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Correlation of Vitamin D3 Levels with Disease Activity in Rheumatoid Arthritis- an observational study

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Abstract
Introduction-Vitamin D is avidly involved in the process of innate and adaptive immune activation. A fall in vitamin D levels leads to the activation of tissue-damaging autoimmunity.Serum vitamin D levels are observed to be reduced in RA, however, to date there is still a paucity of literature on its correlation with markers of disease including ESR.
Aims and objectives- 50 newly diagnosed cases of RA were included to assess vitamin D3 levels. The levels were correlated with disease duration, markers of disease activity, disease severity, and level of hemoglobin in RA patients.
Results- The mean age of patients was 43.6 ± 15.9 years with a female to male ratio of 6.14:1. The mean vitamin D level was 18.01 ± 6.08, indicating an overall deficient vitamin D status. While 74% were vitamin D deficient, 22% had insufficient vitamin D levels, and 4% had adequate vitamin D levels. There was a significant correlation between serum vitamin D level with disease activity, disease duration, ESR level,hemoglobin level, and VAS scores (p-values< 0.00001,<0.001,<0.001, 0.04, and 0.04, respectively).
Conclusion- In conclusion, there is a high prevalence of vitamin D deficiency in RA patients. The levels are very strongly related to every aspect of disease severity. Vitamin D supplementation must be done in every case of connective tissue disorder.
Key words: *vitamin D3, Rheumatoid arthritis, ESR, DAS 28 ESR*

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I. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory connective tissue disorder, that primarily affects the synovial joint lining.[1] Being an autoimmune disorder, RA has a multisystem involvement. Globally the estimated prevalence of the disease is between 0.5% to 1%.[2] RA has complex pathogenesis, with activation of T cells, B cells, osteoclasts, chondrocytes, fibroblasts, dendritic cells, and proteolytic enzymes. The activation of these inflammatory mediators leads to the damage of synovium, bone, cartilage, and tendons. Additionally, these autoimmune mechanisms also lead to several extra-articular and systemic manifestations.[3,4]

The immune cells activated in RA express receptors for vitamin D. Vitamin D is avidly involved in the process of innate and adaptive immune activation. Vitamin D is responsible forupregulating the immune system.A fall in vitamin D levels leads to the activation of tissue-damaging autoimmunity.[3]

A handful of autoimmune diseases are attributed to vitamin D dysregulation, namely, inflammatory bowel disease, insulin-dependent diabetes mellitus, systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis.[5]There is still a paucity of data on the impact of rheumatoid arthritis severity on the levels of serum vitamin D in the Indian literature. Keeping this in mind, we conducted this study with the primary objective to assess the correlation of serum vitamin D levels with the severity of RA. Secondary objectives were In this study, we will determine the link between vitamin D levels and RA in the local population.The secondary objective was the quantification of vitamin D3 deficiency, and correlating it with the extent of disease activity in RA.

II. Materials And Methods

This cross-sectional study was conducted at our tertiary care hospitalover 12 months between July 2020 to June 2021,after obtaining due approval from the institutional ethics board. The study population included patients over the age of 16 years newly diagnosed with Rheumatoid Arthritis according to the 2010 ACR-EULAR criteria.[5]

Cases of Rheumatoid arthritis who were already on treatment with any disease-modifying anti-rheumatic drugs(DMARDS) orsteroids were excluded. Additionally, patients who failed to give consent were also excluded.

A total of 50 randomly chosen patients of RA were recruited for the study. The clinic-epidemiological data of cases were recorded in a pre-structured proforma. All the cases underwent detailed clinical examination with regards to the pattern of joint involvement, types, and the number of joints, the severity of RA, duration of symptoms, and the presence of any extra-articular manifestations.The mode of onset of RA, preceding history of infectionbefore the onset of disease, history, family history, and personal history were also noted. A subjective assessment of pain was done using the visual analog scale (VAS) between 0 to 10, with 0 being no pain and 10 being the worst pain possible.

ACR-EULAR criteria[5]

This criteria rates the RA disease severity of patients on a scale of 0-10 points. The points are assigned for separate domains of signs and symptoms, joint involvement, duration of symptoms, serology, and acute phase reactants. Any patients who scored 6 or more points on the scale were considered to have definite RA.

A detailed systemic examination was also done in all cases.A locomotor system examination was conducted to ascertain the pattern of joint involvement and signs of inflammation.

Cases were subjected to routine investigations including hemogram, renal and liver profile, and erythrocyte sedimentation rate (ESR) level.

Disease Activity Score 28 ESR severity score

Disease Activity Score 28 (DAS 28) ESR severity score was deduced and disease activity was calculated. In our study the DAS score of participants was divided into the following categories, remission (<2.6), low (<3.2), moderate (3.2-5.1), and high (>5.2).

Serum Vitamin D level

The serum 25(OH) vitamin D level assessment of the blood sample was done by electro-chemiluminescent assay technique using vitamin D kits.

If any patient was found to have serum vitamin D deficiency, the levels were categorized into normal (>30 ng/dl), insufficient (20-30 ng/dl), and deficient (<20 ng/dl). Cases with vitamin D levels < 30 ng/ml were classified as having hypovitaminosis D.[6]

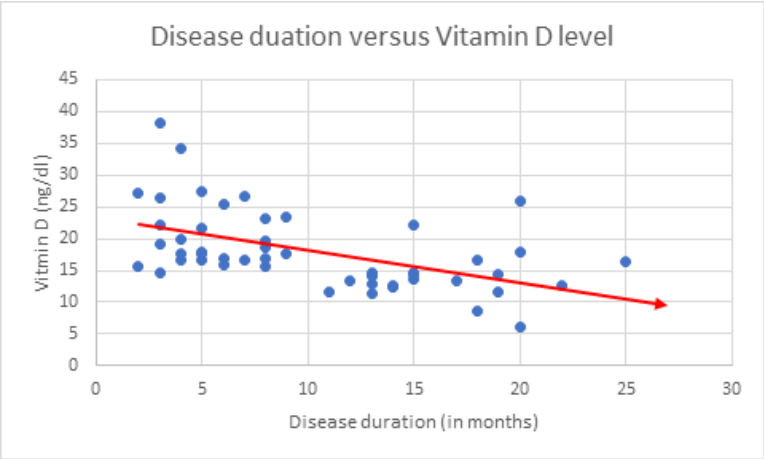
Serum rheumatoid factor positivity was also assessed in all the patients. Anti-CCP (cyclic citrullinated peptide) antibody levels were measured in clinical ambiguous cases.

The serum Vitamin D levels were correlated with the level of ESR, disease severity, hemoglobin level, and subjective pain level (VAS scale).

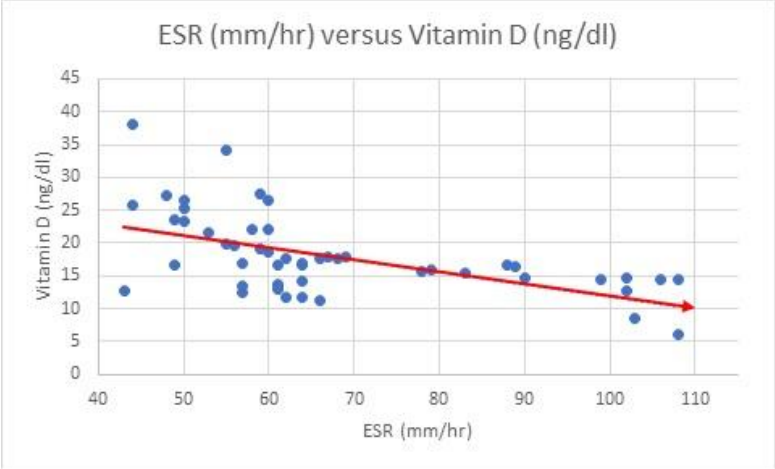
III. Results

In this study, 50 patients between the ages of 16 to 73 years were included. The mean age of patients was 43.6 ± 15.9 years. There was a bimodal peak of age distribution in our study with 11 (22%) patients between the age group of 20-29 years and 11 (22%) between 40-49 years of age. There was a significantly higher proportion of females (86%)than males (14%). The female to male ratio of our subjects was 6.14:1.

The duration of symptoms varied between 3 months to 30 months. The mean duration of symptoms was 9.16 ± 1.02 months. As far as joint involvement was concerned 21 (42%) patients had a monoarticular presentation, and 29(58%) had oligoarticular involvement. Rheumatoid factor was positive in 33 (66%) cases and negative in 17 (34%) cases. These 17 cases were further subjected to Anti-CCP ab was done only in patients who were negative for rheumatoid factor. Anti-CCP antibody was found to be positive in 16 patients.



While analyzing ESR levels, 28 (56%) cases had ESR levels between 60-100mm/hr indicating an inflammatory state, 9 (18%) patients had even higher levels with ESR >100mm/hr, whilethe remaining 13 (26%) cases had ESR below 60 mm/hr.



The mean DAS 28 ESR of study participants was 5.09 ± 0.34.None of the cases were under remission or had a low DAS 28 ESR score. While 46 (92%) patients scored between 3.2 and 5.1, the remaining 4 (8%) scored higher than 5.2.

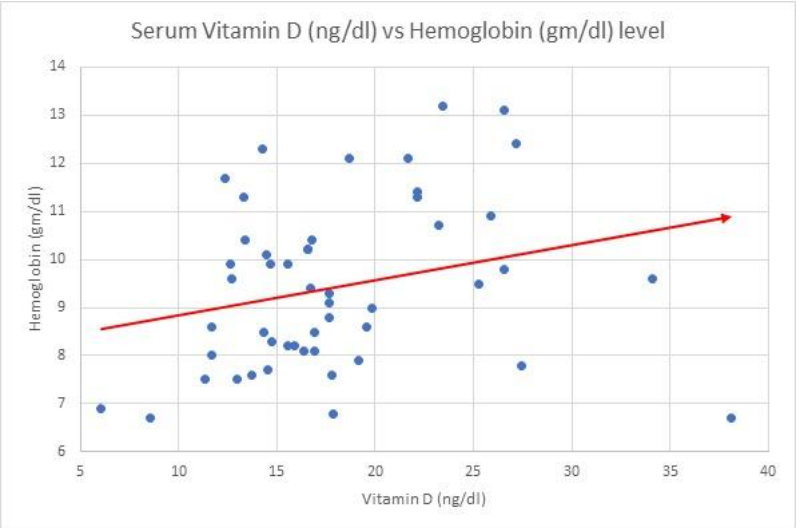
We found that a majority of RA patients were either vitamin D deficient or had insufficient serum vitamin D levels.

The mean vitamin D level of our study participants was 18.01 ± 6.08, indicating an overall deficient vitamin D status in our subjects.Out of 50 cases, 37 (74%) cases were vitamin D deficient having levels <20 ng/dl, 11 (22%) had insufficient vitamin D levels (between 20-30 ng/dl), while the remaining 2 (4%) had an adequate level of vitamin D (>30 ng/dl) (table 1).

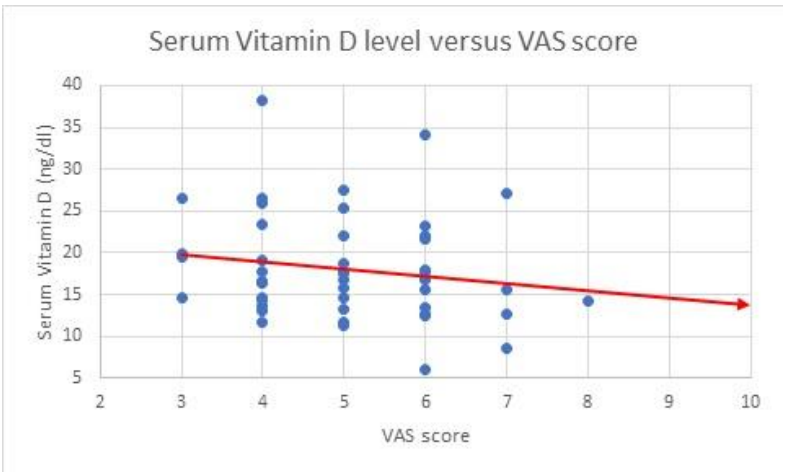
According to the DAS 28 ESR score, 46 (92%), had moderate disease activity, while the remaining 4 (8%) had high disease activity. While comparing the disease activity with serum vitamin D levels 33 (66%) cases with moderate disease activity had serum vitamin D levels lower than 20 ng/dl. While all 4 patients with high disease activity had serum vitamin D levels less than 20ng.dl. There was a significant association between low vitamin D levels and high disease activity (p-value was < 0.00001) (table 2).

There was also a negative correlation between disease duration and serum vitamin D level (r= -0.51, p-value<0.001) (figure 1). There was also a significant negative correlation between rising ESR levels and falling serum vitamin D levels (r= -0.56, p-value<0.001) (figure 2).

In our study, the hemoglobin levels of study participants ranged from 6.7 gm/dl to 13.2 g/dl. The mean hemoglobin level was 9.43 ± 1.72 g/dl. While correlating the hemoglobin levels of patients with serum vitamin D levels we found a significant positive correlation. The value of correlation coefficient (r) was 0.29 (p value= 0.04). The relationship between the variables was strong (figure 3).



While correlating the VAS score of patients with serum vitamin D levels we found a significant negative correlation. The value of correlation coefficient R= -0.28 (p value=0.04)indicates that cases with low vitamin D levels scored poorer on VAS (figure 4).



IV. Discussion

RA is an autoimmune chronic inflammatory disease with an unknownetiology. The disease is characterized by marked asymmetric and peripheral polyarthritis. The disease has a multifactorial role ingenetic and environmental factors. Of late, various authors have identified the role of vitamin D deficiency in the pathogenesis of RA, among other connective tissue and autoimmune disorder. Vitamin D possesses an immunoregulatory activity that is mediated via its vitamin D receptors (VDRs). These VDRs are present on activated T cells, B cells, and other antigen-presenting cells.[9]Vitamin D has a complex interplay with the immune system, by regularizing the differentiation of lymphocytes, natural killer cells, and macrophages, and controlling the secretion of inflammatory cytokines.[10,11]

In this study, we measured the vitamin D levels in 50 treatment-naïve cases of RA. We also compared the levels of vitamin D between cases having different stages of disease activity. The mean age of patients was 43.6 ± 15.9 years. We found a bimodal peak of age distribution, with the first peak between 20-29 years and the second peak of incidence between 40-49 years of age. The concept of the bimodal peak has been widely observed in adult-onset juvenile RA. However, cases in our study had only adult-onset RA.[12]

The female to male ratio was 6.14:1 with 86% females. Similar results have also been reported by Meena et al. RA is seen twice or thrice more frequently in women.[13] This is due to a strong link between disease activity and high estrogen levels. This suggests the role of genes located on sex chromosomes along with a strong Th1 response.[14]

In this study, we observed that maximum cases of RA had deficient or insufficient vitamin D levels. The mean vitamin D level was 18.01 ± 6.08ng/dl. While 74% of cases were vitamin D deficient having levels <20 ng/dl, 22% had insufficient vitamin D levels (between 20-30 ng/dl). In fact, only 4% had adequate vitamin

D levels. Statistically, there was a highly significant association between low vitamin D levels and high disease activity (p-value was < 0.00001).Similar results have also been reported by Meena et al.[13] and Cen et al.[15]Merlino et al.[16] also found an inverse correlation between higher intake of vitamin D and the risk of RA. Another similar case-control study noted that patients RA patients without vitamin D supplementation had high disease activity than those who were on vitamin D supplements.[17]Another study by Sabbagh et al. also found patients with highly active systemic autoimmune rheumatic diseases(SARDs) had significantly lower vitamin D levels.[18]These studies indicate that there is a dire need for baseline evaluation of serum vitamin D levels in all newly diagnosed cases of RA.

Similar results have also been noted while assessing the levels of serum vitamin D3 in patients with other connective tissue and autoimmune disorders. Kareem et al.[19], Ibrahim et al.[20], and Yagiz et al.[21]observed that apart from RA, patients with Systemic Lupus Erythematosus,Behcet'sdisease, and Ankylosing spondylitis also had significantly lower levels of serum vitamin D3 that the control population. All these reports further reinforce the theory that vitamin D is avidly linked with the pathogenesis of autoimmune disorders. In their study, Sharma et al.also found a significant correlation between low serum vitaminlevelsvel and high disease activity in RA patients.[22]

In our study we also found a highly significant correlation between high ESR levels and low serum vitamin D levels (p-value<0.001). ESR is perhaps the oldest acute phase reactant. High ESR is attributed to high viscosity and its interplay with the red cells. In inflammatory disorders, the albumin/globulin ratio is disturbed, responsible for raised plasma viscosity. Plasma viscosity, or more precisely the albumin/globulin ratio, is altered in an acute phase reaction and is probably the most significant factor affecting ESR. ESR is a universally accepted marker of disease activity in RA, along with CRP.

Kostoglou-Athanassiouet al.also found a negative correlation between vitamin D3 and ESR levels with a correlation coefficient of -0.11.[23] We found an even stronger correlation between the two variables (r= -0.56). The fact that serum vitamin D levels were so closely correlated with the levels of ESR, suggests that vitamin D levels could also be used as an adjuvant or perhaps even a substitute for assessing the disease activity in RA patients. However, there is still a paucity of literature analyzing the close correlation between the two variables.

This study also found a significantly negative correlation between disease duration and vitamin D levels (r= -0.51, p-value<0.001).Another noteworthy finding of our study wasa significantly negative correlation between the VAS score of patients and serum vitamin D levels (r= -0.28; p value=0.04). We also found a significantly positive correlation between hemoglobin level and serum vitamin D level (r=0.29; p value= 0.04). Since rheumatoid arthritis is characterized by anemia of chronic disease, low hemoglobin levels are expected to be seen in severe uncontrolled RA. The fact that hemoglobin level was significantly associated with vitamin D level further reinforces the fact that vitamin D is a key marker of disease activity in RA.

Our study is perhaps one of its kind exploring the association of vitamin D levels with multiple markers of disease activity including disease duration, ESR, disease severity (DAS 28 ESR), hemoglobin level, and VAS scores. Although our study was limited by the small sample size, absence of a control group, and lack of follow-up post-treatment, the findings of this study strongly favor the utilization of serum vitamin D3 levels as both a diagnostic and prognostic marker for RA.

V. Conclusion

In conclusion, there is a high prevalence of vitamin D deficiency in RA patients. The levels are very strongly related to every aspect of disease severity. Vitamin D supplementation must be done in every case of connective tissue disorder. Since vitamin D deficiency is strongly linked to diffuse musculoskeletal pain, administration of vitamin D early in the course of the disease could aid in preventing osteoporosis and help in pain relief in RA patients.

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TABLE 1: DISTRIBUTION OF PATIENTS ACCORDING TO SERUM VITAMIN D LEVELS

Vitamin D (ng/dl)	Disease activity	Number of patients	Percentage
<20	Deficient	37	74%
20-30	Insufficient	11	22%
>30	Normal	2	4%
Total		50	100%

TABLE 2: CORRELATION OF SERUM VITAMIN D LEVEL WITH DISEASE ACTIVITY

Disease Activity	Serum Vitamin D (ng/dl) level		
	<20	20-30	>30
Moderate	33	1	2
High	4	0	0

Figure legends
Figure 1- Correlation between disease duration and vitamin D3 level
Figure 2- Correlation between ESR and vitamin D3 level
Figure 3- Correlation between disease duration and vitamin D3 level
Figure 4- Correlation between hemoglobin level and vitamin D3 level

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