

Subject Area:

Vitamin D level in Rheumatoid arthritis and its correlation with the disease activity

Amany Fayez Hakim
Mataria Teaching Hospital

Soha Sayed Shaaban
Mataria Teaching Hospital, doc_soha@yahoo.com

Follow this and additional works at: <https://jmisr.researchcommons.org/home>



Part of the [Medical Sciences Commons](#), and the [Medical Specialties Commons](#)

Recommended Citation

Hakim, Amany Fayez and Shaaban, Soha Sayed (2019) "Vitamin D level in Rheumatoid arthritis and its correlation with the disease activity," *Journal of Medicine in Scientific Research*: Vol. 2: Iss. 2, Article 11. DOI: https://doi.org/10.4103/JMISR.JMISR_7_19

This Original Study is brought to you for free and open access by Journal of Medicine in Scientific Research. It has been accepted for inclusion in Journal of Medicine in Scientific Research by an authorized editor of Journal of Medicine in Scientific Research. For more information, please contact m_a_b200481@hotmail.com.

Vitamin D level in Rheumatoid arthritis and its correlation with the disease activity

Soha Sayed Shaaban^a, Amany Fayeze Hakim^b

Departments of ^aRheumatology and ^bRehabilitation, Mataria Teaching Hospital, Cairo, Egypt

Abstract

Objective

Vitamin D has an immunomodulatory and anti-inflammatory action, and its deficiency may cause several autoimmune disorders, including rheumatoid arthritis (RA). The relationship between vitamin D level and the severity of RA is of mere interest to several researchers.

Patients and methods

This prospective study included 40 cases of RA and 20 healthy controls, of age group between 40–70 years. Serum Vitamin D levels were measured and compared in RA patients and controls. Vitamin D levels in RA patients were measured in three different groups; active RA group, inactive RA group and control.

Results

Sixty-five percent patients of active RA were Vitamin D deficient versus only 40% of inactive RA patients. The serum Vitamin D levels were also significantly lower in the RA patients (mean value of 18.09 ± 8.99 ng/ml), as compared to the controls (mean value of 29.67 ± 11.34 ng/ml). There was an inverse significant correlation between serum Vitamin D levels and RA disease activity as measured by DAS28. The mean serum Vitamin D levels were 18.81 ± 6.679 ng/ml, 14.42 ± 6.856 ng/ml, 9.83 ± 6.791 ng/ml, in low disease activity, moderate disease activity, and high disease activity groups, respectively.

Conclusion

Vitamin D deficiency is more common in autoimmune diseases as RA and may be one of the leading cause of increased disease activity.

Keywords: Disease activity, rheumatoid arthritis, Vitamin D

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that usually affects the synovial joints, causing significant morbidity and shortened life expectancy [1]. Vitamin D (25-hydroxyvitamin D [25(OH) D]) changes the expression of genes that affect cellular functions such as proliferation, differentiation, apoptosis, and angiogenesis [2]. It is known that 1, 25-dihydroxy vitamin D3 [1, 25(OH) 2 D3] inhibits IFN- γ secretion and negatively regulates IL-12 production by downregulating NF-kB [3]. When administered in vivo, 1,25(OH)2 D3 was found to have a preventative effect on autoimmune diseases [4], and other studies have revealed that vitamin D deficiency is linked to many autoimmune

diseases [5,6]. The action of vitamin D depends on vitamin D receptor (VDR), and activation of VDR results in inhibition of pro-inflammatory T cells and DC differentiation.

Furthermore, VDR agonists induce T regulator and natural killer cells and thus suppress autoimmunity [7], and the VDR polymorphism has been known to confer susceptibility to RA [8]. A low vitamin D level may increase the RA risk [9]. However, studies on vitamin D level in RA patients compared to healthy controls and on the relationship between

Correspondence to: Soha Sayed Shaaban, MD, Rheumatology and Rehabilitation, Cairo, Egypt, Tel: 2+01006000829. E-mail: doc_soha@yahoo.com

Access this article online

Quick Response Code:



Website:
www.jmsr.eg.net

DOI:
10.4103/JMISR.JMISR_7_19

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

How to cite this article: Shaaban SS, Hakim AF. Vitamin D level in Rheumatoid arthritis and its correlation with the disease activity. J Med Sci Res 2019;2:152-6.

serum vitamin D levels and RA activity have shown mixed results [10].

AIM OF THE WORK

To evaluate the prevalence of vitamin D deficiency in active RA patients in comparison with healthy controls.

PATIENTS AND METHODS

Our prospective study included 60 patients selected from the outpatient clinic of Mataria Teaching Hospital. Age ranged from 40 to 70 years. All patients are diagnosed on clinical radiological basis according to ACR/EULAR 2010 classification criteria. Our patients are divided into three groups: one group included 20 patients with active RA evaluated for vitamin D level and disease activity score 28 (DAS28). The second group included 20 patients with inactive RA evaluated for vitamin D level, and a third control group included 20 control group of healthy individuals. Patients having overlap autoimmune, endocrinal diseases, and renal impairment were excluded. All participants were interviewed regarding personal details. Detailed history was taken from cases regarding age of onset of symptoms, progression of disease, pattern of joint involvement, presence of any swelling, pain in the joints, and drug history (if any). DAS28 of patients with RA was calculated according to the guidelines of American College of Rheumatology, which indicated the disease severity, that is, low-, moderate-, and high-disease activity. Calculation of DAS28 score was done by following measures.

- (1) Number of swollen joints (out of 28).
- (2) Number of tender joints (out of 28).
- (3) Erythrocyte sedimentation rate (ESR).
- (4) The patient was asked to make a 'global assessment of health' (indicated by marking on a 10-point line between very good and very bad).

These results were formulated into a mathematical equation to detect the overall DAS [10]:

$$\text{DAS28} = 0.56\sqrt{(28\text{TJC})} + 0.28\sqrt{(28\text{SJC})} + 0.70 \text{Ln} \\ (\text{ESR}) + 0.014\text{VAS}$$

where TJC is the tender joint count; SJC, swollen joint count; Ln, log; VAS, visual analog scale.

Disease activity is classified based on the DAS28 value as follows: remission (<2.6), low (2.6–<3.2), moderate (≥3.2–5.1), and high (≥5.1) [10]. All patients were subjected to laboratory investigations in the form of complete blood count, ESR, C-reactive protein (CRP), RF, liver function tests, kidney function, and complete urine analysis. Vitamin D level was estimated.

RESULTS

In this study, we found that serum vitamin D levels were significantly lower in active RA group (mean value of 13.89 ± 7.60 ng/ml), as compared with inactive RA

Table 1: Comparison of serum vitamin D levels in active rheumatoid arthritis group and inactive rheumatoid arthritis group

	Control group (n=20)	Active rheumatoid (n=20)	Inactive rheumatoid (n=20)
Vitamin D			
Mean±SD	29.67±11.34	13.89±7.60	22.29±8.44
Range	11-48	4-27	10-38
Deficient [n (%)]	6 (30.0)	13 (65.0)	8 (40.0)
Insufficient [n (%)]	2 (10.0)	7 (35.0)	8 (40.0)
Sufficient [n (%)]	12 (60.0)	0 (0.0)	4 (20.0)
DAS [n (%)]			
Remission	20 (100.0)	0 (0.0)	20 (100.0)
Low	0 (0.0)	7 (35.0)	0 (0.0)
Moderate	0 (0.0)	4 (20.0)	0 (0.0)
High	0 (0.0)	9 (45.0)	0 (0.0)

DAS, disease activity score.

group (mean 22.29 ± 8.44) and the control group (mean value of 29.67 ± 11.34 ng/ml) (Table 1).

We found that the range of ESR in patients with RA was 12–75 mm/h with mean 35.45 ± 17.00 mm/h, whereas the range of ESR in the control group was 8–34 mm/h, with mean of 17.25 ± 7.66 mm/h. The range of CRP in patients with RA was 0.6–45 mg/l, with median of 6 mg/l (4.5–8.89 mg/l), whereas the range of CRP in the control group was 0–7 mg/l, with a median of 4 mg/l (3–5.5 mg/l).

There was an inverse correlation between both ESR and CRP and vitamin D level in active and inactive RA groups; the *P* value was less than 0.01.

The range of vitamin D level was 4–38 ng/ml with a mean of 18.09 ± 8.99 in patients with RA, whereas in the control group, the level of vitamin D ranged from 11 to 48 ng/ml, with a mean of 29.67 ± 11.34 (Table 2). Obviously, there is a high significant value between vitamin D level and patients with RA, as shown that [12] 52.5% of patients with RA had vitamin D deficiency, 15 (37.5%) of patients with RA had insufficient level of vitamin D, whereas four (10%) of patients with RA had sufficient vitamin D (Fig. 1).

In this study, the DAS in 20 patients with active RA was found as follows: 0 (0%) of patients with RA were in remission (DAS28 score, <2.6), seven (35%) with low-disease activity (DAS28 score, 2.7–3.2), four (20%) with moderate-disease activity (DAS28 score, 3.3–5.1), and nine (45%) with high-disease activity (DAS28 score, >5.1) (Table 1, Fig. 2).

There was a highly significant difference between all the patients with rheumatoid arthritis (patients with active and inactive RA together), with range of 10–38 and a mean of 22.29 ± 8.438 in patients with remission, a range of 10–27 and a mean of 18.81 ± 6.679 in patients with low activity, a range of 8–24 and a mean of 14.42 ± 6.856 in patients with moderate

Table 2: The range of vitamin D level in patients with rheumatoid arthritis in comparison with the control group

	Control group (n=20)	RA ^a group (n=40)	Test	P	Significance
Vitamin D					
Mean±SD	29.67±11.34	18.09±8.99	4.303 ^b	0.000	HS
Range	11-48	4-38			
Vitamin D level					
Deficient	6 (30.0)	21 (52.5)	17.559	0.000	HS
Insufficient	2 (10.0)	15 (37.5)			
Sufficient	12 (60.0)	4 (10.0)			

Hs, highly significant; RA, rheumatoid arthritis. ^aX² test. ^bIndependent *t* test. *P* value more than 0.05, non significant; *P* value less than 0.01, highly significant.

Table 3: Comparison between the range of vitamin D level and DAS in all rheumatoid patients (active and inactive RA patients together)

DAS	All rheumatoid group				
	Vitamin D		Test	P	Significance
	Mean±SD	Range			
Remission	22.29±8.438	10-38	5.767 ^a	0.003	HS
Low	18.81±6.679	10-27			
Moderate	14.42±6.856	8-24			
High	9.83±6.791	4-22			

P-value > 0.05: Non significant; *P*-value < 0.05: Significant; *P*-value < 0.01: Highly significant. ^aOne Way ANOVA test.

Table 4: Correlation between DAS 28 and vitamin D level in active and all rheumatoid groups together

DAS	Vitamin D			
	Active rheumatoid		All rheumatoid group	
	<i>r</i>	<i>P</i>	<i>R</i>	<i>P</i>
	-0.766**	0.000	-0.719**	0.000

P-value > 0.05: Non significant; *P*-value < 0.05: Significant; *P*-value < 0.01: **Highly significant. Spearman correlation coefficient.

activity, and the range of 4–22 and a mean of 9.83 ± 6.791 in patients with high DAS (Table 3, Fig. 3).

Moreover, there is an inverse correlation between DAS 28 and the level of vitamin D in active and all rheumatoid groups together (*P* < 0.01) (Table 4, Fig. 4). These data provide further support that vitamin D plays an immunomodulatory role in inflammatory arthritis.

DISCUSSION

RA is a chronic autoimmune inflammatory disease presented with asymmetric, peripheral polyarthritis, and many environmental and genetic factors play a role in the development of this disease.

Several studies suggest that vitamin D deficiency increases the risk of various autoimmune diseases such as RA, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, and type I diabetes mellitus. Vitamin D has immune-regulatory activity, which is mediated through VDRs

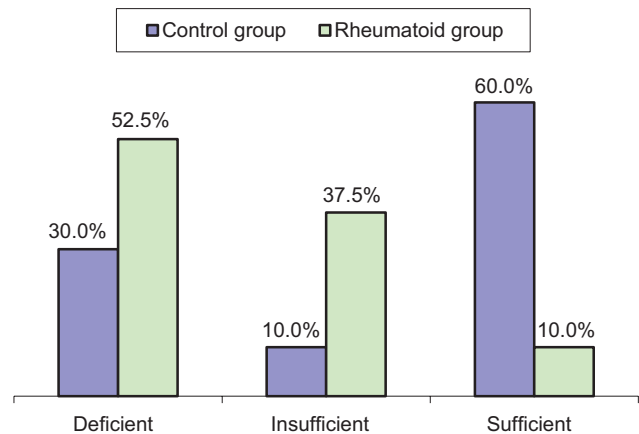


Figure 1: The range of vitamin D level in patients with RA in comparison with the control group. RA, rheumatoid arthritis.

present on antigen-presenting cells, and activated T and B lymphocytes. Vitamin D interacts with the immune system through its actions on the regulation and differentiation of lymphocytes, macrophages, and natural killer cells, and interfering in the production of cytokines.

In this study, vitamin D levels were measured in 40 patients with RA (20 active RA and 20 inactive RA) and compared with 20 patients of controls. Vitamin D levels in patients with RA were assessed in different stages of disease activity to assess the correlation between the three groups. The age of patients in the RA group ranged from 40 to 70 years, and the majority were females.

Overall, 65% of active RA and 40% of inactive RA enrolled for this study were vitamin D deficient, whereas 30% of control participants had deficiency of vitamin D. The serum vitamin D levels were significantly lower in active RA group (mean value of 13.89 ± 7.60 ng/ml), as compared with inactive RA group (mean 22.29 ± 8.44) and the control group (mean value of 29.67 ± 11.34 ng/ml) (Table 1).

Disease activity of RA was assessed according to the value of DAS28 score. There was a significant inverse correlation between serum vitamin D levels and RA disease activity; serum vitamin D level was 20 (50%) in patients with RA who were in remission (DAS28 score, <2.6), seven (37.5%) with low-disease activity (DAS28 score,

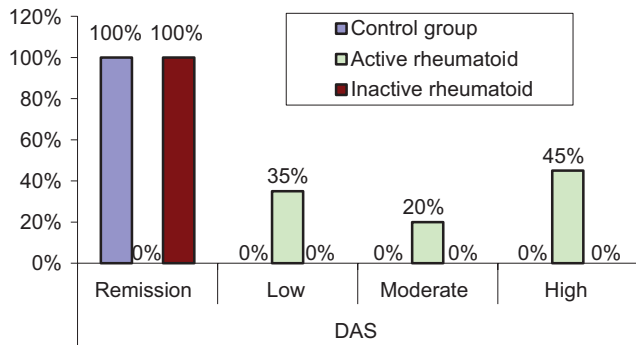


Figure 2: The disease activity score (DAS) in patients with active RA in comparison with inactive RA and control groups. RA, rheumatoid arthritis.

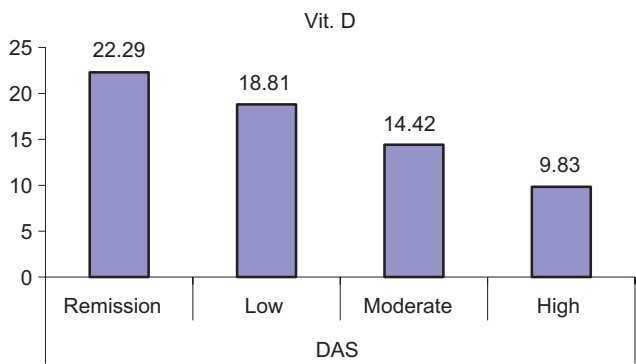


Figure 3: Comparison between the range of vitamin D level and DAS in all patients with rheumatoid arthritis (patients with active and inactive RA together). DAS, disease activity score; RA, rheumatoid arthritis.

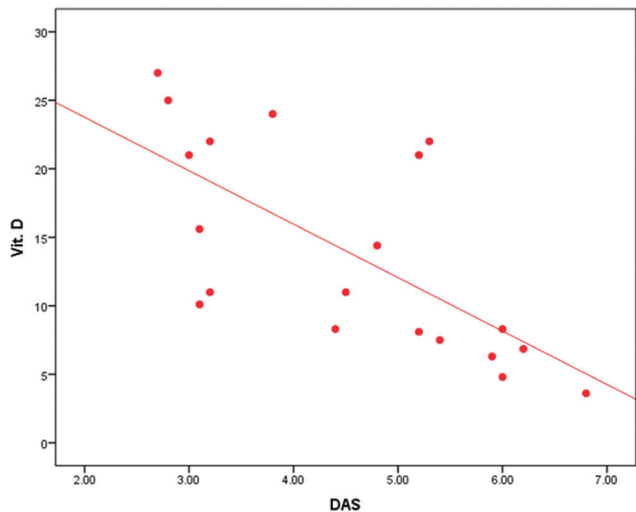


Figure 4: Correlation between DAS 28 and vitamin D level in active and all rheumatoid groups together. P -value > 0.05 : Non significant; P -value < 0.05 : Significant; P -value < 0.01 : Highly significant. •: One Way ANOVA test.

2.7–3.2), four (20%) with moderate-disease activity (DAS28 score, 3.3–5.1), and nine (22.5%) with high-disease activity (DAS28 score, >5.1) (Table 1, Fig. 2). These differences were highly significant ($P < 0.01$).

Ibrahim *et al.* [12], Yagiz *et al.* [13], and Kareem *et al.* [14] found decreased levels of vitamin D in patients with RA, systemic lupus erythematosus, Behcet’s disease and ankylosing spondylitis, as compared with controls, thus supporting the role of vitamin D in the pathogenesis, activity, and treatment of autoimmune diseases.

Similar findings were reported in the study of Cen *et al.* [15] as the mean serum vitamin D level was significantly lower in patients with RA (35.99 ± 12.59 nmol/l) as compared with the normal participants (54.35 ± 8.20 nmol/l).

A study of Sabbagh *et al.* [16] found that inadequate vitamin D level in patients with systemic autoimmune rheumatic diseases had strong association with disease activity in patients with RA. This study pointed on proper evaluation of vitamin D level and recommended intake of a proper dose of vitamin D in such patients.

However, Merlino *et al.* [17] showed an inverse association between increased intake of vitamin D and the risk of RA. They analyzed their data from a prospective cohort study of 29 368 women without a history of RA through a baseline study that took 11 years of follow-up, where 152 cases of RA were diagnosed. Increased intake of vitamin D was inversely associated with increased risk of RA.

In another study of 100 patients with RA and 100 controls who do not receive vitamin D supplements realized that patients with high-disease activity had the lowest vitamin D levels (18.23 ± 8.2 nmol/l) compared with patients with moderate (35.13 ± 15.2 nmol/l) and low (38.05 ± 7.3 nmol/l) disease activity. Serum vitamin D was negatively correlated with DAS28, which was statistically significant. Significantly lower vitamin D values were detected in patients who were not responding to treatment and were not in disease remission [11].

Studies done by Yassin *et al.* [18] and Azzeh and Kensara [19] showed similar results observed in Egypt and Saudi Arabia and concluded that vitamin D insufficiency is highly prevalent and linked to the severity of patients with RA.

A review by Bragazzi and colleagues pointed out that the role of vitamin D supplementation in the prevention of RA manifestations is unclear in view of studies showing contrasting findings with regards to the association between vitamin D levels and RA. This study highlights the high prevalence of decreased vitamin D level in RA and the immunomodulatory role of vitamin D in the development of RA and other autoimmune diseases. This study also pointed on the inverse relationship between vitamin D levels and the severity of disease activity in RA [20].

An Indian study found that 90% of patients with RA were either vitamin D deficient or insufficient. The mean serum vitamin D level of patients with RA was significantly low in comparison with healthy controls. Levels of vitamin D in patients with high-disease activity were significantly lower compared with those in patients with moderate-disease and

low-disease activity, and vitamin D level had significant negative correlation with DAS28 score [21].

Meta-analysis of 1143 patients with RA and 963 controls showed the prevalence of patients with vitamin D deficiency was significantly higher in RA group in comparison with the control group (55.2 vs. 33.2%; $P = 0.023$), as the mean serum vitamin D level in the RA group was also significantly lower in comparison with the control group. This meta-analysis highlighted on the significant inverse correlation between vitamin D levels and DAS28 [22].

CONCLUSION

Vitamin D deficiency is common in patients with RA and may be a leading cause of developing active RA. Decreased level of vitamin D is associated with increased disease activity. Proper evaluation of vitamin D level is mandatory in all patients of RA to prescribe the recommended dose of vitamin D.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Harris ED Jr.: Rheumatoid arthritis. Pathophysiology and implications for therapy. *N Engl J Med* 1990; 322:1277–89.
- Cantorna MT: Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence? *Proc Soc Exp Biol Med* 2000; 223:230–3.
- Boonstra A, Barrat FJ, Crain C, Heath V, Savelkoul HF, O'garra A. α , 25-Dihydroxyvitamin D₃ has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. *J Immunol* 2001; 167:4974–80.
- Koizumi T, Nakao Y, Matsui T, *et al.* Effects of corticosteroid and 1,24R-dihydroxy- vitamin D₃ administration on lymphoproliferation and autoimmune disease in MRL/MP-lpr/lpr mice. *Int Arch Allergy Appl Immunol* 1985; 77:396–404.
- Kamen D, Aranow C. Vitamin D in systemic lupus erythematosus. *Curr Opin Rheumatol* 2008; 20:532–7.
- Cutolo M, Otsa K, Paolino S, Yprus M, Veldi T, Seriola B. Vitamin D involvement in rheumatoid arthritis and systemic lupus erythematosis. *Ann Rheum Dis* 2009; 68:446–7.
- Wen H, Baker JF. Vitamin D, immunoregulation, and rheumatoid arthritis. *J Clin Rheumatol* 2011; 17:102–7.
- Lee YH, Bae SC, Choi SJ, Ji JD, Song GG. Associations between vitamin D receptor polymorphisms and susceptibility to rheumatoid arthritis and systemic lupus erythematosus: a meta-analysis. *Mol Biol Rep* 2011; 38:3643–51.
- Gatenby P, Lucas R, Swaminathan A. Vitamin D deficiency and risk for rheumatic diseases: an update. *Curr Opin Rheumatol* 2013; 25:184–91.
- Prevo M, Van't Hof M, Kuper H, Van Leeuwen M, Van De Putte L, Van Riel P. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38:44–8.
- Wells G, Shea B, O'connell D, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; 2000.
- Ibrahim MH, Bakheet MS, Sater KA, Shakoor MA. Relationship between Vitamin D and disease activity in some rheumatic diseases. *Wyno Acad J Med Sci* 2013; 2:52–6.
- Yagiz AE, Ustun N, Paksoy H, Ustun I, Mansuroglu A, Guler H, *et al.* Association of Vitamin D with disease activity in rheumatoid arthritis and ankylosing spondylitis. *J Clin Anal Med* 2015; 6:486–9.
- Kareem MI, Mohammed RH, Abozaid HS, Rayan MM, Mohamed AM, Fathi NA. Hypo-vitaminosis D in patients with rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis. *J Clin Cell Immunol* 2015; 6:1–6.
- Cen X, Liu Y, Yin G, Yang M, Xie Q. Association between serum 25-hydroxyvitamin D level and rheumatoid arthritis. *Biomed Res Int* 2015; 2015:913804.
- Sabbagh Z, Markland J, Vatanparast H. Vitamin D status is associated with disease activity among rheumatology outpatients. *Nutrients* 2013; 5:2268–75.
- Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG, *et al.* Vitamin D intake is inversely associated with rheumatoid arthritis: Results from the Iowa women's health study. *Arthritis Rheum* 2004; 50:72–7.
- Yassin A, Gareeb H, Mohamed NA, Samy C. The relationship between Vitamin D and disease activity in Egyptian patients with rheumatoid arthritis. *Int Trends Immun* 2014; 2:122–7.
- Azzeh FS, Kensara OA. Vitamin D is a good marker for disease activity of rheumatoid arthritis disease. *Dis Markers* 2015; 2015:260725.
- Bragazzi NL, Watad A, Neumann SG, Simon M, Brown SB, Abu Much A, *et al.* Vitamin D and rheumatoid arthritis: An ongoing mystery. *Curr Opin Rheumatol* 2017; 29:378–88.
- Sharma R, Saigal R, Goyal L, Mital P, Yadav RN, Meena PD, *et al.* Estimation of Vitamin D levels in rheumatoid arthritis patients and its correlation with the disease activity. *J Assoc Physicians India*. 2014; 62:678–81.
- Lee YH, Bae SC. Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: A meta-analysis. *Clin Exp Rheumatol* 2016; 34:827–33.