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ORIGINAL ARTICLE

Role of vitamin D supplementation in improving disease activity in rheumatoid arthritis: An exploratory study

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Abstract

Aim: The aim of this exploratory study is to estimate the relationship between vitamin D (vit D) deficiency and active rheumatoid arthritis (RA), and the role of supplementation in improving disease activity.

Method: A randomized recruitment, consent screening, open-label interventional study was conducted in patients who fulfilled American College of Rheumatology/European League Against Rheumatism 2010 criteria for diagnosing RA and on stable disease-modifying anti-rheumatic drugs (DMARDs) for 3 months. Serum vit D levels and Disease Activity Score of 28 joints/C-reactive protein (DAS28-CRP) disease activity status were estimated at the first visit. Subjects with low vit D levels and DAS28-CRP > 2.6 were supplemented with vit D for 12 weeks, and were assessed for improvement in disease activity and serum vit D levels.

Results: One hundred and fifty RA patients of mean age 49 ± 12.1 years, mean duration of illness 78 ± 63 months, and on treatment with DMARDs for 44 ± 39 months were recruited for the study. Of these, 73 (49%) subjects were found to have DAS28-CRP > 2.6 and serum vit D below 20 ng/mL. The patients received vit D supplement of 60 000 IU/week for 6 weeks, followed by 60 000 IU/month for a total duration of 3 months. Disease activity and vit D status were assessed for 59 (80.8%) patients who reported at the end of 12 weeks of treatment. Mean DAS28-CRP of these patients showed a statistically significant improvement from 3.68 ± 0.93 at baseline to 3.08 ± 1.11 after supplementation ($P = 0.002$). Serum vit D levels improved from 10.05 ± 5.18 to 57.21 ± 24.77 ng/mL ($P < 0.001$) during the period.

Conclusion: Supplementation of vit D in RA patients with persisting disease activity and vit D deficiency contributed to significant improvement in disease activity within a short duration.

Key words: DAS28, rheumatoid arthritis, vit D, vitamin D.

INTRODUCTION

Rheumatoid arthritis (RA), a chronic, inflammatory multisystem autoimmune disease characterized by persistent synovitis, affects 0.8–1.0% of the global population and is predominant among women.[1] RA leads to severe deformities in patients who failed to achieve low disease activity or clinical remission. Vitamin D (vit D), a fat-soluble vitamin mainly synthesized in the skin during sunlight exposure, facilitates intestinal absorption, and calcium and phosphorus metabolism. It has been demonstrated to play a major role in the immune system functioning, apart from musculoskeletal health and calcium homeostasis. Moreover, vit D is attributed to confer anti-inflammatory and immune-modulating properties. Hence, its deficiency is associated with increased inflammation.[2] Vit D deficiency has been reported from different parts of the world, particularly in southern countries, where more than 90% of the affected are elderly people.[3–7] Vit D deficiency is also frequent in the younger population.

Vit D deficiency prevails in epidemic proportions all over the Indian subcontinent, with prevalence in a

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majority of the general population. Subclinical vit D deficiency is highly prevalent in both urban and rural settings, and across all socio-economic and geographic strata. In India, vit D deficiency is likely to play an important role in the increased prevalence noted for certain diseases, such as rickets, osteoporosis, cardiovascular diseases, diabetes, cancer and tuberculosis.[8] Many Indian studies have reported low 25(OH)-vit D (25-hydroxyvitamin D) levels in the general population, in spite of abundant sunshine and exposure.[9] About 40% of apparently healthy children from North India who belong to the age group 3 months–12 years and upper socioeconomic status are found to be vit D deficient.[10] The prevalence of hypovitaminosis D (< 20 ng/mL) among young adults is around 70% with a slightly higher preponderance in women (76%).[11]

Vit D deficiency has been linked to the occurrence of autoimmune disorders, including RA. A study published in 2010 found that women living in the northeastern US were more likely to develop the disease because of the development of vit D deficiency due to reduced sunlight exposure.[12] A similar association with vit D deficiency from decreased solar exposure in northern latitudes has also been observed for multiple sclerosis, Crohn's disease and other autoimmune diseases. Vit D receptor found on several immune cells and in *in vitro* studies, indicate that vit D metabolites modulate T-cell proliferation and dendritic cell functions.[13,14] Epidemiological data also imply that vit D deficiency may be a risk factor for the development of autoimmune and other chronic diseases.[5,15] Studies on RA have demonstrated that low levels of vit D are very common.[16–19] A recent study from the US has indicated that 42 of 145 post-menopausal women with RA had vit D deficiency and the highest prevalence is among African-Americans.[20,21] Reports also suggest an inverse relation between serum vit D and disease activity or disability in patients with RA.[18,21–23]

Controversies do exist regarding the optimum level of serum 25(OH)D in a healthy population. Most experts agree that serum vit D levels < 20 ng/mL represent deficiency. However, some experts recommend a higher minimum target level of 30 ng/mL of 25(OH)D in a healthy population.[24] With this background, we hypothesized that vit D deficiency could be one of the causes for persisting disease activity in RA patients, and selective replacement of vit D should help improve the disease activity. Therefore, an exploratory study was conducted to assess the influence of vit D on the disease activity of RA in randomly selected patients. Some of the vit D-deficient patients were also supplemented with recommended amounts of vit D, in order to assess the improvement in disease activity, if any.

METHODS

The randomized recruitment, consent screening, open-label interventional study was approved by our institutional ethics committee. Patients, previously diagnosed with RA in our medical centre and on regular follow-up, were randomly selected for screening. Patients who fulfilled the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2010 criteria for diagnosis of RA and not having any other overlapping connective tissue disorders were recruited randomly based on their visit number to the outpatient clinic. The patients being treated with maximum permissible disease-modifying anti-rheumatic drugs (DMARDs) in combinations were recruited, and so also the patients in whom there was no possibility or need for increasing DMARDs. The change was not possible because the patient either had attained lower disease activity or had been prescribed the maximum tolerable dose of triple or double drug combinations. Methotrexate was prescribed up to 25 g/week orally, and/or leflunomide 20 mg and/or hydroxychlororquine 200 mg once daily. Patients who were on regular vit D and calcium supplementation, those who refused consent, who were not regularly on DMARDs and follow-up, and whose disease assessment was not possible, were excluded from the study after screening. The patient's clinical data including duration of illness, severity of pain, tender joint counts (TJC) and swollen joint counts (SJC), serum vit D levels, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were recorded. An independent joint assessor performed joint examinations and pain assessment. Visual analogue scale (VAS) for pain was assessed by the patients. All the patients except those in group 1 were put back into regular care. Serum vit D levels were estimated by chemiluminescence immunoassay platform (Roche Cobas e411, Minato-ku, Tokyo, Japan). ESR was determined by Westergren's method and CRP by the nephelometric method. Disease activity scores were calculated based on the three variables using the standard formula.[25]

Figure 1 shows the randomization of patients and the design of the study. Following clinical evaluation, patients were divided into four groups, depending on Disease Activity Score of 28 joints/CRP (DAS28-CRP) > 2.6 (high) or < 2.6 (low), and vit D < 20 (low vit D) or > 21 ng/mL (normal vit D): group 1: high disease

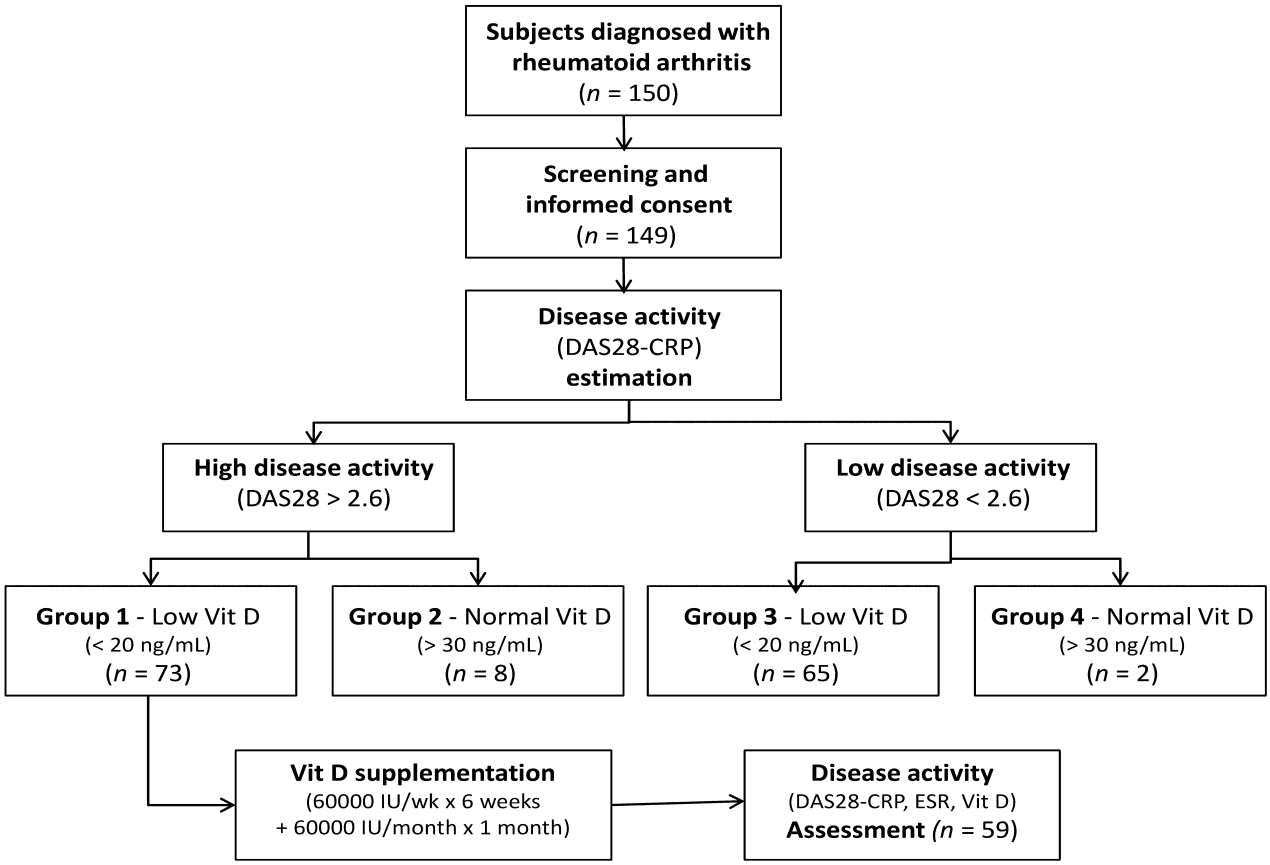

Figure 1 Randomization of subjects and study design.

activity with low vit D; group 2: high disease activity with normal vit D; group 3: low disease activity with low vit D; and group 4: low disease activity with normal vit D. The patients in group 1 fulfilled the criteria of having active disease, that is, DAS28-CRP score above 2.6 were recruited into open-label vit D supplementation at 60 000 IU once weekly for 6 weeks, followed by once monthly for a total duration of 3 months. These patients were reassessed for disease activity, including ESR, CRP and vit D levels at the end of 3 months of treatment.

Statistical analysis

Student's *t*-test was performed using VassarStats, an online statistical computation website (vassarstats.net). Correlation statistics were performed between vit D levels and other disease variables.

RESULTS

Out of the 150 RA patients screened, 149 were selected for study. One of the patients was excluded from the study due to the development of interstitial lung disease (ILD) during the course of study. The demographic data and baseline disease activity parameters of the patients are as follows: male/female 9 (6%)/140 (94%), mean ± SD age 49 ± 12.1 years, duration of illness 78 ± 63 months, duration of treatment with DMARDs 44 ± 39 months, TJC-66 joints 6.65 ± 10.2, TJC-28 joints 4.07 ± 6.13, SJC-64 joints 2.28 ± 3.84, SJC-28 joints 1.10 ± 2.13, CRP 7.68 ± 11.99 mg/L, ESR 30.80 ± 20.18 mm/h, DAS28-ESR 3.69 ± 1.18, DAS28-CRP 2.91 ± 1.14, and serum vit D of 27.49 ± 16.5 ng/mL. There were associated co-morbidities such as diabetes in 23, hypertension in 23, hypothyroidism in 13, asthma in three, and benign prostatic hyperplasia (BPH) in one patient. These 149 patients were divided into four groups depending on their disease activity (DAS28-CRP) and serum vit D levels, as shown in Fig. 1. Group 1 had 73 patients, group 2 had eight, group 3 had 65, and group 4 had two patients, respectively. Since number

of patients was not adequate in groups 2 and 4, they were excluded from further analysis.

Demographic and disease activity parameters of groups 1 and 3 are compared in Table 1. There was a significantly lower level of vit D in the patients with persisting active disease compared to patients with low disease activity (LDA) or remission (group 3). The patients with vit D deficiency had prolonged duration of disease. However, there was no correlation between duration of illness and the vit D levels. Out of the 73 patients in group 1 who were supplemented with vit D, only 59 patients completed the study. The remaining 14 patients did not report for reassessment within the window period, and hence, were considered as drop-outs from the study.

Demographic and other laboratory parameters were measured at baseline (visit 1) and at the end of study (visit 2) for the 59 patients who completed study (Table 2). Statistically significant improvement in disease activity parameters, such as TJC, SJC, VAS (pain), DAS28-ESR, and DAS28-CRP has been observed after vit D supplementation. As per EULAR response criteria, the 59 patients who completed the follow-up after vit D supplementation were grouped as 'good responders' and 'no responders' based on their baseline disease activity and the change in DAS28 score (Table 3). Among the 26 out of 59 patients who had responded (44%), 23 demonstrated moderate disease activity (DAS28 score < 3.2). Only three out of 22 patients with disease activity > 3.5 responded. More than 50% of patients (19/33 patients) who were grouped as 'failure to improve' demonstrated higher disease activity.

DISCUSSION

The present study suggests significant deficiency of vit D in patients with persisting active disease. Vit D supplementation caused improvement in the disease activity in more than 50% of the patients. Ninety percent of the present study population (139/149) had vit D levels lower than the cut-off value of 20 IU/dL. This observation follows the trend of previous published data for normal populations, where it has been reported to be from 70–100%.[26] In the present study, 69 out of 149 (46%) subjects were having LDA or remission, which is in line with the previously reported data for the population studied from our institution.[27]

In order to evaluate patients with normal levels of vit D and low or high activity, it would require screening of more patients; however, an estimated 73 patients were recruited for the intervention group. Since the primary objective was to evaluate the influence of its supplementation on disease activity and overall outcome, only two groups with sufficient numbers of subjects

Table 1 Demographics, disease activity and related parameters of vitamin D-deficient groups

Parameter	Group 1 (high DAS, low vit D)	Group 3 (low DAS, low vit D)	*P*-value‡
Number of subjects (*n*)	73	65	
Gender (M/F)	8/65	11/54	0.310
Age (years)	47.2 ± 12.2†	50.0 ± 11.5	0.169
Duration of illness (m)	92.3 ± 68.8	59.2 ± 47.8	0.001
Duration of treatment (m)	49.5 ± 42.4	39.8 ± 35.0	0.144
CRP	9.49 ± 13.3	4.31 ± 4.47	0.002
ESR	34.3 ± 22.3	25.1 ± 16.1	0.006
DAS ESR	4.38 ± 0.99	2.77 ± 0.60	< 0.01
DAS CRP	3.63 ± 0.94	1.97 ± 0.37	< 0.01
VAS score	3.73 ± 2.06	1.54 ± 1.93	< 0.001
TJC-66	10.4 ± 11.0	1.03 ± 1.69	< 0.01
TJC-28	6.67 ± 6.80	0.50 ± 0.75	< 0.01
SJC-64	3.57 ± 4.34	0.55 ± 2.00	< 0.01
SJC-28	1.94 ± 2.68	0.07 ± 0.32	< 0.01
RF	157.4 ± 188.6	205.9 ± 241.3	0.196
Vit D (ng/mL)	10.5 ± 5.91	13.0 ± 6.35	0.015

†All values are mean ± SD. ‡$P(T \leq t)$, two-tailed *t*-test. CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; vit, vitamin; VAS, visual analogue scale for pain.

Table 2 Disease activity and related parameters of group 1 (high DAS, low vitamin D) subjects

Parameter	Visit 1	Visit 2	*P*-value‡
Number of subjects (*n*)	59	59	
CRP	9.02 ± 13.31†	11.64 ± 16.20	0.339
ESR	31.77 ± 15.81	37.12 ± 20.74	0.118
DAS ESR	4.43 ± 0.97	3.91 ± 1.13	0.009
DAS CRP	3.68 ± 0.93	3.08 ± 1.11	0.002
VAS scale	3.77 ± 2.06	2.79 ± 2.23	0.015
TJC-66	11.0 ± 11.6	6.18 ± 9.46	0.015
TJC-28	7.61 ± 8.50	4.20 ± 5.94	0.013
SJC-64	3.79 ± 4.63	1.84 ± 3.75	0.013
SJC-28	1.94 ± 2.75	0.98 ± 2.45	0.047
Hemoglobin	12.11 ± 1.35	12.21 ± 1.47	0.726
Vitamin D (ng/mL)	10.05 ± 5.18	57.21 ± 24.77	< 0.000

†All values are mean ± SD. ‡$P(T \leq t)$, two-tailed *t*-test. CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale for pain.

Table 3 Classification of group 1 (high DAS, low vitamin D) subjects after vitamin D supplementation based on EULAR response with DAS28-CRP

Baseline DAS28-CRP	EULAR criteria		
	Good (≥ 1.2)	Moderate (> 0.6 ≤ 1.2)	No (≤ 0.6)
≤ 3.2	13†	10†	14†
> 3.2 ≤ 5.1	0	3†	16†
≥ 5.1	0	0	3†

†Number of rheumatoid arthritis patients who responded as per the classification criteria. CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; EULAR, European League Against Rheumatism.

were considered for analysis (i.e., supplementation and assessment of disease activity were performed for group 1 and the baseline characteristics of group 1 were compared with group 3). Vit D levels were significantly lower in patients with active disease (group 1) than without (group 3). However, both the groups had vit D levels lower than the normal range. Moreover, the duration of illness was significantly different between the groups, in addition to expected differences in all the parameters of disease activity. However, there was no significant correlation between duration of disease and vit D levels (data not shown).

Turhanoğlu *et al.*[28] have found an inverse relationship between RA activity (DAS28) and serum levels of vit D in a cohort of 65 patients. They found that serum vit D levels in patients with RA were similar to those in healthy controls. In the present study, the proportion of vit D levels in patients concurs with the previously noted incidence in the same population, suggesting that vit D deficiency is comparable. Patients with persisting disease demonstrated severe deficiency, when the minimum cut-off value of the vit D levels was considered as deficiency. Craig *et al.* (a study of 266 patients) and Kostoglou-Athanassiou *et al.* (a study of 44 patients) have demonstrated similar results.[21,29] Cutolo *et al.*[22] found that plasma levels of vit D were inversely correlated with RA disease activity, showing a circannual rhythm (more severe in winter). Similarly, Rossini *et al.*[30] have concluded that vitamin deficiency is very common in RA patients, and 25(OH)D levels are inversely associated with disease activity and disability scores.

Contradictory to these findings, Baker *et al.*[31] have shown that serum levels of vit D did not correlate with RA activity, and response to treatment was similar in patients with different levels of vit D. Salesi *et al.*[32] have also reported non-significant improvement in efficacy of oral vit D in patients with active RA receiving stable doses of methotrexate.

The present study has demonstrated the benefit of vit D supplementation in improving disease activity parameters. Moderate EULAR response was noted in 44% of the subjects (Table 3). The best response was seen in patients who achieved lower disease activity with optimum or maximum permissible DMARDs. In the present study population, only three of the 22 patients with moderate to severe disease activity showed such a response. Around 30% of the subjects in routine clinical practice show inadequate response or refractory disease, in spite of the maximum permissible dose of DMARDs. This explains the low response rate (3/22) seen in patients with severe disease activity, irrespective of the vit D intervention. Probably the patients in Baker's study who demonstrated no response to vit D activity might have had severe active disease.[31] The selection of subjects in different studies may have been the cause of differences between the results of vit D supplementation and response of RA.

The present study suggests that moderate vit D deficiency may not be directly responsible for persisting disease, while severe deficiency may be responsible for simmering mild disease. There is evidence to suggest that vit D does have anti-inflammatory and immune response stabilizing activity with reference to RA.[33] Merlino *et al.*[33] have reported that intake of vit D reduced the incidence of RA in 29 368 middle-aged (55–69 years) women in an 11-year follow-up study. It was also demonstrated that serum levels of vit D in patients with ESR > 24 were significantly lower than those with ESR < 24.

Although no significant improvement or change in inflammatory parameters (both ESR and CRP) was noted, statistically significant changes were seen in joint count and pain scale measures. Significant change is DAS28 score was also noted, because the joint counts form the major component in calculating the score. The plausible reason for no significant differences in ESR and CRP could be the requirement of a larger patient population to show a significant difference, due to the variable nature of these measures. The other possible explanation is that the impact of vit D levels on inflammation might be trivial. Vit D may improve the pain perception (pain threshold) of the patients, and thereby the TJC and pain scale. But these explanations fail to clarify the observation of reduced swollen joint count, which is a reliable indicator of inflammation.

In view of this, there is a possibility of benefit from a trial with supplementation of vit D in patients with a milder persisting disease. It may be worthwhile to supplement vit D after patient evaluation for vit D deficiency. The other possibilities of routine vit D estimation and supplementation to improve the outcome, in combination with conventional DMARDs, need further evaluation. The current study is moderately powered, especially for subgroup analysis for outcome based on disease activity. Selecting patients by randomization has helped to circumvent the expected entry bias, but the major limitation of the study is that it is open-labelled and there is no placebo control arm. Blinding the independent joint assessor on intervention might have helped to reduce the observer bias, but the placebo effect cannot be ruled out.

CONCLUSION

The present study demonstrates that severe vit D deficiency could be one of the reasons for persisting disease activity in RA. On intervention with oral supplementation of vit D in patients with deficiency, there were significant improvements in DAS28-ESR and DAS28-CRP.

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AUTHOR CONTRIBUTIONS

Dr. S. Chandrashekara has contributed in designing the concept and writing the manuscript. Dr. Anand Patted has contributed in data collection, recruitment of patients, and data analysis.

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