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SCIENTIFIC INVESTIGATIONS

Vitamin D Deficiency in Patients Referred for Evaluation of Obstructive Sleep Apnea

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Study Objectives: A recent study reported an association between obstructive sleep apnea (OSA) and low vitamin D levels. In this study, we measured vitamin D levels in patients referred for evaluation of suspected OSA and sought to identify associated risk factors for vitamin D deficiency. Our objective was to determine whether evaluations of patients with suspected OSA should include routine screening for vitamin D deficiency.

Methods: Using a cross-sectional study design, we measured vitamin D levels in consecutively enrolled patients referred for an OSA evaluation to Dr. Lutfi Kirdar Kartal Training and Research Hospital in Istanbul, Turkey. We conducted full-night polysomnography and compared vitamin D levels both between patients with OSA and patients without OSA and across the various severity levels of OSA. We evaluated the association between vitamin D levels and various clinical and demographic characteristics, including the apnea-hypopnea index and body mass index.

Results: From April 2014 to June 2015, 195 patients were referred for OSA evaluation. Of these, 181 patients (93%) consented to participate and underwent full polysomnography and measurement of vitamin D levels. The mean ± standard deviation age was 49 ± 12 years and body mass index of 31 ± 6 kg/m^2. Polysomnography led to the diagnosis of OSA in 162 of the patients (89.5%): 52 (32%) were categorized as having mild OSA, 38 (23.5%) as having moderate OSA, and 72 (44.5%) as having severe OSA. Vitamin D level was 15.5 ± 11.6 ng/mL (95% confidence interval; 13–17 ng/mL) and 134 patients (74%) met the criterion for vitamin D deficiency (< 20 ng/mL). Sex, vitamin D levels, and percentage of patients with vitamin D deficiency were similar in patients with and without OSA (P > .05). Vitamin D levels were similar across OSA severity categories (P = .68). We found no association between vitamin D levels and the apnea-hypopnea index or body mass index.

Conclusion: A large proportion of patients referred for OSA evaluation had vitamin D deficiency. Vitamin D levels did not differ by OSA diagnosis status or severity. Patients referred for polysomnography should undergo routine screening for vitamin D deficiency as well as clinically indicated treatment to prevent associated comorbidities.

Keywords: obstructive sleep apnea, vitamin D deficiency, vitamin D level

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by recurrent, partial, or complete upper airway obstruction resulting in intermittent hypoxia during sleep. OSA is associated with obesity and diabetes, and is also a risk factor for hypertension and coronary artery disease.[1]

Recent reports have suggested that patients with OSA have a higher prevalence of vitamin D deficiency than healthy patients.[2,3] Vitamin D plays a key role in calcium absorption and homeostasis, and is obtained both from dietary sources and through the skin via exposure to sunlight. The accepted definition of vitamin D deficiency is vitamin D levels less than 20 ng/mL in serum[4–6]; such deficiency can lead to additional comorbidities, including multiple bone disorders.[6]

Obesity is a risk factor for vitamin D deficiency. Vitamin D is fat soluble and stored in adipose tissue. Obese individuals have more subcutaneous fat, which reduces the release of vitamin D from the skin into circulation.[7,8] Obesity is also a risk factor for OSA.[1] It is not known whether there is a direct and causal association between OSA and vitamin D deficiency, but recent studies have reported that patients with OSA have lower vitamin D levels than patients without OSA.[2,3] Other studies, however, have reported that only female patients and those with severe OSA are at increased risk for vitamin D deficiency.[9,10]

BRIEF SUMMARY

Current Knowledge/Study Rationale: There are contradictory results about association between obstructive sleep apnea and vitamin D levels. In this study we aimed to determine whether evaluations of patients with suspected OSA should include routine screening for vitamin D deficiency.

Study Impact: In this study, we found that the majority of patients referred to the sleep center for OSA evaluation had vitamin D deficiency. The recognition that vitamin D deficiency seems common in the referred patients supports screening and potentially treatment when clinically indicated.

Given the clinical importance of vitamin D deficiency and the fact that there have been contradictory results with regard to whether patients with OSA are at greater risk, this study seeks to describe vitamin D levels in a cohort of consecutively enrolled patients referred to our sleep center for evaluation of OSA and identify risk factors for vitamin D deficiency. Our objective was to determine whether screening for vitamin D deficiency should be a routine part of evaluating patients suspected of having OSA.

METHODS

Ethics Statement

The institutional review board at Dr. Lutfi Kirdar Kartal Training and Research Hospital in Istanbul, Turkey reviewed and approved the study. All study participants provided written informed consent.

Study Population

We screened all patients referred to the sleep laboratory at Dr. Lutfi Kirdar Kartal Training and Research Hospital with symptoms of snoring, witnessed apnea, or daytime sleepiness between April 2014 and June 2015 and invited them to participate in our study. Prior to polysomnography and a blood draw, patients provided sociodemographic and clinical information using a standardized form. We measured height, weight, and blood pressure; calculated body mass index (BMI); performed physical examinations; and collected information on tobacco smoking history and comorbid conditions. After completion of overnight polysomnography, we performed a blood draw and analyzed it for vitamin D levels using a Roche Cobas E411 autoanalyzer (Roche, Germany) with an electrochemiluminescence immunoassay. Analyses included all consenting participants who provided vitamin D measurements.

Polysomnography

The standard overnight polysomnography included electroencephalography, electrooculography, submental and bilateral leg electromyographs, and electrocardiography recordings. We measured air flow with a nasal pressure transducer and an oronasal thermistor, respiratory effort via respiratory inductance plethysmography, and arterial oxyhemoglobin saturation via a finger pulse oximeter. Experienced technicians collected and digitalized all signals using computerized polysomnography systems (Comet Grass: Astro-Med, Inc., West Warwick, Rhode Island, United States and Viasys Cephalo-Pro, SomnoStar: VIASYS Healthcare, Hoechberg, Germany) in accordance with established standards.[11] Certified sleep specialists, experienced in sleep medicine, scored sleep stages using the 2012 American Academy of Sleep Medicine (AASM) scoring system.[12] Disease classifications followed the International Classification of Sleep Disorders, Third Edition.[13] Grading of the apnea-hypopnea index (AHI) followed AASM's 1999 criteria as follows: an AHI less than 5 was normal, an AHI higher than 5 but less than 15 was mild, an AHI higher than 15 but less than 30 was moderate, and an AHI higher than 30 was severe.[14]

Statistical Analysis

Data analysis used SPSS version 17.0 software (SPSS, Inc., Chicago, Illinois, United States). The chi-square test compared categorical variables between groups. Comparison of means between patients with OSA and control groups used a *t* test, with descriptive statistics given as mean ± standard deviation. When there were more than three groups and their distribution was normal, we used the analysis of variance test, which evaluated the three OSA severity groups and controls. The Spearman rank correlation evaluated the relationships between the AHI, BMI, and vitamin D level. Logarithmic transformation evaluated variables that were not normally distributed. We considered a value of $P < .05$ as statistically significant for all measures.

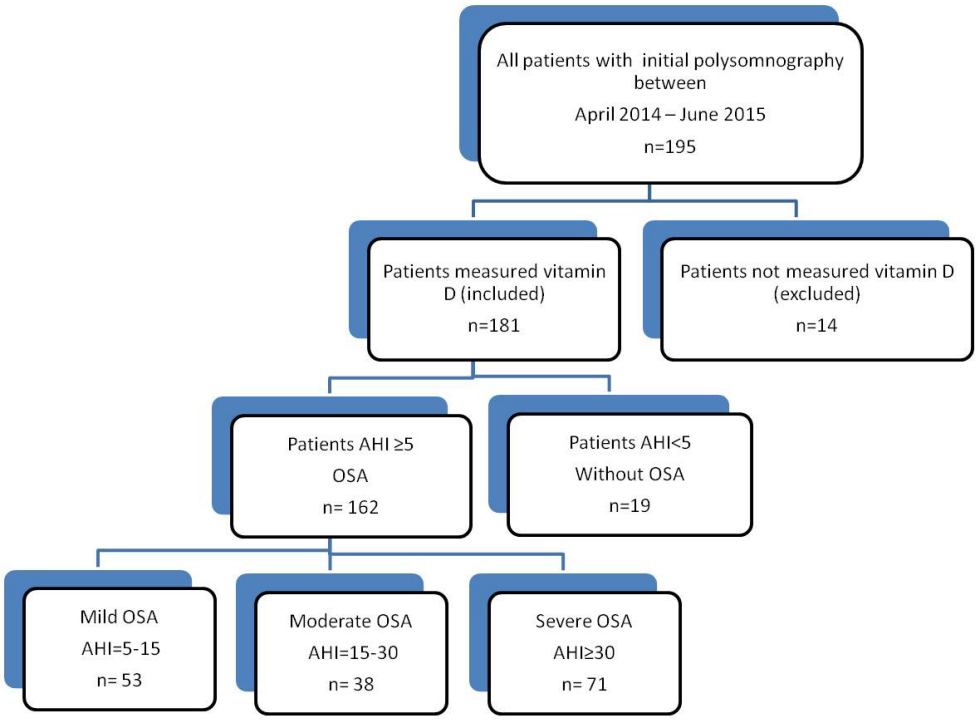
RESULTS

In total, 195 patients completed full polysomnography. Of these, 181 patients (93%) consented to participate and underwent measurement of vitamin D levels. Fourteen subjects who did not give consent to participate or did not undergo measurement of vitamin D levels were not included in analyses. The mean ± standard deviation age of the 181 remaining patients providing vitamin D levels and full polysomnography was 49 ± 12 years, 60% were male, and BMI was 31 ± 6 kg/m^2. Of these, 162 patients (89.5%) received a diagnosis of OSA. Evaluation of the patients' severity of OSA showed 53 (32%) were graded as mild, 38 (23.5%) as moderate, and 71 (44.5%) as severe. Conversely, 19 patients showed no evidence of OSA on polysomnography (**Figure 1**). The mean age and BMI in the OSA group were higher than in those without OSA (50 years versus 38 years, $P < .001$; 32 kg/m^2 versus 26 kg/m^2, $P < .001$, respectively). Both groups had male predominance. (63% versus %27, $P = .47$).

Vitamin D levels were not normally distributed. The mean vitamin D level was 15.5 ± 11.6 ng/mL (95% confidence interval; 13–17 ng/mL). Vitamin D levels were less than 30 ng/mL in 161 patients (89%) and less than 20 ng/mL in 132 (73%). In both patients with OSA (75%) and those without OSA (68%) there was a large proportion of subjects with vitamin D deficiency, and we found no statistically significant difference in vitamin D deficiency between these groups ($P = .55$). There was a significantly higher proportion of female patients in the vitamin D deficiency group compared to the group without deficiency (44.6% versus 24.5%, $P = .041$). No other evaluated characteristics were significantly different between those patients with vitamin D deficiency and those without, including age, BMI, presence of OSA, diabetes, hypertension, cardiovascular disease, hypothyroidism, and smoking (all $P > .05$) (**Table 1**).

The percentage of patients with vitamin D levels less than 20 ng/mL was not significantly different between patients with and without OSA ($P = .55$). As vitamin D levels are known to have seasonal variability, we included the date of the study as a covariate, but there was still no difference between the groups ($P = .95$). Mean vitamin D levels showed no difference between patients with and those without OSA ($P = .89$), nor between the various OSA severity groups ($P = .68$) (**Figure 2**).

Figure 1—Distribution of the patients



AHI = apnea-hypopnea index, OSA = obstructive sleep apnea.

Table 1—Characteristics of patients with and without vitamin D deficiency.

	Patients With Vitamin D Deficiency vit D < 20 ng/mL (n = 132)	Patients Without Vitamin D Deficiency vit D ≥ 20 ng/mL (n = 49)	*P* Value
Age (y), mean ± SD	48.3 ± 11.7	50.7 ± 13.3	.24
Female sex	44.6%	26.5%	.041
BMI (kg/m^2), mean ± SD	31.2 ± 6.1	30.4 ± 4.8	.40
AHI (events/h), mean ± SD	31.5 ± 28.6	32.1 ± 31.6	.90
Presence of obstructive sleep apnea	90.9%	89.7%	.78
Presence of diabetes	26.5%	34.6%	.35
Presence of hypertension	40.9%	38.7%	.35
Presence of cardiovascular disease	21.2%	14.2%	.39
Presence of hypothyroidism	10.6%	12.2%	.79
Presence of smoking	40.9%	55.1%	.19

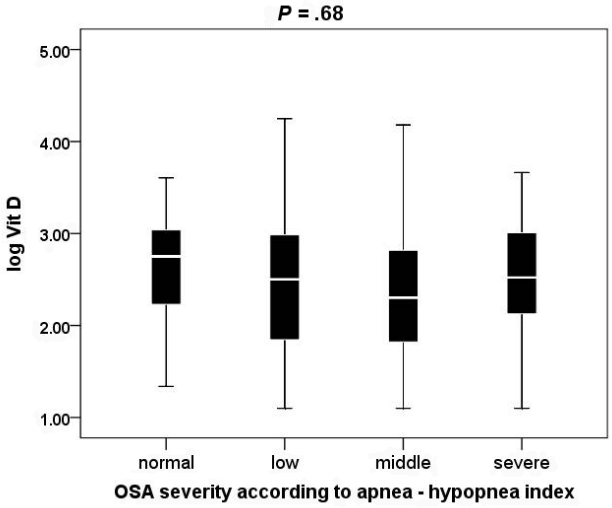
AHI = apnea-hypopnea index, BMI = body mass index, SD = standard deviation, vit = vitamin.

There was no correlation between vitamin D levels and the AHI ($P = .35$, $r = -0.06$) (**Figure 3**) or BMI ($P = .30$, $r = -0.07$) (**Figure 4**). Even after stratification by sex, there was no correlation between vitamin D levels and AHI (males: $P = .12$, $r = -0.18$; females: $P = .59$, $r = -0.05$). In addition, there was no correlation between vitamin D levels and diabetes, age, oxygen desaturation index, or minimum oxygen saturation (all $P \geq .1$).

DISCUSSION

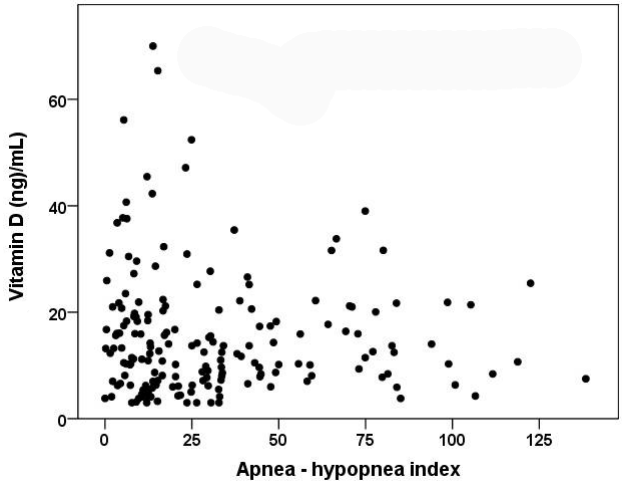
Our study found that the majority of patients referred to our sleep center in Istanbul, Turkey, for OSA evaluation had vitamin D deficiency, defined as vitamin D levels less than 20 ng/mL in accordance with internationally accepted definitions.[4–6] This deficiency was present regardless of OSA status, with 75% of patients with an OSA diagnosis and 68% of patients without OSA having vitamin D deficiency. Although a significant proportion of patients had vitamin D deficiency, we did not find any differences in vitamin D levels related to OSA severity grade or AHI, and there was no correlation between vitamin D levels and BMI. The absence of associations for vitamin D levels with either BMI or severity of OSA is contrary to other published studies.[2,3,9,10] Because vitamin D levels vary seasonally, decreasing in autumn and winter, and increasing in spring and summer,[5] we also investigated seasonal changes in vitamin D levels by stratifying analyses by the date of polysomnography. However, we found no

Figure 2—Vitamin D level of all apnea-hypopnea index severity groups.



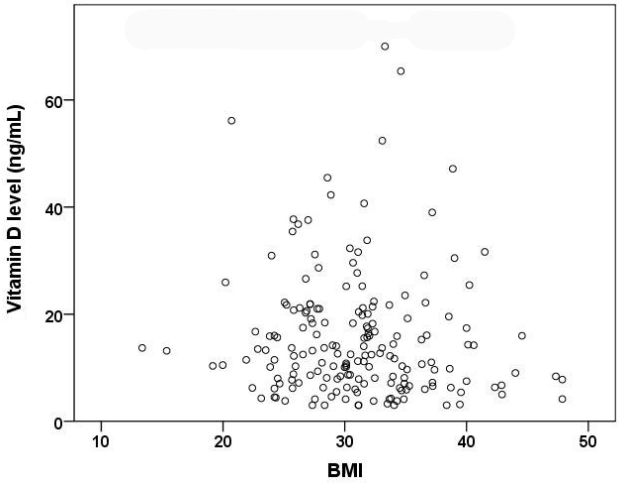
OSA = obstructive sleep apnea; Vit = vitamin.

Figure 3—Correlation between vitamin D level and apnea-hypopnea index in the study population.



P = .35; r = −0.06.

Figure 4—Correlation between vitamin D level and body mass index in the study population.



P = .30; r = −0.07. BMI = body mass index.

significant relationship between season and vitamin D levels in our cohort.

The clinical practice guidelines of the Endocrine Society recommend screening of populations at risk for vitamin D deficiency and that all adults who have vitamin D deficiency receive treatment to prevent osteoporosis and cardiovascular diseases.[5] Defining the populations at risk for deficiency can be challenging; a large population-based study conducted in Turkey reported diagnosed vitamin D deficiency in 47% of the general population, with a mean vitamin D level of 22.8 ng/mL.[15] Other studies have reported that populations in developing countries, including Turkey, have low vitamin D levels.[16] Recent health initiatives investigating the vitamin D levels of general medical patients evaluated at our hospital has shown mean vitamin D levels to be 18.5 ng/mL. The mean vitamin D level in our study population of patients referred for polysomnography was notably lower (15 ng/mL) than that of the general Turkish population, suggesting that such sleep center patients are at great risk for vitamin D deficiency and should be screened.

Studies have shown that obese subjects are more likely to have vitamin D deficiency compared to nonobese patients.[7,18,19] Some have postulated that obese individuals might avoid sunlight to explain this association.[7] It is also well established that OSA is associated with obesity,[1] and although obesity is not the only reason for referral to sleep centers, the condition is present in more than 60% of the patients referred.[20] In evaluating the relationship between obesity, vitamin D deficiency, and OSA, Erden and colleagues[2] recently reported an inverse correlation between BMI and vitamin D level, as well as lower vitamin D levels in patients with OSA than in controls. However, the control group consisted of study subjects who did not undergo PSG testing, and the AHI levels of the control group are not reported. Consistent with our findings, the authors did not find any differences in vitamin D measurements associated with severity of OSA.[2] The subjects referred to our laboratory and in whom OSA was not diagnosed were still overweight, which could have influenced the results. These patients already carry the risk of vitamin D deficiency because of obesity.

Other studies have reported additional clinical characteristics associated with deficiency, which were not present in our cohort. For example, Kerley and colleagues[3] showed that patients with OSA had more vitamin D deficiency than patients without OSA, and also reported that the BMI and AHI were inversely correlated with vitamin D level.[3] Bozkurt et al.[9] found that BMI was higher in severely obese patients and that vitamin D level was inversely correlated with BMI. However, they reported that vitamin D levels were not different in controls (n = 47) and patients with OSA (n = 139). In their cohort, female subjects with moderate and severe OSA had lower vitamin D levels than those with mild OSA and controls.[9] In both reports, the study population consisted of subjects referred to the sleep laboratory and who underwent PSG; subjects with AHI less than 5 were considered

as the control group. However, in our study, there were no BMI-associated differences in vitamin D levels, though we did find that female patients were more likely to have vitamin D deficiency.

Finally, Mete et al.[10] did not find any significant difference in either vitamin D levels or the percentage of patients who had vitamin D deficiency among patients with OSA and controls (150 with OSA and 32 without OSA who were referred for sleep study), though their subgroup analysis did report that patients with severe OSA had lower vitamin D levels and more vitamin D deficiency than other OSA groups, as well as controls.[10] A study by Barcelo et al. found an inverse association between vitamin D level and diabetes and metabolic syndrome in patients with OSA.[21] In our cohort, 52 patients had diabetes and this finding was not associated with vitamin D levels.

Our study has limitations. First, the number of patients without OSA (n = 19) was small. This is a limitation common to the published literature on this topic, with the referenced studies also having relatively small control groups. The small sample size of the control group may result in us erroneously concluding that there is no relationship between OSA status and vitamin D deficiency. However, we believe that the absence of differences in vitamin D levels based on severity of OSA in 162 patients underscores that the risk factors for and associations with vitamin D deficiency are complex and cannot be explained solely based on BMI or OSA status and severity. Second, the patients were referred to a specialized center for polysomnography in Istanbul, Turkey; as such, there is a risk of referral bias, and the results may not be generalizable to other settings. Third, because this was a cross-sectional study, it provides little insight into potential causal mechanisms. However, the recognition that vitamin D deficiency seems common in our referred patients supports screening and potentially treatment when clinically indicated.

In conclusion, the majority of patients referred to our sleep laboratory in Istanbul, Turkey had vitamin D deficiency (defined as vitamin D levels less than 20 ng/mL), with mean vitamin D levels being lower than the vitamin D levels reported in the general Turkish population.[15] Contrary to other reports, our study found that vitamin D levels were not significantly different between patients with and those without OSA. Because of this, we conclude that patients referred for polysomnography should be screened for vitamin D deficiency and receive clinically indicated treatment to prevent associated comorbidities.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
AHI, apnea-hypopnea index
BMI, body mass index
OSA, obstructive sleep apnea
Vit D, vitamin D

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DISCLOSURE STATEMENT

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