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Gastroesophageal Reflux Disease and Sleep Disorders: Evidence for a Causal Link and Therapeutic Implications

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Abstract

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Gastroesophageal reflux disease (GERD) and sleep disturbances are both common health problems. There is a significant association between disturbed sleep and GERD, and this may be bidirectional. Sleep disorders may induce gastrointestinal (GI) disturbances, while GI symptoms also may provoke or worsen sleep derangements. Reflux of gastric acid is a less frequent event during sleep, however, acid clearance mechanisms (including swallowing, salivation and primary esophageal motility) are impaired during sleep resulting in prolongation of acid contact time. Nighttime reflux can lead to sleep disturbance and sleep disturbance may further aggravate GERD by prolonged acid contact time and heightened sensory perception. This may facilitate the occurrence of complicated GERD and decreased quality of life. However, the interplay between sleep problems and GERD is complex, and there are still relatively limited data on this issue. Further investigation of sleep-related GERD may identify common pathophysiological themes and new therapeutic targets.

Keywords: Sleep, Gastroesophageal reflux disease

Introduction

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Gastroesophageal reflux disease (GERD) is a common and chronic condition. At least 20% of adults in the United States report having heartburn once a week or more.[1,2] Insomnia is a symptom describing difficulty initiating or maintaining sleep, or the experience of nonrefreshing sleep, and is also a very common condition; about 10% of adults in the United States report having sleep insufficiency.[3]

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At least 50% of patients with sleep disturbance seen in primary care practices have comorbid conditions.[3] Specifically, Taylor et al.[4] found a higher prevalence of gastrointestinal (GI) problems in those with chronic insomnia compared with those without insomnia (33.6% vs. 9.2%; Odd ratio (OR) 3.33, 95% confidence interval (CI), 1.83-6.05). Among patients with frequent heartburn, the majority reported difficulties initiating sleep or maintaining sleep through the night. Sleep disturbances can have a significant impact on an individual's health and quality of life,[5] resulting from decreased daytime functioning.

In this review, we aimed to address the complex relationships between GERD and sleep. We wished to address the following questions: (1) Does GERD contribute to the development of sleep disturbance, or vice versa? (2) If there is a significant association, is it explained by confounding or other comorbidities? (3) What physiological evidence supports a causal link? (4) Should coexisting sleep derangements in GERD change specific treatment strategies?

Systematic literature reviews, with defined inclusion and exclusion criteria, were conducted to identify the available evidence to support each statement. Literature searches were conducted in English language publications in Medline, confined to human subjects in the past 5 years. We included the following keywords in our search including "gastroesophageal reflux" or "gastroesophageal" and "reflux" or "gastroesophageal reflux" or "GERD" and "sleep". We excluded non-English language trials or studies in pediatric or adolescent patients, or meeting abstracts. Symptomatic GERD had to be diagnosed by a symptom questionnaire or by a physician. Reflux esophagitis was defined by upper endoscopy.

1. Is GERD associated with the development of sleep disturbance or vice versa, and is a link explained by confounding or comorbidities?

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Sleep disturbances are common; so are GI symptoms. Is there really an association or is this observation due to chance? Recent epidemiologic studies have revealed a significant association between GERD and sleep disturbance indicating this is not a chance finding.

1) Prevalence of sleep disturbances among patients with GERD

Several epidemiologic studies have shown that nighttime heartburn is prevalent and that individuals who experience nighttime heartburn have associated sleep disturbances resulting in alterations in daytime performance (Table 1, Fig. 1).[6-16] A large population-based, cross sectional study based on 2 large health surveys of 1984-1986 and 1995-1997 was performed in 65,333 participants (70% of adult population) in Norway.[6] They found an association between GERD symptoms and sleep problems, including insomnia (OR, 3.2; 95% CI, 2.7-3.7), sleeplessness (OR, 3.3; 95% CI 2.9-3.8) and problems falling asleep (OR 3.1, 95% CI, 2.5-3.8), adjusting for age, sex, smoking, obesity and socioeconomic status. Further they showed that the association between GERD symptoms and sleep persisted after adjusting for other comorbid conditions, such as depression or anxiety, which were themselves also associated with sleep disturbances. However, their study had inherent limitations including a cross sectional study design and reliance on self-reported symptoms of reflux and sleep. In another study based on data from the 2006 US National Health and Wellness Survey, Mody et al.[7] observed that 19% of 62,833 respondents experienced heartburn at least twice a month, and among them, 89% experienced nighttime GERD symptoms, 68% sleep difficulties, 49% difficulty initiating asleep, and 58% difficulty maintaining sleep. They showed the presence of GERD was associated with more than

twice the likelihood of experiencing sleep difficulties, and more specifically subjects with nighttime GERD symptoms experienced 1.5 times more sleep difficulties compared to subjects with daytime only GERD symptoms. In addition, they showed that among adults with GERD symptoms, sleep difficulties were associated with greater use of health care resources and loss of work productivity, and increased impairment of daily activities.[7] Adults with GERD symptoms who experienced sleep difficulties had 5.5% greater work productivity loss than those without sleep difficulties, equating to a loss of 2.75 weeks of lost productivity per year per sufferer compared with those without sleep difficulties.[7] Although this study also had limitations including being a web-based study subject to selection bias, these findings have been replicated in other studies.[17-19]

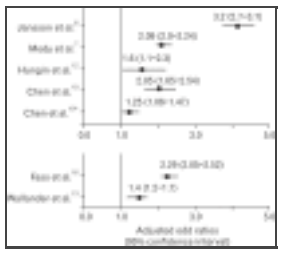

Figure 1

Epidemiologic data show the adjusted odds ratios (ORs) from case-control studies examining the association between sleep disturbance and gastroesophageal reflux disease. Upper four studies show a consistent and significant association with sleep disturbance **...**

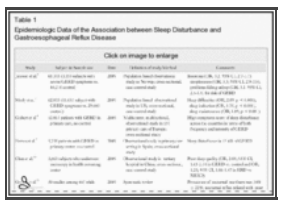

Table 1

Epidemiologic Data of the Association between Sleep Disturbance and Gastroesophageal Reflux Disease

In another large multicenter, multinational, observational study conducted as a series of parallel, locally managed studies at 134 primary care sites across six European countries (RANGE; Retrospective Analysis of GERD), sleep disturbances were common among subjects with GERD symptoms in all countries both in terms of frequency and intensity.[8] Similar data have been reported from a primary care study in Spain.[9] Recent systematic reviews have also reported that nocturnal GERD symptoms and sleep disturbances increased the likelihood of medical consultation.[11,12]

Reflux esophagitis at upper endoscopy has been observed to be associated with an increased risk for sleep disturbance. Among 3,663 individual who underwent endoscopy at a Chinese referral center,[10] reflux symptom were associated with two fold increased odds of a sleep disturbance (OR, 1.25; 95% CI, 1.06-1.47) and the severity of reflux esophagitis was also related to sleep disturbance (OR 1.25, 95% CI 1.06-1.46 in erosive reflux disease vs. non-erosive reflux disease). Other studies have also observed that sleep-related GERD is associated with higher esophagitis grades and Barrett's esophagus.[20,21]

Overall, there are convincing data that sleep disturbances are a common feature in patients with GERD symptoms, and the association is not due to chance or obvious confounding. However, these data do not establish a causal role for sleep disturbances in GERD or vice versa.

2) GERD in patients with primary sleep disturbances

A substantial proportion of adults with objective sleep disturbance experience GERD (Table 1, Fig. 1). In a multicenter, longitudinal cohort study of sleep-disordered breathing, 24.9% (3,806/15,314) reported having GERD. Body mass index, daytime sleepiness, insomnia, hypertension and asthma were strong predictors for nighttime heartburn.[16] Usage of benzodiazepines was a risk factor for GERD among subjects with sleep-disordered breathing (OR, 1.43; 95% CI, 1.09-1.88).[16] Others have

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observed similar associations.[13,22]

Limited data suggest a relationship between symptomatic obstructive sleep apnea (OSA) and GERD. The prevalence of GERD has been shown about 58-62% of patients with OSA,[23,24] however, these results may all be confounded by obesity. Apnea may increase trans-diaphragmatic pressure and decrease intra-thoracic pressure, favoring GERD.[25] Moreover, apnea might induce gastric dilatation, decrease gastric emptying, and induce transient lower esophageal sphincter relaxations.[26] Further, greater respiratory effort increases the pressure gradient across the lower esophageal sphincter and eventually facilitates the retrograde movement of gastric contents. However, other studies have failed to show significant relationship between GERD and OSA.[27,28] Moreover, in a recent study applying simultaneous recordings of high resolution manometry (impedance and pH monitoring) and polysomnography, the pressure of the upper esophageal sphincter and esophago-gastric junction increased during OSA despite decreased esophageal body pressure, and the incidence of GERD was not different from controls.[29] Although the relationship between OSA and GERD is not clear, treatment of OSA has been shown to improve GERD[30] and continuous positive airway pressure (CPAP) has been demonstrated to reduce the total 24 hour esophageal acid contact time.[31,32]

2. Pathophysiological evidence for a causal link between GERD and sleep disturbance

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There is considerable evidence to indicate that GERD can be affected by abnormal sleep physiology. Conversely, it is also possible that disturbed sleep enhances perception of intra-esophageal reflux events. However, few studies have been conducted and these have shown inconsistent results (Table 2, Fig. 2).

Figure 2

Possible pathophysiology of sleep disturbance and gastroesophageal reflux disease (GERD).

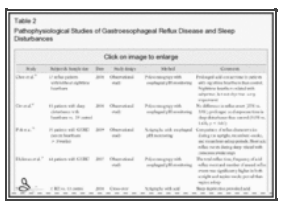

Table 2

Pathophysiological Studies of Gastroesophageal Reflux Disease and Sleep Disturbances

1) Normal physiologic change during sleep

GERD is usually a postprandial event and is a normal physiologic response to gastric distension after eating, which induces a transient relaxation of the lower esophageal sphincter, but notably esophageal physiology and esophageal acid clearance during sleep differ from wakefullness.[33] Acidification of the distal esophagus produces a marked increase in the secretion of saliva and its bicarbonate concentration whilst awake. In addition, in response to an acidic distal esophagus, there is a marked increase of swallowing and in subsequent primary peristalsis of the esophagus.[34] However, this secretory and motor response to acid exposure in the distal esophagus is different during sleeping. Swallowing frequency is almost not existent during sleep; swallows only occur during brief arousals.[34] Salivary secretion ceases during sleep, and sleep facilitates proximal acid migration into the esophagus.

2) GERD induced conscious arousals may provoke sleep disturbance

In a small sample of GERD patients who underwent polysomnography and 24-hr esophageal pH

monitoring assessing the impact of GERD on sleep, Dickman et al.[31] showed that most reflux event occurred during stage 2 sleep and 90% of reflux event were associated with a short arousal. In addition, the supine awake period in patients with GERD has been shown to shorten the reflux time period.[35] In another recent study using 24-hr esophageal pH monitoring and actigraphy, a validated watch-like ambulatory digital recording system in determining sleep duration and awakening, Poh et al.[36] confirmed that short-duration reflux events during the sleep period were associated with conscious awakenings. Thus, it is conceivable that nocturnal reflux events might evoke frequent conscious awakenings during sleep.

Thus conscious awakening may interrupt sleep; a high arousal index has been shown to be associated with poor quality of sleep. Physiologically, hyperarousal may be associated with activation of neuroendocrine systems including the autonomic nervous system (ANS) and the hypothalamic pituitary adrenal axis. These arousals might lead to increased sympathetic activation manifested by events such as increased heart rate or blood pressure; such autonomic arousals can result in poor sleep quality in the absence of electroencephalographic evidence of cortical arousal. Indeed, hyperarousal has been demonstrated to disrupt sleep patterns.[37] However, there were few studies that have specifically addressed the nighttime response of the ANS to acid reflux events. Interestingly, simultaneous cardiac and ambulatory pH monitoring revealed that esophageal acid exposure during sleep was associated with parasympathetic fluctuation with a superimposed sympathetic interaction.[38]

3) Prolonged acid contact time during sleep disturbances may provoke GERD

The occurrence of GERD cannot be evaluated by symptoms during sleep.[34] 24-hr esophageal pH monitoring studies combined with simultaneous polysomnography have established that GERD occurs less frequently during sleep.[39-41] However, prolonged acid contact time during sleep has been shown in GERD patients.[42,43] Using simultaneous monitoring of esophageal pH and polysomnography, a recent study was conducted in 81 patients with sleep disturbance and heartburn and 39 controls with neither sleep problem nor heartburn.[43] This study showed no difference in reflux event (27% vs. 33%), but acid exposure time was longer in patients with sleep disturbances than controls.[43]

4) Disturbed sleep-induced hyperalgesia may cause GERD

In a cross-over study evaluating sleep deprivation and perception in the esophagus, Schey et al.[44] studied 10 patients with reflux esophagitis (Los Angeles classification B-D) and 10 healthy controls; after sleep deprivation, the GERD patients had a significant decrease in lag time to symptom report, an increase in intensity rating, and an increase in acid perfusion sensitivity score, as compared to nights of good sleep. Normal subjects did not demonstrate any differences in the stimulus response to acid between sufficient sleep and sleep deprivation. They concluded that sleep deprivation may provoke hyperalgesia in patients with GERD. However, further studies are needed to confirm these findings.

5) Medication use for sleep disturbance can provoke or aggravate GERD

Some medications used to manage sleep disturbances may aggravate GERD. For example, benzodiazepines have been shown to be significantly associated with heartburn during sleep in an epidemiologic study.[16] In both animal models and humans, benzodiazepines decreased basal lower esophageal sphincter pressure and increased the number of gastroesophageal reflux events.[45] Non-benzodiazepine hypnotics include zolpidem; this binds to gamma-aminobytyric acid (GABA)-A receptors, facilitating sleep onset, and reducing the arousal threshold. Recently, one study showed that

zolpidem reduced the arousal response to nocturnal acid exposure and increased the duration of each esophageal acid reflux event in healthy individuals and patients with GERD.[46]

3. What are the treatment implications if GERD and sleep disturbances are related?

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Theoretically the vicious cycle of GERD inducing poor sleep that in turn aggravates GERD further may be interrupted by more aggressive acid reducing therapy. Several studies have evaluated the efficacy of PPI therapy for sleep disturbances in patients with GERD but few randomized blinded placebo controlled clinical trials are available (Table 3).[47-50] Johnson and colleagues[47] performed a large multicenter randomized double-blind placebo-controlled trial utilizing esomeprazole 40 mg, 20 mg, or placebo for 6 weeks in 675 adults with GERD-associated sleep disturbance. Fifty percent of the esomeprazole-treated subjects had resolution of nighttime heartburn, and by 4 weeks, 73% of the esomeprazole-treated subjects had resolution of their GERD-associated sleep disturbance. Both doses of esomeprazole resulted in improved sleep quality, reduced lost work hours, and increased work productivity. In another study using rabeprazole for sleep-related GERD with 24-pH esophageal monitoring study with polysomnography, Orr et al.[48] observed that rabeprazole reduced overall acid reflux, and improved subjective indices of sleep quality. However, they failed to show any objective improvement of sleep parameters after acid suppression.

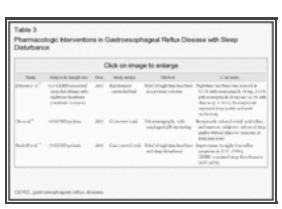

Table 3

Pharmacologic Interventions in Gastroesophageal Reflux Disease with Sleep Disturbance

A retrospective observational study in 56 patients with GERD who took double dose proton pump inhibitor (PPI) with/without additional ranitidine was conducted to evaluate symptom relief by a patient's interview.[49] The addition of ranitidine administered at bedtime to patients taking double dose of PPI therapy led to an improvement in overall symptoms and GERD-associated sleep disturbance. Another study suggested that the addition of a nocturnal H_2RA (histamine-2 receptor antagonist) or PPI after taking a morning dose of PPI decreased nocturnal acid breakthrough with improvement of daytime functioning.[50] Unfortunately, other data suggested tachyphylaxis with H_2RAs in nocturnal acid breakthrough.[51]

Data regarding the impact of fundoplication on sleep parameters has been very limited. Eleven patients with heartburn undergoing fundopication 8 to 10 weeks after surgery all reported an improvement of subjective sleep disturbances but not the objective sleep parameters.[52]

Conclusion

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This review has addressed the complex relationships between GERD and sleep. Epidemiologic data suggest that GERD has a modest but important association with sleep disturbance, and this association appears to be bidirectional. The link appears to not be explained by comorbidity. Medical treatment of nighttime GERD appears to improve subjective sleep disturbances but objective data may not improve. Further studies are needed to investigate sleep architecture and brain function in GERD patients that is not detected by traditional polysomnography.[36,44] Data on non-acidic reflux and the potential relationship with sleep disturbance is also needed (e.g., by using impedance and high resolution manometry). A better understanding of the relationships between sleep and GERD may allow the

clinician to manage these patients more effectively in the future.

Footnotes

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Conflicts of interest: None.

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