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Role of vitamin D in flare ups of rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects about 1% of the human population. Its incidence increases between 25 and 55 years and is the most common type of chronic inflammatory arthritis. Genetic as well as environmental factors may cause activation of Th1 by MHC and catalyses production of IL-1, IL-6, and TNFα [1-5].

Vitamin D (Vit D) can increase innate immunity. Epidemiologic evidence confirms a relationship between Vit D deficiency and increased autoimmune diseases which is related to Vit D receptors [1-7].

Vit D downregulates MHCII (major histocompatibility complex II) and inhibits Th1 and Th2 and then decreases IL-17, IL-6, IL-1, and TNFα. Activated Vit D also inhibits the monocytes' precursors with its immunomodulatory effects. Calcitriol (1,25-dihydroxyvitamin D_3, OHD) has effects on B lymphocytes and induce B cell apoptosis without influencing primary differentiation of these cells. Such antiproliferative, antiinflammatory, and immunomodulatory effects causes Vit D to be effective as an adjuvant agent in the treatment of many autoimmune diseases like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), diabetes mellitus type I (DM type I), and inflammatory bowel diseases (IBD) [2-8].

Drugs used in the treatment of RA have numerous potential side effects but in some progressive types of disease combination therapy is administered, which increases the cost of treatment and also possible complications due to drug side effects [8-13]. Osteopenia and osteoporosis are common complications due to chronic inflammation in diseases. Vit D is used in arthritis rheumatoid prevention and control [6]. Some studies suggest that higher doses of Vit D result in better disease control, while other studies showed higher prevalence and severity of autoimmune diseases like RA in areas with fewer hours of sunshine [11]. In this study, we investigated the administration of Vit D in controlling disease activity and reducing dosages of disease-modifying antirheumatic drugs (DMARDs).

Materials and methods

After approval of institutional ethics committee (Reg no. P/17/1/49188), this double-blinded, randomized, placebo-controlled clinical trial was conducted from October 2012 to February 2013. Participants were selected from known RA patients referred to the rheumatology clinics of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. After complete explanation of the study process to participants, written consent was obtained from all participants.

Inclusion criteria

Patients with RA that was diagnosed based on new 2010 ACR-EULAR criteria were enrolled in this study. Disease was controlled at the time of admission and patients had been in remission during the past 2 months. Remission based on ACR-ECULAR criteria was determined by (1) number of tender joints ≤1, (2) number of swollen joints ≤1, (3) C-reactive protein (CRP) ≤1 mg/dl, and (4) patient global assessment ≤1 (range 0–10).

The Vit D level was checked using Roch kits (Germany). Patients with Vit D levels under 30 ng/dl were included in the study.

Exclusion criteria

Patients with symptoms of RA that were overlapped by other rheumatologic disease (overlap syndrome) and patients with abnormal calcium and phosphorus or normal Vit D levels were excluded from the study.

Based on α=0.05, β=0.02, δ=R/6, and d=1 and using the statistical relationship a total of 40 patients were needed for each

$$N = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 \delta^2}{d^2}$$

group.

Data were collected using a questionnaire and included questions on age, sex, complete drug history, visual analogue score (VAS), and numbers of involved, swollen and painful joints. Activity level was calculated based on disease activity score 28 (DAS28):

Also if needed, the level of CRP, ESR,

$$(DAS28 = 0.56 \times \sqrt{tender28} + 0.28 \times \sqrt{swollen28} + 0.70 \times ESR + 0.014 \times VAS)$$

ALP, Ca, P, and Vit D were measured repeatedly during follow-ups and registered.

Tab. 1 Frequency of recurrence among study groups and related p value

Group		Recurrence		
		Yes	No	Total
Vit D	n	7	33	40
	%	17.5	82.5	100
Placebo	n	11	29	40
	%	27.5	72.5	100

Fisher's exact testp value=0.42.

Tab. 2 Frequency of prednisolone, methotroxate (*MTX*) and hydroxychloroquine (*HCQ*) dose decrease in study groups and related p values

Group		Dose decreased			
		No	Yes	Total	p
Prednisolone					
Vit D	n	17	23	40	0.26
	%	42.5	57.5	100	
Placebo	n	23	17	40	
	%	57.5	42.5	100	
MTX					
Vit D	n	25	15	40	0.22
	%	62.5	37.5	100	
Placebo	n	31	9	40	
	%	77.5	22.5	100	
HCQ					
Vit D	n	35	5	40	0.71
	%	87.5	12.5	100	
Placebo	n	37	3	40	
	%	92.5	7.5	100	

Fisher's exact test.

All lab test costs were paid from the study budget; study participation for the patients was free of cost.

Patients in intervention group were administered one Vit D pearl weekly, while patients in the control group were administered placebo pearls in a similar fashion. Vit D pearls (50,000 unit/pearl) and placebo were similar and were produced by the same company (Zahravi Pharmaceutical Company, Tabriz, Iran) with 24 pearls packaged in similar sachets. The sachets were labeled by the statistician based on the patients' group. All drugs and laboratory tests costs were covered by study funds and the study was free of cost for participants. One sachet was given to each patient and the code of each sachet was recorded in each patient's documents. Patients were followed for 6 months. They were requested to bring the sachet to each of their visits to ensure compliance and were recommended to call the researcher if any problems arose. If any signs or symptoms of disease flare were observed, the DAS28 was calculated based on needed factors as mentioned previously using online software designed to calculate this score [14].

After finishing the study follow-up time, groups of patients were identified using the drug sachets codes. All registered data were transferred into SPSS-11 software and analyzed using Fisher's exact test and Mann–Whitney test.

Results

A total of 80 RA patients with Vit D deficiency were enrolled in this study: 34 women and 6 men were included in the Vit D group, while 36 women and 4 men participated in the placebo group (p=0.73). There were no differences between groups according to age (45±8.66 vs. 42.7±9.77 for case and control groups, respectively, p=0.26) and mean serum Vit D (p=0.33).

A flare was observed in 7 patients (17.5%) of the Vit D group and 11 patients (27.5%) of the placebo group, while no disease flare was observed in the other 33 patients (82.5%) in the Vit D and 29 patients (72.5%) in the placebo group. Based on Fisher's exact test, there was no statistical significant difference between groups, while this difference could be significant clinically (**Tab. 1**).

Absolute risk reduction (ARR) is about 10% which relative risk reduction (RRR) is about 36% and number needed to treat (NNT) is 10 patients, which means that with Vit D treatment in 10 patients, 1 patient will have no flare (CI −0.817 to −0.278). Also after logistic regression, the odds ratio (OR) was estimated to be about 1.17 which shows that not using Vit D in the placebo group caused a 17% increased risk of recurrence, but the difference in this context is not statistically different (p=0.82).

Vit D did not cause a need for lower doses of prednisolone administration. ARR is 15%, RRR 26%, and NNT 7 patients (CI −1.22 to 1.37). There was a similar result with MTX (ARR 15%, RRR 19.3%, and NNT 7 patients) and hydroxychloroquine (**Tab. 2**).

There was no significant discrepancy during flared patients of two groups according age, sex, serum Vit D level, and DAS28 score.

Flare was compared between patients with a normal Vit D level (patients who excluded from the study) and the study Vit D group (patients with Vit D deficiency who received Vit D during the study). RA flared in 13 patients (17.6%) with normal Vit D and in 7 patients (17.5%) of the Vit D study group. The difference was not significant (p=1.00; Fisher's exact test).

Discussion

Most of previous studies investigated the effect of Vit D on active RA. However, there are many confounding factors which effect such a study design; thus, we investigated RA patients who were in remission. Although the previous studies demonstrated that Vit D decreases incidence and activity of RA, we did not detected any effects of Vit D on recurrence, and in patients with normal serum Vit D levels no discrepancy compared to our case (Vit D administered) group was found. Merlino et al. [15] followed 29,368 women between 55 and 69 years without RA diagnosis for 11 years about Vit D administration (as regimen or supplements) and concluded that Vit D lowers the incidence of rheumatoid arthritis. Andjelkovic et al. [9] divided 19 RA patients into highly active and moderately active groups and administered 2 µg of oral calcidiol to both groups. After 3 months, 45% of patients were in remission and 44% had symptomatically recovered which illustrates the immunomodulatory effects of calcidiol with low hypercalcemic effects. This study had no control group and its sample size was smaller than our study. In the 2010 Turhanoğlu et al. [2] study, no difference was found according to mean serum 25-OHD levels between 65 RA patients and 40 healthy participants. They also divided RA patients into three groups of low, moderate, and high activity. Patients in the high and moderate activity groups had lower Vit D levels than the low activity group which shows an inverse relationship between serum Vit D levels and disease activity [2]. There was no intervention in this study.

Epidemiologic study confirms that decreased level of Vit D increases the risk of autoimmune diseases progression like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), diabetes mellitus type I (DM type I), and inflammatory bowel diseases (IBD) [7-16]; and preventive treatment with Vit D for high-risk people is recommended [17]. On the other hand, there is another large scale epidemiologic study which refutes such a relationship [18], but there is also controversy concerning this matter.

In a study by Nielen et al. [19], serum Vit D in 79 paraclinical susceptible RA patients was compared to 139 healthy controls during the 5 years prior to the emergence of symptoms in the RA group. There were no differences according to Vit D levels.

Based on our study, about 51.9% of RA patients had Vit D deficiency; in a study performed in five Iranian cities, the prevalence of Vit D deficiency was reported to be about 45.2% in a middle-aged population [20]. In another study in Isfahan, this rate was reported to be about 50.8%. There is no strong evidence on a relationship between seasons and RA incidence but in some seasons a deterioration of the patients' conditions may be observed [21].

In another 2010 study, 266 newly diagnosed RA patients were assessed according to Vit D levels and disease activity for 3 years. About 50% of patients were Vit D deficient. There was no significant relationship between pain, swelling, and DAS28 with Vit D level [22]. These results are concomitant with our findings.

A study in the United States investigated 62 RA patients in terms of Vit D and DAS28 levels. About 61% of patients had low Vit D levels (less than 30 ng/ml). An inverse relationship was also found between Vit D level and high disease activity (DAS28 >2.6), while the relationship between the Vit D level and controlled disease (DAS28 <2.6) was not significant. These results confirm correlation between high and moderate activity of disease and Vit D levels [23]. In our study, results were not significant at any level of disease activity possibly due to our patients being in remission.

Abstract · Zusammenfassung

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Role of vitamin D in flare ups of rheumatoid arthritis

Abstract

Introduction. Rheumatoid arthritis (RA) is one of the most prevalent autoimmune diseases worldwide. Some researchers have suggested that the serum vitamin D (Vit D) level may relate to disease activity. The current study was designed to identify the correlation between vitamin D prescription and prevention of relapses in rheumatoid arthritis.
Patients and method. A double blinded, randomized controlled trial study was performed using 80 RA patients. RA was controlled and patients were in remission during the past 2 months. Serum level of Vit D in the studied patients was below 30 ng/dl. Patients were randomly allocated to receive Vit D or placebo. In the 6-month follow-up period, the Disease Activity Score 28 (DAS28) was used in case of relapses as an index of RA activity to compare the two groups.
Results. The flare rate was not different between two groups (p>0.05). The odds ratio of the rate of decline in patients of the trial group compared with the control group was 1.17 (not significant; p>0.05). The mean DAS28 between the two patient groups was not significant (p>0.05).
Conclusion. A low Vit D level was not identified to be a risk factor for RA severity or flare ups; however, although not statistically significant, Vit D treatment might be clinically effective. Further studies are needed with more emphasis on the issue of cost effectiveness and clinical importance to provide more information.

Keywords

Flare · Rheumatoid arthritis · Vitamin D · Autoimmune diseases · Vitamin D deficiency

Rolle von Vitamin D bei Schüben der rheumatoiden Arthritis

Zusammenfassung

Einleitung. Die rheumatoide Arthritis (RA) gehört weltweit zu den häufigsten Autoimmunerkrankungen. Manche Forscher vermuten, dass die Aktivität der Erkrankung mit dem Vitamin-D-Spiegel im Serum zusammenhängt. In der vorliegenden Studie sollte die Beziehung zwischen der Verschreibung von Vitamin D und der Prävention von RA-Rezidiven ermittelt werden.
Patienten und Methoden. An 80 RA-Patienten wurde eine doppelblinde, randomisierte, kontrollierte Studie durchgeführt. Die Erkrankung war unter Kontrolle, die Patienten hatten sich in den vorausgegangenen 2 Monaten in Remission befunden. Der Serum-Vitamin-D-Spiegel lag bei den eingeschlossenen Patienten unter 30 ng/dl. Die Teilnehmer wurden in 2 Gruppen randomisiert. Eine erhielt Vitamin D, die andere Placebo. Im 6-monatigen Follow-up wurde im Falle eines Rezidivs der Disease Activity Score 28 (DAS28) herangezogen, um die beiden Gruppen bezüglich der RA-Aktivität zu vergleichen.
Ergebnisse. Die Gruppen unterschieden sich nicht hinsichtlich der Rate an Schüben (p>0,05). Die Odds Ratio der Abnahme betrug für Patienten in der behandelten Gruppe im Vergleich zur Kontrollgruppe 1,17 (nicht signifikant; p>0,05). Auch hinsichtlich des durchschnittlichen DAS28 fand sich in den beiden Gruppen keine Signifikanz (p>0,05).
Schlussfolgerung. Ein niedriger Vitamin-D-Spiegel erwies sich nicht als Risikofaktor für Schübe oder die Schwere der RA. Allerdings könnte die Vitamin-D-Behandlung, wenn auch ohne statistische Signifikanz, klinisch wirksam sein. Weitere Studien mit stärkerem Gewicht auf der Kosteneffektivität und klinischen Bedeutung sind notwendig.

Schlüsselwörter

Schub · Rheumatoide Arthritis · Vitamin D · Autoimmunerkrankung · Vitamin-D-Mangel

A study performed in Washington during 2011 with about 850 RA patients found 83% of patients to have Vit D insufficiency (Vit D <30) and 43% of patients to have deficiency (Vit D <20). Deficiency was higher in anti-CCP-positive patients and Caucasians. In this study a relationship was also found between Vit D deficiency and the numbers of painful joints and also CRP level [24].

A study on 1191 RA patients and 1019 healthy controls in Italy did not find significant difference between two groups but in RA patients, Vit D was inversely related to disease activity [25].

In a study performed in Isfahan (Iran), 117 active RA patients (mean DAS28 =5.5) were divided into two case and control groups. Results showed that oral Vit D supplement has no significant effect on disease activity [26]. In the present study, we surveyed RA patients in remission as there are some confounding factors during treatment, and discrimination between the effects of therapeutic protocol drugs and Vit D is difficult.

In the present study, we evaluated the effect of Vit D on prevention of flares in controlled rheumatoid arthritis but Vit D deficient patients and compared it to placebo. Follow-up duration was 6 months. The recurrence in Vit D group was lower than placebo (17.5% vs. 27.5%), which is clinically important, but not statistically different. As accepted by other studies, Vit D is effective in patients with severe and highly active RA but not on activity or recurrence among low active or remitted patients.

Conclusion

Based on current studies [21, 22] and also our survey, Vit D deficiency is not a risk factor for activation or flare of RA patients in remission. Because of a clinically (but not statistically) important lower recurrence rate among the Vit D group compared to the placebo group and considering with harmless, inexpensive Vit D pearls, we recommend oral Vit D supplements as an adjuvant therapy for RA. More studies are needed with more stress on cost effectiveness as well as clinical importance.

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Compliance with ethical guidelines

Conflict of interest. A. Dehghan, S. Rahimpour, H. Soleymani-Salehabadi, and M. Bagher Owlia state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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