Effect of vitamin D on the recurrence rate of rheumatoid arthritis

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Abstract. Rheumatoid arthritis (RA) is an autoimmune disease that is characterized by chronic inflammation affecting target tissues including the joints, bones, and synovial membrane. However, the etiology and pathogenesis of RA remains to be determined, and investigations into the treatment of RA are imperative. Vitamin D (Vit D) was previously found to be associated with the activity of RA and exerts therapeutic benefits. The aim of the present study was to investigate the effect of Vit D on the recurrence rate of RA. A total of 377 patients with RA at remission stage were divided into the normal Vit D group and the Vit D-deficient group according to their Vit D levels at baseline. The patients in the Vit D-deficient group were further randomly allocated to receive treatment with or without Vit D. The patients were followed up for 24 months, and the visual analogue scale, as well as the number of pain and swelling joints were recorded every 2-3 months. In addition, C-reactive protein and the blood sedimentation rate were measured every 2-3 months to assess the recurrence of RA based on disease activity score 28 (DAS28). The recurrence rate of RA was 16.7, 19.0 and 29.5% for the normal Vit D group (n=168), Vit D treatment subgroup (n=84), and non-Vit D treatment subgroup (n=88), respectively. The recurrence rate of the normal Vit D group was lower, compared to the non-Vit D treatment subgroup, and the difference was statistically significant. However, the difference was not statistically significant between the Vit D treatment subgroup and non-Vit D treatment subgroup. In conclusion, a decreased level of Vit D is a risk factor for the recurrence of RA.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation affecting target tissues including the joints, bones, and synovial membrane. RA causes a high rate of disability and ultimately leads to death in patients (1). However, the etiology and pathogenesis of RA have yet to be determined. Thus, investigations into treatment strategies for RA are crucial. Currently, most studies are based on the premise that RA develops through an antigen-triggered 'challenge-chained immune reaction' process, with infection and autoimmune responses playing central roles in the development and progression of RA, while genetic and environmental factors are important influencing factors that may activate Th1 cells and increase the secretion of cytokines including interleukin-1 (IL-1), IL-6 and TNF-α through the major histocompatibility complex (2,3). These cytokines are useful in mediating the continuous activation of B cells and eventually induce synovial lesions (2,3).

Vitamin D (Vit D) decreases the production of IL-17, IL-6, IL-1 and tumor necrosis factor-α (TNF-α) by inhibiting the immune response of Th1 cells. In addition, activated Vit D may inhibit the precursors of monocytes by immune modulation effects and inhibit the apoptosis of B-cells (4). It has been previously demonstrated that Vit D is associated with the activity of RA and exerts therapeutic benefits (5,6). Although in previous studies the association between Vit D and RA was investigated, to the best of our knowledge, no study has investigated whether Vit D affects the recurrence rate of RA or whether Vit D supplementation has various benefits for RA patients through reduction of the recurrence of RA, thereby proving useful for the long-term remission of RA, or reducing the application of slow-acting drugs. In this randomized, open-label clinical study, we investigated the effect of Vit D on the recurrence rate of RA and found that a decreased level of Vit D in the groups examined in the present study is a risk factor for the recurrence rate of RA.

Materials and methods

Patients characteristics. RA patients, who were treated at the outpatient service of the Department of Rheumatism and Immunology, Xuzhou Central Hospital (Jiangsu, China), between October 2010 and February 2014, were enrolled. A questionnaire was used to collect general data including age, gender, disease duration, and medical history in the previous 2-3 months, visual analogue scale (VAS) score, patient global assessment and number of swelling and pain joints of the patients. In addition, levels of C-reactive protein (CRP), blood sedimentation rate (ESR), Ca, P and 25(OH)D3 of patients were also measured. The inclusion criteria that applied were: i) patients met the American College of Rheumatology and European League Against Rheumatism (ACR-EULAR)

Table I. Demographic data and baseline disease characteristics.

| Characteristics | Normal Vit D group (n=168) | Vit D-deficient group | | P-value |
		Vit D treatment subgroup (n=84)	Control subgroup (n=88)	
Age (years)	43.1±7.1	44.2±7.5	41.7±8.6	0.32
Male patients, n (%)	20 (11.9)	12(14.2)	10 (11.3)	0.82
Disease duration (years)	5.2±2.4	4.9±2.1	5.1±2.2	0.78
Remission time (months)	8.2±4.1	7.9±4.6	8.6±3.8	0.73
Vit D level (ng/ml)	37.6±7.1	20.6±9.1	21.3±8.5	0.71[a]

[a]Comparison of the Vit D level between the Vit D treatment and non-Vit D subgroups. Vit D, vitamin D.

classification criteria for RA issued in 2010 (7); ii) patient was in a remission phase in the previous 2-3 months, according to the ACR-EULAR 2010 criteria (8), with <1 swelling joint and 1 tender joint, CRP <1 mg/dl, and patient global assessment ≤1 (range 0-10); and iii) patient did not receive glucocorticoids or Vit D during the previous 2-3 months, although the patients remained on maintenance treatments with slow-acting drugs. Patients with one or more of the following features were excluded: i) other comorbid rheumatic diseases; ii) poor compliance to previously used treatment method; or iii) serum calcium >2.75 mmol/l or serum phosphorus >1.61 mmol/l.

The study was approved by the Ethics Committee of the Clinical Trial Center of the Xuzhou Center Hospital (20101016-10). Written informed consent was obtained from all the patients prior to entering the study.

Treatment method. This randomized, controlled, open-label study was conducted between October 2010 and February 2014. The included RA patients were first divided into the normal Vit D and Vit D-deficient groups according to their baseline Vit D levels (cut-off value, 30 ng/dl). Random numbers were generated by a computer to allocate patients in the Vit D-deficient group, the Vit D treatment subgroup and the non-Vit D treatment subgroup (control group). For the patients in the Vit D treatment subgroup, alfacalcidol (0.25 μg, twice a day) was administered as the treatment, while for patients in the control group and non-Vit D treatment subgroup the previously used treatment method was continued (Table II). Patients were followed up every 2-3 months during the 24-month follow-up period, and VAS and the number of swelling or tender joints were recorded. In addition, CRP and ESR levels were measured. The activity level was calculated based on the disease activity score 28 (DAS28). When DAS28 ≥3.2 it was deemed as RA recurrence. The Vit D3 level of the patients was also measured at the end of follow-up. In addition, Ca and P levels were measured for the patients who received alfacalcidol. If patients receiving alfacalcidol were found with a serum calcium level >2.75 mmol/l or serum phosphorus >1.61 mmol/l, treatment of alfacalcidol was discontinued and additional treatments were performed to reduce serum calcium and phosphorus. Enzyme-linked immunosorbent assay (ELISA) kits (Roche,

Basel, Switzerland) were used to determine Vit D3 levels, and blood samples were preserved in the dark.

Statistical analysis. SPSS 16.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Analysis of variance and the t-test (two-sample/group t-test and least significant difference test) were used for comparison of quantitative data. The Chi-square test was used for comparison of qualitative data. P<0.05 was considered to indicate a statistically significant result.

Results

General characteristics. A total of 377 eligible patients were included in the present study, of which 185 patients had normal Vit D levels and 192 patients had Vit D deficiency, which indicated a Vit D deficiency rate of 50.9%. The 192 patients with Vit D deficiency were subdivided into the Vit D treatment subgroup (n=93, comprising 77 women and 16 men) and the non-Vit D treatment subgroup (n=99, comprising 83 women and 16 men). Table I shows the demographic and clinical characteristics of the patients at baseline. No significant difference in age, gender, disease duration, and remission time at study entry was identified for the three groups. In addition, the Vit D level was not significantly different between the Vit D treatment and non-Vit D treatment subgroups. Table II provides the treatment methods applied at study entry for the patients, and the data show there was no statistically significant difference. Vit D levels at baseline were significantly different between the recurrent patients in the Vit D treatment and non-Vit D treatment subgroups (Table III).

Recurrence rate. After 24 months of follow up, the number of patients lost to follow up and who failed to comply with treatment requirements in the normal Vit D group, Vit D treatment subgroup and control subgroup was 17, 9 and 11, respectively. Thus the actual number for the three groups of complete follow up was 168 (comprising 149 women and 19 men), 84 (comprising 72 women and 12 men), and 88 (comprising 78 women and 10 men) for the the normal Vit D group, Vit D treatment subgroup and non-Vit D subgroup, respectively.

Table II. Treatment methods of patients at study entry.

| | | Vit D-deficient group | | |
Treatment	Normal Vit D group (n=168)	Vit D treatment subgroup (n=84)	Control subgroup (n=88)	P-value[a]
Methotrexate	30	16	16	>0.05
Leflunomide	22	12	10	
Tripterygium and methotrexate	16	10	8	
Methotrexate and hydroxychloroquine	60	28	32	
Leflunomide and methotrexate	40	18	22	

[a]P>0.05, comparing each treatment method for the three groups. Vit D, vitamin D.

Table III. Comparison of the general characteristics of the patients with recurrence.

| | | Vit D-deficient group | | |
Characteristics	Normal Vit D group (n=168)	Vit D treatment subgroup (n=84)	Control subgroup (n=88)	P-value
Age (year)	42.1±6.2	41.2±6.6	41.7±5.8	0.74
Disease duration (years)	5.0±1.9	4.9±1.7	5.1±2.1	0.89
Remission time (months)	8.1±3.9	7.9±4.1	8.2±3.7	0.94
Vitamin D level (ng/ml)	36.8±6.7	25.5±8.9	20.9±8.6	0.0039[a]

[a]Comparison of Vit D level between patients with disease recurrence in the Vit D treatment and non-Vit D subgroups. Vit D, vitamin D.

Table IV. Comparison of recurrence rate for the three groups.

| | | | P-value | | |
Group	No. of patients with recurrence	No. of patient without recurrence	Comparison between three groups	Comparison between Vit D treatment subgroup and non-Vit D subgroup	Comparison between normal Vit D group and non-Vit D subgroup
Normal Vit D group (n=168)	28	140	0.05	0.11	0.02
Vit D-deficient group					
Vit D treatment subgroup (n=84)	16	68			
Non-Vit D subgroup (n=88)	26	62			

Vit D, vitamin D.

RA recurrence was identified in 28 of the 168 patients with normal Vit D (recurrence rate of 16.7%) compared with 26 patients in the non-Vit D treatment subgroup (recurrence rate of 29.5%), and the difference was statistically significant (P=0.02). No patient in the Vit D treatment subgroup discontinued because of high calcium or high phosphorus. However, 16 patients in the Vit D treatment subgroup were identified as having RA recurrence, yielding a recurrence rate of 19.0%, which was not statistically different from the recurrence rate in the non-Vit D treatment subgroup (29.5%) (P=0.11) (Table IV).

Discussion

Previous studies have demonstrated that Vit D supplementation reduces the prevalence and activity of RA (5,9-11). However, few studies have investigated the effects of Vit D on the recurrence rate of RA. In this randomized, open-label clinical study, remission phase RA patients with decreased Vit D levels were treated with or without Vit D, and the recurrence rate of RA was compared. The results showed that the recurrence rate was statistically different between the normal Vit D and Vit D-deficient groups. The results suggest that a low Vit D level constituted a risk factor for RA recurrence. Treatment with alfacalcidol increased the Vit D levels in patients; however, the recurrence rate was not statistically different between the Vit D treatment and non-Vit D treatment subgroups.

RA is an autoimmune disorder with a complex pathophysiology. Genetic and environmental factors contribute to the development of RA. 1,25-Dihydroxyvitamin D3 has been hypothesized to decrease chondrolysis by the IL-1A-mediated production of matrix metalloproteinases, and thus, deficiency is a potential trigger for cartilage damage in RA (9). Epidemiological studies have demonstrated that a reduced Vit D level was associated with an increased risk for the development and progression of autoimmune diseases including RA, systemic lupus erythematosus, and type 1 diabetes (10-12). Increased intake of Vit D has also been associated with a reduced risk of developing RA. In a study by Merlino *et al*, data from 29,368 women aged between 55 and 69 years were analyzed (13). Following administration of Vit D administered in these women for 11 years, no RA was found, suggesting that Vit D reduces the incidence or RA. Merlino *et al* reported an inverse association between Vit D levels and the risk of RA (13). In basal pretreatment conditions, a proportional inverse relationship among the levels of 25(OH)D and the tender joint counts, HAQ scores, CRP levels, and the DAS28 scores was observed. Each increase of 10 ng/ml in the level of 25(OH)D was associated with a decrease in the DAS28 score of 0.3 and in the CRP level of 25% (14). Kröger *et al* studied 143 Finnish women with RA and found that the lowest values of serum Vit D were identified in patients with the highest disease activity (15). In a study with 19 patients with RA treated with traditional disease-modifying anti rheumatic drugs (DMARDs), oral supplementation with high doses of alfacalcidol for 3 months reduced the severity of the symptoms in 89% of the patients, 45% of whom achieved complete remission, and 44% had satisfactory results. No significant adverse effects were identified, and the serum calcium levels were within normal limits for all the patients during the period of the study (16).

Vit D, closely associated with RA, is cost-effective with few side effects. Vit D is recommended for the preventive treatment for high-risk individuals with RA (17). Therefore, a lack of Vit D treatment recommendations for patients with RA in remission is due to the lack of studies available on the effect of Vit D on the RA recurrence rate. A single study focusin on Vit D and the recurrence rate of RA was performed in Iran, between October 2012 and February 2013, with a total of 80 RA patients with Vit D deficiency being enrolled and randomly allocated to receive Vit D or placebo in the 6-month follow-up period. The study showed that the flare rate was not different between two groups (18). The main drawbacks of this study were the small sample size, lack of controls with RA patients of normal Vit D levels, and the shorter observation time period of 6 months.

In the present study, the effect of Vit D on the recurrence rate of RA was evaluated in 340 RA patients in remission after a follow-up period of 24 months. Based on this study, ~50.9% of RA patients in remission had Vit D deficiency. This finding was consistent with findings by Dehghan *et al* (18).

The results of the present study have shown that the recurrence rate was 16.7, 19.0 and 29.5% for patients in the normal Vit D group, Vit D treatment subgroup, and non-Vit D treatment subgroup. The recurrence rate of the normal Vit D group was lower, compared with that of the non-Vit D treatment subgroup, and the difference was statistically significant, suggesting that a decreased level of Vit D is a risk factor for RA recurrence. The findings of the present study demonstrate that the recurrence rate of the normal Vit D group was lower and treatment of patients with a standard dose of Vit D potentially increased the level of Vit D and reduced the recurrence rate of RA, although the difference was not statistically significant. This finding may be due to the fact that the Vit D level of the Vit D treatment subgroup following treatment remained below the normal range. Therefore, more studies are required to investigate whether increasing the dose of Vit D is beneficial to patients in order to recover normal Vit D levels, and thus affect the recurrence rate of RA. Vit D may exert important effects on autoimmune diseases, and the adverse effects of Vit D are substantially lower than slow-acting drugs.

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