

Overlap Syndrome of Functional Dyspepsia and Irritable Bowel Syndrome - Are Both Diseases Mutually Exclusive?

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Among functional gastrointestinal (GI) disorders, functional dyspepsia (FD) and irritable bowel syndrome (IBS) are important to public health around the world and are frequently encountered in general practice. Upper GI symptoms such as heartburn, postprandial fullness, early satiety, epigastric pain or burning and lower GI symptoms such as constipation and diarrhea often coexist. Although the prevalence of FD-IBS overlap would be influenced by the selection of the study population, the overlap rate of FD-IBS could be in the range of 11%-27%. Specifically, FD-IBS overlap is associated with more severe symptoms than FD alone or IBS alone. Since clinical overlap, especially FD-IBS overlap, is very common, the 2 syndromes should not be treated in a mutually exclusive fashion.

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Key Words

Dyspepsia; Epigastric pain syndrome; Health-related quality of life; Irritable bowel syndrome; Postprandial distress syndrome

Introduction

Epidemiological studies suggest a considerably high rate of overlap between functional dyspepsia (FD) and irritable bowel syndrome (IBS). According to the recent systematic review and metaanalysis,¹ the prevalence of IBS in subjects with dyspepsia is 37% (95% CI, 30%-45%) as compared to 7% (95% CI, 5%-10%) in those without. The pooled odds ratio for IBS in subjects with dyspepsia was 8 (95% CI, 5.74-11.16) as compared to that

in those without dyspepsia. However, the original studies used an older classification such as Manning's, Rome I or II, than Rome III and also did not exclude organic diseases, possibly resulting in the contamination with peptic ulcer diseases or reflux esophagitis.

Prevalence of Overlap Between Functional Dyspepsia and Irritable Bowel Syndrome

There are a few evaluations of overlap between FD and IBS

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based on the Rome III classification. Kaji et al² conducted a cross-sectional study to examine the prevalences of gastroesophageal reflux, FD and IBS, their overlap rates, and the health-related quality of life (HRQOL) for each disease and each overlap syndrome, as compared with the corresponding values in healthy controls in a Japanese health check-up population. Of the 2,680 eligible subjects, 269 (10.0%) were diagnosed as having FD, and 381 (14.2%) as having IBS. Overlaps between FD and IBS were found in 92 patients (3.4%). Overlap significantly worsened the HRQOL in most domains, except in the “role emotional” domain. The HRQOL was particularly poor in the mental component summary for overlapping IBS.² On the other hand, Nakajima et al³ conducted a survey in a general gastroenterology outpatient clinic of 1,378 consecutive patients. Among them, 29 (2.1%) were diagnosed as having FD, and 33 (2.4%) as IBS. Overlaps between FD and IBS were found in 12 (0.9%).

Wang et al⁴ investigated 3,014 patients who responded to their questionnaires (male:female = 47.2:52.8, response rate 89%) at a general gastroenterology outpatient clinic. FD-IBS overlap was observed in 151 (5.0%) patients, while 457 (15.2%) and 329 (10.9%) were classified as having FD alone and IBS alone, respectively.⁴ As compared with that in the non-IBS cohorts, the OR of having FD among IBS was 2.09 (95% CI, 1.68-2.59). Patients with FD-IBS overlap had higher severity scores for the symptom of postprandial fullness (2.4 ± 1.5 vs 1.7 ± 1.6 , $P < 0.001$) and overall FD symptoms (6.7 ± 2.9 vs 5.8 ± 2.8 , $P < 0.05$) than those with FD alone. The only independent risk factor for FD-IBS overlap versus FD alone was the presence of postprandial fullness (OR, 2.67; 95% CI, 1.34-5.31).⁴

Lee et al⁵ investigated the differences in depressive mood and quality of life (QOL) among Korean patients with FD, IBS and FD-IBS overlap diagnosed by the Rome III definition. According to their report,⁵ out of 279 subjects, 70 (25.1%) and 124 (44.4%) were diagnosed as having FD and IBS, respectively. Patients with FD-IBS overlap and those with FD alone showed higher Beck Depressive Inventory scores than normal subjects ($P < 0.001$ and $P = 0.02$, respectively), whereas those with IBS alone showed no differences in scores from normal subjects ($P = 0.17$). All of the SF-36 (the 36-item Short Form general health survey) subscores of the FD-IBS overlap cohorts were significantly lower than those in normal subjects ($P < 0.05$). Depressive mood was significantly related to FD and FD-IBS overlap, but not to IBS alone. Patients with FD-IBS overlap had a worse QOL than patients with FD alone or IBS alone.⁴ Furthermore, according to the recent report by Park,⁶ the sensi-

tivity and specificity of the Rome III classification in discriminating functional gastrointestinal disorders (FGIDs) from organic diseases of the upper gastrointestinal (GI) tract were 60% and 53%, respectively, while the values of the lower GI tract were 80% and 50%, respectively, partially supporting the use of the Rome III criteria in Korea.⁵

Data on the impact of FD on the HRQOL in the general population are scarce. Aro et al⁷ explored the impact of FD based on the Rome III classification on the HRQOL in the general population. Among 1,001 cohorts, 202 (20%) individuals reported uninvestigated dyspepsia (UID), and 157 (16%) reported FD. FD-IBS overlap had a significant impact on bodily pain ($P < 0.01$) and general health ($P < 0.05$).⁷

Although Hori et al⁸ used the Rome II criteria, they examined concurrent GI symptoms in FD and IBS in a total of 186 college students who filled out a questionnaire administered to determine whether they had UID or IBS. The diagnosis of UID, IBS and UID + IBS overlap was made in 12 (6.7%), 40 (22.1%) and 8 (4.4%) patients, respectively and a significant prevalence of UID + IBS overlap was observed (66.7% IBS in UID; 20.0% UID in IBS).⁸ Although Corsetti et al⁹ also used Rome II criteria for the diagnosis of FD in their questionnaire survey of 309 consecutive FD patients to assess the dyspepsia and IBS symptom patterns, 54% of the patients had FD alone, whereas 46% had FD + IBS. FD-IBS overlap patients were more likely to be female (75% vs 60%, $P < 0.01$) and to have greater weight loss (5.4 ± 0.6 vs 3.5 ± 0.4 kg, $P < 0.05$). Coexisting IBS did not increase the risk of dyspepsia, however, the overall symptom severity was significantly higher in the patients with FD-IBS overlap (12.4 ± 0.4 vs 9.8 ± 0.3 , $P < 0.01$). FD-IBS overlap patients had a lower threshold for first perception (2.9 ± 0.3 vs 3.8 ± 0.3 mmHg, $P < 0.05$) and for discomfort (7.9 ± 0.4 vs 9.5 ± 0.5 mmHg, $P < 0.05$) and a greater prevalence of hypersensitivity to gastric distention (44% vs 28%, $P < 0.05$).⁹

Recently, we performed a web-based survey comprised of Rome III criteria for FD, the Gastrointestinal Symptom Rating Scale, and questions to determine demographic information among subjects registered for Japanese clinical trial programs.¹⁰ Cluster analysis revealed 3 distinct clusters: cluster associated with diarrhea, cluster associated with constipation and cluster associated with neither diarrhea nor constipation. Cluster associated with constipation and cluster associated with diarrhea were significantly linked to the presence of FD, suggesting that FD was more prevalent among participants with bowel symptoms than in those without. Furthermore, FD patients with bowel

symptoms had more severe dyspepsia symptoms than those without.

Although GI symptoms are quite common in the general population, different methods for the survey show different epidemiologies, and the effects of psychosocial and behavioral factors on the symptoms have been studied, mainly by subgroup analysis. According to the Japanese questionnaire survey focusing on GI symptoms and the psycho-behavioral background in members of a registered panel via e-mail and postal mail, despite the difference in the prevalence of GI symptoms, that is, 47% in the electronic survey and 25% in the postal one, similar proportions of symptom subtypes and patterns of overlaps were obtained with such 2 methods.¹¹ While 56% were diagnosed as having FD, and 58% as having IBS in the electronic survey, 57% were diagnosed as having FD, and 55% as having IBS in the postal one. FD-IBS overlap was found in 24% in the electronic survey and in 23% in the postal one. Subjects who have higher scores for psycho-behavioral problems had a higher prevalence of FD and IBS symptoms. The data suggest that psycho-behavioral conditions may affect the development of functional GI symptoms, regardless of the subtype of GI disorders, and can explain the high proportion of overlap among the subtypes.¹¹

Taken together, the above-mentioned prevalence of FD-IBS overlap would be altered depending on the selected study population. The rate of FD-IBS overlap could be in the same range, such as 11.4%,⁶ 16.5%,² 23.8%,⁴ 24.0%³ and 27.6%⁵ (Table).

Influence of Each Subtype of Functional Dyspepsia or Irritable Bowel Syndrome on the Presence of Functional Dyspepsia-Irritable Bowel Syndrome Overlap

A general definition of FD, to be used mainly for clinical

Table. Prevalence of Overlap Between Functional Dyspepsia and Irritable Bowel Syndrome

	FD alone (n [%])	IBS alone (n [%])	FD-IBS overlap (n [%])
Wang et al ⁴	306 (48.2)	178 (28.0)	151 (23.8)
Nakajima et al ³	17 (34.0)	21 (42.0)	12 (24.0)
Kaji et al ²	177 (31.7)	289 (51.8)	92 (16.5)
Lee et al ⁵	28 (18.4)	82 (53.9)	42 (27.6)
Park ⁶	72 (43.1)	76 (45.5)	19 (11.4)

FD, functional dyspepsia; IBS, irritable bowel syndrome.

purposes, and although further research on more specific definitions is ongoing, is provided under category B1: functional dyspepsia (FD) in Rome III classification. However, particularly for pathophysiological and therapeutic approach, it is recommended in Rome III that new entities of meal-induced dyspeptic symptoms as postprandial distress syndrome (PDS): B1a, and epigastric pain and burning as epigastric pain syndrome (EPS): B1b, should be used.¹² These 2 subcategories such as PDS and EPS seem very useful in clinical practice as well as in the investigative settings. According to the report by Wang et al,⁴ more patients with PDS alone had IBS than those with EPS alone. Patients with FD-IBS overlap were more likely to be classified as the PDS + EPS subtype, had more frequent presence of the postprandial fullness symptom, one of major symptoms of PDS ($P < 0.001$), and overall FD symptom ($P < 0.01$) than those with FD alone. Furthermore, patients with FD-IBS overlap were less likely to be classified as the EPS alone ($P < 0.01$) compared to those classified as FD alone. By the multivariate logistic regression analysis, only the presence of postprandial fullness (OR, 2.67; 95% CI, 1.34-5.31; $P < 0.01$) had a statistically significant and independent effect on the probability of FD-IBS overlap. On the other hand, subtypes of IBS did not differ between patients with constipation type-IBS (IBS-C) and diarrhea-type IBS (IBS-D). In addition, neither IBS-D (OR, 1.44; 95%CI, 0.93-2.22; $P = 0.10$) nor mixed-type IBS (IBS-M) (OR, 1.62; 95% CI, 0.77-3.40; $P = 0.21$) was identified as risk factor for FD-IBS overlap versus IBS alone in the multivariable analysis. Aro et al⁷ reported the data on the impact of PDS and EPS on QOL. The impact of PDS is statistically significant compared with controls except for Role Emotional and the results are consistently the same when analyzing for the possible confounders such as anxiety, depression and use of proton pump inhibitors. Patients with EPS had a statistically relevant impairment of HRQOL only in 2 domains such as Bodily Pain and Vitality compared with nondyspeptic cohorts. Namely, PDS seems to damage HRQOL in all SF-36 domains more than EPS.

In addition, non-erosive reflux disease is more frequently overlapped with FD, especially with EPS and presents with significantly increased frequency of IBS.¹³

Pathophysiology Leading to Functional Dyspepsia-Irritable Bowel Syndrome Overlap

FD and IBS are common functional disorders without de-

defined pathophysiology and are known as multifactorial syndromes. The pathophysiological factors for the generation of FD or IBS would be listed as visceral hypersensitivity, central abnormal deregulation for sensory perception, GI dysmotility, and abnormal alteration of the intestinal flora, GI inflammation, and psychosocial factors. Although such a mechanistic investigation is further preceded in the research field in IBS, the detail of pathophysiology in FD-IBS overlap has not been fully explored. However, as these 2 syndromes (FD and IBS) would have common causative factors, the high prevalence of FD-IBS overlap is considered to be easily acceptable.

Abnormalities of psychosocial or central nervous factors, which would affect the whole GI tract, could be a possible causative factor in the pathogenesis of FD-IBS overlap. Savas et al¹⁴ examined the 1-year prevalence of IBS and dyspepsia symptoms and their associations with depression, anxiety and post-traumatic stress disorder (PTSD) among women veterans receiving primary care at a Women's Clinic, Veteran Affairs (VA) Medical Center. They reported that women with IBS-dyspepsia overlap showed higher scores of anxiety (IBS: 24 vs 12, $P < 0.001$ and dyspepsia: 26 vs 12, $P < 0.001$), depression (IBS: 22 vs 11, $P < 0.001$ and dyspepsia: 23 vs 11, $P < 0.001$) and PTSD (IBS: 87 vs 69, $P < 0.001$ and dyspepsia: 86 vs 69, $P < 0.0005$), and age- and ethnicity-adjusted logistic regression analyses revealed a 3- to 46-fold increase in the OR of IBS and dyspepsia among women with depression, anxiety or PTSD.¹⁴ Although gastric sensorimotor dysfunction, psychosocial factors and somatization are all implicated in the development of FD symptoms according to the report by Van Oudenhove et al,¹⁵ symptom severity and weight loss in FD are determined by psychosocial factors (depression or history of abuse) and somatization, and to a lesser extent by gastric sensorimotor function, but not by FD-IBS overlap. On the other hand, Kindt et al¹⁶ in Belgium investigated the 5-year evolution of symptoms in a clinical FD population to identify factors associated with the outcome and indicated that the dyspepsia symptom score (DSS) at the initial visit and trait anxiety were longitudinally associated with the DSS at follow-up, with a trend found for weight loss; depression, chronic fatigue and IBS at follow-up were cross-sectionally associated with DSS.

On the other hand, GI inflammation and altered immune responses could be another candidate as the cause of FD-IBS overlap. Patients with IBS show a greater degree of inflammatory cell infiltration than healthy controls. Mast cells and eosinophils interact with T lymphocytes and may alter the enteric nerve and smooth muscle functions. Examination of 48 IBS patients with

either diarrhea or constipation,¹⁷ 12 patients with microscopic colitis, 20 patients with ulcerative colitis, and 24 healthy controls, indicated that as compared to male IBS patients, female IBS had greater numbers of mast cells ($P = 0.066$), but lesser numbers of CD3+ and CD8+ T cells ($P < 0.01$ and $P < 0.001$, respectively). Such mucosal mast cell infiltration in IBS patients was significantly associated with the frequency of abdominal bloating ($P < 0.05$) and with dysmotility-like dyspepsia ($P = 0.001$), but not with ulcer-like dyspepsia.¹⁷ According to the report by Walker et al,¹⁸ intraepithelial lymphocytes in IBS-C were significantly increased ($P = 0.005$) and mast cells were significantly increased in the second part of the duodenum in IBS ($P < 0.001$), while eosinophils were significantly increased in the duodenal bulb and second part of the duodenum in FD ($P < 0.001$), suggesting that duodenal mast cell hyperplasia is linked to IBS, and eosinophilia to FD.

Recently, it has been revealed that previous infectious gastroenteritis is often followed by postinfectious FD (PI-FD)¹⁹ or postinfectious IBS (PI-IBS).²⁰ Porter et al²¹ recently conducted a matched, case-control study describing the epidemiology and risk determinants of IBS, functional constipation, functional diarrhea and dyspepsia using electronic medical encounter data in active-duty US military personnel, and demonstrated a significant association between infectious gastroenteritis and all FGIDs (OR, 2.64; $P < 0.001$), with the highest frequency of functional diarrhea (OR, 6.28; $P < 0.001$) and IBS (OR, 3.72; $P < 0.001$), and a moderate frequencies of functional constipation (OR, 2.15; $P < 0.001$) and FD (OR, 2.39; $P < 0.001$). According to Kindt et al²² and Suzuki²³, PI-FD is associated with persistent focal T cell aggregates, decreased CD4+ cells and increased macrophage counts surrounding the crypts, indicating an impaired ability of the immune system to terminate the inflammatory response after an acute insult.

Since the etiology of FD is still uncertain, it is not surprising that *Helicobacter pylori*, a major pathogen in the stomach,²⁴⁻²⁶ has been implicated in the pathophysiology of so called dyspepsia. Many trials reporting the efficacy of *H. pylori* eradication therapy for FD including non-ulcer dyspepsia have given conflicting results but there is a clear indication that *H. pylori* eradication treatment is effective in at least a subset of patients with FD or non-ulcer dyspepsia.^{27,28} The recent meta-analysis also suggests that *H. pylori* eradication at 12 months has a small but statistically significant benefit in the treatment of FD (relative risk [RR] of remaining dyspepsia with *H. pylori* eradication therapy = 0.91; 95% CI, 0.87-0.99). While statistically significant, the clinical

significance of this finding is less clear because the effect is small, that is, 15 *H. pylori*-positive dyspeptic patients will need to be treated to achieve just one cure.²⁹ On the other hand in Asia, Gwee et al³⁰ conducted a double blind, randomized, placebo-controlled trial of *H. pylori* eradication for FD was conducted in Singapore population. Forty-one patients received active treatment consisting of a 1-week course of omeprazole 20 mg once daily, clarithromycin 250 mg twice daily and tinidazole 500 mg twice daily whereas another 41 patients received matching placebo tablets. They reported on ITT analyses, that while symptom resolution was observed in 24% of patients on active treatment, only 7% was found on the placebo ($P = 0.02$; 95% CI, 1.1-17.7). In addition, their report shows that among patients with *H. pylori* eradicated on active treatment the symptom resolution rate was 39%, whereas it was 3% among patients in the placebo who had persistent *H. pylori* infection,³⁰ suggesting that patients with FD in Asian population might benefit more from treatment for *H. pylori* infection.

On the aspects of pathophysiology of dyspepsia in *H. pylori* infection, we recently reported in mice that after long-term *H. pylori* infection, gastric emptying was significantly accelerated with a significant thickening of the muscular layers of the stomachs that was manifest in the hyperplasia of myocytes.³¹ We also examined the expression profile of microRNAs (miRs), which is recently reported to be involved in the pathogenesis of GI disorders including cancers.^{32,33} In *H. pylori*-infected mice, the muscle-specific miRs such as *miR-1*, *miR-133a* and *miR-133b* were significantly down-regulated in the stomachs with an enhancement of the expression of histone deacetylase 4 and serum response factor, which are reported target genes of *miR-1* and *miR-133* and to enhance the muscular hyperproliferation. Accelerated gastric emptying may be possibly through the disturbed gastric accommodation due to the alterations in muscular layer modification, providing a novel insight into the molecular pathogenesis of dyspepsia associated with *H. pylori* infection.³¹

There might be a reason to consider *H. pylori*-associated dyspepsia as an organic disease and to deal with it as a different disease entity from FD.^{34,35} A new classification based on the pathophysiology and specific symptoms needs to be considered to further the diagnostic and therapeutic advances in this field.

Racial Differences in the Epidemiology of Irritable Bowel Syndrome and Dyspepsia

There is a paucity of data on racial differences in the epidemiology of IBS alone and UID alone as compared to that of the “overlap syndrome.” According to a random survey of 990 subjects who completed a questionnaire which included the Rome II criteria for IBS and FD,³⁵ among African Americans, the prevalences of IBS alone, UID alone and their overlap were 0.6%, 17% and 7.3%, respectively, while among Caucasian Americans, they were 0%, 13% and 13%, respectively. All but 4 patients with IBS had UID. Among patients with UID, overlap syndrome was seen in 30% of African Americans, as compared to 50% of Caucasian Americans. African Americans below the poverty line were more likely to have UID than overlap (22% vs 10%). As compared to African Americans, Caucasians with overlap syndrome were likely to be married and to be living in an urban area. There was a higher prevalence of overlap syndrome (UID-IBS) among Caucasians with lower levels of education. UID-IBS overlap was 2.5 times more likely to occur among Caucasians than among African Americans.³⁶ However, among UID patients, there might be considerable numbers of patients with peptic ulcer disease or erosive esophagitis.

Conclusion

The concept of FD-IBS overlap syndrome is important for determining the independent therapeutic approach for such disease conditions of FD alone or of IBS alone, by treating them as a disease of the entire gut as a single organ. Under such concept of disease overlap, FD and IBS can be recognized as being frequently coexisting and not mutually exclusive syndromes.

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