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## Role of vitamin d levels in rheumatoid arthritis and its correlation with disease severity

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### Abstract

**Objective:** Deficiency of Vitamin D has been linked in the pathogenesis of many autoimmune diseases such as diabetes mellitus type 1 and multiple sclerosis. Deficiency of vitamin D has been associated with high susceptibility of the development of rheumatoid arthritis (RA) and also with increased disease activity in patients with RA. The objective of this study was to evaluate the status of vitamin D in patients with RA, assess the correlation between serum level of Vitamin D and disease severity. **Materials and Methods:** This was a prospective, comparative study conducted on 100 participants, 50 cases of RA and 50 healthy controls, all in the age group of 18–75 years. Serum Vitamin D levels were measured and compared in cases and controls.

**Results:** Ninety two percent patients belonging to the RA group were Vitamin D deficient, whereas only twenty four percent belonging to the control group had Vitamin D deficiency. There was a significant inverse correlation between serum Vitamin D levels and RA disease severity. The mean serum Vitamin D levels were 34.36ng/ml, 32.25±0.395ng/ml, 22.70±4.787ng/ml and 16.41±2.911ng/ml in the remission, low disease activity, moderate disease activity, and high disease activity groups, respectively.

**Conclusion:** Vitamin D insufficiency and deficiency are more common in patients with RA. In this study Vitamin D deficiency was related to RA patients with older age, RA with female gender and a higher degree of RA activity.

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

### Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease mainly characterized by synovitis and joint destruction. Etiology of RA is unknown. It is a chronic autoimmune disorder characterized by systemic features and joint involvement which affects 1% of the world's adults [1, 2]. It can lead to significant morbidity and mortality. Role of Vitamin D deficiency in the pathogenesis of RA was the interest of the study. The role of Vitamin D in modulating immune function is supported by the discovery of Vitamin D receptors (VDRs) in peripheral mononuclear blood cells [3, 4]. Vitamin D causes down regulation of antigen-presenting cells, inhibition of T-cell proliferation, and decreased production of T helper cell-1 cytokines IL-2, interferon gamma and tumor necrosis factor-alpha[5,6]. Researchers have related Vitamin D deficiency with several autoimmune disorders, including insulin-dependent diabetes mellitus, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) [7-10]. It has been suggested that Vitamin D is an extrinsic factor capable of affecting the prevalence of autoimmune diseases. The immunomodulatory activities of Vitamin D might be particularly efficient in RA patients and support a therapeutic role of Vitamin D in these patients [11]. The VDRs have been demonstrated in macrophages, chondrocytes, and synoviocytes in rheumatoid synovium and at sites of cartilage erosion in RA patients [5, 6, 11]. In RA patients, measurement of Vitamin D levels is particularly important as its deficiency is highly prevalent in this group [12-14]. Vitamin D may also have a role in modulating RA disease activity and is already known to be important in osteoporosis and falls and fractures, which are common in RA. The antiproliferative, immunomodulatory, and anti-inflammatory properties of Vitamin D could be exploited to treat a variety of autoimmune rheumatic diseases, from RA to SLE, and possibly also multiple sclerosis, type 1 diabetes or inflammatory bowel diseases [15].

The relationship between the severity of RA and levels of Vitamin D is a subject of immense interest and therapeutic implications, hence in this study we compared the serum levels of Vitamin D in the healthy population and in RA patients to correlate the levels of Vitamin D with the RA disease activity.

**Materials and Methods**

This was a prospective comparative study conducted in the department of Orthopedics in Government Medical College and Rajindra Hospital Patiala. A total of 100 participants were included, and they were divided into 2 groups. Group I included 50 cases of RA and Group II included 50 healthy controls, all participants were in the age group of 18–75 years. Permission was sought from the institutional ethics committee and written informed consent was taken from each participant before enrolling him/her for the study.

**Inclusion criteria**

Both males and females in the age group of 18–75 years having RA according to the criteria of American College of Rheumatology-European League against Rheumatism 2010

**Exclusion criteria**

1. Patients having age less than 18 yr or more than 75yr
2. Patients suffering from malnutrition, hepatic or renal dysfunction
3. Patients who are on medication affecting serum calcium levels, Vitamin D metabolism (such as anticonvulsants, diuretics, and thyroxin).
4. Patients suffering from hyperparathyroidism, hyperthyroidism, diabetes mellitus.
5. Patients on Vitamin D supplementation in the past 6 months
6. Patients currently enrolled in another investigational study.
7. Patients who were not willing to participate in the study.

The patients were included from Out Patient Department of Orthopaedics, Government Medical College and Rajindra Hospital, Patiala after fulfilling the required inclusion criteria. All patients were interviewed regarding their personal details, and detailed history were taken from cases regarding age at onset of symptoms, the progression of disease and pattern of joint involvement, the presence of any swelling and pain in the joints, and drug history (if any). Disease activity score of 28 joints (DAS28) of RA patients were calculated as per the guidelines of American College of Rheumatology, which indicated the disease severity, that is low, moderate, and high disease activity. DAS28 score was calculated by following measure

1. Counting the number of swollen joints (out of 28)
2. Counting the number of tender joints (out of 28)
3. Taking blood to measure the erythrocyte sedimentation rate (ESR)
4. Asking the patient to make a “global assessment of health” (indicated by marking on a 10 point line between very good and very bad).

Above results were incorporated into a mathematical formula to produce the overall disease activity score [16]:

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

(Here TJC = Tender joint count, SJC = Swollen joint count,

Ln = log, VAS = Visual analog scale)

Disease severity was assessed according to the value of DAS28score as follows:

1. Remission: DAS28  $\leq 2.6$
2. Low disease activity: DAS28  $> 2.6 \leq 3.2$
3. Moderate disease Activity: DAS28  $> 3.2 \leq 5.1$
4. High disease Activity: DAS28  $> 5.1$ .

The investigations carried out in all the participants participating in this study were ESR, RA factor, anticitrullinated cyclic peptide antibody (wherever required), Vitamin D3 level, complete blood count, renal function tests, serum uric acid and liver function tests. Vitamin D3 levels above 30ng/ml were considered as sufficient. X-rays of involved joints and X-ray chest were done wherever needed.

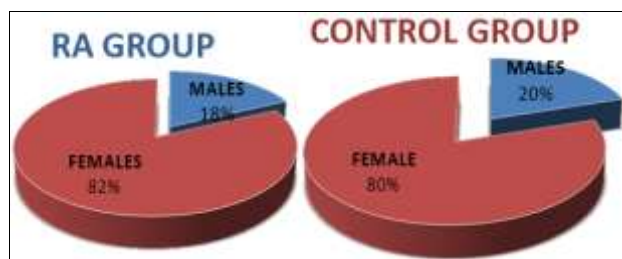
**Results**

The study consisted of 50 patients diagnosed with RA and 50 age and sex matched apparently healthy individuals as control. Average age of patients in RA group was 50.37±11.68 years, whereas the average age of participants in the control group was 50.67 ± 10.65 years. Among the 50 patients in the RA group, 9 (18%) were males and 41 (82%) were females. Among the 50

1. participants in the control group, 10 (20%) were males and 40 (80%) were females [Table 1].

**Table 1:** Number of Males and Females in each group

Group	Number	Males	Females
Rheumatoid arthritis	50	9	41
Control	50	10	40



The mean serum calcium levels were 8.61±0.485 mg/dl in the RA group and 9.31±0.432mg/dl in the control group [Table 2]. Forty-six patients (92%) belonging to the RA group had serum Vitamin D levels <30ng/ ml, that is, they were Vitamin D deficient, whereas only 12 participants (24%) belonging to the control group had Vitamin D deficiency. The mean serum Vitamin D levels were 20.49±6.044ng/ml in patients of RA and 33.71±7.402ng/ ml in the control group [Table 2].

**Table 2:** Mean serum calcium and vitamin D levels in the study groups

Group	Number	Mean serum calcium (mg/dl)	Mean serum vitamin D (ng/ml)
Rheumatoid arthritis	50	8.61±0.485	20.49±6.044
Control	50	9.31±0.432	33.71±7.402

In this study, out of 50 patients of RA, 1 patient (2%) was in the remission group (DAS28 score <2.6), 3 patients (6%) in the low disease activity group (DAS28 score 2.7–3.2), 22 patients (44%) in the moderate disease activity group (DAS28 score 3.2–5.1), and 24 patients (48%) in the high disease activity group (DAS28 score >5.1).

The mean serum calcium levels were 8.9 mg/dl, 8.92±0.0243mg/dl, 8.68±0.458mg/dl, and 8.49±0.517mg/dl in the remission, low disease activity, moderate disease activity, and high disease activity groups, respectively [Table 3]. The mean serum Vitamin D levels were 34.36ng/ml, 32.25±0.395ng/ml, 22.70±4.787ng/ml, and 16.41±2.911ng/ml in the remission, low disease activity, moderate disease activity, and high disease activity groups, respectively [Table 3].

**Table 3:** Mean serum calcium and vitamin D levels in rheumatoid arthritis patients according to their disease activity

Disease severity group	Number of cases	Mean serum calcium (mg/dl)	Mean serum Vitamin D (ng/ml)
Remission	1	8.9	34.36
Low	3	8.92±0.0243	32.25±0.395
Moderate	22	8.68±0.458	22.70±4.787
High	24	8.49±0.517	16.41±2.911

## Discussion

Most of the RA patients have poor nutritional status which can predispose to low Vitamin D levels. Patients with RA are on multiple drug therapy including steroids which affect Vitamin D metabolism. These factors reinforce the significance of Vitamin D monitoring in RA patients.

Vitamin D deficiency and insufficiency are common among persons having inadequate sun exposure. Pakchotanon *et al.* [17] in a study upon Thai RA patients reported that cutaneous Vitamin D synthesis is markedly reduced during November through February in countries located above 37 degree latitude because of the decreasing number of UVB photons reaching the surface of earth. They reported that though Vitamin D deficiency and insufficiency was more in Thai RA patients as compared to controls, yet it was less than that found in RA cases from United States and European countries. According to them Latitude influences the zenith angle of sun and

Thailand was closer to equator than those countries. The mainland of India is between 8°4' and 37°6' latitude and that can affect cutaneous synthesis of vitamin D.

Cen *et al.* [18] in their study reported that the mean serum Vitamin D level was significantly lower in RA patients (35.99 ± 12.59 nmol/L) as compared to the normal participants (54.35 ± 8.20 nmol/L). Patients with RA in our study (92%) had higher rates of Vitamin D deficiency and insufficiency as compared with controls. However in control group 76% patients have Vitamin D levels in sufficient range and 24% had Vitamin D levels in insufficiency range.

Merlino *et al.* [11] also demonstrated an inverse association between greater intake of Vitamin D and RA risk. They analyzed data from a prospective cohort study of 29,368 women without a history of RA at study baseline, and through 11 years of follow-up, 152 cases of RA were diagnosed. Greater intake of Vitamin D was inversely associated with risk of RA. In our study we found that rheumatoid arthritis patients with moderate and high disease activity (92%) had low Vitamin D levels <30ng/ml, (48% patients had levels <20ng/ml) while RA patients with low disease activity had high Vitamin D levels.

Sabbagh *et al.* [19] also found inadequate Vitamin D status in patients with systemic autoimmune rheumatic diseases (SARDs), along with considerably strong association with disease activity in RA cases. This study indicated the need for proper evaluation of Vitamin D status in these patients to ensure the intake of the recommended amount of Vitamin D.

Studies conducted by Ibrahim *et al.* [20], Yagiz *et al.* [21] and Kareem *et al.* [22] found significantly lower Vitamin D levels in patients with RA, SLE, ankylosing spondylitis, and Behcet's disease as compared to control population thus supporting the possible role of Vitamin D in the pathogenesis, activity and treatment of various autoimmune diseases.

Most of the patients with RA in our study were females (82%). Pakchotanon *et al.* [17] also reported most of their RA cases were middle aged or elderly women and had Vitamin D levels less than 30 ng/ml. We had 92 % RA patients with Vitamin D less than 30ng/ml and most of them were females in age group of more than 40 years.

Kerr *et al.* [23] found that serum Vitamin D correlated with TJC only in patients with deficiency but not in those with 25(OH) D insufficiencies. Results observed in this study as regards the association of Vitamin D and VAS-pain comes in agreement with the concept of the association between hypovitaminosis D and musculoskeletal pain. Although TJC and VAS-pain were inversely associated with Vitamin D concentration in the univariate analysis, these associations failed to meet significance following multivariate adjustments whereas SJC and DAS28-CRP remained statistically significant following adjustments for age and sex, suggesting that the association of TJC and VAS-pain is explained primarily by the disease activity.

## Conclusion

Vitamin D insufficiency and deficiency are common in patients with RA. In our study Vitamin D deficiency was related to RA patients with older age, RA with female gender and a higher degree of RA activity. Vitamin D levels had no relation with functional disability or radiological damage in RA. In our opinion regular Vitamin D monitoring in RA cases is invaluable in determining current disease activity and may prove to be a key factor in ultimate disease outcome.

**Conflict of interest:** None

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