

Relationship between Vitamin D Level and Disease Activity in Rheumatoid Arthritis

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Abstract

Background: Vitamin D is thought to have immunomodulatory and anti-inflammatory properties, and a lack of it has been related to several autoimmune illnesses, including rheumatoid arthritis (RA). The link between serum Vitamin D levels and the severity of RA is of great interest.

Objectives: This study aimed to determine the relationship between vitamin D level and disease activity score in rheumatoid arthritis.

Methods: In this cross-sectional study we enrolled 100 patients aged between 18 and 80 in the rheumatology department at Shahid Doctor Hemn Teaching Hospital/Rheumatology and Rehabilitation center in Sulaymaniyah, from January to July 2023. All of them were diagnosed with rheumatoid arthritis. Cobas 6000 machine was used to estimate vitamin D levels. DAS28 (ESR) was used to evaluate the disease activity score in all patients.

Results: There was no significant correlation between vitamin D and disease activity ($p=0.271$). Vitamin D deficiency increased with age, especially 41-60 and 61-80 age groups ($p=0.041$). Higher disease activity among those with lower economic status, lower among those with good economic status ($p=0.018$). Smoking status correlated with disease activity, non-smokers generally moderate, others varying levels ($p=0.028$).

Conclusion: There was no significant relation between vitamin D level and disease activity score in rheumatoid arthritis.

Keywords: rheumatoid arthritis, vitamin D, disease activity

Background

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that is characterized by polyarticular inflammatory arthritis and a variety of extra-articular symptoms. Over all 0.5 to 1% of general population are affected with rheumatoid arthritis.^{1 2}

A numerical scoring system called the Disease Activity Score (DAS 28) is used to determine the activity of rheumatoid arthritis (RA). The score considers the quantity of swollen and tender joints, the degree of inflammation determined by a blood test called C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), and the patient's subjective evaluation of the severity of their disease by using a visual analogue scale (VAS).^{3,4}

Vitamin D is a precursor to steroid hormone that chemically converted in the liver and kidney: at the beginning to 25OHD an objective indicator of vitamin D status in the liver, and then to the main bioactive form, 1,25-dihydroxyvitamin D (1,25(OH)₂ D) in the kidney. ⁵

Vitamin D's main function was formerly associated with Calcium and phosphate metabolism and bone homeostasis, however current research findings have revealed its key significance in immune system modulation.⁶ By regulating both innate and adaptive immune systems, vitamin D reduces the inflammatory response⁵ and might contribute to the development and progression of RA. There are conflicting findings from research that looked at the relationship between RA disease activity and vitamin D levels.² There is still discussion and continuing study surrounding the link between vitamin D levels and RA disease activity, and additional research is required to completely understand this interaction.⁷ This study aims to determine the relationship between vitamin D level and disease activity score in rheumatoid arthritis in Sulaymaniyah, Iraq.

Objectives

The aim of this study is to estimate the Relationship Between Vitamin D level and Disease Activity Score in Rheumatoid Arthritis. Also, to determine the relation between confounding factors (eg: Body Mass Index (BMI), Age, Sex, Smoking, economic stats) and disease activity score in rheumatoid arthritis.

Methods

All included participants were diagnosed as rheumatoid arthritis by rheumatologists according to ACR/EULAR classification criteria. Patients with 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.

Data Collection

All participants were interviewed regarding personal details and detailed history was taken from patients regarding age, sex, BMI, economic state, smoking and also regarding family history and seropositivity of rheumatoid arthritis.

Sample Size Calculation

The design of the study is cross-sectional study and one group. The below equation was used; $n = (Z\alpha)^2 * P(1-P) / d^2$. The total sample size was 100 cases. n = the sample size, P = prevalence of the variable under the study, d = the difference the investigator wishes to detect, $Z\alpha = 1.96$.

Disease Activity and Vitamin D assessment

Disease Activity Score 28 (DAS28) was used to measure the disease activity as per the American College of Rheumatology, and the following measures did the calculation:

1. Number of tender joints counting (out of 28 joints)
2. Number of swollen joints counting (out of 28 joints)
3. Measuring of erythrocyte sedimentation rate (ESR)
4. Visual Analogue Scale (VAS) by asking the patient to make a health global assessment (by marking a point line from 0 to 10 as very good to very bad).

The disease severity was assessed as follows:

- DAS28 < 2.6 (remission)
- DAS28 2.7 – 3.2 (low disease activity)
- DAS28 3.3 – 5.1 (moderate disease activity)
- DAS28 > 5.1 (high disease activity)

Serum vitamin D level was measured by using cobas 6000 machine and calculated in (ng/ml). According to the results the participants vitamin D level was classified in to following groups:

- Vitamin D (< 20 ng/ml): deficiency
- Vitamin D (20-32 ng/ml): Insufficiency

- Vitamin D (32-88 ng/ml): sufficiency
- Vitamin D (> 88ng/ml): toxicity

Statistical Analysis

For this cross-sectional study, the "IBM SPSS Statistics version 26" was used for the analysis of the data and both descriptive and inferential statistics were used. Furthermore, a P-value of (≤ 0.05) was considered as statistically significant associations. In addition, Pearson Chi-Square was used to find out the significancy of association between independent and dependent variable pairs.

Results

This cross-sectional study was conducted on 100 (22 male and 79 female) patients with a mean age of 54.46 (21-80) years. A majority of them had a negative family history (61%) and positive seropositivity (82%). Moreover, 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%) (See Table 1). Regarding body mass index (BMI), 27 (27%) of the participants had normal weight, 34 (34%) were overweight, 38 (38%) were obese, and only 1 (1%) was underweight (see Table 5). Furthermore, 48 (48%) had low economic state, while 6 (6%) and 46 (46%) had good and moderate economic states, respectively (see Table 3). Majority of the patients 71 (71%) were non-smokers, while 11 (11%) were ex-smokers, 10 (10%) passive smokers, and only 8 (8%) were current smokers (see Table 4).

The results of the study revealed that there was not a statistically significant correlation between DAS28 (ESR) score (disease activity) and vitamin D level (p-value=0.271), such that patients with different levels of vitamin D were not significantly different in terms of their disease activity (See Table 1).

Table (1). 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	

According to the results, there was a statistically significant correlation between the patients' age and their vitamin D levels (p -value=0.041), such that deficiency and insufficiency of vitamin D increased with an increase in the patients' age, and the age groups (41-60) years and (61-80) years had higher levels of vitamin D deficiency and insufficiency (See Table 2).

Table (2). 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	

According to the results, there was a significant correlation between the patients' economic status and their disease activity (DAS28 (ESR) scores) (p -value=0.018), such that disease activity was higher among those with moderate and low economic status, while patients with good economic status had lower DAS28 (ESR) scores) (See Table 3).

Table (3). Correlation between economic status and DAS28 ESR scores

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

As demonstrated by the results, there was a statistically significant correlation between the patients' smoking status and their DAS28 ESR scores (disease activity) (p -value=0.028), such that 4% of the ex-smokers had low disease activity, 3% had moderate disease activity, and 2% had a high disease activity. Moreover, 1% of passive smokers had low disease activity, 4% had moderate disease activity, and 2% had high disease activity. Also, 2% of current smokers had moderate and 1% had high disease activity. Disease activity was moderate among most of the non-smokers (36%), low among 15%, and high among 13%(See Table 4).

(Table 4).

			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	

Regarding the correlation between body mass index (BMI) and disease activity score (DAS28), the results showed that there was not a statistically significant correlation between disease activity and BMI (p-value= 0.319) (see Table 5).

Table (5). Correlation between body mass index (BMI) 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)		
BMI Groups (Kg/M*2)	Under Weight (< 18.50)	Count (% Of Total)	0	0	1	0	1	0.319
	Normal (18.50 - 24.99)	Count (% Of Total)	6	5	12	4	27	
	Over Eight (25.00 - 29.99)	Count (% Of Total)	7	7	16	4	34	
	Obese (30.00 - 40.00)	Count (% Of Total)	4	6	16	10	36	
	Morbid Obesity (> 40)	Count (% Of Total)	0	2	0	0	2	
Total		Count (% Of Total)	17	20	45	18	100	

Discussion

This study aimed to explore the potential correlation between vitamin D levels and disease activity scores in individuals diagnosed with rheumatoid arthritis (RA). The objective to enhance our understanding of the potential impact of vitamin D on disease activity in RA patients. The results suggest that there is no significant association between vitamin D levels and disease activity evaluated by the Disease Activity Score-28 ESR (DAS28-ESR) for Rheumatoid Arthritis. The current study result are consistent with findings of three distinct studies conducted by Matsumoto et al. (2015), Baker et al. (2012), and Raczkiwicz et al. (2015) cited in the text reported no significant correlation between measured vitamin D levels and disease activity, as evaluated by the DAS28 score, in individuals diagnosed with rheumatoid arthritis (RA). These studies did not provide evidence supporting a link between vitamin D levels and the severity or progression of RA.^{8,9,10} There are number of studies having results concluding relation between

Vitamin D level and disease activity score, Higgins et al. (2013) claiming that patients with vitamin D deficiency had higher average DAS28 scores, supported by elevated visual analog scores. Furthermore, their findings confirmed the prevalence of vitamin D deficiency among individuals with rheumatoid arthritis.¹¹ Additionally, Lee et al. (2016) conducted another study demonstrating a significant inverse correlation between vitamin D levels and DAS28 scores.¹² In general, the findings from two studies conducted by Guan et al. (2020) and Dupuis et al. (2021) have revealed an inverse relationship between vitamin D levels and disease activity scores in rheumatoid arthritis (RA), as assessed by the Disease Activity Score 28 (DAS28). These studies indicate that higher levels of vitamin D are associated with lower DAS28 scores, which reflect less active disease. This suggests that maintaining sufficient levels of vitamin D may contribute to the reduction of RA disease severity and progression by modulating immune function in a manner that suppresses autoimmune processes underlying rheumatoid inflammation. Although further research is still needed, the current evidence suggests a protective role of vitamin D against active RA.^{13,14} It can be stated that the relationship between vitamin D levels and disease activity in rheumatoid arthritis is complex and inconsistent across studies due to various factors. In the present study, the heterogeneity of patient populations, variability in vitamin D measurement methods, and presence of confounding factors like medications can influence the study results. Additionally, the timing of vitamin D assessment relative to disease evaluation, as well as potential publication bias, may impact findings. Given limitations of individual studies, more well-designed prospective research is required to understand how disease activity is associated with vitamin D levels in rheumatoid arthritis patients, accounting for diverse patient characteristics and minimizing influencing factors.

The results of our study indicate a significant association between age and the presence of vitamin D deficiency and insufficiency, 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 Kavadiachanda et al. (2023), which also observed a positive correlation between age and vitamin D levels.¹⁵ 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.^{16,17}

Based on the findings, a notable correlation exists between economic status and the severity of rheumatoid arthritis (RA), wherein individuals with lower income brackets exhibit higher Disease Activity Score-28 (DAS28) scores compared to those with higher income. This suggests that socioeconomic factors significantly influence disease activity levels among patients with rheumatoid arthritis. A study conducted by Dey et al. (2022) observed a connection between low socioeconomic status and unfavorable disease outcomes in individuals diagnosed with RA. This finding aligns with existing evidence indicating that patients from lower socioeconomic backgrounds with rheumatoid arthritis tend to experience inferior disease outcomes when compared to their counterparts with higher socioeconomic status.¹⁸ In an

independent inquiry conducted by Molina et al. (2015), it was uncovered that individuals with lower socioeconomic status tended to initiate disease-modifying antirheumatic medications at a later stage. Both low socioeconomic standing and delayed treatment initiation are individually associated with unfavorable clinical outcomes among patients with rheumatoid arthritis. The authors suggest implementing strategies to reduce treatment delays for individuals with rheumatoid arthritis from lower socioeconomic backgrounds, as this may contribute to improving their clinical condition.¹⁹

The disease activity levels in rheumatoid arthritis (RA) patients appear to be influenced by their smoking status. A higher proportion of ex-smokers and passive smokers demonstrated moderate to high Disease Activity Score-28 (DAS28) compared to non-smokers, who exhibited moderate activity. Even current smokers displayed a higher prevalence of moderate to high disease activity. These findings suggest that smoking can directly and indirectly impact the severity of RA, possibly through past exposure. Similarly, Kim (2018) observed that passive smokers had significantly higher DAS28-ESR and DAS28-CRP scores than non-smokers during the follow-up period. Moreover, Roelsgaard et al. (2020) reported that smoking cessation in RA patients was associated with reduced disease activity and improved lipid profiles.^{20,21}

A study conducted by Rydell et al. (2018) reported that smoking cessation among individuals with rheumatoid arthritis (RA) was associated with reduced disease activity and improved lipid profiles.¹⁹ Similarly, Saevarsdottir et al. (2015) identified significant associations between current smoking, baseline erosions, DAS28, and its inflammatory components, namely C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).^{22,23} The existing literature investigates the relationship between body mass index (BMI) and disease activity in patients with rheumatoid arthritis (RA), with a specific focus on DAS28. Son et al. (2021) identified a negative correlation between BMI and baseline DAS28, suggesting that higher BMI is associated with lower disease activity at the initiation of treatment²⁴. According to the findings of George et al. (2016), individuals with a body mass index (BMI) exceeding 30 kg/m² exhibited less improvement in the Disease Activity Score 28 (DAS28) compared to those with a BMI ranging from 20 to 30 kg/m². Specifically, obese patients achieved the DAS28 response criteria at a rate of 50%, whereas overweight patients attained it at a rate of 75%.²⁵ Furthermore, Witkam et al. (2023) noted a more robust association between poorer Disease Activity Score 28 (DAS28) outcomes in RA patients with a BMI of 30 or higher compared to those with lower BMI. In summary, the available evidence indicates a general correlation between higher body mass index (BMI) and elevated disease activity levels at the initial stage of RA. Moreover, it suggests that individuals with higher BMI experience less improvement in disease activity over time. Furthermore, this negative impact appears to be more prominent among obese populations with RA.²⁶

This study investigated the relationship between various factors and disease activity as measured by DAS28 in rheumatoid arthritis patients. The study found no significant correlation between vitamin D levels and DAS28 scores. Patients with average BMI appeared to have slightly lower DAS28 scores than overweight and obese groups. Older patients and those with lower socioeconomic status tended to have

higher vitamin D deficiency and disease activity. Smoking status also seemed to influence DAS28, as non-smokers generally showed moderate activity while current and former smokers exhibited variable activity. However, the cross-sectional design and small sample size limited the conclusions. Larger longitudinal studies are still needed to better understand how factors like BMI, age, economic status, smoking, and their potential impacts on vitamin D levels may influence disease activity as assessed by DAS28 scores.

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