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Symptoms of gastro-oesophageal reflux disease and the severity of obstructive sleep apnoea syndrome are not related in sleep disorders center patients

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SUMMARY

Background: Studies suggest obstructive sleep apnea syndrome (OSAS) frequently manifests in patients with gastroesophageal reflux disease (GERD) and that there may be a causal relationship.
Aim: To determine the relationship between OSAS and symptoms of GERD.
Methods: Consecutive patients referred to the Sleep Disorders Center (SDC) 18 years and older with polysomnographically defined OSAS were evaluated prospectively for GERD using a validated symptoms questionnaire. The GERD and OSAS relationship was assessed by 1) determining frequency of GERD in patients with and without OSAS; 2) ascertaining the relationship between OSAS severity categories and presence of GERD; 3) examining GERD score in relation to those factors that might affect both GERD and OSAS, e.g. obesity.
Results: One thousand and twenty-three SDC patients met entry citeria. Amongst participants, GERD was common (29% of women and 17% of males) and OSAS extremely common (58% of women and 80% of males). GERD score did not correlate with OSAS variables. The severity of OSAS did not influence the prevalence of GERD.
Conclusion: In a large group of patients referred to a sleep disorders center, there was no relationship between OSAS and GERD symptoms. Also, there was no relationship between the severity of OSAS and the likelihood of GERD symptoms.

INTRODUCTION

Clinicians and interested researchers disagree whether or not obstructive sleep apnoea syndrome (OSAS) causes gastro-oesophageal reflux disease (GERD). In a 1989 letter, Samelson suggested that the negative intrathoracic pressures generated during obstructive apnoea events precipitated reflux.[1] A year later, Diaz *et al.* reported that five OSAS patients treated with continuous positive airway pressure (CPAP) administration manifested improvement in GERD.[2] In 1992, a study using both a 24-h pH monitor and polysomnography in six OSAS patients with night-time GERD found that both OSAS and GERD improved after the administration of nasal CPAP thus supporting the hypothesis of an OSAS—GERD cause–effect relationship. However, the authors could not establish a specific linkage between GERD and apnoea events.[3]

More recent studies[4–8] showed that OSAS patients frequently manifest GERD, but did not establish a cause–effect relationship. For example, Ing *et al.*[6] determined that OSAS patients manifested more reflux and greater time with an oesophageal pH below 4.0. However, respiratory events preceded only 11% of the reflux events. In addition, the putative OSAS–GERD

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cause–effect relationship is questioned by a recent study of 228 patients. This study paired a validated GERD questionnaire and nocturnal oximetry desaturations (as a proxy for apnoeic and hypopnoeic events) to investigate the relationship between OSAS and GERD.[9] The authors found no relationship between these surrogate measures of GERD.

To date, studies have manifested flaws such as a small number of subjects, lack of complete polysomnography, as well as the inherent difficulty in assessing GERD. GERD is defined as '…any symptomatic clinical condition or histopathological alteration resultant from episodes of GER'.[10] Unfortunately, no unassailable gold standard exists for the diagnosis of GERD. One candidate, the expensive and relatively invasive 24-h pH probe testing, has problems with sensitivity and reliability.[11] For example, two studies revealed that 22 and 26% of patients with upper endoscopy documented erosive oesophagitis manifested normal 24-h pH probe test results.[12, 13] Finally, in clinical practice the 24-h pH probe is not indicated for the routine evaluation of GERD but instead for the diagnosis of atypical symptomatology and for the assessment of subjects considering antireflux surgery.[14] Upper endoscopy also suffers flaws as a tool for diagnosing GERD.[14]

However, multiple investigators do note the validity of establishing GERD on the basis of symptoms.[15–17] In fact, clinicians typically diagnose and treat patients with GERD on just such clinical grounds. Therefore, this study used a succinct validated questionnaire specifically designed for the diagnosis of GERD[18] in a large number of consecutive Sleep Disorders Center (SDC) patients completing full polysomnography. The authors hypothesized that using a validated GERD questionnaire and polysomnography (the gold standard for the diagnosis of OSAS) would provide data bolstering the contention that OSAS causes GERD.

MATERIALS AND METHODS

Study population

The investigators selected the study population from 1342 consecutive patients referred to the Eastern Virginia Medical School/Sentara Norfolk General Hospital SDC. Included subjects were new SDC patients ≥18 years of age, who completed study questionnaires as well as a diagnostic polysomnogram. Those patients previously diagnosed with OSAS were excluded from the study. The Institutional Review Board at Eastern Virginia Medical School approved the study.

Study design and data collection

All patients underwent a standard history and physical examination including review of medications and computation of body mass index (BMI).

Before PSG (a study of sleep that incorporates electroencephalography, electro-oculography, electromyography, respiratory and cardiac monitoring), patients completed a brief 10-item GERD questionnaire that was the sole tool used to diagnose GERD in this study.[18] The questionnaire addresses both frequency and severity of GERD symptoms. This scale was developed utilizing content validation via literature review, expert opinion, patient interviewing and extensive psychometric evaluation. Additional validation included convergent and predictive accuracy against doctor diagnosis. Research on this questionnaire identified a score of 15.5 or greater (S. Adlis, 2001, personal communication) as indicating GERD (from a range of 0–50).

Doctors ordered polysomnograms as indicated by the patient's intake interview and physical examination. The polysomnogram determined the presence and severity of OSAS. The apnoea hypopnoea index (AHI) was defined as the number of apnoea and hypopnoea events per hour. The complete cessation of airflow for 10 or more seconds defined apnoea. Hypopnoea events were characterized by a 50% decrement in airflow and 2% desaturations. The investigators defined OSAS by an AHI of 10 or greater. OSAS was subcategorized as mild, 10–19 events/h; moderate, 20–39 and severe, ≥40. Diplomates of the American Board of Sleep Medicine reviewed and interpreted all polysomnograms. During a follow-up office visit after the polysomnogram, the investigators reviewed the study results and discussed treatment options with patients.

Statistical analysis

Statistical analyses were completed using the statistical software program (SPSS, Chicago, IL, USA). Non-normally distributed data (AHI and the GERD score) were transformed using 1+ natural log of AHI and the GERD score. Untransformed mean values are used in the paper while the statistical values are from the results using the transformed data. The relationship between OSAS and GERD was examined in several ways. We examined the

Pearson correlation on the transformed data and examined the Spearman's rho correlation between the GERD score and OSAS frequency [including supine and rapid eye movement (REM) sleep events] on the untransformed data. The GERD score was examined in relation to factors that might affect GERD and OSAS including age, BMI and the use of antireflux medications. Using an ANOVA, the relationship between severity categories of OSAS and the presence of GERD was analysed. Finally, the investigators computed a linear regression analysis with variables potentially related to GERD, i.e. age, BMI, caffeine use, alcohol intake, non-steroidal anti-inflammatory drugs (NSAIDS), AHI, arousal index, supine AHI, REM sleep AHI and smoking.

RESULTS

Study subjects description

A total of 1023 subjects completed the study. Gender, ages, BMI, GERD scores and AHI for the analysed groups are in Table 1. There was no difference in age between men and women. Both men and women were obese as defined by a BMI $\geq$ 30 kg/m^2 with the women having a greater BMI than men ($t = 4.91$, d.f. = 1022, $P < 0.001$).

About 71% of the study group had OSAS. Of the men, 80% had OSAS ($n = 491$) while of the women 58% had OSAS ($n = 235$; $\chi^2 = 55.9$, d.f. = 1, $P < 0.001$). Male subjects manifested a higher AHI (Table 1; $t = 8.64$, d.f. = 1021, $P < 0.001$). In contrast to the apnoea diagnosis, 29% of women and 17% of men had a GERD score of $\geq$15.5. Women (mean = 10.7 $\pm$ 11.7) scored higher than men (mean = 6.9 $\pm$ 8.8; $t = 5.94$, d.f. = 1021, $P < 0.001$).

Table 1. Number, sex, age, BMI, AHI and GERD score of study subjects

	N	Age (year)	BMI (kg/m^2)	AHI	GERD
Total	1023				
Mean		49.3	35.4	33.4	8.4
s.d.		12.5	8.6	31.9	10.2
Median		48.0	34.0	22.4	5.0
Men	617 (60%)				
Mean		49.6[1]	34.4[2]	40.1[3]	6.9[4]
s.d.		12.4	7.5	32.9	8.8
Median		49.0	33.0	30.9	3.3
Women	406 (40%)				
Mean		49.0	37.0	23.1	10.7
s.d.		12.5	9.9	27.2	11.7
Median		48.0	35.0	13.0	7.0

AHI, apnoea hypopnoea index; BMI, body mass index; GERD, gastro-oesophageal reflux disease.
[1] Difference in age between men and women was not significant.
[2] Women had a greater BMI than men ($P < 0.001$).
[3] Men had more frequent apnoea events than women ($P < 0.001$).
[4] Women had higher GERD scores than men ($P < 0.001$).

Correlations with GERD scores with Bonferroni corrections

Age did not correlate with GERD ($r = -0.022$). There was a small positive correlation with BMI ($r = 0.089$, $P < 0.05$). Over all subjects, the GERD score did not significantly correlate with sleep apnoea variables (overall AHI, supine AHI, REM sleep AHI, maximum apnoea duration or arousals from sleep).

No significant correlation existed between GERD and alcohol use, smoking and caffeine use. Positive correlations occurred between GERD and antireflux medication use [antacids, $r = 0.090$; H_2-blockers, $r = 0.179$; proton-pump inhibitors (PPIs), $r = 0.246$ and prokinetic agents, $r = 0.117$]. These were all significant at a probability of <0.05 or better. Use of NSAIDs had a slight but significant positive correlation with GERD ($r = 0.090$). Also, those with higher GERD scores took more GERD medications. The score increased from 6.3 $\pm$ 8.7 for those taking no medication ($n = 726$), to 13.1 $\pm$ 11.6 for those taking one GERD medication ($n = 272$), to 19.0 $\pm$ 11.8 for those taking two or more GERD medications ($n = 25$; F = 65.4, d.f. = 2, $P < 0.001$).

Group overlap

Figure 1 demonstrates that OSAS severity was not related to the percentage of patients with GERD (Pearson $\chi^2 = 2.349$, d.f. = 3, $P = 0.503$), i.e. there was no increase in the percentage of patients with GERD symptoms as the severity of apnoea increased. Although the majority of our patients had OSAS (71%), only 22% had GERD and only 15% of our patients had both GERD and OSAS (Pearson $\chi^2 = 2.376$, d.f. = 3, $P = 0.498$). Likewise, there was no relationship between the use of GERD medications and the severity of OSAS (Table 2).

Regression

A binary logistic regression using the sleep-respiratory variables in addition to age, BMI, caffeine use, alcohol use, smoking and NSAID use indicated a relatively low

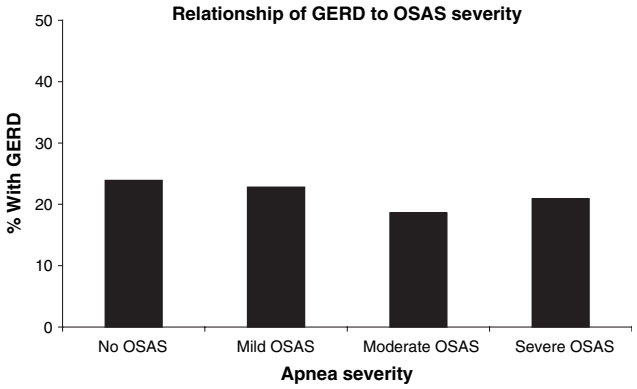

Figure 1. Percentage of patients with gastro-oesophageal reflux disease (GERD) and obstructive sleep apnoea syndrome (OSAS). There was no relationship between the percentage of patients with GERD and the severity of OSAS (Pearson $\chi^2 = 2.37$, d.f. = 3, $P = 0.49$).

Table 2. GERD Medication and OSAS severity

	No OSAS	Mild OSAS	Moderate OSAS	Severe OSAS
No GERD Rx (%)	76.1	77.2	81.4	79.1
GERD Rx (%)	23.9	22.8	18.6	20.9
N	297	180	226	320

No apnoea, AHI < 10; mild, AHI = 10–19.9; moderate, AHI = 20–39.9; severe AHI ≤ 40.
GERD, gastro-oesophageal reflux disease; OSAS, obstructive sleep apnoea syndrome; Rx, medications.

r^2 of 0.038. The only significant predictor was BMI ($P = 0.014$). None of the sleep apnoea variables predicted GERD.

To address the possibility that a GERD–OSAS relationship might occur solely in those with the largest BMI, we stratified the study participants into four BMI groups: (i) normal (BMI: <25 kg/m^2); (ii) overweight (BMI: 25–29.9 kg/m^2); (iii) obese (BMI: 30–39.9 kg/m^2) and (iv) severely obese (BMI: ≥40 kg/m^2). Using an ANOVA, we determined that there was no three-way interaction among these variables, i.e. there was no relationship to the presence of GERD at any BMI group for either men or women (F = 0.319, d.f. = 3, 1007, P = N.S.). In addition, there was no two-way interaction between the presence of GERD and gender (F = 0.537, d.f. = 1, 1007, P = N.S.) or between the presence of GERD and BMI group (F = 0.996, d.f. = 3, 1007, P = N.S.).

The difference between men and women in sleep apnoea became most marked in the largest BMI group. That is it was males who were apt to display the most severe sleep apnoea. This was reflected in a gender by BMI interaction (F = 3.460, d.f. = 3, 1007, P = 0.016).

DISCUSSION

A plausible and perhaps intuitive hypothesis is that OSAS causes or exacerbates GERD. The large negative intrathoracic pressures generated during apnoeic events may draw gastric contents into the oesophagus, particularly in the context of arousals and movements that accompany respiratory instability. Previous work has indeed demonstrated nocturnal GER events during sleep to follow short-lived arousals.[19] An auxiliary hypothesis is that even small amounts of refluxed material might lead to a swallow with subsequent reduction in lower oesophageal sphincter pressure and larger amounts of reflux.[3] Data do demonstrate that OSAS patients frequently have GERD and more than one study has demonstrated that CPAP treatment attenuates GERD. A recent study in a large group of patients not only demonstrated improvement in GERD with the application of CPAP but also a weak relationship between AHI and nocturnal reflux.[20] As noted previously, the working hypothesis of the present study was that patients with OSAS would be more likely to have GERD and that OSAS was likely a causative factor.

The results of this study however, run counter to the argument that OSAS and symptoms of GERD are related. In over 1000 SDC patients, there was no correlation between the presence or absence of GERD and OSAS. Additionally, there was no evidence for an increased likelihood of GERD with increasing severity of the AHI. This was despite increasing BMI with increasing AHI, a trend that could have predisposed subjects to an increased likelihood of GERD. As an example, one study of over 1500 Olmstead County residents demonstrated a BMI >30 kg/m^2 to be associated with an increased risk for GERD symptoms.[17]

A causal relationship between these two common syndromes should have eventuated in an increased frequency of GERD overall in OSAS subjects when compared to those without OSAS. In addition, it is plausible that with increasing severity of OSAS, more GERD would have occurred in a dose–response relationship. Again, this was not found. Finally, it is of interest that men were less likely than women in our study to have GERD. This could have been due at least

in part to our women subjects manifesting a higher BMI. This reduced likelihood of GERD in men was in spite of the fact that their AHI was higher than women.

Antireflux medications such as PPIs could reduce GERD scores and hence potentially confound this study. If the use of medications was in fact masking GERD symptoms in GERD patients with OSAS, then a positive correlation with OSAS should have been found. This however was not the case. In fact, more patients without sleep apnoea than with sleep apnoea were taking GERD medications (Table 2).

Our results are consistent with other pertinent reports. For example, one previously noted study,[4] did not find a relationship between severity of OSAS by AHI and GERD as documented by pH probe. A more recent investigation with 228 patients also utilizing a validated questionnaire (GERQ) did not establish a relationship between OSAS and GERD.[9] Finally, as in this study recent work also utilized both polysomnography and a validated GERD questionnaire (GERD Symptom Checklist) to investigate OSAS and GERD. In 136 patients, the authors stated that their data '…failed to show a causal link between GERD and OSA'.[21] Thus when one includes this study, three different studies utilizing three different validated questionnaires comprising some 1387 patients have not found a correlation between OSAS and GERD. The strengths of the present study are that it uses a validated GERD questionnaire, diagnoses OSAS according to the 'gold standard', the nocturnal polysomnogram, and that it is the largest study to date. The authors believe that the GERD symptomatology in OSAS patients may stem from promoting factors such as obesity (via increased intra-abdominal pressure) and perhaps the use of alcoholic beverages (although in our study no such relationship was found).[22] Men and women in this study were obese and in fact the mean BMI for those with an AHI of >40 almost reached severe obesity at 39 kg/m^2. Interestingly, a recent study using a validated gastrointestinal (GI) questionnaire revealed that the severely obese (mean BMI 47.8 kg/m^2) noted more severe GI symptoms including GERD.[23]

Although CPAP improves GER and suggests that OSAS could be causative of GERD, it is possible that CPAP operates through different mechanisms to improve apnoea and GERD. CPAP both increases intrathoracic pressure and may increase lower oesophageal sphincter pressure.[24] In the second instance, CPAP may work to alleviate GERD through a mechanism that would have little to do with OSAS. In addition, one study has demonstrated that CPAP reduces regurgitant reflux in achalasia, an unrelated illness to OSAS.[25] Finally, Kerr *et al.* have shown that GERD is reduced by CPAP in patients without OSAS.[24] The causal link between OSAS and GERD because CPAP attenuates both pathological events is therefore, tenuous.

A potential criticism of this study would be that all patients were referred to the SDC, i.e. no subjects from the general population were studied. However, an unselected Olmstead County population manifested a prevalence of weekly or greater GERD symptoms of 19.8%[26] similar to this study. In addition, a study by Valipour *et al.* of consecutive sleep disorders patients[9] found a prevalence of weekly or greater GERD symptoms of 23.2%. In a study of 1000 primary care adult patients from our catchment area, 24% admitted to symptoms of GERD.[27] Some other studies have found a higher percentage of GERD symptoms. For example, two studies noted frequencies of GERD in OSAS of 60[9] and 62%.[13] However, these studies asked for symptoms within the last 12 and 6 months while the validated questionnaire in this study asked for GERD symptoms within the last 4 weeks.

A recent report did use a validated questionnaire and suggested that there was a significant correlation of GERD symptoms and the AHI.[28] This study however, was relatively small (94 total patients; 26 patients with OSAS and reflux symptoms present). The potential for type 1 error is readily apparent, especially given that the association of OSAS and GERD was not the primary intent of the study.

It is also worth noting that from the standpoint of BMI, this study's population was not grossly dissimilar from the general medical population. Recent work by the authors that obtained 1000 primary care patients from this same south-eastern Virginia referral community revealed a mean BMI of 30.2 kg/m^2.[27] At least from the standpoint of weight (a risk factor for both GERD and OSAS) both study patients and our primary care patients in this community would be identified as obese under current National Institutes of Health guidelines. Nevertheless a large-scale study investigating OSAS and GERD that also includes normal controls would be of interest.

Potentially this study would have been strengthened by the use of a 'more objective' measure such as the 24-h pH probe or upper endoscopy. However, in a study of this size large-scale use of such a measure would not be feasible and again gastroenterologists do not agree

that there is a 'gold standard' in the diagnosis of GERD.[12] The authors recognize that this study did not replicate the previously alluded findings of Green *et al.*[20] that demonstrated a weak relationship between AHI and reflux. However, that study did not utilize a validated questionnaire to assess GERD although it used 'widely accepted' terminology. Finally, a recent small study using the 24-h pH probe and polysomnography revealed a correlation between severity of OSAS and the percentage time oesophageal pH measured <4. However, only 7% of reflux episodes occurred during sleep and the timing of respiratory and reflux events did not correlate.[29] Despite the findings of this study it remains possible that a subgroup of OSAS patients do suffer increased GERD as a consequence of their sleep disordered breathing. Symptoms of GERD and histological findings do not always correlate. It is recognized that there is a lack of correlation of the severity of symptoms of GERD and the severity of acid exposure or related erosive oesophagitis. Given that this study uses a validated symptom assessment for GERD rather than pH measurement, we are unable to comment as to potential differences for acid contact time in OSAS patients.[30, 31] Further work using both validated GERD questionnaire and 24 h pH probe testing would be enlightening.

In conclusion, this study indicates that OSAS is not associated with GERD as defined by symptoms. Shared risks such as obesity probably explain the fact that patients with OSAS frequently note symptoms of GERD. Nevertheless, adult patients with both OSAS and GERD may have both syndromes respond to the administration of nasal CPAP. The authors recognize that CPAP is not a validated treatment for GERD. However, a well done population-based study has reported that 2% of women and 4% of men aged 30–60 years have OSAS.[32] In addition, researchers utilizing a validated questionnaire have determined that approximately 58% of Olmstead County, MN, USA adult subjects admitted to reflux at some time in the past year and over 19% at a weekly or greater frequency.[25] Therefore, given the complications of GERD and the costs entailed in the use of long-term PPIs, this ancillary benefit of CPAP may not be trivial.

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