Original Article

Vitamin D deficiency and interleukin-17 relationship in severe obstructive sleep apnea–hypopnea syndrome

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Abstract:

PURPOSE: We aimed to assess Vitamin D (VD) abnormalities in patients with severe obstructive sleep apnea–hypopnea syndrome (OSAHS), to study its association with clinical and polygraphic data, and to correlate VD levels with interleukin-17 (IL-17).

METHODS: Ninety-two patients with severe OSAHS were consecutively enrolled between September 2014 and February 2016 and compared to age-, sex-, and body mass index (BMI)-matched controls. Anthropometric parameters and medical history were collected. The serum levels of VD and IL-17 were determined by radioimmunoassay and enzyme-linked immunosorbent assay, respectively.

RESULTS: Ninety-two severe OSAHS patients and thirty controls were enrolled in the study. All OSAHS patients had VD deficiency. The mean level of VD was at 7.9 ng/ml among OSAHS group versus 16.8 ng/ml among control group. IL-17A levels were elevated (20.3 pg/ml) in OSAHS group compared to healthy group (10.05 pg/ml). VD levels were negatively correlated with nocturia severity ($r = -0.26$; $P = 0.01$) and positively correlated with mean O_2 saturation ($r = 0.59$; $P = 0.02$) and lowest O_2 saturation ($r = 0.3$; $P = 0.03$). IL-17 levels were positively correlated with nocturia severity ($r = 0.24$; $P = 0.03$) and negatively correlated with mean O_2 saturation ($r = -0.42$; $P = 0.03$). A significant negative association was observed between IL-7 and VD levels ($r = -0.64$, $P = 0.2\ 10^{-4}$). The magnitude of this correlation was higher for important nocturia, lower $MSaO_2$, or higher BMI.

CONCLUSIONS: VD deficiency in patients with severe OSAHS is common with a negative association between IL-17 and VD serum levels. Hypoxia could play an important role in this association. Further studies are needed to clarify this relationship.

Key words:

Inflammation, interleukin-17, obstructive sleep apnea, Vitamin D

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is a common chronic sleep disorder. Its pathogenesis is uncertain and likely to be multifactorial including many processes such as inflammation and oxidative stress.[1] Inflammation plays a crucial role in OSAHS due to the occurrence of recurrent hypoxia.[2] The hypoxia with repetitive short cycles of desaturation followed by rapid reoxygenation is associated with inflammation through the induction of adhesion molecules and C-reactive protein (CRP) in vascular endothelial cells and leukocytes.[3,4] Recent studies reported that individuals with OSAHS have lower Vitamin D (VD) concentrations compared to healthy individuals.[5-7] Moreover, it has been reported that VD can establish homeostasis between regulatory and suppressor T-cell functions to modulate inflammatory process.[8] However, the mechanism involved in the VD deficiency in OSAHS is not completely understood. In fact, VD acts through various mechanisms such as secretion of cytokines. Numerous studies have described increased levels of systemic biomarkers of inflammation, including interleukin-6 (IL-6) and CRP, in patients with OSAHS.[5-17] IL-6 is involved in inducing the differentiation of Th17 cells in

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both human and mice.[12,13] Recently, Ying *et al*.[18] reported that IL-17A serum levels are increased in OSAHS patients and positively correlated with the disease severity. This proinflammatory cytokine induces chemokine production in various tissues to recruit monocytes and neutrophils to the site of inflammation. It acts synergistically together with tumor necrosis factor-α (TNF-α) and IL-1 and represents a critical IL in inflammatory response in OSAHS.[19] We hypothesized that IL-17 may be expressed differentially in OSAHS patients and correlated with VD expression. Since the inflammatory disorders and VD deficiency are more common in severe OSAHS, we aimed first to assess VD abnormalities in severe OSAHS patients and to study its association with clinical and polygraphic parameters and second to correlate VD levels with IL-17.

Methods

Ninety-two patients with severe OSAHS were consecutively enrolled between September 2014 and February 2016 in La Rabta Pulmonary Department, Tunis, Tunisia. We included patients with severe OSAHS undergoing polygraphic cardiorespiratory monitoring (Cidelec 102L, France) diagnosed according to the American Academy of Sleep Medicine criteria[20] and defined by apnea–hypopnea index (AHI) ≥30/h. The controls were volunteers who had no sleep disorders and similar to the patients group in terms of age, sex, and body mass index (BMI). Included participants had to show none of the following criteria: Clinical signs of acute inflammatory or autoimmune disease, cancer, parathyroid disorders, chronic renal disease, chronic liver disease, sarcoidosis, osteoporosis, or heart failure and were taking corticosteroids, calcium, or VD supplements. This study was approved by the Ethics Committee of the Rabta Hospital of Tunis. Verbal informed consent was obtained from all the participants.

Respiratory polygraphy

The presence and severity of OSAHS were determined by overnight polygraphy using measurements of oxygen saturation, airflow, snoring, heart rate, nasal, and suprasternal pressure. Sleep-disordered breathing events were scored manually by the same physician, according to the American Academy of Sleep Medicine criteria.[20] Apnea was defined as a decrease in airflow more than 90% for at least 10 s relative to baseline. Hypopnea was defined as a decrease in airflow relative to baseline more than 30%, with an associated oxygen desaturation more than 3% for at least 10 s.[20] The AHI was defined as the number of apneas and hypopneas per hour of sleep. Patients were diagnosed with severe OSAHS if the AHI was ≥30. Oxygen desaturation index (ODI) and the mean and the lowest O_2 saturation values were measured overnight for each patient.

Anthropometric parameters and medical history were collected. We evaluated excessive daytime somnolence by means of the Epworth Sleepiness Scale (ESS).[21] The height and waist circumference (WC) of the patients and controls were measured in cm. Obesity was assessed with BMI. It was calculated dividing weight (kg) by square of height (m). According to BMI, 18–24.9 kg/m^2 was accepted as normal weight, 25–29.9 kg/m^2 as overweight, 30–39.9 kg/m^2 as obese, and over 40 kg/m^2 as morbid obese. Nocturia was defined as waking at night one or more times to void. For each participant, the number of voids/night was specified.

Measurement of interleukin-17 and Vitamin D serum levels

Blood samples were taken for VD and IL-17 measurement. The collected serum was immediately shielded from direct light and stored at −20°C. The serum IL-17 levels were determined by enzyme-linked immunosorbent assay following the manufacturer's instructions and using the eBioscience kit (San Diego, CA, USA). The serum concentrations of VD were assayed with a radioimmunoassay kit (DiaSorin, Stillwater, MN, USA). VD level values were used as a continuous variable and were categorized in descriptive analyses as desirable (or sufficient) when scores were at least 30–40 ng/mL, insufficient between 20 and 30 ng/mL, and deficient when <20 ng/mL.[22]

Statistical analysis

A statistical software package was used for all measures (SPSS for Windows, version 11.0, Maasachussets, USA). Descriptive data were expressed as mean and standard deviation. To check the data for normality, we used Shapiro–Wilk test. The majority of variables were not normally distributed. Therefore, we utilized nonparametric tests. The Mann–Whitney test was performed for pairwise comparisons. Correlations were assessed with Pearson's or Spearman's correlation analysis as appropriate for normally distributed or skewed variables, respectively. Logistic regression was used to assess the relevant correlations between serum data (VD and IL-17), BMI, ESS, and different polygraphic parameters. Paired *t*-tests were used to compare differences between OSAS cases and matched controls.

$P < 0.05$ was considered statistically significant.

Results

Demographic and sleep characteristics of participants

Ninety-two patients (52.2% male, 47.8% female) with severe OSAHS and thirty controls (56.7% male, 43.3 female) were enrolled with a mean age of 52.3 ± 12.7 years and 45.7 ± 14.7 years, respectively. The mean BMI was 36.2 ± 6 in the OSAHS group. Nocturia and sleepiness were reported by 60.9 and 80.4% of patients, respectively. In the OSAHS group, ODI, mean arterial oxygen saturation ($MSaO_2$), and lowest arterial oxygen saturation ($LSaO_2$) were 55.8 ± 16.9 events/h, 91% ±5.1%, and 74.7% ±8.2%, respectively. The characteristics of patients with OSAHS and controls are shown in Table 1.

Evaluation of serum Vitamin D levels and symptoms

All patients with severe OSAHS had VD deficiency. The mean level of VD in OSAHS group was at 7.9 ± 2.9 ng/ml. There was no difference in VD levels according to age or gender. The level of VD was lower in patients with hypertension ($P = 0.05$) and diabetes mellitus ($P = 0.02$). There was no significant difference in serum VD levels according to other comorbidities. We did not find a correlation between VD serum levels and BMI, and there was no significant difference between VD levels among different BMI classes ($P > 0.05$). Patients with nocturia had lower VD levels ($P = 0.007$) [Table 2]. Moreover, VD levels decreased more when nocturia was more important ($r = -0.26$, $P = 0.01$). No correlation was found with ESS scores. There was no association between serum VD levels and AHI score

of severe OSAHS patients (r = −0.016, P = 0.9). However, there was a positive correlation between serum VD levels and lowest O_2 saturation. We also found that serum VD levels were positively correlated with mean SaO_2 ≤92% (r = 0.59, P = 0.02). Table 3 demonstrates the correlation between VD and different parameters.

Elevated levels of serum interleukin-17 was observed in patients with obstructive sleep apnea–hypopnea syndrome

The mean of IL-17 serum levels in the OSAHS group was 20.3 ± 3.9 pg/ml. IL-17 levels were positively correlated with nocturia (r = 0.24; P = 0.03). Patients with ESS >11 had significantly higher IL-17 levels (P = 0.02). A negative correlation was also found between IL-17 levels and $MSaO_2$ (≤92%).

Table 1: Demographic, clinical, and polygraphic data of obstructive sleep apnea-hypopnea syndrome patient group

	OSAHS patients (n=92)	Controls (n=30)
Demographic data		
Age (years)	52.3±12.7	45.7±14.7
Percentage of male	52.2	56.7
Body mass index (kg/m^2)	36.2±6	32±4.2
Current smokers	40	40
Alcohol	7	10
Medical history (%)		
Hypertension	52.2	0
Diabetes	35.9	0
Statin use	21.7	0
Coronaropathy	8.7	0
Nocturia	60.9	6.7
Sleepiness	80.4	0
Sleep-disordered breathing		
Epworth Sleepiness Scale Score	12.1±5.7	-
AHI (events/h)	55.7±17.8	-
Mean SaO_2 (%)	91±5.1	
Lowest SaO_2 (%)	74.7±8.2	-
Oxygen desaturation index (events/h)	55.8±16.9	-
Biomarker levels		
Vitamin D (ng/ml)	7.9±2.9	16.8±3.1
IL-17 (pg/ml)	20.3±3.9	10.05±3

AHI = Apnea-hypopnea index, OSAHS = Obstructive sleep apnea-hypopnea syndrome, SaO_2 = Oxygen saturation

We did not find association between IL-17 levels and other symptoms or comorbidities. Table 3 demonstrates the correlation between IL-17 and different parameters.

Correlation between Vitamin D and interleukin-17

A significant negative correlation was observed between IL-7 and VD levels (r = −0.64, P = 0.2 10^{-4}). This correlation was studied among different subgroups according to BMI (≥35), ESS (>11), nocturia severity (>3), and $MSaO_2$ (≤92). Of all these parameters, the correlation between VD and IL-17 levels was highest for nocturia >3. The magnitude of correlation between VD and IL-17 levels was also higher for $MSaO_2$ ≤92 and for BMI ≥35 than for all patients [Figure 1].

Case–control study

To further assess whether there was any relationship between OSAHS and VD or IL-17, we examined VD and IL-17 levels between OSAHS cases and controls after matching for potential confounders such as age, gender, and BMI [Table 1].

The analysis of OSAHS cases and controls matched for important determinants of VD and OSAHS revealed that VD levels were significantly decreased in OSAHS. The mean level of VD in control group was 16.8 ± 3.1 ng/ml, and VD deficiency was found among 40% of control group. On the other hand, the serum levels of IL-17 in the OSAHS group were higher than that in the control group. The mean level of IL-17 in control group was 20.3 ± 3.9 pg/ml.

Discussion

Previous cross-sectional reports showed that VD deficiency was widespread in OSAHS, whereby the proportion of participants with VD deficiency was markedly higher in severe OSAH compared to mild or moderate OSAHS. The inflammatory disorders were also more common in severe OSAHS. In the light of these findings, we aimed to assess the relationship between VD abnormalities and IL-17 in patients with severe OSAHS.

Our results are consistent with those of the literature and provide further new observations. First, we confirmed the emerging lines of evidence that patients with severe OSHAS suffered from low VD and had higher serum levels of IL-17 than control group. Second, we found that nocturia severity

Table 2: Obstructive sleep apnea-hypopnea syndrome findings and serum data of Vitamin D and interleukin-17

	Mean level Vitamin D (ng/ml)	P	Mean level IL-17 (pg/ml)	P
Male/female (49/43)	7.5±2.9/8.4±2.9	0.1	20.7±3.8/19.9±4.1	0.3
Current smokers (n=32)	6.6±2.7/8.5±2.9	0.01	21.1±3.9/20.1±3.9	0.5
Alcohol (n=7)	6.3±1.9/8.1±3	0.1	20.6±2.5/20.2±4	0.8
Hypertension (n=48)	7.3±2.8/8.5±2.9	0.05	20.7±4/19.9±3.8	0.3
Diabetes (n=33)	6.9±2.5/8.4±3	0.02	20.9±4/20.3.9	0.3
Arrhythmia (n=8)	8.9±3/7.8±2.9	0.3	18.8±3.3/20.5±4	0.2
Coronaropathy (n=8)	7±2.8/8±2.9	0.3	20.1±3.6/20.3±4	0.9
Stain use (n=20)	8.1±3.4/7.8±2.8	0.8	19.9±4/20.4±3.9	0.6
Sleepiness (n=74)	8±2.8/7.1±2.8	0.3	20±3.8/21.7±4.5	0.1
Nocturia (n=56)	7.2±2.5/9±3.4	0.007	21±3.5/19.3±4.5	0.04
Fatigue (n=45)	7.9±3/7.8±3	0.9	20±3.8/20.7±4.2	0.7

IL-17 = Interleukin-17

was negatively correlated with VD serum levels and positively with IL-17 serum levels. Finally, we demonstrated that the serum levels of IL-17 were negatively correlated with serum levels of VD in patients with severe OSAHS. The magnitude of this correlation was higher for important nocturia, lower $MSaO_2$, or higher BMI.

VD has long been known to contribute to bone health by facilitating the absorption of calcium. Recently, considerable attention was given to its possible immune and inflammatory benefits.[23-26] Data about VD status in OSAHS of Tunisian patients were lacking. In the present study, low VD level was frequent among both controls and patients with OSAHS. The frequency of hypovitaminosis D among Tunisian healthy controls in the study of Meddeb *et al*.[27] was also surprisingly common (47.6%) as similar to other sunny countries such as Italy, Spain, and Greece.[28] Insufficient VD dietary intake, higher parity, and wearing the veil could explain VD deficiency in Tunisian healthy participants. In our study, all patients had VD deficiency with a very low serum level of VD. Our results are similar to those of urban morbidly obese population (8.8 ng/ml) in the United Kingdom.[29] It is not surprising that a mostly obese population with severe OSAHS had severe VD deficiency. Moreover, some data suggested that myopathy related to VD deficiency may be most pronounced at very low VD levels (<12 ng/ml).[30]

Table 3: Correlation between Vitamin D, interleukin-17 serum levels, and Obstructive Sleep Apnea-hypopnea Syndrome parameters

	r (*P*)	
	Vitamin D	IL-17
Age	−0.062 (0.6)	0.083 (0.4)
Body mass index	−0.025 (0.8)	0.05 (0.7)
Nocturia severity	−0.26 (0.01)	0.24 (0.03)
Epworth Sleepiness Scale score	0.28 (0.8)	0.49 (0.7)
Apnea-hypopnea index (events/h)	−0.016 (0.9)	0.081 (0.6)
Mean SaO_2%*	0.59 (0.02)	−0.42 (0.03)
Lowest SaO_2%	0.3 (0.03)	−0.11 (0.2)
Oxygen desaturation index (events/h)	−0.12 (0.4)	0.035 (0.8)

*Subgroup with mean $SaO_2 \leq 92\%$. IL-17 = Interleukin-17, SaO_2 = Oxygen saturation

This VD deficiency has been linked to several health problems including asthma, diabetes, chronic kidney disease, multiple sclerosis, and cardiovascular disease.[23,24] Recent findings suggest that VD deficiency may also be associated with OSAHS, and VD is believed to have a role in sleep balance, but the mechanism is not completely clear.[25,26] Several factors may be involved in VD deficiency among patients with OSAHS (age, obesity, and inflammation). OSAHS prevalence was reported to increase at the age of 18–45 years and form a plateau between the ages of 55 and 65 years. On the other hand, people over age 50 years have an increased risk of VD deficiency and the risk increases with age. In our study, there is no correlation between age and VD levels. It has been reported that obesity, major risk factor of OSAHS, is associated with VD deficiency.[31] However, the association between VD and obesity is controversial. Among community-dwelling older men, the association between VD deficiency and sleep apnea was explained by confounding greater BMI and larger neck circumference.[32] The association between obesity and lower VD levels is explained by several factors. Poor dietary habits that lead to obesity usually provide a poor source of VD intake. In addition, restricted physical activity is frequent among obese participants limiting their exposure to sunlight that could decrease VD

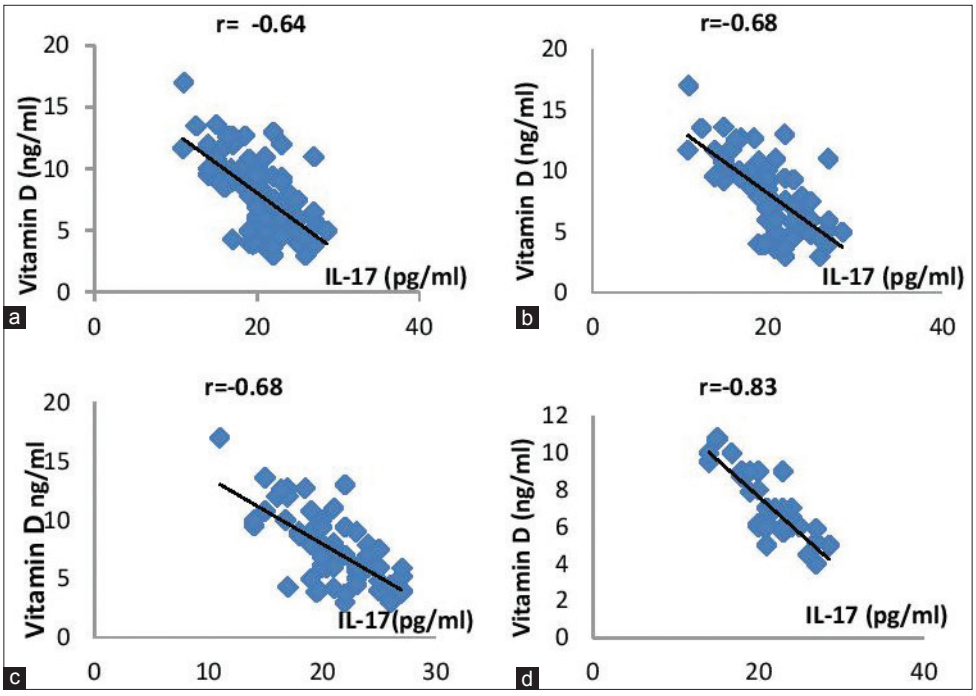

Figure 1: Vitamin D and interleukin-17 correlation: (a) all patients; (b) subgroup with mean $SaO_2\% \leq 92\%$; (c) subgroup with body mass index ≥35; (d) subgroup with nocturia >3; there was a negative significant correlation between Vitamin D and interleukin-17 ($P < 10^{-3}$)

levels. Moreover, it is known that VD bioavailability and its metabolic clearance are affected by inflammatory cytokines upregulated in adiposity.[32] In our study, we did not find a correlation between BMI and VD levels. These findings are in agreement with those of the study of Mete *et al*.[26] In fact, BMI did not fully explain the association between AHI and VD. In other studies, low VD levels in OSAHS are explained partially by the exposure lack to sunlight due to the need for sleep during daytime or by hypoxemia, which is frequently observed in these patients, by myopathy, inflammatory rhinitis, and/or tonsillar hypertrophy.[7,33] In our study, we did not find a correlation between VD and ODI; however, there was a significant association between VD levels and the lowest and mean SaO_2. This finding was reported in other studies and could suggest that hypoxia is a presumptive factor involved in VD deficiency in patients with OSAHS, as in chronic obstructive pulmonary diseases.[34] However, VD-binding protein (VDBP) modifies VD serum level in response to chronic hypoxia. Hence, further investigation of VDBP serum levels in patients with OSAHS before and after continuous positive airway pressure (CPAP) treatment would be required to clarify this association.[35] On the other hand, recent reports showed that OSAHS is an inflammatory disorder.[36] Therefore, it is possible that the VD deficiency interferes with OSAHS through an upregulation of inflammatory pathways. In our study, we reported a significant negative correlation between VD and IL-17 serum levels. This decrease in VD concomitant with an increase in IL-17 levels was described in chronic hepatitis C liver disease.[37] This could be attributed to the finding that VD suppresses proinflammatory cytokines and increases anti-inflammatory cytokines. The impact of VD on the behavior of Th17 cells was studied in various diseases, and it has been reported that VD suppresses IL-17 and IL-23 expression.[38,39] The regulatory effect on Th17 cells by VD happens by reducing retinoic acid-related orphan receptor-γt expression.[38] Data about IL-17 among OSAHS patients are scarce, and to the best of our knowledge, this is the first study which accesses the relationship between IL-17 and VD in OSAHS. In the study of Ying *et al*.,[18] adults with OSAHS exhibit an increase in circulating Th17 cells and high levels of IL-17A. In contrast to Treg cells, Th17 cells can promote the activation, proliferation, and effector functions of numerous immune cells. The authors concluded that the relationship between OSAHS and inflammation may be partially explained by an increased frequency of Th17 cells associated with a reduced frequency of Treg cells.[40,41] Previous studies proposed that OSAHS modulated the expression and secretion of inflammatory cytokines from fat and other tissues.[42-44] However, other authors concluded that CRP, TNF-α, and IL6 levels in patients with OSAHS are elevated, independently of obesity, and are related to increased metabolic and cardiovascular diseases, sleepiness, and fatigue.[45-48] In our study, there is no association between IL-17, VD, and BMI. Hence, it can be hypothesized that OSAHS is associated with VD deficiency and serum levels of IL-17 increase independently of obesity. The anti-inflammatory properties of synthetic Vitamin D receptor (VDR) agonists could be exploited to treat a variety of inflammatory diseases. Treatment with VDR agonists inhibits the T-cell production of IL-17.

VD and IL-17 disturbance were significantly more frequent among patients with nocturia. The criteria of the OSAHS severity are a combination of the severity of daytime sleepiness and the value of AHI. However, according to numerous studies, nocturnal urination of more than three times per night could predict OSAHS severity, and the $LSaO_2$, $MSaO_2$, and ODI had been considered as measures of OSA severity.[49] In the present study, the severity of VD deficiency correlated with the frequency of nocturnal urination. The mechanism of nocturia in patients with OSAHS has not been fully elucidated. The association between OSAHS and nocturia in the older population is frequent due to the increased rate of urological symptoms in elderly patients. It is known that patients develop more nocturia as they age. Umlauf *et al*.[50] proposed that the obstructive respiratory events generate negative intrathoracic pressure, causing the heart to receive a signal of volume overload. Moreover, hypoxia and hypercapnia have been suggested as the possible mechanism underlying increased left ventricular afterload.[51] The normal physiological response to atrial stretch is to excrete atrial natriuretic peptide (ANP). In a recent meta-analysis,[52] the authors thought that the beneficial effect of CPAP treatment on nocturia may be due to reduced release of ANP. CPAP therapy can effectively relieve obstruction of the airway, avoiding excessive expansion of the cardiac atrium induced by intrathoracic negative pressure. Moreover, CPAP can effectively reduce nighttime hypoxemia, thereby avoiding pulmonary hypoxic contraction. Nocturia should not be viewed as a single disorder. It can be caused by combinations of various factors, such as natriuresis induced by OSAHS, or fluid transfer from leg edema. Moreover, a relationship of VD levels and male lower urinary tract symptoms has been reported in population-based samples. Thirsty in central nervous system is inhibited by VD analogs through reduced renin-angiotensin activity in paraventricular nucleus. Polydipsia and polyuria may be caused by a lack of VD.[53]

We did not find a correlation between VD, ESS, and AHI. Nevertheless, we found correlation between VD/IL-17 and nocturia, $MSaO_2$ and $LSaO_2$. The correlation between IL-17 and VD is higher for nocturia >3 and $MSaO_2 \leq 92\%$. Then, it can be suggested that the magnitude of this correlation increases with the severity of SAHOS, and hypoxia could play an important role in this association. Repetitive hypoxia-reoxygenation cycles have been shown to be associated with activation of the proinflammatory factors.[14,15] This negative correlation between VD and IL-17 in different OSAHS parameters may highlight how these cytokines might be involved with VD in OSAHS.

Limitations

In this study, we did not use polysomnography, gold standard method for sleep-disordered breathing. The polygraphic cardiorespiratory monitoring could be underestimating respiratory events from OSAHS since it cannot evaluate the sleep stages and arousals during the night.

Conclusions

Our study is a pilot study that provides important information on VD levels OSAHS in the Mediterranean region and its correlation with clinical data and IL-17 serum levels. As a pro-inflammatory cytokine, IL-17 may be an important factor linking OSAHS to systemic inflammation. To understand the mechanisms of serum VD deficiency in OSAHS patients and its association with inflammation, our future studies will focus

on the use of VD supplementation in patients with OSAHS and its impact on clinical symptoms, OSAHS severity, and inflammatory biomarkers.

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Conflicts of interest
There are no conflicts of interest.

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