The Relation between the Serum Level of 25 (OH) Vitamin D and Disease Activity among Patients with Rheumatoid Arthritis

Eman Ahmed Hamed, Marwa Ahmed Abdel-Aziz, Marwa Maher Abdelaziz*, Doaa Kamal Mohamed.
Rheumatology, Rehabilitation and Physical Medicine Department, Faculty of Medicine, Assiut University, Assiut, Egypt.
***Corresponding Author:** Marwa Maher Abdelaziz.
E-mail:marwamaher128@gmail.com

Abstract

Introduction: Rheumatoid arthritis is a chronic progressive autoimmune disease. Rheumatoid arthritis is a multifactorial disease, but the exact mechanism is unknown. Vitamin D is a fat-soluble vitamin that has an immunomodulatory effect. Its effect depends on the regulation and secretion of different cytokines. So, in this study, we discussed the relationship between Vitamin D serum levels and disease activity in Rheumatoid arthritis patients.

Patients and Methods: The present study was a prospective cohort study. It included 30 cases of rheumatoid arthritis who had attended the Rheumatology, Rehabilitation, and Physical Medicine Department at Assiut University Hospitals, Assiut, Egypt. The Clinical disease activity index and disease activity score 28-ESR index were used to evaluate Rheumatoid arthritis disease activity. Serum vitamin D level was evaluated.

Results: The mean age of the studied Rheumatoid arthritis cases was 45.77 ± 8.50 years (range; 25 to 60 years); all are females. The median Vitamin D level was 17.78nmol/L (range; 7.95 – 48.04nmol/L). According to the Disease Activity Score 28 scale, 26.7% of cases have mild disease activity, 73.3% have moderate to high disease activity, and according to the Clinical Disease Activity Index scale, 46.7% have mild disease activity, and 53.3% have moderate to high disease activity, with no significant difference in serum vitamin D level and different Disease activity score 28 and Clinical disease activity index categories (P=0.682, and 0.186) respectively.

Conclusion: Based on the current finding, we could conclude that serum Vitamin D level has no association with Rheumatoid arthritis disease activity. However, further larger studies are needed to evaluate the potential role of Vitamin D in Rheumatoid arthritis etiopathogenesis and its relation to disease activity.

Keywords: Rheumatoid arthritis, Disease activity, Vitamin D.

Introduction:

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease. It is characterized by progressive synovial inflammation and proliferation that leads to joint destruction, bony erosions, and permanent disabilities (1).In the long run, it can also cause extra-articular complications.

RA affects mostly 0.1–2.0% of the population worldwide. Generally, females are more likely to develop RA than males (2). RA is presented by

chronic symmetrical polyarticular arthritis, which mostly affects small joints of the hands, feet, and wrists (3).

Although the underlying mechanism is still unknown, a combination of genetic, environmental, and immunological variables participate in RA pathogenesis (4). Both innate and adaptive immune cells, together with cytokines secreted by T-lymphocytes and macrophages, participate in the pathogenesis of RA (5). Natural killer cells, dendritic cells, macrophages, and neutrophils are innate immune response-related cells, and T and B lymphocytes are examples of adaptive immune response cells (6). Tumor necrosis factor (TNF)-α and interleukin (IL)-6 are two main cytokines in the pathogenesis of RA. Other cytokines that participate in the pathogenesis are IL-17, IL-21, IFN-α and β, IL-1, IL-18, IL-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (7).

Vitamin D is a fat-soluble vitamin. It is obtained from sunlight exposure, especially ultraviolet-B (UVB) rays, diet, and supplements (8). The regulation of calcium and phosphorus absorption in the intestine is the main function of Vitamin D, which is important for musculoskeletal health (9). It also has an immunomodulatory effect that depends on regulating the secretion of different cytokines(10). Vitamin D participates in innate and adaptive immune responses by binding to Vitamin D receptors (VDR). These receptors are expressed by multiple immune cells as macrophages, dendritic cells, B and CD4+ and CD8+ T cells, and these cells can synthesize an enzyme called 1-α-hydroxylase (CYP27B1), which is responsible for activation of the inactive form of 25(OH)D3 to the active form which is 1,25(OH)2D3 (10). So, Vitamin D can suppress autoimmunity by binding to VDR receptors and regulation of cytokines secretion (10).

Thus, the main purpose of the current study is to evaluate the relationship between serum Vitamin D levels in RA patients and RA disease activity.

Patients and Methods:

This is a descriptive hospital-based cohort study conducted at the Rheumatology, Rehabilitation, and Physical Medicine Department in Assiut University Hospitals, Assiut, Egypt, between the 1st of January 2020 and the end of December 2021. It was approved by the regional ethics committee at Assiut University (IRB No. 17101118). Before their enrollment in the current study, each participant provided written informed consent.

(A) Patients:

The current study included Thirty adult female patients with RA who were diagnosed with the disease following the 2010 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) criteria (11).

Patients with arthritis caused by diseases other than RA (such as crystal arthropathies, seronegative spondylo-arthritis, etc.) and those with other autoimmune diseases (such as dermatomyositis, systemic lupus erythematosus, systemic sclerosis) were excluded.

(B) Data Collection:

All eligible participants underwent a thorough history taking, physical examination, and routine investigations, including complete blood picture (CBC), acute phase reactants: erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP), random blood glucose

(RBG), liver function test (LFT), kidney function test (KFT), complete urine analysis, rheumatoid factor (RF), Anti-CCP, and serum level of 25 hydroxy-vitamin D (25 OH vitamin D). The disease activity score (DAS) 28-ESR index and clinical disease activity index (CDAI) were used to assess the disease activity.

(C) Statistical Analysis:

Version 22 of SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) was used for all statistical computations. The data were presented as numbers (percentages). They were compared using the Fisher Exact or Chi-square ($\chi 2$) test or presented as mean ± standard deviation (±SD) or median and range. A P-value <0.05 level is considered significant.

Results

Baseline Data:

The mean age of the studied RA cases was 45.77 ± 8.50 years (range: 25 to 60

Years). All studied cases were non-workers females, who were mainly non-smokers, except for 20.0%, who were passive smokers.

The median disease duration among the 30 RA cases studied was six years, ranging from one year to 20 years.

The mean Vitamin D level among the studied RA cases was 19.06 ± 9.51 (range; 7.95 – 48.04).

Regarding the line of treatment received by the studied RA patients, it was found that hydroxychloroquine was the most frequent drug taken by all studied cases, followed by Leflunomide (76.7%), sulfasalazine (33.3%), methotrexate (30.0%), and steroid (6.7%) **(Table 1)**.

Table (1): Baseline data of the studied 30 rheumatoid arthritis cohort

Baseline data	RA group (n=30)
Age (year)	
• Mean ± SD	45.77 ± 8.50
• Median (range)	49 (25 – 60)
Smoking status, n (%)	
• Non-smoker	24 (80.0%)
• Passive smoker	6 (20.0%)
Disease duration (years), median (range)	6 (1 – 20)
Vitamin D	
• Mean ± SD	19.06 ± 9.51
• Median (range)	17.78 (7.95 – 48.04)

Baseline data	RA group (n=30)	
Type of treatment		
• Hydroxychloroquine	30	(100.0%)
• Vitamin D and Calciun supplements	30	(100.0%)
• Leflunomide	23	(76.7%)
• Sulfasalazine	10	(33.3%)
• Methotrexate	9	(30.0%)
• Steroids	2	(6.7%)

RA: rheumatoid arthritis.

Clinical Manifestations:

Clinical manifestations of the studied RA cases were summarized in Table 2. 18 cases (60.0%) suffered from morning stiffness with symmetrical manifestation in all studied cases. Three cases (10.0%) suffered from deformities. Nine cases (30.0%) have swollen joints with a median of 7 joints (range; 1 – 17) joints, and 23 cases (76.7%) have tender joints with a median of 6 joints (range; 1 – 22) joints.

Table (2): Clinical manifestation among 30 rheumatoid arthritis cohort

Clinical manifestation	N	(%)
• Morning stiffness	18	(60.0%)
• Symmetry	30	(100.0%)
• Deformities	3	(10.0%)
• Total swollen joint	9	(30.0%)
• Median (range)		7 (1 – 17)
• Total tender joint	23	(76.7%)
• Median (range)		6 (1 – 22)

Laboratory Data:

All baseline laboratory data of studied RA cases are summarized in Table 3.

Table (3): Baseline laboratory data among 30 rheumatoid arthritis cohort

Laboratory data	Mean ± SD	Median (range)
Hemoglobin (g/dl)	11.92±1.30	12.0 (9.3 – 13.8)
Red blood corpuscles (10^6/ul)	4.32± 0.49	4.4 (3.0 – 5.3)
Platelets (10^3/ul)	286.80±73.44	273 (142 - 418)
Leucocytes (10^3/ul)	6.65±3.45	5.5 (3.5 – 21.5)
Aspartate transaminase (u/l)	19.70±5.51	20.8 (10.4 – 34.5)
Alanine transmarine (u/l)	16.43±6.21	15.9 (6.3 – 28.3)
Total protein (g/l)	72.81±6.22	72.7 (54.8 – 83.9)
Albumin/globulin ratio	1.34±0.18	1.3 (1.1 – 1.8)
Uric acid (mg/dl)	4.71±0.51	4.7 (3.7 - 5.7)
Urea (mmol/l)	3.99±1.21	3.6 (2.3 - 7.6)
Creatinine (umol/l)	56.85±10.65	53.9 (43.0 – 89.0)
Blood glucose (mmol/l)	5.16±0.52	5.2 (4.2 – 6.2)
ESR	43.83±27.38	44.0 (5.0 – 100.0)
CRP	6.72±6.40	5.0 (0.4 – 25.8)

Level of Vitamin D and Activity of RA Disease:

According to the DAS28 scale, eight cases (26.7%) have mild disease activity, and 22 (73.3%) have moderate to high disease activity. According to the CDAI scale, 14 cases (46.7%) have mild disease activity, and 16 (53.3%) have moderate to high disease activity. No significant difference was observed in the serum vitamin D level and the different DAS 28 and CDAI categories (P=0.682 and 0.186), respectively, as in Table 4.

Table (4): Comparison of the serum Vitamin D according to DAS 28 and CDAI categories among the studied 30 RA cohort

Disease activity	Total (n=30)	Vitamin D			P-value
		Deficiency < 20, n=20	insufficiency 21 – 29, n=6	Sufficiency 30 – 100, n=4	
DAS 28 categories					0.682
• On remission to mild	8 (26.7%)	6 (30.0%)	(33.3%)	0 (0.0%)	
• Moderate to high	22 (73.3%)	14 (70.0%)	(66.7%)	4 (100.0%)	
CDAI					0.186
• On remission to mild	14 (46.7%)	11 (55.0%)	(50.0%)	0 (0.0%)	
• Moderate to high	16 (53.3%)	9 (45.0%)	(50.0%)	4 (100.0%)	

Discussion

Rheumatoid arthritis is a chronic multifactorial autoimmune disease. The exact cause that elicits RA is still not known (1). The pathogenesis of RA depends on the proliferation and activation of macrophage-like synovio-cytes (MLSs) and fibroblast-like synovio-cytes (FLSs). These cells produce multiple cytokines, such as tumor necrosis factor (TNF)-α and IL-6, to initiate the inflammatory process (12). Our study discussed the relationship between serum Vitamin D levels and disease activity in RA patients, as vitamin D is believed to have an immunomodulatory function. The results showed that our study participants' mean Vitamin D serum level ranged between deficiency and insufficiency, and there is no significant relationship between serum Vitamin D level and RA disease activity (whether DAS28 or CDAI). However, studies done on this point were scarce, and also reported conflicting findings.

In agreement with our results, the studies of Gopal et al. and Pakchotanon et al. showed no significant relation between

RA disease activity and vitamin D serum levels according to the DAS28 score. The

study of Gopal et al. also revealed no improvement in disease activity after

vitamin D supplementation. Still, vitamin D supplementation can only improve the physical activity of RA patients (13, 14). Similarly, the study of Matsumoto et al. did not find an association between serum 25(OH)Vitamin D and RA disease activity, and also, a study of Baker et al., which was performed on 499 patients with active RA, did not observe any association between vitamin D deficiency and DAS28 (15, 16).

Contrary to our findings, the studies of Rossini et al., Gheita et al., and Chen et al. showed a substantial inverse relation between RA disease activity and serum 25(OH) Vitamin D (17-19).

These conflicting results could be attributed to different factors that affect vitamin D serum levels and RA pathogenesis, which include different ethnicity, disease duration, disease severity, treatments used, vitamin D supplementations, and gender of patients.

Conclusion

Based on the results of the current study, we concluded that serum Vitamin D level has no association with RA disease activity, which was assessed using DAS and CDAI scores. However, we recommended further larger studies, specifically in our ethnic group, to evaluate the role of Vitamin D in RA pathogenesis and its effect on disease activity and determine if Vitamin D supplementation can affect RA disease activity.

References

1. Lin Y-J, Anzaghe M, Schülke S. Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. Cells. 2020;9(4):880.
2. Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. Rheumatol Int. 2021;41(5):863-77.
3. van der Woude D, van der Helm-van Mil AHM. Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2018;32(2):174-87.
4. Zhou S, Lu H, Xiong M. Identifying Immune Cell Infiltration and Effective Diagnostic Biomarkers in Rheumatoid Arthritis by Bioinformatics Analysis. Front Immunol. 2021;12.
5. Edilova MI, Akram A, Abdul-Sater AA. Innate immunity drives pathogenesis of rheumatoid arthritis. Biomed J. 2021;44(2):172-82.
6. Falgarone G, Jaen O, Boissier M-C. Role for Innate Immunity in Rheumatoid Arthritis. Joint Bone Spine. 2005;72(1):17-25.
7. Kondo N, Kuroda T, Kobayashi D. Cytokine Networks in the Pathogenesis

   of Rheumatoid Arthritis. Int J Mol Sci. 2021;22(20):10922.
8. Jeon S-M, Shin E-A. Exploring vitamin D metabolism and function in cancer. Exp Mol Med. 2018;50(4):1-14.
9. Khazai N, Judd SE, Tangpricha V. Calcium and vitamin D: Skeletal and extraskeletal health. Curr Rheumatol Rep. 2008;10(2):110-7.
10. El-Sharkawy A, Malki A. Vitamin D Signaling in Inflammation and Cancer: Molecular Mechanisms and Therapeutic Implications. Molecules. 2020;25(14):3219.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.
12. Jang S, Kwon E-J, Lee JJ. Rheumatoid Arthritis: Pathogenic Roles of Diverse Immune Cells. Int J Mol Sci. 2022;23(2):905.
13. Gopal K, Thevarajah M, Ng CM, Raja J. Effects of vitamin D on disease activity and serum interleukin-6 in rheumatoid arthritis. Int J Rheum Dis. 2019;22(5):834-41.
14. Pakchotanon R, Chaiamnuay S, Narongroeknawin P, Asavatanabodee P. The association between serum vitamin D Level and disease activity in Thai rheumatoid arthritis patients. Int J Rheum Dis. 2016;19(4):355-61.
15. Matsumoto Y, Sugioka Y, Tada M, Okano T, Mamoto K, Inui K, et al. Relationships between serum 25-hydroxycalciferol, vitamin D intake, and disease activity in patients with rheumatoid arthritis--TOMORROW study. Mod Rheumatol. 2015;25(2):246-50.
16. Baker JF, Baker DG, Toedter G, Shults J, Von Feldt JM, Leonard MB. Associations between vitamin D, disease activity, and clinical response

to therapy in rheumatoid arthritis. Clin Exp Rheumatol. 2012;30(5):658-64.

17. Rossini M, Maddali Bongi S, La Montagna G, Minisola G, Malavolta N, Bernini L, et al. Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants, and associations with disease activity and disability. Arthritis Res Ther. 2010;12(6)

18. Gheita TA, Sayed S, Gheita HA, Kenawy SA. Vitamin D status in rheumatoid arthritis patients: relation to clinical manifestations, disease activity, quality of life and fibromyalgia syndrome. Int J Rheum Dis. 2016;19(3):294-9.

19. Chen J, Liu W, Lin Q, Chen L, Yin J, Huang H. Vitamin D deficiency and low bone mineral density in native Chinese rheumatoid arthritis patients. Int J Rheum Dis. 2014;17(1):66-