Vitamin D status and association with disease activity and quality of life in patients with rheumatoid arthritis

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Abstract

Aim: The aim of this study is to determine the vitamin D level in patients with RA (Rheumatoid Arthritis) and association with clinic and laboratory parameters and quality of life. Material and Method: Out of 111 patients with RA and 107 healthy controls who were admitted to Ahi Evran University Training and Research Hospital were included in this study. Patients underwent clinical, laboratory, functional, and quality of life examination. Laboratory tests used for patient evaluations included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein level (CRP). Disease activity was calculated by DAS28 (Disease Activity Score) and functional and quality of life was examined by RAQoL (Rheumatoid Arthritis Quality of Life), HAQ (Health Assessment Questionnaire). Larsen score was calculated to assess the radiographic damage. Results: There was no significant difference between the patient and control groups regarding age, sex and vitamin D level (p > 0.05). There were no correlation between vitamin D and Larsen score, RAQoL, HAQ, ESR, and CRP (p > 0.05). We found negative correlation between DAS28 (Disease Activity Score) and vitamin D (r = -0.416, p = 0.014). We found negative correlation between morning stiffness and vitamin D (r = -0.454, p = 0.007). We found negative correlation in the group with vitamin D deficiency (r = -0.454, p = 0.007). There was a negative correlation between morning stiffness and vitamin D deficiency (r = -0.454, p = 0.007). There was a negative correlation between DAS28 score and vitamin D deficiency (r = -0.416, p = 0.014). Discussion: This study presents a negative correlation between serum vitamin D level and DAS28. Since vitamin D has autoimmune roles, deficiency or inadequacy can cause flaring in patients with RA. In the light of these findings, we recommend vitamin D supplementation.

Keywords
Rheumatoid Arthritis; Vitamin D; Disease Activity; Deficiency; Autoimmune Role
Introduction
Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease that involves predominantly joints. The typical course of the disease presents synovial inflammation, cartilage damage and bone resorption [1]. The pathogenesis of RA is not still fully understood but some susceptibility factors may include genetic factors, environmental triggers, and activation of the acquired and natural immunity [2]. Vitamin D is a hormone that plays a major role in regulation of bone metabolism and its insufficiency causes rickets in children and osteomalacia in adults. The 25-hydroxy-vitamin D (25-OH-D) has been mentioned to inhibit T-cell expansion and down-regulate inflammatory cytokines and 1,25-dihydroxy vitamin D3 [1,25 (OH)2D3] discourage IFN-γ and IL-12 secretion [2,3]. Data indicate that sufficient vitamin D levels have a protective role against autoimmunity through inhibiting T cell expansion and inflammatory mediators in inflammatory rheumatic diseases including RA [4-6]. Also, some studies reported the association between seasonal variations in serum levels of vitamin D, disease activity and latitude in patients with RA [7,8]. Furthermore, it has been showed increasing vitamin D had no association to relative risk of developing RA [10]. However, contradictory results have been published in the literature about vitamin D and RA activity [7-24]. It has been reported that vitamin D has a negative correlation between DAS28, CRP and HAQ values [25]. Therefore, the aim of the present study was to evaluate the vitamin D level in patients with RA and association with clinic and laboratory parameters and quality of life.

Material and Method
Patients
Out of 111 patients (aged between 30 and 84 years) with RA and 107 healthy controls who were admitted to Ahi Evran University Training and Research Hospital were included in this study. The inclusion criteria were to be a volunteer patient with a rheumatoid arthritis disease. Exclusion criteria were the presence of chronic medical disorders requiring medical treatments, fractures, infectious diseases, malignant tumors, unstable hypertension, severe cardiovascular problems, major hepatic and renal insufficiency, hemorrhagic diseases, serious anemia, pregnancy, psychiatric disorder, and systemic inflammatory disease except RA. All the patients were diagnosed by the same physician (SS) at the Physical Medicine and Rehabilitation clinic. Laboratory tests used for patient evaluations included complete blood count, erythrocyte sedimentation rate, C-reactive protein level, fasting blood glucose level, hepatic and renal function tests, rheumatoid factor, and thyroid function tests. The patients who met the inclusion and exclusion criteria were admitted to the hospital outpatient clinic. The patients were fully informed about the nature and purpose of the study. Written informed consents were obtained. The study was approved by the ethics committee (Approval number: 2017-04/31).

Outcome Measures
Demographic and clinical features and measurements were performed before participation. Patient data, included age, gender, smoking history, disease duration, health assessment questionnaire (HAQ), Rheumatoid arthritis quality of life (RAQoL), disease activity score (DAS28), Larsen score, Hemoglobin, platelet, white blood cell, rheumatoid factor, sedimentation (ESR), C-Reactive protein (CRP), serum vitamin D level, number of tender joints, number of swelling joints.

Disease activity was examined by disease activity score (DAS28) including 28 joints, ESR, patient VAS (visual analogue scale) (0-100), where 0 = best and 100 = worst, and both swollen and tender joint number. DAS28 scores is defined high ( > 5.1), moderate (3.2 < 5.1) and slightly active disease ( ≤ 3.2) respectively [26]. It is calculated as follows:

\[ \text{DAS28} = 0.56\times(\text{TJC28}) + 0.28\times(\text{SJC28}) + 0.014\times\text{GH} + 0.70\times\ln(\text{ESR}) \]

TJC = tender joint count and SJC = swollen joint count. Larsen score was analyzed by the same physician from hand radiography. Wrist, 2-5 proximal interphalangeal and 2-5 metacarpophalangeal joint were assessed. Radiography was scored 0 to 5 points, where 0 = no abnormalities, 1 = slight abnormalities, 2 = small but define erosions, 3 = medium erosions, 4 = severe destructive abnormalities, 5 = mutilating abnormalities [27]. Health status was measured by HAQ. HAQ includes 20 activities of daily living with four answers (0 = any difficulty, 1 = some difficulty, 3 = much difficulty, 4 = inability) were classified into eight groups. The score is assigned to the highest point in each group. Patients were asked to use any device or aids, or help from another person [28]. Life quality was assessed by RAQoL in patients with Rheumatoid arthritis. RAQoL was formed of 30 items with a yes/no (1/0) response [29]. All the measurements were taken by the same physician. All patients received medical immunosuppressive treatment. The patients did not receive vitamin D supplementation.

Statistical analyses
Descriptive statistical methods including frequency distribution tables, graphs, central and distribution tendencies were utilized to analyze the data. Kolmogorov-Smirnov test was utilized 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 defined at \( p < 0.05 \). Data analysis was performed using SPSS version 20.0 Software.

Results
The demographic features of the patient and control group were displayed in Table 1. There was no significant difference between the patient and control groups regarding age, sex and vitamin D level \(( p > 0.05)\). There was no correlation between vitamin D level and Larsen score, RAQoL, HAQ, ESR and CRP \(( p > 0.05)\). The negative correlation was found between DAS28 and vitamin D level \(( r = -0.416, p = 0.014)\). We found negative correlation between morning stiffness and vitamin D \(( r = -0.454, \ldots)\).
Patients with RA were divided into two groups with D vitamin deficiency (0-19 ng/mL) (n = 34) and D vitamin (> 20 ng/mL). There was a negative correlation with morning stiffness in the group with vitamin D deficiency (r = -0.454, p = 0.007) and a negative correlation between DAS28 score and vitamin D deficiency (r = -0.416, p = 0.014).

Table 1. Demographic features of Rheumatoid Arthritis and Healthy Control

|                  | RA (n=111) | Control (n=107) | p     |
|------------------|------------|----------------|-------|
| Female           | 84 (%75.7) | 82 (%76.6)     |       |
| Male             | 27 (%24.3) | 25 (%23.4)     | 0.132 |
| Age              | 56.96±12.40| 56.67±11.95    | 0.908 |
| Disease duration (years) | 8.48±8.89 |               |       |
| Morning stiffness (minutes) | 22.93±24.32 |             |       |
| VAS (0-10)       | 4.76±2.49  |               |       |
| Patient Global Assessment | 4.76±2.49 |             |       |
| Doctor Global Assessment | 4.71±2.49 |             |       |
| DAS28            | 3.56±1.45  |               |       |
| Hgb (12.6-17.4 g/dL) | 13.10±1.63 |             |       |
| Pts (130-450 10^3/L) | 290.76±99.34 |           |       |
| WBC (4-10.2 10^3) | 7.18±2.49  |               |       |
| RF (0-14 IU/mL)  | 73.53±136.96|              |       |
| ESR (mm/h)       | 22.77±18.36|               |       |
| RAQol (0-30)     | 9.95±6.49  |               |       |
| CRP (0.015-0.50 mg/dL) | 1.15±3.12 |           |       |
| Vitamin D (20-60 ng/mL) | 24.93±15.08 | 26.37±18.33 | 0.973 |
| Larsen score     | 15.60±18.92|               |       |
| Number of swelling joint | 1.84±3.33 |             |       |
| Number of tender joints | 4.84±4.95 |             |       |
| HAQ score        | 1.07±0.58  |               |       |

Discussion

This study investigated vitamin D level and association with disease activity and quality of life in patients with RA and healthy controls. The results indicated that there is no significant difference in vitamin D levels in patients with RA compared with healthy controls. And also in the RA group, there was a negative correlation between DAS-28 and morning stiffness. This negative correlation also persisted when vitamin D was lower than 20 ng/mL. But we didn't note any correlation between acute-phase response rather than causing inflammation [40].

There are some limitations in our study. First, the patient's long-term follow up was not conducted. Second, we did not note clothing, sun exposure and season. Third, we did not measure vitamin D receptors.

In conclusion, this study presents a negative correlation between serum vitamin D level and DAS28. This study concluded that serum vitamin D can be measured as an alternative marker in patients with RA.

Since vitamin D has autoimmune roles, deficiency or inadequacy can cause flaring in patients with RA. In the light of these findings, we recommend vitamin D supplementation.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national re-
Conflicts of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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