a high degree of suspicion. Taking vitamin D supplements may be necessary to prevent or reverse the progression of the disease.

References

1. High prevalence of vitamin D inadequacy and implications for health. Holick MF. *Mayo Clin Proc.* 2006;81:353–373.
2. Epidemiology and genetics of rheumatoid arthritis. Silman AJ, Pearson JE. *Arthritis Res.* 2002;4 Suppl 3:0–72.
3. Pathogenesis of rheumatoid arthritis [Article in Croatian] Branimir Anić, Mayer. <https://pubmed.ncbi.nlm.nih.gov/25427390/> *Reumatizam.* 2014;61:19–23.
4. Vitamin D and the immune system. Aranow C. *J Investig Med.* 2011;59:881–886.
5. The importance of vitamin D levels in autoimmune diseases [Article in English, Portuguese] Marques CD, Dantas AT, Fragozo TS, Duarte AL. <https://pubmed.ncbi.nlm.nih.gov/21125142/> *Rev Bras Reumatol.* 2010;50:67–80.
6. Sparks, J. A. Rheumatoid Arthritis. *Ann. Intern. Med.* 170, Itc1– itc16, <https://doi.org/10.7326/aitc201901010> (2019).
7. Lee, Y. H. & Bae, S. C. Vitamin D level in

rheumatoid arthritis and its correlation with the disease activity: a meta-analysis. *Clin. Exp. Rheumatol.* 34, 827–833 (2016)

8. Herly, M. et al. The D-vitamin metabolite 1,25(OH)₂ D in serum is associated with disease activity and Anti-Citrullinated Protein Antibodies in active and treatment naive, early Rheumatoid Arthritis Patients. *Scand. J. Immunol.* 88, e12704,
9. Hazlewood, G. S. et al. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis. *BMJ* 353, i1777, <https://doi.org/10.1136/bmj.i1777> (2016).
10. Di, F. M. et al. Hypovitaminosis D in recent onset rheumatoid arthritis is predictive of reduced response to treatment and increased disease activity: a 12 month follow-up study. *BMC. Musculoskelet. Disord.* 16, 53 (2015).
11. Quintana-Duque, M. A. et al. The Role of 25-Hydroxyvitamin D as a Predictor of Clinical and Radiological Outcomes in Early Onset Rheumatoid Arthritis. *J. Clin. Rheumatol.* 23, 33–39, <https://doi.org/10.1097/rhu.000000000000477> (2017).
12. K. Gopinath and D. Danda, “Supplementation of 1,25 dihydroxy vitamin D3 in patients with treatment naive early rheumatoid arthritis: a randomised controlled trial,” *International Journal of Rheumatic Diseases*, vol. 14, no. 4, pp. 332–339, 2011.
13. A. R. Broder, J. N. Tobin, and C. Putterman, “Disease-specific definitions of vitamin D deficiency need to be established in autoimmune and non-autoimmune chronic diseases: a retrospective comparison of three chronic diseases,” *Arthritis Research & Therapy*, vol. 12, no. 5, article R191, 2010.
14. M. Rossini, S. M. Bongi, G. la Montagna et al., “Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability,” *Arthritis Research & Therapy*, vol. 12, no. 6, article R216, 2010.
15. R. Pakchotanon, S. Chaiamnuay, P. Narongroeknawin, and P. Asavatanabodee, “The association between serum vitamin D Level and disease activity in Thai rheumatoid arthritis patients,” *International Journal of Rheumatic Diseases*, 2013.
16. K. Gopinath and D. Danda, “Supplementation of 1,25 dihydroxy vitamin D3 in patients with treatment naive early rheuma-

- toid arthritis: a randomised controlled trial," *International Journal of Rheumatic Diseases*, vol. 14, no. 4, pp. 332–339, 2011
17. M. Bukhari, B. Harrison, M. Lunt, D. G. I. Scott, D. P. M. Symmons, and A. J. Silman, "Time to first occurrence of erosions in inflammatory polyarthritis: results from a prospective community-based study," *Arthritis & Rheumatism*, vol. 44, no. 6, pp. 1248–1253, 2001.
 18. E. Zold, P. Szodoray, J. Gaal et al., "Vitamin D deficiency in undifferentiated connective tissue disease," *Arthritis Research & Therapy*, vol. 10, no. 5, article R123, 2008
 19. M. Hewison, L. Freeman, S. V. Hughes et al., "Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells," *Journal of Immunology*, vol. 170, no. 11, pp. 5382–5390, 2003
 20. Sukharani N, Dev K, Rahul F, Bai P, Ali A, Avinash F, Kammawal Y, Kumar N, Rizwan A. Association Between Rheumatoid Arthritis and Serum Vitamin D Levels. *Cureus*. 2021 Sep 24;13(9):e18255.
 21. Xiaomin Cen, Yuan Liu, Geng Yin, Min Yang, Qibing Xie, "Association between Serum 25-Hydroxyvitamin D Level and Rheumatoid Arthritis" *BioMed Research International*, vol. 2015, Article ID 9138
 22. Herly, M., Stengaard-Pedersen, K., Vestergaard, P. et al. Impact of season on the association between vitamin D levels at diagnosis and one-year remission in early Rheumatoid Arthritis. *Sci Rep* 10, 7371 (2020)
 23. Atwa MA, Balata MG, Hussein AM, Abdelrahman NI, Elminshawy HH: Serum 25-hydroxyvitamin D concentration in patients with psoriasis and rheumatoid arthritis and its association with disease activity and serum tumor necrosis factor-alpha. *Saudi Med J*. 2013, 34:806-13.
 24. Haque UJ, Bartlett SJ: Relationships among vitamin D, disease activity, pain and disability in rheumatoid arthritis. *Clin Exp Rheumatol*. 2010, 28:745-7
 25. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG: Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum*. 2004, 50:72-7.
 26. R. Pakchotanon, S. Chaiamnuay, P. Narongroeknawin, and P. Asavatanabodee, "The association between serum vitamin D Level and disease activity in Thai rheumatoid arthritis patients," *International Journal of Rheumatic Diseases*, 2013
 27. H. J. Haga, A. Schmedes, Y. Naderi, A. M. Moreno, and E. Peen, "Severe deficiency of 25-hydroxyvitamin D₃(25-OH-D₃) is associated with high disease activity of rheumatoid arthritis," *Clinical Rheumatology*, vol. 32, no. 5, pp. 629–633, 2013.
 28. M. Cutolo, K. Otsa, K. Laas et al., "Circannual vitamin D serum levels and disease activity in rheumatoid arthritis: Northern versus Southern Europe," *Clinical and Experimental Rheumatology*, vol. 24, no. 6, pp. 702–704, 2006.
 29. Haga HJ, Schmedes A, Naderi Y, Moreno AM, Peen E: Severe deficiency of 25-hydroxyvitamin D₃ (25-OH-D₃) is associated with high disease activity of rheumatoid arthritis. *Clin Rheumatol*. 2013, 32:629-33
 30. Furuya T, Hosoi T, Tanaka E, Nakajima A, Taniguchi A, Momohara S, Yamanaka H: Prevalence of and factors associated with vitamin D deficiency in 4,793 Japanese patients with rheumatoid arthritis. *Clin Rheumatol*. 2013, 32:1081-7.