Original Article

Assessment of Vitamin D in Rheumatoid Arthritis and Its Correlation with Disease Activity

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Abstract

Background: Vitamin D is believed to have an immunomodulatory and anti-inflammatory action, and its deficiency has been linked with several autoimmune disorders, including rheumatoid arthritis (RA). The relationship between the severity of RA and serum levels of Vitamin D is a subject of immense interest and therapeutic implications. **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. Vitamin D levels in RA patients were also assessed in different stages of disease activity to assess the correlation between the two. **Results**: Eighty-four percent patients of RA were Vitamin D deficient versus only 34% of controls. The serum Vitamin D levels were also significantly lower in the RA patients (mean value of 21.05 ± 10.02 ng/ml), as compared to the controls (mean value of 32.87 ± 14.16 ng/ml). There was a significant inverse correlation between serum Vitamin D levels and RA disease activity. The mean serum Vitamin D levels were 35.28 ± 9.0 ng/ml, 33.80 ± 4.1 ng/ml, 22.47 ± 6.18 ng/ml, and 14.21 ± 6.97 ng/ml in the remission, low disease activity, moderate disease activity, and high disease activity groups, respectively. **Conclusions**: Vitamin D deficiency is more common in RA patients and may be one of the causes leading to development or worsening of the disease.

Keywords: Disease activity, rheumatoid arthritis, Vitamin D

Introduction

Vitamin D promotes absorption of calcium in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts.[1,2] In addition, Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by Vitamin D.[3,4]

The role of Vitamin D in modulating immune function is supported by the discovery of Vitamin D receptors (VDRs) in peripheral mononuclear blood cells.[5,6] Vitamin D causes downregulation 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.[7,8] Researchers have related Vitamin D deficiency with several autoimmune disorders, including insulin-dependent diabetes mellitus, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).[9-12] It has been suggested that Vitamin D is an extrinsic factor capable of affecting the prevalence of autoimmune diseases.[13]

The immunomodulatory activities of Vitamin D might be particularly efficient in RA patients and support a therapeutic role of Vitamin D in these patients.[14] The VDRs have been demonstrated in macrophages, chondrocytes, and synoviocytes in rheumatoid synovium and at sites of cartilage erosion in RA patients.[7,8,15] In RA patients, measurement of Vitamin D levels is particularly important as its deficiency is highly prevalent in this group.[16-18] 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

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to treat a variety of autoimmune rheumatic diseases, from RA to SLE, and possibly also multiple sclerosis, type 1 diabetes or inflammatory bowel diseases.[19] The relationship between the severity of RA and levels of Vitamin D is a subject of immense interest and therapeutic implications, hence the study was undertaken to compare the serum levels of Vitamin D in the healthy population and RA patients and to correlate Vitamin D levels with the RA disease activity.

Materials and Methods

This was a prospective comparative study conducted in the department of Medicine of a tertiary care teaching hospital of Punjab, India. 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. The data were collected by the first author as per the detailed questionnaire.

Inclusion criteria

Both males and females in the age group of 18–75 years having RA according to the American College of Rheumatology-European League Against Rheumatism 2010 criteria[20] were enrolled in this study.

Exclusion criteria

Patients with malnutrition, hepatic and renal dysfunction, hyperparathyroidism, hyperthyroidism, diabetes mellitus, and patients on Vitamin D supplementation in the past 6 months or on medications that can affect bone and Vitamin D metabolism (anticonvulsants, diuretics, and thyroxin) were excluded from this study.

All participants were interviewed regarding personal details, and detailed history was 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 was calculated as per 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. 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).

These results were incorporated into a mathematical formula to produce the overall disease activity score:[21]

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

(Here TJC = Tender joint count, SJC = Swollen joint count, Ln = log, VAS = Visual analog scale)

Disease severity was assessed according to the value of DAS28 score as follows

- Remission: DAS28 ≤2.6
- Low disease activity: 2.6 <DAS28 ≤3.2
- Moderate disease Activity: 3.2 <DAS28 ≤5.1
- High disease Activity: DAS28 >5.1.

The investigations carried out in all the participants participating in this study were ESR, RA factor, anti-citrullinated cyclic peptide antibody (wherever required), Vitamin D3 level, complete blood count, renal function tests, serum uric acid, liver function tests, urine examination, and electrocardiogram. X-rays of involved joints and X-ray chest were done if needed.

25(OH)-Vitamin D Xpress ELISA Kit was used for the quantitative measurement of Vitamin D3 {25 (OH)-D3} in serum. The estimation process was done in Biotek ELX-800 autoanalyzer. The assay utilized a competitive ELISA technique with a selected monoclonal antibody recognizing 25(OH)-Vitamin D. Normal serum Vitamin D levels were taken as 30–70 ng/ml or 75–175 nmol/L. Observed values of Vitamin D levels were recorded and analyzed in both the groups and correlated with the disease activity of RA. Statistical analysis was done to know the significance of this relationship. Statistical analysis was performed using GraphPad InStat software (version 3.05 for Windows, SanDiego, CA, USA). At 95% confidence interval, $P < 0.05$ was considered statistically significant.

Results

The mean age of patients in the RA group was 44.92 ± 13.06 years, whereas the mean age of participants in the control group was 44.02 ± 11.65 years. Among the 50 patients in the RA group, 7 (14%) were male and 43 (86%) were female. Among the 50 participants in the control group, 8 (16%) were male and 42 (84%) were female. The mean serum calcium levels were 8.54 ± 0.62 mg/dl in the RA group and 9.01 ± 0.59 mg/dl in the control group [Table 1]. This difference was statistically significant ($P < 0.05$). Forty-two patients (84%) belonging to the RA group had serum Vitamin D levels <30 ng/ml, that is, they were Vitamin D deficient, whereas only 17 participants (34%) belonging to the control group had Vitamin D deficiency. The mean serum Vitamin D levels were 21.05 ± 10.02 ng/ml in patients of RA and 32.87 ± 14.16 ng/ml in the control group [Table 1, Figure 1]. This difference was also statistically significant ($P < 0.05$).

In this study, out of 50 patients of RA, 6 patients (12%) were in the remission group (DAS28 score <2.6), 3 (6%) in the low disease activity group (DAS28 score 2.7–3.2), 19 (38%) in the moderate disease activity group (DAS28 score 3.3–5.1), and 22 patients (44%) in the high disease activity group (DAS28 score >5.1). The mean serum calcium levels were 8.96 ± 0.75 mg/dl,

8.83 ± 0.05 mg/dl, 8.76 ± 0.60 mg/dl, and 8.19 ± 0.47 mg/dl in the remission, low disease activity, moderate disease activity, and high disease activity groups, respectively [Table 2]. These differences were statistically significant ($P < 0.05$). The mean serum Vitamin D levels were 35.28 ± 9.0 ng/ml, 33.80 ± 4.1 ng/ml, 22.47 ± 6.18 ng/ml, and 14.21 ± 6.97 ng/ml in the remission, low disease activity, moderate disease activity, and high disease activity groups, respectively [Table 2, Figure 2]. These differences were also statistically significant ($P < 0.05$).

Discussion

RA is a chronic inflammatory disease of unknown etiology marked by asymmetric, peripheral polyarthritis. Etiology of RA is still unknown, and many environmental and genetic factors play a role in the development of this disease.

Various studies done so far suggest that Vitamin D deficiency increases the risk of developing autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, Type I diabetes mellitus, SLE, and RA. Vitamin D has immunoregulatory activity which is mediated through VDRs present on antigen presenting cells, activated T-lymphocytes, and activated B-lymphocytes. Vitamin D seems to interact with the immune system through its actions on the regulation and differentiation of cells such as lymphocytes, macrophages, and natural killer cells, besides interfering in the production of cytokines.

In this study, Vitamin D levels were measured in 50 patients with RA and compared with an equal number of age- and sex-matched controls. Vitamin D levels in RA patients were also assessed in different stages of disease activity to assess the correlation between the two. The mean age of patients in the RA group was 44.92 ± 13.06 years, and the majority (86%) were female, whereas the mean age of participants in the control group was 44.02 ± 11.65 years and 84% were females.

Table 1: Mean serum calcium and vitamin D levels in the study groups

Group	Number	Mean serum calcium (mg/dl)	Mean serum vitamin D (ng/ml)	*P*
Rheumatoid arthritis	50	8.54±0.62	21.05±10.02	<0.05
Controls	50	9.01±0.59	32.87±14.16	

Table 2: Mean serum calcium and vitamin D levels in rheumatoid arthritis patients according to their disease activity

Group (according to disease activity)	Number	Mean serum calcium (mg/dl)	Mean serum vitamin D (ng/ml)	*P*
Remission	6	8.96±0.75	35.28±9.0	<0.05
Low	3	8.83±0.05	33.80±4.1	
Moderate	19	8.76±0.60	22.47±6.18	
High	22	8.19±0.47	14.21±6.97	

Eighty-four percent patients of RA enrolled for this study were Vitamin D deficient, whereas only 34% of control participants had deficiency of Vitamin D. The serum Vitamin D levels were significantly lower in the RA group (mean value of 21.05 ± 10.02 ng/ml, as compared to the control group (mean value of 32.87 ± 14.16 ng/ml) [Table 1, Figure 1]. RA disease activity was assessed according to the value of DAS28 score. There was a significant inverse correlation between serum Vitamin D levels and RA disease activity. The mean serum Vitamin D levels were 35.28 ± 9.0 ng/ml, 33.80 ± 4.1 ng/ml, 22.47 ± 6.18 ng/ml, and 14.21 ± 6.97 ng/ml in the remission, low disease activity, moderate disease activity, and high disease activity groups, respectively [Table 2, Figure 2]. These differences were statistically significant ($P < 0.05$).

Similar findings were reported by Cen *et al*.[22] in their study, wherein 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).

Merlino *et al*. 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.[14]

Another study with 100 RA patients and 100 controls, not on Vitamin D supplements, noticed that patients with high disease activity had the lowest Vitamin D levels (18.25 ± 8.3 nmol/L) compared to 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 found in patients who were poorly responding to treatment, and were not in a state of disease remission.[23]

Sabbagh *et al*. 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.[24]

Studies conducted by Ibrahim *et al*.,[25] Yagiz *et al*.[26] and Kareem *et al*.[27] 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.

A recent Indian study found that 90% of RA patients were either Vitamin D deficient or insufficient. The mean serum Vitamin D level of RA patients was significantly low in comparison to healthy controls. Levels of Vitamin D in patients with high disease activity were significantly lower compared to those in patients with moderate- and low-disease activity and Vitamin D level had significant negative correlation with DAS28 score.[28]

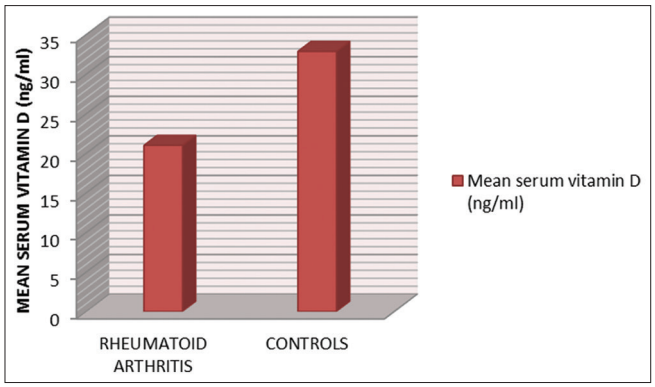

Figure 1: Mean serum Vitamin D levels in rheumatoid arthritis patients and controls

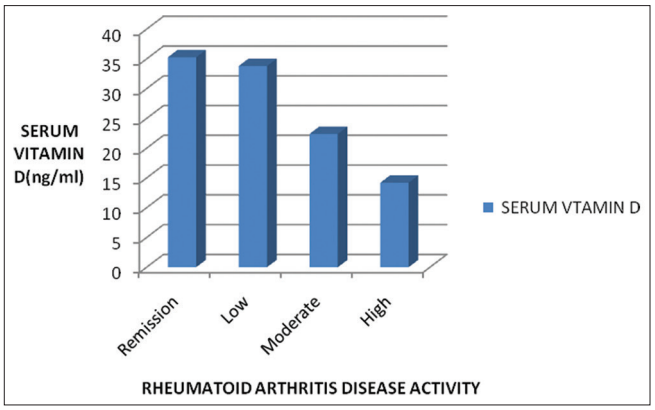

Figure 2: Mean serum Vitamin D levels in rheumatoid arthritis patients according to their disease activity

Studies by Yassin *et al*.[29] and Azzeh and Kensara[30] observed the same results in Egyptian and Saudi patients with RA and concluded that Vitamin D insufficiency is highly prevalent and linked to disease severity in patients with RA.

Recent meta-analysis of 1,143 RA patients and 963 controls showed that the prevalence of Vitamin D deficiency was significantly higher in the RA group than in the control group (55.2% vs. 33.2%; $P = 0.023$), and the mean serum Vitamin D level in the RA group was also significantly lower than that in the control group. This meta-analysis also showed a significant inverse correlation between the Vitamin D levels and DAS28.[31]

A recent review by Braqazzi *et al*., however, pointed out that the potential role of Vitamin D supplementation in preventing the manifestations of RA is unclear in view of studies showing contrasting findings with regards to the association between Vitamin D levels and RA. Therefore, further research is essential to confirm the relationship between RA susceptibility and Vitamin D deficiency and to ascertain whether Vitamin D plays a role in preventing the manifestation of RA.[32]

Strength of the study

This study highlights the high prevalence of hypovitaminosis D in RA and thus the possible immunomodulatory role of Vitamin D in the development of RA and other autoimmune diseases. This study also emphasizes the inverse relationship between Vitamin D levels and the severity of disease activity in RA.

Limitations of the study

This was a single-center study with a small sample size.

Conclusions

Vitamin D deficiency is more common in RA patients and may be one of the causes leading to development or worsening of RA. In RA, as the disease activity increases, the serum Vitamin D levels tend to decrease. There is a need for proper evaluation of Vitamin D status in all RA patients to ensure the intake of the recommended amount of Vitamin D. Further research is required so that the antiproliferative, immunomodulatory, and anti-inflammatory properties of Vitamin D could be exploited to treat a variety of autoimmune rheumatic diseases.

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Conflicts of interest

There are no conflicts of interest.

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