Obstructive Sleep Apnea and Keratoconus: A Systematic Review and Meta-analysis

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BACKGROUND: Despite the increasing number of studies focused on the association between obstructive sleep apnea (OSA) and keratoconus (KC), to date, no comprehensive meta-analysis or systematic review was published.

OBJECTIVE: The objective of this study was to evaluate the association between OSA and KC.

DATA SOURCES: Sources of data were PubMed, Scopus, and Web of Science databases.

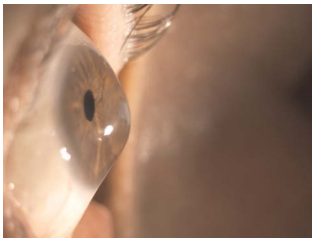
STUDY ELIGIBILITY CRITERIA: The criteria for study eligibility were case-control studies and cohort studies reporting data on the association of OSA with KC with risk ratio, odds ratio, or hazard ratio with 95% confidence intervals or sufficient raw data for calculation.

STUDY APPRAISAL AND SYNTHESIS METHODS: Meta-analysis was conducted with a random-effects model using odds ratio with 95% confidence interval as the effect size. Heterogeneity was evaluated using the Q and I^2 tests. Sensitivity analysis and assessment of publication bias were performed.

RESULTS: Five studies (four case-control studies and one cohort study) published between 2012 and 2016 and involving 33,844 subjects (16,922 patients with KC, 16,922 controls) were included in this meta-analysis. A significant association between OSA and KC has been shown (pooled odds ratio, 1.841; 95% confidence interval, 1.163 to 2.914; $P = .009$). A significant heterogeneity was observed ($Q = 15.8$, $I^2 = 74.6\%$). There was no evidence of significant publication bias ($P = .07$). The sensitivity analyses indicated the stability of results.

LIMITATIONS: Heterogeneity across the studies was observed. Data from four hospital-based case-control studies and one large population-based cohort study were combined. Most of the included studies ascertained OSA by the Berlin Questionnaire, which is a screening tool.

CONCLUSIONS: This meta-analysis provides significant evidence that OSA is associated with KC. Therefore, a proper screening for OSA is warned for KC patients for the prevention of various cardiovascular comorbidities. Further prospective studies are warranted to explore more in-depth the casual relationship between the two conditions.



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Obstructive sleep apnea is characterized by recurrent episodes of apnea during sleep caused by upper airway obstruction, leading to transient hypoxemia and hypercapnia and sleep disruption.[1] Common symptoms include excessive daytime sleepiness, fatigue, morning headache, snoring, irritability, poor concentration, and memory loss. The condition has been identified as an independent risk factor for multiple systemic disorders, such as systemic hypertension,[2] cardiovascular disease,[3] and stroke.[4] In parallel, obstructive sleep apnea has been linked with various ocular disorders, including keratoconus,[5] floppy eyelid syndrome,[6] glaucoma,[7] nonarteritic ischemic optic neuropathy,[8] and central serous chorioretinopathy.[9] Furthermore, untreated obstructive sleep apnea is associated with reduced work productivity and motor vehicle crashes resulting in injury and fatality. Continuous positive airway pressure therapy is the first-line treatment of obstructive sleep apnea and has been shown to reduce the breathing disturbances and daytime sleepiness and improve sleep quality, quality of life, and blood pressure. Alternative treatment options, including oral appliances and upper airway surgery, are available for patients in whom continuous positive airway pressure is not well tolerated or unsuccessful.[1–4]

Lately, the association between obstructive sleep apnea and keratoconus has been increasingly studied, mostly with conflicting results. Gupta et al.[5] reported a prevalence of 18% of obstructive sleep apnea among patients with keratoconus, which is much higher than previously reported in general population (between 1 and 5%).[1,10,11] Other studies reported inconsistent results, possibly due to differences in study population, and incomplete adjustment for potential confounding variables.[12–16] The association between obstructive sleep apnea and keratoconus could influence the life expectancy of keratoconus patients.[17,18] This issue is of particular interest because the incidence and prevalence of keratoconus were recently found to be 5- to 10-fold higher than previously reported.[19] However, recent studies found no significant changes in mortality between keratoconus patients and controls.[20,21]

The current systematic review and meta-analysis was designed to assess whether evidence of the association between obstructive sleep apnea and keratoconus exists. To the best of our knowledge, this is the first meta-analysis to investigate this association.

METHODS

Search Strategy

We developed an a priori protocol that defined eligibility criteria, search strategy, outcomes of interest, and analysis methods. We

systematically searched the literature using the following electronic databases: PubMed, Scopus, and Web of Science. The key words "keratoconus" AND ("sleep apnea" OR "OSA" OR "OSAS" OR "sleep-related breathing disturbance") were used in the literature search. No language restriction was applied. The last search was conducted on February 1, 2019. In addition, the reference lists of selected retrieved articles were scanned manually to identify any additional studies.

Study Selection

Articles evaluating the association between keratoconus and obstructive sleep apnea were considered eligible if they met the following inclusion criteria: (1) case-control, cross-sectional, or cohort design; and (2) evaluation of the association between keratoconus and obstructive sleep apnea with risk ratio, odds ratio, or hazard ratio with 95% confidence intervals or sufficient raw data for calculation. Conference proceedings and abstracts, letters, reviews, editorials, and studies without raw data available for retrieval were excluded.

After removing duplicate publications, two independent reviewers (MP and GG) independently screened the titles and abstracts of all identified citations. Then, the full texts of citations judged as potentially eligible were obtained and independently screened for eligibility by the same two reviewers. Any disagreement in the determination of the eligibility of each study was resolved by discussion with all authors.

Data Extraction and Quality Assessment

Two reviewers (MP and GG) independently extracted data from the studies with a pilot-tested data extraction form. The following data were obtained from each study: last name of the first author, publication year, journal, study location, study design, study population characteristics, numbers of patients with keratoconus and controls, and event rate (the frequency of occurrence of obstructive sleep apnea) in patients with keratoconus and in control subjects. In case of discrepancies between the two reviewers, the articles were revisited and agreed on by discussion. The methodological quality of each study was assessed by two independent reviewers (MP and GG) using the Newcastle-Ottawa Scale for quality of case-control studies in meta-analyses.[22] This tool for assessing the quality of nonrandomized studies evaluates three quality domains (selection of study groups, comparability of groups, and ascertainment of outcome) divided across eight specific items. A maximum of one star is assigned for each item, with the exception of the item related to comparability that allows for the assignment of two stars. Thus, the maximum for each study is nine stars, and studies with fewer than five are judged to be at high risk of bias.

Data Analysis

To examine the association between keratoconus and obstructive sleep apnea, the summary odds ratio with 95% confidence intervals was estimated by pooling the odds ratio of each study using the random-effects models, which considered both within- and between-study variation.[23] Heterogeneity was evaluated by the Q and I^2 tests. Sensitivity analysis was performed by removing one study at a time from the full meta-analysis to verify whether the results would change. Potential publication bias was assessed by both visual evaluation of funnel plots and the Egger test.[24] All statistical analyses were conducted using the Comprehensive Meta-Analysis software (version 3; Biostat, Inc., Englewood, NJ).

RESULTS

Literature Search

The flowchart showing the selection process for the included studies is presented in Fig. 1. A total 46 articles were initially identified. After the screening of titles and abstracts, 10 articles were retrieved for full-text review. Finally, five articles that met the inclusion criteria were included in the study.[12–16]

Characteristics of Studies

The selected studies were published between 2012 and 2016 and included a total number of 16,922 patients with keratoconus and 16,922 control subjects. The characteristics of the studies are reported in Table 1. Three studies were conducted in the United States,[14–16] one in Turkey,[12] and one in Iran.[13] Four studies had a case-control design,[12–15] whereas one was a retrospective cohort study based on data extracted from a large health care claims database.[16] The presence of obstructive sleep apnea was ascertained by the Berlin Questionnaire for Sleep Apnea in three studies,[12,13,15] by polysomnography in one study,[14] and by a previous diagnosis of sleep apnea in one study.[16] The total quality score of studies according to the Newcastle-Ottawa Scale ranged between 5 and 8 of a maximal score of 9. The most common shortcomings among the studies were the lack of cases and controls matched for body mass index, the ascertainment of obstructive sleep apnea by an investigator not blinded to case-control status, and the lack of description of the nonresponse rate (Table 2).

Quantitative Analysis

The forest plot of the association between obstructive sleep apnea and keratoconus is shown in Fig. 2. The presence of keratoconus was significantly associated with obstructive sleep apnea, conferring a pooled odds ratio of 1.841 (95% confidence interval, 1.163 to 2.914; $P = .009$). A significant heterogeneity was observed ($Q = 15.8$, $I^2 = 74.6\%$). The exclusion of any single study at a time from the full meta-analysis did not significantly alter the pooled odds ratio, which ranged from 1.554 (95% confidence interval, 1.027 to 2.352; $P = .04$) to 2.225 (95% confidence interval, 1.558 to 3.178; $P < .001$). No significant publication bias was detected by the Egger test ($P = .07$). A metaregression was performed to assess the effect of body mass index on the odds ratio; however, the result was not statistically significant ($P = .10$).

DISCUSSION

Although an increasing number of studies focused on the association between obstructive sleep apnea and keratoconus have been recently published, to our knowledge, no meta-analysis or systematic review was performed before. This meta-analysis of cohort and case-control studies aimed at investigating the relationship between these two conditions. A significant association of keratoconus with obstructive sleep apnea was found. Based on the pooled odds ratio, patients with keratoconus were 1.8 times as likely to have obstructive sleep apnea compared with control subjects. The association was stable after sensitivity analysis, and no evidence of publication bias was detected, suggesting that the results of the meta-analysis are robust.

Although the pathophysiological bond between keratoconus and obstructive sleep apnea remains somewhat elusive, several possible pathogenic mechanisms may exist behind this association. Matrix

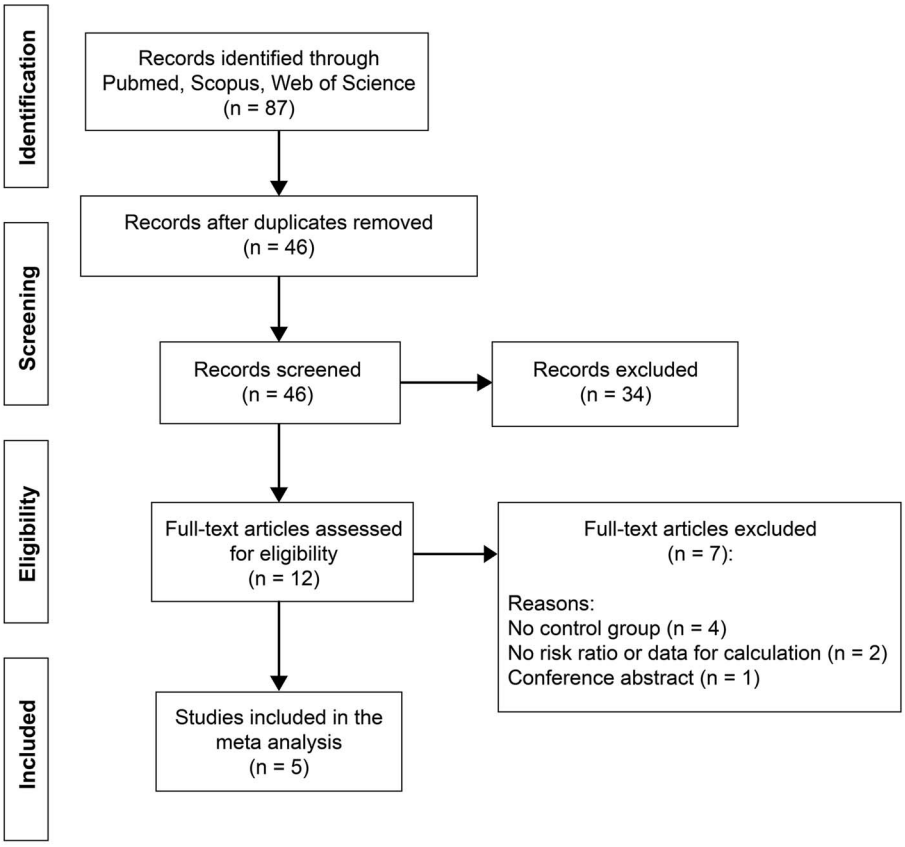

FIGURE 1. Flowchart describing the selection of studies.

metalloproteinases are proteolytic enzymes promoting the degradation of extracellular matrix components in response to stress or injury.[25] Patients with obstructive sleep apnea have increased serum levels and activity of matrix metalloproteinases-9 compared with obese controls.[26] Similarly, matrix metalloproteinases-9 tear levels are increased in patients with keratoconus and seem to play a pivotal role in the development and progression of corneal thinning and ectasia.[27–29] In addition, the intermittent hypoxia followed by reoxygenation that occurs in obstructive sleep apnea causes the generation of reactive oxygen species,[30,31] which have been implicated in the pathogenesis of tissue damage in keratoconus.[32–34]

Furthermore, eye rubbing during sleep may represent another possible mechanism of corneal damage in obstructive sleep apnea and keratoconus patients. In fact, this pattern has been recognized as a significant risk factor for keratoconus,[35,36] and patients with obstructive sleep apnea are more likely to sleep while their hands are found near their faces.[5] Mechanical trauma during sleep is also linked with floppy eyelid syndrome, a condition characterized by loose, easily everted upper eyelids and chronic papillary conjunctivitis, which is also significantly associated with both obstructive sleep apnea and keratoconus.[37–39] This mechanical theory is supported by the observation that the laterality of the preferred sleeping position coincided with that one eye more affected by floppy eyelid syndrome and keratoconus.[37,40] However, increased matrix metalloproteinases-9 levels and ischemia-reperfusion injury have been postulated as having an etiological role also in floppy eyelid syndrome, suggesting that a common inflammatory pathway may link those three conditions.[14,37] Because keratoconus is considered a heterogeneous disease with highly variable presentation and progression, it is possible that a distinct subset of patients

TABLE 1. Characteristics of the studies included in the meta-analysis

			Sample size		Age (y)		Body mass index (kg/m^2)		
First author (year)	Country	Design	Keratoconus	Controls	Keratoconus	Controls	Keratoconus	Controls	Odds ratio
Gencer et al. (2014)[12]	Turkey	Case-control	146	146	25.0	24.0	23.2	23.4	1.406
Naderan et al. (2015)[13]	Iran	Case-control	616	616	25.3	25.7	24.4	24.8	2.027
Pihlblad and Schaefer (2013)[14]	United States	Case-control	15	15	39.1	40.2	31.9	30.0	12.130
Saidel et al. (2012)[15]	United States	Case-control	92	92	47.0	48.7	29.9	27.2	3.054
Woodward et al. (2016)[16]	United States	Cohort	16,053	16,053	40.4	40.4	NA	NA	1.235

TABLE 2. Quality of the studies included in the meta-analysis assessed by the Newcastle-Ottawa Scale

	Selection				Comparability		Exposure			
First author (year)	S1	S2	S3	S4	C1	C2	E1	E2	E3	No. stars
Gencer et al. (2014)[12]	*	*		*	*		*	*		6
Naderan et al. (2015)[13]	*	*	*	*	*	*		*		7
Pihlblad and Schaefer (2013)[14]	*	*	*	*	*	*		*		7
Saidel et al. (2012)[15]	*	*	*	*				*		5
Woodward et al. (2016)[16]	*	*	*	*	*		*	*	*	8

C1 = comparability of cases; C2 = controls on the basis of the analysis; E1 = ascertainment of exposure; E2 = same method of ascertainment for cases and controls; E3 = nonresponse rate; S1 = adequate case definition; S2 = representativeness of the cases; S3 = selection of control; S4 = definition of control.

presents the association of floppy eyelid syndrome, corneal ectasia, and collapsible upper airways.

Corneal biomechanical alterations play a key role in the pathophysiology of keratoconus and occur before the clinical appearance of the disease.[41] In particular, eyes with keratoconus present decreased corneal hysteresis and corneal resistance factor.[42,43] Similarly, biomechanics of the upper airways may be altered in obstructive sleep apnea, leading to their frequent collapse.[44] Two recent studies evaluated corneal biomechanics in patients with obstructive sleep apnea without any sign of keratoconus and reported a reduction of corneal hysteresis and corneal resistance factor in patients with severe disease.[45,46] Thus, obstructive sleep apnea could be associated with a reduced corneal mechanical stability predisposing to ectasia, even in the absence of frank keratoconus. Genetic factors may be involved in the abnormal biomechanical behavior of the cornea and upper airways; in fact, genetic disorders of the connective tissue, such as Ehlers-Danlos syndrome, are associated with both keratoconus and obstructive sleep apnea.[47]

The link between obstructive sleep apnea and keratoconus seems to be complicated by several potential confounding variables, such as body mass index, age, sex, ethnicity, and other systemic diseases. Obesity is a well-recognized risk factor for obstructive sleep apnea,[48] whereas conflicting results have been reported regarding its association with keratoconus.[49] The body mass index of patients with keratoconus and control subjects was at or above the obesity limit in two of the five studies included in this meta-analysis.[14,15] Conversely, in the study by Gencer et al.,[12] body mass index was within the reference range, and no significant association between obstructive sleep apnea and keratoconus was found. In addition, also in the study by Naderan et al.,[13] body mass index was within the reference range, but a higher prevalence of obstructive sleep apnea was found in the keratoconus group, even after adjusting for this variable. We performed a metaregression to evaluate the effect of body mass index on the association between obstructive sleep apnea and keratoconus, but the results of the analysis were not significant. We could not include in the metaregression other variables because of the low number of studies included in the meta-analysis. Thus, the effect of demographical and clinical characteristics on the association between obstructive sleep apnea and keratoconus has yet to be defined; further studies are needed so this issue is suitably addressed.

The relationship between obstructive sleep apnea and keratoconus has important clinical implications to be taken into account by eye care providers. Obstructive sleep apnea represents a serious public health problem because of its many comorbidities and remains a severely underdiagnosed condition.[50] Unrecognized and untreated obstructive sleep apnea is associated with a significant increase in cardiovascular events and mortality.[51] Therefore, patients with keratoconus may benefit from proper screening for obstructive sleep apnea, particularly if at high risk.

This meta-analysis suffers from some limitations, First, heterogeneity was observed across the studies, which had significant differences regarding patients' characteristics such as age, sex, and body mass index. The association estimate resulting from the meta-analysis could not be adjusted for these relevant covariates. Therefore, the summary estimate of effect should be interpreted with caution. Second, data from four hospital-based case-control studies were combined with one large population-based cohort study, which accounted for most patients included in the meta-analysis.

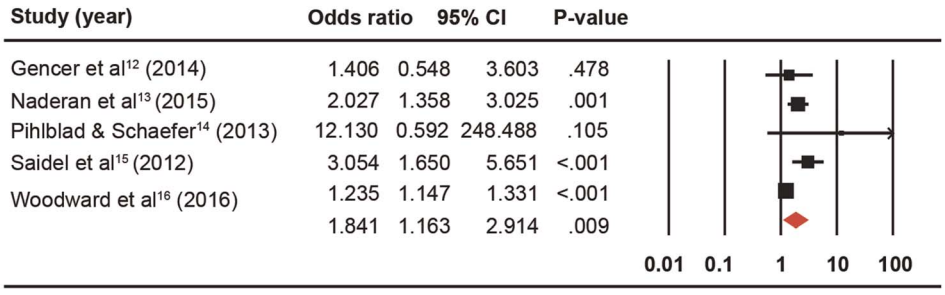

FIGURE 2. Forest plot of the association between obstructive sleep apnea and keratoconus. Squares represent study-specific odds ratio (size of the square reflects the study weight), horizontal lines represent 95% confidence intervals (CIs), and the diamond represents the pooled odds ratio, which was computed by using a random-effects model.

This difference in the experimental design could have contributed to heterogeneity. In addition, patients with keratoconus examined in a hospital may have severe coexisting diseases in comparison with patients seen in community-based practice. Third, only one of the included studies ascertained obstructive sleep apnea with polysomnography,[14] whereas most of them used the Berlin Questionnaire,[12,13,15] which stratifies the risk of obstructive sleep apnea but does not really identify patients affected by the condition. Although the questionnaire is a useful screening tool, its validity may vary in different populations, and its specificity is lower compared with criterion standard polysomnography.[52] In addition, self-reporting the personal snoring severity and daytime fatigue may lead to a recall bias and misclassification. Only one previous study evaluated prospectively patients with keratoconus using polysomnography, reporting a 38% prevalence of obstructive sleep apnea, with a higher risk in obese patients.[53] However, this study did not include a control group, and thus, it could not be included in the meta-analysis.

In conclusion, the published evidence indicates that keratoconus is associated with an increased risk of obstructive sleep apnea. Because underdiagnosed obstructive sleep apnea is associated with higher cardiovascular risk and premature mortality, eye care providers should consider the referral of patients with keratoconus to sleep specialists, particularly for those at higher risk of obstructive sleep apnea. Further well-designed longitudinal prospective studies are needed to examine any common causality in the relationship between the two conditions.

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