

Characteristics of Sleep Disturbances in Patients with Gastroesophageal Reflux Disease

Narika Iwakura¹, Yasuhiro Fujiwara¹, Masatsugu Shiba¹, Masahiro Ochi², Takashi Fukuda³, Tetsuya Tanigawa¹, Hirokazu Yamagami¹, Kazunari Tominaga¹, Toshio Watanabe¹ and Tetsuo Arakawa¹

Abstract

Objective Gastroesophageal reflux disease (GERD) is strongly associated with sleep disturbances; however, the detailed differences in the characteristics of sleep disturbances between GERD and non-GERD patients are unknown. The aim of the present study was to analyze the clinical characteristics as well as health-related quality of life in GERD and non-GERD patients with sleep disturbances.

Methods Three hundred and fifty patients, including 124 patients with GERD and 226 patients without GERD, completed a self-administered questionnaire that evaluated clinical information. The Pittsburg Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS) and 8-item Short-Form Health Survey (SF-8) were also used. Sleep disturbance was considered to be present if the PSQI was >5.5.

Results The prevalence of sleep disturbances was significantly higher in the GERD patients (66/124, 53.9%) than in the non-GERD patients (89/226, 39.3%). Depression and anxiety were significantly more common in the subjects with sleep disturbances than in those without sleep disturbances, although there were no differences between the GERD and non-GERD patients. Among the subjects with sleep disturbances, daytime sleepiness was more common in the GERD patients than in the non-GERD patients. The subjects with sleep disturbances had a poorer health-related quality of life. The physical components of quality of life were impaired, particularly in the GERD patients with sleep disturbances.

Conclusion GERD patients with sleep disturbances commonly experience daytime sleepiness and an impaired health-related quality of life, especially in terms of physical components.

Key words: gastroesophageal reflux disease, sleep disturbances, daytime sleepiness, health-related quality of life

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Introduction

Gastroesophageal reflux disease (GERD) is caused by the reflux of gastric contents into the esophagus and is characterized by symptoms such as heartburn. A systematic review reported that the prevalence of GERD (defined as the onset of heartburn and/or acid regurgitation at least weekly) in Western countries is 10-20%, with a lower prevalence in

Asia (1). However, the frequency of GERD in Asia, including Japan, has recently been reported to be increasing (2). Several studies have also reported that GERD is strongly associated with sleep disturbances (3-10). For example, Shaker et al. reported that 79% of 1,000 adults with GERD have nighttime heartburn. Among these individuals, 75% reported that GERD symptoms affected their sleep, 63% believed that these symptoms negatively affected their ability to sleep well, 40% believed that sleep difficulties caused by night-

¹Department of Gastroenterology, Osaka City University Graduate School of Medicine, Japan, ²Department of Internal Medicine, Meijibashi Hospital, Japan and ³Department of Gastroenterology, Minamiosaka Hospital, Japan

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Correspondence to Dr. Narika Iwakura, m1111620@med.osaka-cu.ac.jp

time heartburn impaired their ability to function the following day and 42% stated that they accepted the fact that they could not sleep through the night (3). Such impairment of sleep in patients with GERD results in socioeconomic complications, through reduced work productivity and daily life activities (11, 12), leading to considerable economic loss and lower health-related quality of life (HR-QOL).

Sleep disturbances are common in the general population. In 2008, the National Sleep Foundation's Sleep in America Poll demonstrated that approximately half of all participants reported non-refreshing sleep a few nights per week or more, with 42% reporting frequently waking at night and 26% reporting difficulty in falling asleep (13). Nationwide epidemiological studies in Japan have shown that the prevalence of sleep disturbances is approximately 17.3-22.3% for men and 20.5-21.5% for women (14-17). In addition, a nested case cohort study conducted in the UK indicated that there is a clear association between sleep disturbances and smoking, excessive alcohol consumption, psychiatric disorders (stress and depression), cardiovascular diseases (heart failure and coronary heart disease) and gastrointestinal diseases, including GERD and irritable bowel syndrome (18).

Nevertheless, the specific clinical features of sleep disturbances in GERD patients are unknown. Therefore, the aim of the present study was to compare the characteristics of sleep disturbances between GERD patients and non-GERD patients using several self-administered questionnaires.

Materials and Methods

Study subjects

This study was part of a cross-sectional study conducted between April 2012 and November 2013 at Osaka City University, Meijibashi and Minamiosaka hospitals to examine the associations between sleep disturbances and gastrointestinal diseases. The GERD patients included in this study were adult outpatients (age >20 years) who visited the participating hospitals during the survey period and experienced heartburn symptoms at least twice a week, irrespective of treatment with acid-suppressive drugs. The control patients were outpatients who had undergone endoscopic resection of superficial gastric cancers or colonic polyps but did not exhibit GERD symptoms. The exclusion criteria included: (1) employment in overnight positions; (2) pregnancy and nursing; (3) severe psychiatric diseases, such as major depression; (4) severe malignant disease; and (5) severe sleep disorders, such as obstructive sleep apnea syndrome, that required continuous nasal positive airway pressure. This study was approved by the Osaka City University Ethics Committee, and informed consent was obtained from all participants.

Questionnaire

All participants were asked to complete a self-administered questionnaire that evaluated clinical informa-

tion (age, sex, height, body weight, smoking status, alcohol drinking habits, caffeine intake, history of disease, current medications and comorbidities), presence or absence of snoring and apnea, sleep disturbances, daytime sleepiness, mental health and HR-QOL. Body mass index (BMI) was calculated as bodyweight divided by height squared (kg/m^2).

Pittsburg sleep quality index

A Japanese version of the Pittsburg Sleep Quality Index (PSQI) was used to assess sleep disturbances occurring within the month before the assessment (19). The PSQI consists of 17 individual items that generate the following seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep difficulty, hypnotic use and daytime dysfunction. Each component score ranges from 0 to 3, and the sum of all the component scores provides one total score, with higher scores indicating poorer sleep (20). In the Japanese version, a PSQI >5.5 has a sensitivity of 80.0-85.7% for various patient groups and a specificity of 86.6% for control subjects (19). We defined cases of sleep disturbance as those involving patients with a total PSQI of >5.5 (19).

Epworth sleepiness scale

The Epworth Sleepiness Scale (ESS) measures a subject's general level of daytime sleepiness (21). It consists of eight self-rated items, scored from 0 to 3, that measure the subject's habitual "likelihood of dozing or falling asleep" in common situations of daily living. The ESS score represents the sum of individual items. A high ESS score indicates that the subject is sleepier during the daytime. An ESS score of ≥ 11 indicates daytime sleepiness (22).

Insomnia severity index

The Insomnia Severity Index (ISI) consists of seven questions and summed scores for all seven items (23). The total scores are categorized into four degrees of severity: no clinically significant insomnia (0-7), mild insomnia (8-14), moderate insomnia (15-21) and severe insomnia (22-28).

Hospital anxiety and depression scale

The Hospital Anxiety and Depression Scale (HADS) is designed to identify cases of anxiety disorders and depression (24) and is divided into an anxiety subscale (HADS-A) and depression subscale (HADS-D). Each subscale contains seven items, with the value of each item ranging from 0 to 3 and the sum of all the seven items ranging from 0 to 21. Higher HADS scores indicate that the subject is more depressive or anxious; the recommended diagnostic cutoff is >8 for both subscales (25).

Health-related quality of life

The health-related quality of life (HR-QOL) was assessed according to the Japanese version of the 8-item Short-Form Health Survey (SF-8) (26). The SF-8 is a questionnaire derived from the longer 36-item Short-Form Health Survey (SF-36) and was developed to estimate the HR-QOL based on the scores for eight domains and two summary items: physical functioning (PF), role physical (RF), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role emotional (RE), mental health (MH),

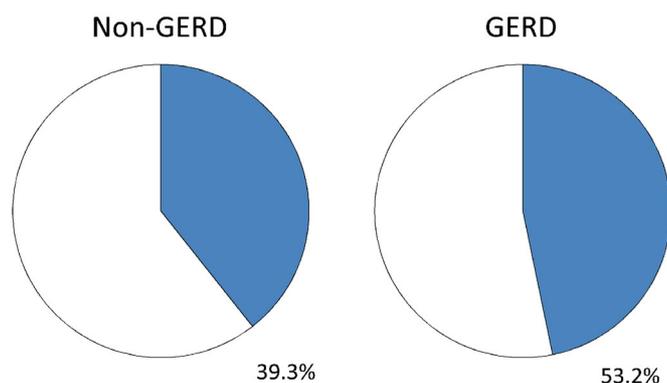


Figure 1. Prevalence of sleep disturbances in GERD and non-GERD patients.

physical component summary (PCS) and mental component summary (MCS). The PF, RP and BP scales correlate most highly with the physical component and contribute most to the scoring of the PCS score. The mental component correlates most highly with the MH and RE scales, which subsequently contribute most to the scoring of the MCS score. Three of the scales (VT, GH and SF) have noteworthy correlations with both components (26-28). Importantly, the SF-8 score shows a high correlation with the SF-36 score. The scores for PCS and MCS were calculated according to the manual of the Japanese version of the SF-8.

Statistical analysis

The data are presented as the mean \pm standard deviation for continuous variables and as numbers for categorical variables. Comparisons of categorical data between groups were performed using the chi-squared test, whereas continuous data were compared using the *t*-test. The statistical analyses were performed using the IBM SPSS software program version 21.0 for Windows (SPSS Inc., Tokyo, Japan). All statistical tests were two-sided, and a *p* value of <0.05 was considered to be statistically significant.

Results

Prevalence of sleep disturbances and clinical characteristics of the study subjects

Sleep disturbances were reported in 66 of 124 (53.3%) GERD patients and 89 of 226 (39.3%) non-GERD patients (Fig. 1), suggesting that the prevalence of sleep disturbances was significantly higher in the GERD patients ($p < 0.05$). The clinical characteristics of the GERD and non-GERD patients according to the presence and absence of sleep disturbances are shown in Table 1. Although the GERD patients with sleep disturbances were predominantly female, there were no differences in age, BMI, smoking, alcohol drinking, bedside drinking, caffeine intake habits or the presence of snoring or apnea between the four groups.

The rates of ISI were significantly higher in both the GERD and non-GERD patients with sleep disturbances than

in the GERD and non-GERD patients without sleep disturbances; however, no differences were found between the GERD and non-GERD patients (Table 2). The classification of the severity of insomnia according to the ISI indicated that, among the GERD patients with sleep disturbances, 37% had mild insomnia, 35% had moderate insomnia and 8% had severe insomnia. In contrast, among the non-GERD patients with sleep disturbances, 43% had mild insomnia, 34% had moderate insomnia and 1% had severe insomnia. Similarly, the total PSQI as well as each PSQI subscale score were higher in the patients with sleep disturbances. Only the scores for daytime dysfunction were significantly higher in the GERD patients with sleep disturbances than in the non-GERD patients with sleep disturbances. Although there were no differences in the ESS scores among the four groups, the prevalence of a positive ESS score was significantly higher in the GERD patients with sleep disturbances (Table 2).

Prevalence of depression and anxiety in the controls and GERD patients according to the presence of sleep disturbances

Fig. 2 shows the prevalence of depression and anxiety in the four groups. The prevalence of depression and anxiety was higher in both the GERD and non-GERD patients with sleep disturbances than in those without sleep disturbances, although there were no differences between the GERD and non-GERD patients.

Differences in HR-QOL between the controls and GERD patients with and without sleep disturbances

The scores for all HR-QOL domains and summary scores, such as PCS and MCS, were significantly lower in the subjects with sleep disturbances than in those without sleep disturbances among both the GERD and non-GERD patients. Interestingly, the scores for BP and VT and the PCS scores were significantly lower in the GERD patients with sleep disturbances than in the non-GERD patients with sleep disturbances (Fig. 3).

Discussion

Approximately half of all the GERD patients in the present study experienced sleep disturbances, as assessed by the PSQI. Several reports have found that the prevalence of sleep disturbances in GERD patients ranges between 40% and 68% (3, 4, 7, 8, 10), which is similar to the findings of our study, although the precise definition of sleep disturbances differs in each study. It should be noted that our observed prevalence of sleep disturbances in the non-GERD patients was higher (39%) than that seen in the general Japanese adult population (approximately 20%), as we chose to assess outpatients as controls.

Numerous factors can affect sleep; in particular, psychological factors play crucial roles in the onset of sleep disturbances (14, 29, 30). The present results showed that the

Table 1. Characteristics of the Study Subjects.

| | Non-GERD | | GERD | |
|--------------------------|---------------------------------------|-----------------------------------|--------------------------------------|-----------------------------------|
| | Without sleep disturbances n = 137 | With sleep disturbances n = 89 | Without sleep disturbances n = 58 | With sleep disturbances n = 66 |
| Age | 66.3 ± 0.8 | 67.1 ± 1.2 | 64.7 ± 1.8 | 66.0 ± 1.7 |
| Male sex | 55.5% | 49.4% | 56.9% | 33.3% |
| BMI (kg/m ²) | 22.6 ± 0.3 | 21.7 ± 0.4 | 22.6 ± 0.5 | 22.4 ± 0.4 |
| Smoking (%) | 18.9% | 15.9% | 15.5% | 13.6% |
| Alcohol drinking (%) | 55.5% | 47.1% | 55.2% | 36.4% |
| Bedside drinking (%) | 11.7% | 19.3% | 13.8% | 16.7% |
| Caffeine intake (%) | 38.0% | 30.7% | 41.4% | 39.4% |
| Snoring (%) | 56.9% | 48.3% | 56.9% | 60.0% |
| Apnea (%) | 14.6% | 15.9% | 24.6% | 15.6% |

Table 2. Sleep Disturbance Parameters of the Study Subjects.

| | Control | | GERD | |
|---------------------|-------------------------------------|---------------------------------|------------------------------------|---------------------------------|
| | Without sleep disturbances n=137 | With sleep disturbances n=89 | Without sleep disturbances n=58 | With sleep disturbances n=66 |
| ISI | 4.08 ± 0.32 | 11.93 ± 0.57 ^a | 4.64 ± 0.44 | 12.85 ± 0.70 ^b |
| ESS score | 5.59 ± 0.35 | 5.83 ± 0.38 | 5.40 ± 0.43 | 6.73 ± 0.50 |
| ESS score ≥11 (%) | 8.1 | 6.7 | 8.6 | 19.7 ^c |
| PSQI-total | 3.13 ± 0.12 | 8.37 ± 0.25 ^a | 3.59 ± 0.15 | 8.68 ± 0.32 ^b |
| PSQI-component | | | | |
| Sleep quality | 0.92 ± 0.04 | 1.66 ± 0.07 ^a | 0.93 ± 0.05 | 1.79 ± 0.09 ^b |
| Sleep latency | 0.43 ± 0.05 | 1.48 ± 0.11 ^a | 0.64 ± 0.10 | 1.39 ± 0.13 ^b |
| Sleep duration | 0.71 ± 0.06 | 1.28 ± 0.08 ^a | 0.64 ± 0.07 | 1.45 ± 0.10 ^b |
| Sleep efficiency | 0.15 ± 0.05 | 0.97 ± 0.12 ^a | 0.17 ± 0.06 | 0.79 ± 0.13 ^b |
| Sleep difficulty | 0.59 ± 0.04 | 1.02 ± 0.04 ^a | 0.66 ± 0.07 | 1.08 ± 0.05 ^b |
| Hypnotic use | 0.07 ± 0.03 | 1.21 ± 0.14 ^a | 0.10 ± 0.06 | 1.11 ± 0.17 ^b |
| Daytime dysfunction | 0.26 ± 0.04 | 0.78 ± 0.07 ^a | 0.45 ± 0.08 | 1.08 ± 0.10 ^{bc} |

^a p < 0.01 versus control without sleep disturbances, ^b p < 0.01 versus GERD without sleep disturbances, ^c p < 0.01 versus control with sleep disturbances.

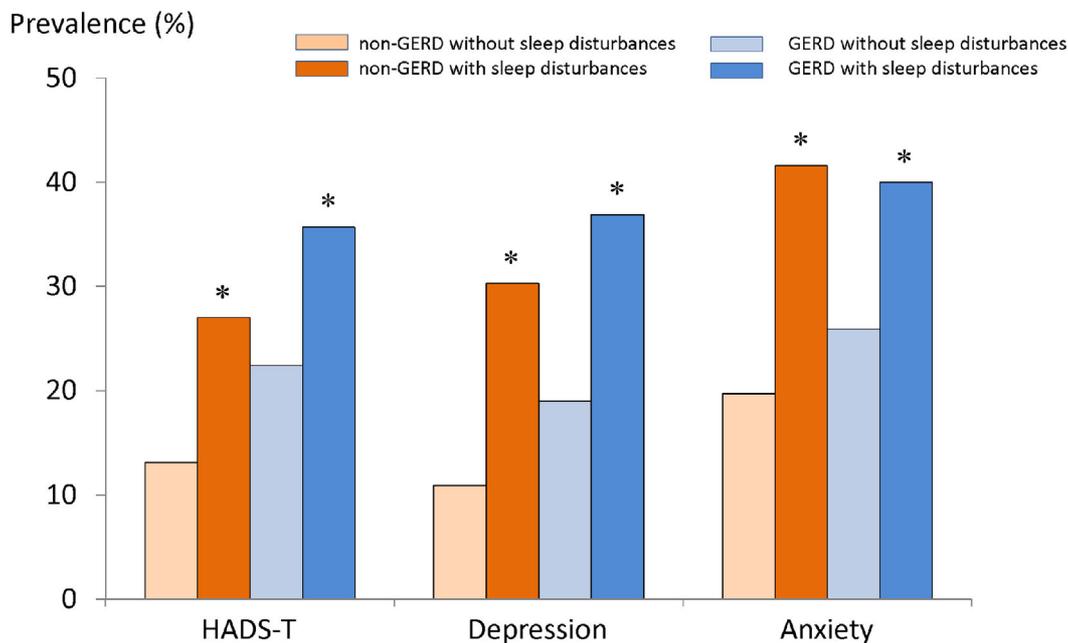


Figure 2. Prevalence of depression and anxiety in GERD and non-GERD patients according to the presence or absence of sleep disturbances. *p<0.01 versus non-GERD patients without sleep disturbances. **p<0.01 versus GERD without sleep disturbances.

prevalence of depression and anxiety was high in the subjects with sleep disturbances, although there were no differences between the GERD and non-GERD patients. These results suggest that depression and/or anxiety are associated

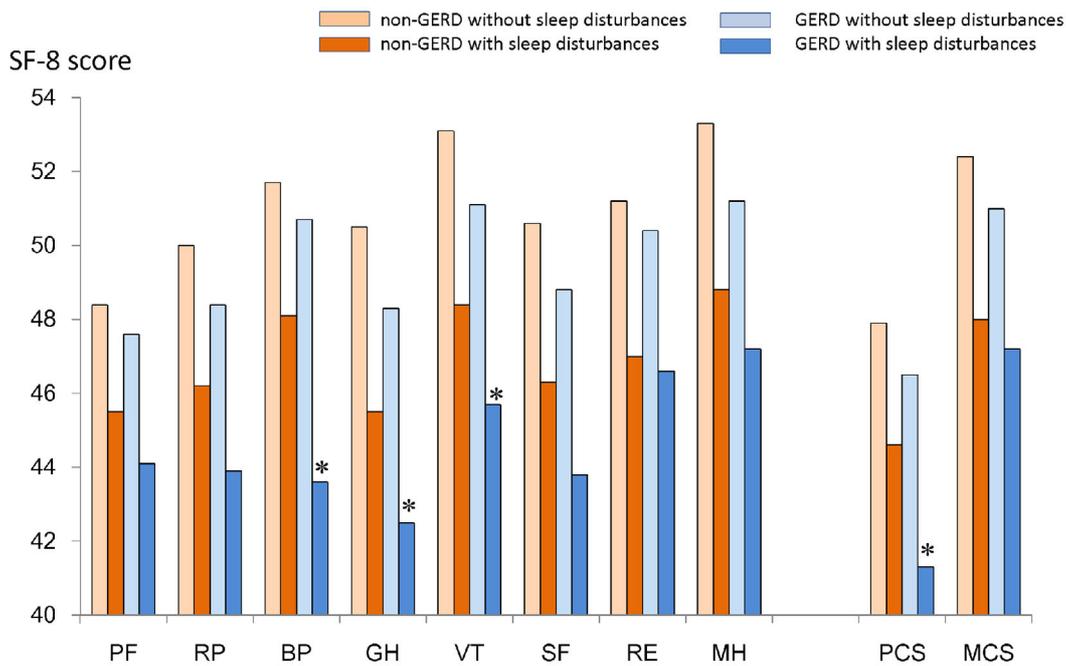


Figure 3. Health-related quality of life in GERD and non-GERD patients. * $p < 0.05$ versus control with sleep disturbances. PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health perception, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health, PCS: physical component summary, MCS: mental component summary

with sleep disturbances, but are not specific to GERD patients. This speculation is supported by two large epidemiological studies. Jansson et al. conducted a population-based study among 65,333 subjects in Norway, including 3,153 patients with reflux symptoms, and found that GERD was associated with insomnia (OR, 3.2), sleeplessness (OR, 3.2) and difficulty falling asleep (OR, 3.1), after adjusting for several confounding factors, including anxiety and depression (31). In addition, Mody et al. analyzed data from the 2006 US National Health and Wellness Survey, which included 11,685 patients with GERD and 29,634 patients without GERD, and reported that GERD was significantly associated with difficulty sleeping (OR, 2.09) after adjusting for eight factors, including age, race, sex, marital status, education, number of physical comorbidities, presence of psychiatric conditions and BMI (8).

In the current study, daytime sleepiness was significantly more common in the GERD patients with sleep disturbances than in the non-GERD patients with sleep disturbances. The exact reasons for the association between daytime sleepiness and GERD were unknown; however, this finding suggests that sleep disturbances in GERD patients might be due to obstructive sleep apnea. Although polysomnography was not used in this study, there were no differences in the incidence of reported symptoms, such as snoring and apnea, between the GERD and non-GERD patients or among the GERD patients with and without sleep disturbances, suggesting that obstructive sleep apnea may not play a major role in the pathophysiology of sleep disturbances in GERD patients. In addition, several studies have demonstrated that there is in-

sufficient evidence of a causal relationship between obstructive sleep apnea and GERD, and the two disorders are likely associated based on similar risk factors, such as obesity (32).

Several studies have shown that the HR-QOL is impaired in GERD patients, especially those with sleep disturbances (4, 8, 33). Our findings are consistent with these results, and the current data also showed that the scores for the physical components of the HR-QOL were significantly lower in the GERD patients. Therefore, the development of sleep disturbances in GERD patients might be due to physical conditions, such as nighttime heartburn, acid regurgitation or chest pain. This hypothesis is supported by our previous study that showed that acid reflux directly causes sleep disturbances via sleep fragmentation and poor sleep quality (34).

Our study is associated with several limitations. First, we defined sleep disturbances based on the results of a self-administered questionnaire; therefore, objective sleep parameters obtained using polysomnography or actigraphs were not evaluated. Second, we included patients taking acid-suppressive drugs. Several clinical trials have demonstrated that proton pump inhibitors significantly reduce the incidence of subjective sleep disturbances in patients with GERD (35-37). Therefore, the prevalence of sleep disturbances in the GERD patients in the present study might be underestimated. However, we underline the finding that the prevalence of sleep disturbances in our study is similar to that seen in previous reports. This may be due to the nature of the enrolled study subjects; namely, patients with GERD

symptoms at least twice weekly who were likely also on acid-suppressive medications. Third, we did not evaluate the severity of GERD symptoms in this study. In the future, a detailed study is required to assess the association between sleep disturbances and the severity of GERD symptoms using the F-scale. Fourth, the non-GERD patients in this study included patients with functional dyspepsia. Since some studies have reported that functional dyspepsia is associated with sleep disturbances (38, 39), the prevalence of sleep disturbances in the non-GERD patients was likely underestimated in this study. Finally, we did not include all confounding factors in our analysis, although it is difficult to systematically analyze all factors associated with sleep disturbances.

In conclusion, approximately half of the GERD patients in this study experienced sleep disturbances. Daytime sleepiness was more common in GERD patients with sleep disturbances. Prevalence of anxiety and depression was high in patients with sleep disturbances, suggesting that psychological factors are not specific for the sleep disturbances observed in GERD. Moreover, GERD patients with sleep disturbances had poorer scores on the physical components of HR-QOL.

The authors state that they have no Conflict of Interest (COI).

References

- Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* **54**: 710-717, 2005.
- Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. *J Gastroenterol* **44**: 518-534, 2009.
- Shaker R, Castell DO, Schoenfeld PS, Spechler SJ. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup survey conducted on behalf of the American Gastroenterological Association. *Am J Gastroenterol* **98**: 1487-1493, 2003.
- Farup C, Kleinman L, Sloan S, et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. *Arch Intern Med* **161**: 45-52, 2001.
- Suganuma N, Shigedo Y, Adachi H, et al. Association of gastroesophageal reflux disease with weight gain and apnea, and their disturbance on sleep. *Psychiatry Clin Neurosci* **55**: 255-256, 2001.
- Fass R, Quan SF, O'Connor GT, Ervin A, Iber C. Predictors of heartburn during sleep in a large prospective cohort study. *Chest* **127**: 1658-1666, 2005.
- Kusano M, Kouzu T, Kawano T, Ohara S. Nationwide epidemiological study on gastroesophageal reflux disease and sleep disorders in the Japanese population. *J Gastroenterol* **43**: 833-841, 2008.
- Mody R, Bolge SC, Kannan H, Fass R. Effects of gastroesophageal reflux disease on sleep and outcomes. *Clin Gastroenterol Hepatol* **7**: 953-959, 2009.
- Jung HK, Choung RS, Talley NJ. Gastroesophageal reflux disease and sleep disorders: evidence for a causal link and therapeutic implications. *J Neurogastroenterol Motil* **16**: 22-29, 2010.
- Fujiwara Y, Kohata Y, Kaji M, et al. Sleep dysfunction in Japanese patients with gastroesophageal reflux disease: prevalence, risk factors, and efficacy of rabeprazole. *Digestion* **81**: 135-141, 2010.
- Dean BB, Crawley JA, Schmitt CM, Wong J, Ofman JJ. The burden of illness of gastro-oesophageal reflux disease: impact on work productivity. *Aliment Pharmacol Ther* **17**: 1309-1317, 2003.
- Dubois RW, Aguilar D, Fass R, et al. Consequences of frequent nocturnal gastro-oesophageal reflux disease among employed adults: symptom severity, quality of life and work productivity. *Aliment Pharmacol Ther* **25**: 487-500, 2007.
- Swanson LM, Arnedt JT, Rosekind MR, et al. Sleep disorders and work performance: findings from the 2008 National Sleep Foundation Sleep in America poll. *J Sleep Res* **20**: 487-494, 2011.
- Kim K, Uchiyama M, Okawa M, Liu X, Ogihara R. An epidemiological study of insomnia among the Japanese general population. *Sleep* **23**: 41-47, 2000.
- Kim K, Uchiyama M, Liu X, et al. Somatic and psychological complaints and their correlates with insomnia in the Japanese general population. *Psychosom Med* **63**: 441-446, 2001.
- Doi Y, Minowa M, Okawa M, Uchiyama M. Prevalence of sleep disturbance and hypnotic medication use in relation to sociodemographic factors in the general Japanese adult population. *J Epidemiol* **10**: 79-86, 2000.
- Doi Y, Minowa M, Uchiyama M, Okawa M. Sleep-medication for symptomatic insomnia in the general population of Japan. *Sleep Biol Rhythms* **3**: 149-157, 2005.
- Wallander MA, Johansson S, Ruigomez A, Garcia Rodriguez LA, Jones R. Morbidity associated with sleep disorders in primary care: a longitudinal cohort study. *Prim Care Companion J Clin Psychiatry* **9**: 338-345, 2007.
- Doi Y, Minowa M, Uchiyama M, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. *Psychiatry Res* **97**: 165-172, 2000.
- Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* **28**: 193-213, 1989.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* **14**: 540-545, 1991.
- John MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth Sleepiness Scale: failure of the MSLT as a gold standard. *J Sleep Res* **9**: 5-11, 2000.
- Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* **2**: 297-307, 2001.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* **67**: 361-370, 1983.
- Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* **52**: 69-77, 2002.
- Fukuhara S, Suzukamo Y. Manual of the SF-8 Japanese version: Institute for Health Outcomes & Process Evaluation Research. Kyoto, 2004.
- McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* **31**: 247-263, 1993.
- Ware JE, Kosinski M, Kellar SD. SF-36 Physical and Mental Summary Scales: A User's Manual. The Health Institute, Boston, MA, 1994.
- Owens JF, Matthews KA. Sleep disturbance in healthy middle-aged women. *Maturitas* **30**: 41-50, 1998.
- Papadimitriou GN, Linkowski P. Sleep disturbance in anxiety disorders. *Int Rev Psychiatry* **17**: 229-236, 2005.
- Jansson C, Nordenstedt H, Wallander MA, et al. A population-based study showing an association between gastroesophageal reflux disease and sleep problems. *Clin Gastroenterol Hepatol* **7**: 960-965, 2009.

32. Morse CA, Quan SF, Mays MZ, Green C, Stephen G, Fass R. Is there a relationship between obstructive sleep apnea and gastro-oesophageal reflux disease? *Clin Gastroenterol Hepatol* **2**: 761-768, 2004.
33. Fujiwara Y, Arakawa T, Fass R. Gastroesophageal reflux disease and sleep disturbances. *J Gastroenterol* **47**: 760-769, 2012.
34. Nakahara K, Fujiwara Y, Tsukahara T, et al. Acid reflux directly causes sleep disturbances in rat with chronic esophagitis. *PLoS One* **9**: e106969, 2014.
35. Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. *Am J Gastroenterol* **100**: 1914-1922, 2005.
36. Johnson D, Crawley JA, Hwang C, Brown K. Clinical trial: esomeprazole for moderate-to-severe nighttime heartburn and gastro-oesophageal reflux disease-related sleep disturbances. *Aliment Pharmacol Ther* **32**: 182-190, 2010.
37. Fass R, Johnson DA, Orr WC, et al. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. *Am J Gastroenterol* **106**: 421-431, 2011.
38. Lacy BE, Everhart K, Crowell MD. Functional dyspepsia is associated with sleep disorders. *Clin Gastroenterol Hepatol* **9**: 410-414, 2011.
39. Futagami S, Yamawaki H, Izumi N, et al. Impact of sleep disorders in Japanese patients with functional dyspepsia (FD): nizatidine improves clinical symptoms, gastric emptying and sleep disorders in FD patients. *J Gastroenterol Hepatol* **28**: 1314-1320, 2013.