



## Relationship Between Vitamin D level and Disease Activity in Rheumatoid Arthritis

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### Abstract

**Background and objectives:** A lack of vitamin D can cause several autoimmune illnesses, including rheumatoid arthritis. The link between serum Vitamin D levels and the severity of rheumatoid arthritis is of great interest. This study aims to assess the correlation between disease activity and serum vitamin D levels in rheumatoid arthritis patients.

**Methods:** In this cross-sectional study, 100 patients with rheumatoid arthritis were recruited from Rheumatology and Rehabilitation department in Sulaymaniyah from January to July 2023. The patient's medical files and relevant examinations were used to collect the required data. Disease activity was assessed using the Disease Activity Score 28 based on tender and swollen joints and erythrocyte sedimentation rate.

**Results:** Forty-five percent and 18% of the patients had moderate and high disease activities, respectively. Vitamin D deficiency and insufficiency were found in 44% and 36%, respectively. Disease activity was not correlated with vitamin D levels ( $p=0.271$ ). The patients were 21 to 80 years old. Vitamin D deficiency rose with increasing age, especially in 41-60 and 61-80 age groups ( $p=0.041$ ). Patients with lower economic status (46%) had a heightened level of disease activity, whereas those with a favorable economic status (6%) demonstrated lower disease activity ( $p=0.018$ ). Eight percent of the patients were current smokers. A significant correlation was observed between smoking status and disease activity; non-smokers generally moderate, others varying levels ( $p=0.028$ ).

**Conclusion:** Vitamin D levels in rheumatoid arthritis patients had no significant relation with disease activity.

**Keywords:** Disease activity, Rheumatoid arthritis, Vitamin D

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## Introduction

As a persistent, systemic autoimmune disorder, rheumatoid arthritis is characterized by inflammatory arthritis which can affect multiple joints and is accompanied by various extra-articular manifestations. Women are two to three times more likely than men to develop rheumatoid arthritis. According to 2002 statistics, 0.5 to 1% of general population are affected with rheumatoid arthritis.<sup>1,2</sup> Disease Activity Score (DAS 28) - erythrocyte sedimentation rate DAS28 - ESR is a numerical scoring system which is employed to assess rheumatoid arthritis (RA) activity. This scoring system takes into account a number of different factors, including the subjective assessment of disease activity by patients using a visual analogue scale (VAS), the inflammation level specified through blood tests such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and the number of swollen and tender joints.<sup>3,4</sup> As a precursor to a steroid hormone, vitamin D experiences chemical conversion in the kidney and liver. Initially, it is converted to 25-hydroxyvitamin D (25OHD) which is used as an objective indicator of vitamin D status in the liver. Afterwards, it undergoes additional conversion within the kidney to transform into the main active form called 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub> D).<sup>5</sup> Initially, the main function ascribed to Vitamin D was intricately linked to the regulation of calcium and phosphate levels in the body, as well as maintaining bone homeostasis. However, new scientific breakthroughs in studies have revealed the crucial significance of Vitamin D in the modulation of the immune system.<sup>6</sup> Through its regulatory influence on both the adaptive and innate immune systems, Vitamin D exerts a downregulating effect on the inflammatory response, potentially playing a role in the development and progression of rheumatoid arthritis (RA).<sup>5</sup> Nevertheless, research investigations examining the correlation

between disease activity in RA and Vitamin D levels have produced conflicting results.<sup>2</sup> This disparity in findings underscores the need for further clarification and in-depth examination of the intricate association between RA disease activity and Vitamin D levels. The existing scientific discourse is characterized by ongoing discussions, and additional studies are indispensable to unravel the complete nature of this interaction.<sup>7</sup> The current study aims at determining the correlation between scores of disease activity and levels of vitamin D in patients with rheumatoid arthritis in Sulaymaniyah, Kurdistan region, Iraq. This research was primarily aimed at assessing the relationship between disease activity scores and vitamin D levels in individuals diagnosed with rheumatoid arthritis. Additionally, the current investigation was aimed at exploring the relation between potential confounding variables like age, smoking habits, and socioeconomic status, and disease activity scores in patients with RA.

## Patients and methods

Classification criteria set forth by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) were utilized by rheumatologists to diagnose RA patients. Patients having history of diabetes mellitus, kidney and liver dysfunction, hyperparathyroidism, hyperthyroidism, patients on vitamin D supplementation and those who were on medications that affects vitamin D metabolism (diuretics, thyroxin, and anticonvulsants) were excluded. Patients younger than 18 years or older than 80 years were also excluded. Ethical approval was obtained from the Ethics Committee in Kurdistan Higher Council of Medical Specialties, and informed consent was obtained from the participants. Comprehensive personal interviews were conducted with all participants, encompassing inquiries into individual characteristics, and a meticulous patient history was obtained, with particular emphasis on age,





economic state, and smoking. The study design was single-group cross-sectional study. The formula  $n = (Z\alpha)^2 * P(1 - P)/d^2$  was employed to compute the study sample size. In this formula,  $n$  represents the sample size,  $P$  denotes the prevalence of the variable being investigated,  $d$  signifies the desired detectable difference, and  $Z\alpha$  corresponds to the critical value of 1.96. The sample in this particular study consisted of a total of 100 cases. Disease Activity Score 28 (DAS28) was used to measure the disease activity as per the American College of Rheumatology. For this purpose, tender joints (out of twenty-eight joints) and swollen joints (out of twenty-eight joints) were counted, and erythrocyte sedimentation rate (ESR) was measured. Moreover, Visual Analogue Scale (VAS) was employed by requesting the patients to indicate their evaluation using a scale with scores between 0 (excellent health) and 10 (extremely poor health). To interpret the data, DAS28 scores below 2.7 were interpreted as remission, DAS28 scores between 2.7 and 3.2 as low activity of disease, DAS28 scores between 3.3 and 5.1 as moderate activity of disease, and DAS28 scores over 5.1 as high activity of disease. Serum vitamin D level was measured by using Cobas 6000 machine and calculated in (ng/ml). According to the collected data, vitamin D level below 20 ng/ml was interpreted as deficiency, vitamin D level between 20 and 32 ng/ml as insufficiency, vitamin D level between 32 and 88 ng/ml as sufficiency, and vitamin D level over 88 ng/ml as toxicity. Data analysis in the current investigation was carried out using the "IBM SPSS Statistics version 26" software. Descriptive and inferential statistical methods were employed to examine the data. A significance level of  $\leq 0.05$  was adopted to determine statistically significant associations. Additionally, Pearson Chi-Square was utilized to figure out the significance of associations between independent and dependent variable pairs.

## Results

The results of DAS28 showed 17 (17%) remission, 20 (20%) low, 45 (45%) moderate, and 18 (18%) high disease activity scores. In addition, vitamin D levels were deficient among 44 (44%), insufficient among 36 (36%), and sufficient among 20 (20%) as shown in Table (1). As revealed by the results, the level of vitamin D had no statistically significant correlation with DAS28 (ESR) score (disease activity) ( $p$ -value=0.271), such that patients with different levels of vitamin D were not significantly different regarding their disease activity as shown in Table (1). The patients' age ranged from 21 to 80 years, with 58% of them being 41-60, 30% being 61-80, and 12% being 20-40. Their age was found to be significantly correlated with the levels of their vitamin D ( $p$ -value=0.041), such that an increase in the patients' age results in deficiency and insufficiency of vitamin D, and higher levels of vitamin D insufficiency and deficiency were seen in the age groups (41-60) years and (61-80) years as shown in Table (2). As revealed by the results, 48 (48%) had low economic state, while 6 (6%) and 46 (46%) had good and moderate economic states, respectively. The results indicated a significant correlation ( $p$ -value=0.018) between the economic status of the patients and their disease activity. Specifically, individuals with moderate and low economic status exhibited higher disease activity, whereas those with good economic status demonstrated lower DAS28 (ESR) scores as shown in Table (3). Most of the patients 71 (71%) did not smoke, while 11 (11%) were ex-smokers, 10 (10%) passive smokers, and only 8 (8%) were current smokers. The results revealed that 4%, 3%, and 2% of ex-smokers exhibited low, moderate, and high disease activities, respectively. Similarly, among passive smokers, low activity of disease was observed in 1% of them, moderate activity in 4%, and high activity in 2%. High and moderate levels of disease activity were





observed among 1% and 2% of the current smokers, respectively. Most of non-smokers had moderate activity of disease (36%), while 15% had low activity of disease, and 13% had high activity of disease. According to the

results, a significant correlation (p-value=0.028) between the smoking status of the patients and their DAS28 ESR scores which reflect disease activity as shown in Table (4).

**Table (1):** This table describes the Association between DAS28 ESR scores and vitamin D levels

DAS28 (ESR) Score		Vitamin D Level (ng/ml)			Total	p-value
		Deficiency (<20)	Insufficiency (20-32)	Sufficiency (33-88)		
Remission (<2.7)	Count (% of Total)	9	6	2	17	0.271
Low (2.7-3.2)	Count (% of Total)	9	9	2	20	
Moderate (3.3-5.1)	Count (% of Total)	15	17	13	45	
High (>5.1)	Count (% of Total)	11	4	3	18	
Total	Count (% of Total)	44	36	20	100	

**Table (2):** This table describes the Association between age groups and Vit. D level

Age groups (year)		Vitamin D Groups (ng/ml)			Total	p-value
		Deficiency (<20)	Insufficiency (20-32)	Sufficiency (33-88)		
20-40	Count (% of Total)	4	5	3	12	0.041
41-60	Count (% of Total)	33	17	8	58	
61-80	Count (% of Total)	7	14	9	30	
Total	Count (% of Total)	44	36	20	100	



**Table (3):** This table describes the correlation between economic status and DAS28 ESR scores

Economic status		DAS28 (ESR) Scores				Total	p-value
		Remission (<2.7)	Low (2.7-3.2)	Moderate (3.3-5.1)	High (>5.1)		
Good	Count (% of Total)	0	1	4	1	6	0.018
	Count (% of Total)	6	14	15	13	48	
	Count (% of Total)	11	5	26	4	46	
	Count (% of Total)	17	20	45	18	100	

**Table (4):** This table describes the correlation between smoking status and disease activity score (DAS28)

			DAS28 (ESR) Groups				Total	p-value
			Remission (<2.7)	Low (2.7-3.2)	Moderate (3.3-5.1)	High (>5.1)		
Smoking	Ex-smoker	Count (% of Total)	2	4	3	2	11	0.028
	None	Count (% of Total)	7	15	36	13	71	
	Passive smoker	Count (% of Total)	3	1	4	2	10	
	Current smoker	Count (% of Total)	5	0	2	1	8	
Total		Count (% of Total)	17	20	45	18	100	

## Discussion

This study aimed to explore the link between disease activity and vitamin D levels in rheumatoid arthritis patients. The findings showed no significant relationship between disease activity and vitamin D levels,

consistent with previous studies by Raczkiewicz et al., Baker et al., and Matsumoto et al. whose studies did not provide substantial evidence for a correlation between vitamin D levels and RA severity or progression.<sup>8,9,10</sup> Multiple studies have shown a correlation between vitamin D levels





and disease activity scores in rheumatoid arthritis (RA) patients. For example, Higgins et al. found that vitamin D deficiency was associated with higher DAS28 scores and increased visual analog scores in RA patients.<sup>11</sup> Lee et al. also reported an inverse relationship between DAS28 scores and vitamin D levels.<sup>12</sup> Similarly, Guan et al. and Dupuis et al. demonstrated that higher vitamin D levels were linked to lower DAS28 scores in patients with rheumatoid arthritis, indicating less active disease.<sup>13,14</sup> These findings suggest that maintaining sufficient vitamin D levels may reduce RA severity and progression by modulating immune function. However, the correlation between disease activity and vitamin D levels in RA is complex and inconsistent due to various factors such as patient heterogeneity, measurement methods, confounding factors, and timing of assessments. Further prospective research with meticulous design is needed to better understand this correlation, considering diverse patient characteristics, and minimizing the impact of influencing factors. As indicated in the current study, age and the presence of vitamin D insufficiency and deficiency were significantly associated, with older adults being more susceptible to lower levels of vitamin D. Several factors likely contribute to this relationship, including reduced exposure to sunlight and diminished capacity for vitamin D synthesis as individuals age. These findings align with a study by Kavadichanda et al., which also observed a positive correlation between age and vitamin D levels.<sup>15</sup> Furthermore, other studies have reported that the elderly population faces risks such as vitamin D deficiency, decreased vitamin D intake, increased adipocyte percentage, diminished vitamin D synthesis, and limited engagement in outdoor activities.<sup>16,17</sup> Based on the findings, a significant correlation exists between economic status and the severity of

rheumatoid arthritis (RA), with lower-income individuals showing higher disease activity (DAS28 scores) compared to higher-income groups. As pointed out by similar studies, low socioeconomic status is associated with unfavorable disease outcomes in RA patients. Patients from lower socioeconomic backgrounds tend to have worse outcomes than those from higher socioeconomic backgrounds.<sup>18</sup> Delayed initiations of disease-modifying antirheumatic medications is more common among individuals with lower socioeconomic status. Both low socioeconomic standing and delayed treatment initiation are linked to poor clinical outcomes in RA patients. The authors recommend strategies to reduce treatment delays for RA patients from lower socioeconomic backgrounds to improve their clinical condition.<sup>19</sup> Smoking status impacts disease activity in RA patients. Ex-smokers and passive smokers had higher levels of disease activity compared to non-smokers, while current smokers had the highest prevalence of moderate to high disease activity. Smoking has both direct and indirect effects on RA severity, potentially influenced by previous exposure to smoking. In a similar study, passive smokers showed significant increases in DAS28-ESR and DAS28-CRP scores compared to non-smokers during the follow-up period.<sup>20</sup> Moreover, Roelsgaard et al. remarked that smoking cessation in RA patients was associated with reduced disease activity and improved lipid profiles.<sup>21</sup> In their study, Rydell et al. reported that smoking cessation among individuals with rheumatoid arthritis (RA) was associated with reduced disease activity and improved lipid profiles.<sup>19</sup> Similarly, Saevarsdottir et al. pointed out that smoking is significantly associated with baseline erosions, DAS28, and its inflammatory components, namely erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).<sup>22,23</sup>





## Conclusion

This study examined factors and disease activity in rheumatoid arthritis patients. Vitamin D levels were not correlated with disease activity. Age was associated with vitamin D deficiency. Lower socioeconomic status was linked to higher disease activity. Smoking status affected disease activity, with non-smokers having moderate activity and current/former smokers showing variable activity. However, limited by small sample size and cross-sectional design. Larger longitudinal studies needed to understand how age, economic status, smoking, and vitamin D levels influence disease activity.

## Conflict of interest

None

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