—Review—

Sleep Disorders in Functional Dyspepsia and Future Therapy

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Abstract

Sleep disorder is a common medical problem. Sleep disorder has been associated with several diseases, including pulmonary disease, gastroesophageal reflux disease (GERD) and fibromyalgia. Interest in sleep phenomenology and gastrointestinal functioning has recently increased, because sleep disorder causes significant morbidity, as evidenced by the increased need for general medical and mental health treatment for emotional problems. A number of studies have found an association between sleep disorders and functional gastrointestinal (GI) disorders. Although arousal from sleep serves several protective roles, such as increase in the speed of esophageal clearance and in airway refluxes to prevent aspiration, awakening from sleep unfortunately induces impairment of sleep quality. Some investigations about the relationship between psychogenic factors and gut motility are controversial. In addition, reports of alterations in gut motility during sleep have also been contradictory. We have evaluated sleep disorder in functional dyspepsia (FD) patients using Pittsburgh Sleep Quality Index (PSQI) score. In our recent data, PSQI score of FD patients was significantly higher compared to that in healthy volunteers. Another study has reported that the distribution of subjects who thought that they got enough sleep was significantly lower for the FD/irritable bowel syndrome (IBS) subjects than for control subjects. Several studies have reported that anti-acid therapy and prokinetic agents are effective for certain FD patients. In addition, previous study has reported tricyclic antidepressants (TCA) drugs are effective for some FD patients. Finally, new drug, actiamide, a muscarinic antagonist and cholinesterase inhibitor, significantly improves Postprandial Distress Syndrome (PDS) symptoms. It might be critical issues for determination of precise mechanism for functional gastrointestinal disorders to clarify the relationship between gut motility and sleep disorders.
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Key words: functional dyspepsia, functional gastrointestinal disorders, gastric motility, sleep disorders

Introduction

Sleep disorder is a common medical problem. 50% or more of American adults experiencing 1 or more symptoms that indicate insomnia at least a few nights per week. An epidemiological survey on insomnia demonstrated that from 17.3% to 22.3% of

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the general Japanese population suffer from sleep disorders[1–3]. Interest in sleep phenomenology and gastrointestinal functioning has recently increased. Sleep disorder causes significant morbidity, as evidenced by the increased need for general medical and mental health treatment for emotional problems[4]. Then, sleep disorder has been associated with several diseases, including pulmonary disease, gastroesophageal reflux disease (GERD) and fibromyalgia[5]. Interestingly, a number of studies have found an association between sleep disorders and functional GI disorders[6–8]. Sleep disorder reported by patients with GERD is substantially improved by the use of proton-pump inhibitor (PPI) therapy or anti-reflux surgery[9]. There were a few reports concerning the relationship between sleep disorders and functional dyspepsia (FD)[10,11]. The clarification for sleep disorder and gastrointestinal functioning promises to create a new dimension in the understanding of the pathophysiology of a variety for functional gastrointestinal disorders.

Pathophysiology of Patients with Functional Dyspepsia (FD)

FD has been subclassified into two new disease categories under the Rome III classification criteria: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS)[12]. Most patients with FD complain of various symptoms related to the intake of meals; however, the pathophysiology of FD remains poorly defined[13,14]. A number of potentially important abnormalities have been reported in patients with FD, including impaired fundic accommodation [15], gastric hypersensitivity to distention[16], abonormal duodenojejunal motility[17], duodenal motor and sensory dysfunction[18], duodenal hypersensitivity[19], hereditary factors[20,21], *Helicobacter pylori (H. pylori)* infection[22] and other infections. In our previous study, in post-infectious FD patients, migration of activated macrophages stimulated by Monocyte Chemoattractant Protein-1 (MCP-1) in the duodenal mucosa might contribute to the development of clinical symptoms[23]. Although the Rome III criteria exclude gastroesophageal reflux symptoms from the panel of clinical symptoms of patients with FD, some degree of overlap between the symptoms of non-erosive reflux disease (NERD) and FD is inevitable. Impairment of gastric motility such as gastric emptying is strongly associated with the pathophysiology of FD, which is one of the most common gastrointestinal disorders[24]. We have previously reported that the Tmax value as the point of maximun speed of gastric emptying for a marker of gastric emptying in PDS patients was significantly greater compared with that of healthy volunteers[25]. We have reported that prokinetics such as mosapride citrate, improve clinical symptoms by affecting the Tmax value in PPI-resistant NERD patients with impaired gastric emptying[26]. In addition, we have also reported that nizatidine significantly improved both gastric emptying and clinical symptoms in FD patients with impaired gastric emptying[27]. Therefore, we have considered that Tmax and $T_{1/2}$ values representing the time when 50% of the initial gastric content was emptied using ^{13}C-acetate breath test were the useful marker for treatment of FD patients.

Sleep Disorders and Functional Gastrointestinal Disorders

Reflux events that occur during arousal are usually postprandial and rapidly cleared. During sleep, however, acid clearance is prolonged and the number of total reflux episodes is decreased. Nighttime heartburn is present in about 70% of GERD patients in the USA. A majority of these patients experience sleep difficulties[28]. Although arousal from sleep serves several protective roles, such as an increase in the speed of esophageal clearance and in airway reflexes to prevent aspiration, awakening from the sleep unfortunately induces impairment of sleep quality[29]. Yi et al. have reported that NERD patients have greater Pittsburgh Sleep Quality Index (PSQI) scores than do healthy subjects[30]. Kusano et al. have reported that sleep disorders, such as inability to sleep, difficulty falling asleep, and awakening in the night, are present in 56.3% of patients with heartburn[31]. Goldsmith et al. have shown that irritable bowel syndrome (IBS) symptoms also correlate with the

quality of the previous night's sleep[32]. We have also evaluated sleep disorder in FD patients using PSQI score. A Japanese version of the PSQI[33] was used to measure the patient's recent history of sleep quality and the sleep duration during the month immediately preceding the study. Our data also shows that diarrhea and constipation are significantly (p=0.002; p=0.002) associated with the global PSQI score (submitted data)[34].

Relationship between Gut Motility and Psychogenic Factors in Functional Gastrointestinal Disorders

Psychiatric illness is common in functional gastrointestinal disorders such as IBS and FD and has been proposed to contribute to symptom development. In addition, emotional disorders are also common in FD. Psychiatric disorders in IBS include depression, anxiety, neuroticism, somatization, hypochondriasis, and stress. Investigators report elevations in both state anxiety and trait anxiety, a stable personality trait, in FD[35]. Therefore, it is possible that both sleep disorders and functional GI disturbances might result from an underlying psychological problem, such as depression and anxiety. Oudenhove et al. have reported that state-anxiety is significantly and negatively correlated with discomfort threshold and pain threshold[35]. Geeraerts et al. have reported that experimentally induced anxiety is associated with decreased gastric compliance and accommodation to a meal and with increased epigastric symptom score during a standard nutrient challenge in healthy volunteers[36]. Rhudy et al. have also demonstrated lower somatic pain thresholds in healthy volunteers during anxiety induced by uncertain expectation of pain[37]. Some studies have suggested that the presence of anxiety can modulate gut function and produce gastrointestinal disorders[38–40]. In addition, De la Roca-Chiapas JM et al. have reported that $T_{1/2}$ is positively correlated with state-anxiety[40]. In contrast, Johnston et al. have reported that there was no significant difference between either State-Trait Anxiety Inventory (STAI)-trait or STAI-state, and functional heartburn or erosive esophagitis[41]. However, in our data, there was not significant correlation between Tmax value or $T_{1/2}$ and STAI-trait/-state scores (submitted data)[34].

Sleep Disorders and Functional Dyspepsia

Some studies concerning about gastric motility during sleep are controversial. There are no conclusive results with regard to either the motor functioning of the stomach, or its ultimate consequence, gastric emptying[42]. In addition, further studies, including studies of the basic electrical properties of the stomach, might be needed to clarify the relationship between sleep disorders and gastric motility in patients with FD.

Actually, in our recent data, PSQI score of FD patients was significantly higher compared to that in healthy volunteers[34]. Miwa et al. have also reported that the percentage of subjects who thought that they got enough sleep was significantly lower for the FD/IBS subjects than for control subjects[43]. In addition, Lacy et al. have reported that PSQI scores are higher in patients with FD whose symptoms are moderate or severe[11].

Treatment for Functional Dyspepsia and Future Therapy

Talley et al. have reported that smoking, alcohol, aspirin and NSAID were not associated with an increased risk of functional dyspepsia in outpatients undergoing endoscopy[44]. Carvalho et al. have reported that food intolerance has no apparent effect on food pattern or nutritional status in most patients with FD[45]. They have investigated forty-one functional dyspepsia patients and 30 healthy volunteers answered a questionnaire to identify eating habits and food intolerance and then wrote a 7-day alimentary diary. In contrast, Pilichiewicz et al. have reported that a high-fat meal induces more symptoms than an isocaloric high-carbohydrate meal[46]. Furthermore, the relationship between *H. pylori* infection and FD patients remains controversial. The main reason for *H. pylori* eradication in patients with FD may be related more

to other potential beneficial effects than to symptomatic improvement[47]. In addition, further studies will be needed to evaluate the effect of eradication therapy against FD patients in long-term period[48].

Several studies have reported that anti-acid therapy and prokinetic agents are effective for certain FD patients. Lacy et al. have reported that twelve randomized controlled trials (RCTs) compared H_2RAs (histamin H_2 receptor antagonist) with placebo evaluating a total 2,183 participants. An average of 54% of subjects had a statistically significant improvement in dyspeptic symptoms with H_2RA therapy compared with 40% in the placebo arm[49]. A comparison of PPI therapy to H_2RA therapy with nonulcer dyspepsia showed a trend towards a better outcome based on global dyspepsia cure with a PPI, although the difference was not statistically significant[50]. Epigastric pain and postprandial fullness were improved by H_2RA therapy compared with placebo with no significant improvement in other individual symptoms. Then, PPIs have been widely used to treatment of dyspeptic symptoms and in patients with the diagnosis of FD. Evidence from RCTs suggests that PPIs have limited efficacy of PPIs against FD and should be prescribed only if patients have co-existing reflux symptoms. Although prokinetic agents are conceptually appealing given their potential to improve gastric emptying, and are commonly used throughout the world, treatment results in patients with FD have been underwhelming.

Systemic reviews have shown that tricyclic antidepressants (TCAs) are effective for chronic pain syndromes[51] and IBS[52]. Clinicians have also used TCAs to treat FD, but the evidence for their efficacy is limited[53]. RCTs in healthy volunteers have shown that TCAs do not affect gastric motor function[54] or improve satiety[55] after a drink test.

New drug, actiamide, a muscarinic antagonist and cholinesterase inhibitor, improves gastric motility and gastric emptying in rodents and dogs. Matsueda et al. have reported significant improvement in PDS symptoms in patients treated with acotiamide[56].

Conclusions

Sleep disturbance, appetite loss and depression are closely associated with the pathophysiology of FGIDs. It might be critical issues for determination of precise mechanisms for functional gastrointestinal disorders to clarify the relationship between gastrointestinal functioning and sleep disorder.

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References

1. 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 Epidermiol 2000; 10: 79–86.
2. Kim K, Uchiyama M, Okawa M, Liu X, Ogihara R: An epidemiological study of insomnia among the Japanese general population. Sleep 2000; 23: 41–47.
3. Kim K, Uchiyama M, Liu X, et al.: Somatic and psychological complains and their correlates with insomnia in the Japanese general population. Psychosom Med 2001; 63: 441–446.
4. Weissman MM, Greenwald S, Nino-Murcia G, Dement WC: The morbidity of insomnia uncomplicated by psychiatric disorders. Gen Hosp Psychiatry 1997; 19: 245–250.
5. Parish J: Sleep-related problems in common medical conditions. Chest 2009; 135: 563–572.
6. Fass R, Fullerton S, Tung S, Mayer EA: Sleep disturbances in clinic patients with functional bowel disorders. Am J Gastroenterol 2000; 95: 1195–2000.
7. Jarrett M, Heitkemper M, Cain KC, Burr RL, Hertig V: Sleep disturbance influences gastrointestinal symptoms in women with irritable bowel syndrome. Dig Dis Sci 2000; 45: 952–959.
8. Goldsmith G, Levin JS: Effect of sleep quality on symptoms of irritable bowel syndrome. Dig Dis Sci 1993; 38: 1809–1814.
9. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group: The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006; 101: 1900–1920.
10. Vege SS, Locke GR 3rd, Weaver AL, Farmer SA, Melton LJ 3rd, Talley NJ: Functional gastrointestinal disorders among people with sleep disturbances: a population-based study. Mayo Clin Proc 2004; 79: 1501–1506.
11. Lacy BE, Everhart K, Crowell MD: Functional dyspepsia is associated with sleep disorders. Clin Gastroenterol Hepatol 2011; 9: 410–414.

12. Tack J, Talley NJ, Camilleri M, et al.: Functional gastroduodenal disorders. Gastroenterology 2006; 130: 1466–1479.
13. Talley NJ, Zinsmeister AR, Schleck CD, Melton LJ 3rd: Dyspepsia and dyspepsia subgroups: a population-based study. Gastroenterology 1992; 102 (Pt 1): 1259–1268.
14. Castillo EJ, Camilleri M, Locke GR, et al.: A community-based, controlled study of the epidemiology and pathophysiology of dyspepsia. Clin Gastroenterol Hepatol 2004; 2: 985–996.
15. Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J: Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 1998; 115: 1346–1352.
16. Lunding JA, Tefera S, Gilja OH, et al.: Rapid initial gastric emptying and hypersensitivity to gastric filling in functional dyspepsia:effects of duodenal lipids. Scand J Gastroenterol 2006; 41: 1028–1036.
17. Holtmann G, Goebell H, Talley J: Impaired small intestinal peristaltic refluxes and sensory thresholds are independent functional disturbances in patients with chronic unexplained dyspepsia. Am J Gastroenterol 1996; 91: 485–491.
18. Samsom M, Verhagen MA, vanBerge Henegouwen GP, Smout AJ: Abnormal clearance of exogenous acid and increased acid sensitivity of the proximal duodenum in dyspeptic patients. Gastroenterology 1999; 116: 515–520.
19. Takahashi Y, Amano Y, Yuki T, et al.: Influence of acid suppressants on gastric emptying: cross-over analysis in healthy volunteers. J Gastroenterol Hepatol 2006; 21: 1664–1668.
20. Shimpuku M, Futagami S, Kawagoe T, et al.: G-protein β3 subunit 825CC genotype is associated with postprandial distress syndrome with impaired gastric emptying and with the feeling of hunger in Japanese. Neurogastroenterol Motil 2011; 23: 1073–1080.
21. Holtmann G, Siffert W, Haag S, et al.: G-protein beta 3 subunit 825 CC genotype is associated with unexplained (functional) dyspepsia. Gastroenterology 2004; 126: 971–979.
22. Quigley EM: Gastric motor and sensory function, and motor disorders of the stomach. In Gastrointestinal and liver disease, pathophysiology／diagnosis／management (Feldman M, Friedman LS, Sleisenger MH, eds), 2002; pp 691–714, WB Sanders, Philadelphia.
23. Futagami S, Shindo T, Kawagoe T, et al.: Migration of eosinophils and CCR2-/CD68-double positive cells into the duodenal mucosa of patients with postinfectious functional dyspepsia. Am J Gastroenterol 2010; 105: 1835–1842.
24. Quigley EM: Gastric emptying in functional gastrointestinal disorders. Aliment Pharmacol Ther 2004; 20(suppl 7): 56–60.
25. Shindo T, Futagami S, Hiratsuka T, et al.: Comparison of gastric emptying and plasma ghrelin levels in patients with functional dyspepsia and non-erosive reflux disease. Digestion 2009; 79: 65–72.
26. Futagami S, Iwakiri K, Shindo T, et al.: The prokinetic effect of mosapride citrate combined with omeprazole therapy improves clinical symptoms and gastric emptying in PPI-resistant NERD patients with delayed gastric emptying. J Gastroenterol 2010; 45: 413–421.
27. Futagami S, Shimpuku M, Song JM, et al.: Nizatidine improves clinical symptoms and gastric emptying in patients with functional dyspepsia accompanied by impaired gastric emptying. Digestion 2012; 86: 114–121.
28. 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 Gastroenterology 2003; 98: 1487–1493.
29. Gerson LB, Fass R: A systemic review of the definitions, prevalence, and response to treatment of nocturnal gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2009; 7: 372–378.
30. Yi CH, Hu CT, Chen CL: Sleep dysfunction in patients with GERD: erosive versus nonerosive reflux disease. Am J Med Sci 2007; 334: 168–170.
31. Kusano M, Kouzu T, Kawano T, Ohara S: Nationwide epidemiological study on gastroesophageal reflux disease and sleep disorders in the Japanese population. J Gastroenterol 2008; 43: 833–841.
32. Goldsmith G, Levin JS: Effect of sleep quality on symptoms of irritable bowel syndrome. Dig Dis Sci 1993; 38: 1809–1814.
33. Doi Y, Minowa M, Okawa M, et al.: Development of the Japanese version of the Pittsburgh Sleep Quality Index. Jpn J Psychiatr Treat 1998; 13: 755–763 (in Japanese).
34. Futagami S, Izumi N, Shimpuku M, 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 in press.
35. Van Oudenhove L, Vandenberghe J, Geeraerts B, et al.: Relationship between anxiety and gastric sensorimotor function in functional dyspepsia. Psychosom Med 2007; 69: 455–463.
36. Geeraerts B, Vandenberghe J, Van Oudenhove L, et al.: Influence of experimentally induced anxiety on gastric sensorimotor function in humans. Gastroenterology 2005; 129: 1437–1444.
37. Rhudy JL, Meagher MW: Fear and anxiety: divergent effects on human pain thresholds. Pain 2000; 84: 65–75.
38. Lorena SL, Tinois E, Brunetto SQ, Camargo EE, Mesquita MA: Gastric emptying and intragastric distribution of a solid meal in functional dyspepsia: influence of gender and anxiety. J Clin Gastroenterol 2004; 38: 230–236.
39. Monnikes H, Tebbe JJ, Hildebrandt M, et al.: Role of stress in functional gastrointestinal disorders. Evidence for stress-induced alterations in gastrointestinal motility and sensitivity. Dig Dis 2001; 19: 201–211.
40. De la Roca-Chiapas JM, Solis-Ortiz S, Fajardo-Araujo M, Sosa M, Cordova-Fraga T, Rosa-Zarate A: Stress profile, coping style, anxiety, depression, and gastric emptying as predictors of functional dyspepsia: a case-control study. J Psychosom Res 2010; 68: 73–81.
41. Johnston BT, Lewis SA, Love AH: Stress, personality and social support in gastro-oesophageal reflux

disease. J Psychosom Res 1995; 39: 221–226.
42. Orr WC: Gastrointestinal physiology. In Principl Pract Sleep Med, 3ed. 2000; pp 279–288.
43. Miwa H: Life style in persons with functional gastrointestinal disorders-large-scale internet survey of lifestyle in Japan. Neurogastroenterol Motil 2012; 24: 464–471.
44. Talley N, Weaver AL, Zinsmeister AR: Smoking, alcohol, and nonsteroidal anti-inflammatory drugs in outpatients with functional dyspepsia. Am J Gastroenterol 1994; 89: 524–528.
45. Carvalho RV, Lorena SL, Almeida JR, Mesquita MA: Food intolerance, diet composition, and eating patterns in functional dyspepsia patients. Dig Dis Sci 2010; 55: 60–65.
46. Pilichiewicz AN, Feltrin KL, Horowitz M, et al.: Functional dyspepsia is associated with a greater symptomatic response to fat but not carbohydrate, increased fasting and postprandial CCK, and diminished PYY. Am J Gastroenterol 2008; 103: 2613–2623.
47. Chey WD, Moayyedi P: Uninvestigated dyspepsia and non-ulcer dyspepsia-the use of endoscopy and the roles of Helicobacter pylori eradication and antisecretory therapy. Aliment pharmacol Ther 2004; 19 suppl 1: 1–8.
48. Futagami S, Shimpuku M, Yin Y, et al.: Pathophysiology of Functional dyspepsia. J Nippon Med Sch 2011; 78: 280–285.
49. Lacy BE, Talley NJ, Locke GR 3rd, et al.: Review article: current treatment options and management of functional dyspepsia. Aliment Pharmaol Ther 2012; 36: 3–15.
50. Blum AL, Arnold R, Stolte M, Fischer M, Koelz HR: Short course acid suppressive treatment for patients with functional dyspepsia: results depend on Helicobacter pylori status. Gut 2000; 47: 473–480.
51. Saarto T, Wiffen PJ: Antidepressants for neuropathic pain. Cochrane Detabase Syst Rev 2007; 4: CD005454.
52. Ford AC, Talley N, Schoenfeld PS, Quigley EM, Moayyedi P: Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systemic review and meta-analysis. Gut 2009; 58: 367–378.
53. Talley NJ, Herrick L, Locke GR: Antidepressants in functional dyspepsia. Exper Rev Gastroenterology Hepatol 2010; 4: 5–8.
54. Talley NJ, Camilleri M, Chitkara DK, et al.: Effects of desipramine and escitalopram on postprandial symptoms induced by the nutrient drink test in healthy volunteers: a randomized, double-blind, placebo-controlled study. Digestion 2005; 72: 97–103.
55. Choung RS, Cremonini F, Thapa P, Zinsmeister AR, Talley NJ: The effect of short-term, low-dose tricyclic and tetracyclic antidepressant treatment on satiation, postnutrient load gastrointestinal symptoms and gastric emptying: double-blind, randomized, placebo-controlled trial. Neurogastroenterol Motil 2008; 20: 220–227.
56. Matsueda K, Hongo M, Tack J, et al.: Clinical trial: dose-dependent therapeutic efficacy of acotiamide hydrochloride (Z-338) in patients with functional dyspepsia-100 mg t.i.d.is an optimal dosage. Neurogastroenterol Motil 2010; 22: 618–e173.

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