The effect of vitamin D deficiency on fatigue and depression in patients with axial spondyloarthritis

Aksiyal spondiloartritli hastalarda D vitamini eksikliğinin yorgunluk ve depresyon üzerine etkisi

Abstract

Aim: In this study, we aimed to examine the effect of vitamin D deficiency on fatigue and depression in patients with axial spondyloarthritis (Ax-SpA).

Methods: This cross-sectional study included 141 Ax-SpA patients. Demographic information of the patients was recorded. The Hospital Anxiety and Depression Scale, Visual Analog Scale, Fatigue Severity Scale, and Ankylosing Spondylitis Disease Activity Score were used to evaluate depression, anxiety, pain, fatigue, and disease activity levels, respectively. Vitamin D levels were classified as deficiency (<10 ng/ml), insufficiency (11–20 ng/ml), and normal (>20 ng/ml).

Results: A total of 141 patients enrolled in the study (67 female and 74 male). Vitamin D levels were deficient in 14.2%, insufficient in 56%, and sufficient in 29.8% of cases. In the evaluation of fatigue, 20.6% of the cases were evaluated as normal, 60.3% as tired, and 19.1% as chronically tired. Although fatigue was detected in 79.4% of Ax-SpA patients, fatigue scores were not associated with vitamin D deficiency (p=0.191). There were no significant differences between the vitamin D groups (deficiency, insufficiency, and normal) in fatigue and depression scores, sex, disease duration, and activity.

Conclusion: Vitamin D deficiency is not associated with fatigue, depression, or disease activity in patients with Ax-Spa. Regardless of vitamin D deficiency, patients with depression and fatigue should be evaluated and managed appropriately, and the management of vitamin D deficiency should not be ignored.

Keywords: Depression; fatigue; spondylarthritis; vitamin D deficiency

Öz

Amaç: Bu çalışmada aksiyal spondiloartrit (Ax-SpA) hastalarında D vitamini eksikliğinin yorgunluk ve depresyon üzerine etkisini incelemeyi amaçladık.

Yöntemler: Bu kesitsel çalışmaya 141 Ax-SpA hastası dahil edildi. Hastaların demografik bilgileri kaydedildi. Hastaların depresyon, anksiyete, ağrı, yorgunluk ve hastalık aktivite düzeylerini değerlendirmek için, sırasıyla Hastane Anksiyete ve Depresyon Ölçeği, Görsel Analog Ölçeği, Yorgunluk Şiddeti Ölçeği ve Ankilozan Spondilit Hastalık Aktivite Skoru kullanıldı. D vitamini düzeyleri eksiklik (<10 ng/ml), yetersizlik (11-20 ng/ml) ve normal (>20 ng/ml) olarak sınıflandırıldı.

Bulgular: Araştırmaya toplam 141 hasta (67 kadın, 74 erkek) katılmıştır. D vitamini düzeyi olguların %14.2'sinde eksik, %56'sında yetersiz ve %29.8'inde yeterliydi. Yorgunluk değerlendirmesinde olguların %20,6'sı normal, %60,3'ü yorgun, %19,1'i kronik yorgun olarak değerlendirildi. Ax-SpA hastalarının %79,4'ünde yorgunluk tespit edilmesine rağmen yorgunluk skorlarının D vitamini eksikliği ile ilişkili olmadığı görüldü (p=0,191). D vitamini grupları (eksiklik, yetersizlik ve normal) arasında yorgunluk ve depresyon skorları, cinsiyet, hastalık süresi ve aktivitesi açısından anlamlı fark yoktu.

Sonuç: Ax-Spa'lı hastalarda D vitamini eksikliği yorgunluk, depresyon veya hastalık aktivitesi ile ilişkili değildir. D vitamini eksikliğinden bağımsız olarak, depresyon ve yorgunluk şikayeti olan hastalar uygun şekilde değerlendirilmeli ve tedavi edilmeli, D vitamini eksikliğinin tedavisi de göz ardı edilmemelidir.

Anahtar Sözcükler: Depresyon; D vitamini eksikliği; spondiloartrit; yorgunluk

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INTRODUCTION

Axial spondyloarthritis (Ax-SpA) is a chronic inflammatory disease that primarily affects the axial skeleton (1). The term Ax-SpA includes nonradiographic axial spondyloarthritis (nr-Ax-SpA) and ankylosing spondylitis (AS) (2). Complaints such as pain, fatigue, limited mobility, sleep disturbance, anxiety, and depression were observed in patients with Ax-SpA. Clinically, the most common symptom after pain and morning stiffness is fatigue (1,3).

Fatigue is characterized by extreme tiredness at rest, lack of energy that impairs daily activities, and difficulty initiating or maintaining voluntary activities (4). Overall, nearly 25% of the healthy adults and approximately 50–67% of the Ax-SpA patients had fatigue (1,3,5). Physical manifestations such as pain, stiffness, sleep disturbances, reduced spinal mobility, and fatigue in patients with Ax-SpA have psychological consequences such as anxiety and depression (6). Anxiety was reported in 22.5% and depression in 44% of Ax-SpA patients (7).

Vitamin D is a fat-soluble vitamin important for mineral and bone metabolism. Comorbid disorders such as autoimmune, neurological, and neuromuscular diseases have been linked to vitamin D levels. Inverse correlations have been observed between vitamin D levels and pain symptoms, including fibromyalgia and rheumatic illnesses (8). Pain and fatigue were linked to lower vitamin D levels (9,10).

This study investigated the effects of vitamin D deficiency on fatigue and depression in patients with Ax-SpA. Determining the relationship between vitamin D deficiency and conditions that may affect treatment, such as fatigue and depression, will contribute to treatment.

MATERIAL AND METHODS

Study design and participants

This study was approved by Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Prof Dr Cemil Taşcıoğlu City Hospital (date: 26.01.2021, decision no: 20). The study was performed between February and April 2021, and followed the guidelines outlined in the Declaration of Helsinki. This study included Ax-SpA patients who met the Axial Assessment of Spondyloarthritis International Society Ax-SpA classification criteria (11). Other inclusion criteria were ages 18–65 years and having had a vitamin D laboratory test performed in the last 1 month. All participants provided written informed consent. Patients with acute and post-acute infectious disorders; cancer; substance abuse; and past or present neurological, psychiatric, or other chronic inflammatory conditions were excluded from the study. In the same session, participants who volunteered to participate in the study underwent interviews and completed questionnaires.

Age, sex, body mass index (BMI), degree of education, current smoking status, and current treatments were the demographic information gathered. On outpatient admission, disease activity, pain intensity, fatigue, anxiety, and depression were assessed. The patients were divided into three groups according to the Vitamin D levels. The groups were compared in terms of disease activity, pain intensity, fatigue, and depression-anxiety.

The primary outcome of this study was the relationship between vitamin D deficiency, fatigue, and depression, and the secondary outcome was the frequency of vitamin D deficiency and fatigue in patients with Ax-SpA.

Materials

The Fatigue Severity Scale (FSS) evaluates fatigue and consists of nine questions. Each question is scored between 1 and 7. The Turkish validation of the FSS was conducted by Armutlu et al. There were nine questions in total, scaled between 1-7 on this scale. Scores below 2.8 are considered normal, between 2.8 and 6.1 are considered tired, and above 6.1 are considered chronic fatigue, respectively (12).

The Hospital Anxiety and Depression Scale is used to assess the risk and severity of anxiety and depression. It comprises of two subscales: anxiety and depression. The threshold values for the Turkish versions of the Anxiety and Depression subscales were 10 and 7, respectively. The questionnaire had a total of 14 questions, seven of which measured depression, and seven measured anxiety. Each response to a question was scored between 0 and 3. Depression and anxiety were scored independently (13).

Table 1. Descriptive and clinical characteristics of AxSpA patients

		n(%)//median(min-max)//mean±sd
Gender	female	67 (47.5%)
	male	74 (52.5%)
Age		40 (20-65) / 41.6±9.8
BMI		26.9(18.0-39.1) / 27.0±4.4
Smoking status	smoker	58 (41.1%)
	nonsmoker	83 (58.9%)
Education	primary	91 (64.5%)
	secondary	31 (22%)
	university	19 (13.5%)
Disease duration		48 (4-384) / 75.2±72.1
B-DMARD	none	23 (16.3%)
	adalimumab	45 (31.9%)
	etanercept	24 (17%)
	golimumab	14 (9.9%)
	sekukinumab	20 (14.2%)
Vitamin D	sertolizumab	15 (10.6%)
ASDAS-crp		3.1 (1.3-6.0) / 3.1±1.1
	<1.3	26 (18.4%)
	1.3-2.1	61 (43.3%)
	>2.1	54 (38.3%)
Fatigue		4.6 (0.0-7.0) / 4.5±1.8
	<2.8	29 (20.6%)
	2.8-6.1	85 (60.3%)
	>6.1	27 (19.1%)
HADd		7 (0-20) / 7.2±4.6
HADa		6 (0-21) / 6.8±4.8
VASr		6 (0-10) / 5.8±2.6
VASa		5 (0-10) / 5.5±3.9
VASn		6 (0-10) / 6.0±2.9

n: number; min: minimum; max: maximum; sd: standart deviation; AxSpA: axial spondyloarthritis; BMI: body mass index, B-DMARD: biological disease-modifying antirheumatic drugs; ASDAS-crp: Ankylosing Spondylitis Disease Activity Score- C reactive protein; HAD: hospital anxiety, depression (d: depression, a: anxiety), VAS: visual analog scale (r: rest, a: activity, n: night)

The Ankylosing Spondylitis Disease Activity Score includes acute-phase reactants and patient-reported measurements. It is used to evaluate the severity of the illness (14).

The Visual Analog Scale scores patient's pain on a pain scale with 0 representing "no pain" and 10 representing "most severe pain" possible (15).

Statistical Analyses

Power analysis was performed using G*Power (v3.1.7) to determine the number of samples. At 80% power 0.05 alpha significance level, taking into account possible losses, the total sample size was estimated to include n=130 (female and male) patients.

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 25.0, for Windows (SPSS Inc.; Chicago, IL, USA). Shapiro-Wilk and Kolmogorov-Smirnov tests were used to check for normal distribution. Continuous variables are shown as the mean, standard deviation, or median (minimum-maximum), and categorical variables are shown as numbers (n) and percentages (%). The

Table 2: Comparison of parameters acccording to vitamin D levels

			VitaminD <10ng/ml (n:20)	VitaminD 10-20ng/ml (n:79)	VitaminD >20ng/ml (n:42)	p
Age[a]			39.6±9.4	41.3±10	45±26.5	0.297
Gender	**Male[b]**		9 (45%)	43 (54.4%)	22 (52.4%)	0.752
	Female[b]		11 (55%)	36 (45.6%)	20 (47.6%)	0.752
BMI [a]			28.4±4.8	26.7±4.5	26.8±3.8	0.508
Disease duration[a]			33 (12-180)	60 (4-384)	48 (10-264)	0.345
Smoking		**Smoker[b]**	5 (25%)	34 (43%)	19 (45.2%)	0.278
		Nonsmoker[b]	15 (75%)	45 (57%)	23 (54.8%)	0.278
		HADSa[c]	6 (0-15)	6 (0-21)	6.5 (0-18)	0.948
		HADSd[c]	6 (0-15)	7 (0-20)	8 (0-19)	0.331
		·ASDAScrp[c]	3.1 (2.3-5)	3.1 (1.3-5.6)	3,2 (1.3-6)	0.260
		FATIGUE[c]	4.9 (1-7)	4.2 (0.6-7)	5.3 (0-7)	0.191
		VASr[c]	7 (0-9)	5 (0-10)	7 (0-9)	*0.048*
		VASa[c]	7 (0-9)	5 (0-10)	6.5 (0-10)	*0.030*
		VASn[c]	8 (0-10)	5 (0-10)	7.5 (0-10)	*0.017*

(a) mean±sd; (b) number (percentage); (c): median (minimum-maximum), p<0,05
BMI: body mass index, ASDAS-crp: Ankylosing Spondylitis Disease Activity Score-crp;
VAS: visual analog scale (r:rest, a: activity, n: night),
HAD: hospital anxiety, depression (d: depression, a: anxiety)

Table 3: Comparison of parameters acccording to fatigue severity

			<2,1 (n:29)	2.1-6.3 (n:85)	>6.3 (n:27)	p
Age[a]			29.0±3.2	41.1±5.1	56.4±4.3	*0.000*
Gender	**Male[b]**		16 (55.2%)	37 (43.5%)	14 (51.9%)	0.451
	Female[b]		13 (44.8%)	48 (56.5%)	13 (48.1%)	0.451
BMI [a]			28.4±4.8	27.4±3.9	37.8±6.0	0.508
Disease duration[a]			36 (4-180)	48 (6-264)	108 (6-384)	*0.001*
Smoking		**Smoker[b]**	10 (34.5%)	36 (42.4%)	12 (44.4%)	0.849
		Nonsmoker[b]	19 (65.5%)	49 (57.6%)	25 (55.6%)	0.849
		HADSa[c]	3.0 (0-19)	6.0 (0-18)	11 (0-21)	*0.003*
		HADSd[c]	5.0 (0-11)	7.0 (0-16)	10 (0-20)	*0.013*
		·ASDAScrp[c]	2.5 (1.3-5)	3.2 (1.3-6.0)	3.6 (1.5-5.1)	0.163
		Vitamin D	13 (7.3-44)	17 (7-45)	19 (7.4-43)	0.136
		VASr[c]	5.0 (0-9)	6.0 (3-10)	8.0 (3-10)	*0.058*
		VASa[c]	3.0 (0-9)	5.0 (1-10)	7.0 (1-10)	0.019
		VASn[c]	5.0 (0-10)	6.0 (2-10)	8.0 (2-10)	*0.197*

(a) mean±sd; (b) number (percentage); (c): median (minimum-maximum), p<0,05
n: number; BMI: body mass index; ASDAS-crp: Ankylosing Spondylitis Disease Activity Score-C reactive protein; VAS: visual analog scale (r:rest, a: activity, n: night); HAD: hospital anxiety, depression (d: depression, a: anxiety)

Kruskal-Wallis test, ANOVA and Pearson's chi-square tests were used for intergroup analysis. The results were evaluated bilaterally at 95% confidence interval, significance level of p <0.05.

RESULTS

A total of 141 participants (67 females and 74 males) with a mean age of 41.6 ± 9.8 (range: 20–65) years and a mean BMI of 26.9 ± 4.4 kg/cm2 were enrolled in the study. Vitamin D deficiency was detected in 70.2% of the patients (deficient in 14.2% of the cases, insufficiency in 56%). Among all the patients, 79.4% had fatigue (60.3% as tired and 19.1% as chronically tired). Table 1 shows the descriptive and clinical characteristics of patients with Ax--SpA. A comparison of the parameters acccording to vitamin D levels is presented in Table 2. Even though the fact that 79.4% of Ax-SpA patients had fatigue, this was not due to a vitamin D deficiency (p=0.191). A comparison of the parameters acccording to fatigue severity is presented in Table 3. Fatigue was associated with older age, longer disease duration, depression, and anxiety.

DISCUSSION AND CONCLUSION

The effect of vitamin D deficiency, on fatigue and depression in patients with Ax-SpA was investigated in the present study. Fatigue was found in 79.4% and low vitamin D levels were detected in 70.2% of the patients. Both fatigue and vitamin D levels were higher in patients with Ax-SpA, which is consistent with the literature (1,16).

In Ax-SpA, fatigue is a major symptom reported in 50–70% of patients and, this is related to disease activity, mental health status, functional capacity, and poor quality of life (1,3,5,17). Although no association was found between fatigue and disease activity in this study, fatigue was associated with depression and anxiety. A predominance of fatigue has been reported in females (1,5). The fatigue rate in this study was slightly higher than those reported in the literature. We believe that the higher number of female patients may have contributed to this discrepancy."

Vitamin D deficiency was found in 51.2% of the spondyloarthritis patients (18). Deficiency of vitamin D was detected in 14.2% of the cases in this study. Sun exposure and dietary intake were not assessed in the present study. Perhaps the lower deficiency in this study was because of the patients who received vitamin D supplementation. The relationship between fatigue and vitamin D levels in various diseases has been investigated, but no clinically significant relationship has been reported (19-21). In one study, a weak correlation was found between vitamin D levels and fatigue in patients with Rheumatoid arthritis (RA), which was not statistically significant. They observed that pain, anxiety, depression, and sleep disturbance were associated with fatigue. (22). The association between vitamin D levels and fatigue in patients with Ax-SpA has only been examined in one study. In patients with Ankylosing spondylitis (AS), there is no correlation between vitamin D levels and fatigue (23). They reported that spinal pain, disease activity, functional impairment, and quality of life were factors contributing to fatigue in the Ankylosing spondylitis (AS) group. (23). In this study, fatigue was associated with older age, longer disease duration, active pain, depression, and anxiety.

Another study conducted in patients with inflammatory bowel found no relationship between fatigue and vitamin D levels (21). Similar to previous studies the current study found no association between vitamin D intake and fatigue. Contrary to these findings, individuals with fatigue had a very high prevalence of low vitamin D levels, and after vitamin D levels normalized, a significant decline in fatigue symptom scores was observed (10).

The pathophysiology of fatigue in patients with Ankylosing spondylitis (AS) is multifactorial. Patient-reported risk factors for the development of fatigue include ongoing inflammation in the disease process, high disease activity, pain, stiffness, sedentary life, depression, malnutrition, and sleep disturbances (24). We may not have discovered a connection between vitamin D levels and patient fatigue due to the factors that contribute to fatigue. Depression was associated with reduced vitamin D levels. (25). However, one study found no evidence of the meaningful therapeutic benefit of vitamin D supplementation in treating depression (26). In this study, we were unable to identify a link between depression and vitamin D deficiency.

Despite effects of vitamin D insufficiency depression, and fatigue are comorbidities of Ax-SpA.

No association was observed between the vitamin D levels and disease activity. Similar studies have not found an association between vitamin D levels and disease activity (16,27). Additionally, vitamin D deficiency was associated with pain in this study. Vitamin D administration was found to lessen pain in chronic musculoskeletal illnesses in the literature (9). In contrast to these results, another study showed no association between pain and vitamin D levels. (28).

It is generally accepted that depression and fatigue symptoms Symptoms of depression and fatigue negatively affect treatment responses. In the treatment approach for these patients, it is recommended that they review their psychological status and provide the necessary support, in addition to their current treatment (29).

This study had some limitations. First, because this study's design was cross-sectional, we were unable to determine whether vitamin D deficiency, fatigue, or depression were causally related. Second, we did not include a control group. Third, we did not investigate whether fibromiyalgia and sleep disorders are important causes of fatigue and depression.

Fatigue, depression, and disease activity were not associated with vitamin D deficiency in patients with Ax-Spa. Regardless of vitamin D deficiency, patients with depression and fatigue should be properly referred to and managed. Although vitamin D deficiency did not affect fatigue or depression in patients with Ax-SpA, vitamin D treatment should be considered. The association between fatigue and vitamin D levels may be better understood through additional research that takes into account the limitations of this study.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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