

# Association of Disease Activity with Vitamin D in Early Rheumatoid Arthritis

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## ABSTRACT

**Objective:** Aim of the present study is to find out the level of vitamin D in patients of early rheumatoid arthritis and investigate association of vitamin D deficiency with the disease activity in rheumatoid arthritis.

**Methods:** A case control study comprising 90 case of early rheumatoid arthritis and 80 age and sex matched control carried out at tertiary care hospital in western province of Uttar Pradesh India between January 2017 and June 2021. Baseline data along with vitamin D level was recorded in both the group. Disease activity was recorded using clinical disease activity index (CDAI) in all patients of rheumatoid arthritis.

**Results:** Vitamin D deficiency was significantly higher in rheumatoid arthritis patients compared to healthy control from same geographic region (56.7% vs 32.5%, p value = 0.002%). Disease activity assessed by clinical disease severity index (CDAI) was inversely correlated with vitamin D level ( $r = -0.23$ , p-value 0.028) and. Joint pain was also inversely correlated with vitamin d level ( $r = -0.37$ , p value <0.0001). However, there was no significant association of vitamin D level with joint swelling, tenderness and erythrocyte sedimentation rate.

**Conclusions:** In our study vitamin D deficiency was more common in patients of rheumatoid arthritis. Disease activity and joint pain were inversely correlated with vitamin D level. However, there was no significant association of vitamin D level with joint swelling and tenderness.

Key words: vitamin D, rheumatoid, arthritis, CDAI , joint, tenderness

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to deformity and significant physical disability. It is the most common form of chronic inflammatory arthritis afflicting 1% of the adult population.<sup>1</sup> In addition to joint involvement, it induces systemic complications such as cardiovascular and cardiopulmonary dysfunction, and reduces life expectancy by about 3–10 years.<sup>2</sup> Early diagnosis and appropriate therapeutic intervention is crucial to prevent permanent joint destruction and disability. At present, "early" RA is regarded as patients with symptom duration < 3 months as early disease.<sup>3</sup> Although a precise etiology remains elusive, the current understanding is that RA is a multifactorial disease,

wherein complex interactions between host and environmental factors determine the overall risk of disease susceptibility, persistence and severity.<sup>4</sup> Pathophysiological process in Rheumatoid arthritis is marked by neutrophils, macrophages, T cells, B cells and dendritic cells infiltrating the synovium of joints and causing inflammation. Vitamin D is a steroid hormone with pleiotropic and tissue-specific effects due to wide expression of the nuclear vitamin D receptor in many different tissues and the many genes that are targeted by its actions.<sup>5</sup> Vitamin D not only plays a major role in the regulation of bone mineral homeostasis but also plays a role in cell function such as cell proliferation, differentiation, apoptosis, and angiogenesis.<sup>6</sup> Appropriate level of vitamin D has been reported to reduce the risk of some chronic inflammatory or autoimmune conditions such as various cancers, infectious diseases, type 1 diabetes, multiple sclerosis, and autoimmune rheumatic disease.<sup>7</sup> Many studies have focused on the role of low vitamin D level in the pathogenesis of rheumatoid arthritis and found an inverse relationship between serum levels of 25-hydroxyvitamin D and disease activity or functional impairment.<sup>8-10</sup> However, some studies have found no role of vitamin D level in development of rheumatoid arthritis.<sup>1</sup> There are very few studies about vitamin D in early rheumatoid arthritis. Therefore, this study was carried out to estimate the level of vitamin D in early rheumatoid arthritis and investigate the association of vitamin D level and the disease activity

## 2. Materials & Methods

The study was a case control study carried out at UP University of medical sciences located in rural area of western Uttar Pradesh India from January 2017 to June 2021. Institute ethical committee initiated study after approval. Total 1924 adult patients presenting to Orthopedic and Medicine OPD of the hospital with joint pain and swelling were screened for presence of definitive rheumatoid arthritis. Of these 427 patients were found to have definitive rheumatoid arthritis as per the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria. Of these, 90 patients having duration of symptoms less than 3 month were included in the study. Exclusion criteria were patients already on vitamin D supplementation or having disease known to affect serum vitamin D level. 80 age and sex matched apparently healthy individual were selected from the attendants of the patients for control group. Informed written consent were obtained from the all the subjects before inclusion in the study.

### Vitamin D

Vitamin D was measured in the form of 25-hydroxy-vitamin D (25(OH)-D) by chemiluminescent microparticle immunoassay using Abbott Architect i-1000 (Abbott Park, IL, USA). The lower limit of detection of the assay is 2.8 ng/ml and the upper limit of detection of the assay is 147.8ng/ml. Levels of 25-hydroxyvitamin D are stratified as follows: Deficiency (<20 ng/ml), Insufficiency (20–29 ng/ml) and Sufficiency ( $\geq 30$  ng/ml).<sup>11</sup>

### Measures of RA Disease Activity

In addition to 25(OH)-D levels, baseline evaluations included tender and swollen joint counts (0–28), patient self reported global assessment for disease activity (PDGA) on the scale of 0-10, Evaluator Disease Global Assessment(EDGA) on scale of 0-10, subcutaneous nodules (present vs. absent), prior use of glucocorticoids, self-reported comorbidity (including a history of renal disease, liver disease) and use of disease-modifying anti-rheumatic drugs (DMARDs), measurement of haemoglobin, erythrocyte sedimentation rate(ESR), C-reactive protein(CRP)( mg/L), rheumatoid factor (RF) positivity, kidney function test and liver function test. Disease activity was assessed by Clinical Disease Activity Index (CDAI) scoring using formula:  $CDAI = TJC + SJC + PDGA + EDGA$ , where TJC is the Tender Joint

Count, SJC is the Swollen Joint Count, PDGA is the Patient's Disease Global Assessment visual analogue score (VAS) 0–10 cm, and EDGA is the Evaluator/Assessor's Disease Global Assessment (VAS 0–10 cm). Disease severity was assessed according to the value of CDAI score as follows; Remission:  $\leq 2.8$ , Low disease activity: 2.9-10, Moderate disease Activity: 11.1-22, High disease Activity.<sup>12, 13</sup>

#### Statistical Analysis

Data was analyzed using IBM SPSS version 23. Mean values were calculated for all continuous variable, along with their standard deviations. Correlation between two variables was analysed using pearson correlation coefficient. ANOVA and student t test were used for comparison of means between the groups. Influence of vitamin D on disease severity were assessed using multivariate regression analysis. P value of less than 0.5 was considered for statistical significance.

### 3. Result

Clinical characteristics of study participants are presented in Table 1.

**Table 1: Base line characteristics of cases and control**

	RA (n=90)	Control(n=80)	P value
Age, years mean (SD)	39.8(11.6)	37.3(10.1)	0.13
Gender,% female	68.9	71.3	0.5
Smoking (%)	1.1	2.5	0.49
Diabetes	6.7	0	0.02
Hypertension	1.3	3.3	0.37
BMI(kg/m <sup>2</sup> )	19.8(5.5)	20.5(5.8)	0.46
Hemoglobin(gm/dl)	10.5(2.1)	13.2(1.4)	<0.001
ESR( mm/hr)	43.5(12.7)	7.9(3.9)	<0.001
Serum vitamin D level	29.3(10.3)	35.2(11.9)	0.001
Low Vitamin D (%)	56.7	32.5	0.002

RA, rheumatoid arthritis; BMI body mass index, ESR Erythrocyte Sedimentation Rate

Compared with the control group, the level of serum 25-OH-D in RA patients was significantly lower (19.46 $\pm$ 8.20 vs. 23.18 $\pm$ 6.71, p=0.001).

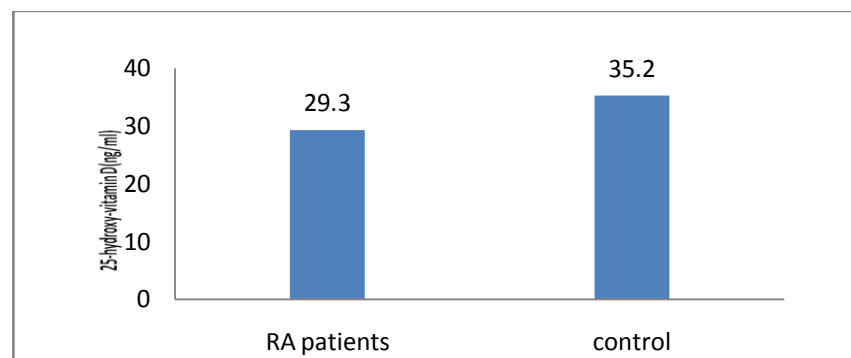
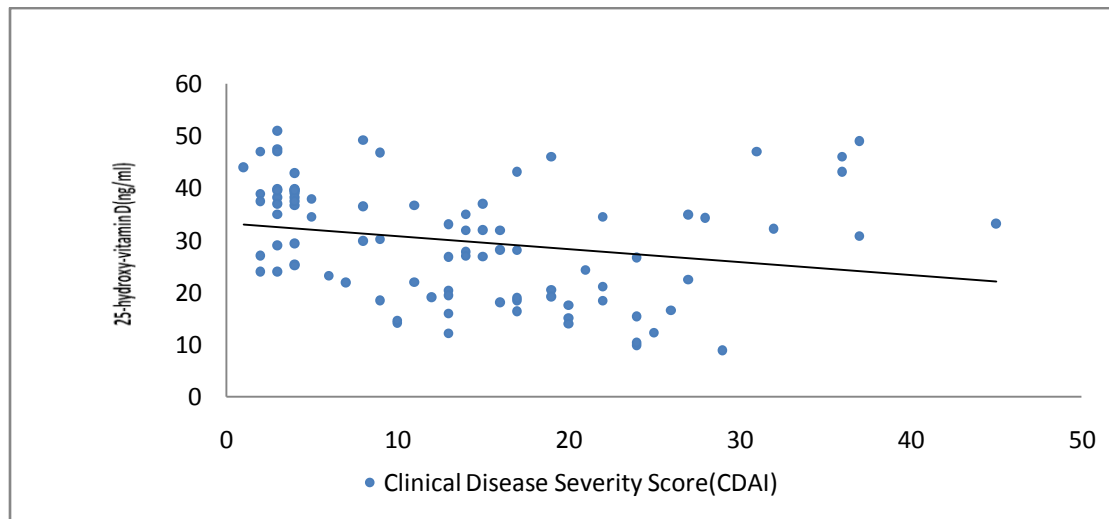


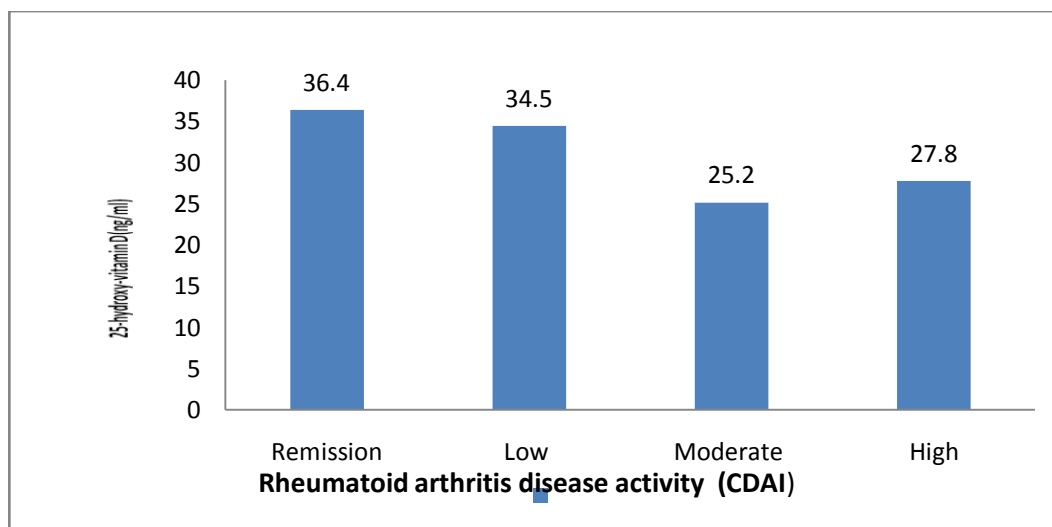
Figure1: Mean vitamin d level in RA patients and control (p value=0.001). RA, rheumatoid arthritis

Prevalence of vitamin D deficiency was 56.7 % in rheumatoid arthritis whereas 32.5% in control group. In 84% patients RF was positive whereas one patient was RF positive in control group. CRP was positive in all the patients of RA.



**Figure 2:** Correlation of clinical disease severity with vitamin D level in patients of rheumatoid arthritis ( $r = -0.23$ ,  $p\text{-value} = 0.028$ )

Clinical Disease severity index was inversely correlated with vitamin D level ( $r = -0.23$ ,  $p\text{-value} = 0.028$ )(Fig 1 &2). Patient's pain score was also inversely correlated with level of vitamin D( $r = -0.367$ ,  $p\text{-value} < 0.001$ ). Level of vitamin D was not related to joint swelling( $r = -0.105$ ,  $p\text{-value} = 0.325$ ), joint tenderness( $r = -0.117$ ,  $p\text{-value} = 0.271$  or ESR( $r = -0.116$ ,  $p\text{-value} = 0.278$ ). Vitamin D level was not significantly different in RF positive patient compared to RF negative patients. In multivariate regression analysis, vitamin D level was not found to be associated with CDAI.



**Figure 3:** Mean serum Vitamin D levels in rheumatoid arthritis patients in different disease activity assessed by (CDAI)

#### 4. Discussion

In our study 56.7 % of the patient were vitamin D deficient compared to healthy control from same region. This was in accordance with the study carried out by Meena et al where vitamin D deficiency was significantly higher in patient of rheumatoid arthritis (84% vs 34%).<sup>14</sup> In a study carried out by Yanan WANG et al, about 48.7% of RA patients had vitamin D deficiency.<sup>15</sup> In an another study carried out by Dehghan et al, the prevalence of vitamin D deficiency was reported to be about 51.9%.<sup>16</sup> Our observation was also similar to the study conducted by Craigel et where prevalence of vitamin D deficiency was 50% among African American patients of rheumatoid arthritis. However, it is difficult to compare vitamin D deficiency in different geographic area mainly because of difference in climatic condition like sun expose, dietary habbit. Mean vitamin D level was significantly lower in RA patients as compared to control (29.3ng/ml vs 35.2ng/ml, p value =0.001). This finding was in accordance with the study conducted by Cen et wherein the mean serum Vitamin D level was significantly lower in RA patients ( $35.99 \pm 12.59$  nmol/L) as compared to the normal participants ( $54.35 \pm 8.20$  nmol/L).<sup>17</sup>

In our study level of vitamin D was inversely correlated with joint pain score and CDAI. Our finding was similar to the study conducted by Patel et al in which vitamin D level was lower in 309 patients of rheumatoid arthritis experiencing more disease activity at the early stage and after one year of follow-up in.<sup>18</sup> Similar observation was reported by Craigel et a where pain score and severity of the disease was inversely associated with vitamin D level in univariate analysis.<sup>9</sup> Although they used DAS28 score for assessing disease activity whereas in present study we used CDAI score due its simplicity for easy bedside calcuculation. In study carried out by Abourazzak et al, vitamin D level was inversely associated with swelling and tenderness of the joints.<sup>6</sup> However, In our study vitamin D level was not significantly associated with the swelling and tenderness of the joint. This may be due to the small sample size of our study. In our study level of vitamin D were not significantly different in RF positive patient compared to RF negative patient.

Recent studies have focused on the immunologic role of Vitamin D which is independent of its classical role in calcium metabolism.<sup>19-22</sup> The pathogenesis of RA involves both innate and adaptive immune activities. Adaptive CD4+ T cells are critical in the pathogenesis of RA. For example, T cells are a source of RANKL, leading to osteoclast activation and subsequent joint destruction in RA.<sup>23</sup> The immunomodulatory effects of vitamin D on adaptive immunity are both indirect and direct.<sup>24</sup> Vitamin D is able to downregulate the expression of proinflammatory cytokines by monocytes, such as Interleukin 6 (IL-6) and Tumor Necrosis Factor  $\alpha$  (TNF $\alpha$ ), which are part of the inflammatory milieu allowing B and T cells activation and proliferation.<sup>25</sup> Obervation that T cells from the inflamed joints of RA patients are insensitive to 1,25-(OH)<sub>2</sub>D3 indicates that RA disease is associated with a corruption of vitamin D signalling that may be fundamentally important for RA disease pathology.<sup>26</sup> Therefore role of vitamin D in pathogenesis of rheumatoid arthritis appears to be more complex than we think.

Limitations of our study was small sample size. There are many confounders like dietary intake, level of sun exposure which may influence the level of vitamin were not taken into consideration

#### Conclusions

In our study disease, vitamin D level was significantly lower in early rheumatoid arthritis than the control from same geographic region. Disease severity assessed by clinical disease severity index was inversely associated with the level of vitamin D. joint pain was also inversely associated with vitamin D level.

However joint swelling and joint tenderness and ESR was not found to be associated with level of vitamin D.

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