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Research Article

Serum level of vitamin D in obstructive sleep apnea patients with fibromyalgia syndrome

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Abstract

Objectives: The aim of this study was to investigate the serum concentration of vitamin D in patients with obstructive sleep apnea syndrome (OSAS) alone and with coexisting fibromyalgia syndrome (FMS) and to assess the relationship to pain.

Methods: A total of 60 patients diagnosed with OSAS and 40 healthy individuals whose age and sex were analogous to the patient group were included in this study. The OSAS patients were examined for FMS according to the American College of Rheumatology criteria, and 27 cases were identified. Group 1 consisted of patients with OSAS alone (n=33) and Group 2 comprised patients with FMS+OSAS (n=27). Serum samples were analyzed using an ultra-performance liquid chromatography analyzer (Thermo Dionex Ultimate 3000; Thermo Fisher Scientific, Inc., Waltham, MA, USA).

Results: A comparison of the OSAS and FMS+OSAS groups with the healthy individuals revealed that the vitamin D level was significantly lower in the patient groups (Group 1: p=0.001, Group 2: p=0.038). No statistically significant difference was found in the vitamin D level between the subgroups of OSAS and FMS+OSAS. A weak negative correlation was determined between the number of the tender points (r=-0.428) and the vitamin D level in the subjects with FMS (p=0.013). In addition, the oxygen desaturation values of the FMS+OSAS and OSAS patient groups were significantly different (p=0.001).

Conclusion: Patients with OSAS and FMS+OSAS had a low vitamin D level, which should be considered when planning treatment strategies.

Keywords: Fibromyalgia syndrome, obstructive sleep apnea syndrome, vitamin D

Obstructive sleep apnea syndrome (OSAS) is a disease defined by recurrent episodes of upper airway obstruction and sporadic oxygen desaturation during sleep. Patients with OSAS suffer from a low quality of life as a consequence of persistent deficient quality sleep. The prevalence of OSAS has been reported at 1% to 5% in various studies and is more common in males than females [1].

Fibromyalgia syndrome (FMS) is a relatively new, yet now commonly seen disorder characterized by various symptoms, such as tender points, musculoskeletal pain, sleep disturbance, memory problems, and fatigue lasting for at least 3 months. FMS is seen more frequently in women than men; however, the exact etiology and pathogenesis of FMS remains unclear [2].

Vitamins are essential nutrients required in very small amounts for normal development and health. Vitamins are classified as fat soluble or water soluble. Among the fat-soluble vitamins, vitamin D has a crucial role [3]. Although the main function of vitamin D is to provide adequate amounts of calcium and phosphate for a healthy mineralized skeleton, it is now also considered an important immunomodulatory hormone be-

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cause vitamin D receptors (VDRs) are found throughout the human body. Many extra-skeletal diseases, such as cancer, autoimmune, cardiovascular, neurologic and psychiatric disorders are associated with vitamin D deficiency [4].

Serum 25(OH) vitamin D is routinely measured to assess vitamin D status. Based on the current literature, physicians generally use the following classification: A vitamin D level of 5-10 ng/mL is evaluated as moderate deficiency, 10-20 ng/mL represents mild deficiency, >20 ng/mL is a sufficient level, and >100 ng/mL is regarded as toxic [5]. The concentration of serum vitamin D can be influenced by various factors, and has been reported to affect the duration of quality sleep [6]. Research studies have found VDRs in some areas of the brain, including the hypothalamus, which regulates the sleep-wake cycle [7]. A high concentration of vitamin D has been noted to have a converse relationship with sleep disorders. Therefore, vitamin D supplementation has been associated with improved sleep quality as both a therapeutic and a preventative aid for sleep disorders and related conditions [8]. Epidemiological studies have noted that dietary intake of vitamin D was associated with sleep duration and uninterrupted sleep [9, 10]. However, the literature results are inconsistent. In addition, a deficiency of vitamin D has been shown to be common in patients with fibromyalgia (FM) [11].

Given these data, this study was designed to investigate the serum concentration of vitamin D in OSAS patients with and without FM. Although there are various recently published studies about sleep disorders in FMS patients, the number of OSAS cases with coexisting FMS examined is limited. The objective of this study was to evaluate the relationship between the vitamin D level and the severity of OSAS, as well as the possible effect of vitamin D concentration on the assessment of fatigue and pain in OSAS patients with FMS. The results of this study may promote future research related to vitamin D and sleep disorders.

Materials and Methods

This clinical study included 60 patients aged ≥18 years diagnosed with OSAS who had common complaints of snoring, daytime hypersomnia, widespread musculoskeletal pain, and a stiff back in the morning. A total of 40 healthy control subjects of similar age and gender were also enrolled. Sleep tests were performed with the OSAS patients, and the presence of FMS was diagnosed based on the current criteria published by the American College of Rheumatology in 1990 [12]. The OSAS groups were classified according to the Apnea-Hypopnea Index (AHI) measuring the number of apneas or hypopneas per hour of sleep: 5-15 is considered mild, 15-30 is a moderate score, and >30 reflects a severe condition. [13]. The Fibromyalgia Impact Questionnaire (FIQ) was first developed by Burchardt et al. [14] to determine the effect of FMS by measuring physical activity and how FMS patients feel. Lower scores indicate a mild FMS impact, while higher scores indicate severe FMS. In this study, the FIQ and a visual analog scale (VAS) were employed to evaluate the OSAS patients. Group 1 comprised 33 patients with OSAS alone, and OSAS patients who were subsequently also diagnosed with FMS in the department of physical therapy were categorized as Group 2. Tender points were recorded for all of the patients diagnosed with FMS, and the presence and severity of widespread pain was determined using a VAS [15]. Patients were asked to score their pain level on a 10 cm scale. In all, 27 patients were identified for Group 2. All of the patient groups had minimal exposure to sunlight due to their lifestyle. Patients who used vitamin D replacement therapy and those with certain diseases known to affect vitamin D metabolism (such as chronic degenerative, inflammatory, rheumatic, or endocrine disorders, and cancer) were excluded. After 10-12 hours of fasting, 10 mL of venous blood was drawn into serum separator gel tubes between 8:00 and 10:00 am, centrifuged at 4000 rpm for 10 minutes, and the serum was separated. Serum specimens were transferred to polypropylene tubes and stored at -80°C until the assay was performed and the samples were brought to room temperature before analysis.

The serum vitamin D level of the patients and the healthy individuals was measured using a ClinRep Complete Kit (RECIPE Chemicals+Instruments GmbH, Munich, Germany) and a Thermo Dionex Ultimate 3000 ultra performance liquid chromatography (UPLC) analyzer (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The results were reported as ng/mL. This study protocol was approved by the Namık Kemal University Research Ethics Committee (2015/60/05/05).

Statistical analysis

SPSS Statistics for Windows, Version 17.0 software (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis of the study variables. Normal distribution of the variables was tested with the Shapiro-Wilk test. Student's t-test (in homogeneous groups) and the Mann-Whitney U test (in heterogeneous groups) were used to compare parameters between groups. The Pearson test was used to analyze correlation. The relationship between vitamin D level and the number of tender points, fatigue, and VAS score was evaluated using Pearson correlation analysis, as the data did not provide parametric distribution. A value of $p<0.05$ was considered statistically significant. The numerical values obtained were expressed as mean±SD or median and minimum-maximum values.

Results

Age, gender distribution, and the results of the FIQ, AHI, oxygen desaturation level, and the median and minimum-maximum values of the vitamin D level of the patients with OSAS (Group 1), FMS+OSAS (Group 2), and the control group are provided in Table 1. When the patient groups were compared with the control group, the vitamin D concentration was significantly lower among the patients (Group 1: $p=0.001$, Group 2: $p=0.038$) (Fig. 1). There was no statistically significant differ-

Table 1. Comparison of demographic, FIQ, AHI, oxygen desaturation, and vitamin D levels of the study groups

	Control group (n=40)	OSAS group (n=33)	FMS+OSAS group (n=27)
Demographic information			
Gender, n (%)			
Male	17 (42.5)	23 (57.5)	9 (33.3)
Female	23 (69.7)	10 (30.3)	18 (66.7)
Age (years)	58.7±10.0	61.4±7.5	57.00±9.3
Parameters of FMS and OSAS			
FIQ	-	-	64.12 (35.07-89.94)
AHI	-	33.60 (0.0-104.2)	16.80 (0.6-118.4)
Oxygen desaturation	-	81.00 (54.0-97.0)	83.00 (50.0-93.0)
Biochemical measurement			
Vitamin D (ng/mL)	26.20 (10.1-55.4)	17.60 (3.3-32.7)	20.55 (2.1-34.6)

Results are presented as median (min-max) or mean±SD. AHI: Apnea hypopnea index; FIQ: Fibromyalgia impact questionnaire; FMS: Fibromyalgia syndrome; OSAS: Obstructive sleep apnea syndrome

ence in the vitamin D level between the FMS+OSAS and OSAS patient groups (p=0.246). Moreover, there was no significant difference in the vitamin D level between the OSAS groups according to the AHI classification (normal, mild, moderate, severe) (p=0.118) (Fig. 2). The Pearson correlation analysis between the number of tender points, fatigue measurement, VAS values, and vitamin D in Group 2 is presented in Table 2. It was observed that there was a weak negative correlation between the number of tender points and the vitamin D concentration of patients with FMS (p=0.013). As the vitamin D concentration decreased, the number of tender points increased (Fig. 3). However, there was no correlation between the vitamin D level and either the VAS score (r=-0.017; p=0.468) or fatigue (r=-0.045; p=0.415), also shown in Table 2. The oxygen desaturation value of the FMS+OSAS and OSAS patient groups was significantly different (p=0.001).

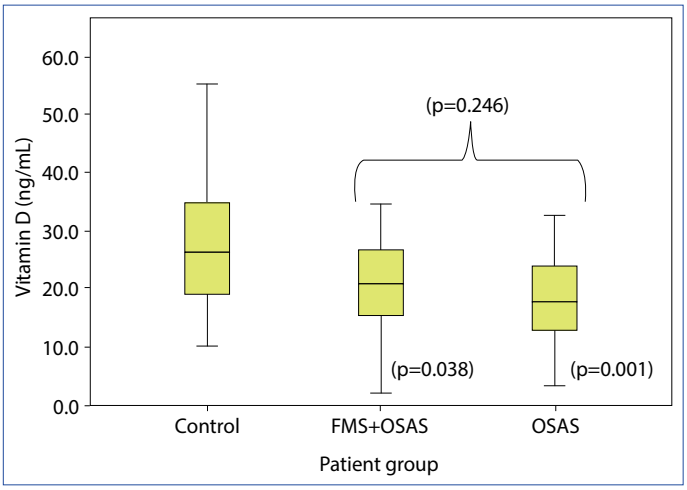

Figure 1. The vitamin D concentration was significantly lower in the patient groups.

FMS: Fibromyalgia syndrome; OSAS: Obstructive sleep apnea syndrome.

Discussion

Although vitamin D is a fat-soluble vitamin, it has a very high importance as a hormone in human metabolism because it is produced in the body and acts in different regions other than where it is produced. The role of vitamin D in human health was first established in the early 1900s based on the effect of vitamin D supplementation in the treatment of rickets. Understanding of the importance of vitamin D and its relationship to various diseases continues to gradually increase. Studies conducted in recent years have demonstrated that vitamin D deficiency is a preliminary risk factor for both skeletal and non-skeletal clinical disorders, including diabetes, coronary heart disease, multiple sclerosis, cancer, tuberculosis, and infections, and it is currently used for both prevention and as a supplementary treatment for coronavirus 2019 [4].

In this study, the vitamin D concentration was significantly lower in both groups of OSAS patients than in the healthy individuals (p=0.001). Our results are supported by the findings of Archontogeorgis et al. [16], who also observed that patients with OSAS had lower vitamin D concentrations than healthy control subjects. Similarly, Abbas et al. [13] found a lower vitamin D level in an OSAS group compared with healthy controls. No significant difference in the vitamin D level of the OSAS subgroups classified by AHI value (normal, mild, moderate, severe) was recorded in our study (p=0.181). Yassa et al. [17] also found no significant difference in vitamin D level according to OSAS severity (mild, moderate, severe) or a significant correlation with AHI values. Vitamin D deficiency may not be the predominant factor determining the severity of OSAS.

Carlander et al. [18] found that low vitamin D levels in OSAS patients were associated with low sunlight exposure and excessive sleepiness during the day. These data were supported by our results. Exposure to sunlight is acknowledged to be a primary source of vitamin D.

Factors that may cause sleep disorders in FMS patients have been investigated using sleep test analysis in various studies

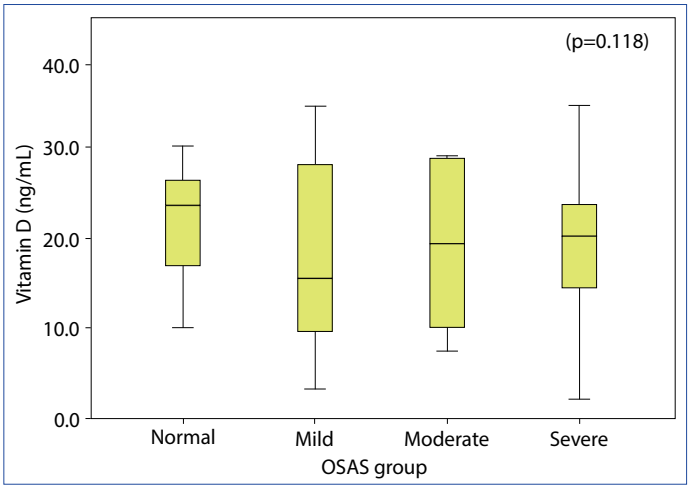

Figure 2. There was no significant difference in the vitamin D level in OSAS patients according to Apnea-Hypopnea Index classification.

FMS: Fibromyalgia syndrome; OSAS: Obstructive sleep apnea syndrome.

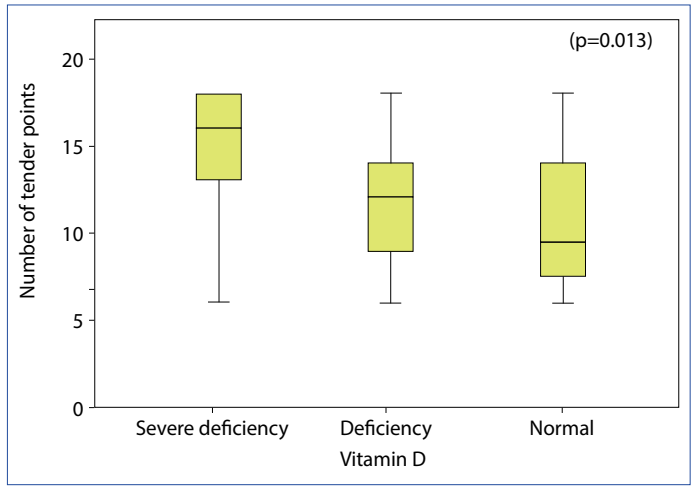

Figure 3. The relationship between vitamin D concentration and the number of tender points.

Severe deficiency of vitamin D was defined as <5 ng/mL, deficiency as 5-20 ng/mL, and normal level as 20-100 ng/mL.

[19]. A high rate of sleep irregularities has been found in patients with FMS in the majority of the research [20]. Moreover; patients with OSAS generally report complaints such as frequent sleep interruptions, non-restorative sleep, and daytime sleepiness. The presence of complaints in OSAS patients of widespread skeletal muscle pain and tender points led to the idea that patients with OSAS may have also FMS [21]. Significant improvements have been observed in FMS symptoms after 3 weeks of continuous positive airway pressure treatment in patients with sleep-disordered breathing [22]. Based on these results, we hypothesized that a deficiency of vitamin D might be related to FMS symptoms and OSAS. In our study, the patients were first diagnosed with OSAS and then evaluated in terms of FMS. We compared the vitamin D concentration of OSAS patients with coexisting FMS and OSAS alone. There is currently little in the literature regarding the presence of FMS in patients with OSAS. We sought to investigate the possibility that another pathology might also be involved in these symptoms in addition to the sleep disorder. We thought that sleep disturbance and morning fatigue complaints, which are common symptoms in both FMS and OSAS, might be related to vitamin D deficiency. Reports of a low serum vitamin D concentration in patients with FMS have indicated that inadequate sunlight exposure may lead to movement difficulty [23].

Table 2. Pearson correlation of vitamin D level with the number of tender points, fatigue measurement, and VAS values in FMS+OSAS patients

	Vitamin D	
	r	p
Number of tender points	-0.428	0.013
Fatigue	-0.045	0.415
VAS	-0.017	0.468

There was a weak negative correlation between the number of tender points and vitamin D level. FMS: Fibromyalgia syndrome; OSAS: Obstructive sleep apnea Syndrome; VAS: Visual analog scale

Our results indicated that the vitamin D concentration in the FMS+OSAS patient group (Group 2) was statistically significantly lower than that of the healthy individuals (p=0.038). However, evaluation of the relationship between vitamin D and the intensity of pain revealed no significant correlation between vitamin D concentration and VAS scores (p=0.468). Similarly, in a study conducted by Dogru et al. [24], no statistically significant difference was seen in the VAS values of patients with low and normal vitamin D levels.

Vitamin D deficiency is primarily exhibited by pain in the musculoskeletal system and is an early symptom of osteomalacia [25]. Vitamin D deficiency is related to muscle weakness through the reduction of VDRs and VDR binding sites [26]. Vitamin D deficiency especially affects type II collagen fibrils, which provide strength to the musculoskeletal system. Lewis et al. [27] have suggested that FMS may suppress the production of vitamin D via the parathyroid axis, a mechanism similar to that involved in rickets.

In a large study conducted in the USA by Prabhala et al. [28], it was determined that severe myopathy was related to vitamin D deficiency. They reported that pain symptoms and muscle weakness decreased dramatically after vitamin D supplementation and the authors suggested that the vitamin D level should be evaluated in patients with non-specific musculoskeletal pain. Shinchuk and Holick [29] reported that vitamin D deficiency should be considered in the differential diagnosis of patients with musculoskeletal pain, FMS, chronic tiredness, or muscle inflammation.

In a cross-sectional study, De Rezende et al. [30] compared a control group consisting of 92 healthy subjects who were age and gender compatible and not suffering chronic musculoskeletal pain with 87 patients diagnosed with FMS to assess

vitamin D concentration. There was no statistically significant difference between the groups in terms of the mean vitamin D concentration that clarified the relationship between pain and a deficiency of vitamin D. They also reported that there was no correlation between the severity of pain and vitamin D concentration. We found a weak correlation between the number of the tender points related to pain and vitamin D level in subjects with FMS. Vitamin D supplementation may help to relieve pain in these patients.

Sleep disruption diminishes sleep quality in patients with OSAS, and absent or incomplete rapid eye movement sleep has been observed. Moreover, hypoxic conditions promote increased or continuous inspiratory effort throughout the entire period of absent airflow in OSAS patients [31]. Evaluation of the oxygen desaturation values in this study yielded a significant difference between the FMS+OSAS and OSAS groups (p=0.001). İnönü Köseoğlu et al. [32] also found that OSAS oxygen desaturation values were statistically significant in an analysis of rapid eye movement and OSAS.

In conclusion, the presence of common symptoms, such as non-restful sleep, morning headaches, and widespread musculoskeletal pain strongly suggests that there is a relationship between vitamin D deficiency and OSAS and FMS. It is our hope that our study will promote and support additional research of the role of vitamin D deficiency in the pathogenesis of these diseases with coinciding symptoms. Since the small sample size of this study represents a limitation, we plan to conduct a larger and more comprehensive study group in the future. Another shortcoming of this study is the lack of power analysis. Investigation of managed dietary intake of vitamin D in a homogenous population will provide stronger results than are currently available. Nonetheless, the results of this early study offer useful information for future research and treatment strategies in this area.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Ethics Committee Approval: This study was approved by the ethics board of Namık Kemal University Faculty of Medicine Clinical Research Ethics Committee (Date: 04.06.2015/Number: 2015/60/05/05).

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