ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Relation Between Obstructive Sleep Apnea Syndrome and 25-Hydroxyvitamin D Levels in Patients at High Altitude

Yüksek Rakımda Obstruktif Uyku Apnesi Sendromu ile 25-Hidroksivitamin D Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Aim: *Present study's objective is to investigate the relationship between serum 25-hydroxyvitamin D and the severity of sleep apnea at altitude.*

Material and Method: *Fifty obstructive sleep apnea syndrome patients and 18 persons without apnea participated in this study. Apnea Hypopnea Index scores were measured with polysomnography during the night and classified as AHI<15:control, 15≥AHI<30 moderate, and AHI≥30 severe obstructive sleep apnea. In addition, the serum 25-hydroxyvitamin D levels of the patients were also measured.*

Results: *In the logistic regression analysis, it was found that there was an independent correlation between the apnea-hypopnea index and 25-hydroxyvitamin D (AUROC=0.658, p=0.028). We found a significant difference between the control and obstructive sleep apnea groups for 25-hydroxyvitamin D (p<0.05). A significant relationship has been found between moderate and severe obstructive sleep apnea groups for vitamin D deficiency and average vitamin D (p<0.0001).*

Conclusion: *We found an independent association between 25-hydroxyvitamin D and obstructive sleep apnea severity at high altitudes. An interesting point of our study is that our study has been conducted at a high altitude region with an elevation of more than 1768 meters. Therefore, effective vitamin D management may help prevent obstructive sleep apnea syndrome development, and patients' medical status can be improved.*

Key words: *25-Hydroxyvitamin D; polysomnography; obstructive sleep apnea syndrome; altitude*

ÖZET

Amaç: *Mevcut çalışmada, yüksek rakımlı coğrafi bölgede yaşayan hastalarda obstrüktif uyku apne sendromunun şiddeti ile serum 25-hidroksivitamin D düzeyleri arasındaki ilişkinin araştırılması amaçlandı.*

Materyal ve Metot: *Çalışmaya obstrüktif uyku apne sendromu olan 50 hasta ve 18 sağlıklı birey katıldı. Apne Hipopne İndeksi skorları tüm gece polisomnografisi ile ölçüldü ve AHI<15:kontrol, 15≥AHI<30 orta derecede obstrüktif uyku apnesi ve AHI≥30 şiddetli obstrüktif uyku apnesi olarak sınıflandırıldı. Hastaların serum 25-hidroksivitamin D düzeyleri ölçüldü.*

Bulgular: *Lojistik regresyon analizinde apne hipopne indeksi ile 25-hidroksivitamin D düzeyleri arasında bağımsız korelasyon görüldü (AUROC=0,658, p=0,028). Kontrol grubu ile obstrüktif uyku apnesi grubu arasında 25-hidroksivitamin D düzeyleri ile istatistiksel olarak anlamlı fark vardı (p<0,05). D vitamini eksikliği ve normal D vitamini düzeyleri için orta ve şiddetli obstrüktif uyku apnesi grupları arasında anlamlı ilişki gözlendi (p<0,0001).*

Sonuç: *Yüksek rakımda yapılan mevcut çalışmada 25-hidroksivitamin D düzeyleri ile obstrüktif uyku apnesi şiddeti arasında bağımsız bir ilişki olduğunu gözlemlendi. Çalışmamız rakımı 1768 metreden fazla olan yüksek rakımlı bölgede yapılmıştır. Vitamin D düzeylerinin dikkatli yönetimi, obstrüktif uyku apne sendromu gelişiminin önlenmesinde tıbbi durumlarının iyileştirilmesinde yardımcı role sahip olabilir.*

Anahtar kelimeler: *25-hidroksivitamin D; polisomnografi; obstrüktif uyku apne sendromu; yüksek rakım*

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Introduction

Obstructive sleep apnea syndrome (OSA) is a combination of unexplained severe daytime sleepiness with at least five respiratory events (apnea or hypopnea) per sleep hour. Apnea is defined as a respiratory arrest for at least 10 seconds in adults during sleep, while hypopnea is defined as a reduction of ventilation for at least 50% compared to the baseline value for a minimum of 10 seconds. The evaluation of the diagnosis and the severity is measured with apnea hypopnea index (AHI) which consists average apnea and hypopnea count during sleep[1]. Gominak et al.[2] suggested that the sleep disorder epidemic in the world may be associated with vitamin D and there are potential epidemiological, anatomical connections between sleep disorders and vitamin D.

Discovery of receptors for vitamin D in brainstem areas responsible for sleep maintenance suggests that sleep management is affected by vitamin D. Immunological mechanisms overlapping with OSA and vitamin D make it necessary to address this issue[3]. Current study intended to investigate the relationship between vitamin D levels and sleep apnea severity in patients living in high altitude conditions.

Material and Methods

Sixty-eight patients who underwent nocturnal polysomnography in Kafkas University central sleep laboratory were included in the study. All patients were residing in Kars region for at least 24 months. All participants have given written consent. Ethics commission confirmation from Kafkas University Faculty of Medicine with Session No: 08, Approval No: 163 were obtained. This study was conducted at high altitude Kars region, Turkey which has an altitude more than 1768 meters.

According to recods during nocturnal poysomnography; apnea hypopnea index results were classified as following; AHI<15 as control group, 15≥AHI<30 as moderate OSA group and AHI≥30 as severe OSA group. 25-hydroxyvitamin D (25(OH)D) measurements were obtained from all participants and were classified as following; <20 ng/ml defined as vitamin D deficiency, 20–29 ng/ml defined as vitamin D insufficiency and ≥30 ng/ml defined as normal.

Patients with kidney failure, malignancy, active infection, rheumatoid arthritis, malabsorption, ankylosing spondylitis, collagen tissue disease, sarcoidosis, acute myocardial infarction, thyroid and parathyroid disease, bone metabolism disease, hepatic dysfunction, celiac disease were excluded from the study. Patients using calcium preparations, vitamin D, bisphosphonate, calcitonin, antiepileptic and steroid were omitted.

All participants underwent physical examination, height and body weight measurement. Body mass index (BMI) were defined as dividing weight (kilograms) and square of height (meters) (kg/m^2).

Serum 25-hydroxyvitamin D level was measured with analyzer Cobas e 411 (Roche Diagnostics GmbH, Mannheim, Germany). Polysomnography measurements were made at night time in the Kafkas University Medical School Center of Sleep Disorders, which is accredited by the Turkish Association of Sleep Medicine. Polysomnography device Embla N7000 system (Medcare; Reykjavik, Iceland) was used. During the polysomnography session; measurements of electroencephalography, body position measurements, electrocardiography, electrooculography, thoracoabdominal movements, submental muscle electromyography, nasal pressure, finger-tip oxygen saturation with finger oximeter, anterior tibialis electromyography, oronasal airflow measurement via thermal sensor were performed. Patient information, gender, height and body weight of the patients were recorded by the technician before the polysomnography.

Statistical Analysis

Statistical analysis of the study was obtained using the IBM SPSS 20.0 (IBM Inc. Chicago, IL.) Program. "Kolmogorov-Smirnov normality test" was used to analyze whether the distributions were normal or not, and "Levene test" was used to determine the homogeneous variance equality. Continuous variables were expressed as mean ± standard deviation or median, and categorical variables were expressed as patient count and percentages. In normal distribution data; the chi-square test was used in the analysis of categorical variables and the Independent t-test was used in the analysis of numerical variables. In comparing the variables; when hypotheses for continuous variables were confirmed One-Way ANOVA was used and when it was not provided Kruskal-Wallis H Test and Mann-Whitney U test was used.

Evaluating for different results from One-Way ANOVA, Tamhane Test was used in case of non-homogenous condition and Tukey Test was used in case of the homogenous condition. Paired-Samples' t-test was used to investigate the binary correlation of the variables. The Spearman's Degree Correlation test was used when the variables were homogeneous in the correlation analysis, and the Kendall correlation test was used when the variables were not homogeneous. In all comparisons, $p<0.05$ was considered significant and assessed at 95% confidence level.

Results

Forty-one of the patients were male (60.29%) and 27 (39.21%) were female. According to the polysomnographic results, 34 patients had severe OSA, 16 patients had moderate OSA and 18 of the patients were classified as the healthy control group. The distribution of the groups according to gender was given in Table 1.

In terms of variables such as age, sex, height, weight and BMI; age and weight showed a significant difference. There was no difference in height and BMI. Mean and standard deviation values of the age in moderate and severe apnea groups were found to be similar. In all OSA groups, the mean values of the height were not statistically significant and close to each other. The distribution of groups according to demographic variables was given in Table 2.

There was not a relation between the apnea hypopnea index and BMI ($p>0.05$). There was nor an association between vitamin D and BMI.

Statistically significant difference was found between moderate and severe OSA groups for vitamin D deficiency and normal 25(OH)D levels ($p<0.0001$). Significant difference was found between the control group and OSA group for 25(OH)D levels ($p<0.05$). The mean 25(OH)D was found to be highest in the control group (Table 3).

In the logistic regression analysis, it is found that there was an independent correlation between apnea hypopnea index and 25(OH)D (AUROC=0.658, $p=0.028$). ROC curve analysis of 25(OH)D is shown in Fig. 1.

Table 1. *Distribution of the patients according to the gender*

	Control	Moderate OSAHS	Severe OSAHS	Total
Male	9 (21.95%)	12 (29.26%)	20 (48.78%)	41 (60.29%)
Female	9 (33.33%)	4 (14.81%)	14 (51.85%)	27 (39.70%)
Total	18 (26.47%)	16 (23.52%)	34 (50.00%)	68 (100%)

Table 2. *Distribution of demographic characteristics of the patients according to the groups*

Variables	AHI <15 (N=18)	15≤AHI <30 (N=16)	30≤AHI (N=34)	p value
Age (Years)	41.1±12.5	52.8±11.7	53.5±11.2	<0.0001*
Gender (F/M)	9/9	4/12	14/20	1.000
Height (cm)	168.8±9.88	171.5±8.0	163.0±20.8	0.401
Weight (kg)	80.4±18.5	91.0±11.7	100.6±15.1	<0.0001*
BMI (kg/m^2)	28.2±6.67	31.1±5.45	36.8±7.47	0.241

AHI: Apnea Hypopnea Index.

Table 3. *Relation of groups to 25-Hydroxyvitamin D (ng/ml)*

	Control	Moderate OSA	Severe OSA	p value	P
Vitamin D deficiency	10.3±3.63	13.7±3.68	11.5±4.17	<0.0001*	
Vitamin D insufficiency	23.5±2.15	23.7±3.93	22.9±1.77	0.2329	<0.0001*
Normal vitamin D	72.75±0.00a	33.5±0.00a	44.4±19.0	<0.05*	

OSA: Obstructive Sleep Apnea Syndrome.

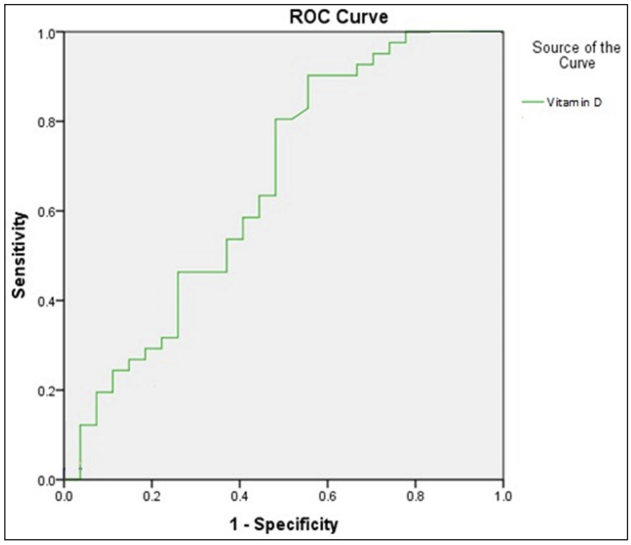

Figure 1. *ROC curve analysis of 25-Hydroxyvitamin D (AUC=0.658, 95% CI = 0.519–0.797, p=0.028)*

Discussion

In our study relation of apnea hypopnea index and serum 25-OH vitamin D in sleep apnea patient group and healthy controls were analyzed. For 25(OH) D levels, significant statistical difference was found between the control group and obstructive sleep apnea patients ($p<0.05$). For vitamin D deficiency and normal 25(OH)D levels we found significant difference between moderate and severe OSA groups ($p<0.0001$). In the logistic regression analysis, it is found that there was an independent association between apnea hypopnea index and 25(OH)D (AUROC=0.658, p=0.028).

Obstructive sleep apnea syndrome is a prominent threat for mortality and can be cause of morbidity. Risk factors include obesity and the winter season[4–7]. Metabolic disorders such as systemic inflammation, hyperglycemia, hyperlipidemia, increased bone density loss may also be associated with sleep apnea[8–10]. Lower vitamin D level is also related to the winter season, obesity, systemic inflammation and metabolic disorders[11,12]. 25(OH)D receptor existence in the brain regions responsible for sleep control has potential implications for obstructive sleep apnea syndrome etiology[13–16]. Presentation and severity of obstructive sleep apnea syndrome may be affected by vitamin D.

Lin et al.[8] have reported that high-sensitivity C reactive protein, one of the inflammation markers, is related to the severity of OSA, independent of other factors such as obesity. Vitamin D is also reported to be associated with systemic inflammation[17,18]. The transcription factor NF-κB, and tumor necrosis factor-alpha and interleukin-8 expression are increased in relation to sleep hypoxia[17]. NF-κB has an enhancing effect on the inflammatory cascade by upregulating interleukin-8, tumor necrosis factor-alpha cytokines[18]. Vitamin D is also known to have effects on these transcription factors and cytokines[19,20]. These overlapping features of OSA and vitamin D in the inflammatory processes suggest that the relationship between these two entities should be investigated[21].

At high altitudes, changes in breathing patterns are observed during sleep which comprises apnea intervals. Studies investigating between the high altitude and the severity of obstructive sleep apnea have been performed in only small patient groups[22]. Researchers reported that in OSA patients hypoxemia deteriorates at altitudes up to 2590 meters[23]. However, optimal treatment approaches and effects of high altitude on the severity of the disease in OSA patients living at high altitudes are largely unknown[24].

In another study 25(OH)D was found reduced in severe OSA patients[25]. A study reported that compared to control group, 25(OH)D were lower in the OSA patients[26]. Our research results are consistent with the studies conducted in Turkey, although our study was performed at a higher altitude. Our study is conducted at Kars, Turkey which has an elevation of more than 1768 meters. In a recent study conducted at a lower altitude than our study, it is reported that severe OSA patients had a higher prevalence of vitamin D deficiency[27]. Reports of research found that vitamin D deficiency in the severe OSA group was found to be highest compared to moderate and non-OSA groups[4]. Another study reported that decreased vitamin D was related with risk of AHI meausurement 30 or more[28]. The significant decrease of 25(OH)D in the severe obstructive sleep apnea group in our study was consistent with the literature.

In our study we found independent association between 25-hydroxyvitamin D and obstructive sleep apnea severity at high altitude. An interesting part of our study is the independent association between AHI and 25(OH)D levels (AUROC=0.658, p=0.028). Our findings may indicate that 25(OH)D may be attributed to obstructive sleep apnea etiology and the disease severity. An interesting point of our study is

that our study has been conducted at a high altitude region, which has an elevation of more than 1768 meters. Measurement of 25(OH)D levels in obstructive sleep apnea patients and, if necessary, adding 25(OH) D into the treatment may be considered as an appropriate option.

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