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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Psoriasis is associated with risk of obstructive sleep apnea independently from metabolic parameters and other comorbidities: a large hospital-based case-control study

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Abstract
Purpose Obstructive sleep apnea (OSA) represents a breathing disorder during sleep with significant health consequences. Few studies have examined the prevalence of OSA in psoriatic patients and whether OSA may be associated with psoriasis risk. We aimed to explore: (1) the inverse relationship, that is whether psoriasis might represent an independent predictor of OSA and its severity considering important predisposing factors and (2) the psoriatic phenotype related to severe OSA.
Methods In a large hospital-based case-control study, we examined a total of 253 patients with OSA and a control group of 104 subjects without OSA, who underwent full nocturnal polysomnography and dermatologic examination.
Results The prevalence of psoriasis was significantly greater in OSA patients than in controls ($p = 0.03$). Psoriasis was associated with OSA risk ($p = 0.04$) but not severity of OSA, sleepiness severity or sleep efficiency, independently from age, gender, anthropometric features, and significant comorbidities. The phenotype of a psoriatic patient suffering from severe OSA is not different from that of a patient with severe OSA and is not associated with psoriasis severity indexes. OSA psoriatic patients were not compliant with CPAP treatment in comparison with OSA patients without psoriasis.
Conclusion Psoriasis may represent an independent risk factor for OSA above and beyond significant comorbidities, anthropometric and metabolic parameters. Physicians should be aware of the bi-directional association of psoriasis and OSA. Managing psoriasis may be a potential target for preventing OSA as well as the potential cardiovascular mortality related to OSA and psoriasis.

Keywords Apnea · Comorbidity · Obesity · Obstructive sleep apnea · Psoriasis · Sleep efficiency

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Abbreviations

AHI	Apnea-hypopnea index
BMI	Body mass index
CVD	Cardiovascular disease
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
DLQI	Dermatology life quality index
ECG	Electrocardiogram
EEG	Electroencephalogram
ESS	Epworth sleepiness scale
HIF-1α	Hypoxia-inducible factor 1-alpha
HPA	Hypothalamic-pituitary-adrenal
IGF	Insulin growth factor

IL	Interleukin
IR	Insulin resistance
NC	Neck circumference
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NPSG	Nocturnal polysomnography
OSA	Obstructive sleep apnea
PASI	Psoriasis area and severity index
ROS	Reactive oxygen species
SD	Standard deviation
t2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor-α
UAW	Upper airway
VEGF	Vascular endothelial growth factor
WC	Waist circumference

Introduction

Obstructive sleep apnea (OSA), also referred to as obstructive sleep apnea-hypopnea, represents a common breathing disorder in which a person frequently stops breathing during sleep because of complete or partial occlusion of the upper airway resulting in recurrent hypoxia and sleep fragmentation [1–4]. Recent studies have shown that the estimated prevalence of sleep-disordered breathing has increased [5, 6]. In the HypnoLaus study, the prevalence of moderate-to-severe sleep-disordered breathing, defined as an apnea-hypopnea score of 15 or higher, is almost 23.4% for women and 49.7% for men in the general population [5]. OSA is often associated with comorbidities such as obesity, insulin resistance (IR), type 2 diabetes mellitus (t2DM), and cardiovascular disease (CVD) with important underlying factors such as activation of inflammatory mechanisms, sympathetic stimulation, and hypercoagulability [2–4].

Psoriasis, which affects 2–4% of the population worldwide, constitutes a chronic, systemic, T cell immune-mediated inflammatory skin disorder with expanded Th-1, Th-17, and Th-22 cell populations, characterized by cutaneous and joint manifestations [7, 8]. Psoriasis is associated with a range of comorbidities exhibiting an overlapping pathology such as obesity, metabolic diseases and CVD [9–11]. OSA and psoriasis share common outcomes with the inflammatory component as the main hypothesized pathogenetic mechanism [12].

Until today, few epidemiologic studies have examined the association of OSA and psoriasis [4, 13–18]. The majority of these studies have focused on the prevalence of OSA in psoriatic patients and the risk of psoriasis in OSA patients [4, 16, 17] finding that OSA may be an independent risk factor for psoriasis. However, there is a Janus face in the association between psoriasis and OSA [15]. The bidirectional relationship between OSA and psoriasis, and in particular whether psoriasis may be a risk factor for OSA, was demonstrated in one large Danish cohort study, showing that psoriasis was related with increased risk of OSA as well as OSA was related with increased risk of psoriasis [18].

Hence, the aim of the present study was to investigate the prevalence of psoriasis in OSA patients in a large hospital-based case-control study using polysomnographic data and to explore whether psoriasis might represent an independent predictor of OSA and its severity considering important predisposing factors, including obesity. Another objective of our study was to determine the psoriatic phenotype related to severe OSA.

Material and methods

Study design

In this hospital-based case-control study, a total of 253 consecutive OSA patients (200 men and 53 women) from the Sleep Laboratory of the Pulmonary Department, who underwent full nocturnal polysomnography and met the study criteria, agreed to participate from July 2009 to July 2012. The study criteria included the following: age > 18 years, non-pregnancy and the ability to provide informed consent.

During the same chronic period, a consecutive volunteer control group without OSA ($N = 104$) was randomly selected from the Outpatient Clinic and the Laboratory Department of the same hospital among those who came for an annual check-up examination. All subjects were examined for OSA by the sleep specialist (KV) of the Sleep Laboratory.

All participants had a physical examination and completed a full medical interview. The collecting data included weight, height, body mass index (BMI), waist (WC), and neck circumference (NC), and the Mallampati score for assessing upper airway, blood pressure, tobacco smoking, presence of other comorbidities such as hypertension and t2DM, and concomitant medications. Interviews and measurements were performed under similar conditions at the same time in the morning. BMI was calculated as weight (kg)/height (m^2). To determine the WC, we located the upper hip bone and placed a measuring tape at the level of the uppermost part of the hipbone around the abdomen. Blood pressure was recorded after subjects had been sitting for 5 min. The Epworth Sleepiness Scale (ESS) questionnaire was also completed as a validated tool for screening daytime sleepiness [19].

All participants were examined for psoriasis by the same dermatologists (EP, DK). The Psoriasis Area and Severity Index (PASI) and the Dermatology Life Quality Index (DLQI) scores were employed to assess psoriasis severity and extent. A full medical history of psoriasis features was obtained including age of onset, disease duration, presence of arthritis, and history of previous use and number of

systemic classical or biological treatment (retinoids, methotrexate, azathioprine, cyclosporin and biologic agents). The study was approved by the Attikon General Hospital of Athens University School of Medicine Review Board (274/30/07/09). All participants gave written informed consent.

Nocturnal polysomnography

All participants underwent a diagnostic NPSG. The diagnosis of OSA was confirmed by NPSG, which started at 22:00 and finished at 6:00 in the following morning, using a computerized system (ALICE 5 Philips/Respironics). NPSG was performed according to standard procedures, including sleep staging by monitoring central and occipital channels of the electroencephalogram (C4-A1, C3-A2, O1-A2, O2-A1), electrooculogram, and electromyogram (submental and anterior tibialis). Respiratory efforts were monitored with piezoelectric transducers placed around the chest and the abdomen and oximetry to measure oxygen desaturation. Electrocardiogram (ECG) and heart rate were monitored using the standard limb leads. Finally, snoring and body position were assessed by a snoring sensor and a body position sensor, respectively. Nocturnal studies were scored in 30-s epochs following the 2007 American Academy of Sleep Medicine criteria for sleep staging [20].

An apnea was defined as a cessation of airflow (≥90% compared with baseline) for ≥10 s. A hypopnea was defined as a reduction in baseline airflow or in thoracoabdominal movement ≥30% with ≥4% desaturation lasting ≥10 s. Apnea-hypopnea index (AHI) is the major disease severity index for OSA [2] and was assessed by full NPSG as the sum of the number of apneas and hypopneas per hour of sleep. The severity of OSA was based on the following frequencies of apnea/hypopnea episodes during total sleep time: mild 5–14.9, moderate-to-severe 15–29.9, and severe ≥30 events per hour of sleep. The sleep technician (SG) was not aware of the study objectives.

Statistical analysis

Statistical analysis of the data was performed using SPSS® version 22. Initially, data were assessed using chi-square test and Fisher's exact test for categorical variables, *t* test for normally distributed variables and Mann-Whitney *U* test for not normally distributed variables. Partial Spearman correlation coefficients (*r*) were used as measurements of correlation for continuous variables adjusting for BMI. Subsequently, analysis was undertaken through multivariable logistic regression models in order to evaluate the independent association of psoriasis with the risk of OSA and severe OSA, characterized by an AHI score ≥ 30, taking into account demographic: age and gender, anthropometric/metabolic parameters: overweight/obesity and central obesity, as well as presence of hypertension, t2DM, and smoking status. A two-sided *p* value of less than 0.05 was considered as significant.

Results

Clinical characteristics of OSA patients and controls without OSA are depicted in Table 1. Mean age and frequency of gender were similar in both groups. OSA patients presented higher BMI, WC, NC, and Mallampati score ($p < 0.001$). Also, they presented more frequently hypertension, t2DM, and a smoking history ($p < 0.05$). The prevalence of psoriasis was significantly greater in patients with OSA (9.5%) than in controls (2.9%, $p = 0.03$) and the general Greek population (being estimated to 3.16%, $p = 0.003$) [21].

Table 2 portrays the clinical and laboratory characteristics of OSA psoriatic patients and OSA patients without psoriasis. All patients presented similar age, gender, BMI, WC, NC, Mallampati and AHI scores, sleep efficiency, and smoking history ($p > 0.05$). OSA patients without psoriasis presented statistically significantly higher ESS score ($p = 0.04$). On the contrary, more psoriatic patients with OSA had hypertension ($p = 0.03$), t2DM ($p = 0.03$), and were significantly less compliant to continuous positive airway pressure (CPAP) treatment ($p < 0.001$). The CPAP use was less than 4 h per night and less than 70% of the nights per week. Psoriatic patients had a mean PASI score of 11.3 ± 8.9, a mean DLQI score of 10.7 ± 4.1 and a mean duration of psoriasis 11.3 ± 9.1 years. 45.8% of psoriatic patients received systematic therapy and 12.5% suffered from psoriatic arthritis. In psoriatic patients, adjusting for BMI, AHI, ESS scores, and sleep efficiency were not correlated with psoriasis features such as PASI and DLQI scores as well as psoriasis duration (adjusted $p > 0.05$). WC and NC were positively associated with AHI (adjusted $r = 0.59$, $p = 0.003$ and $r = 0.55$, $p = 0.006$, respectively) and ESS scores (adjusted $r = 0.40$, $p = 0.048$). Finally, AHI score was positively associated with ESS (adjusted $r = 0.40$, $p = 0.048$), negatively associated with sleep efficiency (adjusted $r = -0.52$, $p = 0.01$), and ESS score was negatively associated with sleep efficiency (adjusted $r = -0.48$, $p = 0.02$).

Tables 3 and 4 display multivariable logistic regression models that were performed in order to explore the independent association of psoriasis with risk of OSA and severe OSA (characterized by an AHI score ≥ 30), adjusting for age, gender, overweight/obesity, central obesity, presence of hypertension, and t2DM. Psoriasis was associated with risk of OSA ($p = 0.04$) independently from age, gender, overweight/obesity, central obesity, smoking history, and presence of hypertension and t2DM (Table 3). Similar results were obtained when we used BMI instead of overweight/obesity. On the contrary, psoriasis was not associated with increased risk of severe OSA ($p = 0.13$), adjusting for the abovementioned parameters (Table 4). The same results were yielded when we used NC

Table 1 Clinical characteristics of patients with OSA ($N = 253$) and hospital-based controls without OSA ($N = 104$)

Variables	Patients with OSA $N = 253$	Controls without OSA $N = 104$	p value
Age (years), mean (SD)	52.8 (11.9)	54.3 (10.5)	0.25
Gender (%, N)			
Male	79.1 (200)	78.8 (82)	0.97
Female	20.9 (53)	21.2 (22)	
Height (m), mean (SD)	1.72 (0.08)	1.72 (0.08)	0.63
Weight (kg), mean (SD)	97.9 (17.2)	78.9 (14.5)	**<0.001**
BMI (kg/m^2), mean (SD)	33.2 (5.9)	26.5 (4.6)	**<0.001**
Overweight/obesity, BMI ≥25 kg/m^2, (%, *N*)	96 (243)	46.1(48)	**<0.001**
Waist circumference (cm), mean (SD)	114.7 (12.8)	97.8 (13.1)	**<0.001**
Central obesity, WC ≥102 cm in males and ≥88 cm in females, (%, *N*)	86.2 (218)	38.5(40)	**<0.001**
Neck circumference (cm), mean (SD)	43.5 (4.2)	38.6 (4.2)	**<0.001**
Mallampati score (%, *N*) (≥ 3)	71.9 (182)	11.5(12)	**<0.001**
Presence of psoriasis (%, *N*)	9.5 (24)	2.9 (3)	**0.03**
Presence of hypertension (%, *N*)	54.1 (137)	22.1 (23)	**<0.001**
Presence of diabetes type 2 (%, *N*)	14.6 (37)	5.8 (6)	**0.02**
Smoking history			
Current smokers (%, *N*)	58.9 (149)	31.7 (33)	**<0.001**

Data are expressed as number (percentage) or mean ± standard deviation

BMI body mass index, *SD* standard deviation, *WC* waist circumference

In bold are statistically significant results when $p < 0.05$

Table 2 Clinical and laboratory characteristics of patients with OSA and psoriasis ($N = 24$) and OSA patients without psoriasis ($N = 229$)

Variables	All patients with OSA $N = 253$	OSA patients with psoriasis $N = 24$	OSA patients without psoriasis $N = 229$	p value
Age (years), mean (SD)	52.8 (11.9)	50.7 (13.6)	53 (11.8)	0.43
Gender (%, *N*)				
Male	79.1 (200)	79.2 (19)	79 (181)	0.98
Female	20.9 (53)	20.8 (5)	21 (48)	
Height (m), mean (SD)	1.72 (0.08)	1.73 (0.1)	1.72 (1.03)	0.42
Weight (kg), mean (SD)	97.9 (17.2)	100.9 (15.6)	97.5 (17.3)	0.33
BMI (kg/m^2), mean (SD)	33.2 (5.9)	33.8 (5.8)	33.1 (6.5)	0.57
Obesity, BMI ≥30 kg/m^2 (%, *N*)	67.9 (172)	75 (18)	67.2 (154)	0.44
Waist circumference (cm), mean (SD)	114.7 (12.8)	115.8 (11.8)	114.5 (12.9)	0.62
Neck circumference (cm), mean (SD)	43.5 (4.2)	44.2 (3.9)	43.4 (4.3)	0.39
AHI score, mean (SD)	39.1 (25.6)	29.9 (22.7)	40.1 (25.7)	0.05
Mallampati score (%, *N*) (>3)	71.9 (182)	79.2 (19)	71.2 (163)	0.41
Epworth sleepiness score, mean (SD)	8.6 (4.7)	7 (3.7)	8.8 (4.8)	**0.04**
Sleep efficiency, mean (SD)	92.5 (10.9)	94.3 (5.9)	92.3 (11.3)	0.17
Compliance (%, *N*)	48.6 (123)	4.2 (1)	53.3 (122)	**<0.001**
Presence of hypertension (%, *N*)	54.1 (137)	75 (18)	52.4 (120)	**0.03**
Presence of diabetes type 2 (%, *N*)	14.6 (37)	29.2 (7)	13.1 (30)	**0.03**
Smoking history				
Current Smokers (%, N)	58.9 (149)	66.6 (16)	58.1 (133)	0.42
Psoriasis duration, years, mean (SD)	–	11.3 (9.2)	–	–
Presence of arthritis (%, *N*)	–	12.5 (3)	–	–
Patients who received systemic therapy for psoriasis (%, *N*)	–	45.8 (11)	–	–
PASI score, mean (SD)	–	11.3 (8.9)	–	–
Range		2–35		
DLQI score, mean (SD)	–	10.7 (4.1)	–	–
Range		4–23		

Data are expressed as number (percentage) or mean ± standard deviation

AHI apnea hypopnea index, *BMI* body mass index, *DLQI* dermatology life quality index, *PASI* psoriasis area severity index, *SD* standard deviation

In bold are statistically significant results when $p < 0.05$

Table 3 Association of age, gender, overweight/obesity, central obesity, presence of hypertension, diabetes type 2, smoking status, and psoriasis with risk of OSA in 253 cases suffering from OSA and 104 hospital-based non-apneic controls; adjusted odds ratios (OR) and their 95% confidence intervals (95% CI)

Variable	Category or increment	*p* value	OR	95% CI
Age	1 year more	0.16	0.98	0.95–1.01
Gender	Male vs female	0.71	1.15	0.55–2.43
Overweight/obesity	Yes vs no	**<0.001**	8.34	3.07–22.66
Central obesity	Yes vs no	**0.01**	2.76	1.23–6.21
Hypertension	Yes vs no	0.09	1.77	0.90–3.48
Diabetes type 2	Yes vs no	0.41	1.59	0.52–4.88
Smoking status	Yes vs no	**0.001**	3.04	1.62–5.73
Psoriasis	Yes vs no	**0.04**	13.31	1.19–48.93

In bold are statistically significant results when $p < 0.05$

AHI: apnea hypopnea index

instead of central obesity assessed by the WC. Similarly to the risk of severe OSA, psoriasis was not associated with sleepiness severity or sleep efficiency in multivariable analyses ($p > 0.05$, data not shown).

Table 5 portrays the clinical and laboratory characteristics of psoriatic patients with severe OSA and those with mild and moderate OSA. We have found that psoriatic patients manifesting severe OSA were frequently males ($p = 0.05$), taller ($p = 0.02$), heavier ($p = 0.007$), obese ($p = 0.03$), with higher WC and NC ($p = 0.03$ and $p = 0.005$, respectively), and a higher ESS score ($p = 0.07$, though not significant at $\alpha = 0.05$). They presented lower sleep efficiency ($p = 0.005$). Psoriatic patients in both groups had similar PASI and DLQI scores and a similar psoriasis duration.

Discussion

Until now, many studies have evaluated the increased prevalence of comorbidities and risk factors in psoriatic patients [22–27]. Few studies have examined the association of OSA and psoriasis focusing particularly on the prevalence of OSA and its severity in psoriasis as well as whether OSA may be a risk factor of psoriasis, which is the inverse relationship in comparison to our study aim [4, 13–16, 28]. These studies have indicated a higher prevalence of OSA in psoriatic population compared to controls [14, 29, 30] without taking into consideration important confounders [15]. In our previous study focusing on psoriatic population, we have found that psoriasis or psoriasis characteristics (PASI and DLQI) were not independently related to OSA but only BMI and hypertension were associated with OSA in psoriasis patients adjusting for important confounders [13]. Four large epidemiologic studies have particularly examined whether OSA may be a risk factor of psoriasis [4, 16–18]. Yang et al. reported an increased risk of subsequent psoriasis in Taiwanese OSA patients but without considering other comorbidities as well as anthropometric and metabolic parameters, notably BMI, WC, and NC [4]. In the Nurses' Health Study, Cohen et al. found that women with OSA presented a significantly increased risk of incident psoriasis (determined by using a questionnaire) adjusting for anthropometric variables and comorbidities [16]. In a large case-control study from Israel, Shalom et al. found that the prevalence of OSA in patients with psoriasis was increased compared to the control group and that OSA was significantly associated with psoriasis independently from important confounders including obesity [17]. Similar to the latter results, in a large Danish cohort study, Egeberg et al. found that OSA was an independent risk factor of subsequent psoriasis [18].

Investigating the inverse relationship, that is the prevalence of psoriasis in OSA patients and the independent effect of psoriasis on OSA risk and its severity, we have found that (1) the prevalence of psoriasis in OSA patients is greater than in the control group and the general Greek population [21] and (2) psoriasis is an independent risk factor for OSA above and beyond important comorbidities, anthropometric measures including also NC, a novel cardiometabolic risk factor which is independent of and synergistic with visceral adipose tissue

Table 4 Association of age, gender, overweight/obesity, central obesity, presence of hypertension, diabetes type 2, smoking status, and psoriasis with risk of severe OSA characterized by an AHI score ≥ 30 in 253 cases suffering from OSA and 104 hospital-based non-apneic controls; adjusted odds ratios (OR) and their 95% confidence intervals (95% CI)

Variable	Category or increment	*p* value	OR	95% CI
Age	1 year more	0.22	0.99	0.96–1.01
Gender	Male vs female	**0.001**	3.58	1.77–7.26
Overweight/obesity	Yes vs no	**0.02**	6.20	1.24–31.06
Central obesity	Yes vs no	**0.001**	4.41	1.79–10.87
Hypertension	Yes vs no	0.08	1.60	0.93–2.76
Diabetes type 2	Yes vs no	0.19	1.66	0.77–3.57
Smoking status	Yes vs no	**0.02**	1.86	1.11–3.12
Psoriasis	Yes vs no	0.13	0.48	0.18–1.23

In bold are statistically significant results when $p < 0.05$

AHI apnea hypopnea index

Table 5 Clinical and laboratory characteristics of psoriatic patients ($N = 24$) with severe OSA, characterized by an AHI score ≥ 30 ($N = 9$), and those with mild and moderate OSA characterized by an AHI score < 30 ($N = 15$)

Variables	All psoriatic patients $N = 24$	Psoriatic patients with severe OSA $N = 9$	Psoriatic patients with mild/moderate OSA $N = 15$	p value
Age (years), mean (SD)	50.7 (13.6)	48.9 (12.6)	51.8 (14.5)	0.61
Gender (%, *N*)				
Male	79.2 (19)	47 (9)	52.6 (10)	0.05
Female	20.8 (5)	0 (0)	100 (5)	
Height (m), mean (SD)	1.73 (0.1)	1.79 (0.09)	1.69 (0.1)	**0.02**
Weight (kg), mean (SD)	100.9 (15.6)	111.4 (12.1)	94.6 (14.2)	**0.007**
BMI (kg/m^2), mean (SD)	33.8 (5.8)	35.2 (3.4)	32.9 (6.8)	0.12
Obesity, BMI ≥30 kg/m^2 (%, *N*)	75 (18)	100 (9)	60 (9)	**0.03**
Waist circumference (cm), mean (SD)	115.8 (11.8)	122.3 (11.5)	111.8 (10.4)	**0.03**
Neck circumference (cm), mean (SD)	44.2 (3.9)	46.9 (3.5)	42.5 (3.2)	**0.005**
Mallampati score (%, *N*) (≥3)	79.2 (19)	36.8 (7)	63.1 (12)	0.89
Epworth sleepiness score, mean (SD)	7 (3.7)	8.7 (2.9)	6 (3.9)	0.07
Sleep Efficiency, mean (SD)	94.3 (5.9)	91.8 (6.2)	98.4 (1.7)	**0.005**
Compliance (%, *N*)	4.2 (1)	11.1 (1)	0 (0)	0.19
Presence of hypertension (%, *N*)	75 (18)	77.7 (7)	73.3 (11)	0.81
Presence of diabetes type 2 (%, *N*)	29.2 (7)	22.2 (2)	0.33 (5)	0.56
Smoking history				
Current smokers (%, *N*)	66.6 (16)	66.6 (6)	66.6 (10)	1.00
Psoriasis duration, years, mean (SD)	11.3 (9.2)	9.7 (5.5)	12.4 (10.8)	0.73
Presence of arthritis (%, *N*)	12.5 (3)	22.2 (2)	6.6 (1)	0.26
Patients who received systemic therapy for psoriasis (%, *N*)	45.8 (11)	44.4 (4)	46.6 (7)	0.91
PASI score, mean (SD) range	11.3 (8.9) 2–35	12.5 (9.1) 4–35	10.6 (9.05) 2–35	0.62
DLQI score, mean (SD) range	10.7 (4.1) 4–23	10.2 (3.5) 4–23	11 (4.6) 5–22	0.64

Data are expressed as number (percentage) or mean ± standard deviation

AHI apnea hypopnea index, *BMI* body mass index, *DLQI* dermatology life quality index, *PASI* psoriasis area severity index, *SD* standard deviation

In bold are statistically significant results when $p < 0.05$

[31]. An important advantage of our research was the use of full NPSG, which is the gold standard objective tool to evaluate breathing sleep disorders and measure sleep efficiency. Only the very recent large cohort study by Egeberg et al. examining the bidirectional association of psoriasis and OSA has found that psoriasis was associated with increased risk of OSA independently from other comorbidities [18]. Nevertheless, this large study did not present any polysomnographic and anthropometric data, as well as OSA severity.

The pathophysiologic mechanisms that interconnect psoriasis, OSA, and obesity are synopsized in Fig. 1. The systemic inflammatory milieu seen in psoriasis [22] in conjunction with the chronic subclinical low-grade inflammation observed in obesity—particularly central obesity [32–34]—may promote the pathogenesis of OSA [35]. Due to stress, depression, nocturnal pruritus and pain, psoriasis induces sleep disturbances, which enhance pro-inflammatory cytokines and activate the hypothalamic-pituitary-adrenal (HPA) axis with increased cortisol secretion [12]. Psoriasis may be considered a risk factor for sleep disturbances, promoting inflammation and, consequently, OSA [12]. Additionally, sleep restriction induces insulin resistance, altered secretion of adipocytokines and ghrelin, increased appetite, craving for carbohydrates, increased BMI, all of which contribute to the development of metabolic syndrome, which, in turn, plays an important role in the pathogenesis of OSA [35, 36]. On the other hand, OSA is considered a systemic inflammatory disorder with increased levels of pro-inflammatory cytokines such as TNF-α, IL-6 and CRP, VEGF, and reactive oxygen species (ROS), due to a higher expression of the transcription factors NF-κB and HIF-1α [37–40]. OSA is characterized by intermittent hypoxia, which enhances the generation of ROS and sleep fragmentation/deprivation, both of which are linked to stimulation of HPA axis, increased cortisol and pro-inflammatory cytokines promoting and exacerbating psoriasis

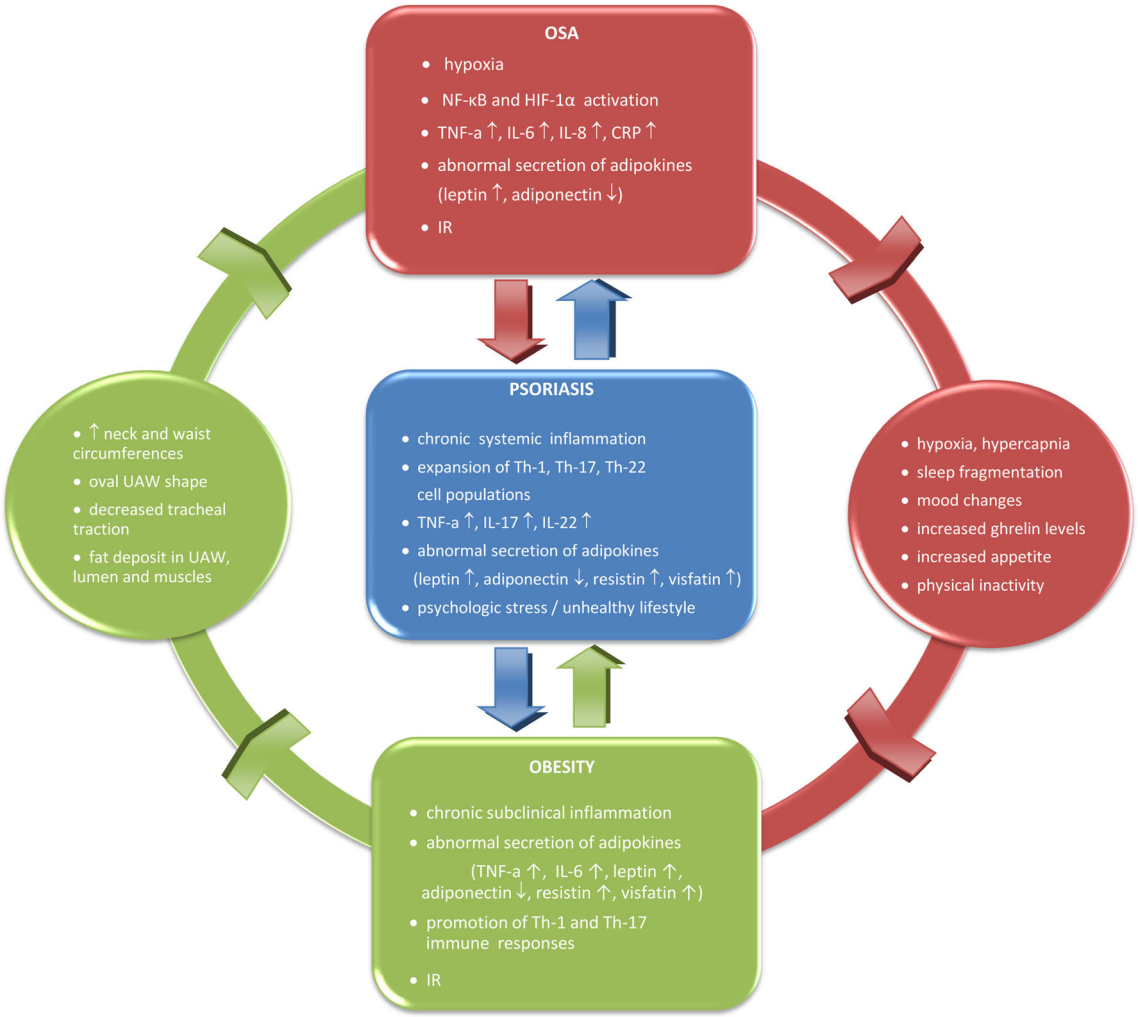

Fig. 1 Pathophysiologic mechanisms that interconnect psoriasis, OSA, and obesity formatting a vicious cycle. *CRP* C-reactive protein, *HIF-1α* hypoxia-inducible factor 1-alpha, *IL* interleukin, *IR* insulin resistance, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *OSA* obstructive sleep apnea, *TNF-α* tumor necrosis factor-α, *UAW* upper airway, *VEGF* vascular endothelial growth factor

[12]. Therefore, beyond obesity, a bidirectional link between OSA and psoriasis may exist because both disease entities share common systemic inflammatory pathogenetic mechanisms involving the Th-1 inflammatory pathway [41, 42]. Besides epidemiological data, evidence that pro-inflammatory cytokines may play a role in the pathogenesis of OSA is not completely solid. However, accumulating evidence from animal studies and a pilot human study with administration of etanercept (a TNF-α inhibitor) in 8 obese patients with sleep apnea supports that pro-inflammatory cytokines participate in the pathogenetic mechanisms leading to OSA and sleepiness [35]. Metabolic syndrome, the constellation of obesity, insulin resistance, dyslipidemia, and hypertension, predisposes to the onset of OSA (and vice versa) through hypercytokinemia, altered secretion of adipocytokines (e.g., hyperleptinemia) and hyperinsulinemia/visceral obesity, which may promote inflammation of the upper airway tissues, reduced muscle contractibility and collapse of the upper airway during sleep [35].

In this study, although psoriasis was not associated with OSA severity, we have found that the differences observed between psoriatic severe and mild-to-moderate OSA patients were similar to the differences seen between severe and mild-to-moderate OSA patients regarding anthropometric parameters. Indeed, an increase in body weight, and, consequently, in BMI was associated with a parallel increase in AHI, the major index of sleep apnea severity [43, 44]. Visceral fat, which is better expressed by WC than BMI, was also correlated with indices of sleep apnea severity [35]. However, psoriasis indexes such as PASI and DLQI scores were not associated with OSA severity in accordance with our previous study [13], probably because psoriatic patients were under treatment (systemic or topical).

Another valuable finding of our study is that OSA psoriatic patients were not compliant with CPAP treatment, considered as an anti-inflammatory approach, for OSA [2, 41], in comparison with OSA patients without psoriasis. This may be

attributed to the psychological profile of the psoriatic patient [45]. Hypertension and t2DM are associated with OSA. However, OSA psoriatic patients presented more frequently hypertension and t2DM than OSA patients without psoriasis. This could be explained by the additional inflammatory burden provoked by psoriasis. Beyond OSA, psoriasis enhances the secretion of IGF-II and IL-17, which are implicated in the pathogenesis of both metabolic syndrome and cardiovascular disease [12]. The non-compliance with CPAP in psoriatic patients with OSA may also be associated with increased metabolic and cardiovascular risks as observed in many but not all studies [35, 46, 47].

Interestingly, OSA patients with psoriasis presented lower AHI and ESS scores than OSA patients without psoriasis. This could be attributed to the fact that almost half of psoriatic patients were under systemic therapy for psoriasis. The administration of etanercept resulted in a significant decrease of sleepiness and AHI in 8 obese patients with OSA, through the inhibition of the pro-inflammatory TNF-α as discussed above [35, 48]. Although one study failed to demonstrate a decrease in AHI in psoriatic patients with OSA treated with anti-TNF-α agent [28], another study has shown improvements in sleep efficiency in patients suffering from rheumatic disease [49]. More prospective randomized controlled trials are needed in order to explore the effects of systemic and biological therapy on apnea severity indices in patients with psoriasis and OSA.

Our study presents certain limitations. It is a case-control study; hence, a cause-effect relationship cannot be established. Although a prospective cohort investigation is the ideal study for establishing the association between psoriasis and OSA, designing prospective cohort studies requires large sample size and many years of follow-up, which is resource- and time- consuming. Nonetheless, we implemented an appropriately powered and controlled study that was sufficient to generate statistically significant associations. Another methodological strength of this research is the adjustment for important risk factors of OSA, mainly obesity, which reinforces the observed associations.

Conclusion

We have found that psoriasis may represent an independent risk factor for OSA above and beyond significant comorbidities, anthropometric and metabolic parameters including also NC. Indeed, the prevalence of psoriasis in OSA patients was greater than in the control group and in the general Greek population. However, psoriasis was not associated with severity of OSA, sleep efficiency, and sleepiness, probably due to the systemic and biological treatment for psoriasis. Further prospective studies are needed to investigate whether systemic, particularly biological, therapy has any effect on apnea severity in patients with psoriasis and OSA. Physicians should be aware of the bidirectional association of psoriasis and OSA. Our results suggest that managing psoriasis may be a potential target for preventing OSA as well as the potential CVD mortality related to OSA and psoriasis.

Compliance with ethical standards

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Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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