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

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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 ± 6.79 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

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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]:

\[
DAS28 = 0.56 \sqrt{(28TJC)} + 0.28 \sqrt{(28SJC)} + 0.70 \ln (ESR) + 0.014 VAS
\]

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 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

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

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

DAS, disease activity score.
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 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,
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.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**