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Report

Psoriasis and obstructive sleep apnea

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Abstract

Background Psoriasis is a chronic inflammatory skin disorder that is associated with the metabolic syndrome and its components. An association between obstructive sleep apnea (OSA) and the metabolic syndrome was previously observed.

Objectives To investigate the association between psoriasis and OSA in a comprehensive community base database.

Materials and methods The study was performed utilizing the medical database of Clalit Health Services. Patients with psoriasis were compared to controls regarding the prevalence of OSA in a case–control study. A logistic multivariate model was used to control for independent covariates.

Results Study included 12 336 patients with psoriasis ≥21 years and 24 008 age- and sex-matched controls. The prevalence of OSA in patients with psoriasis was increased compared to the control group (2.7%, 1.5%, respectively, $P < 0.001$). Multivariate analysis adjusting for age, sex, ethnicity, body mass index, chronic obstructive pulmonary disease, hypothyroidism, hyperlipidemia, and peptic disease demonstrated a significant association between psoriasis and OSA (odds ratio = 1.27, 95% confidence interval 1.08–1.49, $P < 0.001$).

Conclusion We found an association between psoriasis and OSA among a large cohort of patients with psoriasis. Clinicians should take into account that patients with psoriasis may have undiagnosed OSA.

Introduction

Obstructive sleep apnea (OSA) is defined as recurring episodes of termination of the airflow during sleep due to obstruction of airways at the level of the pharynx. When such episodes occur during sleep, the patient experiences a decrease in oxygen saturation and nocturnal asphyxia, which leads to sleep disruption, which in turns leads to excessive daytime sleepiness. OSA occurs in middle-aged persons and has an estimated prevalence of 4% in men and 2% in women. Risk factors for OSA include obesity, age above 40 years, male gender, postmenopausal status in women, nasal obstruction (e.g., due to nasal polyps), anatomic narrowing of the airways (e.g., due to tonsillar hypertrophy), alcohol or sedative intake before bedtime, and tobacco smoking. The gold standard test for OSA diagnosis is a night-time sleep study (polysomnography). OSA is treated by continuous positive airway pressure (CPAP) treatment, which restores regular night-time breathing and reduces snoring. CPAP also decreases the risk for stroke and heart failure and lowers the blood pressure. When left untreated, OSA may increase the risk for development of hypertension, stroke, myocardial infarction, diabetes, cardiovascular disease, and work-related and motor vehicle accidents.[1–7]

In recent years, it has been shown that OSA may be associated not only with anatomic problems such as tonsillar hypertrophy or nasal polyps, but also with chronic inflammation and aberrant immune response. Numerous studies have shown an association between OSA and the metabolic syndrome; however, it is difficult to establish causality between OSA and the metabolic syndrome and it is not clearly defined which is the cause and which the consequence.[7–15]

Psoriasis is an immune disease in which systemic inflammation and cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 play an important role.[7,16,17] As OSA and psoriasis are both associated with chronic inflammation and an abnormal immune response, a possible association between psoriasis and OSA has been raised in recent years. However, data regarding this association are lacking, and the present evidence is still not strong enough. Lower sleep quality for patients with psoriasis vulgaris was described during the past decade by several groups, yet it was attributed mostly to itch and pain caused by skin lesions. Buslau and Benotmane first described an association between psoriasis and OSA in a research letter in 1999.[18] A further few studies reported an association between psoriasis and OSA only recently, yet these suffer several limitations; some were based on small series of patients,[19,20] others were based on self-reported psoriasis

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diagnosis and OSA diagnosis.[21] Other limitations that can be found in these recent reports are the lack of a control group, and more importantly, the absence of any adjustment in the statistical analyses taking into account important confounders such as body mass index (BMI) reflecting obesity, which may underlie the association of psoriasis with OSA. Nevertheless, overrepresentation of OSA among patients with psoriasis remains more than possible, yet it needs to be proven on a solid ground. Therefore, re-evaluation and establishment of stronger evidence regarding the association between psoriasis and OSA is clearly warranted. The aim of the current study was to evaluate the association between psoriasis and OSA in a community-based approach, utilizing the large medical database of Clalit Health Services (CHS).

Materials and methods

For the current study, data mining techniques utilizing the CHS database were used. CHS is the largest healthcare provider in Israel, serving a population of approximately 4 300 000 enrollees. CHS has a comprehensive computerized database with continuous real-time input from pharmaceutical, medical, and administrative computerized operating systems, facilitating epidemiological studies such as the current analysis.

In recent years, we have used the CHS database to study disease associations in patients with psoriasis; the methodology has been previously described.[22–24] In the current study, patients were defined as having psoriasis when there was at least one documented diagnosis of psoriasis in the medical records registered by a CHS dermatologist in the community or when psoriasis was listed in the diagnoses of discharge letters from a hospital affiliated with CHS. The control group was randomly selected from the list of CHS members, excluding patients with a diagnosis of psoriasis, and was frequency matched to cases regarding sex and age, with age being matched within ± 1 year. Data available from the CHS database included age, sex, weight, height, and smoking status. The diagnoses of chronic diseases were extracted from the CHS chronic diseases registry, which is based on data withdrawn from hospital and primary care physicians' reports. The registry is validated by primary physician confirmation of registered diagnoses of chronic diseases. The validity of diagnoses in the register was previously estimated and found to be high for important chronic diagnoses.[25]

The code for OSA in the ICD9-CM is 780.57 ("Other and unspecified sleep apnea"). The CHS coding system is partially based on the ICD9-CM, with all the following diagnoses receiving CHS code 7805: "apnea – sleep," "disorder – sleep," "hypersomnia," "insomnia and sleep apnea," "insomnia not otherwise specified," "obstructive sleep apnea," "other hypersomnia," "sleep apnea," "sleep disorder," and "unspecified sleep disturbance." Therefore, we performed text mining in the diagnoses codes to identify only those patients who had an explicit diagnosis of "sleep apnea." To increase the accuracy of inclusion of patients with sleep apnea, we included only patients for whom the diagnosis of "sleep apnea" was entered at least twice by a CHS primary care physician. Data regarding sedative and hypnotic drug purchase (cumulative dose and duration of therapy in months) was also available. The performance of a polysomnography study (but not the result of the study) was available from billing data within the database. BMI was calculated from the average weight and height data recorded within the last 5 years. Extreme values of height (<1.20 or >2.20) and weight (<35 kg or >250 kg) were assumed typing errors and were ignored.

The study was approved by the institutional review board of Soroka University Medical Center. Publication of the data was approved by the institutional committee of CHS general management.

The distribution of patient's characteristics was compared between patients with and without psoriasis using the chi-squared test for sex and smoking status and the *t*-test for age. The proportions of patients with OSA were compared between the study groups in the entire study sample as well as in a stratified analysis based on age, sex, and other subgroups using the chi-square test. The presence of effect modification was identified using Breslow–Day's test. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented as well. A logistic regression model was used to measure the association between psoriasis and OSA in a multivariate analysis. Interaction terms for statistically significant effect modifiers were added to the multivariate model when appropriate. Statistical analysis was performed using SPSS software, version 15.

Results

The study included 12 336 patients with psoriasis over the age of 21 years and 24 008 age- and sex-matched controls. Descriptive analyses of the characteristics of case and control patients appear in Table 1. The BMI was missing for 12% of patients with psoriasis and 18% of controls. This was, however, the only variable with some missing data. Cases and controls with missing data were therefore excluded from the logistic regression model.

The prevalence of OSA in patients with psoriasis was increased as compared to the prevalence of OSA in the control group (2.7% and 1.5%, respectively, OR = 1.74, 95% CI 1.50–2.03, $P < 0.001$). Table 2 presents the association between OSA and psoriasis in the entire study population, and stratified by age, sex, BMI, ethnicity, and the presence of factors associated with OSA, including peptic disease, hyperlipidemia, chronic obstructive pulmonary disease, hypothyroidism, and purchase of sedative drugs. The association was statistically significant in most subgroups, excluding patients 21–39 years old, patients with peptic disease and non-obese patients.

Table 1 Descriptive characteristics of the study population (n = 36 344)

Characteristic	Psoriasis patients (n = 12 336)	Controls (n = 24 008)	P value
Age (years), mean ± SD	55.6 ± 16.3	54.0 ± 17.1	<0.001
Median	56	55	
Range	21–89	21–89	
Male	6441 (52.2%)	12 096 (50.4%)	0.001
Mean BMI (kg/m^2) (n = 30 538)	30.2 ± 6.7	29.1 ± 6.4	<0.001
BMI categories:			
Underweight (<20 kg/m^2)	311 (2.9%)	731 (3.7%)	<0.001
Normal (20–24.9 kg/m^2)	2116 (19.4%)	4690 (23.9%)	
Overweight (25–29.9 kg/m^2)	3550 (32.6%)	6.738 (34.3%)	
Obesity (30–39.9 kg/m^2)	4037 (37.0%)	6197 (31.6%)	
Severe obesity (>40 kg/m^2)	885 (8.1%)	1263 (6.5%)	
Peptic disease	1166 (9.5%)	1543 (6.4%)	<0.001
Hyperlipidemia	6016 (48.8%)	9111 (37.9%)	< 0.001
COPD	704 (5.7%)	842 (3.5%)	<0.001
Hypothyroidism	1012 (8.2%)	1454 (6.1%)	<0.001
Arab ethnicity	1110 (9.0%)	3794 (15.8%)	<0.001
Sedatives/hypnotics purchased			
Any	2789 (22.6%)	4206 (17.5%)	<0.001
Mean cumulative defined daily dose	32.0 ± 105.5	22.9 ± 87.1	<0.001
Mean cumulative duration (months)	1.3 ± 3.6	1.0 ± 3.1	<0.001
Obstructive sleep apnea	327 (2.7%)	369 (1.5%)	<0.001

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Effect modification by sex was noted (P = 0.033). However, the interaction term for sex and psoriasis was not incorporated into the multivariate model because it did not significantly improve the fit of the model (Table 3). In a multivariate analysis, psoriasis was associated with OSA (OR = 1.27, 95% CI: 1.08–1.49), controlling for age, sex, ethnicity, BMI, chronic obstructive pulmonary disease, hypothyroidism, hyperlipidemia, and peptic disease (Table 3). Sedative use (either as a cumulative dose, or as duration of therapy, or a dichotomous any/none categorization) was not associated with OSA in the multivariate model.

In a sensitivity analysis, we refined the OSA definition as those patients who went through a polysomnography, and had a diagnosis of OSA registered in the electronically medical records at least twice. The prevalence of verified OSA was similarly higher among patients with psoriasis (1.2% vs. 0.7%, P < 0.001, OR = 1.71, 95% CI 1.36–2.13). In the multivariate analysis, the magnitude of the association between verified OSA and psoriasis was very similar to the association of wide-definition OSA and psoriasis, although it was of borderline statistical significance due to the smaller number of verified OSA cases (OR = 1.22, 95% CI 0.97–1.54). The proportion of patients with a diagnosis of OSA who underwent a polysomnography test was similar among psoriasis cases (46%) and controls (47%), making detection bias unlikely. In an additional sensitivity analysis, we imputed missing BMI values with the mean BMI, so that all patients could be included in the regression model. In this model, psoriasis was still associated with OSA (OR = 1.37, 95% CI: 1.16–1.60).

Discussion

In the current study, we observed an association between psoriasis and OSA. This observation is in accordance with previous reports.[21] The association between psoriasis and OSA is biologically conceivable as systemic inflammation plays an important role in both psoriasis and OSA.[7–20]

Several cytokines exhibit a high degree of temporal regulation as well as somnogenic potency such as IL-1 or TNFα. The alteration or dysregulation of these cytokines may lead to sleep dysfunction. The circadian rhythm of TNFα release was previously shown to be significantly disturbed in patients with OSA; nocturnal physiologic peaks of this cytokine's levels almost disappear and an additional daytime peak develops. Patients with OSA present increased levels of inflammatory mediators such as TNFα and IL-6. These abnormalities decrease with CPAP treatment. OSA can induce or aggravate an inflammatory state. Thus, C-reactive protein and serum amyloid A, serum markers of inflammation, are increased in OSA in accordance with disease severity. These levels decrease after treatment for OSA. Activation of inflammatory pathways may be a consequence of the intermittent re-oxygenation that is characteristic of intermittent hypoxia and, thus, represents a variant of reperfusion injury. Re-oxygenation after a brief period of hypoxia as experienced repetitively and systematically by patients with OSA may predispose to cell stress, possibly because of mitochondrial dysfunction. It has been suggested that such events favor the activation of a proinflammatory response as mediated through

Table 2 Stratified analysis of the association between psoriasis and obstructive sleep apnea (n = 36 346)

Subgroups	*n*	OSA in psoriasis cases (n = 12 336)	OSA in controls (n = 24 008)	OR (95% CI)
All	36 344	327 (2.7%)	369 (1.5%)	**1.74 (1.50–2.03)*****
Sex				
Males	18 537	228 (3.5%)	279 (2.3%)	**1.55 (1.30–1.86)*****
Females	17 807	99 (1.7%)	90 (0.8%)	**2.24 (1.68–2.99)*****
Age (years)				
21–39	7813	14 (0.6%)	19 (0.3%)	1.72 (0.86–3.44)
40–59	14 252	154 (3.2%)	173 (1.8%)	**1.73 (1.39–2.16)*****
60–89	14 279	159 (3.1%)	177 (1.9%)	**1.63 (1.31–2.03)*****
Body mass index categories (n = 30 567)				
Underweight (< 20 kg/m^2)	1042	2 (0.6%)	2 (0.3%)	2.36 (0.33–16.9)
Normal (20–24.9 kg/m^2)	6806	16 (0.8%)	27 (0.6%)	1.32 (0.70–2.45)
Overweight (25–29.9 kg/m^2)	10 288	58 (1.6%)	107 (1.6%)	1.03 (0.74–1.43)
Obesity (30–39.9 kg/m^2)	10 234	179 (4.4%)	175 (2.8%)	**1.60 (1.29–1.98)*****
Severe obesity (> 40 kg/m^2)	2168	61 (6.9%)	45 (3.5%)	**2.04 (1.37–3.03)*****
Peptic disease				
Without peptic disease	33 635	265 (2.4%)	304 (1.4%)	**1.77 (1.50–2.10)*****
With peptic disease	2709	62 (5.3%)	65 (4.2%)	1.28 (0.89–1.83)
Hyperlipidemia				
Without hyperlipidemia	21 217	110 (1.7%)	148 (1.0%)	**1.77 (1.37–2.27)*****
With hyperlipidemia	15 127	217 (3.6%)	221 (2.4%)	**1.51 (1.24–1.83)*****
COPD				
Without COPD	34 798	278 (2.4%)	340 (1.5%)	**1.64 (1.40–1.93)*****
With COPD	1546	49 (7.0%)	29 (3.4%)	**2.10 (1.31–3.36)****
Hypothyroidism				
Without hypothyroidism	33 878	290 (2.6%)	340 (1.5%)	**1.72 (1.46–2.02)*****
With hypothyroidism	2466	37 (3.7%)	29 (2.0%)	**1.87 (1.13–3.06)***
Ethnicity				
Jewish	31 440	308 (2.7%)	340 (1.7%)	**1.65 (1.41–1.93)*****
Arab	4904	19 (1.7%)	29 (0.8%)	**2.26 (1.26–4.05)****

CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; OSA, obstructive sleep apnea; PH, pulmonary hypertension..

*$P < 0.05$.

**$P \leq 0.01$.

***$P \leq 0.001$.

the transcription factor, nuclear factor $\kappa\beta$, a master regulator of inflammatory gene expression that is also active in psoriasis. An increase in inflammatory cytokines and adhesion molecules has been demonstrated in patients with OSA. Levels of circulating soluble adhesion molecules, which mediate adhesion of leukocytes to the vascular endothelium, such as intracellular adhesion molecule-1, are elevated in patients with OSA and improve with CPAP therapy.[7]

Several studies have shown that sleepiness is affected by some medications that neutralize TNFα. Examples include thalidomide, etanercept, and infliximab. Obese patients with OSA presented significant and marked decrease in sleepiness after treatment with etanercept. This effect was reported to be much more effective than CPAP. Disturbances in sleep and alertness were reported to improve in patients with rheumatoid arthritis with infliximab treatment, suggesting a central effect through inhibition of circulating TNFα in both psoriasis and OSA.[7,26]

Table 3 Multivariate logistic regression models for obstructive sleep apnea (n = 30 567)

Variable	OR	95% CI	*P* value
Psoriasis	1.27	1.08–1.49	0.003
Age (per 5 years)	0.94	0.91–0.97	<0.001
Male sex	3.90	3.23–4.70	<0.001
Body mass index (per 1 kg/m^2)	1.10	1.08–1.12	<0.001
Peptic disease	2.17	1.76–2.68	<0.001
Chronic obstructive pulmonary disease	1.77	1.36–2.30	<0.001
Hyperlipidemia	1.54	1.29–1.84	<0.001
Hypothyroidism	1.39	1.05–1.85	0.021
Arab ethnicity (vs. Jewish ethnicity)	0.49	0.35–0.67	<0.001

CI, confidence interval; OR, odds ratio.

Our observation of an association between psoriasis and OSA may also shed light on several unsolved issues in psoriasis and pruritus. For example, Gupta *et al.*, have investigated

pruritus associated with nocturnal wakening.[31] It might be claimed that nocturnal wakening in patients with psoriasis is organic (e.g., due to OSA) and not psychogenic. In addition, previous reports have demonstrated an alleged association between intake of methotrexate or methoxypsoralen and sleep disorders in patients with psoriasis.[32–34] Once again, it is possible that the alleged association between OSA and the intake of these medications is confounded by the higher prevalence of OSA in patients with psoriasis.

As the association between psoriasis and OSA is clinically relevant, in the following paragraphs we describe the approach to the diagnosis and treatment of OSA, as should be known to practicing dermatologists.

The symptoms of OSA are divided into daytime and nighttime symptoms.[1–6] Daytime symptoms of OSA are excessive daytime sleepiness, being tired after the morning awakening, poor concentration, memory problems, irritability, and mood changes. Night-time symptoms of OSA include loud snoring and gasps that arouses patient from sleep, and disrupted sleep. In patients with OSA, a spouse may also witness apneic episodes at night.[1–6]

The differential diagnosis of OSA in the context of patients with psoriasis is depression with excessive daytime sleepiness or respiratory disorders with nocturnal awakenings such as chronic obstructive pulmonary disease or congestive heart failure. Untreated, OSA appears to progress in severity. The morbidity and mortality due to OSA is usually due to arrhythmias, ischemic heart disease, or hypertension on the one hand, and motor vehicle accidents on the other.

Our study has several strengths. In the current study design, patients were defined as having psoriasis when there was at least one documented diagnosis of psoriasis in the medical records registered by a CHS dermatologist in the community or when psoriasis was listed in the diagnoses of the discharge letters from a hospital. The definition of OSA was based on a diagnosis of OSA registered twice in the medical record, rather than using more strict criteria such as the results of a polysomnography study. In sensitivity analyses, when we restricted the case definition of OSA to include patients with a diagnosis of OSA registered twice in the database and performing polysomnography, the magnitude of the association did not change, both in the univariate and in the multivariate analysis suggesting that the association we observed is frank. A detection bias seems unlikely, as patients with suspected OSA will be referred to a sleep study regardless of having psoriasis. Our data support that assumption, with similar rates of referral to a sleep study test among patients with suspected OSA, whether they had psoriasis or not.

Nonetheless, our study suffers several limitations. First, due to its retrospective nature underestimation of the true frequency of OSA is possible. Second, we could not determine the temporal relationship between the diagnoses of psoriasis and OSA, as the precise dates of diagnoses are not available in our database. The CHS database undergoes a continuous validation process during which diagnoses are being validated or removed. As part of this quality control process the dates of diagnoses can be changed, hence the temporal data are not reliable. Therefore, we cannot definitely ascertain whether OSA appeared first and led to the diagnosis of psoriasis or vice versa, as it was not part of our study objectives. Another limitation is the underdiagnosis of OSA in the present study; even among psoriasis cases, the prevalence of OSA was 3.5% in males and 1.7% in females, as compared with 4% and 2% in the general population.[7] Nevertheless, in spite of these limitations, the present study reveals important data supporting the association between psoriasis and OSA.

Physicians attending to patients with psoriasis must bear this association in mind. Dermatologists should consider initial screening by appropriate questionnaire, several easy-to-use questionnaires for the screening of OSA are suggested.[35] Proper early treatment may avert preventable morbidity and even mortality.

In conclusion, our observation supports previous reports of an association between psoriasis and OSA. Physicians who treat patients with psoriasis should be attentive of this association and consider the possible diagnosis of OSA in patients with psoriasis. When OSA is suspected, dermatologists should consider referring the patients for consultation to an appropriate specialist.

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