TÜBİTAK

Turkish Journal of Medical Sciences
http://journals.tubitak.gov.tr/medical

Turk J Med Sci
(2021) 45: 2524-2533

Research Article

doi: 10.3906/sag-2101-83

The effects of vitamin D supplemantation on prognosis in patients with mild obstructive sleep apnea syndrome

Feride AYYILDIZ[1,*], Hilal YILDIRAN[1], Nigar AFANDIYEVA[2], Özlem GÜLBAHAR[2], Oğuz KÖKTÜRK[3]
[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Gazi University, Ankara, Turkey
[2]Department of Medical Biochemistry, Faculty of Medicine, Gazi University, Ankara, Turkey
[3]Department of Chest Diseases, Faculty of Medicine, Gazi University, Ankara, Turkey

Received: 07.01.2021 **Accepted/Published Online:** 24.06.2021 **Final Version:** 21.10.2021

Background/aim: The aim of this study was to investigate the effect of vitamin D on the disease prognosis and biochemical parameters in patients with mild obstructive sleep apnea syndrome (OSAS).

Materials and methods: Nineteen adult male individuals (18–65 years) who were diagnosed with mild OSAS after polysomnography and had low vitamin D levels were included in the study. Each week, patients took 50.000 IU Vitamin D3 supplementation for 8 weeks. Polysomnography, biochemical parameters FBG (fasting blood glucose), lipid profile (TG, TC, LDL-C, HDL-C, VLDL-C), calcium, phosphorus, parathormone, calcitonin, serum 25(OH)D, insulin, CRP, TNF-α, IL-6, and IL-10 of patients were evaluated at the beginning of study and at the end of the study. All assessments, including polysomnography, were repeated after 8 weeks.

Results: Serum vitamin D levels were initially 19.5 ± 5.01 ng/mL and increased to 41.8 ± 10.51 ng/mL ($p < 0.001$) at the end of the study. FBG, TC and HOMA-IR of the patients were significantly decreased ($p < 0.05$). CRP, TNF-α, IL-6, and IL-10 levels were also correlated with serum vitamin D levels ($p < 0.05$). There was a significant decrease in number of obstructive apneas, apneas and hypopneas, apnea index, hypopnea index, and apnea hypopnea index of the patients ($p < 0.05$).

Conclusion: As a result, it is thought that vitamin D supplementation may have a positive effect on the disease prognosis of mild OSAS.

Key words: Vitamin D supplementation, obstructive sleep apnea, biochemical parameters, inflammation

1. Introduction

Among the sleep disorders, obstructive sleep apnea syndrome (OSAS) has the highest prevalence (1%–5%) [1,2]. OSAS is defined as a disease with daytime sleepiness, loud snoring and witnessed apnea in the presence of at least five airway obstructions per hour in sleep [2]. Obstructive sleep apnea syndrome is not only a disease affecting daily life, but associated with many diseases such as coronary artery disease, diabetes mellitus (DM) and stroke as well [3,4]. These diseases accompanying OSAS and OSAS itself have been found to be associated with the inflammatory process, and proinflammatory mediators (IL-1 beta, IL-6, IL-8, CRP, and TNF-α) have been seen to increase in these diseases [5,6]. Besides, intermittent hypoxia induces inflammation and causes impairment in lipid metabolism or stimulation of lipolysis [7,8]. The hyperlipidemia resulting from excessive lipolysis [7] triggers insulin resistance and inflammation [8].

Polysomnography (PSG) is the gold standard technique in the diagnosis of OSAS [9], and continuous positive airway pressure (CPAP) is the gold standard treatment in patients with moderate and severe OSAS with apnea-hypopnea index (AHI)> 15. However, CPAP treatment is recommended in mild obstructive sleep apnea (OSA) (AHI: 5–15) if symptoms are pronounced and/or in the presence of cardiovascular and cerebrovascular risk factors [10]. Since the severity of mild OSAS worsens over time, it is also thought that active and effective treatment may be required for mild OSAS. Although severe OSA is associated with an increased risk of cardiovascular disease (CVD), mild OSA is associated with a higher prevalence of CVD and significant cardiovascular (CV) comorbidity [11]. In addition, if OSA is not treated, the risk development of CVD may increase [12]. Despite these risks, it has been emphasized that the acceptance rate of CPAP is low in mild OSAS [11]. In a study, while the rate of acceptance to use CPAP is 61.88% in severe OSAS and 37.37% in moderate OSAS, this rate is only 10% in mild OSAS ($p < 0.001$) [11]. It has been reported that getting the device for a certain fee or the high price of the device affects its use, and the rate of use increases in the countries where the CPAP device is provided free of charge [11].

As stated in the consensus report of OSAS in Turkey, the gold standard treatment method in OSAS is positive airway pressure (PAP) treatment. However, contrary to current scientific practices, in order to report devices such as air pressure/bilevel positive airway pressure (CPAP/BPAP) in the practices of Social Security Institution (SSI), "the apnea index (AI) must be at least 15

*Correspondence: feridecelebi_dyt@hotmail.com

or apnea-hypopnea index (AHI) must be at least 30, or the respiratory disturbance index (RDI) must be at least 30". If the RDI is between 5 and 30, costs of the devices are covered by the institution if some risk factors accompanying OSAS (daytime sleepiness, hypertension, cognitive impairment) are reported [10].

Recently, vitamin D deficiency has been reported to play a role in the development of sleep disorders [13]. It was observed that serum 25-hydroxyvitamin D (25(OH)D) level was lower in OSAS than in the control group [14]. Some studies have shown that serum 25(OH)D levels decrease as OSAS intensity increases [15–17]. Vitamin D deficiency has been reported to pose a risk for OSAS by causing increased adenotonsillar hypertrophy, airway muscle myopathy, and/or chronic rhinitis [13]. Chronic low serum vitamin D level also increases the risk of restriction in nasal airflow [13]. In addition, low serum vitamin D levels cause an increased risk of diseases such as autoimmune diseases, chronic rhinitis, CVD, diabetes, and tonsillar hypertrophy. This is associated with an increase in inflammatory cytokines (TNF-α, IL-1, and prostaglandin D2 (PD2)), which are also effective in regulating sleep, with the change of immunomodulation and increased susceptibility to infections [13]. Besides, the level of IL-6 increase [18] and serum 25(OH)D level decrease in OSAS [19]. In human studies, they have attributed high serum vitamin D levels to a decrease in inflammatory cytokines such as CRP, IL-6, and TNF-α in healthy individuals [20,21]. The same relationship has been observed in proinflammatory conditions such as diabetes, atherosclerosis, and inflammatory polyarthritis [19]. While high serum vitamin D is known to have positive effects in the inflammatory process, the effect of continuous positive airway pressure (CPAP) treatment applied in the treatment of OSAS on inflammation is contradictory [22–24].

The low rate of CPAP acceptance/use in mild OSAS suggests that different treatment practices should be tried in mild OSAS. Studies on vitamin D supplementation in OSAS are limited in the literature. The aim of this study is to evaluate the effects of vitamin D supplementation on disease prognosis and biochemical parameters in individuals who do not have a routine treatment, do not accept CPAP use, and have a diagnosis of mild OSAS with vitamin D deficiency.

2. Materials and methods

Nineteen male volunteer adults with vitamin D deficiency (<30 mg/dL) were included in this study. They aged between 19 and 64 and applied to Gazi University Faculty of Medicine, Sleep Disorders Center between March 2016 and May 2018 with the complaint of sleep disorder. They were diagnosed with mild OSAS after fullnight polysomnography (AHI: 5–15). Since this disease is seen more frequently in men and the proportion of men applying to the study center is higher, only male individuals were included in the study. A group of patients who did not receive/accept any treatment including CPAP was studied. The power was calculated with Minitab 16.0 program. According to the program, the full power was calculated as 85.59% for 19 individuals.

Those who took vitamin-mineral or fish oil supplements in the last 6 months, who had liver and kidney dysfunction, those who had normal vitamin D levels, those who take a medication affecting vitamin D level (such as steroids and anticonvulsant), who are diagnosed with cancer, who follow a diet, and those who do not want to participate in the study were excluded. Vitamin D supplementation is also contraindicated in patients with vitamin D hypervitaminosis, hypercalcemia, hypercalciuria, calcium-containing kidney stones, and calcium hypersensitivity. Therefore, these patients were not included in the study.

2.1. Research plan

Forty patients who met the determined criteria were included in the study. Vitamin D supplementation (D3 oral solution) was applied to all individuals for 8 weeks. PSG findings, biochemical parameters (fasting blood glucose (FBG), lipid profile, calcium, phosphorus, parathormone, calcitonin, (25(OH)D), insulin, C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10) were evaluated at the beginning and after 8 weeks. However, two patients refused to take vitamin D supplementation at the beginning of the study; 14 patients initially agreed to be included in the study but did not take a vitamin D supplementation regularly; 4 patients did not agree to come for analysis to be performed at the end of the study although they regularly took vitamin D supplementation for 8 weeks. One of the participants did not accept PSG for the second time, so only blood findings were analyzed. For these reasons, the study was completed with 19 patients (Figure).

2.2. Evaluation of polysomnography

All individuals included in the study were diagnosed with mild OSAS with an AHI value between 5–15 from polysomnography (PSG) [25] performed at Gazi University Faculty of Medicine, Sleep Disorders Center for one night. At the end of the study, PSG was repeated. The Natus neurology Grass Technologies (Twin PSG Clinical Software) was used for PSG. The scoring PSG was performed manually by the same person.

2.3. Vitamin D supplementation

It was recommended to take 50.000 IU vitamin D supplement once a week for individuals with an initial serum 25(OH)D level of <30 ng/mL for 8 weeks according to the recommendation of the Endocrine Society [26]. Individuals included in the study were reminded by phone every week that they should receive supplementations.

2.4. Biochemical parameters

Blood samples were taken at the beginning and end of the study after 8 hours of fasting and in pyrogen-free tubes. Calcium, phosphorus, parathormone, calcitonin, 25(OH)D, insulin, CRP, cytokines (TNF-α, IL-6, and IL-10) analyses of the biochemical parameters of these samples fasting

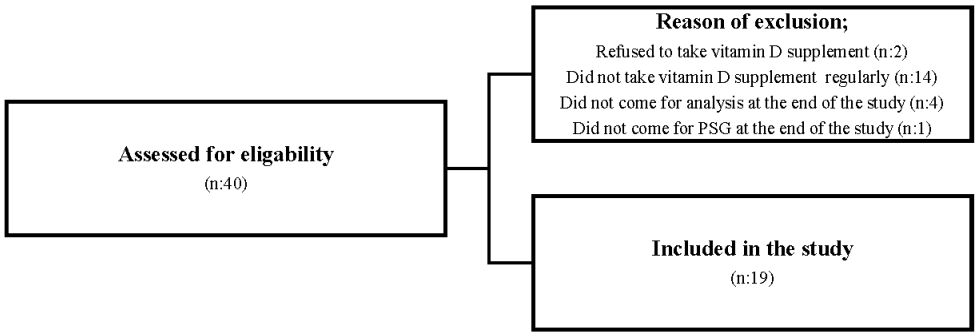

Figure. Study flow.

blood glucose (FBG), lipid profile (triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C) were done at Gazi University Central Biochemistry Laboratory. Serum FBG, lipid profile, calcium, and phosphorus levels were studied with photometric method by using auto-analyzer (Beckman Coulter AU5800) and using ready to use kits (Beckman Coulter). Serum parathormone, insulin, and serum 25(OH)D levels were studied with chemiluminescent method by using auto-analyzer (Beckman Coulter DXI 800) and ready to use kits (Beckman Coulter). Serum calcitonin levels were studied with chemiluminescent method by using auto-analyzer (Siemens Immulite 2000 XPI) and ready to use kits (Siemens). Serum CRP levels were studied with nephelometric method. In the analysis of cytokines, ELISA method was employed by using ready to use kits (Diasource).

Individuals' blood glucose, insulin level, and homeostatic model assessment insulin resistance (HOMA-IR) were calculated as HOMA-IR = fasting glucose (mg/dL) X fasting insulin (uIU/mL)/405 and individuals with HOMA value ≥2.7 are considered to have insulin resistance [27].

2.5. Statistical evaluation of data

The obtained data were evaluated in SPSS v. 22.0 statistical package program. The information about the categorical variables of the individuals is given in terms of frequency and percentage, and differences were examined with chi-square (χ^2) analysis. For the assessment of quantitative data, mean ($\bar{x}$) and median, standard deviation (SD), and lower and upper values were tabulated. The normality of the distributions was examined with the Kolmogorov–Smirnov test. HDL-C, calcitonin, TG, parathormone show normal distribution, while other biochemical parameters do not show normal distribution. For variables with normal distribution, paired-sample t test in paired differences, and the differences of those without normal distribution assumption were examined with Wilcoxon sign test. Also, the t-test was used for number of respiratory events during the entire sleep, nonrapid eye movement (NREM) sleep phase and supine position (total apnea, hypopnea, apnea + hypopnea). The Wilcoxon sign test was used to evaluate respiratory events in rapid eye movement (REM) sleep phase and nonsupine position. The correlation between biochemical parameters and the mean serum 25(OH)D levels of individuals was used Spearman correlation. All examinations were made statistically and interpreted at a 95% confidence level. In order to highlight the significance, values with $p < 0.05$ are shown in the table with (*).

3. Results

This study included 19 volunteer male individuals diagnosed with mild OSAS. The mean age of the patients is 44.1 ± 10.39 years (23–63 years). 63.2% of individuals have undergraduate and graduate education. While the rate of self-employed is 52.6%, the rate of civil servants is 21.1%. The marital status of 94.7% of the participants in the study is married. In 47.4% of individuals, there are additional diseases other than OSAS. Cardiovascular diseases are present in 44.4% of those diagnosed with additional diseases, while nervous system diseases are present in 33.0%. In initial of study, the mean BMI of individuals was 28.3 ± 3.49 kg/m^2 and 28.4 ± 3.41 kg/m^2 at the end of the study ($p = 0.133$). It was observed that the rate of obese individuals (BMI ≥ 30 kg/m^2) was the same (31.6%) at the beginning and end of the study. During the period from the beginning to the end of the study, no suggestions regarding nutrition and physical activity were made to the patients and no changes were made. In addition, there was no significant difference between individuals' body weight at the beginning and end of the study ($p > 0.05$) (not shown in the table).

3.1. Vitamin D levels of individuals

Vitamin D levels of individuals (n:19) are shown in Table 1. Serum vitamin D level was 19.5 ± 5.01 ng/mL before vitamin D supplementation while it increased to 41.8 ± 10.51 ng/mL after vitamin D supplementation ($p < 0.001$). According to initial serum vitamin D level of the individuals, 52.6% of the individuals were deficient and 47.4% of them were insufficient. At the end of the study, there was no individual with a deficiency of vitamin D while 89.5% of them had sufficient vitamin D levels. When the exposure of individuals to daylight was questioned, it was 51.1 ± 48.66 min/day (10.0–180.0 min/day) at the beginning while it was 58.2 ± 63.03 min/day (15.0–240.0 min/day) ($p > 0.05$) at the end of the study (not shown in the table).

3.2. Biochemical parameters of individuals

The evaluation of individuals' biochemical parameters at the beginning and end of the study is shown in Table 2. While the mean FBG level was 95.7 ± 7.97 mg/dL at the beginning of the study, it decreased to 90.0 ± 8.26 mg/dL after vitamin D supplementation, and the mean HOMA-IR values decreased from 2.3 ± 1.09 to 1.8 ± 0.83. These decreases are statistically significant (p = 0.003 and p = 0.040, respectively). It was found that initial TC level decreased from 206.8 ± 43.55 mg/dL to 188.3 ± 53.17 mg/dL, and this decrease was statistically significant (p = 0.044). Although the initial mean serum HDL-C, LDL-C, VLDL-C, calcium, phosphorus, parathormone, calcitonin, insulin, CRP, TNF-α, IL-6, and IL-10 levels decreased at the end of the study, this difference was not statistically significant (p > 0.05). Although the mean TG levels of individuals increased at the end of the study, this increase was not significant (p = 0.709).

Correlation of biochemical parameters according to the mean serum 25(OH)D levels of individuals is given in Table 3. Initially, there was no significant correlation between vitamin D levels and biochemical findings (p > 0.05). After the supplementation, a significant negative correlation was observed between vitamin D level and levels of CRP (r: –0.477 p = 0.034), TNF-α (r: –0.450 p = 0.047), and IL-6 (r: –0.560 p = 0.010); while a significant positive correlation was found with IL-10 (r: 0.549 p = 0.012) level.

Table 1. Vitamin D levels of individuals (%).

	Initial		Final	
Serum 25(OH)D level (ng/mL)	n	%	n	%
<20 (insufficiency)	10	52.6	-	-
20–30 (deficiency)	9	47.4	2	10.5
30–100 (normal)	-	-	17	89.5
	19.5 ± 5.01 ng/mL		41.8 ± 10.51 ng/mL*	

*(p < 0.001). Since the number of observations is insufficient, statistical difference could not be evaluated in other parameters.

3.3. Evaluation of polysomnography results of individuals

According to the polysomnography (PSG) results of the individuals, the number of respiratory events during the entire sleep is shown in Table 4. After using vitamin D supplements, the mean AHI decreased from 8.9 ± 2.05 to 5.5 ± 2.43 (p < 0.001). At the same time, the number of apnea + hypopnea, apnea index, and hypopnea index decreased significantly (p = < 0.001, p = 0.015 and p = 0.004, respectively). There was a significant decrease in the number of obstructive apnea (p = 0.012), as well as a significant decrease in the number of all apneas (p = 0.012) and the number of hypopneas (p = 0.001) (Table

Table 2. The evaluation of individuals' biochemical parameters ($\bar{x}$±SD).

	Initial	Median	Min	Max	Final	Median	Min	Max	Z/t	p
FBG (mg/dL)	95.7 ± 7.97	94.5	80.0	112.0	90.0 ± 8.26	90.0	68.0	105.0	–3.474	0.003*
TC (mg/dL)	206.8 ± 43.55	203.5	127.0	286.7	188.3 ± 53.17	189.3	22.4	265.3	–2.016	0.044*
HDL-C (mg/dL)	41.8 ± 10.10	41.0	25.8	65.0	41.7 ± 10.20	39.9	25.2	62.6	–0.205	0.837
LDL-C (mg/dL)	130.4 ± 34.57	131.7	73.2	187.0	126.7 ± 28.48	120.9	78.0	170.0	–0.900	0.380
VLDL-C (mg/dL)	34.4 ± 20.19	27.5	13.2	102.1	31.0 ± 14.55	27.8	11.7	72.0	–1.344	0.179
TG (mg/dL)	172.4 ± 100.69	137.5	66.4	508.0	175.8 ± 130.28	139.4	58.5	656.7	–0.373	0.709
Calcium (mg/dL)	9.6 ± 0.27	9.6	9.2	10.2	9.5 ± 0.30	9.4	8.8	10.0	–1.809	0.086
Phosphorus (mg/dL)	3.3 ± 0.46	3.3	2.4	4.47	3.2 ± 0.45	3.2	2.2	4.1	–0.752	0.461
Parathormone (pg/mL)	49.2 ± 23.96	43.7	23.4	136.2	44.3 ± 18.99	35.7	21.1	89.0	–0.747	0.455
Calcitonin (pg/mL)	4.9 ± 6.12	2.6	2	28.1	4.4 ± 5.27	2.2	2.0	24.0	–1.363	0.173
Insulin (ng/mL)	10.0 ± 4.75	9.9	3.2	22.5	8.0 ± 3.45	8.5	2.87	12.8	–1.814	0.085
HOMA-IR	2.3 ± 1.09	2.2	0.7	4.9	1.8 ± 0.83	1.7	0.6	3.28	–2.202	0.040*
25(OH)D (ng/mL)	19.5 ± 5.01	18.5	11.0	27.7	41.7 ± 10.51	42.0	22.98	67.0	9.439	<0.001*
CRP (mg/L)	3.0 ± 1.01	3.0	1.4	5.85	2.8 ± 0.71	3.0	1.8	4.8	–1.587	0.129
TNF-α (pg/mL)	13.3 ± 26.36	7.1	3.8	124.8	12.6 ± 13.79	8.1	4.4	67.7	–1.791	0.073
IL-6 (pg/mL)	28.3 ± 7.81	26.1	191	48.7	27.7 ± 8.87	25.2	17.8	48.2	–0.915	0.360
IL-10 (pg/mL)	5.5 ± 6.35	3.8	1.8	31.8	5.5 ± 4.87	4.8	1.8	24.8	–0.819	0.413

*p < 0.05. FBG: Fasting blood glucose, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, VLDL-C: Very low density lipoprotein cholesterol, TC: Total cholesterol, TG: Triglyceride, HOMA-IR: Homeostatic model assessment insulin resistance, 25(OH)D: 25-hydroxyvitamin D, CRP: C-reactive protein, TNF-α: Tumor necrosis factor alpha, IL-6: Interleukin-6, IL-10: Interleukin-10.

Table 3. Correlation of biochemical parameters according to the mean serum 25(OH)D levels of individuals.

	Initial		Final	
	r	p	r	p
FBG (mg/dL)	–0.399	0.081	–0.396	0.084
TC (mg/dL)	–0.065	0.786	–0.542	0.014*
HDL-C (mg/dL)	0.221	0.349	–0.282	0.228
LDL-C (mg/dL)	–0.255	0.278	–0.506	0.023*
VLDL-C (mg/dL)	–0.072	0.764	–0.108	0.649
TG (mg/dL)	–0.072	0.764	–0.047	0.845
Calcium (mg/dL)	–0.005	0.982	–0.264	0.262
Phosphorus (mg/dL)	0.070	0.768	–0.222	0.347
Parathormone (pg/mL)	–0.176	0.458	–0.423	0.063
Calcitonin (pg/mL)	0.305	0.190	–0.178	0.452
Insulin (uIU/mL)	–0.186	0.431	–0.079	0.741
HOMA-IR	–0.245	0.297	–0.109	0.647
CRP (mg/L)	–0.223	0.344	–0.477	0.034*
TNF-α (pg/mL)	0.047	0.843	–0.450	0.047*
IL-6 (pg/mL)	–0.171	0.470	–0.560	0.010*
IL-10 (pg/mL)	–0.269	0.251	0.549	0.012*

* $p < 0.05$. FBG: Fasting blood glucose, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, VLDL-C: Very low density lipoprotein cholesterol, TC: Total cholesterol, TG: Triglyceride, HOMA-IR: Homeostatic model assessment insulin resistance, 25(OH)D: 25-hydroxyvitamin D, CRP: C-reactive protein, TNF-α: Tumor necrosis factor alpha, IL-6: Interleukin-6, IL-10: Interleukin-10.

4). According to the PSG results of individuals, respiratory events were evaluated in the NREM sleep phase (Table 4). It was seen that there was a significant decrease in AHI value after supplementation ($p = 0.002$). While the decrease in the number of obstructive apnea was not significant, the decrease in the number of all apneas was statistically significant ($p = 0.035$). At the same time, the number of hypopnea, apnea + hypopnea, and hypopnea index also decreased significantly after the take of vitamin D ($p < 0.05$). When respiratory events were evaluated in REM sleep phase according to the PSG results of individuals, in addition to the significant decrease in AHI value ($p = 0.005$) in the REM stage after using vitamin D, the number of obstructive apnea, the number of all apneas, the number of hypopnea, the number of apnea + hypopnea, and the hypopnea index also decreased significantly ($p < 0.05$) (Table 4).

According to PSG results of individuals, respiratory events were evaluated according to the nonsupine/supine sleep position (Table 5). The initial AHI value in the nonsupine position was an average of 4.3 ± 3.84, and then it decreased to 2.7 ± 3.99. However, while the decrease in AHI value was not significant, it was seen that there was a significant decrease only in the number of apnea + hypopnea ($p = 0.017$). According to the supine sleep position, the AHI value at the beginning of the study was 16.3 ± 12.34, then it decreased to 12.2 ± 9.57 at the end of the study ($p = 0.009$). In addition, the number of hypopnea and apnea + hypopnea decreased significantly ($p < 0.05$).

Oxygen desaturation index (ODI) decreased significantly after using vitamin D in NREM ($p = 0.027$) and REM ($p = 0.016$). When the desaturation status of individuals was evaluated according to the PSG results during the entire sleep period, ODI decreased significantly at the end of the study ($p = 0.014$). There was no significant change in the mean oxygen saturation (SpO_2). Although an increase in sleep time was observed in individuals with $SpO_2 > 90\%$ after vitamin D supplementation, this increase was not significant ($p = 0.053$) (Not shown in the table).

4. Discussion

Obstructive sleep apnea syndrome is a disease affecting daily life and associated with many diseases such as coronary artery disease, diabetes mellitus, and stroke [3,4]. When OSAS is not treated, it is difficult to control blood pressure and the risk of developing CVD such as arrhythmias, coronary artery diseases, congestive heart diseases, stroke may increase [12]. The importance of early and accurate diagnosis of OSAS is important in terms of both improving individuals' health and preventing the burden it can put on healthcare [28]. PAP treatment is safe and effective, and its side effects are minor and reversible [29]. However, the rate of accepting to use CPAP in OSAS has been found to be low [11].

It has been reported that serum 25(OH)D levels are lower in individuals with OSAS than healthy individuals, and the level of vitamin D decreases as OSAS severity increases [14–17]. On the contrary, Li et al. [30], showed that the serum 25 (OH) D level was not decreased in mild OSA patients compared with the controls. However, the serum 25 (OH) D level in moderate and severe OSA patients was lower than that in the controls. Liguori et al. [31] reported that serum 25(OH)D deficiency for OSAS is a risk factor for men. In the study, the mean serum vitamin D of male individuals was 19.5 ± 5.01 ng/mL while it increased to 41.8 ± 10.51 ng/mL after supplementation ($p < 0.001$). In another study, as a result of the vitamin D supplement given to 200 individuals for 6 months, it was observed that only 60 individuals had a statistically significant level of vitamin D increase (normal level) [32]. In this study, while the vitamin D level of individuals was in the "deficient" class before vitamin D supplementation, 89.5% (n: 17) of the vitamin D level reached a sufficient level after supplementation. For those who do not reach a sufficient level despite vitamin D support, it is thought that vitamin D supplementation will depend on duration and individual differences such as VDR polymorphism differences, genetics, age, and BMI.

An increase in TC, LDL-C, VLDL-C, TG levels, and a decrease in HDL-C level pose a risk for CVD [33]. In a study, LDL-C decreased significantly and HDL-C increased significantly in individuals diagnosed with OSAS after vitamin D supplementation (n:10). However, in that study,

Table 4. The number of respiratory events during the entire sleep according to the polysomnography (PSG) results of the individuals ($\bar{x}$±SD).

	Initial				Final					
	$\bar{x}$±SD	Median	Min	Max	$\bar{x}$±SD	Median	Min	Max	Z/t	p
Number of respiratory events during the entire sleep										
Obstructive apnea	18.7 ± 13.30	17.0	0.0	45.0	10.3 ± 8.56	9.0	0.0	31.0	−2.787	0.012*
Total apnea	22.4 ± 14.93	21.0	0.0	58.0	13.3 ± 9.12	12.0	0.0	33.0	−2.803	0.012*
Hypopnea	34.7 ± 17.69	30.0	7.0	63.0	22.3 ± 15.33	18.0	5.0	58.0	−3.960	0.001*
Apnea + hypopnea	59.0 ± 17.57	60.0	34.0	98.0	35.6 ± 16.51	33.0	11.0	70.0	−5.195	<0.001
Apnea index	3.8 ± 1.94	3.4	0.6	7.8	2.3 ± 1.44	2.4	0.1	5.4	−2.727	0.015*
Hypopnea index	4.8 ± 2.30	4.6	1.1	9.1	3.0 ± 1.96	2.8	1.1	8.3	−3.419	0.004*
AHI	8.9 ± 2.05	8.8	5.9	12.3	5.5 ± 2.43	5.1	1.4	10.8	−5.768	<0.001
Respiratory events in NREM sleep phase										
Obstructive apnea	10.9 ±12.42	7.0	0.0	39.0	6.1 ± 5.17	5.0	0.0	19.0	−1.951	0.067
Total apnea	14.2 ±13.94	10.0	0.0	40.0	8.4 ± 6.57	8.0	0.0	21.0	−2.285	0.035*
Hypopnea	18.3 ± 9.18	18.0	2.0	39.0	13.1 ± 8.47	11.0	2.0	31.0	−2.715	0.014*
Apnea + hypopnea	32.4 ±16.25	33.0	7.0	59.0	21.5 ± 9.92	20.0	6.0	36.0	−3.640	0.002*
Apnea index	3.1 ± 2.74	2.2	0.2	8.8	2.0 ± 1.57	1.7	0.2	6.3	−2.047	0.570
Hypopnea index	3.7 ± 1.87	3.6	0.3	8.5	2.9 ± 2.26	2.4	0.5	9.1	−2.448	0.026*
AHI	7.3 ± 3.26	7.7	1.2	13.3	4.5 ± 1.86	4.9	1.0	7.6	−3.684	0.002*
Respiratory events in REM sleep phase										
Obstructive apnea	7.6 ± 7.89	3.0	0.0	20.0	4.0 ± 6.32	1.0	0.0	23.0	−2.260	0.024*
Total apnea	8.6 ± 8.57	8.0	0.0	24.0	4.6 ± 6.48	2.0	0.0	23.0	−2.204	0.028*
Hypopnea	12.5 ± 10.42	10.5	0.0	30.0	6.1 ± 8.31	3.0	0.0	35.0	−2.562	0.010*
Apnea + hypopnea	23.4 ± 17.2	24.0	0.0	60.0	10.4 ± 12.20	5.0	0.0	38.0	−3.289	0.001*
Apnea index	5.8 ± 5.23	5.1	0.0	14.0	3.9 ± 5.31	1.6	0.0	17.9	−1.293	0.196
Hypopnea index	8.7 ± 7.23	9.4	0.0	21.0	4.3 ± 5.25	2.4	0.0	20.2	−2.045	0.041*
AHI	14.1 ± 9.89	14.7	0.0	35.1	7.9 ± 9.06	4.1	0.0	30.5	−2.809	0.005*

*p < 0.05. AHI: apnea hypopnea index, NREM: nonrapid eye movement, REM: rapid eye movement.

it was stated that 90.0% of individuals received CPAP treatment as well as vitamin D supplementation [34].

There is another study showing that CPAP treatment reduces LDL-C and TC and increases HDL-C [35]. Therefore, whether this effect is a result of vitamin D or CPAP has not been revealed clearly. In this study, a group of patients with mild OSAS who did not receive/accept any treatment, including CPAP was studied. At the end of the study, TC level decreased significantly and after vitamin D supplementation, a significant negative relationship between serum vitamin D level and some parameters (TC level (r: −0.475 p = 0.033) and LDL-C level (r: −0.446 p = 0.049)) was revealed. Barbalho et al. [36] reported that vitamin D supplementation caused a significant decrease in TC, and a negative significant correlation between TC and LDL-C and serum vitamin D levels would have a positive effect for CVD. The positive contribution of vitamin D to the lipid profile may be due to the anti-inflammatory effect of vitamin D and reducing oxidative stress [33]. This study suggests that the positive effect of vitamin D supplementation on the lipid profile may have a positive effect against the risk of developing CVD in OSAS.

In OSAS, proinflammatory mediators have been shown to increase IL-1 beta, IL-6, IL-8, CRP, and TNF-α [5,6]. Serum vitamin D is thought to have a positive effect on cardiovascular health by inhibiting inflammatory cytokine release [32]. Although it is thought that low vitamin D level may increase systemic inflammation [13], it is emphasized that the anti-inflammatory response that plays a role in the relationship between metabolic dysfunction and OSAS is not clear [37]. In individuals diagnosed with mild and moderate OSAS, no significant change in plasma IL-6, IL-10, CRP, or TNF-α has been reported after 6 months of CPAP treatment [23]. At the end of this study, although serum CRP, TNF-α, and IL-6 levels decreased in this study, this decrease was not

Table 5. The number of respiratory events according to the nonsupine/supine sleep position ($\bar{x}$±SD).

	Initial				Final					
	$\bar{x}$ ± SD	Median	Min	Max	$\bar{x}$ ± SD	Median	Min	Max	Z/t	p
Nonsupine position										
Obstructive apnea	4.3 ± 6.97	1.0	0.0	27.0	1.4 ± 2.00	1.0	0.0	7.0	–1.789	0.074
Total apnea	5.2 ± 7.01	2.0	0.0	27.0	2.2 ± 2.49	1.0	0.0	7.0	–1.566	0.117
Hypopnea	6.9 ± 6.16	5.0	0.0	22.0	5.1 ± 9.67	2.0	0.0	43.0	–0.865	0.398
Apnea + hypopnea	12.0 ± 9.15	12.0	0.0	39.0	7.3 ± 11.1	4.0	0.0	50.0	–2.395	0.017*
Apnea index	2.1 ± 3.37	1.2	0.0	13.7	0.8 ± 1.07	0.4	0.0	4.1	–1.320	0.187
Hypopnea index	2.1 ± 2.23	1.5	0.0	8.3	1.8 ± 3.19	0.7	0.0	10.6	–0.983	0.326
AHI	4.3 ± 3.84	2.8	0.0	14.2	2.7 ± 3.99	1.4	0.0	14.7	–1.871	0.061
Supine position										
Obstructive apnea	14.1 ± 11.69	13.0	0.0	39.0	8.6 ± 8.92	8.0	0.0	31.0	–1.636	0.102
Total apnea	17.4 ± 12.91	14.0	0.0	46.0	10.7 ± 9.30	9.0	0.0	33.0	–1.824	0.085
Hypopnea	26.5± 13.21	24.0	6.0	51.0	14.3 ± 9.54	11.0	5.0	37.0	–3.161	0.002*
Apnea + hypopnea	44.0 ± 15.73	41.0	19.0	74.0	25.0 ± 15.14	20.0	8.4	68.0	–3.860	0.001*
Apnea index	7.4 ± 8.89	4.2	1.1	39.3	4.7 ± 3.75	3.5	0.2	14.5	–1.492	0.136
Hypopnea index	8.8 ± 5.21	8.2	1.3	20.2	7.4 ± 7.95	4.5	1.1	29.0	–2.509	0.012*
AHI	16.3 ± 12.34	13.5	4.5	59.5	12.2 ± 9.57	9.3	2.6	34.8	–2.604	0.009*

*p < 0.05. AHI: apnea hypopnea index.

statistically significant (p > 0.05). However, there was a statistically significant negative correlation between vitamin D and proinflammatory cytokines after supplementation (r: –0.477 p = 0,034; r: –0.450 p = 0.047; r: –0.560 p = 0.010, respectively), and a positive correlation (r: 0.549 p = 0.012) was found with IL-10, which is an anti-inflammatory cytokine. This effect of vitamin D [13], which is directly related to inflammation, is thought to contribute positively to the disease prognosis.

It is predicted that insulin resistance and inflammation, which is common in OSAS, can be improved by vitamin D supplementation [38]. Low vitamin D levels are known to be associated with hyperglycemia, hyperinsulinemia, decreased beta cell function, and insulin resistance [39]. In one study, the intervention group was given 50.000 IU of vitamin D once a week for 8 weeks, and it was observed that FBS decreased significantly in both groups compared to the baseline. While the fasting insulin level and HOMA-IR decreased significantly in the group receiving the supplement, there was no difference in BMI value compared to the baseline [40]. Similarly, in this study, it was observed that FBS and HOMA-IR values decreased significantly, but the decrease in insulin level was not significant. In another study, individuals with a diagnosis of OSAS (n: 10) showed a significant decrease in FBS after vitamin D supplementation. However, in that study, it was seen that 90.0% of individuals received CPAP treatment as well as vitamin D supplementation [34]. It is thought that there is a need for a further study to examine the effect of vitamin D supplement to be applied with CPAP.

Because CPAP, which is the gold standard treatment in patients with OSAS, has relatively poor compatibility, 31% of patients with OSAS who have been prescribed CPAP never starts treatment, and 15% of individuals stops using the device after 10 months of use ever starts [41], an active and effective alternative treatment may be required for mild OSAS [11]. In this study, the effects of vitamin D supplementation on disease findings in mild OSAS patients with vitamin D insufficiency were investigated, and after using vitamin D supplements, the mean AHI of patients decreased from 8.9 ± 2.05 to 5.5 ± 2.43 (p < 0.001). In addition to the significant decrease in the number of obstructive apnea (p = 0.012), a significant decrease was seen in the number of all apneas (p = 0.012) and the number of hypopneas (p = 0.001). Apnea + hypopnea number, apnea index, and hypopnea index also decreased significantly (p = < 0.001, p = 0.015 and p = 0.004, respectively). There was a significant decrease in the number of obstructive apnea (p = 0.012), as well as a significant decrease in the number of all apneas (p = 0.012) and the number of hypopneas (p = 0.001). In addition, there was a significant positive correlation between serum vitamin D level and sleep efficiency and continuity (r: 0.666 p = 0.002 and r: 0.627 p = 0.007, respectively). It is thought that the take of vitamin D in treatment, due to its positive effects, in mild OSAS patients with insufficient of vitamin D will have a positive effect on the prognosis of the disease.

In adults, it is characteristic that upper respiratory tract obstructions are seen in NREM sleep in OSAS [42]. In this study, it was seen that there was a significant decrease in the NREM sleep period AHI value and the number of total apnea (p < 0.05). At the same time, the number of

hypopnea, apnea + hypopnea, and hypopnea index decreased significantly after the use of vitamin D ($p < 0.05$). Also, it is known that REM related sleep disorder is more common in mild and moderate OSAS. The low tonus experienced in the muscles during sleep causes atony especially by peaking in the REM stage, and respiratory disorders have been reported to occur more easily. It is also emphasized that sleep-related respiratory disturbance associated with REM is the initial stage of OSAS [43]. In the REM stage after supplementation, the AHI value, the number of obstructive apnea, the number of all apneas, the number of hypopnea, the number of apnea + hypopnea, and the hypopnea index also decreased significantly ($p < 0.05$).

The vast majority of patients with mild OSAS are said to have the presence and severity of symptoms associated with body position and often show position-related apnea. It may cause partial or entire blockage in the airway in the supine position especially due to the retraction of the chin and tongue [11]. In mild OSAS, it has been shown that there is a lower apnea index and better sleep efficiency in the position dependent group comparing to the nonposition dependent group [44]. At the beginning of this study, it was observed that the mean AHI in the nonsupine position was 4.3 ± 3.84 while it was 16.3 ± 12.34 in the supine position. Similarly, it was shown in another study that the AHI value decreased by more than approximately 50% when switching from supine to lateral position [45]. In this study, it was observed that the decrease in supine position was statistically significant even though there was a decrease in AHI value in nonsupine position after vitamin D supplementation ($p = 0.009$). Positional therapy is often used for mild OSAS, but it has only moderate efficacy and poor compatibility [11]. In this study, when respiratory events were examined according to nonsupine sleep position in mild OSAS with the support of vitamin D, there was a significant decrease in the number of apnea + hypopnea ($p = 0.017$); in addition to AHI value, the number of hypopnea, apnea + hypopnea index and hypopnea index significantly decreased ($p < 0.05$) in the supine position. It is thought that the decrease in especially supine position is important in mild OSAS. In case of vitamin D insufficiency, it is thought that vitamin D supplementation may have a positive effect in the treatment of position-related respiratory events in mild OSAS.

In a meta-analysis that examined the effect of loss of body weight by intraoral device, CPAP, exercise, and diet, CPAP treatment was shown to be the most effective method for the development of saturation during sleep in complete solution of OSAS (AHI, reduction in ODI) [46]. Nerfeld et al. [47] found that ODI improved, excessive daytime sleepiness decreased, but AHI did not decrease with 13% body weight loss in 33 obese OSAS individuals. In the present study, both AHI and ODI ($p = 0.014$) decreased significantly with the support of vitamin D. However, there was no significant change in the mean SpO_2. Although it was observed that there was an increase in the sleep time, in which SpO_2 was above 90% (90%–100%), after the use of vitamin D, this increase was not significant ($p = 0.053$). Studies to be carried out by increasing the number of samples can be effective in seeing this significance.

The present study has some limitations. Firstly, the control group could not be included in the study due to the low number of individuals diagnosed with mild OSAS. Because, generally individuals with severe and moderate OSAS apply to the Sleep Disorders Center. Secondly, since this disease is seen more frequently in men and the proportion of men applying to the study center is higher, only male individuals were included in the study. Besides, the study is the first study on vitamin D supplementation in mild OSAS in Turkey. We think this study will be useful for further studies on this issue.

5. Conclusion

The low rate of CPAP acceptance/use in mild OSAS suggests the need to try different treatment practices in mild OSAS. For this purpose, this study was planned to investigate the effect of vitamin D supplementation on disease prognosis and biochemical parameters in mild OSAS patients with vitamin D deficiency. At the end of the study, it was observed that vitamin D supplementation had a positive effect especially on the regulation of insulin resistance and lipid profile and on many sleep parameters. In mild OSAS, which is known to increase in severity as the disease progresses, monitoring the serum vitamin D levels of patients and vitamin D supplementation in case of deficiency and insufficiency may be a preventive treatment to prevent the course of the disease from worsening. However, studies on vitamin D supplementation in OSAS are quite limited in the literature. For this reason, it is thought that studies with higher sample sizes that can clearly demonstrate the effects of vitamin D use and the dose and duration of vitamin D in OSAS are needed.

Conflict of interest

There is no conflict of interest.

Acknowledgment

We would like to thank Onur Toka (PhD) who works as a consultant for statistical analysis.

Funding

The costs of the analysis of biochemical parameters of the individuals participating in the study and the kits to be used for the analysis were covered from the budget deserved in Gazi University Teaching Staff Training Program.

Informed consent

The study protocol was approved by the decision of Gazi University Clinical Research Ethics Committee on 03.07.2017. A voluntary consent form was signed by the individuals participating in the research. Because vitamin

D supplementation studies are within the scope of the Phase IV study, ethical approval numbered 93189304-514.04.01-E.235801 and dated 11.28.2017 was taken from the board of Turkish Medicines and Medical Devices Agency Clinical Research Committee. All participants provided informed consent.

References

1. Hong S, Chen YF, Jung Y, Kwon YD, Liu SYC. Hypoglossal nerve stimulation for treatment of obstructive sleep apnea (OSA): a primer for oral and maxillofacial surgeons. Maxillofacial Plastic and Reconstructive Surgery 2017; 39: 27. doi: 10.1186/s40902-017-0126-0
2. Epstein LJ, Kristo D, Strollo PJ, Friedman N, Malhotra A et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of Clinical Sleep Medicine 2009; 5 (3): 263-276.
3. Cowie MR. Sleep apnea: state of the art. Trends in Cardiovascular Medicine 2017; 27 (4): 280-289. doi: 10.1016/j.tcm.2016.12.005
4. Neighbors CL, Noller MW, Song SA, Zaghi S, Neighbors J et al. Vitamin D and obstructive sleep apnea: a systematic review and meta-analysis. Sleep Medicine 2017; 43 (1): 100-108. doi: 10.1016/j.sleep.2017.10.016
5. Köktürk O, Ulukavak Çiftçi T, Mollarecep E, Çiftçi B. Elevated C-reactive protein levels and increased cardiovascular risk in patients with obstructive sleep apnea syndrome. International Heart Journal 2005; 46: 801-809. doi: 10.1536/ihj.46.801
6. Alberti A, Sarchielli P, Gallinella E, Floridi A, Floridi A et al. Plasma cytokine levels in patients with obstructive sleep apnea syndrome: a preliminary study. Journal of Sleep Research 2003; 12 (4): 305-311. doi: 10.1111/j.1365-2869.2003.00361.x
7. Sniderman AD, Cianflone K. Substrate delivery as a determinant of hepatic apoB secretion. Arteriosclerosis, Thrombosis, and Vascular Biology 1993; 13 (5): 629-636. doi: 10.1161/01.atv.13.5.629
8. Köktürk O, Kanbay A. Insulin resistance in patients with obstructive sleep apnea syndrome. Eurasian Journal of Pulmonology 2003; 15 (2): 135-136. doi: 10.5152/solunum.2013.027
9. Kushida CA, Morgenthaler TI, Littner MR, Alessi CA, Bailey D et al. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. Sleep 2006; 29 (2): 240-243. doi: 10.1093/sleep/29.2.240
10. Demir A, Ursavaş A, Tana Aslan A, Gülbay B, Çiftçi B et al. Türk Toraks Derneği Obstrüktif Uyku Apne Sendromu Tanı ve Tedavi Uzlaşı Raporu. Türk Toraks Dergisi 2012; 13 (Suppl 1): 1-73 (in Turkish).
11. Huang YC, Lin CY, Lan CC, Wu YK, Lim CS et al. Comparison of cardiovascular co-morbidities and CPAP use in patients with positional and non-positional mild obstructive sleep apnea. BMC Pulmonary Medicine 2014; 14 (1): 140-153. doi: 10.1186/1471-2466-14-153
12. Budhiraja R, Budhiraja P, Quan SF. Sleep-disordered breathing and cardiovascular disorders. Respiratory Care 2010; 55 (10): 1322-1332.
13. McCarty DE, Chesson AL, Jain SK, Marino AA. The link between vitamin D metabolism and sleep medicine. Sleep Medicine Reviews 2014; 18 (4): 311-319. doi: 10.1016/j.smrv.2013.07.001
14. Upala S, Sanguankeo A. Association between 25-hydroxyvitamin D and obstructive sleep apnea: a systematic review and meta-analysis. Journal of Clinical Sleep Medicine 2015; 11 (11): 1347-1347. doi: 10.5664/jcsm.5208
15. Mete T, Yalcin Y, Berker D, Ciftci B, Guven S et al. Obstructive sleep apnea syndrome and its association with vitamin D deficiency. Journal of Endocrinological Investigation 2013; 36 (9): 681-685. doi: 10.3275/8923
16. Erden ES, Genc S, Ustun I, Ulutas KT, Bilgic HK et al. Investigation of serum bisphenol A, vitamin D, and parathyroid hormone levels in patients with obstructive sleep apnea syndrome. Endocrine 2014; 45 (2): 311-318. doi: 10.1007/s12020-013-0022-z
17. Kerley CP, Hutchinson K, Bolger K, McGowan A, Faul J et al. Serum vitamin D is significantly inversely associated with disease severity in Caucasian adults with obstructive sleep apnea syndrome. Sleep 2016; 39 (2): 293-300. doi: 10.5665/sleep.5430
18. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. Sleep 2007; 30 (9): 1145-1152. doi: 10.1093/sleep/30.9.1145
19. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? British Journal of Nutrition 2003; 89 (5): 552-572. doi: 10.1079/BJN2003837
20. De Vita F, Lauretani F, Bauer J, Bautmans I, Shardell M et al. Relationship between vitamin D and inflammatory markers in older individuals. Age 2014; 36 (4): 9694. doi: 10.1007/s11357-014-9694-4
21. Liefaard MC, Ligthart S, Vitezova A, Hofman A, Uitterlinden AG et al. Vitamin D and C-reactive protein: a Mendelian randomization study. PloS One 2015; 10 (7): e0131740. doi: 10.1371/journal.pone.0131740
22. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF et al. CPAP versus oxygen in obstructive sleep apnea. New England Journal of Medicine 2014; 370 (24): 2276-2285. doi: 10.1056/NEJMoa1306766
23. Stradling J, Craig S, Kohler M, Nicoll D, Ayers L et al. Markers of inflammation: data from the MOSAIC randomised trial of CPAP for minimally symptomatic OSA. Thorax 2015; 70 (2): 181-182. doi: 10.1136/thoraxjnl-2014-205958
24. Hudgel DW. Critical review: CPAP and weight management of obstructive sleep apnea cardiovascular co-morbidities. Sleep Medicine Reviews 2016; 37: 14-23. doi: 10.1016/j.smrv.2016.12.001
25. Ruehland WR, Rochford PD, O'donoghue FJ, Pierce RJ, Singh P et al. The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. Sleep 2009; 32 (2): 150-157. doi: 10.1093/sleep/32.2.150
26. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanle DA et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism 2011; 96 (7): 1911-1930. doi: 10.1210/jc.2011-0385
27. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 1998; 21 (12): 2191-2192. doi: 10.2337/diacare.21.12.2191
28. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep

Medicine clinical practice guideline. Journal of Clinical Sleep Medicine 2017; 13 (3): 479-504. doi: 10.5664/jcsm.6506
29. Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA et al. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep 2006; 29 (3): 375-380. doi: 10.1093/sleep/29.3.375
30. Li X, He J, Yun J. The association between serum vitamin D and obstructive sleep apnea: an updated meta-analysis. Respiratory Research 2020; 21: 294. doi: 10.1186/s12931-020-01554-2
31. Liguori C, Romigi A, Izzi F, Mercuri NB, Cordella A et al. Continuous positive airway pressure treatment increases serum vitamin D levels in male patients with obstructive sleep apnea. Journal of Clinical Sleep Medicine 2015; 11 (6): 603-607. doi: 10.5664/jcsm.4766
32. Verrusio W, Andreozzi P, Renzi A, Musumeci M, Gueli N et al. Association between serum vitamin D and metabolic syndrome in middle-aged and older adults and role of supplementation therapy with vitamin D. Annali Dell'ıstituto Superiore Di Sanita 2017; 53 (1): 54-59. doi: 10.4415/ANN_17_01_11
33. Şahin M. Soru 1–Kolesterol hipotezi nedir? Kardiyovasküler hastalıklara neden oluyor mu? Bu konuda elimizdeki kanıtlar nelerdir? Turk Kardiyoloji Derneği Arşivi 2016; 44 (4): 1-141 (in Turkish).
34. Kerley CP, Hutchinson K, Bramham J, McGowan A, Faul J et al. Vitamin D improves selected metabolic parameters but not neuropsychological or quality of life indices in OSA: a pilot study. Journal of Clinical Sleep Medicine 2017; 13 (1): 19-26. doi: 10.5664/jcsm.6378
35. Nadeem R, Singh M, Nida M, Kwon S, Sajid H et al. Effect of CPAP treatment for obstructive sleep apnea hypopnea syndrome on lipid profile: a meta-regression analysis. Journal of Clinical Sleep Medicine 2014; 10 (12): 1295-1302. doi: 10.5664/jcsm.4282
36. Barbalho SM, Tofano RJ, De Campos AL, Rodrigues AS, Quesada K et al. Association between vitamin D status and metabolic syndrome risk factors. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2018; 12 (4): 501-507. doi: 10.1016/j.dsx.2018.03.011
37. Leon-Cabrera S, Arana-Lechuga Y, Esqueda-León E, Terán-Pérez G, Gonzalez-Chavez A et al. Reduced systemic levels of IL-10 are associated with the severity of obstructive sleep apnea and insulin resistance in morbidly obese humans. Mediators of Inflammation 2015; 2015: 493409. doi: 10.1155/2015/493409
38. Bozkurt NC, Cakal E, Sahin M, Ozkaya EC, Firat H et al. The relation of serum 25-hydroxyvitamin-D levels with severity of obstructive sleep apnea and glucose metabolism abnormalities. Endocrine 2012; 41 (3): 518-525. doi: 10.1007/s12020-012-9595-1
39. Karefylakis C, Särnblad S, Ariander A, Ehlersson G, Rask E et al. Effect of Vitamin D supplementation on body composition and cardiorespiratory fitness in overweight men-a randomized controlled trial. Endocrine 2018; 61 (3): 388-397. doi: 10.1007/s12020-018-1665-6
40. Osati S, Homayounfar R, Hajifaraji M. Metabolic effects of vitamin D supplementation in vitamin D deficient patients (a double-blind clinical trial). Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2016; 10 (2): 7-10. doi: 10.1016/j.dsx.2016.01.007
41. Wolkove N, Baltzan M, Kamel H, Dabrusin R, Palayew M. Long-term compliance with continuous positive airway pressure in patients with obstructive sleep apnea. Canadian Respiratory Journal 2008; 15 (7): 365-369. doi: 10.1155/2008/534372.
42. Balbani AP, Weber SA, Montovani JC. Update in obstructive sleep apnea syndrome in children. Revista Brasileira de Otorrinolaringologia 2005; 71 (1): 74-80. doi: 10.1016/s1808-8694(15)31288-x
43. Lakadamyalı H, Fıratgüven S, Çiftçi B, Eyüboğlu FÖ. Hızlı göz hareketleri ile ilişkili obstrüktif uyku apnesendromu: antropometrik ve polisomnografik bulgular. Tuberküloz ve Toraks Dergisi 2012; 60 (1): 13-19 (in Turkish).
44. Oksenberg A, Arons E, Radwan H, Silverberg DS. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic and multiple sleep latency test data. Chest 1997; 112 (3): 629-639. doi: 10.1378/chest.112.3.629
45. Isono S, Tanaka A, Nishino T. Lateral position decreases collapsibility of the passive pharynx in patients with obstructive sleep apnea. Anesthesiology: The Journal of the American Society of Anesthesiologists 2002; 97 (4): 780-785. doi: 10.1097/00000542-200210000-00006
46. Iftikhar IH, Bittencourt L, Youngsted SD, Ayas N, Cistulli P et al. Comparative efficacy of CPAP, MADs, exercise-training, and dietary weight loss for sleep apnea: a network meta-analysis. Sleep Medicine 2017; 30 (1): 7-14. doi: 10.1016/j.sleep.2016.06.001
47. Nerfeld P, Nilsson BY, Mayor L, Uddé J, Friberg D. A two-year weight reduction program in obese sleep apnea patients. Journal of Clinical Sleep Medicine 2010; 6 (5): 479-486.