Cardiovascular Risk Factors in Patients with Obstructive Sleep Apnea

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Abstract
Obstructive Sleep Apnea (OSA), characterized by intermittent and repeated upper airway obstruction during sleep, is a common disorder with well-established cardiovascular comorbidities. However, cardiovascular risk factors are not routinely assessed in patients with OSA, in spite of current research indicating a significant reduction of cardiovascular disease with proper identification and management. The purpose of this study was to identify cardiovascular risk factors which are significantly associated with obstructive sleep apnea.

We performed a case-control retrospective study by searching health records of 1105 patients with diagnosed OSA and 2007 age-matched randomly selected controls without the diagnosis of OSA. For each subject, we collected the following information: gender, BMI, weight, diabetes mellitus type II, hyperlipidemia, hypertension, ischemic heart disease, pulmonary hypertension, congestive heart failure, cardiomyopathy, atrial fibrillation, peripheral vascular disease, smoking status, carotid disease, and history of cerebrovascular attacks.

Significant association was found between OSA and gender (p < 0.001), obesity (p < 0.001), atrial fibrillation (p < 0.001), congestive heart failure (p < 0.001), diabetes mellitus type II (p < 0.001), ischemic heart disease (p < 0.001), and smoking (p < 0.001). However, OSA was not found to be significantly associated with carotid disease (p = 0.368), hypertension (p = 0.978), or vascular disease (p = 0.149).

Overall, we found a significant association between OSA and several cardiovascular risk factors and by reporting these associations, we hope to increase awareness among clinicians with the ultimate goal of improving the overall health of the patient.

Introduction
Obstructive Sleep Apnea (OSA), the most common and treatable type of sleep apnea, is characterized by intermittent and repeated upper airway obstruction during sleep. Punjabi\(^1\) reports that as many as 7% of men and 5% of women in Western Countries are affected by this disorder. In patients with certain cardiac conditions, such as coronary artery disease\(^2\) and acute myocardial infarction\(^3\), OSA has long been established to have a much higher prevalence. In addition, OSA is a recognized independent risk factor for cardiac, neurologic, and perioperative comorbidities\(^4\). Given its high prevalence, it is unfortunate that OSA remains undiagnosed in up to 82% of women and 93% of men\(^4\).

Timely and successful management of OSA, such as with continuous positive airway pressure (CPAP), has been shown to significantly reduce the risk of both fatal and non-fatal cardiovascular events\(^5\). The Framingham study\(^6\) recognized several risk factors, such as age, sex, systolic blood pressure, total cholesterol, smoking behavior, and diabetes, whose interaction overtime produces cardiovascular disease. A risk function, which uses these risk factors has been developed, which produces an estimate of developing cardiovascular disease over a fixed time, such as the next 10 years\(^6\). Identification of these risk factors provides the basis for recommendations to lower the modifiable risk factors.

In spite of the well-established associations between OSA and cardiovascular diseases, cardiovascular risk factors are not routinely assessed during diagnosis or management of OSA. Similarly, OSA is not always suspected in patients with cardiovascular disease. Very few studies have associated OSA with cardiovascular events, and no large epidemiological studies have thus far been undertaken to study multiple cardiovascular risk factors in patients with OSA in the United States. Gilat et al\(^7\) studied 2797 patients with OSA for cardiovascular risk factors, but their study was performed entirely in Israel, which we believe differs from the United States in enough ways to warrant a similar study in the United States. The purpose of this study was to identify specific cardiovascular risk factors in patients with OSA
in the United States. Increased awareness of the existence of these risk factors should facilitate timely interventions of not only OSA, but also the associated cardiac risk factors, thereby leading to improvement of overall health of the patient.

Methods

Data for this project was obtained from the health records of patients at Altru Health System in Grand Forks, North Dakota. Altru Health System is the second largest healthcare provider and a level II trauma center in the state of North Dakota and serves a population of more than 225,000 from northeast North Dakota and northwest Minnesota.

We performed a case-control retrospective study of patients who were diagnosed with obstructive sleep apnea from January 1, 2009 to October 31, 2014. A case to control ratio of 2:1 was maintained. Diagnosis of OSA at Altru Health System is based on overnight polysomnography score of 5 or more on the apnea-hypopnea index. Cases were selected from the clinical database using ICD-9 code of 327.23 after comprehensive review of inpatient and outpatient records. Control population included randomly selected patients, matched for age, without a diagnosis of OSA in their clinical records.

The following data was collected from cases and controls: age, gender, BMI, weight, diabetes mellitus type II, hyperlipidemia, hypertension, ischemic heart disease, pulmonary hypertension, congestive heart failure, cardiomyopathy, atrial fibrillation, peripheral vascular disease, smoking status, carotid disease, and history of cerebrovascular attacks.

Our study was approved by the Institutional Review Boards of both the University of North Dakota and Altru Health System. SPSS 21.0 for Windows was used to analyze demographic and clinical characteristics of patients. Frequencies and relative percentages were computed for each categorical variable. Chi-square tests and Fisher’s exact tests were performed to determine which categories were significantly different from one another, and t-test and ANOVA were used to compare continuous variables. All p values were two-sided, and p value < 0.05 was considered to be significant. Missing data were excluded from analysis.

Results

During the study period, a total of 1105 subjects carried a diagnosis of obstructive sleep apnea. 2007 subjects from the same period were selected as controls, which led to a sample size of 3112 and a case to control ratio of 64.5% to 35.5%.

Of the 3112 subjects, 1798 (57.8%) were female and 1314 (42.2%) were male (Table 1). We found that cases were significantly less likely to be females (37.5% vs. 69%; \( p < 0.001 \)).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 3112)</th>
<th>Cases (n = 1105)</th>
<th>Controls (n = 2007)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1798 (57.8)</td>
<td>414 (37.5)</td>
<td>1384 (69)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1314 (42.2)</td>
<td>691 (62.5)</td>
<td>623 (31)</td>
<td></td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Normal or Overweight</td>
<td>1366 (43.9)</td>
<td>210 (19)</td>
<td>1156 (57.6)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1746 (56.1)</td>
<td>895 (81)</td>
<td>851 (42.4)</td>
<td></td>
</tr>
</tbody>
</table>

Three categories of Body Mass Index (BMI) were defined: normal (which includes underweight subjects) with a BMI < 25 kg/m\(^2\), overweight with a BMI between 25 kg/m\(^2\) and 29 kg/m\(^2\), and obese with
BMI > 29 kg/m². 482 (15.5%) of the subjects were determined to have normal BMI, 884 (28.4%) to be overweight, and 1746 (56.1%) to be obese. For the purposes of this study, normal and overweight subjects were combined into a single group (Table 1) and it was found that cases were significantly more likely to be obese (81% vs. 42.2%; p < 0.001).

Table 2. Presence of cardiovascular risk factors in patients with OSA and controls

<table>
<thead>
<tr>
<th>Cardiovascular Risk Factor, n (%)</th>
<th>Total (n = 3112)</th>
<th>Cases (n = 1105)</th>
<th>Controls (n = 2007)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>247 (7.9)</td>
<td>136 (12.3)</td>
<td>111 (5.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Carotid Disease</td>
<td>30 (1)</td>
<td>13 (1.2)</td>
<td>17 (0.8)</td>
<td>0.368</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>153 (4.9)</td>
<td>117 (10.6)</td>
<td>36 (1.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>842 (27.1)</td>
<td>440 (39.8)</td>
<td>402 (20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1784 (57.3)</td>
<td>520 (47.1)</td>
<td>1264 (63)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2040 (65.6)</td>
<td>724 (65.5)</td>
<td>1316 (65.6)</td>
<td>0.978</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>28 (0.9)</td>
<td>22 (2)</td>
<td>6 (0.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>154 (4.9)</td>
<td>134 (12.1)</td>
<td>20 (1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>61 (2)</td>
<td>27 (2.4)</td>
<td>34 (1.7)</td>
<td>0.149</td>
</tr>
</tbody>
</table>

A total of 247 subjects had a history of atrial fibrillation (AF) and cases were found to be significantly more likely to have suffered from this condition (12.3% vs. 5.5%; p < 0.001). Congestive heart failure was found in 153 subjects and was significantly more likely in patients with OSA (10.6% vs. 1.8%; p < 0.001). Diabetes mellitus was found in 842 subjects and patients with OSA were significantly more likely to be diabetic (39.8% vs. 20%; p < 0.001). Patients with OSA were also more likely to have suffered from ischemic heart disease (2% vs. 0.3%; p < 0.001). Smoking history was also more likely to be associated with cases (12.1% vs. 1%; p < 0.001).

However, there was at least one well-recognized cardiovascular risk factor, hyperlipidemia, which was found to be significantly less likely to be associated with cases (47.1% vs. 63%; p < 0.001).

There were also some cardiovascular risk factors which were not found to be significantly associated with OSA. Carotid disease was found in 1.2% of cases and 0.8% of controls and showed no significant association (p = 0.368) with OSA. Similarly, 65.5% of cases and 65.6% of controls had hypertension, demonstrating no significant association between OSA and hypertension (p = 0.978). Similarly, no significant association could be found between vascular disease and OSA (p = 0.149).

Three of the studied cardiovascular risk factors did not have sufficient prevalence to be analyzed for their association with OSA. Only one subject had pulmonary hypertension, one suffered from cardiomyopathy, and four from cerebrovascular attack(s). These risk factors will not be discussed further.

Discussion

Obstructive sleep apnea is a common disorder with many harmful associations and sequelae. It is characterized by intermittent and cyclic cessation of airflow during sleep, mediated by neurotransmitters. Its prevalence has substantially increased in the past two decades, yet many patients remain undiagnosed. Even in patients diagnosed with OSA, comorbidities are not always assessed. This is particularly concerning for cardiovascular comorbidities because successful management of OSA has been shown to improve cardiovascular disease as well.
Although the pathogenesis of cardiovascular consequences of OSA has not been completely established, several studies implicate intermittent hypoxia as the critical element responsible for immediate and long-term sequelae\textsuperscript{10}. A patient with OSA has at least five occurrences of apnea or hypopnea per hour and each of these occurrences results in hypoxia which resolves only upon arousal and subsequent restoration of airway patency. Morgan et al\textsuperscript{11} have long shown that each episode of hypoxia results in sympathetic activation via carotid chemoreflex stimulation. Xie et al\textsuperscript{12} have gone further to propose that systemic hypertension can be elevated due to this sympathetic activation. However, their study was based on a sample size of seven, and was performed on healthy individuals during wakefulness. Although the proposed mechanism by Xie et al\textsuperscript{12} does appear to logically follow from the study by Morgan et al\textsuperscript{11}, we did not find a significant association between OSA and systemic hypertension. We conclude that the association may not be present in all patients, or that it is a result of limitations of our study which are discussed below. It is also to be noted that Xie et al\textsuperscript{12} had a very small sample size.

We found a significant association of OSA with cardiovascular diseases such as ischemic heart disease that are a result of endothelial dysfunction. This parallels the findings of Kato et al\textsuperscript{13} who found impaired endothelial-mediated vasodilation in patients with OSA compared to matched controls. One possible mechanism that has been proposed to explain endothelial injury in cardiovascular diseases in the context of OSA is hypoxia mediated reduction of molecular oxygen resulting in the formation of free radicals and subsequent free radical-mediated endothelial damage. Ip et al\textsuperscript{14} generate some hope by finding that impairment of endothelial function is reversible. Further substantiating this mechanism, Grebe et al\textsuperscript{15} found that endothelial function improved significantly in patients with OSA after supplementation with vitamin C, which reduces hypoxia mediated endothelial damage.

In a review of heart failure in patients with OSA, Lyons and Bradley\textsuperscript{18} report that OSA contributes to heart failure by exposing the heart to intermittent hypoxia, increasing preload and afterload, initiating sympathetic nervous activity, and causing endothelial dysfunction. Our study found a significant association between OSA and congestive heart failure, corroborating the report. However, it remains to be determined whether successful management of OSA can in itself significantly reduce the morbidity and mortality due to congestive heart failure.

Although the pathophysiology of atrial fibrillation is not entirely understood, it is believed to entail an intricate interaction of triggers, substrates, and autonomic influences\textsuperscript{19}. Findings by Morgan et al\textsuperscript{11} that hypoxia results in sympathetic (autonomic) activation, which were discussed above, provide a possible etiology for the significant association we found between OSA and atrial fibrillation. Prystowsky et al\textsuperscript{19} categorize OSA as a reversible cause of atrial fibrillation and state that the number of episodes of atrial fibrillation can be reduced by modifying risk factors such as OSA.

Sleep deprivation and sleep fragmentation, which are characteristic features of OSA, have been shown to correlate with insulin resistance in obese individuals\textsuperscript{20}. These findings by Cizza et al\textsuperscript{20} substantiate our report of a significant association between OSA and diabetes mellitus type II, a disease that stems from insulin resistance.

Our study has identified several cardiovascular risk factors with significant associations with OSA in the United States, some of these associations were in deed different from what Gilat et al\textsuperscript{7} found in Israel. We hope that this knowledge empowers clinicians in this country to assess patients suffering from OSA for these specific factors, ultimately leading to improvement of overall health of the patient.

In spite of uncovering several associations supported by current literature, the present study has its own limitations. It suffers from a common shortcoming of retrospective studies where the reported associations cannot determine temporal relationships. Although we strongly believe that the current study is more representative of population in the United States than the study by Gilat et al\textsuperscript{7}, the sample for the present study was obtained from a single health system whose patients were drawn largely from a well demarcated geographic area. For our findings to be more representative of the general
population of the United States, we recommend expansion of our project to a multi-site or a multi-center study.

Acknowledgments

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References


