—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\(^9\). 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\(^1\). Then, sleep disorder has been associated with several diseases, including pulmonary disease, gastroesophageal reflux disease (GERD) and fibromyalgia\(^2\). Interestingly, a number of studies have found an association between sleep disorders and functional GI disorders\(^6\). Sleep disorder reported by patients with GERD is substantially improved by the use of proton-pump inhibitor (PPI) therapy or anti-reflux surgery\(^7\). There were a few reports concerning the relationship between sleep disorders and functional dyspepsia (FD)\(^10\). 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)\(^8\). Most patients with FD complain of various symptoms related to the intake of meals; however, the pathophysiology of FD remains poorly defined\(^11\). A number of potentially important abnormalities have been reported in patients with FD, including impaired fundic accommodation\(^12\), gastric hypersensitivity to distention\(^13\), abnormal duодenojejunal motility\(^14\), duodenal motor and sensory dysfunction\(^15\), duodenal hypersensitivity\(^16\), hereditary factors\(^17\), *Helicobacter pylori* (*H. pylori*) infection\(^18\) 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\(^19\). 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\(^20\). We have previously reported that the Tmax value as the point of maximum speed of gastric emptying for a marker of gastric emptying in PDS patients was significantly greater compared with that of healthy volunteers\(^21\). 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\(^22\). In addition, we have also reported that nizatidine significantly improved both gastric emptying and clinical symptoms in FD patients with impaired gastric emptying\(^23\). 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\(^24\). 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\(^25\). Yi et al. have reported that NERD patients have greater Pittsburgh Sleep Quality Index (PSQI) scores than do healthy subjects\(^26\). 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\(^27\). Goldsmith et al. have shown that irritable bowel syndrome (IBS) symptoms also correlate with the
quality of the previous night’s sleep. We have also evaluated sleep disorder in FD patients using PSQI score. A Japanese version of the PSQI 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).

**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. 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. 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. Rhudy et al. have also demonstrated lower somatic pain thresholds in healthy volunteers during anxiety induced by uncertain expectation of pain. Some studies have suggested that the presence of anxiety can modulate gut function and produce gastrointestinal disorders. In addition, De la Roca-Chiapas JM et al. have reported that T1/2 is positively correlated with state-anxiety. 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.

However, in our data, there was not significant correlation between Tmax value or T1/2 and STAI-trait-state scores (submitted data).

**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. 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. 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. In addition, Lacy et al. have reported that PSQI scores are higher in patients with FD whose symptoms are moderate or severe.

**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. Carvalho et al. have reported that food intolerance has no apparent effect on food pattern or nutritional status in most patients with FD. 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. 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
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to other potential beneficial effects than to symptomatic improvement\(^8\). In addition, further studies will be needed to evaluate the effect of eradication therapy against FD patients in long-term period\(^6\).

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\(_2\)RAs (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\(_2\)RA therapy compared with 40\% in the placebo arm\(^9\). A comparison of PPI therapy to H\(_2\)RA 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\(^9\). Epi gastric pain and postprandial fullness were improved by H\(_2\)RA 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\(^3\) and IBS\(^5\). Clinicians have also used TCAs to treat FD, but the evidence for their efficacy is limited\(^6\). RCTs in healthy volunteers have shown that TCAs do not affect gastric motor function\(^8\) or improve satiety\(^9\) 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 actiamide\(^8\).

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

41. Johnston BT, Lewis SA, Love AH: Stress, personality and social support in gastro-esophageal reflux
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