The Relationship between Serum Level of Vitamin D3 and the Severity of New Onset Rheumatoid Arthritis Activity

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a systemic inflammatory disease which typically involves wrists, ankles, and finally every joint. Some of studies have reported a reverse relationship between the level of vitamin D and RA severity.

Aim: The present study was carried out in order to check the potential relationship between the level of vitamin D and RA severity.

Materials and Methods: Ninety-three patients with RA with onset in recent three months (new onset RA), and 31 patients without RA were chosen as the control group. The patients all aged under 75 years and were diagnosed by a rheumatologist. The serum level of vitamin D was measured through blood test by chemiluminescence method by taking a blood sample of 5 cc. The relationship between the average level of vitamin D and disease severity was analyzed based on scoring scale of DAS28 in different groups with RA. The significant level of the above mentioned tests was set at $p<0.05$. Data analysis was carried out using SPSS 20.0.

Results: The results of the present study indicated that there was no significant relationship between the two groups in terms of the serum level of vitamin D. Since the subgroups of the patients are not homogenous in terms of age and based on disease severity, ANOVA and chi-square were used to modify this heterogeneity and compare vitamin D levels in patients based on disease severity. The results indicated that there was a significant difference between the three groups of patients in terms of disease severity, such that disease severity rose with a decrease in the serum level of vitamin D, (p-value <0.001).

Conclusion: There was a significant reverse relationship between the serum level of vitamin D and RA severity based on Das Score 28. Therefore, it is recommended that if there is a lack of or insufficient amounts of this vitamin in the body, vitamin D supply needs to be optimized along with other standard medications in order to reduce the RA severity.

INTRODUCTION

RA is a systemic inflammatory disease whose outstanding sign is chronic symmetrical polyarthritis (synovitis) which can typically involve wrists, ankles, and every joint. This disease is affected by age and gender, such that its incidence increases with an increase in age and also hormonal changes in women [1,2].

Inflammation is caused by synovial proliferation and deformation results from tendon strain caused by bone erosion which is normally irreversible [1]. Severity and activity of the disease is measured according to the score obtained in DAS28 scale [3].

The results of immunological studies indicate that vitamin D deficiency causes many chronic and immune diseases [4]. The results of recent studies have indicated that 1 & 25-dihydroxy vitamin D in vitro secretion of cytokines and proliferation controls T cells [5-7]. The results of numerous studies have indicated a reverse relationship between the level of vitamin D and the RA severity [8,9]. Some studies, observed that disease severity had a significantly reverse relationship with serum level of vitamin D and DAS28 scale [8,9]. Moreover, others reported that the level of vitamin D is significantly lower in RA patients [10].

On the other hand, some studies have indicated that there is no relationship between serum level of vitamin D and affliction with disease [11]. Due to the contradictory results regarding the effect of serum level of vitamin D on the RA severity, the present study aimed to investigate this issue by selecting an appropriate sample, including a control group, and homogenizing the groups. Therefore, the present study was aimed at investigating the relationship between serum level of vitamin D and severity of new onset RA.

MATERIALS AND METHODS

This was a cross-sectional study that was done in Khoosetan province of Iran. Sampling was carried out using a non-randomized sequential method. Ethical approval was obtained and all participants consented for trial.

Inclusion criteria: Sample size was 124, divided into three groups of 31 patients with rheumatoid arthritis in various stages of disease and 31 patients without rheumatoid arthritis. Diagnosis of rheumatoid arthritis was based on ACR 2010 criteria, age of below 75 years, and beginning and diagnosis with the past three months.

Exclusion criteria: Consumption of any active form of vitamin D over the last three months except for Calcium D-Glucarate containing 200 units vitamin D, history of kidney or liver diseases, and pregnancy. During this trial, all the groups received similar treatment. Methotrexate with a dose of 0.2 mg/kg, hydroxychloroquine with a dose of 6 mg/kg and prednisolone with a dose of 5 mg daily. None of the participants used any other biologic agent or NSAIDs and other drugs that may relief or decrease symptoms.

The serum level of vitamin D was measured through blood test via chemiluminescence method using Architect lab kit made in Germany by taking a blood sample of 5 cc. The group with RA was divided into three groups based on the serum level of vitamin D. The first group had vitamin D deficiency (under 10 ng/ml), the second group had an insufficient level of vitamin D (between 10 and 29 ng/ml), and the third group had normal levels of vitamin D (over 30 ng/ml) [3].

In the next phase, the relationship between the level of vitamin D and disease severity in different groups with RA was analyzed by an expert and a statistician based on the scoring of DAS28 scale.

The control and experimental groups were homogenized and matched in regard to their age, gender, BMI, diet and consumption of supplements containing vitamin D from the beginning.

According to scores obtained in DAS28 scale, severity and activity of disease measured, results are presented in [Table/Fig-1].

Data collection instrument: All data including age, gender, medicine consumed by patients, and examinations were collected through primary data tables. The required examinations were conducted in Pardis University Center, and the kit utilized for each examination was the same.

Instrument	Score range	Thresholds of disease activity			
		Remission	Low	Moderate	High
Disease activity score in 28 joints (DAS28)	0-9.4	≤2.6	≤3.2	>3.2 and<5.1	>5.1

[Table/Fig-1]: Instruments used to measure rheumatoid arthritis activity [3].

STATISTICAL ANALYSIS

In order to analyze the collected data, descriptive statistical methods including frequency distribution tables, graphs, and central and distribution tendencies were utilized. Kolmogorov-Smirnov test used to check the normality of data distribution. Comparing the qualitative values of the two groups was carried out using independent-samples t-test or its non-parametric equivalent. Chi-square test was employed to examine the relationship between qualitative variables. The significance level was set at $p<0.05$. Data analysis was conducted using SPSS version 20.0 Software.

RESULTS

In the beginning, for demographic variables, the participants were compared in terms of their age, gender, and disease severity [Table/Fig-2]. Age distribution in the patients and healthy group and the three patient groups was normal based on disease severity. The results of age comparison indicated that there was no significant difference between the groups in regard to their age (p>0.05). The results of that test showed that the two groups were not equal in terms of gender. However, the three groups (mild, moderate, and severe) were similar in this regard.

Our data showed that there was no significant difference in mean vitamin D level between healthy and patient groups (p-value = 0.61). We used covariance analysis to compare vitamin D level and disease activity between patient groups with mild, moderate and

Variable	Experimental group	Control group	p-value
Age	45.71	42.74	0.15
Gender			
Male	17 (17.5%)	12(38.7%)	0.014
Female	80 (82.5%)	19(61.3%)	
BMI	25.69	25.09	0.31
Vit D level	33.4788	30.0323	0.63

[Table/Fig-2]: Baseline characteristics of participants.

severe activity. Our data suggested that there is a reverse correlation between level of vitamin D and disease activity, while increasing of disease activity, level of vitamin D decreased. (p-value=0.013). Spearman correlation confirmed these correlations too, (r=-0.28, p-value=0.006). Results are shown in [Table/Fig-3] in details.

DISCUSSION

Similar to the results of the present study, the results of the cross-sectional study carried out by Sahebari M et al., on the relationship between the level of vitamin D and RA severity indicated that there was no significant difference between the two groups of the patients and the control ones in terms of serum level of vitamin D [12]. In that study, although the serum level of vitamin D of patients with new onset RA was lower than those with RA of longer periods, the difference did not show any significant relationship between disease severity and vitamin D level. However, in our study, with a drop in the level of vitamin D in patients with new onset RA, disease severity (DAS28) increased significantly (p-value<0.001). The limitations and similarities of that study and the present one include the fact that both were cross-sectional and aetiology of these differences in the level of vitamin D was not found. Our study; however, considered confounding factors like diet and consumption of vitamin D supplements that can affect the level of vitamin D were omitted in the present study. Similar results were also reported in a cohort study carried out by Cote J et al., on the relationship between incidence of RA and vitamin D level. The results of that study indicated that the relationship was not significant [11]. On the contrary, the results of the present study, the one carried out by Gheita TA et al., and the study conducted by Kostoglou-Athanassiou I et al., showed that the average serum level of vitamin D was lower in the patients with RA than the control group [10,13]. On the other hand, the results of the present study indicated a reverse relationship between vitamin D level and disease severity. However, that study included a smaller sample and background fibromyalgia in some patients which could affect the real results of the study. In that study; moreover, a significant reverse relationship was observed between the patients' BMI and disease severity while there was not such a relationship in the present study.

Another cross-sectional study was carried out by Pakchotanon R et al., on 239 patients. They observed that there was no significant relationship between serum level of vitamin D and disease severity. Another fact related to that study compared to the present study was that although the sample size was appropriate (239 patients), but the serum level of vitamin D in most individuals of control group was low and between 20 and 30 ng/dl [14].

Zakeri Z et al., carried out a cross-sectional study in Iran and observed a significant reverse relationship among serum level of vitamin D, morning stiffness, the number of swollen and tender joints and disease severity based on DAS Score 28. Although the results were in agreement with the present study, the sample size of that study was smaller (66 participants) than the present one; moreover, it did not have a control group [15].

			Category of Vitamin D levels				Total	p-value
			Deficient	Insufficient	Sufficient	Potential intoxication		
Group	Mild	Count	1	10	19	2	32	
		%	3.1%	31.3%	59.4%	6.3%	100.0%	
	Moderate	Count	5	19	9	0	33	
		%	15.2%	57.6%	27.3%	0.0%	100.0%	
	Severe	Count	2	20	10	0	32	
		%	6.3%	62.5%	31.3%	0.0%	100.0%	0.013
Total		Count	8	49	38	2	97	
		%	8.2%	50.5%	39.2%	2.1%	100.0%	

[Table/Fig-3]: Relation between level of Vitamin D and disease activity.

LIMITATION

In this study, samples were selected from a general clinic and may not represent the whole population.

It is suggested that other studies are required with a larger sample size and with the wider population.

CONCLUSION

The results of our study indicate that there is a significant reverse relation between the serum level of vitamin D and RA severity based on DAS Score 28, such that disease severity rises with a drop in the serum level of vitamin D.

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REFERENCES

[1] Boulware DW, Heudebert GR. Lippincott's Primary Care Rheumatology: Lippincott Williams & Wilkins; 2012.

[2] Firestein GS. Evolving concepts of rheumatoid arthritis. Nature. 2003;423(6937):356-61.

[3] Firestein GS, Budd R, Gabriel SE, O'Dell JR, McInnes IB. Kelley's Textbook of Rheumatology: Elsevier Health Sciences; 2012.

[4] Grazio S, Grubišić F, Kavanagh HS, Naglić ĐB, Anić B, Bakula M, et al. Vitamin D serum level, disease activity and functional ability in different rheumatic patients. The American Journal of the Medical Sciences. 2015;349(1):46-49.

[5] Hansen KE, Bartels CM, Gangnon RE, Jones AN, Gogineni J. An evaluation of high-dose vitamin D for rheumatoid arthritis. Journal of Clinical Rheumatology: practical reports on rheumatic & musculoskeletal diseases. 2014;20(2):112.

[6] Marques CDL, Dantas AT, Fragoso TS, Duarte ÂLBP. The importance of vitamin D levels in autoimmune diseases. Revista Brasileira de Reumatologia. 2010;50(1):67-80.

[7] Topilski I, Flaishon L, Naveh Y, Harmelin A, Levo Y, Shachar I. The anti inflammatory effects of 1, 25 dihydroxyvitamin D3 on Th2 cells in vivo are due in part to the control of integrin mediated T lymphocyte homing. European Journal of Immunology. 2004;34(4):1068-76.

[8] Rossini M, D'Avola G, Muratore M, Malavolta N, Silveri F, Bianchi G, et al. Regional differences of vitamin D deficiency in rheumatoid arthritis patients in Italy. Reumatismo. 2013;65(3):113-20.

[9] Patel S, Farragher T, Berry J, Bunn D, Silman A, Symmons D. Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. Arthritis & Rheumatism. 2007;56(7):2143-49.

[10] Gheita TA, Sayed S, Gheita HA, Kenawy SA. Relationships between serum 25-hydroxycalciferol, vitamin D intake and disease activity in patients with rheumatoid arthritis -TOMORROW study. Mod Rheumatol. 2014;11:01-05.

[11] Cote J, Berger A, Kirchner LH, Bili A. Low vitamin D level is not associated with increased incidence of rheumatoid arthritis. Rheumatology International. 2014;34(10):1475-79.

[12] Sahebari M, Mirfeizi Z, Rezaieyazdi Z, Rafatpanah H, Goshayeshi L. 25 (OH) vitamin D serum values and rheumatoid arthritis disease activity (DA S28 ESR), a cross-sectional study. Caspian J Intern Med. 2014;5(3):148-55.

[13] Kostoglou-Athanassiou I, Athanassiou P, Lyraki A, Raftakis I, Antoniadis C. Vitamin D and rheumatoid arthritis. Therapeutic advances in endocrinology and metabolism. 2012;3(6):181-87.

[14] Pakchotanon R, Chaiamnuay S, Narongroeknawin P, Asavatanabodee P. The association between serum vitamin D Level and disease activity in Thai rheumatoid arthritis patients. International Journal of Rheumatic Diseases. 2016;19(4):355-61. Epub 2013 Nov 13.

[15] Zakeri Z, Sandoughi M, Mashhadi MA, Shahbakhsh S. Serum vitamin D level and disease activity in patients with recent onset rheumatoid arthritis. International Journal of Rheumatic Diseases. 2016;19(4):343-47.

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