

# Relationship Between Serum Vitamin D Level and Disease Severity in Rheumatoid Arthritis

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## ABSTRACT

**BACKGROUND AND OBJECTIVE:** Rheumatoid arthritis is an autoimmune disease that causes joint pain and reduces daily activities. The aim of this study was to evaluate the serum of vitamin D and its relationship with the severity of the disease in patients with rheumatoid arthritis referred to Allameh Hehlool hospital in Gonabad.

**DESIGN AND METHODS:** This cross-sectional-analytical study was performed on 92 patients referred to the rheumatology clinic of Allameh Behlool Gonabad Hospital in 2021. After obtaining the permission of the ethics committee, the samples were selected based on the desired criteria. Serum vitamin D levels in patients were measured, and data were collected using a patient information checklist and DAS28-CRP activity questionnaire. Data were analyzed using SPSS software version 16 and using statistically appropriate tests at a significance level less than 5%.

**RESULTS:** The mean age of the patients was  $53.05 \pm 12.33$  years and most of them (58.7%) were women. Serum vitamin D level was sufficient in 65.2% of patients and the severity of the disease was in the remission in 48.9% of them. The results of chi-square test showed a significant relationship between serum vitamin D levels and disease severity in patients ( $P < .001$ ).

**CONCLUSIONS:** Serum vitamin D levels were inversely related to disease severity and in most patients with severe disease severity, serum vitamin D levels were inadequate. vitamin D supplementation is recommended in patients with rheumatoid arthritis.

**KEYWORDS:** Vitamin D, rheumatoid arthritis, DAS28-CRP questionnaire, C-reactive protein, diseases severity

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## Introduction

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disorder of unknown cause. This autoimmune disease leads to inflammation in multiple joints, resulting in destruction of articular cartilage and bone erosion.<sup>1,2</sup> Important genetic and environmental risk factors play a role in the susceptibility to rheumatoid arthritis.<sup>3</sup> RA can occur in patients of any age. The lifetime risk of RA is 3.6% (1 in 28) for women and 1.7% (1 in 59) for men.<sup>3,4</sup> A systematic study conducted on the global frequency of RA in the last decade of the last century estimated the general prevalence of RA at 0.24%.<sup>5</sup> The prevalence of this disease in White breeds is about 1%, but varies between 0.1% (Africa) and 5% (Indian breeds).<sup>6</sup> According to the study of the Davatchi and colleagues in several cities of Iran, including Tehran, Zahedan, and so on, the prevalence of rheumatoid arthritis has been reported 0.37%.<sup>7</sup> A study by

Jamshidi et al<sup>8</sup> In 2014 on the frequency and characteristics of rheumatoid arthritis in Tehran showed that this prevalence was 6 times higher in women than men.

RA is a systemic inflammatory disease that can affect any organ in the body, but in many cases affects the joints of the limbs symmetrically and attacks other organs if left untreated. Common symptoms of systemic inflammation include fever, general weakness, and fatigue.<sup>9</sup> The most well-known antibodies in RA are rheumatoid factor (RF) and anti-citrulline protein (ACPA) antibodies, which are present long before the onset of the disease.<sup>10</sup>

Vitamin D, as one of the most important vitamins needed in the body, plays an important role in bone formation, including the physiological system, including the immune system.<sup>11</sup> Some studies have shown an association between deficiency of this disease because of its significant role in immune responses



**Table 1.** DAS28-CRP score interpretation that measure of disease activity in rheumatoid arthritis (RA).

RESULTS		CHANGES IN THE DAS28 SCORE COMPARED WITH THE BASELINE SCORE		
		MORE THAN 1.2	BETWEEN 0.6 AND 1.2	LESS THAN 0.6
Value in DAS28	Less than 3.2	Good	Moderate	Poor
	Between 3.2 and 5.1	Moderate	Moderate	Poor
	More than 5.1	Moderate	Poor	Poor

**Table 2.** Characteristics of the study participants.

VARIABLE	MEAN ± STANDARD DEVIATION
Age (years)	53.05 ± 12.33
Duration of illness (years)	6.78 ± 4.12
Serum level of Vitamin D (ng/mL)	44.63 ± 23.86
C-Reactive Protein (CRP) (mg/L)	12.86 ± 4.30

and the prevalence and severity of autoimmune diseases such as rheumatoid arthritis. A recent study showed a reduction in the risk of RA in healthy individuals and a reduction in symptoms and disease progression in patients with rheumatoid arthritis by taking Vitamin D.<sup>12</sup> Meena et al<sup>13</sup> showed that 84% of patients with RA were deficient in Vitamin D. In contrast, only 34% of controls had Vitamin D deficiency. The results showed that Vitamin D deficiency is more common in RA patients and may be one of the reasons for the progression or worsening of the disease. Esalatmanesh et al<sup>14</sup> displayed that in patients with active rheumatoid arthritis, Vitamin D levels were lower. Due to the different absorption of Vitamin D by various people in diverse communities due to different nutritional patterns and exposure to different light and also due to contradictory results, we decided to measure the serum level of Vitamin D in RA patients and relationship with the severity of the disease for the first time in Gonabad.

## Materials and Methods

The current research was a cross-sectional investigation, with permission obtained from the Graduate Council of the Medical School and the Research Ethics Committee of Gonabad University of Medical Sciences (IR). All RA patients are registered in the rheumatology clinic of Allameh Bahloul Hospital. First, we have assigned numerical code to all the 200 registered RA patients. Second, we have selected 86 RA patients by simple random sampling method. If any selected RA patient was not willing to participate, we have invited the next person for the study interview. Sampling was within 3 months between (September to November 2021) of the patient's visit or telephone request to visit the clinic and perform the examination.

Using the formula and also considering the 95% confidence level, 80% test power, 0.05 error, 86 sample sizes was calculated. Patients with informed consent of inclusion criteria, with

definitive diagnosis of rheumatoid arthritis and age over 18 years were included in this study. Exclusion criteria include using Vitamin D, pregnancy or lactation, patients with other rheumatic conditions, autoimmune or inflammatory (overlap), chronic liver or kidney disease, and patients with various malignancies. To collect information, a checklist of patient information (age, sex, and duration of the disease) and a questionnaire of activity and severity of the disease (DAS28-CRP) were used (Table 1). The DAS28 questionnaire consisted of 4 items: number of swollen and sensitive joints (SJC and TJC), visual analog scale, general health assessment of patients (VAS-GH; 0=best, 100=worst), and CRP. Show the activity of the disease. The severity of disease activity in each individual is scored according to DAS28-CRP as follows. Also, the validity and reliability of this tool have been reviewed and confirmed in various studies.<sup>15</sup>

To measure the level of CRP in the serum, a nephelometer kit from Jenravi Company (made in China) was used. To measure the serum level of Vitamin D, we used ELISA 25-Hydroxy Vitamin D kits of the manufacturer, Pishgaman Sanjesh, from Iran. The validity of kit has been investigated in previous studies.<sup>16-19</sup> We defined sufficient = more than 30 ng/mL, insufficient = 10-30 ng/mL) and deficiency = less than 10 ng/mL).<sup>16</sup>

## Data analysis

All statistical analyses were performed using SPSS software (version 16.0) through Student's T-test and the Chi-square test. Frequency (percent) and mean ± standard deviation (SD) was used to describe qualitative and quantitative variables, respectively. The default normality of quantitative variables was examined using the Kolmogorov-Smirnov test. The Ordinal regression model was adopted to predict behavior of ordinal-level dependent variable () with a set of independent variables. A *P*-value less than .05 was considered statistically significant.

## Results

In this research, the mean age of patients was 53.05 ± 12.33 years. Taking into account the loss of the sample, we selected 92 people, of which 58.7% women (54) and 41.3% men (38). According to the above table, the mean of the Vitamin D in the patients was 44.63 ± 23.86 ng/mL. Also, the co-efficient of variation (CV) of Vitamin D and CRP measurements, were 0.53% and 0.33%, respectively. The average level of Vitamin D in men is 47.52 ± 24.6 and in women is 42.61 ± 23.32 ng/mL, which difference was not statistically significant (*P*= .334) (Table 2).

**Table 3.** Relationship between disease severity based on criteria (DAS28-CRP) and serum level of Vitamin D.

SERUM LEVEL OF VITAMIN D	INSUFFICIENT		SUFFICIENT		TOTAL		CHI-SQUARE TEST RESULT
	NUMBER	(%)	NUMBER	(%)	NUMBER	(%)	
Remission	0	0	45	75	45	48.9	$\chi^2=52/26$ $df=3$ $P<.001$
Low	7	21.9	7	11.7	14	15.2	
Moderate	10	31.2	6	10	16	17.4	
High	15	46.9	2	3.3	17	1.5	
Total	32	100	60	100	92	100	

**Table 4.** Results of ordinal regression model on the factors associated with disease severity.

VARIABLE NAME	COEFFICIENT	STANDARD ERROR	SIGNIFICANT
Disease severity=Remission	-5.23	1.47	$P<.001$
Disease severity=Low	-4.05	1.42	.004
Disease severity=Moderate	-2.45	1.38	.076
Age	-0.007	0.019	.707
Sex	-0.289	0.461	.531
Duration of the disease	-0.004	0.059	.941
Serum levels of Vitamin D	-0.097	0.015	$P<.001$

Disease severity = High, is reference.

Considering that the serum level of Vitamin D (Variable 1) has 3 levels (deficiency/insufficient/sufficient) and the disease severity (Variable 2) has 4 levels (remission/low/moderate/high), the expected frequency of more than 20% of the cells was less than 5 and the fit of the chi-square test was wrong, we had to combine similar levels together (deficient and insufficient groups). According to Table 3, most of the patients had adequate Vitamin D levels (65.2%) and were in a remission state in terms of disease severity. there was a significant relationship between serum Vitamin D levels and disease severity ( $P<.001$ ). Most people with inadequate serum Vitamin D levels were in severe condition (46.9%) and most people with adequate serum levels were in remission state (75%).

The results of the Table 4 show that all variables are inversely associated to the severity of the disease due to the negative coefficient. For instance, each unit increase in Vitamin D score was associated with  $e^{-0.097}$  units decrease in having a severe level of the disease ( $B=-0.097$ ). Based on ordinal regression analysis, the chance of a person suffering from a severe level of the disease decreases with an increase in the level of Vitamin D. That is, the higher the level of Vitamin D, the lower the chance of developing severe disease. It is also significant ( $P<.001$ ).

## Discussion

our results showed, the mean serum level of the Vitamin D in patients with rheumatoid arthritis was  $44.63 \pm 23.86$  ng/mL

and in 65.2% of patients there was sufficient amount of this Vitamin. Consistent with this analysis, Mena et al<sup>13</sup> in India reported the mean serum level of the Vitamin D at  $31.68 \pm 14.13$  with the aim of investigating the relationship between serum Vitamin D levels and disease severity in patients with rheumatoid arthritis. In Salesi et al,<sup>20</sup> as well as Kavoodi et al,<sup>21</sup> The mean serum levels of the Vitamin D were  $105.61 \pm 29.3$  and  $152.21 \pm 35.92$  ng/mL, respectively. These values (Vitamin D levels) were much higher than the values obtained in the current research. This difference in results can be related to the time and place of the study or the sample size. In contrast to our study, Kaykhaei et al<sup>22</sup> showed the frequencies of Vitamin D deficiency in general population were 85.2%, also 89% of women and 80.3% men had deficiency. Similar to our study, according to Shamsian et al<sup>23</sup> study, 68.8 % of people were deficient in Vitamin D. The Vitamin D levels in males were significantly lower than those in females. Hovsepian et al<sup>24</sup> study presented the prevalence of mild, moderate, and severe Vitamin D deficiencies among the adult population was 19.6%, 23.9%, and 26.9% respectively, that was lower than our study. Also, the prevalence of Vitamin D deficiency in Asian countries among adult population was reported to be 14% to 59%,<sup>19-21</sup> that is more than Vitamin D deficiency in our research. Several studies in different parts of Iran and in different age-groups have shown the high prevalence of Vitamin D deficiency.<sup>13-17</sup> In a similar study in Tehran among

the general population, aged 20 to 64 years. Hashemipour et al<sup>14</sup> reported that the prevalence of severe, moderate, and mild Vitamin D deficiencies was 9.5%, 57.6%, and 14.2%, respectively. Bani-Issa et al<sup>25</sup> in United Arab Emirates showed Vitamin D deficiency in adult were 74%, which was higher than our result.

Also, according to Caraba et al,<sup>26</sup> in early RA patients with moderate and high disease activity, low serum levels of Vitamin D were associated with disease activity, increased insulin resistance, and endothelial dysfunction. Also, in the investigation of Kerr et al<sup>27</sup>, Noroozi et al,<sup>28</sup> and the Esalatmanesh et al,<sup>14</sup> 81%, 57%, and 73.14% of patients, respectively, had normal Vitamin D levels. These findings were consistent with the results of the existing study. However, in the investigation of Abbasi et al<sup>29</sup> and Shadmanfar et al,<sup>30</sup> which aimed to investigate the relationship between serum Vitamin D levels and the severity of rheumatoid arthritis, 68.6% and 77% of patients had serum Vitamin D levels less than They had a normal amount. The difference between the results of this study and the findings of this study can be related to the difference in the measurement method, the difference in the kits and also the time interval for measuring the serum level of the Vitamin D.

Determination of CRP level in patients with rheumatoid arthritis referred to the rheumatology clinic of Allameh Behloul Hospital in Gonabad showed that the serum level of CRP was  $12.86 \pm 5.30$  mg/L in these patients. In the study of Plant et al<sup>31</sup> in patients with RA, the mean serum CRP level of the patients was  $13.14 \pm 6.21$ . The results of the study by Plant et al<sup>31</sup> were consistent with the findings of our study. In contrast to this study, in Reyhani et al,<sup>32</sup> the mean serum CRP level in women with RA was  $7.3 \pm 12.68$  mg/L. Heydari et al<sup>33</sup> evaluate the value of CRP changes in predicting therapeutic response in rheumatoid arthritis. The mean CRP level of the studied patients was  $28.17 \pm 11.31$  mg/L. This high level of CRP and its higher than the values obtained in this study is probably due to receiving appropriate treatment in patients, which was the Word criterion for the study. Findings of this study in relation to determining the severity of the disease using a questionnaire (DAS28) showed that 48.9% of the patients were in the remission, 15.2% in the mild, 17.4% in the moderate, and 18.5% in the severe. In contrast to this study, the mean cases of the disease in the study of Shadmanfar et al<sup>30</sup> (12% remission, 8% weak, 62% moderate, and 18% high activity) and the study by Kavoodi et al (5.2% high, 50.4% moderate (28.1% low and in 16.3% remission) was more than our study.<sup>20</sup>

Also, contrary to this study, in Abbasi et al,<sup>29</sup> the severity of the disease was reported to be low by 56.2%, 21.5% moderate, and high in 22.2%, the proportion of mild cases was higher. Severe cases of the disease in this study were higher

than the Salesi et al<sup>21</sup> (Mean DAS28 score in the studied patients was  $5.5 \pm 1.2$ ). The mean severity of the disease was reported in Patel et al's<sup>34</sup> study, in Turhanoğlu et al's<sup>35</sup> study and in Wervers et al's<sup>36</sup> study. The disease was very different. Therefore, the existence of this difference in the results can be justified according to the different community and also the different climatic conditions of the studied areas. agreeing to the consequences of this survey, there was a important association between disease severity and serum Vitamin D levels, so that all patients whose disease severity was in the range of extinction had sufficient Vitamin D serum levels and disease severity in people with inadequate Vitamin D serum levels. It was intense. Although in some investigations, no relationship has been reported between disease activity and Vitamin levels, in most studies in this field similar results have been obtained.

Also, in Braun-Moscovici et al<sup>37</sup> study, 42% and in Oelzner study, 32% of patients with rheumatoid arthritis were deficient in Vitamin D.<sup>38</sup> Consistent with this study, Shadmanfar et al,<sup>30</sup> as well as Abbasi et al,<sup>29</sup> In line with this results, increased the severity of the disease in patients with lower serum levels of the Vitamin D; Reported. Unlike this study, in the investigation of Kavoodi et al,<sup>20</sup> no significant relationship was observed between serum Vitamin D levels and disease severity. Patel et al's<sup>34</sup> inspection, serum Vitamin D levels were related to disease activity and every 10 ng/mL rise in Vitamin levels was accompanied by a 0.3 decrease in rheumatoid disease activity based on DAS28 and a 25% decrease in CRP. The reverse connection among serum Vitamin D levels and disease activity based on the DAS28 system was also confirmed in a 2006 study by Cutolo et al.<sup>39</sup> In the researches of Noroozi et al,<sup>28</sup> as well as in Kavoodi et al,<sup>20</sup> there was no important association between serum levels of Vitamin D and disease activity. But studies by Higgins et al<sup>40</sup> also showed that Vitamin D deficiency was more common in RA. In a study by Merlino et al,<sup>41</sup> effect of Vitamin D intake, both as a diet and as a supplement, on the incidence of RA was investigated. In an 11-year follow-up, higher intake of the Vitamin D, both nutritionally and as a supplement, was related with a lesser danger of RA. The limitations of this study are due to the nature of the study, which is cross-sectional, the inability to investigate the effective factors, as well as the lack of investigation of other inflammatory and hematological indicators and the single-center nature of the study. In conclusion, most patients with rheumatoid arthritis in this study had adequate serum Vitamin D levels. The severity of the disease was also in the remission state in most patients. The outcomes of this research presented that serum Vitamin D levels were significantly and inversely associated with disease severity in patients with rheumatoid arthritis. According to the results of this study, the use of Vitamin D as a complementary method in the treatment of patients with rheumatoid arthritis can be effective.

## Declarations

### Ethics Approval and Consent to Participate

The Ethics Committee of Gonabad University of Medical Sciences approved this research (approval code: IR. GMU. REC.1400.082). All patients provided a written informed consent to participate in the study.

### Consent for Publication

Not applicable.

### Author Contributions

**Farhang Soltani Bajestani:** Conceptualization; Investigation; Methodology; Supervision; Writing—review & editing. **Nasim Khajavian:** Investigation; Methodology; Software; Writing—review & editing. **Davoud Salarbashi:** Conceptualization; Writing—original draft; Writing—review & editing. **Mojtaba Kafili:** Conceptualization; Investigation; Methodology; Writing—original draft. **Fatemeh Ashori:** Investigation; Methodology. **Jafar Hajavi:** Conceptualization; Investigation; Methodology; Project administration; Supervision; Writing—original draft; Writing—review & editing.

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### Availability of Data and Materials

The data underlying this article are available in the article.

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