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Editorial

Role of Bile Reflux in Functional Dyspepsia: Areas That Need Further Research

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Article: Bile reflux gastropathy and functional dyspepsia
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Functional dyspepsia (FD) is a chronic gastrointestinal disorder defined by upper abdominal symptoms considered to originate from the gastroduodenal region with no structural disease on routine investigation, including upper gastrointestinal endoscopy.[1] A meta-analysis using a broad definition reported that the global prevalence of uninvestigated dyspepsia is 21.0%, with a higher prevalence in women, smokers, users of NSAIDs, and in those with *Helicobacter pylori* infection.[2] In a Korean telephone survey of 5000 subjects who completed the Rome III questionnaire, 7.7% of respondents had dyspepsia symptoms.[3] It is frequently accompanied by gastroesophageal reflux disease or irritable bowel syndrome. Because of the multifactorial nature and heterogeneity of symptoms in FD, the condition's underlying pathophysiology remains unclear. Mechanisms of FD include delayed gastric emptying, disorder of gastric accommodation, hypersensitivity of gastric acid, *H. pylori* infection, inflammation of the duodenum, environmental factors such as spicy food and psychological factors.[4]

Reflux of duodenal contents to the stomach and then to the esophagus is a short-term physiological event rarely leading to symptoms.[5] Excessive duodenogastric reflux (DGR) occurs very commonly in adults secondary to partial gastrectomy, pyloroplasty, and cholecystectomy.[6] The role of DGR of bile in the pathogenesis of FD was investigated in a few studies. One study comparing patients with FD and healthy subjects using bilirubin concentration monitoring (Bilitec 2000, Medtronic) revealed that significant longer periods of bilirubin exposure are observed in patients with FD and the total number of reflux and the number of reflux episode, lasting over 5 minutes were also higher.[7] However, there are few studies on the association of bile reflux, FD, severity of symptoms, and response to treatment in FD patients undergoing cholecystectomy.

In this issue of the *Journal of Neurogastroenterology and Motility*, Lake et al[8] investigated the association of bile reflux gastropathy and FD and identified the predisposing factors in a retrospective study. Patients with dyspepsia who fulfilled the Rome III criteria were included and underwent esophagogastroduodenoscopy and gastric biopsies. A total of 262 patients were included in the study and were stratified into 3 cohorts: bile gastropathy (BG) group (n = 90), non-bile gastropathy (NBG) group (n = 121), and no gastropathy (NG; n = 51). Patients with BG reported significantly more severe abdominal pain than patients with NBG or NG group ($P < 0.05$), and had significantly higher prevalence of

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cholecystectomy (68.0%) than patients with NBG (35.0%) or NG (22.0%) groups. BG patients has significantly higher prevalence of gastric erythema than NBG patients (88.9% vs 63.6%; $P < 0.01$) in endoscopic examination and showed an increase in the prevalence of gastritis (37.8% vs 7.4%), edema (30.0% vs 0.8%), and chronic active inflammation (7.8% vs 1.7%) than the NBG group on pathological examination. According to multivariate regression modeling comparing the BG group (n = 90) vs NBG + NG group (n = 172), cholecystectomy was significantly associated with BG (OR, 6.60; 95% CI, 1.87-23.30; $P = 0.003$). Cholecystectomy was also significantly associated with severe abdominal pain (OR, 2.049; 95% CI, 1.09-3.86; $P = 0.026$) and chronic prescription narcotics than those without cholecystectomy (30.0% vs 14.0%; $P = 0.003$).

This study has limitations because it is retrospective study and has referral bias because this study was conducted in a tertiary center. In addition, since there was no data for *H. pylori*, one of the important causes of FD, there was a possibility that the adjustment for this confounding factor in multivariate analysis was not sufficient. Also, although a small study, contrary to this study, one study reported that FD patients who underwent cholecystectomy were not different from those of FD patient without the surgery history in gastric motility, DGR, and symptom scores.[9] Therefore, further studies are needed on the severity of symptoms and response to treatment in FD patients who underwent cholecystectomy.

For the treatment of dyspepsia with DGR, both sucralfate and rabeprazole therapies are known to be effective treatment options for the dyspeptic symptoms and histologic improvement compared with placebo.[10] Domperidone can also significantly decrease the nocturnal duodenogastric bile reflux compared with placebo in patients with nocturnal dyspeptic symptoms and increased duodenogastric bile reflux time (intragastric bilirubin absorbance > 0.14).[11] Although the treatment options of patients with DGR are not thought to be different from the general FD treatment, in this study, a high rate of taking narcotics in patients who had undergone cholecystectomy was reported. Therefore, when treating FD patients with DGR, it is necessary to consider the possibility of patients not responding well to general FD treatments such as proton pump inhibitors, prokinetics, and mucoprotectives. In order for bile reflux to be recognized as one of the important causes of FD, more studies on pathophysiology and effective therapeutics are needed in the future.

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References

1. Wauters L, Talley NJ, Walker MW, et al. Novel concepts in the pathophysiology and treatment of functional dyspepsia. Gut 2020;69:591-600.
2. Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for uninvestigated dyspepsia: a meta-analysis. Gut 2015;64:1049-1057.
3. Talley NJ. Functional dyspepsia: new insights into pathogenesis and therapy. Korean J Intern Med 2016;31:444-456.
4. Talley NJ, Ford AC. Functional dyspepsia. N Engl J Med 2015; 373:1853-1863.
5. Arslan M, Balamtekin N. The relationship between primary duodenogastric reflux and *Helicobacter pylori* gastritis in children. Dig Dis Published Online First: 19 May 2021. doi:10.1159/000517263.
6. Zullo A, Rinaldi V, Hassan C, Lauria V, Attili AF. Gastric pathology in cholecystectomy patients: role of *Helicobacter pylori* and bile reflux. J Clin Gastroenterol 1998; 27:335-338.
7. Szadkowsko K, Romanowski M, Chojnacki C. [The diagnostic value of 24-hour bile reflux monitoring in patients with functional dyspepsia]. Pol Merkur Lekarski 2009;26:378-381. [Polish]
8. Lake A, Rao SSC, Larion S, Spartz H, Kavuri S. Bile reflux gastropathy and functional dyspepsia. J Neurogastroenterol Motil 2021;27:400-407.
9. Mearin F, Ribot X, Balboa A, MAntolín M, Varas MJ, Malagelada JR. Duodenogasric bile reflux and gastrointestinal motility in pathogenesis of functional dyspepsia. Role of cholecystectomy. Dig Dis Sic 1995;40:1703-1709.
10. Santarelli L, Gabrielli M, Candelli M, et al. Post-cholecystectomy alkaline reactive gastritis: a randomized trial comparing sucralfate versus rabeprazole or no treatment. Eur J Gastroenterol Hepatol 2003;15:975-979.
11. Chen SL, Ji JR, Ping X, et al. Effect of domperidone therapy on nocturnal dyspeptic symptoms of functional dyspepsia patients. World J Gastroenterol 2010;16:613-617.