Cataracts are Associated with the Coexistence of Moderate to Severe Obstructive Sleep Apnea and Diabetes Mellitus

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Background and Objective The individual presence of diabetes mellitus (DM) or obstructive sleep apnea (OSA) is significantly associated with cataract formation, but few studies have examined the association of cataracts with comorbid DM and OSA. Our aim in this study was to confirm the relationship between cataracts and the individual presence of DM or OSA in a large population-based cohort study and evaluate the association between cataracts and the coexistence of OSA and DM.

Methods We included 699 individuals who were enrolled in the Korean Genome and Epidemiology Study and who underwent both nocturnal polysomnography and cataract diagnosis in the study. We assessed the presence and severity of OSA by means of unattended home sleep monitoring. DM was diagnosed based on the fasting blood-glucose level or by the use of antihyperglycemic medications. Cataracts were diagnosed according to the Lens Opacities Classification System III.

Results The prevalence of cataracts tended to increase as OSA worsened. Diabetes patients had a higher prevalence of cataracts than did normal subjects. In multivariate analysis, there was no significant association of cataracts with DM or OSA alone. In the joint analysis of DM and OSA, however, the odds for cataracts were significantly higher in the DM patients with moderate to severe OSA than in the DM patients without OSA, indicating a significant synergy of moderate to severe OSA and DM on cataracts.

Conclusions The concurrent presence of DM and moderate to severe OSA was associated with cataracts. Thus, OSA should be considered in the prevention or treatment of diabetic cataracts.

Key Words Obstructive sleep apnea, Cataracts, Diabetes mellitus, Interaction.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common respiratory symptom affecting 2~4% of the adult population worldwide [1]. OSA is characterized by repeated episodes of partial or complete pharyngeal obstruction during sleep. Such events accompany intermittent hypoxia and arousal, which increase oxidative stress, systemic inflammation, and sympathetic nervous-system surges. It is well known that these abnormal biochemical and physiological disturbances are key mechanisms for the pathogenesis of several chronic systemic diseases seen in patients with OSA, such as cardiovascular diseases and diabetes mellitus (DM) [2,3]. In addition to these systemic diseases, OSA is associated with local complications, including eye disorders. Associations of eye disorders, including glaucoma, floppy eyelid syndrome (FES), non-arteritic anterior ischemic optic neuropathy (NAION), keratoconus, diabetic retinopathy, visual field defects, with OSA have been reported [4-7]. According to a large meta-analysis, OSA was significantly as-
sociated with glaucoma [4,5] and NAION [6]. OSA was not asso-
ciated with diabetic retinopathy, but some evidence has sug-
gested a significant association of OSA with greater severity of
diabetic retinopathy and advanced diabetic retinopathy in type
2 DM patients [7]. Continuous positive airway pressure treat-
ment of OSA improved the symptoms of FES [8] and visual field
loss [9] but did not prevent the development of NAION in pa-
tients with sleep apnea syndrome [10].

Cataracts are a main cause of blindness and visual defects
worldwide. The prevalence of cataracts increases with age. Large
population-based studies have reported the prevalence to be
from 3.9% at 55–64 years to 92.6% at more than 80 years [11-13].
Cataract formation is a multifactorial process. Its risk factors in-
clude increasing age, female sex, genetic factors (e.g., chromo-
some 3 in KCNAB1 and chromosome 21 in CRYAA), lifestyle
factors (e.g., ultraviolet-B exposure, cigarette smoking, and alco-
hol consumption), consumption of carbohydrates with a high
glycemic index, and systemic and medical problems (e.g., type
2 DM, high systemic blood pressure, and metabolic syndrome)
[14]. Although few studies have reported the association of OSA
with cataracts, a recent cross-sectional study reported the mag-
nitude and risk factors of ocular complications in OSA patients
associated with a greater risk of senile cataracts [15]. However,
to our knowledge, no study has investigated the association
between OSA and cataracts in a large population-based prospect-
tive cohort study. Moreover, many studies have identified asso-
ciations between cataracts and DM, but no study has examined
the association between comorbid OSA and DM and the risk
of cataracts. Therefore, we did this study to confirm the relation-
ship between cataracts and the individual presence of DM or
OSA in a large population-based cohort study. We also aimed to
evaluate the association between cataracts and the concurrent
presence of OSA and DM.

**METHODS**

**Subjects**
The study population was participants involved in the com-
unity-based cohort of the Korean Genome and Epidemiology
Study (KoGES). The KoGES began in 2001 with 5020 Koreans
(2523 men and 2497 women) aged 40–69 years. Detailed infor-
mation on the study design and aims is available elsewhere [16,17].
Participants received comprehensive health examinations and
questionnaire-based interviews during every follow-up visit. We
used cataract data for all participants from 2009 to 2010, as well
as sleep data acquired between 2009 and 2011 for OSA. We in-
cluded participants who had undergone both examinations for
ataracts and polysomnography (PSG). After excluding cases
with missing data, we included the data from 699 individuals
(286 men and 413 women) for analysis. All participants provided
informed consent, and the study was approved by the Hu-
man Subjects Review Committee at Korea University Ansan
Hospital (2006AS0045).

**Diagnosis of Cataracts**
The Lens Opacities Classification System III is a standard
system used for grading cataracts. The classification evaluates
four features: nuclear opalescence (NO), nuclear color (NC), cor-
tical cataract (C), and posterior subcapsular cataract (P). NO and
NC are graded on a decimal scale from 1 to 6, based on a set of
six standardized photographs. C and P are graded on a decimal
scale from 1 to 5. The cataract group included participants with
minimal changes (1 < NO, 1 < NC, 1 < C, 1 < P).

**PSG**
Unattended home PSG was done using a portable sleep moni-
toring device (Embletta X-100; Embla Systems, San Carlos, CA,
USA), which consisted of a one-channel electroencephalogram,
electrooculogram, chin electromyogram, a pressure transducer
air-flow sensor, thoracic and abdominal respiratory movements
sensor, electrocardiogram, and pulse oximetry. Using the Amer-
ican Academy of Sleep Medicine scoring manual for respirato-
ry events [18], we defined apnea as a clear decrease in airflow
of at least 90% from a previous baseline for a period of 10 sec-
onds, and hypopnea as a reduction in the oronasal flow ≥ 30%
from a previous baseline, associated with at least 4% oxygen de-
saturation on pulse oximetry. We judged that OSA was present
if the apnea-hypopnea index (AHI) was greater than 5. We de-
ined mild and moderate to severe OSA as 5 ≤ AHI < 15 and
AHI ≥ 15, respectively.

**Questionnaire on Lifestyle, Anthropometric
Measurements, and Definition of Disease**
We calculated body mass index (BMI) by dividing weight in
kilograms by height in meters squared. We obtained information
on physical activity (metabolic equivalent per hour daily, MET),
alcohol intake (g/day), and smoking status (never, former, cur-
cent) by questionnaires at each participant's visit. We defined hy-
pertension (HTN) as systolic/diastolic blood pressure ≥ 140/90
mm Hg or a patient taking antihypertensive drugs. We defined
DM as high fasting blood glucose of greater than 100 mg/dL or
the use of antihyperglycemic medications.

**Statistical Analysis**
The data are expressed as means ± standard deviation. We as-
sessed the significance of the means by using one-way analysis
of variance for continuous variables and a chi-squared test for
categorical variables. We conducted univariate and multivariate
logistic regression analyses to estimate the odds ratio (OR) of
cataracts in relation to DM and OSA severity and reported it with
a 95% confidence interval (CI). The potential confounding vari-
ables included in the multivariate models for DM were age, sex,
BMI, the presence of HTN, alcohol intake (g/day), smoking sta-
Characteristics of Study Samples

The 699 participants who underwent PSG and cataract diagnoses were included in the analysis. The general characteristics of the participants summarized across the severity group of OSA are shown in Table 1. The OSA patients were significantly older and more obese than the normal group. In addition, there were significant differences in alcohol intake, sex distribution, and the presence of diabetes, HTN, and smoking status. Physical activity did not differ across the severity group.

### Prevalence of Cataracts According to DM and OSA Severity Groups

The prevalence of cataracts gradually increased as OSA worsened (Fig. 1A). The prevalence of cataracts was higher in patients with DM than in normal subjects (Fig. 1B).

**Table 1. Characteristics of OSA group**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal (n = 399)</th>
<th>Mild (n = 219)</th>
<th>Moderate/severe (n = 81)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.7 ± 6.4</td>
<td>60.3 ± 7.6</td>
<td>61.7 ± 7.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.9 ± 2.6</td>
<td>25.6 ± 2.8</td>
<td>26.2 ± 3.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Physical activity*</td>
<td>183.8 ± 218.0</td>
<td>221.7 ± 311.3</td>
<td>244.6 ± 296.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Alcohol (g/day)</td>
<td>4.0 ± 10.5</td>
<td>7.3 ± 15.3</td>
<td>10.3 ± 19.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>137 (34.3)</td>
<td>104 (47.5)</td>
<td>45 (55.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Women</td>
<td>262 (65.7)</td>
<td>115 (52.5)</td>
<td>36 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>No</td>
<td>341 (85.5)</td>
<td>160 (73.1)</td>
<td>57 (70.4)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (14.5)</td>
<td>59 (26.9)</td>
<td>24 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>No</td>
<td>303 (75.9)</td>
<td>127 (58.0)</td>
<td>36 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>96 (24.1)</td>
<td>92 (42.0)</td>
<td>45 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Never</td>
<td>300 (75.2)</td>
<td>135 (61.6)</td>
<td>46 (56.8)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>69 (17.3)</td>
<td>65 (29.7)</td>
<td>28 (34.6)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>30 (7.5)</td>
<td>19 (8.7)</td>
<td>7 (8.6)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or n (%). *Average daily metabolic equivalents per hour.

OSA: obstructive sleep apnea.
Association of Cataracts with OSA and DM

confounding variables. The significance remained only when DM coexisted with moderate to severe OSA. Next, we examined the interactions between the DM and OSA severity groups and the ORs for cataracts (Fig. 2) and found significant interactions (p for interactions = 0.004).

DISCUSSION

In this study we confirmed previous findings that the prevalence of cataracts was higher in diabetic patients than in normal subjects. We also found that the proportion of cataracts increased with increases in OSA severity. However, there was no significant association between DM and cataracts or between OSA and cataracts after we accounted for possible confounders. We observed a significant association only when DM coexisted with moderate to severe OSA.

Cataracts are very prevalent ocular disorders in diabetic patients. The risk of developing cataracts is up to five times higher in patients with DM, particularly at earlier ages [19-21]. Several mechanisms (e.g., polyol pathway, osmotic and oxidative stress, and autoimmunity) have been proposed for the development of diabetic cataracts.

Unlike previous findings that reported a significant association of cataracts and DM or OSA alone [15], we failed to observe any significant relationship between them in multivariate analysis. Possible explanations for this discrepancy follow. First, the studies did not consider DM (in a study on the association between OSA and cataracts) or OSA (in a study on the association between DM and cataracts) as confounding variables. Second, previous studies did not use a multivariate analysis taking OSA severity into account. Third, there were differences in study design, sample size, and race. Fourth, there can be some threshold level of

**Table 2. ORs of cataracts according to diabetes and OSA**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>OR (95% CI) p-value</th>
<th>OR (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Normal</td>
<td>Reference</td>
<td>1.94 (1.31–2.89) &lt; 0.01</td>
<td>1.60 (1.00–2.56) 0.05*</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSA</td>
<td>Normal</td>
<td>Reference</td>
<td>1.45 (0.99–2.12) 0.06</td>
<td>0.96 (0.61–1.52) 0.87†</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td></td>
<td>2.45 (1.48–4.06) &lt; 0.01</td>
<td>1.54 (0.83–2.83) 0.17†</td>
</tr>
<tr>
<td></td>
<td>Moderate/severe</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data were adjusted for age, sex, BMI, alcohol, smoking status, physical activity, the presence of HTN, and OSA groups. †Data were adjusted for age, sex, BMI, HTN, alcohol, smoking status, physical activity, and the presence of diabetes and HTN.

**Table 3. ORs of cataracts for the joint effects of diabetes and OSA**

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>OSA</th>
<th>OR (95% CI) p-value</th>
<th>OR (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Reference</td>
<td>1.53 (0.81–2.88) 0.77</td>
</tr>
<tr>
<td></td>
<td>Moderate/severe</td>
<td>(1.00–3.44) (0.54–2.28)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Normal</td>
<td>1.34 (0.86–2.09) 0.65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate/severe</td>
<td>(1.00–3.44) (0.54–2.28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>2.22 (1.22–4.02) 0.30</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.71–3.03)</td>
<td></td>
</tr>
</tbody>
</table>

*Data were adjusted for age, sex, body mass index, alcohol, smoking status, physical activity, and the presence of hypertension.

OSA: obstructive sleep apnea, CI: confidence interval, OR: odds ratio, BMI: body mass index, HTN: hypertension.

**ORs of Cataracts According to DM and OSA**

To estimate the ORs for cataracts according to the presence of DM and the severity of OSA, we did a logistic regression analysis (Table 2). In the crude analysis, the OR for cataracts in the presence of DM was 1.94 (95% CI, 1.31–2.89; p < 0.01) and 2.45 (95% CI, 1.48–4.06; p < 0.01) in the presence of moderate/severe OSA. In the multivariate analysis, however, the significances disappeared.

**Joint Effects of DM and OSA on Cataracts**

The joint analysis for the presence of DM and OSA severity in association with cataracts is shown in Table 3. Crude logistic regression analysis showed a dose-dependent relationship between DM and cataracts according to OSA severity. However, this trend disappeared in the multivariate analysis adjusted for
specific factors or pathways to show cataract phenotype, and the individual presence of diabetes and OSA did not exceed the thresholds.

In addition, we wonder why this significant interaction effect was observed only in diabetic subjects with moderate to severe OSA. The lenses of diabetic patients are vulnerable to oxidative stress, one of the main pathological mechanisms induced by repeated oscillations of hypoxia and reoxygenation in OSA patients, because of their impaired antioxidant capacity [22]. According to a study that examined the oxidative stress levels according to the severity of OSA [23], the subjects who had an AHI > 15, corresponding to greater than moderate OSA, had reduced antioxidant capacities and greater systemic oxidative stress, implying that the oxidative stress in moderate to severe OSA was much higher than in mild OSA. In another study that prospectively investigated the association between NAION and OSA, 89% of NAION patients had AHIs > 15. This study also suggested the importance of OSA severity in the development of ocular diseases. Thus, it is likely that only moderate to severe OSA with higher oxidative stress can lead to cataracts in patients with DM. This hypothesis can be proved by measuring actual levels of oxidative stress according to the severity of OSA.

The strength of our study was that it was a large population-based study. Recent studies have reported possible associations between OSA and eye disorders, but many of these findings were in small case-control series or case reports, limiting the power of the evidence. The limitations of this study were, first, that it was not a prospective study but a cross-sectional study, so it is unclear whether OSA, DM, and cataracts are causally associated or merely share common risk factors. Second, we did not consider other OSA-related factors (e.g., sympathetic activity, hypercapnia, or inspiratory effort) that can play roles in ocular dysfunction. Thus, it is possible that this association was mediated by these additional factors.

In conclusion, this population-based study showed that the coexistence of moderate to severe OSA and DM was significantly associated with cataracts. Additional studies with prospective designs are needed to elucidate the causality among them. It is important for clinicians to understand the synergistic interaction between DM and OSA when evaluating individuals at risk for cataracts. In addition, OSA should be considered in the early detection of diabetic cataracts.

Acknowledgments

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Conflicts of Interest

The authors have no financial conflicts of interest.

Authors’ Contribution


REFERENCES