



Evaluation of Serum Vitamin D Levels in Obstructive Sleep Apnea Syndrome

Obstrüktif Uyku Apne Sendromunda D Vitamini Düzeylerinin Değerlendirilmesi

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Abstract

Objective: The relationship between obstructive sleep apnea syndrome (OSAS) and vitamin D deficiency (VDD) has been an attractive issue for researchers in recent years because both are prevalent conditions with common comorbidities and pathophysiological mechanisms. However, the reported results have often been inconsistent, possibly due to multiple confounders such as obesity. The aim of this study was to assess serum 25-hydroxyvitamin D [25(OH)D] levels in cases screened for OSAS and demonstrate whether there is an association between [25(OH)D] and OSAS.

Materials and Methods: Two hundred and sixty two cases were retrospectively analyzed. The ones with an apnea hypopnea index (AHI) of ≥ 5 /hour were categorized as OSAS patients, and < 5 /hour were classified as non-OSAS controls. Clinical features, polysomnographic indices, and serum 25(OH)D levels were compared between the groups.

Results: Serum 25(OH)D levels were similar between OSAS patients and non-OSAS controls as well as among different disease stages within the OSAS group itself. OSAS patients were then divided into two groups regarding the presence of VDD (< 20 ng/mL). Although no difference was detected in terms of AHI, body mass index (BMI) was significantly increased in the VDD group ($p=0.04$). An inverse correlation was observed between 25(OH)D and BMI ($p=0.037$) in OSAS patients.

Conclusion: The current study demonstrated that neither the presence nor severity of OSAS has a significant association with serum 25(OH)D levels. Our results also confirmed the well-known negative correlation between increased BMI and vitamin D.

Keywords: Obstructive sleep apnea syndrome, 25(OH)D, vitamin D, vitamin D deficiency

Öz

Amaç: Tıkaıcı uyku apne sendromu (TUAS) ve D vitamini eksikliği toplumda yaygın görülen bozukluklardır. Örtüşen patofizyolojik mekanizmalarla birlikte pek çok ortak komorbiditeyi de paylaştıklarından, bu iki durum arasındaki ilişki son yıllarda araştırmacıların dikkatini çeken bir konu olmuştur. Bununla birlikte konuyla ilgili yayınlarda, muhtemelen obezite gibi bir seri karıştırıcı faktörün de etkisinden ötürü, tutarsız sonuçlar bildirilmektedir. Bu çalışmada amaç, TUAS varlığı yönünden araştırılan hastalarda serum 25 hidroksivitamin D [25(OH)D] düzeylerini değerlendirmek ve iki durum arasında gerçek bir ilişki olup olmadığını ortaya koymaktır.

Gereç ve Yöntem: İki yüz altmış iki olgu retrospektif olarak incelendi. Apne hipopne indeksi (AHI) ≥ 5 /saat bulunanlar TUAS hastası olarak kategorize edilirken, AHI < 5 /saat saptananlar kontrol olguları olarak sınıflandı. Klinik bulgular, polisomnografik belirteçler ve serum 25(OH)D düzeyleri gruplar arasında karşılaştırıldı.

Bulgular: Serum 25(OH)D düzeyleri TUAS grubu ve kontrol olguları arasında benzer saptandı. TUAS grubunun kendi içinde yapılan karşılaştırmalarda da; hafif, orta ve ağır hastalık arasında anlamlı farklılık göstermedi. Ardından TUAS hastaları, D vitamini eksikliğine göre [VDE (< 20 ng/mL)] ikiye ayrılarak incelendi. İki grup arasında AHI açısından fark gözlenmezken; VDE bulunan TUAS hastalarında vücut kitle indeksi (VKI) anlamlı olarak yüksek bulundu ($p=0,004$). TUAS hastalarındaki serum 25(OH)D düzeyleri ve VKI arasında negatif korelasyon izlendi ($p=0,037$).

Sonuç: Mevcut bulgular, serum 25(OH)D düzeylerinin TUAS varlığıyla ya da şiddetiyle anlamlı ilişki göstermediğini ortaya koymuştur. Bulgularımız ayrıca VKI artışı ve serum 25(OH)D düzeyleri arasında iyi tanımlanmış negatif korelasyonun varlığını bir kez daha kanıtlamıştır.

Anahtar Kelimeler: Tıkaıcı uyku apne sendromu, 25(OH)D, D vitamini, D vitamini eksikliği

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a frequent disease characterized by excessive daytime sleepiness, snoring, and witnessed apnea arising from intermittent restrictions of the upper airway during sleep, which finally leads to arterial desaturation and sleep fragmentation. Besides causing an increased baseline sympathetic tonus, this typical failure of oxygenation-so-called cyclic intermittent hypoxia-eems to promote the activation of several inflammatory pathways, which remarkably contribute to the cardiovascular consequences (1). Obesity is the most common risk factor and accompaniment at the same time, and OSAS is also known to be associated with numerous further cardiovascular risk (CVR) factors, like hypertension (HT), metabolic syndrome (MS) and diabetes mellitus (DM) (2). It is estimated to affect 3-9% of females and 10-17% of the male population in developed countries and therefore constitutes a significant public health problem (3). Vitamin D deficiency (VDD) is another prevalent condition, with a reported prevalence of 20-100% among adults. Following the current improvement in knowledge of the molecule's critical non-skeletal functions, it has been claimed to predispose various similar disorders associated with immune regulation, homeostasis of vascular tonus, and electrolyte balance (4,5). The biologically active form of vitamin D is "1.25(OH)₂D", which is achieved after two consequent hydroxylation steps; however, the deficiency status and measurements are based on 25(OH)D according to guideline recommendations, as it constitutes the majority in circulation (4). Widespread expression of the signaling components and receptors of vitamin D on cardiovascular structures, as well as immune cells, makes the deficient status a reasonable risk factor for inflammatory atherosclerotic processes and corresponding disorders (5).

Taken together, the relationship between these two common situations, which looks much closed because of some shared comorbidities and pathophysiological mechanisms in the background, has been the subject of interest in many recent studies. In this context, some groups reported no identifiable relationship between the two (6,7), while some others demonstrated a noticeable diminution of 25(OH)D in patients with OSAS-particularly in the severe form-as to non-OSAS counterparts (8). Furthermore, some papers with positive results also suggested a notable correlation between 25(OH)D values and OSAS stage (9).

However, the general opinion regarding contamination of findings by multiple confounders (e.g., obesity, location, gender, season), and thus difficulty in objectively interpreting the results have not been overcome yet (10). In this retrospective cohort, we analyzed 25(OH)D values and polysomnographic (PSG) data among a considerable number of patients, who were screened for OSAS and aimed to clarify the abovementioned ambiguity.

Materials and Methods

Patients

The patient records, who were applied one-night diagnostic polysomnography due to the symptoms indicative of OSAS or excess body mass index (BMI) in a single center's sleep disorders unit between January 2018-2022 December were

retrospectively evaluated. Sex, age, BMI, results of Epworth Sleepiness Scale (ESS) with a Turkish validation (11), and concurrent CVR factors, which include hyperlipidemia, HT, DM, MS, and 25(OH)D values, were recorded. Patients with a history of any medical condition that could impair the metabolism of vitamin D (e.g., renal insufficiency, chronic hepatic failure, and parathyroid disease), patients with a history of multivitamin or vitamin D supplement use, and the ones without available laboratory data regarding 25(OH)D were excluded from this study. Regarding vitamin D, cases with a <20 ng/mL 25(OH)D value were identified to have "VDD," whereas a further decrease indicating <10 ng/mL was categorized as "severe VDD." An interval between 21-29 ng/mL was referred to as "insufficiency" and ≥30 ng/mL values were accepted to be adequate (4). This retrospective study was approved by the Aydın Adnan Menderes University Faculty of Medicine Ethics Committee (no: 2023/106, date: 07.06.2023).

Polysomnography

All cases were subjected to a full night diagnostic polysomnography (SOMNOscreen/Somnomedics GmbH - Randersacker Germany) in the sleep clinic. The PSG records included an electrooculogram and a six-channel electroencephalogram (EEG), chin and leg electromyogram, pulse oximetry, oronasal thermistor, and nasal airflow, electrocardiogram (ECG), body position, and thoracic and abdominal respiratory effort. The PSG data were manually scored under the rules of American Association of Sleep Medicine 2014 v2.4. Regarding respiratory events, a ≥90% decrease in airflow on the thermistor for a minimum of 10 seconds duration was scored as apnea, and a ≥30% diminution in nasal airflow persisting at least 10 seconds accompanied by arousal on EEG or ≥3% desaturation in oximetry was scored as a hypopnea (12). The patient was diagnosed with severe OSAS in the presence of an apnea hypopnea index (AHI) ≥30/hr and moderate OSAS when the corresponding value was between ≥15 - <30/hour. An AHI between ≥5 - <15/hour, together with typical symptoms, was referred to mild OSAS, while AHI <5/hour was accepted as normal (13).

Statistical Analysis

IBM SPSS.20 program was conducted for analysis (SPSS, Inc., Chicago, Illinois). For the assessment of normality, a Shapiro-Wilk test was applied. If normal distribution was present, the data were expressed as mean ± standard deviation and in case of skewed distribution, it was introduced as median (minimum-maximum). Categorical variables were analyzed using the chi-squared test. Considering the normality, the student's t-test or Mann-Whitney U was utilized for pairwise comparisons. Concerning more than two groups, one-way ANOVA or the Kruskal-Wallis test was used accordingly. Bivariate correlations were examined by Spearman's test, and a two-tailed p-value of <0.05 was considered statistically significant.

Results

Two hundred and sixty-two cases fulfilling the inclusion criteria were analyzed. In this study, 66% (n=174) were male, and 34% (n=88) were female. The mean age was 49.9±13.3 years, and

the mean BMI was 32.3 ± 6.9 kg/m². After one-night diagnostic polysomnography, 239 (91%) had an AHI ≥ 5 /hour and were diagnosed with OSAS, whereas AHI was < 5 /hour for the remaining 23 (9%) that were classified as non-OSAS controls. A severe disease grade comprised the majority of patients with OSAS (60%, n=144), while the rate of moderate and mild disease was 26% (n=62) and 14% (n=33), respectively. Among the whole study population, 78% (n=205) had serum 25(OH)D below 20 ng/mL, and out of these individuals with VDD, 41% (n=84) had further reduced levels below < 10 ng/mL, that is referred as "severe VDD". The average 25(OH)D in the study cohort was 14.97 ± 7.86 ng/mL, and only 6% (n=16) had sufficient serum levels indicating ≥ 30 ng/mL. Although age [52 (18-80) vs 40.5 (18-61) years, $p < 0.001$] and BMI [31.6 (18.8-68.7) vs 29.8 (18.9-35.7) kg/m², $p = 0.02$] increased in patients with OSAS, average serum 25(OH)D values were similar between the patients and controls [13.3 (4.2-53.7) vs 16.6 (4.2-36.9) ng/mL, $p = 0.10$]. 25(OH)D levels within the OSAS group also demonstrated no significance according to different disease grades [mild: 17.2 (4.2-37) vs moderate: 13.2 (4.2-34) vs. severe 13.2 (4.2-53.7) ng/mL, $p = 0.32$] (Figure 1). Pairwise comparisons depending on the VDD status of whole cohort [VD_{<20} (25(OH)D < 20 ng/mL) vs VD _{≥ 20} (25(OH)D ≥ 20 ng/mL)] revealed that age, sex, rate of patients with OSAS, AHI and proportion of patients with concurrent CVRs were comparable between the two groups (VD_{<20} vs VD _{≥ 20} , $p > 0.05$) (Table 1). However, the median BMI notably increased in the group of VD_{<20} [31.8 (18.8-68.7) vs 30.1 (20.8-40.3) kg/m², $p = 0.025$], and a borderline negative correlation was detected between 25(OH)D and BMI ($r = -0.122$, $p = 0.05$).

After excluding non-OSAS controls, a similar relation pattern was proper for patients with OSAS. BMI was higher in VD_{<20} patients with OSAS as to VD _{≥ 20} ones [32.0 (18.8-68.7) vs 30.4 (20.8-40.3) kg/m², $p = 0.04$], and a significant inverse correlation was present between serum 25(OH)D level and BMI ($r = -0.0135$, $p = 0.037$) (Figure 2). Although a trend towards increased AHI was observed for VD_{<20} OSAS group, the difference did not reach significance, and the rate of patients with severe disease grade was similar between the two [63% (n=118) for VD_{<20}-OSAS vs 51% (n=26) for VD _{≥ 20} -OSAS, $p = 0.09$]. Sleep

indices yielded from polysomnogram, including total sleep time, sleep efficiency, and proportion of N3 stage, as well as respiratory parameters, including AHI, ODI, desaturation duration (SpO₂ $< 90\%$ duration), and average SpO₂, were similar between the VD_{<20}-OSAS and VD _{≥ 20} -OSAS groups (Table 2).

None of the abovementioned PSG parameters demonstrated significantly correlated with serum 25(OH)D levels in patients with OSAS (Table 3).

Discussion

Current results revealed that neither the presence nor severity of OSAS has a significant association with serum 25(OH)D levels and also confirmed a well-known negative correlation between vitamin D and obesity (14,15).

Table 1. Clinical and laboratory characteristics of the study cohort according to VDD status

Variable	VD _{<20} cases (n=205)	VD _{≥ 20} cases (n=57)	p value
Age (yrs) (min-max)	50 (18-80)	54 (18-77)	0.08
Sex [male, % (n)]	66% (136)	67% (38)	0.69
BMI kg/m ² (min-max)	31.8 (18.8-68.7)	30.1 (20.8-40.3)	0.03*
ESS (min-max)	5 (0-20)	5 (0-12)	0.69
OSAS rate [% (n)]	92% (188)	90% (51)	0.60
AHI	37.5 (0.4-95.2)	32.9 (1-82.9)	0.21
Concurrent CVR [% (n)]	48% (98)	60% (34)	0.11

* $P < 0.05$ denotes statistical significance, VDD: Vitamin D deficiency, VD_{<20} cases (cases with serum 25(OH)D < 20 ng/mL; in other terms cases with VDD), VD _{≥ 20} cases (cases with serum 25(OH)D ≥ 20 ng/mL; in other terms cases without VDD), BMI: Body mass index, CVR: Cardiovascular risk, OSAS: Obstructive sleep apnea syndrome, AHI: Apnea hypopnea index

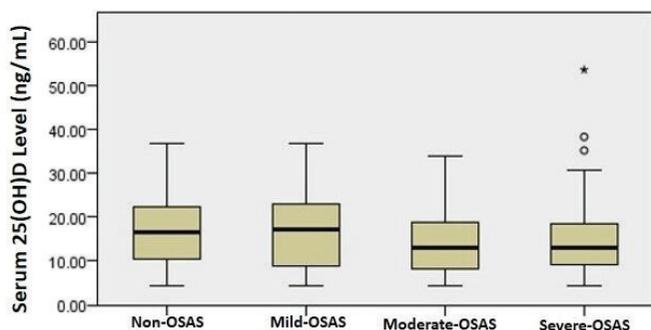


Figure 1. Demonstration of serum 25(OH)D levels in the study population

OSAS: Obstructive sleep apnea syndrome

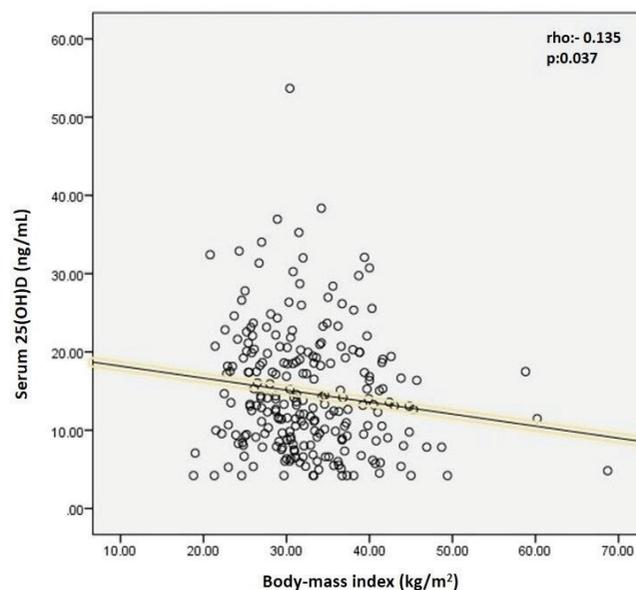


Figure 2. Correlation between BMI and serum 25(OH)D levels in OSAS patients

BMI: Body mass index, OSAS: Obstructive sleep apnea syndrome

Table 2. PSG Features of OSAS patients according to VDD status

Variable	VD _{<20} -OSA patients (n=175)	VD _{≥20} patients (n=51)	p value
Respiratory indices			
AHI (hour)	35.1 (5.3-95.2)	30.1 (7.6-82.9)	0.22
ODI	39.1 (0.8-112.3)	38.04 (5.3-94.1)	0.07
SpO ₂ <90% duration (%)	7.8 (0-98)	3.3 (0-87.9)	0.06
Average SpO ₂	92.5% (71.7-96.1)	92.6% (84.2-96.7)	0.60
Sleep indices			
TST (min)	353.3 (127.5-477.1)	339.5 (138-446.5)	0.44
SE (%)	76.9 (48.7-95.7)	77.3 (49.9-94.5)	0.62
N3 ratio (%)	12.4 (0-48.5)	12.4 (0-31.6)	0.87
*P<0.05 denotes statistical significance, PSG: Polysomnography, OSAS: Obstructive sleep apnea syndrome, VDD: Vitamin D deficiency, VD _{<20} -OSA patients (OSA patients with serum 25(OH)D <20 ng/mL; in other terms OSAS patients with VDD), VD _{≥20} -OSA patients (OSA patients with serum 25(OH)D ≥20 ng/mL; in other terms OSAS patients without VDD), AHI: Apnea hypopnea index, ODI: Oxygen desaturation index, TST: Total sleep time, SE: Sleep efficiency, N3 ratio: Proportion of N3 sleep stage			

Table 3. Spearman correlation of serum 25(OH)D and respiratory indices on PSG in OSAS patients

	rho	p-value
AHI	rho	-0.047
	p-value	0.482
ODI	rho	-0.091
	p-value	0.172
SpO ₂ <90% duration	rho	-0.088
	p-value	0.186
Average SpO ₂	rho	-0.093
	p-value	0.164
P<0.05 denotes statistical significance, PSG: Polysomnography, OSAS: Obstructive sleep apnea syndrome, AHI: Apnea hypopnea index, ODI: Oxygen desaturation index		

The relationship between OSAS and vitamin D has been an attractive issue for researchers in recent years. However, the reported results have often been inconsistent. In 2016, Kerley et al. (9) stated that patients with OSAS have significantly lower serum 25(OH)D levels than controls, and the decrease was parallel to the severity of the disease. A few years later, Archontogeorgis et al. (8) published their cohort analysis from 169 participants, which showed diminished serum 25(OH)D levels in patients with OSAS compared to controls, and presented further findings regarding negative correlations between many hypoxia parameters on polysomnography and 25(OH)D. In contrast, the results of Salepci et al. (6) were completely different. The authors did not observe any significant difference between patients with OSAS and non-apneic individuals, as well as different categories of OSAS, in terms of serum 25(OH)D levels and rate of VDD. According to their results, BMI, AHI, and other hypoxia-related parameters did not demonstrate any correlation with vitamin D. Our results were largely similar to the latter one; however, we detected a significant correlation between BMI and serum 25(OH)D in our sample. The interaction between obesity and vitamin D

has been recognized and extensively studied so far. Dilution effect because of already existing large volume, decreased bioavailability arising from inappropriate dietary patterns or insufficient synthesis from the skin due to a sedentary lifestyle, and consequent decrease in sunlight exposure as well as sequestration of vitamin D throughout the adipose tissue have been all proposed as responsible factors for low 25(OH)D levels among obese individuals (14). Moreover, such confounding effects of obesity could not be excluded in most studies reporting a positive association between OSAS severity and VDD. For instance, on multivariate regression analysis applied for identifying independent associates regarding AHI, Kerley et al. (9) noticed that BMI was markedly more predictive than the other factors, including 25(OH)D and ESS. Erden et al. (16) revealed poorer values of 25(OH)D in severe patients with OSAS as to controls and detected an inverse correlation between 25(OH)D and BMI concerning all subjects, while mean 25(OH)D levels of the 85 patients with OSAS did not show any difference according to disease severity. Although Mete et al. (17) did not find any relation between 25(OH)D and BMI among their patients with OSAS, as well as no difference regarding the pairwise comparison of 25(OH)D levels between patients with OSAS and controls, they demonstrated a lower mean level of 25(OH)D and increased frequency of VDD in severe patients with OSAS after performing subgroup analysis. The authors stated that BMI was similar between patients and controls at the beginning. However, there was an overlooked trend towards an increase of BMI in the severe OSAS group, and a correlation of 25(OH)D and BMI within this group was neither evaluated nor mentioned. More recently, Bouloukaki et al. (18) have disclosed a significant association of vitamin D levels with both AHI and BMI in a quite large population of patients with OSAS and controls and identified severe OSAS -but not increased BMI- as an independent predictor of VDD. During the latter analysis, BMI was considered a categorical variable rather than continuous, and thus it could not be possible to make a clear comment regarding the influence of BMI values up to 30 kg/m² on VDD. Taken together, it would be plausible to suggest that a great magnitude of results from the accumulating data supports -at least could not contradict- our findings indicating an apparent effect of increased BMI on lower 25(OH)D levels and VDD among patients with OSAS. The current study has some limitations based mainly on its retrospective design. First, the size of the groups subjected to comparison was different, favoring patients, especially the ones with severe OSAS. However, it is unignorable that a greater representation of severe OSAS, among all others, is consistent with the plenty of previous literature (16,18) and the real-life data as a result. Second, the sampling term of 25(OH)D, of which the levels are known to display a seasonal variability, was not considered during the assignment of patients to any group (6,19). We consider adjusting for the season would be more appropriate in case of a significant difference between groups to explain the independency of association further, as we observed no difference in terms of 25(OH)D among groups in our study population.

Conclusion

Alterations of vitamin D in the context of OSAS appear to be BMI-dependent, or at least associated. Studying the relevant parameter among the similar size of groups matched for BMI, rather than adjustment, and preferably in a cross-sectional design rather than retrospective, could provide valuable insight regarding this issue.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Aydın Adnan Menderes University Faculty of Medicine Ethics Committee (no: 2023/106, date: 07.06.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.O.A., A.A.G., Concept: U.O.A., A.A.G., Design: U.O.A., A.A.G., Data Collection or Processing: U.O.A., A.A.G., Analysis or Interpretation: U.O.A., A.A.G., Literature Search: U.O.A., A.A.G., Writing: U.O.A., A.A.G.

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