Sleepiness and Vitamin D Levels in Patients with Obstructive Sleep Apnea

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Article

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Abstract: Study Objectives: The aim of this study is to explore the association between serum 25-hydroxyvitamin D [25(OH)D] levels, a marker of Vitamin D status, and excessive daytime sleepiness (EDS), expressed as increased scores of Epworth Sleepiness Scale (ESS), in a group of prospectively enrolled patients with obstructive sleep apnea (OSA). Methods: Newly diagnosed patients with OSA, divided into two groups, those with EDS (ESS>10) and those without EDS (ESS<10). All patients underwent night-polysomnography. Measurement of serum 25(OH)D vitamin was performed using a radioimmunoassay. Results: Totally, 217 patients with OSA (197 males and 20 females) were included. Patients with EDS had higher AHI ($p < 0.001$) values and lower mean serum 25(OH)D levels, compared with those of non-somnolent patients [17.4 (12.2 – 25.7) versus 21.1 (15.3 – 28.8) ng/ml respectively, $p = 0.005$]. In patients with EDS, serum 25(OH)D levels correlated with average oxyhaemoglobin saturation during sleep ($r = 0.194$, $p = 0.043$), and negatively with ESS score ($r = -0.285$, $p = 0.003$), AHI ($r = -0.197$, $p = 0.040$) and arousal index ($r = -0.256$, $p = 0.019$). Binary regression analysis identified Vit D serum levels ($\beta = -0.045$, OR: 0.956, 95% CI: 0.916 – 0.997, $p = 0.035$), total sleep time ($\beta = 0.011$, OR: 1.011, 95% CI: 1.002 – 1.021, $p = 0.016$) and AHI ($\beta = 0.022$, OR: 1.022, 95% CI: 1.003 – 1.043, $p = 0.026$) as independent predictors of EDS in patients with OSA. In patients with EDS, multiple regression analysis indicated that ESS score was negatively associated with Vit D serum levels ($\beta = -0.135$, $p = 0.014$) and minimum oxyhemoglobin saturation during sleep ($\beta = -0.137$, $p = 0.043$). Conclusions: In the present study, EDS in patients with OSA is associated with low levels of Vitamin D, while sleep hypoxia may play a role in this process.

Keywords: vitamin D; sleepiness; obstructive sleep apnea (OSA); sleep apnea; Epworth Sleepiness Scale (ESS)

1. Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep [1]. By definition, these episodes are always accompanied by respiratory effort and result in oxyhaemoglobin desaturation and sleep fragmentation [1]. Currently, OSA is the most frequent breathing disorder during sleep, with an estimated prevalence between 10-17% for men and 3-9% for women in the Western countries [2]. OSA-related symptoms could be

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divided in nocturnal, such as loud snoring and choking sensation during sleep, and diurnal; such as excessive daytime sleepiness (EDS) which among others is recognized as the most common and disabling daytime feature of OSA [3].

EDS is a frequently reported symptom of OSA and it may affect from 19% to 87.2% of patients diagnosed with OSA [4]. Although the prevalence of EDS in OSA exhibits significant variability in epidemiological studies, these evident differences in the prevalence data might be attributed to a complex interplay of several factors, including the methodologies employed for EDS measurement, sample sizes, age, gender, severity of OSA, ethnicity, the presence of comorbidities, and other unrecognized factors that could impact OSA manifestation [5]. EDS is defined as the inability to maintain wakefulness and alertness during the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months [6]. Well-known risk factors for this condition include increased BMI and neck circumference, older age, male gender and anatomical variations causing narrowing of the upper airway [7]. As the syndrome evolves, and while at the same time remains undiagnosed and untreated, EDS becomes debilitating resulting in impaired quality of life, reduced work performance and increased probability for traffic accidents [3].

Vitamin D (Vit D) is a fat-soluble vitamin produced in the skin after exposure to solar radiation. Vit D exists in various forms and serum 25-hydroxyvitamin D [25(OH)D] is recommended as the marker of choice for the evaluation of Vit D status [8]. Interestingly, Vit D insufficiency (defined as Vit D levels < 20 ng/ml) and deficiency (defined as Vit D levels < 10 ng/ml) has an increased prevalence worldwide and is implicated in numerous pulmonary diseases, such as viral and bacterial respiratory infections, asthma, chronic obstructive pulmonary disease and cancer [9]. Recent data reported lower Vit D serum levels in patients with OSA compared with non-apneic individuals, while CPAP treatment showed beneficial effects on Vit D concentrations in this particular population of patients [10,11].

Data regarding the relationship between Vit D serum levels and EDS in OSA is still scarce. Hence, the aim of the present study is to compare Vit D serum levels in OSA patients with and without EDS and to explore potential associations between Vit D levels and the degree of excessive daytime sleepiness in these patients. In addition, secondary endpoints of the study are to examine possible correlations between Vit D levels and different anthropometric and sleep characteristics focusing on the subgroup of patients with EDS.

2. Materials and Methods

Patients

Patients who underwent polysomnography in our Institution and were consecutively diagnosed with OSA have been included in the study.

Patients' recruitment took place between April and October of the same year, in order to avoid significant variations in exposure to sunlight, which could affect Vit D levels. The following exclusion criteria were applied: Vit D supplementation, exclusively central sleep apneas on polysomnography, corticosteroid and/or diuretic therapy, conditions known to affect calcium, phosphorus and Vit D metabolism and absorption, heart failure, inflammatory diseases, cancer, chronic liver or renal disease, osteoporosis and patients with no OSA-related EDS have been excluded [12].

A detailed medical history regarding past medical conditions, known comorbidities, current medication use, with emphasis on Vit D supplements, and tobacco smoking was recorded. A clinical examination and the assessment of anthropometric characteristics (including height, weight, neck circumference, hip, and waist circumference as well as waist/hip circumference ratio and body mass index-BMI) were performed.

OSA was defined as AHI ≥ 15 events/hour of sleep or as AHI ≥ 5 events/hour of sleep accompanied by symptoms of disturbed sleep, such as excessive daytime sleepiness, gasping or choking during sleep, observed loud snoring or breathing interruption [3].

Sleepiness was evaluated using the validated Greek version of the Epworth Sleepiness Scale (ESS) [13], a self-administered questionnaire which comprises eight questions addressing typical

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everyday situations. Responders are asked to rate, with a score from 0 to 3, the possibility of falling asleep in each situation. A score >10 is considered indicative of EDS.

Pulmonary function testing, analysis of arterial blood gases and a 12-lead electrocardiogram were also performed in order for potential coexistent pulmonary and cardiovascular diseases to be excluded.

Polysomnography

Overnight polysomnography, attended by an experienced sleep technician, was performed from 22:00 to 06:00 hours and variables were recorded on a computer system (Alice® 4, Philips Respironics, Murrysville, PA, USA). Sleep staging was based on a standard montage of electroencephalogram, electro-occulogram, electromyogram and electrocardiogram signals. Pulse oximetry was registered and airflow was detected using combined oronasal thermistors for apneas and nasal pressure for hypopneas. Thoracic cage and abdominal motion were detected using inductive plethysmography. Recordings were manually scored according to standard criteria [14]. Apnea was defined as a ≥90% of reduction in airflow for at least 10 sec [14]. Hypopnea was defined as a ≥30% reduction in airflow for at least 10 sec in combination with oxyhaemoglobin desaturation of at least 3% or an arousal registered by the electroencephalogram [14]. The apnea-hypopnea index (AHI) was calculated as the average number of apneas and hypopneas per hour of PSG-recorded sleep time [14].

Blood samples and measurements

Venous blood samples were collected from all participants the morning after polysomnography after at least 8 hours of fasting. Samples were obtained from the antecubital vein and were left to coagulate and then centrifuged (3000 rpm for 10 min). Biochemical parameters regarding renal and liver function, as well as glucose, C-reactive protein (CRP) serum levels and lipid profile were measured using an automated analyzer. Serum concentration of 25(OH)D was determined using a commercial radioimmunoassay kit and the manufacturer's specifications the same day as this of blood sampling (DiaSorin, Stillwater, MN, USA).

Statistical analysis

All analyses were carried out using IBM Statistical Package for Social Sciences (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.). Continuous variables were tested for normality of distribution with the Shapiro-Wilk test. All data are expressed as median (25th - 75th percentile). The chi-squared test was used for comparison of percentages between groups. Correlations were analyzed with Pearson's correlation coefficient, while comparisons between means were studied with the Student's t-test. In case of skewed distribution, the non-parametric Mann–Whitney test was applied. Independent predictors of EDS between the two groups were identified using binary logistic regression analysis. In the EDS group, independent factors of EDS were further determined using multiple linear regression analysis. Reported p-values are two-tailed and significance was defined at $p < 0.05$.

Ethics Approval

The study was carried out in accordance with the Helsinki Declaration of Human Rights and patients gave their informed consent [15]. The study protocol was approved by the Institutional ethics committee (Protocol number: 29/5/13-10-2014).

3. Results

In total, 217 patients with OSA (197 males and 20 females) were recruited and enrolled in the present study. Included patients were middle-aged [age was 55 (46.5 – 62.5) years] and obese [BMI was 35.3 (31.4 – 38.3) kg/m^2], while median serum Vit D levels were of 19.4 (13.3 – 26.5) ng/ml. Females exhibited lower 25(OH)D serum levels compared with males [15.5 (9.7 – 20.6) versus 20.2 (13.4 – 26.7) respectively, $p = 0.048$)].

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Participants were divided according to the presence or not of EDS into two groups: non-sleepy (ESS score ≤ 10), that included 108 patients (96 males and 12 females), and sleepy (ESS score > 10), that included 109 patients (101 males and 8 females). There were no differences between the two groups in terms of gender, age, and BMI. Anthropometric and demographic characteristics of included patients are presented in Table 1.

Table 1. Comparison of anthropometric characteristics between OSA patients with and without EDS.

	OSA patients without EDS n=108	**OSA Patients with EDS n=109**	**p**
Gender (male/female)	96/12	101/8	0.337
Age (years)	55.5 (46 – 64)	54 (47 – 62)	0.839
BMI (kg/m²)	34.3 (30.7 – 37.7)	36 (32.1 – 38.9)	0.103
Neck circumference (cm)	44 (42 – 47)	45 (42 – 48)	0.502
Waist circumference (cm)	121 (113 – 129)	121 (112 – 130)	0.764
Hip circumference (cm)	116 (111 – 124)	116 (110 – 123)	0.937
WHR	1.03 (0.99 – 1.06)	1.03 (0.99 – 1.08)	0.406
Smoking (%)	24.1%	28.4%	0.465

BMI: body mass index; EDS: excessive daytime sleepiness; OSA: obstructive sleep apnea; WHR: waist to hip ratio.

In sleepy patients, the following findings were demonstrated: longer total sleep time, higher sleep efficiency, higher values of arousal index, AHI and worse indices of hypoxia during sleep when compared with patients without EDS. Sleep characteristics of patients are presented in Table 2.

Table 2. Comparison of sleep characteristics between OSA patients with and without EDS.

	OSA patients without EDS n=108	**OSA patients with EDS n=109**	**p**
TST (min)	311 (263 – 339)	340 (311 – 360)	<0.001
N1 (%)	12.3 (5.5 – 18.7)	7.7 (4.4 – 15.3)	0.055
N2 (%)	70.1 (59.2 – 77.9)	72.2 (61.9 – 85.1)	0.046
N3 (%)	7.5 (1.8 – 15.2)	5.2 (0 – 13.6)	0.074
REM (%)	7.5 (1.4 – 12.9)	5.4 (1.3 – 10.5)	0.171
AHI (events/h)	33.9 (15 – 62.3)	54.9 (35.2 – 73)	<0.001
Aver SpO_2 (%)	92 (90 – 94)	91 (89– 93)	0.002
Min SpO_2 (%)	77 (69 – 82)	73 (63 – 79)	0.008
T<90% (%)	11.8 (3.2 – 38.3)	30.9 (12.8 – 59.6)	<0.001
Arousal index	27.5 (13.5 – 35.7)	35.2 (19.2 – 49.5)	0.034

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Sleep efficiency (%)	83.7 (75.7 – 90)	88.6 (80.2 – 92.7)	0.004
ESS score	7 (5 – 9)	14 (12 – 17)	<0.001

AHI: apnea hypopnoea index, Aver SpO_2: average oxyhemoglobin saturation, EDS: excessive daytime sleepiness, ESS: epworth sleepiness scale, Min SpO_2: minimum oxyhemoglobin saturation, N1: sleep stage 1, N2: sleep stage 2, N3: sleep stage 3, OSA: obstructive sleep apnea, REM: rapid eye movement, TST: total sleep time, T<90%: time with oxyhemoglobin saturation <90%.

Additionally, patients with EDS had poorer lipidemic profile, as expressed by higher triglycerides levels and lower HDL-C, compared with patients without EDS. Moreover, sleepy patients with OSA had significantly lower serum 25(OH)D levels than those without EDS [21.1 (15.3 – 28.8) versus 17.4 (12.2 – 25.7) ng/ml respectively, p = 0.005]. Results of blood examinations of patients are presented in Table 3.

Table 3. Comparison of laboratory results between OSA patients with and without EDS.

	OSA patients without EDS n=108	**OSA patients with EDS n=109**	**p**
FEV_1 (% predicted)	93.8 (81.9 – 103)	92.3 (75.9 – 106.8)	0.736
FVC (% predicted)	90.7 (78.1 – 99.3)	85.9 (73.8 – 97.8)	0.137
FEV_1/FVC (%)	86.5 (82 – 110.3)	83 (79 – 95)	0.323
pO_2 (mmHg)	79 (73 – 85.6)	78.5 (68.5 – 86)	0.344
pCO_2 (mmHg)	41 (38.9 – 44)	42 (39 – 45)	0.327
Glucose (mg/dL)	103 (92 – 117)	114 (94.3 – 128.8)	0.078
Creatinine (mg/dL)	0.9 (0.8 – 1)	0.9 (0.8 – 1)	0.316
Cholesterol (mg/dL)	201 (176.8 – 234)	198 (176 – 234.8)	0.735
Triglycerides (mg/dL)	136.5 (98 – 181)	167 (112.5 – 211.8)	0.013
LDL-C (mg/dL)	125.9 (96.3 – 151.5)	118.2 (102 – 142.3)	0.899
HDL-C (mg/dL)	47 (42 – 57.3)	42 (37 – 52)	0.007
AST (U/L)	23 (19 – 27)	21.5 (18 – 27.8)	0.390
ALT (U/L)	25 (17 – 33)	24.5 (20 – 35)	0.604
CRP (mg/dL)	0.25 (0.1 – 0.79)	0.40 (0.20 – 0.66)	0.376
25(OH)D (ng/ml)	21.1 (15.3 – 28.8)	17.4 (12.2 – 25.7)	0.005

ALT: alanine aminotransferase, AST: aspartate aminotransferase CRP: C - reactive protein, FEV1: forced expiratory volume in 1st sec, FVC: forced vital capacity, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, pCO_2: carbon dioxide partial pressure, pO_2: oxygen partial pressure.

Further analysis in the group of sleepy patients showed that serum 25(OH)D levels were positively correlated with average oxyhaemoglobin saturation during sleep (r = 0.194, p = 0.043) and negatively associated with ESS score (r = -0.285, p = 0.003), AHI (r = -0.197, p = 0.040) and arousal index (r = -0.256, p = 0.019). Conversely, among non-sleepy OSA patients, Vit D serum levels were positively associated with average oxyhemoglobin saturation (r = 0.250, p = 0.009) and negatively associated with time with oxyhemoglobin saturation <90% (r = -0.214, p = 0.028) during sleep.

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Age, sex, BMI, indices of oxygenation during sleep (average and minimum oxyhemoglobin saturation and time with oxyhemoglobin saturation <90%), total sleep time, sleep efficiency, AHI, arousal index and Vit D serum levels were included in a binary logistic regression analysis model in order to identify independent predictors of EDS. This analysis revealed that Vit D serum levels (β = -0.045, OR: 0.956, 95% CI: 0.916 – 0.997, p = 0.035), total sleep time (β = 0.011, OR: 1.011, 95% CI: 1.002 – 1.021, p = 0.016) and AHI (β = 0.022, OR: 1.022, 95% CI: 1.003 – 1.043, p = 0.026) emerged as independent predictors of EDS in patients with OSA.

In the group of OSA patients with EDS, correlations of ESS score with other indicators were determined using a multivariate linear regression analysis. In this analysis, ESS score was set as the outcome whereas age, sex, BMI, indices of oxygenation during sleep (average and minimum oxyhemoglobin saturation and time with oxyhemoglobin saturation <90%), total sleep time, sleep efficiency, AHI, arousal index and Vit D serum levels were set as covariates. Results indicated that ESS score was negatively associated with Vit D serum levels (β = -0.135, p = 0.014) and minimum oxyhemoglobin saturation during sleep (β = -0.137, p = 0.043). In the group of OSA patients without EDS, a similar analysis showed that ESS score was positively associated with sleep efficiency (β = 0.138, p = 0.001).

4. Discussion

The present study has reported significantly lower levels of 25(OH)D in patients with OSA and EDS compared with patients with OSA and without EDS. Additionally, Vit D serum levels, AHI and total sleep time were identified as independent predictors of EDS. Finally, 25(OH)D levels were associated with indices of hypoxia during sleep and total sleep time.

Both decreased serum 25(OH)D levels and severity of OSA associated with EDS in the group of patients with OSA. The relationship between EDS and hypovitaminosis D has been a subject of interest in previous studies. In a previous study an association was shown between Vit D status and excessive daytime sleepiness in patients with sleep disorders, of which obstructive sleep apnea was the most prevalent [16]. Interestingly, only in black patients with Vit D deficiency (defined as < 20 ng/mL), VitD levels correlated with sleepiness (r = 0.48, p < 0.05), expressed as scores in ESS≥10 [16]. In addition, multiple lines of evidence indicate that patients with OSA are more prone at Vit deficiency than those without OSA [17,18], and that treatment with CPAP could increase Vit D levels either after short term application and in male patients with OSA [19], and after long term application in sleepy patients and those with severe OSA [20], or more specifically in male obese patients with OSA [11].

In the present study, differences between sleepy and non-sleepy patients with OSA in terms of polysomnographic parameters were noted. Specifically, OSA patients with EDS exhibited increased AHI, total sleep time, arousal index and sleep efficiency, and presented worse hypoxia during sleep compared with those individuals without EDS. These results confirm previous reports on the association of EDS (assessed either by subjective or objective tools [21]) with anthropometric and polysomnographic characteristics in OSA patients, including higher BMI, longer total sleep time, increased arousal index and, as well as decreased minimum oxyhaemoglobin saturation during REM and NREM sleep [22].

Hypoxia may serve as an underlying mechanism explaining the association between hypovitaminosis D and EDS. Previous studies reported a clear link between the impaired oxygenation during sleep and EDS in individuals with OSA, suggesting a potential causal relationship between nocturnal hypoxia and EDS [21,22]. Concurrently, hypoxia and hypoxia-related factors, such as the hypoxia inducible factor-1α subunit (HIF-1α) and the vascular endothelial growth factor (VEGF) are inversely correlated to serum 25(OH)D levels [23,24]. Indeed, in our study we confirmed previous reports that patients with OSA exhibit decreased 25(OH)D levels in comparison to healthy controls, and these diminished 25(OH)D levels are correlated with average oxyhemoglobin saturation and with percentage of time with oxyhaemoglobin saturation <90% during sleep [17]. Thus, over-expression of inflammatory factors promoted by hypoxia during sleep may mediate the relationship between low Vit D levels and increased levels of EDS in OSA patients.

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Moreover, several other pathogenetic mechanisms have been proposed in order to elucidate the link between Vit D and EDS. An underlining hypothesis suggests that low Vit D serum levels could promote EDS through mechanisms involving upregulation of inflammatory mediators and hypnogenic cytokines such as TNF-α, IL-1, IL-6 and prostagladin-2 [25,26]. The relationship between EDS and increased AHI has been proven in some, but not in all studies [27–29]. Excluding AHI, other factors, including metabolic and psychological conditions, may contribute to the increased risk of EDS in OSA patients [30]. EDS has been frequently reported among diabetic patients without OSA and constitutes a risk factor for severe hypoglycemia [26,31]. Recently, reduced serum Vit D levels have been associated with increased insulin resistance in patients with OSA [32]. Similarly, in patients with OSA and EDS associations have been shown between insulin resistance and glucose deregulation [33,34]. Moreover, in a median follow-up of 8.1 years, lower serum Vit D concentrations were associated with increased risk of type 2 diabetes, with daytime sleepiness being the major contributor [35]. Thus, insulin resistance may mediate the emergence of EDS in patients with OSA and Vit D insufficiency.

Notably, studies investigating the association between EDS and Vit D serum levels in conditions other than OSA, have reported conflicting results. In the study of Carlander et al. [36], serum 25(OH)D concentrations were decreased in patients with narcolepsy compared with healthy controls. Patients with narcolepsy were at increased risk of Vit D deficiency compared with non-narcoleptic subjects (72.5% versus 50.9% respectively) [36]. Conversely, another study showed similar levels of 25(OH) D between patients with narcolepsy type 1 and healthy controls [37]. In patients with narcolepsy, no significant association was found between Vit D deficiency and disease duration or severity [37]. OSA is a frequent comorbidity in narcolepsy (about 25%) and may explain the puzzling results regarding the association between Vit D and narcolepsy [38].

Certainly, our study has a number of limitations. Firstly, our data were obtained from middle-aged adults thus caution is needed in extrapolating the results to older patients with OSA. Of note, regression analysis failed to demonstrate age as an influencing factor for EDS in our participants. Secondly, data regarding skin pigmentation, clothing and dietary habits were not recorded in the current study. Nevertheless, the study was conducted in a relatively limited time interval (6 months), and included Caucasian patients, living in the same area, with relatively similar sun exposure and dietary habits. Additionally, the number of included female patients was relatively small and thus the study results should be interpreted with caution. However, at regression analysis, gender was excluded as cofounder regarding the relationship between Vit D deficiency and EDS. It should be noted that the index females/males was the result of an increased male referral and has not resulted from a female exclusion process. Finally, EDS was evaluated using the ESS and not an objective method, such as multiple sleep latency test. However, there is evidence suggesting that ESS can be a valid tool for the evaluation of EDS [39]. Potential mechanisms of EDS in OSA still are not entirely clear [40].

In conclusion, our results suggest that both AHI and Vit D serum levels predict EDS in a group of patients with OSA. Hypoxia during sleep may play an important role in this process. A possible bi-directional relationship between OSA and hypovitaminosis D could partially explain our findings. Further research is necessary in order to better elucidate the interaction between serum Vit D levels and EDS in patients with OSA.

Author Contributions: Author contributions: K. A. and P.S. conception and design of the study; interpretation of data; statistical analysis; drafting of manuscript; critical revision of the manuscript for important intellectual content. N.T.E., E.N., A.V., A.R., K.C., G.T. and P.B.; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. All authors are responsible for interpretation of the findings. All authors critically revised and approved the final version to be published.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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