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<tr>
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<td>Prevalence of Sleep Apnea Syndrome and High Risk Characteristics among Keratoconus Patients</td>
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<td>keratoconus; clinical (human) or epidemiologic studies: risk factor assessment; cornea: clinical science</td>
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</table>
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| Abstract:         | Purpose: To determine the prevalence and risk factors of sleep apnea in keratoconus population.  
Methods: 92 keratoconus patients and 92 controls were classified as high risk or low risk for sleep apnea, using the Berlin Questionnaire or individual history of sleep apnea. Logistic regression was used to investigate risk factors associated with high risk of sleep apnea in keratoconus patients and controls.  
Results: Out of the 92 keratoconus patients, 18 (19.6%) had a positive known history for sleep apnea, and 49 (53.3%) were categorized to be high risk by the Berlin Questionnaire. Out of the 92 control patients, 6 (6.5%) had a positive known history for sleep apnea, and 25 (27.2%) were categorized to be high risk by the Berlin Questionnaire. In keratoconus patients, BMI was only risk factor for sleep apnea, while in control patients, age, BMI and family history of sleep apnea were risk factors for sleep apnea.  
Conclusions: Keratoconus patients are at increased risk for sleep apnea and different risk factors are associated with sleep apnea in keratoconus and controls. Ophthalmologists should consider screening keratoconus patients for obstructive sleep apnea if appropriate. |
We would like to thank the reviewers for their comments. We have made all of the suggested changes to the manuscript.
Prevalence of Sleep Apnea Syndrome and High Risk Characteristics among Keratoconus Patients

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Abstract

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**Keywords:** keratoconus • clinical (human) or epidemiologic studies: risk factor assessment • cornea: clinical science
Introduction

Sleep apnea syndrome is a sleep disorder defined by varying, repetitive episodes of apnea for at least 10 seconds and is associated with a reduction in oxygen saturation[1]. In obstructive sleep apnea, the respiratory disturbance is caused by upper airway obstruction resulting from partial to complete airway collapse[2]. Repeated episodes lead to fragmented sleep, hypoxia, excessive daytime sleepiness, fatigue and automobile accidents[3, 4]. Obstructive sleep apnea can also be life-threatening and has been identified as an independent risk factor for systemic hypertension[5, 6], cardiovascular disease[7-9], and stroke[10, 11]. Untreated obstructive sleep apnea is associated with increased risk of all-cause mortality and can lead to premature death[12, 13].

Obstructive sleep apnea has been associated with a variety of ophthalmic conditions including glaucoma[14, 15], non-arteric ischemic optic neuropathy[16, 17], floppy eyelid syndrome[18-24], retinal vein occlusion[25], and keratoconus [26-29]. Floppy eyelid syndrome, a disorder marked by easily everted upper eyelids and papillary conjunctivitis, has also been linked to obstructive sleep apnea and keratoconus [26, 30-32].

Keratoconus has been linked to obesity[33], although one study reported that keratoconus was associated with a lower body mass index (BMI)[34]. Obesity is also a risk factor for sleep apnea. Identifying risk factors for obstructive sleep apnea helps to address the public health concern of obstructive sleep apnea as intervention can reduce morbidity and mortality. The purpose of the current study was to characterize the risk of sleep apnea in keratoconus patients compared to a non-keratoconus contact lens clinic population.

Methods

Institutional review board approval was obtained prior to the start of this study. Two hundred sixteen keratoconus patients in the cornea clinic were identified by a retrospective chart review with demographic and past medical histories collected at the Department of Ophthalmology, Loyola University Chicago. Keratoconus patients were defined unambiguously by having both clinical and topographical evidence of the disease. We used a modified keratoconus severity score shown in table 3 to identify the keratoconus patients. [46].

These keratoconus patients were then contacted for a telephone survey, which used the Berlin Questionnaire (BQ), an accepted sleep apnea screening tool proven to effectively classify patients into low and high risk categories by calculating BMI and asking questions regarding snoring behavior, daytime somnolence and history of hypertension[35]. Patients were considered high risk for obstructive sleep apnea if they were high risk in a minimum of two of the following categories: snoring behavior (loudness, frequency, observed apneas), daytime sleepiness (tired after sleep, fatigue during day, falling asleep while driving) and high blood pressure or BMI greater than or equal to 30 kg/m² [35]. A past medical history of previously-diagnosed obstructive sleep apnea was also recorded. Patients with a positive history of obstructive sleep apnea were
included as part of the high risk group. Informed consent was acquired via telephone prior to the administration of the survey.

Among the 216 keratoconus patients, 124 were excluded from the study because they could not be reached by telephone or mail, or they could not participate in the questionnaire without a proxy. A proxy would not be able to accurately answer the subjective questions about the patient’s personal feelings about daytime fatigue. This resulted in 92 keratoconus patients who completed the BQ survey.

For the control group we recruited 92 consecutive new patients to the contact lens service. These patients met exclusion criteria for keratoconus and defined as normal according to criteria listed in table 3. Informed consent was given verbally, and the survey was administered during the clinic visit. Responses to the BQ were not linked to clinical outcomes. Subjects found to be at high risk for sleep apnea were referred to the sleep clinic for evaluation. The following patient data was also collected: patient height, weight, age, gender, race, family history of obstructive sleep apnea, and family history of keratoconus.

Statistical Analysis

The patient demographic and clinical characteristics were compared between the keratoconus and control groups using the t-test for continuous variables, or the Chi-square test or the Fisher’s exact test for categorical variables. Univariate logistic regression analysis was used first to identify risk factors associated with high risk for sleep apnea in the keratoconus or control group separately, with the risk of sleep apnea (high or low risk) as the outcome. Those variables that were significant in the univariate analyses were subjected to a further multivariate logistic regression.

Results

Demographic and clinical characteristics of the keratoconus and control groups
Table 1 shows the demographic and clinical characteristics of the keratoconus and control groups. The two groups had similar racial/ethnic distribution and family history of sleep apnea. However, compared with the control group, the keratoconus group had more males (52.2% vs. 32.6%, \( p = 0.007 \)), had higher BMI (29.9±8.56 vs 27.2 ±6.03, \( p = 0.016 \)), higher family history of keratoconus (15.2% vs. 0%, \( p < 0.001 \)), higher history of sleep apnea (19.6% vs. 6.5%, \( p = 0.009 \)), and were more likely to have a high risk of sleep apnea based on BQ/BMI classification (53.3% vs. 27.2%, \( p < 0.001 \)). There was one patient in the keratoconus group who was classified as low risk based on BQ/BMI measures but reported a history of sleep apnea. For further analysis to identify risk factors associated with a high risk of sleep apnea, this patient was counted in the high risk group of sleep apnea patients.

Risk factors associated with high risk of sleep apnea
Table 2 compares demographic and clinical characteristics between high risk and low risk of sleep apnea, separately in the keratoconus and control groups. In the keratoconus
group, only BMI was significantly different between high risk and low risk groups. This is not surprising because BMI, together with BQ, was used for high/low risk classification. In the control group, other than BMI, the high risk group had significantly lower portion of subjects younger than 30 years (0% vs. 22.4%, \( p = 0.009 \)), and more likely to have family history of sleep apnea (32.0% vs. 10.5%, \( p = 0.013 \)). These factors (age, BMI and family history of sleep apnea) were also significant in a multivariate analysis in the control group, suggesting three variables were risk factors in the control group.

**Discussion**

In 1982, Gilbert Smolin suggested an association between keratoconus and obstructive sleep apnea [28]. While the connection between the two diseases is unclear, this study confirms Smolin’s assertion. Our study finds that those with keratoconus are more likely to have obstructive sleep apnea or be at risk for obstructive sleep apnea by the BQ. The keratoconus group had 18 of 92 (19.6%) patients with a history of obstructive sleep apnea. The control group had only 6 of 92 (6.5%) giving a positive history for obstructive sleep apnea. The keratoconus group had 50 of 92 (54.4%) patients with obstructive sleep apnea by history or high risk by BQ. The control group had 25 of 92 (27.2%) patients with a history or high risk of obstructive sleep apnea.

Obstructive sleep apnea is known to be more prevalent in certain populations [38]. Interestingly, the demographics of keratoconus patients do not match well with the obstructive sleep apnea population. While obesity has been associated with both keratoconus and obstructive sleep apnea, most other risk factors are not seen in both diseases. Keratoconus patients tend to be younger and healthier than obstructive sleep apnea patients. In our study, the under 30 year-olds in the keratoconus group had a prevalence of high risk for obstructive sleep apnea significantly more commonly than controls (\( p=0.009 \)).

By no means does this study show a causal relationship, and the intersection of these disease processes is unclear. Nevertheless some commonalities are present. Both keratoconus and obstructive sleep apnea have been associated with floppy eyelid syndrome. Indeed the keratoconic cornea is weak. Corneal hysteresis and corneal resistance factor have been shown to be decreased in keratoconic eyes [39-41]. Similarly, airway biomechanics are altered in obstructive sleep apnea leading to repetitive collapse of the upper airway. This collapse is thought to be due to a variety of factors including central nervous system control and biomechanical factors including upper airway hysteresis [42, 43]. Hypoxia and reperfusion injury have been suggested as possible players in floppy eyelid syndrome [20, 32]. It is tempting to hypothesize reperfusion oxidation injury as a contributor to the development of keratoconus; however without further investigation, we cannot determine a causal relationship.

In this study, we used the BQ. The BQ is inherently prone to recall bias as is any questionnaire. The BQ is especially prone to error as it inquires into factors that the
subject does not have firsthand knowledge (i.e. their own sleeping habits). Another bias may be induced by the composition of the control group. Despite the fact that the control group had 6.5% with a history of obstructive sleep apnea – a reasonable level for the general population[36, 37] - the control group had more female patients than male which may have induced bias as sleep disorders are more common in males[44].

Additionally, this patient population may not represent the broader population of keratoconus patients. Because this is an established university-based practice, the patient population may have more severe disease due to referral practices of community-based practitioners. Those patients with mild disease, or even unrecognized disease, may not be seen in the university-based practices. Such a skew in population is a potential selection bias that would be best overcome by expanding this study to multiple centers. Planning for a further study is currently underway.

Going forward, the real association of keratoconus and obstructive sleep apnea needs to be elucidated. Because the BQ only stratifies risk and does not actually identify those with obstructive sleep apnea, in the future, the exact risk for obstructive sleep apnea in keratoconus patients should be quantified. This would include screening keratoconus patients with overnight diagnostic sleep studies such as the polysomnogram and warrants further investigation.

This study shows that keratoconus patients are at an increased risk for obstructive sleep apnea. Given that obstructive sleep apnea is underdiagnosed [45] and the association shown in this article, ophthalmologists and optometrists should consider screening keratoconus patients for obstructive sleep apnea if appropriate.
References


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Table 1: Demographic and clinical characteristics of keratoconus and control groups
Table 2: Risk Factors Associated with High Risk of Sleep Apnea
Table 3: Keratoconus Severity Grading Scheme
### Table 1: Demographic and clinical characteristics of keratoconus (KC) and control groups

<table>
<thead>
<tr>
<th></th>
<th>KC (N = 92)</th>
<th>Control (N = 92)</th>
<th>p-value b</th>
</tr>
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<tbody>
<tr>
<td><strong>Demographic Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sex (Male)</td>
<td>48 (52.2%)</td>
<td>30 (32.6%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>47.0 ± 13.5</td>
<td>48.7 ± 16.2</td>
<td>0.459</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td>0.345</td>
</tr>
<tr>
<td>White</td>
<td>59 (65.6%)</td>
<td>66 (71.7%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>21 (23.3%)</td>
<td>17 (18.5%)</td>
<td></td>
</tr>
<tr>
<td>Hispanics</td>
<td>10 (11.1%)</td>
<td>7 (7.6%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0 (0%)</td>
<td>2 (2.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sleep Apnea Related Measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>29.9 ± 8.56</td>
<td>27.2 ± 6.03</td>
<td>0.016</td>
</tr>
<tr>
<td>Family history of KC</td>
<td>14 (15.2%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of Sleep Apnea</td>
<td>16 (17.6%)</td>
<td>15 (16.3%)</td>
<td>0.818</td>
</tr>
<tr>
<td>History of Sleep Apnea</td>
<td>18 (19.6%)</td>
<td>6 (6.5%)</td>
<td>0.009</td>
</tr>
<tr>
<td>High Risk of Sleep Apnea</td>
<td>49 (53.3%)</td>
<td>25 (27.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk or History of Sleep Apnea</td>
<td>50 (54.4%)</td>
<td>25 (27.2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a: values are mean ± SD for continuous variables or N(%) for categorical variables  
b: p-values from t-tests for continuous variables, or chi-square or Fisher's exact tests for categorical variables  
c: Combining history of sleep apnea and risk of sleep apnea


Table 2: Risk Factors Associated with High Risk of Sleep Apnea

<table>
<thead>
<tr>
<th>Potential Risk Factors</th>
<th>Keratoconus</th>
<th></th>
<th>Control</th>
<th></th>
<th></th>
<th>P- value a</th>
<th>P- value b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Risk (N = 50)</td>
<td>Low Risk (N = 42)</td>
<td>P- value a</td>
<td>High Risk (N = 25)</td>
<td>Low Risk (N = 67)</td>
<td>P- value a</td>
<td>P- value b</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>30 (60.0%)</td>
<td>18 (42.9%)</td>
<td>0.101</td>
<td>9 (36.0%)</td>
<td>21 (31.3%)</td>
<td>0.672</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>45.9 ± 13.58</td>
<td>48.4 ± 13.39</td>
<td>0.37</td>
<td>57.3 ± 14.91</td>
<td>45.4 ± 15.51</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (≤ 30 years)</td>
<td>7 (14.0%)</td>
<td>5 (11.9%)</td>
<td>0.766</td>
<td>0 (0%)</td>
<td>15 (22.4%)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td>0.499</td>
<td></td>
<td></td>
<td></td>
<td>0.886</td>
</tr>
<tr>
<td>White</td>
<td>31 (62.0%)</td>
<td>28 (70%)</td>
<td></td>
<td>17 (68.0%)</td>
<td>49 (73.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>14 (28.0%)</td>
<td>7 (17.5%)</td>
<td></td>
<td>5 (20.0%)</td>
<td>12 (17.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanics</td>
<td>5 (10.0%)</td>
<td>5 (12.5%)</td>
<td></td>
<td>2 (8.0%)</td>
<td>5 (7.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
<td>1 (4.0%)</td>
<td>1 (1.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>33.9 ± 9.32</td>
<td>25.10 ± 3.93</td>
<td>&lt;0.001</td>
<td>31.7 ± 6.07</td>
<td>25.6 ± 5.11</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of keratoconus</td>
<td>7 (14.0%)</td>
<td>7 (16.7%)</td>
<td>0.723</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Family history of Sleep Apnea</td>
<td>11 (22.0%)</td>
<td>5 (12.2%)</td>
<td>0.222</td>
<td>8 (32.0%)</td>
<td>7 (10.5%)</td>
<td>0.013</td>
<td>0.035</td>
</tr>
</tbody>
</table>

a: univariate logistic regression
b: multivariate logistic regression, including age, BMI and family history of sleep apnea in the control group
### Table 3: Keratoconus Severity Grading Scheme

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Unaffected-atypical</td>
<td>KC Suspect</td>
<td>Affected-Mild</td>
<td>Affected-Moderate</td>
<td>Affected-Severe</td>
<td></td>
</tr>
<tr>
<td>Corneal Scarring</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Slit Lamp Signs</td>
<td>None</td>
<td>No</td>
<td>Maybe</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Axial Pattern</td>
<td>Typical</td>
<td>IP, ASBT or AIBT</td>
<td>ISP, SSP or CSP</td>
<td>KC pattern</td>
<td>KC pattern</td>
<td>KC pattern</td>
</tr>
<tr>
<td>Corneal Power</td>
<td>&lt;47.75</td>
<td>IP</td>
<td>ACP &gt;48.00</td>
<td>Flat &lt;51.00</td>
<td>Flat &gt;51.25&lt;56.00</td>
<td>Flat &gt;56.00</td>
</tr>
<tr>
<td>Spectacle Acuity</td>
<td>&gt;55 letters on Log Mar chart</td>
<td>&gt;55 letters on Log Mar chart</td>
<td>&gt;55 letters on Log Mar chart</td>
<td>&lt;55 letters on Log Mar chart</td>
<td>&lt;45 letters on Log Mar chart</td>
<td>&lt;30 letters on Log Mar chart</td>
</tr>
</tbody>
</table>

ACP=average corneal power  
IP=irregular pattern  
ASBT=asymmetric bow tie  
AIBT=asymmetric inferior bow tie  
ISP=inferior steep pattern  
SSP=superior steep pattern  
CSP=central steep pattern  
KC=Keratoconus  
Slit lamp signs: Fleischer ring, Vogt striae
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