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ORIGINAL RESEARCH

Associations Between Obstructive Sleep Apnea Syndrome, Dry Eye Disease, and CPAP Usage Among Taiwanese Patients: A Retrospective Analysis

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Study Objectives: To evaluate the association between obstructive sleep apnea (OSA) and dry eye disease (DED) and analyze the impact of Continuous Positive Airway Pressure (CPAP) on DED.

Methods: This is a retrospective population-based case-control study. Patients who underwent polysomnography in Taiwan from March 1, 2009, to March 1, 2020, were identified from the database of a sleep center. Patients who were diagnosed with keratoconjunctivitis sicca or tear film insufficiency were included. Patients without data from Schirmer's test, lacking tear break-up time values, or with a history of refractive surgery, Sjögren's syndrome, ocular injuries, or a disability in eyelid closure were excluded. All patients with DED enrolled had DED in both eyes. OSA severity between patients with and without DED was compared.

Results: In total, 86 patients with DED and 86 age-matched patients without DED were enrolled. Significant differences in apnea-hypopnea index values (patients with DED: 29.1 ± 23.4, patients without DED: 17.9 ± 20.2, $P < 0.001$), OSA severity ($P < 0.001$), and lowest oxygen saturation ($P = 0.040$) between patients with and without DED were observed. A multivariate logistic regression model indicated that the use of CPAP was independently associated with DED after adjustments for OSA severity. Patients undergoing CPAP were at greater risk of developing DED than those not undergoing CPAP (Odds ratio: 3.93, 95% confidence interval: 1.47–10.49, $P = 0.006$).

Conclusion: OSA severity is associated with DED and might be attributed to the use of CPAP.

Keywords: dry eye disease, obstructive sleep apnea, continuous positive airway pressure

Introduction

Dry eye disease (DED) is a chronic condition where ocular lubrication is impaired due to poor quality or insufficient quantity of lacrimation on the ocular surface.[1] Instability in the tear film irritates the eye, which may contribute to visual disturbance. The etiology of DED is multifactorial and includes aging, medication side effects, systemic inflammation, and environmental factors. Recent studies have shown a correlation between DED and sleep apnea.[2,3]

Obstructive sleep apnea (OSA) is characterized by repeated episodes of apnea and hypopnea events accompanied by arousal and oxygen desaturation due to sleep-induced airway narrowing.[4] If left untreated, OSA may increase oxidative stress, inflammation, and sympathetic activation, with effects on multiple organs.[5] Irritation of the ocular surface is associated with the release of cytokines, leading to disruption of the microenvironment and homeostasis of the lacrimation system, thereby contributing to DED.[6] Additionally, oxidative stress could contribute to the occurrence of floppy eyelid syndrome, characterized by easily everted and floppy eyelids, leading to tear film abnormality due to secondary lipid tear deficiency and associated rapid tear evaporation.[7]

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Treatments for OSA depend on the severity of the disease. For mild cases, initial treatment may involve dietary adjustments and weight loss. In moderate to severe cases, instead of surgical interventions such as uvulopalatopharyngoplasty, nasal reconstruction, and maxillomandibular advancement,[5] the primary conservative management strategy is continuous positive airway pressure (CPAP), where the goal is to maintain upper airway patency during sleep.[8]

CPAP therapy creates positive intraluminal pressure relative to atmospheric pressure, providing a "pneumatic splint" effect.[9] Recent studies have observed favorable outcomes in OSA-associated ocular disease after treatment with CPAP, but the effects of CPAP on disorders of the ocular surface remain unclear. Several published studies and case reports have indicated that CPAP irritates the ocular surface due to airflow leakage, interruption of the nasal lacrimal system, and a decrease in tear film stability, causing secondary ocular damage. Thus, CPAP is considered a risk factor for DED.[10,11]

However, with its ability to reduce oxidative stress and inflammation, CPAP should, in theory, benefit patients with DED. Several studies have demonstrated that CPAP improves the clinical picture of DED without causing ocular irritation.[12]

In this study, we hypothesize that DED may have a positive correlation with OSA severity, and that CPAP may have an additional impact on inducing ocular symptoms. Our aim is to evaluate the relationship between OSA and DED in patients with sleep disturbance. The severity of OSA in patients with or without DED was compared, and the effect of CPAP on the development of DED was investigated.

Materials and Methods

Ethics Declaration

This retrospective comparative cohort study was conducted at Chang Gung Memorial Hospital (CGMH), Taoyuan, Taiwan. The study was approved by the Institutional Review Board of CGMH (IRB: 201601390B0) and adhered to the tenets of the Declaration of Helsinki. Since this was a retrospective chart review study, informed consents were not necessary. All patient data was encrypted and anonymized to keep confidential.

Patient Selection and Grouping

A total of 14,152 patients who had undergone polysomnography (PSG) were identified from the PSG database of the sleep center. Patients who complained about eye discomfort and dryness with diagnoses of keratoconjunctivitis sicca or tear film insufficiency between March 1, 2009, and March 1, 2020 were included. The medical records for patients included in this study began as early as 2001, and the most recent follow-up was in 2020. All diagnoses were based on the *International Classification of Diseases, Ninth Revision* codes for keratoconjunctivitis sicca (*ICD-9* code: 370.33) and tear film insufficiency (*ICD-9* code: 375.15). A total of 457 patients meeting these criteria were identified, and each patient's medical records were then thoroughly reviewed to validate their diagnosis. Patients were excluded if they (1) lacked Schirmer's test or tear break-up time (TBUT) values or if they had a history of (2) refractive surgery such as Laser-assisted in situ keratomileusis (LASIK) or Small incision lenticule extraction (SMILE), (3) Sjögren's syndrome, (4) any ocular burn injury or major trauma, or (5) facial nerve palsy or other eyelid closure-related disability. Ultimately, a final group of 153 patients were recruited for further analysis. (Figure 1)

Data on basic characteristics, including age at PSG, sex, body mass index (BMI), comorbidities, Schirmer's test results or TBUT values, and first-PSG-related characteristics were recorded. For patients with OSA, their PSG data were used to corroborate their diagnosis. For patients undergoing CPAP treatment, their latest Schirmer's test results or TBUT values were used. In this study, patients' data were collected from 2001 to 2020, and were all Asian population. We adjusted the definition of dry eye disease (DED) according to the 2006 version of the Japanese Dry Eye Society (JDES) criteria, which include three categories: subjective symptoms, epithelial damage, and abnormalities of tears, defined as Schirmer's test value ≤5 mm or a TBUT≤5s. Additionally, we recognized the significance of Schirmer's test as an important indicator for diagnosing the aqueous-deficiency type of dry eye, which may be associated with OSA. As a result, DED was defined as (1) Schirmer's test result ≤ 5 mm for both eyes or (2) TBUT ≤ 5 s. Patients with a different severity of DED in each eye and where the criteria was met in only 1 eye were excluded. Ultimately, a final group of 86 patients were recruited for the dry eye disease (DED) group. A control group was formed; it comprised patients who had undergone PSG from the hospital's PSG database, received a diagnosis of chronic conjunctivitis (*ICD-9* code: 372.1),

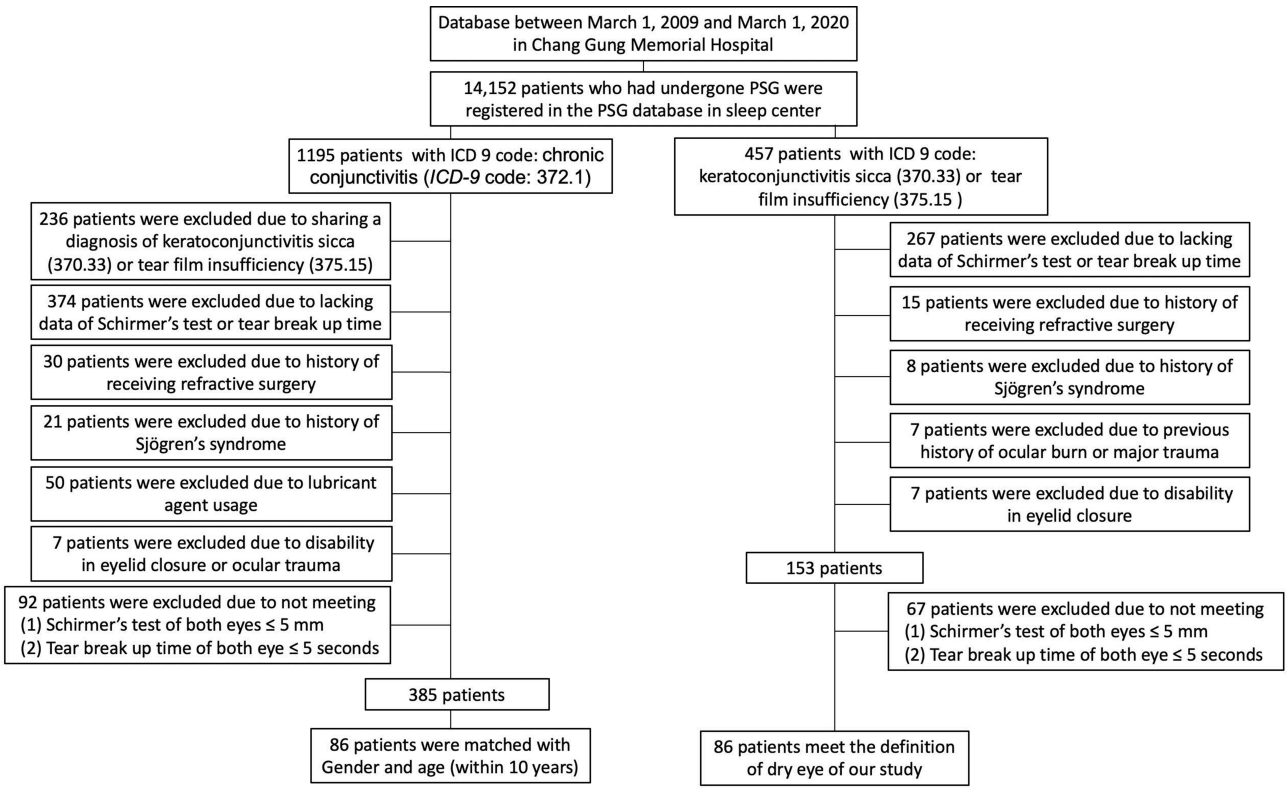

Figure 1 Patient recruitment process. A total of 86 patients, meeting the inclusion criteria, were identified for this study.

and met any of the following criteria: (1) Schirmer's test result > 5 mm for both eyes, (2) TBUT > 5 s for both eyes, (3) no history of treatment using artificial tear products, and (4) not ever having received a diagnosis of tear film insufficiency or keratoconjunctivitis sicca.

All patients underwent PSG at the sleep center of the hospital in a temperature-controlled and sound-attenuated room. During the examination, electroencephalography (EEG) was performed to determine the sleep period. The patients' nasal and oral airflows and oxygen saturation were measured using thermistors and pulse oximetry, respectively. OSA was defined as a decrease in airflow of >80% for at least 10s relative to the normal value. Obstructive hypopnea was defined as a decrease in airflow of >50% for at least 10s relative to the normal value that is an oxygen desaturation of >3%. The apnea-hypopnea index (AHI) was defined as the total number of apnea or hypopnea events per hour of the sleep period recorded using EEG. OSA severity was rated according to AHI scores: no OSA (AHI < 5), mild OSA (5 ≤ AHI < 15), moderate OSA (15 ≤ AHI < 30), and severe OSA (AHI ≥ 30).

Statistical Analyses

Chi-Square test (for categorical data), Student's *t*-test (for continuous data normally distributed), Mann–Whitney U (for continuous data not normally distributed), and multivariate logistic regression model were used for statistical analysis. We used Chi-square test to estimate the sample size as described before.[13] According to the prevalence of OSA reported by Pu et al,[14] we estimated total 172 samples (86 in study group, 86 in control group) given power was 0.8, and alpha was 0.05. All statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA). Categorical data are expressed in terms of the frequency and percentage, whereas continuous data are expressed in terms of the mean and standard deviation. A P-value less than 0.05 was considered statistically significant.

Results

Of the 86 patients with DED in this study, 37 (43%) were male, 49 (57%) were female, and the mean age was 55.9 ± 11.1 years (range, 17–88 years). The control group had the same number of patients and male-to-female ratio as the DED group; the mean age was 56.0 ± 10.7 years (range, 21–81 years). Both groups did not significantly differ in age (P = 0.944); sex (P = 0.878); BMI (P = 0.425); or comorbidities, including diabetes mellitus (P = 0.455), hypertension (P = 1.000), dyslipidemia (P = 0.407), and autoimmune diseases (P = 0.248). The basic characteristics of both groups are summarized in Table 1.

Mean AHI scores, OSA severity, and several PSG parameters for patients with and without DED are presented in Table 2. The mean AHI scores for patients with and without DED were 29.1 ± 23.4 and 17.9 ± 20.2, respectively; the difference between the 2 groups was significant (P < 0.001). The distribution of OSA severity in the 2 groups was as follows: among

Table 1 Demographic Data of Dry Eye Patients and Controls

	Dry Eye (+) Group (N=86)	Dry Eye (-) Group (N=86)	Test Value	P value
Age	55.9 ± 11.1y	56.0 ± 10.7 y	−0.070[a]	0.944
Sex			0.030[b]	0.878
Male	37 (43%)	37 (43%)		
Female	49 (57%)	49 (57%)		
BMI	27.7±4.1	26.0±5.1	−0.797[a]	0.425
Diabetes mellitus	15 (17.4%)	22 (25.6%)	0.693[b]	0.455
Hypertension	34 (39.5%)	34 (39.5%)	0.001[b]	1.000
Hyperlipidemia	23 (26.7%)	32 (37.2%)	0.874[b]	0.407
Autoimmune disease	9 (10.5%)	4 (4.7%)	1.958[b]	0.248

Notes: [a]mann–Whitney *U*-test. [b]Chi-Square test.

Table 2 Polysomnography Parameters for Patients with and without Dry Eye Disease

	Dry Eye (+) Group (N=86)	Dry Eye (-) Group (N=86)	Test Value	P value
AHI	29.1±23.4	17.9±20.2	−13.398[a]	0.000
OSA severity			18.114[b]	0.000
No OSA	15 (17.4%)	24 (27.9%)		
Mild OSA	13 (15.1%)	27 (31.4%)		
Moderate OSA	21 (24.4%)	20 (23.3%)		
Severe OSA	37 (43%)	15 (17.4%)		
Mean Sp O_2	94.3±2.1	94.4±2.1	−0.941[c]	0.347
Average Sp O_2	92.5±3.4	93.1±2.9	−1.358[c]	0.174
Lowest Sp O_2	80.4±9.2	83.1±8.0	−2.057[c]	0.040

Notes: [a]Student's *t*-test. [b]Chi-Square test. [c]Mann–Whitney *U*-test.

patients with DED, 15 (17.4%) did not meet the diagnostic criteria for OSA, 13 (15.1%) had mild OSA, 21 (24.4%) had moderate OSA, and 37 (43%) had severe OSA; among patients without DED, 24 (27.9%) did not have OSA, 27 (31.4%) had mild OSA, 20 (23.3%) had moderate OSA, and 15 (17.4%) had severe OSA. The difference in OSA severity between the 2 groups was statistically significant ($P < 0.001$). Other indicators of sleeping quality, such as oxygen saturation, were also evaluated. The mean, average, and lowest oxygen saturation were 94.3 ± 2.1, 92.5 ± 3.4, and 80.4 ± 9.2 in patients with DED, respectively, and 94.4 ± 2.1, 93.1 ± 2.9, and 83.1 ± 8.0 in patients without DED, respectively, but the difference between the 2 groups showed no significantly difference in the mean oxygen saturation (P=0.347) and the average oxygen saturation (P=0.174) was only statistically significant at the lowest levels of oxygen saturation ($P = 0.040$).

A logistic multivariable regression revealed that CPAP was independently associated with DED after adjustments for OSA severity. Patients who underwent CPAP were at greater risk of developing DED relative to those who did not undergo CPAP (Odds ratio [OR]: 3.93, 95% confidence interval [CI]: 1.47–10.49, $P = 0.006$). However, OSA severity (from mild to severe) was not associated with the occurrence of DED after adjustments for the use of CPAP (P=0.527, 0.403, and 0.376 respectively). The results are presented in Figure 2.

Discussion

Our study aimed to delve deeper into the association between OSA severity, CPAP therapy, and DED. Our findings indicate a correlation between the severity of OSA and DED, which might be attributed to CPAP usage as an important risk factor for DED development.

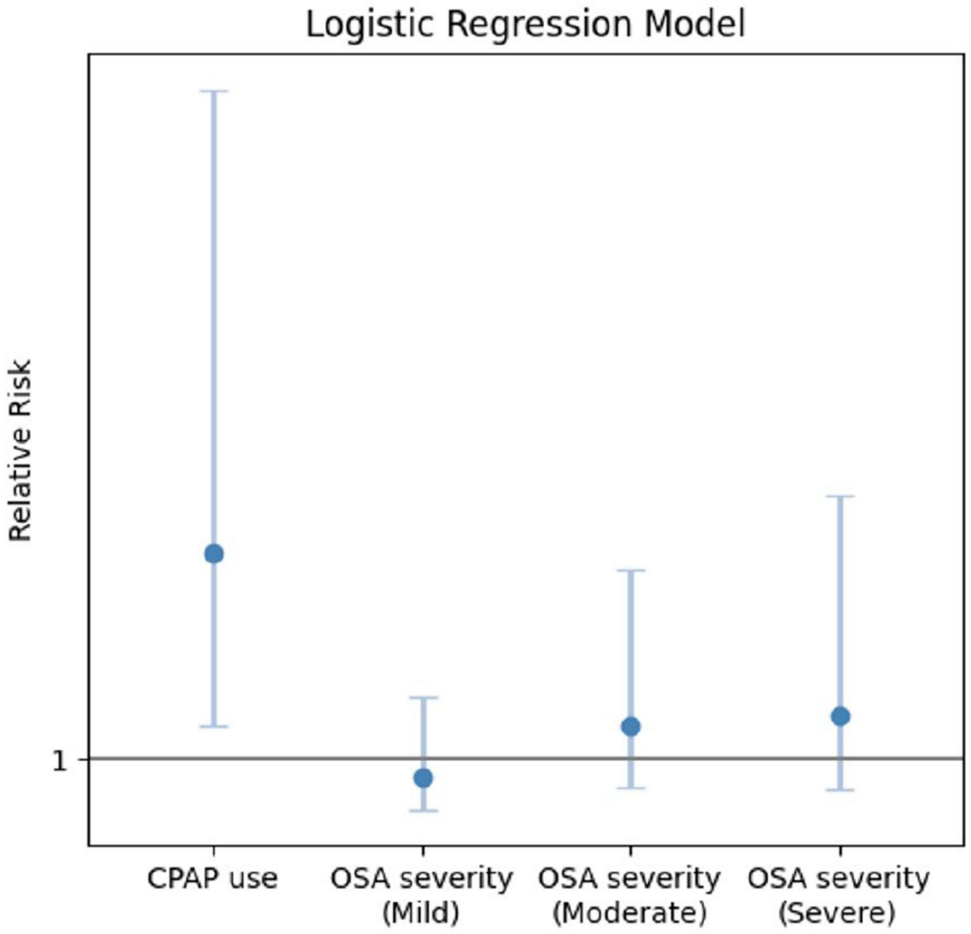

Figure 2 Logistic regression results. The logistic regression results indicate that patients who underwent CPAP were at a greater risk of developing DED (OR: 3.93, 95% CI: 1.47–10.49, P = 0.006). However, no significant association was observed beyond OSA severity: Mild OSA severity (OR: 0.74, 95% CI: 0.29–1.88, P = 0.527); moderate OSA severity (OR: 1.48, 95% CI: 0.59–3.69, P = 0.403); Severe OSA (OR: 1.62, 95% CI: 0.56–4.75, P = 0.376).

DED is characterized by tear film instability and ocular symptoms, including irritation, gritty, scratchy, or burning sensations, eye redness, fatigue, and blurry vision.[15] The diagnostic criteria for DED have evolved with increasing scientific evidence. Currently, diagnosis relies partly on the patient's subjective assessment of ocular discomfort. In this study, we adopted the diagnostic criteria proposed by the Japanese Dry Eye Society, where DED is objectively indicated by a Schirmer's test result of less than 6 mm or a TBUT of less than 6 seconds.[15,16] Sleep disorders, notably, are deemed significant DED risk factors,[17,18] with a hypothesized bidirectional relationship: sleep disturbances alter the ocular surface environment, including hyperosmotic tear, decreased TBUT, and decreased tear secretion,[19] exacerbating DED symptoms, which, in turn, affect sleep quality. Among sleep disorders, OSA is particularly implicated in DED, supported by multiple studies.[2,3,20,21] Thus, our study encompassed patients with DED and without DED as per these criteria, analyzing their PSG data for comparison. Due to the retrospective nature of our study, the non-DED patients we enrolled were all from sleep center database in our hospital, and all patients had done overnight polysomnography. From this database, the way we choose patients as control group was to select patients whose diagnosis were coding with chronic conjunctivitis but had normal Schirmer's test and TBUT without ocular surface abnormalities, and also had no use of lubricant eye drops in the medical records.

Research findings have consistently highlighted a positive correlation between the severity of OSA and the presence of dry eye. In a study published by Karaca et al,[20] 90 patients were recruited and categorized into 4 groups: no, mild, moderate, and severe OSA groups. TBUT and Schirmer's test values were inversely correlated with the severity of OSA. Similarly, another study found that the decrease in TBUT was greater among patients with more severe OSA.[21] Notably, some patients, despite having relatively low TBUT and Schirmer's test values, were not diagnosed with DED, because their Schirmer's test and TBUT values were still more than 5; this was the case even for patients with severe OSA. Therefore, in the present study, we focused on the difference in OSA severity between patients with and those without DED. Among the 192 patients in the study, AHI values, an indicator of OSA severity, were significantly higher in patients with DED, like previous studies. This further demonstrates the association between DED and OSA.

Previous investigations have also established a connection between oxygen saturation levels and the severity of OSA. In one study, the lowest oxygen saturation levels were found to be inversely correlated with the severity of OSA.[22] Furthermore, Avci et al compared several parameters of hypoxia including lowest oxygen saturation in patients with same OSA severity, and found a significant correlation between lowest oxygen saturation and inflammation during sleep.[22,23] Our investigation unveiled DED patients had significantly lower levels of lowest oxygen saturation. This finding lends support to the hypothesis of inflammation affecting the ocular surface in OSA. However, no significant difference in mean and average oxygen saturation between patients with and those without DED was observed in the present study.

To further elucidate the underlying mechanisms linking OSA severity to dry eye symptoms, researchers have explored the inflammatory cascades and signal pathways triggered by OSA-induced hypoxia. Ciftci et al reported a positive relationship between serum levels of interleukin-1, interleukin-6, and tumor necrotic factor (TNF)-a, which are important proinflammatory cytokines, and the severity of OSA.[24] Similar results were discovered in an animal model, showing OSA-induced chronic hypoxia was related to activation of the nuclear factor (NF)-κB signaling pathway in the lacrimal gland and disruption of lipid metabolism.[25] Consequent lipid accumulation and inflammation could trigger the production of reactive oxygen species, resulting in increased oxidative stress. These processes not only affect systemic condition but also interrupted the homeostasis and the microenvironment of the ocular surface.[26,27] If the interactivity among these structures is disturbed, the stability of the tear film may be impaired and will result in DED. In addition, studies on ocular structures in patients with OSA have reported that changes in the morphology of the meibomian gland were especially severe in patients with OSA.[21] Alterations in the microstructure of the meibomian gland were shown to be caused by high concentrations of inflammatory agents.[28] Intact function of the meibomian gland ensures the stability of the tear film by excreting lipid products to the ocular surface.[29] This process forms the outermost layer of the tear film, which prevents the rapid evaporation of lacrimal fluid, hyperosmolarity of the epithelial surface, and epithelial apoptosis.[30] A reduction in tear secretion further delays the removal of inflammatory agents.

CPAP is a risk factor for DED. The main mechanism is believed to be leakage from the ventilator.[31] Retrograde air escape through the nasolacrimal system may also be involved.[32] Matossian et al found that the prevalence and incidence rates of DED were higher in individuals on CPAP and noninvasive ventilators than in the general population, based on

US medical databases.[33] The relationship between ocular irritation and patients with OSA undergoing CPAP has been reported in several studies, but findings have been inconsistent. One prospective study comparing ocular surface findings in 40 patients with OSA undergoing a 4-month CPAP treatment found significantly decreased TBUT values and increased tear evaporation, leading to tear film instability. Additionally, patients reported greater ocular irritation after therapy.[10] By contrast, the attenuation of dry eye symptoms after CPAP has also been reported. Acar et al enrolled 51 patients with OSA undergoing an 18-month CPAP treatment into a study and found that Ocular Surface Disease Index scores decreased and Schirmer's test and TBUT values increased after the administration of CPAP treatment.[9] Kadyan et al reported that patients undergoing CPAP had better tear film and less ocular surface irritation symptoms. These improvements may be attributed to the supine sleep posture enforced by CPAP use, particularly benefiting long-term users who have achieved better mask fits and become accustomed to sleeping in a supine position.[12] However, the improper use of face masks may cause ocular irritation and worsen dry eye symptoms.[34] In the present study, to better understand the relationship between DED and patients with OSA undergoing CPAP, a multivariate logistic regression model test was conducted and indicated that CPAP was independently associated with DED in patients with OSA after adjusting for OSA severity, indicating that patients undergoing CPAP are at greater risk of DED, which supports the hypothesis that CPAP usage jeopardizes the health of the ocular surface. CPAP usage may be more strongly associated with DED than OSA severity. In conclusion, OSA may cause tear film imbalance, and although OSA was associated with decreased Schirmer's test and TBUT values and other impairments of the ocular surface, However, the relationship between OSA and DED may be secondary to the use of CPAP (Figure 3).

This study has several limitations. The definition of dry eye does not fully align with the latest DEWS or JDES criteria. Additionally, due to a lack of data on Ocular Surface Disease Index or Dry eye-related quality-of-life scores, we have limited our patient recruitment to those with documented positive eye irritation or discomfort. Data were obtained from the PSG database of the sleep disease center, and the findings may thus not be generalizable to the general population. The patients included in this study all had sleeping disorders. Due to the retrospective nature of this study, we were not able to standardize the duration of CPAP treatment, and adherence could not be assessed. However, our findings reveal a link between DED and OSA, underscoring the significance of understanding the impact of CPAP on ocular surface health. This emphasizes the importance of awareness and caution in the use of CPAP in such patients. Further large-scale prospective studies are warranted to better understand DED and potential treatment targets.

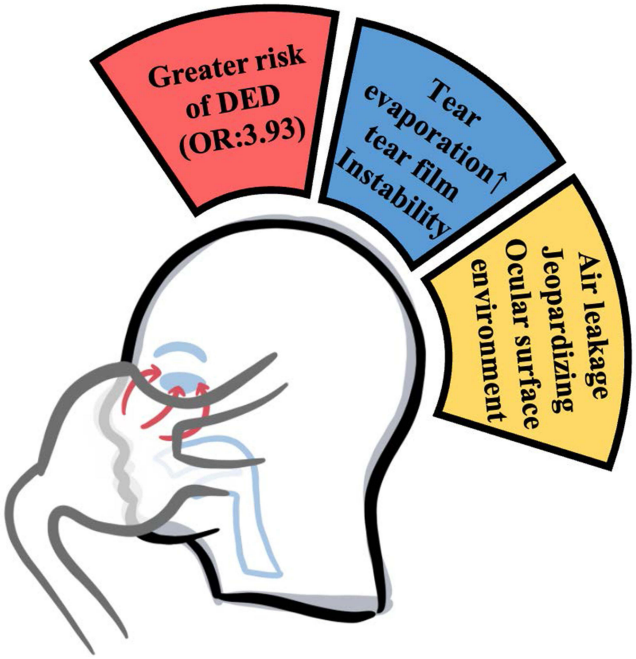

Figure 3 Summary of hypotheses in this study.

Brief Summary

Current Knowledge/Study Rationale: Obstructive sleep apnea (OSA) impacts ocular surface health and contributes to dry eye disease. Yet, the impact of continuous positive airway pressure (CPAP) on dry eye in these patients remains uncertain and conflicting.

Study Impact: While a lower severity of OSA is linked to a reduced risk of dry eye disease, dry eye in patients with a higher severity of OSA is more strongly associated with the use of CPAP. Caution is advised when considering the use of CPAP in these patients, as it may potentially worsen dry eye symptoms.

Abbreviations

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; DED, dry eye disease; EEG, electroencephalography; JDES, Japanese Dry Eye Society; LASIK, Laser-assisted in situ keratomileusis; NF-κB, nuclear factor -κB; OSA, obstructive sleep apnea; PSG, polysomnography; SMILE, Small incision lenticule extraction; TBUT, tear break-up time; TNF, tumor necrotic factor.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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