Arch Clin Exp Med 2018;3(3):127-131. e-ISSN: 2564-6567

DOI:10.25000/acem.440559 Araştırma makalesi / Research article

The impact of vitamin D on rheumatoid arthritis: real or just patient's perception?

Vitamin D'nin romatoid artrit üzerindeki etkisi: gerçek mi yoksa sadece hastanın algısı mı?

Aslı Çalışkan Uçkun [1], Fatma Gül Yurdakul [1], Ayşegül Kılıçarslan [2], Bedriye Başkan [1], Filiz Sivas [1], Semra Duran [3], Hatice Bodur [4]

Abstract

Aim: In this study, our aims were to identify vitamin D levels in rheumatoid arthritis (RA) individuals as compared to controls and the impact of vitamin D levels on both objective and subjective assessments in RA patients.

Methods: The current study was a prospective case-control study conducted on 108 RA patients and 50 age-gender matched healthy controls. We first compared the levels of vitamin D among the RA patients and controls. Demographic and clinical data, parameters of disease activity, inflammatory markers, rheumatoid factor and anti-cyclic citrullinated peptide seropositivity and radiological damage scores were recorded in RA patients. These patients were also demanded to complete RA Quality of Life Questionnaire (RAQoL), fatigue severity scale (FSS) and Health Assessment Questionnaire (HAQ).

Results: D vitamin levels in RA patients were significantly lower than healthy controls (p=0.001). Vitamin D deficiency was determined in 73% of the RA patients and 52% of the controls. Vitamin D deficiency was not associated with disease activity (p=0.862). There was no significant relationship among vitamin D levels and all subjective and objective assessments (p>0.05 for all).

Conclusion: Vitamin D deficiency was common in RA participants than normal population. However, it was not shown that there was a significant relationship between vitamin D levels and objective and subjective assessments of disease, including disease activity, inflammatory markers, rheumatoid factor and anti-cyclic citrullinated peptide seropositivity, radiological damage scores, RAQoL, FSS and HAQ.

Key Words: Rheumatoid Arthritis, Vitamin D, Radiological damage

Öz

Amaç: Bu çalışmadaki amaçlarımız, romatoid artrit (RA) hastalarında D vitamini düzeylerini ve D vitamini düzeylerinin objektif ve subjektif değerlendirmelere etkisini belirlemektir.

Yöntemler: Bu çalışma, 108 RA hastası ve yaş ve cinsiyete göre eşleştirilmiş 50 sağlıklı kontrol üzerinde yapılan bir prospektif olgu-kontrol çalışmasıdır. Öncelikle RA hastaları ve kontroller arasında D vitamini düzeylerini karşılaştırdık. RA hastalarının demografik ve klinik verileri, hastalık aktivitesi parametreleri, inflamatuvar belirteçleri, romatoid faktör ve anti-siklik sitrüllenmiş peptid seropozitifliği ve radyolojik hasar skorları kaydedildi. Hastalardan ayrıca RA Yaşam Kalitesi Anketi (Rheumatoid Arthritis Quality of Life, RAQoL), yorgunluk şiddet ölçeği (Fatigue Severity Scale, FSS) ve Sağlık Değerlendirme Anketi (Health Assessment Questionnaire, HAQ) tamamlamaları istendi.

Bulgular: RA hastalarında D vitamin düzeyleri sağlıklı kontrollerden anlamlı derecede düşüktü (p=0,001). RA hastalarının % 73'ünde ve kontrollerin % 52'sinde D vitamini eksikliği tespit edildi. D vitamini eksikliği, hastalık aktivitesi ile ilişkili değildi (p=0,862). D vitamini seviyeleri ile tüm subjektif ve objektif değerlendirmeler arasında anlamlı bir ilişki bulunamadı (hepsi için p>0,050).

Sonuç: D vitamini eksikliği RA hastalarında normal popülasyona göre daha sık görülmektedir. Ancak, vitamin D düzeyleri ile hastalık aktivitesi, inflamatuvar belirteçler, romatoid faktör ve anti-siklik sitrüllenmiş peptid seropozitifliği, radyolojik hasar skorları ve RAQoL, FSS, HAQ ile ilişkili hastalığın objektif ve subjektif değerlendirmeleri arasında anlamlı bir ilişki bulunduğu gösterilemedi.

Anahtar kelimeler: Romatoid Artrit, D vitamini, Radyolojik hasar

[1] Ankara Numune Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Ankara, Turkey.

[2] Ankara Physical Medicine and Rehabilitation Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Ankara, Turkey.

[3] Ankara Numune Training and Research Hospital, Department of Radiology, Ankara, Turkey.

[4] Yıldırım Beyazıt University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Ankara, Turkey.

Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the author.
Çıkar Çatışması: Yazar çıkar çatışması bildirmemiştir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Geliş Tarihi / Received: 04.07.2018
Kabul Tarihi / Accepted: 04.09.2018
Yayın Tarihi / Published: 30.11.2018

Sorumlu yazar / Corresponding author:
Aslı Çalışkan Uçkun
Adres/Address: Ankara Numune Eğitim ve Araştırma Hastanesi, Talatpaşa Bulvarı No:5 Altındağ / Ankara, Türkiye.
e-posta: draslical@gmail.com
Tel/Phone: 05054953117

Introduction

Vitamin D is a fat-soluble seco-steroid hormone that is synthesized naturally in the human skin by sunlight. In the liver, it is transformed to 25-hydroxyvitamin D [25 (OH)D], which is the most important metabolite for determining the capacity of vitamin D in the body. Thereafter, it is transformed into the biologically active form [1, 25 (OH)2D] [1]. It has been shown that vitamin D takes an important part not only in bone metabolism, but also in the immune system [2, 3].

Rheumatoid arthritis (RA) is a widespread, chronic inflammatory disorder (affecting almost 1% of the world population) characterized by progressive joint destruction and various systemic involvements. Although its etiopathogenesis is not completely understood, various genetic and non-genetic factors have been responsible for RA. It was shown that inadequate vitamin D levels might be an environmental trigger of RA [4]. Another interesting issue is whether vitamin D has an inverse relation with RA activity. The evidence from various studies concerning the link between serum vitamin D concentration and disease activity is inconsistent [5-7]. Some studies also revealed that the impact of inadequate vitamin D levels on disease activity in the RA individuals was associated with more subjective variables (eg, Visual Analog Scale (VAS) pain, tender joint count (TJC)) than a real objective immunomodulatory effect [8]. Both objective and subjective patient-based assessments are required to understand the potential association among RA and the level of vitamin D. Therefore, our aims were to identify vitamin D levels in RA individuals as compared to controls and the impact of vitamin D levels on both objective and subjective assessments in RA patients.

Material and methods

Our prospective case-control study was conducted in the Physical Medicine and Rehabilitation department from October 2017 to March 2018. The ethical approval of the present study (Ethics Committee of Ankara Numune Training and Research Hospital; Decision no/date: 2014-726/03-01-2014) was obtained. All participants gave informed consent to participate in the current study in accordance with the Helsinki Declaration.

Patients with RA based on European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2010 criteria [9], diagnosed at least one year, aged greater than 18 were included. Besides, age-gender matched healthy individuals from participating patients' relatives as control were included. Subjects were excluded if they had hyperparathyroidism, hyperthyroidism, malnutrition, renal and hepatic dysfunction, previous biologic therapy history and received Vitamin D supplementation or drugs which can affect Vitamin D metabolism (i.e. thyroxin, diuretics, and anticonvulsants) in the past 12 months.

Age (years), gender, body mass index (BMI) (kg/m2), waist circumference (cm), smoking status, duration of disease (months), the status of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), morning stiffness time (minute), the patient's assessment of global well-being (10 cm VAS score), TJC (0-28), RA Quality of Life Questionnaire (RAQoL) (0-30) [10,11], fatigue severity scale (FSS) (0-7) [12], and Health Assessment Questionnaire (HAQ) (0-3) [13], swollen joint count (SJC) (0-28) were documented. Serologic evaluation including the serum concentration of 25(OH)D (ng/mL), erythrocyte sedimentation rate (ESR) (mm/h) , and C-reactive protein (CRP) (mg/dL) were analyzed. Finally, all x-ray examinations of the hands in posteroanterior view were estimated considering the van der Heijde modified Sharp score (vdHSS) [14].

Vitamin D level was evaluated with the blood test by the chemiluminescence method. Vitamin D status <20 ng/mL was determined as deficiency, vitamin D status < 10 ng/mL was determined as severe deficiency [15, 16]. We split 108 RA participants into two categories based on 25(OH) D levels-less than 20 ng/mL as cut-off value [17].

The disease activity was assessed using the Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR). All RA participants were categorized into four groups according to their DAS28-ESR: Remission (<2.6), low disease activity (2.6-3.2), moderate disease activity (>3.2–5.1) and high disease activity (DAS28>5.1) [18].

Statistical Analysis

Whole analyses were established using Statistical Package for the Social Sciences-21.0 (SPSS 21.0) software. Shapiro-Wilk test was utilized to test for normality; parametric and nonparametric tests were performed according to results. We used mean ± standard deviation (SD) for normally distributed variables (age, waist circumstance, BMI) and median, minimum-maximum for continuous variables which are not normally distributed. Categorical data are presented as percentages. Differences between patients and controls were checked using Mann-Whitney U test or independent samples T-test according to normality test. The homogeneity of the distributions of categorical variables was determined using chi-square tests. Spearman correlation coefficient was used and the correlation coefficient ranges in value from −1 to +1. P<0.050 was defined as statistically significant.

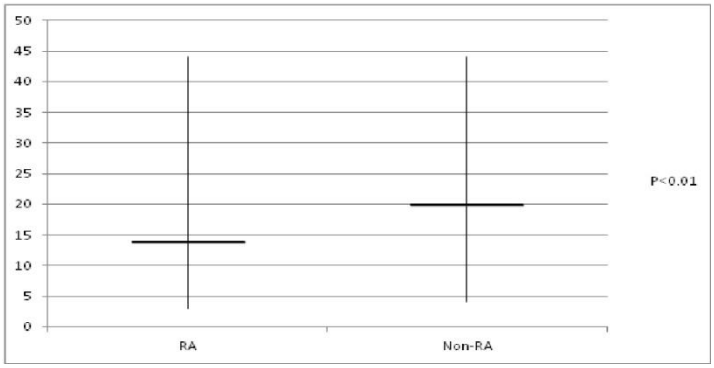
Results

The current study involved 108 participants with RA (female to male ratio: 3) and 50 healthy controls (female to male ratio: 4.56) whose mean ages were 52.66 ±12.23 years and 51.54±9.72 years, respectively. Demographic features of the individuals are summarized in Table 1. There was no significant difference for age, gender, BMI, and smoking status (Table 1), while serum vitamin D concentrations were significantly lower in RA subjects compared to the controls [14.69±9.90 ng/ml, 20.46±9.79 ng/ml, respectively; (p=0.001)] (Figure 1).

Table 1: Demographic and clinical features of RA and healthy controls.

	Patients with RA (n=108)	Control (n=50)	p
Age (years)$^{\mu}$	52.66±12.23	51.54±9.72	0.343
Female sex$^{\pi}$	81(75)	41(82)	0.329
BMI (kg/m^2)$^{\mu}$	28.61±5.86	26.82±5.86	0.064
Current smokers$^{\pi}$	44 (40.7)	20(40)	0.930
Vitamin D level (ng/ml)$^{\mu}$	14.69±9.90	20.46±9.79	0.001

$^{\mu}$: mean±standard deviation, $^{\pi}$: n (%)
RA: Rheumatoid arthritis, BMI: Body mass index.



RA: Rheumatoid arthritis
Figure 1: Vitamin D levels (ng/ml) (Y axis) in the RA and healthy controls.

Variables	All participants (n= 108)	Vitamin D <20 ng/mL (n= 79)	Vitamin D ≥20 ng/mL (n= 29)	P
Age (years)[μ, β]	52.66±12.23 54 (21-79)	51.84±12.16 53 (21-79)	54.89±12.36 56 (23-75)	0.177
Female sex[π]	81 (75)	60 (75.9)	21 (72.4)	0.707
BMI (kg/m^2)[μ, β]	28.61±5.86 28.54 (14.86-45.79)	28.82±5.63 28.72 (18.61-44.14)	28.04±6.53 27.10 (14.86-45.79)	0.390
Waist circumference, (cm)[μ, β]	96.10±14.82 97(58-136)	96.88±14.71 98(65-136)	93.96±15.15 95(58-132)	0.248
Current smokers[π]	44 (40.7)	34 (43)	10 (34.5)	0.423
Disease duration (months)[μ, β]	147±92 132 (12-468)	145±94 120 (12-468)	151±90 144 (12-420)	0.654
RF positivity[π]	80 (74.1)	62 (78.5)	18 (62.1)	0.085
CCP positivity[π]	80 (74.1)	59 (74.7)	21 (72.4)	0.811

Table 2: Comparison of all participants' descriptive data in respect to vitamin D status.
[μ]: mean±standard deviation, [π]: n (%), [β]: median (min-max)
BMI: Body mass index, RF: Rheumatoid factor, CCP: cyclic citrullinated peptide.

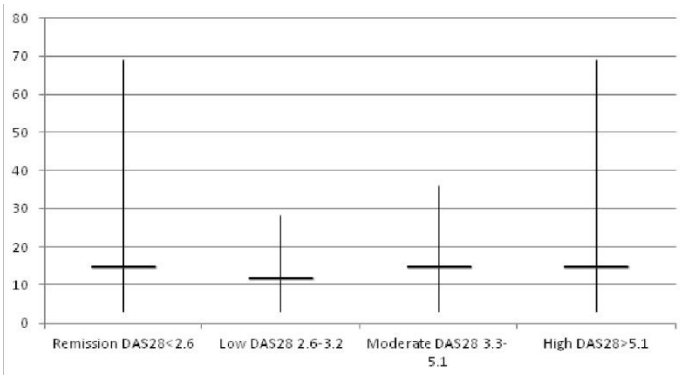
Variables	All participants (n=108)	Vitamin D <20 ng/mL (n=79)	Vitamin D ≥20 ng/mL (n=29)	P
Morning stiffness (minute)[μ, β]	39.72±66.74 5 (0-300)	36.51±63.56 5 (0-300)	48.44±75.26 15 (0-300)	0.472
VAS pain (0–10) [μ, β]	3.63±2.85 3 (0-9)	3.5±2.81 3 (0-8)	3.79±3.0 4 (0-9)	0.758
TJC[μ, β]	8.26±9.57 4 (0-28)	8.77±9.61 7 (0-28)	6.89±9.48 2 (0-28)	0.576
RAQoL[μ, β]	12.75±10.37 11 (0-30)	12.58±10.29 11 (0-30)	13.24±10.77 11 (0-30)	0.803
FSS[μ, β]	3.55±2.07 2.72 (1-6.78)	3.45±2.10 2.55 (1-6.78)	3.82±1.99 3.33 (1-6.78)	0.238
HAQ[μ, β]	0.96±0.80) 0.75 (0-2.75)	0.96±0.79 0.75 (0-2.75)	0.98±0.86 0.75 (0-2.75)	0.942
SJC[μ, β]	0.71±2.28 0 (0-21)	0.79±2.54 0 (0-21)	0.48±1.35 0 (0-6)	0.343
ESR (mm/h)[μ, β]	20.13±13.78 18 (2-90)	20.31±14.22 18 (2-90)	19.65±12.72 18 (4-46)	0.936
CRP (mg/dL)[μ, β]	11.33±15.16 5.82 (0.17-72.72)	11.98±15.89 6.5 (0.2-72)	9.54±13.05 4.54 (0.17-60.5)	0.458
van der Heidje erosion score[μ, β]	6.61±11.76 2.5 (0-71)	6.86±12.09 2.5 (0-71)	5.93±11.01 2.5 (0-57.50)	0.887
van der Heidje joint space narrowing score[μ, β]	15.96±12.17 13.5 (0-56)	16.93±12.57 14 (1-56)	13.34±10.77 13 (0-38.5)	0.182
DAS 28[μ, β]	3.19±1.37 3.01 (0.49-6.55)	3.20±1.37 3.01 (0.49-6.55)	3.15±1.39 3.25 (0.97-6.28)	0.862

Table 3: Comparison of clinical, laboratory, and radiological characteristics in respect to vitamin D status.

[μ]: mean±standard deviation, [π]: n (%), [β]: median (min-max)
SD: Standart deviation, VAS: visual analogue scale, TJC: tender joint count, RAQoL: RA Quality of Life Questionnaire, FSS: fatigue severity scale HAQ: Health Assessment Questionnaire, SJC: swollen joint count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, DAS28: Disease Activity Score 28.

The ratios of severe deficient, deficient, and non-deficient vitamin D levels for RA patients were 40%, 33%, and 27%, respectively. The ratios of severe deficient, deficient, and non-deficient vitamin D levels for non-RA controls were 16%, 36%, and 48%, respectively. There were significant differences between groups in respect of vitamin D status (p=0.005).

Demographic and clinical, laboratory and radiological characteristics in RA individuals are summarized in Table 2 and Table 3, respectively, according to vitamin D status category. Age, gender, BMI, waist circumference, smoking status, disease duration, positivity of RF and anti-CCP were not different between groups. No significant difference was determined among the vitamin D status groups in patient reported subjective assessments (Duration of morning stiffness, VAS, number of tender joints, RAQoL, FSS, HAQ scores), and in objective assessments (SJC, ESR, CRP, radiologic damage scores) (Table 2-3). There was no correlation between DAS28-ESR and the levels of 25(OH) D (p=0.862). Additionally, we demonstrated that the serum concentrations of vitamin D were not significantly different when evaluated according to grades of disease activity (Figure 2).



DAS28: Disease Activity Score 28

Figure 2: Distribution of Vitamin D levels (ng/ml) (Y axis) according to the disease activity scores based on DAS 28.

Discussion

The importance of vitamin D in RA is a still mystery due to conflicting results in the literature. It is another debatable issue whether the impact of vitamin D on disease activity in RA occurs by patient perception effect rather than immune modulator effect. For this reason, the purpose of the current study was to analyze the impact of vitamin D in both the subjective and the objective components in established RA. Our study demonstrated that although vitamin D insufficiency was significantly higher in RA participants than control group, we did not observe any impact of vitamin D deficiency on objective assessments or even subjective assessments.

In countries near equator, where humans synthesize vitamin D on their skin for longer periods during the year, the low incidence of rheumatic disease prompted to research the role of vitamin D on the existence of rheumatic diseases [19]. Besides, an experimental study in 1998 showed that vitamin D receptor agonists reduced disease expression and worsening of arthritis [20]. Thus, various studies to date which had inconsistent results have been conducted to investigate whether there is a connection between the presence of rheumatic diseases and vitamin D level [1, 21]. Factors such as age, gender, BMI, smoking status, living environment, season, receiving vitamin D supplementation may affect the results. Therefore, in order to decrease the influence of confounding factors, we chose healthy controls from patients' relatives who shared the similar living

environment and measured the level of vitamin D in winter to decrease the seasonal effect. We also excluded the participants who received vitamin D supplementation in the past 12 months. Our age-gender matched participants were also similar in terms of smoking status and BMI. Nevertheless, the current study showed that the vitamin D levels were lower in RA participants when compared with healthy participants. Similarly, RA participants had a higher rate of vitamin D deficiency than healthy controls, 73%, 52% respectively. This rate in RA patients is parallel to the data reported to date that demonstrated vitamin D deficiency achieving more than 80% [2]. Our findings were consistent with the recent two meta-analyses regarding the lower levels of D vitamin in RA [4, 19]. In addition to this, another meta-analysis demonstrated that vitamin D intake lowered the chance of developing RA [22]. In the light of all these data, vitamin D deficiency may have a role in the etiopathogenesis of RA, but we should state that low vitamin D levels in our established RA individuals may be dependent on reduced outdoor activities and, thus reduced sun exposure.

Previous studies of the relation among disease activity and vitamin D levels in RA participants demonstrated conflicting findings [19]. Our study demonstrated that serum vitamin D concentrations were not connected with disease activity, its individual objective and subjective components, inflammatory markers, RF and anti-CCP seropositivity, and radiological damage scores. We also assessed serum vitamin D concentration according to disease activity status, due to describing negative relationship between DAS28 and vitamin D levels in only the participants with active RA in some studies [23]. In this manner, we also found no significant differences according to disease activity categories. Although there have been many reports to analyze the connection between the disease activity and vitamin D levels in the RA participants, there were limited studies that conducted in the context of the levels of vitamin D and radiological damage, which is an objective indicator of disease severity. A well-powered longitudinal study by Baker et al. [7], found that vitamin D deficiency (<20 ng/ml) were not related to disease activity, inflammatory markers, and radiographic progression. Another longitudinal study demonstrated that D vitamin levels were associated with disease activity, fatigue, and morning stiffness, but any effect of vitamin D levels on radiographic damage was not shown [17]. Polasik et al. [5], also found no significant association among the vitamin D levels and either disease activity and radiologic damage in the RA participants. Finally, the other two studies showed that while lower vitamin D levels were related with disease activity, not related with radiological structural damage in RA [1, 24]. Although the above-mentioned studies, including ours; two of which were longitudinal, showed different results for various objective or subjective assessments regarding to RA and vitamin D deficiency, none of them found any significant effect of vitamin D deficiency on radiological damage, which is an important objective indicator of disease severity.

Higgins et al. [8] evaluated DAS28-ESR with and without VAS and showed that the level of vitamin D was only correlated with VAS. They emphasized that vitamin D deficiency might cause increased disease activity by affecting pain perception negatively. Therefore, we also evaluated the patients with parameters based on their perception. However, we did not determine any correlation of vitamin D level with the assessments related to patient perception (i.e. VAS, TJC, fatigue, morning stiffness, quality of life, functional disability) as well as in objective assessments (i.e. SJC, inflammatory markers, radiologic damage scores).

There are some limitations in the present study. Firstly, the cross-sectional character of our study did not permit for assessment of the cause-effect relation among vitamin D levels and components of RA. Secondly, we didn't question the patients in terms of their amount/frequency of outdoor activities and sunlight exposure. Finally, this present study included participants with a variable RA duration. Therefore, prospective longitudinal studies in the individuals with similar disease duration and sunlight exposure time are needed to explain impact of vitamin D on RA.

In conclusion, our study demonstrated that serum vitamin D concentrations were lower in RA patients. Vitamin D deficiency may play a role in the etiopathogenesis of RA, but we primarily attribute this result to the reduced outdoor activities and reduced sun exposure in RA individuals than healthy controls. This study also refuted the role of vitamin D on objective or subjective parameters in the patients with RA.

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