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Independent association of obstructive sleep apnea with Barrett's esophagus

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Abstract

Background and Aim: Current guidelines suggest screening at-risk groups of patients for Barrett's esophagus (BE), a precursor to esophageal cancer. Although BE and obstructive sleep apnea (OSA) have common risk factors, including elevated body mass index and gastroesophageal reflux disease (GERD), the relationship between these two conditions has not been well established.

Methods: Retrospectively, all patients who had undergone a polysomnography and esophagogastroduodenoscopy at West Virginia University Hospital from 2013 to 2018 were identified and divided into groups on the basis of the presence or absence of OSA. Clinical course and procedure reports were reviewed to identify relevant variables.

Results: One thousand ninety-one patients met inclusion criteria; 60.9% were female, and mean age of participants was 53.5 years. Univariate analysis revealed that male gender, age, diagnosis of OSA, severity of OSA, and a clinical diagnosis of GERD were associated with BE (P values < 0.05). Multiple logistic regression incorporating age, sex, clinical diagnosis of GERD, smoking history, body mass index, *Helicobacter pylori* status, and presence of hiatal hernia was utilized. Patients with OSA had an increased risk of BE than had those without OSA (P <0.001, odds ratio 3.26 [1.72–6.85]). The risk increased with increasing severity of OSA, categorized in apnea–hypopnea index increments of 10.

Conclusion: Obstructive sleep apnea is associated with BE, a relationship that is independent of other known risk factors. Additionally, this risk increases with increasing severity of OSA. Future efforts should determine if patients with severe OSA need to be screened for BE due to its potential for causing esophageal cancer.

Keywords

Barrett's esophagus; esophageal adenocarcinoma; obstructive sleep apnea

Introduction

Prior studies have identified male gender, increasing age, obesity, and, most importantly, chronic gastroesophageal reflux disease (GERD) as the risk factors associated with the

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development of Barrett's esophagus (BE).[1] Chronic exposure of the distal esophageal mucosal lining to acid reflux induces metaplastic change, which then predisposes the individual to the development of esophageal adenocarcinoma. BE is a mostly asymptomatic condition, and given its potential for malignant transformation, it is usually diagnosed by screening populations at high risk.[2]

Obesity has been linked to the development of BE both through GERD-mediated and GERD-independent mechanisms. By increasing intraabdominal pressure and thus worsening GERD, obesity can prolong exposure of the distal esophageal lining to acid reflux, increasing the risk of BE.[3,4] Conversely, obesity, especially central adiposity, can also induce metaplastic change by GERD-independent mechanisms that comprise an increase in inflammatory milieu with resultant predisposition to metaplasia, as evidenced by increased BE in the absence of reflux.[5,6]

Obstructive sleep apnea (OSA) is becoming increasingly recognized as a widely prevalent disease.[7] OSA shares many risk factors with GERD and BE including advancing age,[8] obesity,[9] and male gender.[10] Although OSA may worsen reflux in patients, a causal relationship between OSA and GERD has yet to be established. Evidence supports both an association of symptoms of OSA with BE that is GERD mediated[11] and one that is independent of gastroesophageal reflux.[12] Thus, it appears that any possible association between OSA and BE in the context of this complex interplay of confounding variables (obesity and GERD) has not been sufficiently explored. We conducted a retrospective case–control study to explore whether OSA is a risk factor for BE and whether this relationship is independent of obesity, GERD, and other known risk factors of BE.

Methods

A retrospective chart review was conducted at West Virginia University Hospital. All patients who underwent a polysomnography from January 2013 to December 2018 and subsequently underwent an esophagogastroduodenoscopy (EGD) were screened for inclusion. Patients were included if they were older than 16 years and whose records included the variables as discussed subsequently. Patients were excluded if the EGD was conducted for an emergent indication that did not allow assessment of BE. Patients with unavailable pathology reports were also excluded from analysis.

Patients were identified using relevant procedure codes from the electronic patient database at West Virginia University Hospital. Data, including demographic characteristics, age, gender, body mass index (BMI), and smoking history, were extracted by two study personnel. Polysomnography reports and EGD procedure reports were then reviewed to ascertain the diagnoses of OSA and BE. Apnea–hypopnea index (AHI) at the time of diagnosis of OSA was noted. BMI of greater than 30 was used as a surrogate marker for central adiposity. The presence of GERD was defined as a documented clinical diagnosis of GERD. In the case of multiple available EGDs, all were reviewed to assess for evidence of BE. The diagnosis of BE was confirmed only in the presence of pathologic confirmation of intestinal metaplasia. Both biochemical-based and EGD-based *Helicobacter pylori* tests

were reviewed. OSA was diagnosed with evidence of AHI of 5 in the presence of symptoms consistent with the disease and AHI greater than 15 in the absence of such symptoms.

The study was reviewed and approved by the institutional review board at West Virginia University before commencement. RedCap software was used for data aggregation,[13] and subsequent statistical analyses were carried out on R statistical software.[14] Data were presented as means and standard deviations (SDs) for continuous variables and as frequencies and proportions for categorical variables. Chi-square and *t* test univariate analyses were conducted to identify variables associated with BE, and associated variables were then incorporated into a multivariable logistic regression model to control for confounders and assess for independent associations. A separate multivariable regression was then fitted that incorporated increasing severity of OSA as reflected by AHI increments of 10 to explore any possible relationship between severity of OSA and Barrett's disease. A separate multivariable model was employed in which OSA was subcategorized as mild, moderate, and severe, based on AHI values of 5 to 15, 15 to 30, and greater than 30, respectively.

Results

A total of 1187 patients underwent both a polysomnography and an EGD during the study period. One thousand ninety-one patients were included after removing patients with incomplete records or emergent procedures. The mean age of study participants was 53.5 years (SD 12.2); 60.9% of the participants were female. Three hundred sixty-three participants (33.4%) were smokers. Seven hundred nine participants (72.6%) were taking proton pump inhibitors at the time of EGD, and 148 participants (15.2%) were taking histamine receptor antagonists. Characteristics of the population are discussed in Table 1.

The mean BMI was 36.5 (SD 9.11). OSA was diagnosed in 74.7%, and BE was diagnosed in a total of 107 participants (9.8%). Univariate analysis revealed that gender, age, OSA, and a clinical diagnosis of GERD were associated with BE (*P* values < 0.05) (Table 2).

Multiple logistic regression was then utilized, incorporating age, gender, a clinical diagnosis of GERD, smoking history, BMI (in incremental categories of 5), and presence of hiatal hernia, to explore the relationship between OSA and BE. Patients diagnosed with OSA on polysomnography had an increased risk of BE ($P < 0.001$), odds ratio 3.24 (95% CI: 1.71–6.81). Age, gender, and the clinical diagnosis of GERD were also independently associated with BE (Table 3).

In a separate multivariable regression model where OSA was graded in AHI increments of 10, an increased risk for BE with every 10-point increase in AHI was found (OR 1.10, 95% CI: 1.02–1.19). BMI, evaluated in increments of 5, was not associated with BE. The association of OSA with BE remained unchanged in a separate model incorporating a binary variable with BMI of greater than 30 used as a surrogate for central adiposity.

In a separate multivariable model, OSA was subcategorized as mild, moderate, and severe, based on AHI values of 5 to 15, 15 to 30, and greater than 30, respectively. An increased risk

of BE was found with increasing severity of OSA in this model as well (OR 1.38, 95% CI: 1.13–1.69).

Discussion

Obstructive sleep apnea has been explored in various studies in the context of GERD. Apneic events can cause negative intrathoracic pressures, postulated to precipitate reflux.[15] Small studies of esophageal pH monitoring in patients with OSA demonstrated prolonged esophageal acid exposure times.[16] On the contrary, compensatory changes in the gastroesophageal junction may prevent reflux during these episodes. Although some data suggest a decrease in reflux events with OSA treatment,[17] there is no consistency regarding temporal associations between apneic episodes and reflux events.[12,18] A study using high-resolution manometry, pH–impedance reflux monitoring, and polysomnography concurrently showed that physiological compensations adequately prevented reflux during apneic episodes.[19] However, factors such as central obesity elevate the risk for BE, at least partly, by GERD-independent mechanisms. This risk enhancement has been postulated to be mediated by inflammatory moieties that are upregulated by obesity. It is to be noted that OSA has been extensively reported to cause oxidative stress and a significant increase in pro-inflammatory cytokines.[20,21] Such a state may lead to a similar GERD-independent increase in Barrett's risk and may explain our findings.

We have found that OSA is associated with BE, and this risk is independent of BMI and GERD. In order to control for BMI-related Barrett's risk associated with obesity, we incorporated 5-point increments of BMI as a covariate in our regression model. As employed by Leggett *et al.*,[12] we also fitted a separate regression model with BMI in excess of 30 as a surrogate marker for central obesity, to control for confounding by GERD-independent Barrett's risk posed by central obesity, but the association between OSA and BE remained unchanged.

The captured cohort likely reflects a higher risk population, as our tertiary care facility is the main referral center for a large underserved catchment area, as reflected in the high rate of Barrett's disease and OSA diagnosis on the respective modalities. The studied population was markedly obese, as evidenced by a mean BMI greater than 30. However, the association of OSA with BE remained unchanged after controlling for BMI.

Helicobacter pylori has also recently garnered much debate as a likely environmental agent that influences both GERD and BE.[22,23] Interestingly, some authors have additionally reported associations between *H. pylori* infection and OSA[24] and associate this pathogen with some inflammatory and metabolic changes seen in OSA. The previous report of BE in the setting of OSA lacked evaluation for *H. pylori*. We additionally controlled our data for *H. pylori*, with no change in association between OSA and BE. Furthermore, in recent studies, *H. pylori*'s role in BE, if at all any, has been observed to be mostly protective.[23]

Regardless of the pathophysiological mechanism responsible for this observed elevated risk of BE in OSA (GERD mediated *vs* GERD independent), treatment of OSA should theoretically mitigate this risk, as both nocturnal reflux and the hypoxia-mediated pro-

inflammatory state show significant abatement with the introduction of continuous positive airway pressure therapy. However, this risk mitigation is yet to be studied by comparing the Barrett risk in the treated and untreated populations of OSA patients. No study in current available scientific literature has assessed the risk of BE in treated *versus* untreated OSA patients. Further prospective studies are needed to establish if the risk of BE in patients with OSA is decreased after they have been adequately treated for their OSA.

The strengths of our study include a large sample size and control for all possible confounders, including those of hiatal hernia and *H. pylori*, which have not been previously studied in this context. Further, the association between OSA and BE remained significant with incremental changes in AHI, lending credence to the notion of a causal association. This association may be clinically relevant when risk stratifying patients for BE screening. One limitation of our study is the lack of anthropometric measurements available in our data, which would allow for a more robust definition of central obesity; however, this poses only a small risk of confounding, as previous studies have reported a BMI of greater than 30 to be an acceptable marker for central obesity and visceral fat.[25,26] We could not study the pathophysiological mechanisms responsible for this association due to the nature of the study.

Conclusion

We provide evidence that OSA is associated with an increased risk for developing BE, with the risk increasing with worsening severity of OSA. This association may be of clinical significance when deciding to perform screening for BE, in patients with comorbid severe OSA.

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Table 1

Characteristics of study population

Variable	Total: *n* (%)	Patients with OSA	Patients without OSA
Gender			
Male	427 (39.1%)	356 (44%)	71 (25.2%)
Female	664 (60.9%)	453 (56%)	211 (74.8%)
Smoking history	363 (33.4%)	249 (30.78%)	114 (40.42%)
Age	53.5 years (SD 12.2)	54.4 years (SD 11.62)	50.92 years (SD 13.43)
Diagnosis of GERD	570 (52.2%)	415 (51.3%)	155 (54.96%)
PPI use	709 (72.6%)	519 (64.15%)	190 (67.38%)
H2 receptor antagonist use	148 (15.2%)	99 (12.24%)	49 (17.38%)
Hiatal hernia	313 (28.69%)	229 (28.31)	84 (29.79%)

GERD, gastroesophageal reflux disease; OSA, obstructive sleep apnea; PPI, proton pump inhibitor.

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Table 2

Univariate analyses

Variable	Patients with Barrett's esophagus *n* (%)	Patients without Barrett's esophagus *n* (%)	Univariate analysis (*P* value)
Male gender	58 (54.21%)	369 (37.50%)	<0.01 †
Age (mean ± SD)	57.74 ± 10	53.06 ± 12.34	<0.01 †
BMI (mean ± SD)	36.15 ± 8.21	36.56 ± 9.20	0.403
Obstructive sleep apnea	97 (90.65%)	712 (72.36%)	<0.01 †
Clinical diagnosis of GERD	69 (64.49%)	501 (50.91%)	0.010 †
Smoking status	38 (35.51 %)	325 (33.03%)	0.682
Helicobacter pylori positivity	7 (6.54%)	48 (4.88%)	0.607
Hiatal hernia	33 (30.84%)	280 (28.46%)	0.685
Presence of central adiposity (BMI > 30)	86 (80.37%)	757 (76.93%)	0.493
Severity of OSA (AHI increments of 10)			0.018 †

† Denotes significance.

BMI, body mass index; GERD, gastroesophageal reflux disease; OSA, obstructive sleep apnea.

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Table 3

Multivariate analysis

Variable	Univanate analysis *P* value	Multiple variable analysis OR (95% CI)	*P* value
Male gender	<0.01†	1.71 (1.13–2.59)	0.012
Age	<0.01†	1.04 (1.02–1.06)	<0.01
BMI (increments of 5)	0.403	0.997 (0.88–1.13)	0.96
Smoking status	0.682	1.09 (0.69–1.68)	0.71
Obstructive sleep apnea	<0.01†	3.26 (1.72–6.85)	<0.01
Hiatal hernia	0.685	0.98 (0.62–1.53)	0.939
GERD	0.010†	2.23 (1.45–3.49)	<0.01
Helicobacter pylori positivity	0.607	1.39 (0.55–3.09)	0.44

†Denotes significance.

BMI, body mass index; GERD, gastroesophageal reflux disease.