Association of Vitamin D with Disease Activity in Rheumatoid Arthritis and Ankylosing Spondylitis

Romatoid Artrit ve Ankilozan Spondilitte Vitamin D'nin Hastalık Aktivitesi ile İlişkisi

Vitamin D ve Hastalık Aktivitesi / Vitamin D and Disease Activity

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Özet

Amaç: Vitamin D eksikliğinin, romatoid artrit (RA) ve ankilozan spondilit (AS) gibi otoimmun hastalıklarda başlatıcı bir neden mi yoksa hastalık aktivitesiyle ilişkili mi olduğu hala merak edilen bir konudur. Çalışmamızın amacı, Th1 baskın hastalıklardan olan RA ve AS hastalarında serum vitamin D seviyeleri ile hastalık aktiviteleri arasındaki ilişkiyi değerlendirmektir. Gereç ve Yöntem: Çalışmamız, retrospektif olarak 92 RA'li hasta, 100 AS'li hasta ve 62 sağlıklı kontrolün dosyalarından elde edilmiş bilgileri içermektedir. Çalışmaya alınanların yaşı, cinsiyeti, hastalık süreleri, kullandığı ilaçlar, vitamin D seviyeleri, kalsiyum, C-reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESH) değerleri kayıt edildi. Hastalık aktiviteleri RA'li hastalarda hastalık aktivite skoru-28 (DAS28) ile, AS'li hastalarda ise bath ankilozan spondilit hastalık aktivite indeksi (BASDAİ) ile değerlendirildi. Bulgular: Vitamin D seviyeleri tüm gruplarda düşüktü. AS hastalarında, vitamin D seviyeleri ile BASDAİ, ESH ve CRP arasında istatiksel olarak negatif korelasyon yoktu (sırasıyla, r = -0.059, *P* = .560, r = -0.072, *P* = .473, r = -0.112, *P* = .268). RA'li hastalarda ise vitamin D düzeyi ile DAS28 arasında anlamlı negatif korelasyon yoktu (r = -0.090, *P* = .392). Tartışma: Çalışmamızda, tüm gruplarda vitamin D seviyeleri düşük bulundu ve bu vitamin D eksikliğinin, RA ve AS'in etyolojisinden ziyade hastalık aktivitesi ile ilişkili olabileceğini akla getirmektedir.

Anahtar Kelimeler

Vitamin D; Romatoid Artrit; Ankilozan Spondilit; Hastalık Aktivitesi

Abstract

Aim: Vitamin D deficiency in autoimmune disorders such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS), whether an initiator cause or associated with disease activity is still wondered. The aim of our study is to investigate the association between serum vitamin D levels and disease activity in subjects with RA and AS which are known to be Th1 dominant diseases. Material and Method: The study included the data of 92 patients with RA, 100 patients with AS and 62 healthy controls, which were retrospectively obtained from the patient files. The age, gender, duration of the disease, medications, levels of vitamin D, calcium, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were recorded. Disease activities were evaluated by Disease Activity Score-28 (DAS28) in patients with RA and Bath Ankylosing Spondylitis Disease Index (BASDAI) in patients with AS. Results: Vitamin D levels were low in all groups. In AS patients, there was no statistical negative correlation among vitamin D levels and BASDAI, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (r = -0.059, *P* = .560, r = -0.072, *P* = .473, r = -0.112, *P* = .268, respectively). In RA patients, there was also no significant negative correlation between vitamin D levels and DAS28 (r = -0.090, *P* = .392). Discussion: In our study, low serum vitamin D levels were found in all groups, and it is suggested that vitamin D deficiency may be associated with the disease activity rather than the etiology of RA and AS.

Keywords

Vitamin D; Rheumatoid Arthritis; Ankylosing Spondylitis; Disease Activity

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory illness with joint involvement as well as extra-articular findings in which etiology has not been fully elucidated. It is 2-4 times more common in women than men. RA can be observed in all age groups with a peak incidence at 40-60 years of age. Genetic and environmental factors have been implied in the etiology.[1,2] Ankylosing spondylitis (AS) is a chronic inflammatory illness that particularly affected the spine, enthesis areas and the peripheral joints. Genetic and environmental factors also had roles in the etiology of this disease which is more commonly diagnosed in men and ranged 20-40 years of age. T helper (Th) cells have significant role in the etiopathogenesis of both illnesses which are known as Th1-dominant disorders.[3,4]

Vitamin D is a hormone regulating calcium homeostasis and protection of skeleton. In addition, it is demonstrated that it is involved in immune function in recent years. This is supported by discovery of vitamin D receptors (VDRs) in peripheral mononuclear blood cells.[5,6] Vitamin D particularly prevents Th1 proliferation and decreases the release of Th1 cytokines including interleukin-2, interferon-α and tumor necrosis factor-α (TNF-α). Furthermore, it was shown that vitamin D addition prevented the onset and progress of inflammatory arthritis in rats.[7,8] However, there are different opinions about the relationship between vitamin D levels and disease activities in RA and AS patients in the literature.[9-17]

The aim of the current study is to detect vitamin D levels and to evaluate association between vitamin D levels and diseases activities in RA and AS patients.

Material and Method

All the cases were admitted to the Physical Medicine and Rehabilitation Department between December 2012 and March 2013. The cases were diagnosed as rheumatoid arthritis regarding American College of Rheumatology criteria[18] and those diagnosed as ankylosing spondylitis regarding modified New York criteria[19] as well as controls who were retrospectively removed from the patient files. The exclusion criteria were intestinal disorders (terminal ileitis, ulcerative colitis), malnutrition, hepatic and renal dysfunction, hyperparathyroidism, hyperthyroidism and medications that can affect bone and vitamin D metabolism (anticonvulsants, corticosteroids, diuretics and thyroxin).

The age and gender of patients, duration of the disease, medications, vitamin D levels, calcium, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were registered. Vitamin D deficiency was defined as <20 ng/ml. The disease activities were evaluated by Disease Activity Score-28 (DAS28) in cases with RA and Bath Ankylosing Spondylitis Disease Index (BASDAI) in cases with AS. The cases with RA were divided into subgroups according to DAS28 as follows: DAS28≤3.2 as mild; 3.2<DAS28≤5.1 as moderate; and DAS28>5.1 as high in terms of disease activity. The patients with AS were divided into subgroups according to BASDAI as follows: BASDAI<4 as mild and BASDAI≥4 as moderate-high in aspect of disease activity.

Statistical analysis was done by SPSS for Windows, version 13 (SPSS, Chicago, IL). Descriptive statistics (frequency, percentage, mean, standard error) were used in the assessment of data. Chi-square test was used for categorical variables, whereas Mann Whitney U test was used in the comparisons of continuous variables. Spearman test was performed as correlation analysis. $p<0.05$ was accepted as the significant level.

Results

There were 92 RA cases, 100 AS cases and 62 controls in the study. Demographic and clinical characteristics of patients and control group were shown in Table 1. There were 24 (26.1%) patients with mild activity, 40 (43.5%) patients with moderate activity and 28 (30.4%) patients with high activity in RA cases. 21 (22.8%) RA patients were using anti-TNF agents while 71 (77.2%) patients were using disease modifying antirheumatic drugs such as methotrexate, leflunomide or sulfasalazine. There were 67 (67%) patients with mild activity, 33 (33%) patients with moderate-high activity in AS subjects. 29 (29%) AS patients were using anti-TNF agents while 71 (71%) patients were using non-steroidal anti-inflammatory drugs or sulfasalazine.

Table 1. Demographic and clinical characteristics of patients and control group

	Sex (F/M)	Age (years)	Disease duration (years)	Vitamin D (ng/ml)
RA (n = 92) Mean±SD	83/9	49.58±13.87	8.83±7.24	14.21±8.00
AS (n = 100) Mean±SD	32/68	40.68±10.55	10.90±9.30	14.50±7.01
Kontrol (n = 62) Mean±SD	35/27	43.85±8.01	-	13.43±5.79

AS: Ankylosing Spondylitis, F/M: Female to Male ratio, RA: Rheumatoid Arthritis, SD: Standard Deviation

Biochemical parameters and complete blood count were within normal range in all groups. Mean vitamin D levels were low in all groups (Table 1). There was no significant difference in vitamin D levels between RA patients and control groups ($p>0.05$). There was also no statistical difference in vitamin D levels between AS and control groups ($p>0.05$). There was vitamin D deficiency in 73 (79.3%) of the patients with RA; in 77 (77.0%) of the patients with AS; and in 53 (85.5%) of the controls. There was no significant difference between RA and control groups, and AS and control groups regarding vitamin D deficiency ($p>0.05$).

In RA patients, mean DAS28 score was 4.30±1.61, whereas mean ESR and CRP levels were 29.83±18.85 mm/h and 17.67±27.69 mg/l, respectively. There was no significant difference in vitamin D levels among RA patients with mild, moderate and high disease activity ($p>0.05$). Also, mean vitamin D levels were low in both anti-TNF using and non using RA patients and there was no statistical difference between these groups (15.47±8.45 ng/ml, 13.84±7.89 ng/ml, $p>0.05$, respectively). In RA patients, there was no statistical negative correlation between DAS28 and vitamin D levels. No such correlation was detected for ESR and CRP (Table 2). Correlations between disease activities and vitamin D levels were shown in Table 2.

In AS patients, mean BASDAI score was 3.28±1.96, whereas mean ESR and CRP levels were 21.54±20.42 mm/h and 11.59±18.61 mg/l, respectively. There was no significant difference in vitamin D levels among AS subjects with mild and moderate-high disease activity ($p>0.05$). Also, mean vitamin D levels were low in both anti-TNF using and non using AS patients and there was no statistical difference between these gro-

Table 2. Correlations between disease activities and vitamin D levels

	DAS28	BASDAI	ESR	CRP
RA (vitamin D)				
r	-0.091	-	0.032	0.060
p	0.393	-	0.768	0.577
AS (vitamin D)				
r	-	-0.059	-0.072	-0.112
p	-	0.560	0.473	0.268

AS: Ankylosing Spondylitis, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, DAS28: Disease Activity Score, ESR: Erythrocyte Sedimentation Rate, RA: Rheumatoid Arthritis, Statistically significant correlation (p<0.05)

ups (14.13±6.83 ng/ml, 14.65±7.12 ng/ml, p>0.05, respectively). In AS patients, there was no statistical negative correlation between vitamin D levels and BASDAI, ESR and CRP (Table 2).

Discussion

Our results demonstrated that vitamin D levels were low in all groups; that there was no statistical negative correlation between vitamin D levels and disease activity, ESR and CRP in patients with AS. However, there was no negative correlation between vitamin D levels and disease activity in patients with RA.

Although vitamin D is necessary in calcium homeostasis, it also contributes to regulation of immune system.[20] Vitamin D levels can be influenced by several factors including dietary habits, life style changes and sunlight exposure.[21] In our study, vitamin D levels were found to be low in both patient and control groups, and there was no significant difference among groups regarding vitamin D levels. In a study on vitamin D levels in cases with inflammatory arthritis, vitamin D levels were determined to be low in patients with RA (15.0±8.4 ng/ml) and AS (12.7±6.9 ng/ml) similar to our study.[15] In another study, vitamin D assays were reported as 19.3 ng/ml in control group, whereas 24.0 and 24.7 ng/ml in female and male patients with RA, respectively.[13] The study by Furuya et al.[22] included 4793 cases with RA, mean vitamin D level was found 16.9 ng/ml and vitamin D deficiency was detected in 71.8% of the cases. In another study, vitamin D deficiency was detected in 26% of the AS patients.[23] In the current study, there was vitamin D deficiency in 73 (79.3%) of the RA patients; in 77 (77.0%) of the AS patients; and in 53 (85.5%) of the controls. Although detection of vitamin D deficiency in both patient and control groups propose that the role of vitamin D in these illnesses should be discussed, this finding can be explained by detection of vitamin D deficiency in a comprehensive assessment of our population and by the fact that our study was conducted during winter and first months of spring where vitamin D deficiency has a peak incidence.[24,25]

Vitamin D exerts its effect via VDRs and inhibits autoimmunity. Thus, there should be a potential relationship among vitamin D deficiency and autoimmune diseases, and it may play a role in the etiopathogenesis of these diseases.[26] In the current study, we determined no significant difference regarding disease activity in terms of vitamin D levels when we divided RA cases based on disease activity as mild, moderate and high. However, we found no statistical negative correlation between vitamin D levels and DAS28. In some previous studies, no significant association was determined between disease activity and vitamin D levels and their results were consistent with our study.[10,14,15] On contrary, some studies reported a significant negative correlation.[9,11-13] These different results may be clarified by number of patients included and variations in disease activity among studies.

Clinical trials demonstrated that vitamin D acts as an endogenous immunoregulator that suppresses active T cells and cell proliferation in AS.[26] In the present study, we observed nonsignificant negative association among vitamin D levels and BASDAI, ESR and CRP in AS patients. Arends et al.[24] revealed that there was no significant association among vitamin D levels and BASDAI, ESR and CRP. The study by Braun-Moscovic et al.[15] also determined no association between vitamin D levels and BASDAI. Mermerci et al.[16] pointed that vitamin D levels were no statistical negatively associated with ESR and CRP and their outcomes are similar to the current study, although there was no significant association between vitamin D level and BASDAI. Lange et al.[17] detected a negative correlation between vitamin D level and BASDAI, ESR and CRP. The differences in the results of these studies may be explained by low sample of the study groups and alterations in the geographic regions, seasons, individual dietary and dressing habits in which the studies are conducted. The major limitations regarding with the present study were the duration and the degree of sun exposure and dietary habits in case of the participants.

Is the problem in the vitamin D deficiency in subjects with RA and AS diseases clear up only by introducing the disease into remission or how much daily vitamin D supplement should be in these patients? Our study did not have enough data for the answer, because the vitamin D levels were also low in the control group. However, it was the interesting that none of these controls were not suffering from musculoskeletal complaints. However, the complaints due to vitamin D deficiency may lead to the delusion which increases the disease activity in cases with RA. It is reported that the clinician should consider this situation when assessing the activation of the disease.[10]

Conclusions

The serum vitamin D levels were low in all groups, therefore, vitamin D supplementation may be needed in RA and AS patients. Also, our study is suggested that vitamin D deficiency may be associated with the disease activity rather than the etiology of RA and AS.

Competing interests

The authors declare that they have no competing interests.

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