



Review Article

Gastroesophageal reflux disease: Evidence for influence on sleep and quality of life

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ABSTRACT

This review addresses current advances in gastroesophageal reflux disease (GERD) and its influence on sleep and health-related quality of life (QOL). Sleep difficulties are highly prevalent among adults with GERD, especially those who experience nighttime symptoms. These sleep difficulties result in substantial costs to the health care system by increasing provider visits. Because continued sleep disruption leads to increased daytime sleepiness and fatigue, nocturnal heartburn can reduce work productivity, as well as reduce function when performing normal daily activities. The continued presence of nocturnal symptoms in routine medical treatment is strongly associated with decreases in health-related quality of life. There is a greater loss of productivity to the employer and poorer health-related QOL (HRQOL) for the patient. Obstructive sleep apnea syndrome and obesity seem to predispose some patients to nocturnal GERD, and the presence of either of these conditions may help to identify patients with symptoms consistent with GERD. Appropriate management of GERD must include treatment of nighttime reflux symptoms that affect difficulty in both initiating and maintaining sleep.

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1. Introduction

Not uncommonly, clinicians observe that patients who are effectively treated for severe heartburn spontaneously, report that they are sleeping better in addition to achieving a resolution of their reflux symptoms. These reports from patients have focused attention on the relationship between gastroesophageal reflux (GER) during sleep and the extent to which this phenomenon results in disturbances of sleep and its associated complications. With the evolution of current knowledge documenting physiologic and psychological changes associated with sleep, as well as a variety of sleep-related problems associated with GER, an awareness of the relationship between sleep and GER disease (GERD) has rapidly emerged. Perhaps the most notable of the more recent focus on gastrointestinal complaints, is the relationship between sleep-related GER and the development of esophageal and extraesophageal complications. In some recent epidemiological studies, which have focused on nighttime heartburn, there has been a particular focus on the issue of nighttime heartburn related

to the consequences of sleep disturbance and reduction in quality of life (QOL).

GERD is a highly prevalent disorder that affects a substantial proportion of the population globally. Fifteen percent of US adults experience symptoms of GERD (heartburn and regurgitation) at least once a week [1]. The fact that symptoms of heartburn are readily treated with antacids, histamine-2 receptor antagonists, and more recently, proton-pump inhibitors, has obscured the frequency and importance of the symptoms of nighttime heartburn. Thus, until recently, clinicians would rarely, if ever, inquire about the frequency, characteristics, and consequences of nighttime heartburn.

2. Nighttime symptoms and sleep disturbances

We have previously attempted to determine whether patients with significant nighttime heartburn had more disturbed sleep and more GER than those without significant nighttime heartburn [2]. Thirty-three reflux patients were stratified into two groups (nighttime heartburn, without nighttime heartburn). After completing questionnaires assessing daytime and nighttime heartburn and subjective sleep with the Pittsburgh Sleep Quality Index (PSQI), all participants underwent 24-hour esophageal pH monitoring and an overnight polysomnographic study. We found

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that the number of reflux events longer than 5 minutes was significantly greater in patients with nighttime heartburn than in those without nighttime heartburn for the total and upright position periods. Acid contact time was significantly greater in patients with nighttime heartburn during the upright period and during the total period. Patients with nighttime heartburn reported significantly greater subjective sleep impairment (8.1 ± 0.7) than those without nighttime heartburn (6.1 ± 0.4 ; $p = 0.02$). It was concluded that patients with significant nighttime heartburn seem to have more acid reflux than those without nighttime heartburn. Nighttime heartburn together with sleep complaints is associated with excessive GER.

Several studies have recently focused attention on both QOL and the sleep disturbance consequences of nighttime heartburn. In understanding how to interpret these data, it is important to understand how “nighttime heartburn” is defined. In general, these studies define nighttime as the time when the patient lies down to attempt to go to sleep until waking in the morning occurs. Among the first of these observations was a survey by Janson and colleagues [3] of the general population in several Scandinavian countries. The authors found a significant relationship between nighttime heartburn at least once a week and daytime sleepiness, daytime tiredness, and snoring. Symptoms of GER were associated with daytime sleepiness [odds ratio (OR) = 2.6], daytime tiredness (OR = 4.5), and disrupted breathing (OR = 3.8). The relationship between snoring and GER at least one night per week showed an OR = 2.75. Another epidemiologic study conducted by Farup and colleagues [1] described the impact of nighttime heartburn on health-related QOL (HRQOL). In this study, nighttime heartburn was reported to be a common symptom in patients with frequent daytime heartburn. The authors reported that 74% of those individuals with frequent heartburn had symptoms of nighttime heartburn. It was also noted that individuals who reported nighttime heartburn were significantly more impaired with regard to QOL than subjects who reported daytime symptoms only. Individuals with nighttime heartburn reported significantly more pain than patients with diabetes and similar pain compared to those

with angina and congestive heart failure. Recently, a strong association between GERD and sleep disturbances as a cause of altered daytime performance has been extensively investigated (Table 1) [2,4–9].

This surprising prevalence of nighttime heartburn has been described in a more recent study by Shaker and colleagues [10]. In this study, a nationwide telephone survey of 1000 adults experiencing heartburn at least once a week was conducted on behalf of the American Gastroenterological Association. The results revealed that 79% of respondents reported experiencing nighttime heartburn. Among these individuals, 75% reported that symptoms altered their sleep, and 63% believed that nighttime heartburn negatively affected their ability to sleep well. Forty percent of patients with nighttime heartburn believed that these nocturnal symptoms impaired their ability to function the following day. Of particular interest was the fact that the prevalence of sleep disturbances among the respondents increased with increasing frequency of nighttime heartburn episodes over the course of a week. That is, individuals who had nighttime heartburn three times a week had complaints of being kept awake (67%) and of waking up during the night (70%). A surprising percentage (16%) of these individuals reported trying sleep medications to treat their presumed GER-related sleep disturbance. Patients with nighttime heartburn had tried a variety of treatment mechanisms in addition to sleeping pills, but with surprisingly poor success. For example, 41% of this patient population indicated that they used prescription medications, but less than half reported that they were satisfied with this treatment approach. A similar percentage of individuals had also tried elevation of the head of the bed, but only 23% reported satisfaction with this treatment approach.

3. Effects of GERD on sleep and HRQOL

Sleep-related GER can result in more than disturbed sleep. Recently, Mody et al examined the relationship between reflux symptoms during sleep, sleep onset, and sleep maintenance insomnia and assessed the effects of reflux-related sleep difficulties

Table 1
Pathophysiological studies of GERD and sleep disturbances.[4]

Date	Individuals (sample size)	Study design	Investigation	Main findings
2007	GERD ($n = 64$)	Observational study	Polysomnography with esophageal pH monitoring	The total reflux time, frequency of acid reflux event and number of sensed reflux events was significantly higher in both the upright and supine-awake period than supine asleep [5]
2007	GERD ($n = 48$)	Observational study	Endoscopy, esophageal pH monitoring	Reciprocal relationship between GERD symptoms/acid exposure and sleep quality [6]
2008	GERD ($n = 33$)	Observational study	Polysomnography with esophageal pH monitoring	Prolonged acid contact time in patients with nighttime heartburn compared to controls. Nighttime heartburn related with subjective, but not objective sleep impairment [2]
2008	GERD ($n = 81$) Controls ($n = 39$)	Observational study	Polysomnography with esophageal pH monitoring	No difference in reflux event (27% vs. 33%); prolonged acid exposure time in sleep disturbance compared to controls (9.5% vs. 1.6%; $p < 0.05$) [7]
2008	RE ($n = 10$) Controls ($n = 10$)	Cross-over case-control study	Actigraphy with acid perfusion test	Sleep deprivation provoked acid hypersensitivity in patients with RE and increased GERD symptom severity [8]
2009	GERD ($n = 39$)	Observational study	Actigraphy with esophageal pH monitoring	Comparison of reflux characteristics during the upright, recumbent-awake, and recumbent-asleep periods. Short acid reflux events during sleep related with conscious awakenings [9]

GERD = gastroesophageal reflux disease; RE = reflux esophagitis.

on QOL, work productivity, and health care resource use [11]. According to their survey of 11,685 respondents with reflux symptoms, 68% experienced sleep difficulties, with 49% reporting sleep onset insomnia and 58% reporting sleep maintenance insomnia. Respondents with reflux symptoms during sleep time were also more likely to have sleep onset insomnia (OR = 1.43) and sleep maintenance insomnia (OR = 1.56) compared to respondents with reflux symptoms only during wakefulness. Furthermore, respondents with reflux with sleep difficulty had more health care provider visits, a loss of 5.5% in their work productivity, and reductions in their HRQOL. Thus, reflux during the sleeping interval affects the ability to sleep, as well as wake-time functioning and QOL.

Among adults with GERD, nighttime symptoms significantly affected sleep difficulties, and sleep difficulties were negatively correlated with HRQOL. The evidence is supported by a study which found that patients with nighttime GERD symptoms reported lower HRQOL than those without nighttime symptoms [1]. Among respondents with GERD who had sleep difficulties, the mean Short-Form (SF)-8 physical and mental summary scores were substantially poorer than those in the general population [1]. After adjusting for differences in personal and clinical characteristics, the differences in SF-8 physical and mental summary scores between those with and without sleep difficulties were >3 points each. A recent study has shown that a 3-point change in the SF-36, and by extension the SF-8, is a clinically meaningful difference [12]. Therefore, the negative effects of sleep difficulties on HRQOL were not only statistically significant, but had meaningful clinical implications. These data are also supported by other epidemiological studies, which indicate that nighttime reflux symptoms are more problematic and may predict GERD with more severe presentations [13,14]. These studies applying an internet survey suggest that individuals with nighttime reflux symptoms have a greater frequency and severity of GERD symptoms, as well as atypical symptoms such as chronic cough, hoarseness, and chest pain. Thus, awareness of significant nighttime symptoms in clinical practice might help identify those individuals at greater risk of developing esophagitis and other complications of GERD, and who thus require more aggressive treatment.

4. Consequences of resolving nighttime symptoms

An epidemiologic study of general symptomatic GERD patients ($n = 6215$) revealed similar results in terms of diminished QOL [15]. Kulig and colleagues found that the generic QOL of these patients was diminished, and that QOL was significantly improved in patients with erosive GERD, non-erosive GERD, as well as Barrett's esophagus, after 2 weeks of treatment with esomeprazole. Baseline QOL in this cohort of GERD patients was comparable to that of patients with coronary artery disease. Treatment resulted in a similar improvement in QOL in all three subpopulations of GERD patients, indicating that endoscopic results and severity appeared to be unrelated to QOL measures. This study indicates that QOL measures can be substantially and significantly improved quickly, with appropriate resolution of symptoms. This study did not address the issue of nighttime GERD.

Other studies have more formally documented the presence of sleep disturbances in patients with nighttime GERD, as well as response to treatment. Chand and colleagues [16] studied 18 patients with erosive esophagitis using subjective GERD rating scales, the PSQI, and ambulatory wrist actigraphy (a device worn on the wrist that monitors motion and provides information on the sleep state). Patients were assessed at 4 and 8 weeks subsequent to treatment with esomeprazole 40 mg/day. In this cohort of patients, the baseline sleep efficiency, determined via wrist actigraphy, was 87%, which is indicative of a significant sleep disturbance. The PSQI

and GERD symptom questionnaire scores were significantly improved after both 4 and 8 weeks of treatment.

Results from a randomized clinical trial involving patients with both nighttime heartburn and sleep disturbance were recently published by Johnson and colleagues [17]. This multicenter, randomized, double-blind, placebo-controlled trial included adults with GERD-associated sleep disturbances and moderate to severe nighttime heartburn, as noted by a subjective patient diary. Patients received either 20 mg or 40 mg of esomeprazole or placebo once daily for 4 weeks. Outcome variables included relief of nighttime heartburn, change in the PSQI global score, and changes in work productivity as assessed by the Work Productivity and Activity Impairment questionnaire. A significantly higher percentage of patients reported relief (no heartburn on six of seven nights), and complete resolution (no heartburn on seven nights) of symptoms with treatment compared with those taking placebo. There was no significant difference between the 40 mg and 20 mg doses of esomeprazole; approximately 50% of treated patients had relief of nighttime heartburn symptoms compared with approximately 13% on placebo. Approximately 82% of patients in the treatment arms reported relief of GERD-associated sleep disturbance compared with 55% on placebo. The PSQI data, which measures general sleep quality, showed a significant improvement to nearly normal levels in both treatment groups. It was documented that approximately 16 work hours were lost due to GERD-related sleep disturbances at baseline; this was improved to approximately 12 hours subsequent to treatment. Using an average total employee compensation cost of \$24.59 (USD) per hour, the cost of hours saved per patient per week was approximately \$290.00 (USD) in the two treatment groups. Indeed, results of a recent internet survey showed that GERD-related symptom severity was strongly associated with work impairment, and that nighttime GERD was associated with substantially greater work impairment, as was symptom severity [18]. In a smaller study using polysomnography to define sleep parameters, rabeprazole 20 mg once daily was shown to improve subjective sleep measures without any change in the objective sleep measures [19]. Additionally, another study done by Dimarino et al, using polysomnography during esophageal pH monitoring, showed that omeprazole 20 mg twice daily improved the objective sleep measures (reflux-related arousals and awakenings) in a group of patients with sleep complaints and GER [20].

In a recent study, Fass et al evaluated the efficacy of dexlansoprazole in relieving nocturnal heartburn, reducing sleep disturbances, improving work productivity, and decreasing nocturnal symptom severity in patients with symptomatic GERD [21]. This randomized, double-blind study enrolled patients ($n = 305$) with frequent, moderate-to-very severe nocturnal heartburn and associated sleep disturbances. They received dexlansoprazole modified release (MR) (not currently available in Taiwan) 30 mg or placebo once daily for 4 weeks. The primary end point was the percentage of nights without heartburn, whereas secondary end points were the percentage of patients with relief of nocturnal heartburn and of GERD-related sleep disturbances over the last 7 days of treatment. Dexlansoprazole MR 30 mg ($n = 152$) was superior to placebo ($n = 153$) in terms of the median percentage of nights without heartburn (73.1 vs. 35.7%, respectively; $p < 0.001$), and relief of nocturnal heartburn and GERD-related sleep disturbances (47.5 vs. 19.6 %, 69.7 vs. 47.9 %, respectively; $p < 0.001$), and led to significantly greater improvements in sleep quality and work productivity and decreased nocturnal symptom severity. It was concluded that in patients with symptomatic GERD, dexlansoprazole MR 30 mg is significantly more efficacious than placebo in providing relief from nocturnal heartburn, in reducing GERD-related sleep disturbances and the consequent impairments in work productivity, and in improving sleep quality and QOL.

5. Obstructive sleep apnea and gastroesophageal reflux

GER is a symptom commonly observed in patients with obstructive sleep apnea (OSA), and patients with both GER and OSA have been shown to have significantly poorer QOL compared with patients with OSA alone [22]. OSA occurs in about 4% of adult men and 2% of adult women [23]. Recent studies have revealed that risk factors for OSA included male sex (OR = 3.7; CI = 1.63–8.19), age > 65 years (OR = 2.4; CI = 0.65–8.54), and BMI (OR = 1.5; CI = 0.68–3.16), which were considered to be of clinical significance [24]. Among these, the most obvious shared risk with GERD is obesity [25]. Further evidence supporting an association between GERD and OSA was provided by a 24-hour esophageal pH monitoring study of 16 patients with OSA, which revealed 80% of those patients had abnormally high esophageal acid exposure times [26]. Furthermore, a study of 16 patients with both OSA and GERD found that improving breathing mechanics with continuous positive airway pressure (CPAP) normalized the esophageal acid exposure in 81% of the patients and reduced the mean acid exposure time of the group from 12.4% before CPAP to 6.8% with CPAP [27]. However, evidence for the relationship between GER and OSA has not been found [26,28].

It is clinically well established that OSA is associated with a profound degree of daytime sleepiness, depression, and irritability, all of which weigh heavily in diminishing QOL. GER exacerbates a significant impairment in QOL to an even greater degree in this patient population (i.e., those with sleep disorders). Despite the intuitive assumption that upper airway obstruction predisposes to GER, <4% of OSA episodes are observed to occur with reflux [20]. GERD was shown to be alleviated during OSA, with pressure changes in both the upper and lower esophageal sphincters [29]. In patients with both GERD and mild OSA, 8-week acid suppression therapy led to a significant resolution in sleep-related GERD, without any improvement in the apnea index [30].

6. Summary and conclusions

Nighttime reflux symptoms, such as heartburn and acid regurgitation, are clinical manifestations that clearly mitigate QOL and work performance; however, they remain to be symptoms which are still commonly ignored. Patients with nighttime GER consistently report that these nighttime symptoms disturb them more than their daytime symptoms, and the resultant disturbance in sleep and impaired daytime performance takes its toll in terms of daily QOL. It is also evident that, although there are many causes of sleepiness, nighttime GER is indeed associated with disturbed sleep, and in a majority of these patients, sleep disturbances and QOL can be markedly improved by eliminating the symptoms of nighttime reflux as treated with acid suppression therapy.

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