

The Relation between Obstructive Sleep Apnea Syndrome and Vitamin D

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ABSTRACT

Introduction: The aim of this study was to assess vitamin D levels in obstructive sleep apnea syndrome (OSAS) and whether there is a relationship between the severity of the disease and vitamin D.

Materials and Methods: In this retrospective study, demographic data, serum 25-Hydroxycholecalciferol [25 (OH) D3], parathyroid hormone (PTH), calcium (Ca), phosphate (P), magnesium (Mg) levels and disease severity [mild, moderate and severe OSAS (AHI = 5-15, 16-30, > 30 / hour)] of patients diagnosed with OSAS by using polysomnography [apnea-hypopnea index (AHI) > 5/hour] and normal patients (AHI < 5/hour)] were evaluated based on hospital records.

Results: Of the 293 subjects whose records were examined, 229 had OSAS (mean age 55.7 ± 11.3 years; age range 26-86 years), whereas 64 subjects were normal (mean age 55.4 ± 13.7 years; age range 24-78 years). 25 (OH) D3 level was significantly lower while BMI and PTH levels were higher in OSAS patients compared to the control group (p < 0.05). 25 (OH) D3 levels were significantly lower in patients with severe OSAS (p < 0.05). In addition, there was a weak negative relationship between AHI and 25 (OH) D3 (p: 0.001, r: -0.328), while a weak positive relationship was observed between PTH (p: 0.001, r: 0.186) and BMI (p: 0.001, r: 0.208).

Conclusion: OSAS patients have vitamin D deficiency, and patients especially with severe OSAS have lower vitamin D deficiency. Therefore, We think that making up of vitamin D deficiency in these patients may be beneficial in reducing the severity of the disease.

Key Words: Obstructive sleep apnea syndrome, 25-hydroxyvitamin D, relation

ÖZET

Amaç: Obstrüktif uyku apne sendromunda (OUAS) D vitamini düzeylerinin belirlenmesi ve hastalık şiddeti ile arasında ilişki olup olmadığı amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmada OUAS ön tanısı nedeniyle polisomnografi yapıp tanı konulan [apne-hipopne indeksi (AHI) > 5/saat] ve normal (AHI < 5/saat) olarak değerlendirilen hastaların demografik verileri, serum 25-Hidroksikolekalsiferol [25(OH)D3], paratiroid hormon (PTH), kalsiyum (Ca), fosfat (P), magnezyum (Mg) düzeyleri ve hastalık şiddeti [hafif, orta ve şiddetli OUAS (AHI=5-15, 16-30, >30/saat)] bilgi işlem kayıtları incelenerek değerlendirildi.

Bulgular: Kayıtları incelenen 293 kişinin 229'da OUAS (ortalama yaş 55,7±11,3 yıl; yaş aralığı;26-86 yıl) mevcut iken 64 kişi normal (ortalama yaş 55,4±13,7 yıl; yaş aralığı;24-78 yıl) idi. OUAS hastalarında 25(OH)D3 seviyesinin kontrol grubuna göre anlamlı bir şekilde daha düşük olduğu ve BMI ile PTH seviyelerinin ise daha yüksek olduğu tespit edildi (p<0.05). Şiddetli OUAS hastalarında 25(OH)D3 düzeyinin anlamlı bir şekilde daha düşük seviyedeydi (p<0.05). Ayrıca AHI ile 25(OH)D3 arasında anlamlı zayıf negatif bir ilişki bulunurken (p:0.001, r:-0.328), PTH (p:0.001, r:0.186) ve BMI (p:0.001, r:0.208) ile arasında ise anlamlı zayıf pozitif bir ilişki tespit edildi.

Sonuç: OUAS hastalarında D vitamini eksikliğinin olduğu ve özellikle şiddetli OUAS hastalarında D vitamini daha düşük olması nedeniyle bu hastalarda D vitamini eksikliğinin yerine konulmasının hastalığın şiddetini azaltmada faydalı olabileceğini düşünmekteyiz

Anahtar Kelimeler: Obstrüktif uyku apne sendromu, 25-hidroksi vitamin D, ilişki

Introduction

Obstructive sleep apnea syndrome (OSAS) is a condition which causes recurrent respiratory dysfunction (apnea, hypopnea) during sleep because of the obstruction of the upper respiratory tract and is a significant health problem that may affect various systems of the body (1). Although the pathogenesis of OSAS is

not known, it might stem from many other causes, including differing mechanisms like inflammation and oxidative stress (2). While obesity is one of the primary factors, agedness, male gender, ethnic origin, and family history are among other risk factors (1).

The data published in the literature emphasizes the relationship between OSAS and a variety of impairments including cardiovascular diseases,

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disordered glucose metabolism, other endocrinopathies and osteoporosis (2, 3). However, contradictory results regarding the relation between vitamin D deficiency and OSAS were reported in some researches (4). The most important indicator of the adequacy of vitamin D is 25-hydroxycholecalciferol [25 (OH) D₃] level. Vitamin D functions best as the regulator of bone metabolism and calcium homeostasis, and its relationship with many non-skeletal pathologies such as cardiovascular diseases, cancer, autoimmune diseases, and diabetes mellitus have been reported (5). In addition, vitamin D receptors were established in many brain regions, hypothalamus included, regulator of changes in the sleep-wake cycle (6).

In our study, 25 (OH) D₃, being a measured type of vitamin D in serum, PTH, calcium, phosphorus, and magnesium levels were investigated in patients with OSAS. The objective was examining the relationship between OSAS and serum vitamin D levels.

Materials and Methods

This retrospective study included 594 patients who underwent all-night polysomnography (PSG) by a technician at the Sleep Disturbance Center of the Pulmonary Diseases Department, Faculty of Medicine, Atatürk University, between January 2016 and December 2018. 293 patients out of 594, age, gender, body mass index (BMI), serum 25 (OH) D₃ levels (30-80 ng/ml, inadequacy; 20-30 ng/ml, deficiency 10-20 ng/ml, severe deficiency <10 ng/ml), parathyroid hormone (PTH:12-88 pg/ml), calcium (Ca:8.8-10.6 mg/dl), phosphate (P:2.5-4.5 mg/dl), magnesium (1.9-2.5 mg/dl) levels and apnea-hypopnea index (AHI) values for disease severity were examined. The study was carried out by the Physical Medicine and Rehabilitation and Pulmonary Diseases Departments, Medical Faculty, Atatürk University. Patients with AHI>5/h were established as OSAS and staged according to their severity. OSAS was divided into 3 groups as mild (AHI=5-15/h), moderate (AHI=16-30/h) and severe (AHI>30/h) (7). Patients with AHI <5/h were regarded as normal and evaluated as a control group. Patients with a disease history or drug use known to affect vitamin D and Ca levels reported in hospital records, or any deficiencies in any of the laboratory parameters were removed from the research. The study protocol was accepted by the Medical Faculty of Atatürk University Ethics Committee (13.02.2019/01;71). The study was

carried out in line with the principles of the Helsinki Declaration.

Statistical Analysis: Statistical analysis was made with SPSS IBM 20.0 version. The assessment of the parameters to normal distribution was evaluated by the Kolmogorov-Smirnov test. Independent T-test and one-way analysis of variance (ANOVA) were applied for comparison of ordinarily distributed parameters. Outcomes were stated as mean \pm standard deviation (SD). Comparison of parameters with non-normal distribution were performed with the Mann-Whitney U (MWU) and Kruskal Wallis tests. As there was no normal distribution in the parameters, the Spearman rank correlation analysis was performed for correlation analysis.

Results

Of the 293 subjects whose records were examined, 229 had OSAS (mean age 55.7 ± 11.3 years; age range 26-86 years), whereas 64 subjects were healthy (mean age 55.4 ± 13.7 years; age range 24-78 years). Demographic and laboratory features of the groups have been summarized in Table 1. Any statistically important variation was not observed between the demographic data of the groups with regards to age and gender ($p > 0.05$), while the patient group showed considerably higher BMI values ($p < 0.05$). With regards to laboratory parameters, the patient group had considerably lower 25 (OH) D₃ levels ($p < 0.05$), while PTH value was considerably higher among the groups ($p < 0.05$). Although P values were in the normal range in both groups, it was considerably lower in the patient group compared with the control group ($p < 0.05$). Any considerable difference was not established between Ca and Mg values between the groups ($p > 0.05$).

As a result of examining the laboratory values according to AHI severity, 25 (OH) D₃ level was found to be deficient in all 3 stages, and the lowest value was found in severe stage patients. Besides, an important variation was observed between moderate and severe stage 25 (OH) D₃ levels ($p < 0.05$), however, any meaningful difference was not observed between mild-moderate and mild-severe stages ($p > 0.05$).

No statistically important difference was observed between the three stages with regard to other laboratory parameters ($p > 0.05$), (Table 2). The analysis of the relationship between AHI and other parameters revealed a considerable weak positive correlation between AHI and BMI values

Table 1. Comparison of demographic, laboratory and apnea-hypopnea index values of the groups

	Patients	Controls	p value
	Mean (min-max)	Mean (min-max)	
Age (Mean±SD)	55.7±11.3	55.4±13.7	0.86
Sex (m/f)	90/139	18/46	0.11
BMI (kg/m ²)	33.3 (23.2-62.4)**	29 (19.3-51.6)	0.001
25(OH)D3 (ng/mL)	14 (0.7-63)**	23.4 (8-80)	0.001
PTH (pg/ml)	50.3 (8-260)**	40.3 (9.4-121)	0.001
Ca (mg/dl)	9.3 (6.9-12.9)	9.4 (7-10.6)	0.302
P (mg/dl)	3.2 (1.6-6.7)*	3.4 (1.6-5.1)	0.031
Mg (mg/dl)	2 (1.3-4.5)	1.9 (1.6-2.6)	0.222
AHI	30.2 (5-116)**	3.1 (0.5-4.7)	0.001

min: minimum; max: maximum, SD: standard deviation, m: male, f: female, BMI: body mass index, 25(OH) D3; 25-hydroxycholecalciferol, PTH: parathyroid hormone, Ca: calcium, P: phosphate, Mg: magnesium, AHI: apnea-hypopnea index, *. p<0.05 was considered as statistically significant between patient and control groups, **. p<0.01 was considered as statistically significant between patient and control groups

Table 2. Serum vitamin D and PTH levels of OSAS patients

	Mild stage	Moderate stage	Severe stage	p value
	Mean (min-max)	Mean (min- max)	Mean (min-max)	
Patients (n)	51	55	123	
25(OH)D3	14 (3-56.4)	16.1 (3-52.1)	12.5(0.7-62.6)*	.042
PTH (pg/ml)	43.4 (12-259)	50.3 (16.3-199)	52.5 (7-259)	.076
Ca (mg/dl)	9.2 (7.7-11.1)	9.3 (8-10.5)	9.4 (6.9-12.9)	.644
P (mg/dl)	3.2 (1.8-5.6)	3.4 (1.7-6.7)	3.2 (1.6-5.6)	.299
Mg(mg/dl)	2 (1.4-4.5)	2 (1.4-2.5)	2 (1.3-3.4)	.945

min: minimum; max: maximum, 25(OH) D3; 25- hydroxycholecalciferol, PTH: parathyroid hormone, Ca: calcium, P: phosphate, Mg: magnesium, *. p<0.05 was considered as statistically significant between disease stages of patients.

Table 3. The relationship between apnea-hypopnea index value and other parameters

	p value	r value
Age (Mean±SD)	.093	.098
Sex (m/f)	.082	-
BMI (kg/m ²)	.001**	.208
25(OH)D3	.001**	-.328
PTH (pg/ml)	.001**	.186
Ca (mg/dl)	.491	.040
P (mg/dl)	.238	-.069
Mg (mg/dl)	.586	.032

SD: standard deviation, m: male, f: female, BMI: body mass index, 25(OH) D3; 25- hydroxycholecalciferol, PTH: parathyroid hormone, Ca: calcium, P: phosphate, Mg: magnesium, *. Correlation is significant at the p<0.05, **. Correlation is significant at the p<0.01.

(p:0.001, r:0.208). Besides, a statistically considerable weak negative correlation was observed between AHI and 25 (OH) D3 (p:0.001, r:-0.328), while a considerable positive weak correlation was ascertained between PTH (p:0.001, r:0.186). Any correlation was not established between other parameters and AHI values (p>0.05), (Table 3).

Discussion

In OSAS patients, 25 (OH) D3 levels were significantly lower whereas BMI and PTH levels were higher than the control group. 25 (OH) D3 levels were considerably lower in patients with severe OSAS. In addition, a significant weak negative relationship was observed between AHI

and 25 (OH) D₃, while a significant weak positive relationship was found between PTH and BMI.

Risk factors related to the etiology of OSAS (male gender, advanced age, obesity, ethnic origin, anatomical abnormalities, etc.) are currently being investigated, and there are ongoing studies.

In addition, vitamin D deficiency is known to cause risk of developing OSAS by causing chronic rhinitis, adenotonsillar hypertrophy, and myopathy in the airway muscles that are involved in the pathophysiology of OSAS (4). Any significant difference was not found between the groups with regard to age and sex. However, average age of the patients was found to be consistent with the literature in terms of being a risk factor for OSAS. The lower number of male patients in our study may be due to the fact that women may apply more frequently with OSAS symptoms such as snoring, apnea, and excessive daytime sleepiness, or that the prevalence of OSAS in women may increase due to the decrease in progesterone hormone in the postmenopausal period (8). In addition, the high number of male patients excluded from the study due to incomplete laboratory data in the records might have contributed to this situation.

Obesity is known to be related to low vitamin D and high PTH levels, as well as an essential risk factor for OSAS (9). In our study, patients with OSAS had higher BMI and PTH values and lower vitamin D levels in accordance with the literature. Furthermore, a considerable weak positive correlation was observed between BMI and AHI values in OSAS patients. This may indicate that OSAS is related to both obesity and low vitamin D levels. Different results have been reported in the literature. In many studies, low vitamin D and high PTH levels were found in patients with OSAS (10-13). However, some studies reported no significant decrease in vitamin D levels in OSAS patients (14-15). In addition, some studies examining the relationship between mild, moderate, and severe OSAS patients and vitamin D levels reported that there was no significant relationship (12,15). However, there are more studies in the literature claiming that vitamin D level decreases as disease severity increases, indicating a negative relationship (10-11,13,16). There are studies indicating that this relationship is significant, especially in patients with severe OSAS (14,17). In addition, some authors suggest that there is a relationship between moderate and severe OSAS and vitamin D levels (10). The study demonstrated that patients with OSAS had significantly lower vitamin D and increased PTH

levels. In addition, when OSAS subgroups are examined; It was established that Vitamin D levels were significantly lower in the group with severe OSAS, while the highest PTH levels were also found in severe OSAS.

It seems that further studies are needed in the literature evaluating the impacts of vitamin D support on the severity of OSAS. In a study including ninety-severe OSAS patients, low vitamin D and high PTH levels were found in the OSAS group similar to our findings, and a considerable increase in vitamin D levels was observed in OSAS patients receiving CPAP for seven days (18). Therefore, increased vitamin D levels as a result of correction of hypoxia in OSAS may explain the relationship between disease severity and vitamin D. There may be many causes of decreased vitamin D levels that are correlated with the severity of the disease in OSAS patients. Low levels of vitamin D might also lead to the development of OSAS. This can be explained by several mechanisms. Vitamin D receptors in skeletal muscles play a role in muscle cell reproduction and variation of mature type II muscle fibers by modulating many transcription factors in muscle cells. Furthermore, vitamin D is known to play a role in sarcomeric muscle contraction by carrying active calcium to the sarcoplasmic reticulum (19). It is reported that vitamin D deficiency may cause proximal myopathy (20). In addition, increased PTH and decreased P levels accompanied by vitamin D deficiency are other factors contributing to muscle weakness (21). Therefore, it has been suggested that a decrease in pharyngeal dilator muscle power in vitamin D deficiency may cause a decrease in pharyngeal patency and predisposition to apnea attacks during sleep (22). But, to our knowledge, there is not sufficient research on the assessment of the impacts of vitamin D replacement therapy on pharyngeal dilator muscle power. But, the outcomes obtained from the randomized studies concerning the impacts of vitamin D support on muscle function showed vitamin D supplementation had a beneficial impact on muscle strength and function in the elderly (23). Beside, OSAS may be a risk factor for vitamin D deficiency. It is stated that OSAS patients may have lower vitamin D synthesis owing to much daytime sleepiness, obesity, limited outdoor activities, and thus, restricted sunlight exposure (24).

In our study, serum Ca and P levels were not considerably different between the groups, but the patient group showed a considerably lower P

levels. This has been shown in similar studies and can be explained by increasing PTH levels to compensate for decreased vitamin D levels (12,25).

There were some shortcomings in our study. The limitations of our study include the effects of many diseases on vitamin D levels, the possibility of vitamin D support even the hospital data did not have any such registration, and that vitamin D levels could be affected by seasonal conditions and nutritional status.

We think that vitamin D is deficient in OSAS patients, and Vitamin D treatment might be beneficial in decreasing the severity of the disease. Since there are conflicting results in the literature regarding the relationship between OSAS and vitamin D, we think that our study will contribute to the literature in this manner.

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