REVIEW

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Current status of functional dyspepsia in Korea

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Dyspepsia refers to group of commonly occurring upper gastrointestinal symptoms. The majority of patients with dyspepsia suffer from functional (nonulcer) dyspepsia. Although there is a lack of epidemiological data from population-based or patient cohort studies in Korea, the current understanding of this condition has been updated using data from various recent research studies, which have facilitated the development of clinical guidelines for functional dyspepsia. According to a survey using the Rome III criteria, more than 40% of respondents who visited primary clinics and tertiary hospitals were defined as having functional dyspepsia, most of who were within a subgroup of patients with postprandial distress syndrome. In addition, a population-based cross-sectional survey revealed considerable overlap between functional dyspepsia and other functional gastrointestinal disorders, including gastroesophageal reflux disease (especially nonerosive reflux disease) and irritable bowel syndrome. In contrast to the results of Western trials, there is insufficient evidence to recommend a *Helicobacter pylori* test-and-treat strategy as an initial management approach to functional dyspepsia in Korea, suggesting the need for early endoscopic evaluation. Additional studies are necessary to adjust the cutoff age for implementation of immediate endoscopic evaluation of patients without alarm symptoms. Considering the prevalence of *H. pylori* infection and the limited efficacy of symptomatic relief after its eradication, further well-qualified studies in Korea are warranted.

Keywords: Functional dyspepsia; Epidemiology; *Helicobacter pylori*

INTRODUCTION

It is well known that functional gastrointestinal (GI) disorders, such as functional dyspepsia (FD) and irritable bowel syndrome (IBS), have a considerable negative socioeconomic impact [1-4]. Although there are limited data regarding the disease burden of functional GI disorders in Korea, an economic analysis of the National Health Insurance Corporation database suggested that these disorders represent a severe burden and are associated with high morbidity in outpatients [5]. FD, which is one of the most common GI disorders encountered in clinical practice, is defined by the Rome III criteria as the presence of chronic dyspeptic symptoms for the previous 3 months, an onset of at least 6 months before diagnosis, and the absence of any structural abnormality (determined by upper GI endoscopy), metabolic cause, or systemic cause explaining the symptoms [6,7]. Multiple theories have been proposed to describe the underlying pathophysiology of FD symptoms, including dysmotility and/or hypersensitivity in the upper GI tract [8].

Many studies have reported the prevalence of FD in population-based settings. However, because the diagnosis is influenced by the criteria used to define FD and by the presence of overlapping disorders, the results of

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such studies are varied. Although there is a lack of qualified research on FD in Korea, recent progress (e.g., inclusion of data from nationwide studies and the suggestion for clinical guidelines) is enhancing our understanding of Korean FD [9,10]. The aim of this review was to describe the current status of FD in Korea from the perspectives of epidemiology, diagnosis, and *Helicobacter pylori* infection.

FD DEFINITIONS

According to the Rome III consensus, FD is defined as the presence of early satiation, postprandial fullness, epigastric pain, or epigastric burning in the absence of an organic, systemic, or metabolic disease that could explain the symptoms (Table 1). This definition differs from previous Rome consensus definitions in that it is limited to only four symptoms that are considered to be key dyspeptic symptoms [6,7]. The number of key symptoms was decreased to four in the Rome III consensus to improve the specificity of the symptom cluster to the gastroduodenal region. Based on population-based and patient cohort studies, the Rome III consensus proposed distinguishing postprandial distress syndrome (PDS) from epigastric pain syndrome (EPS) [6,11-13]. EPS and PDS are thought to have different pathophysiologies because, unlike EPS, PDS appears to be associated with impaired gastric accommodation and increased duodenal eosinophil counts [14]. As such, these two syndromes might have different responses to medication, and distinguishing the two diagnoses would allow for a more rational approach to drug discovery and development. However, the therapeutic implications of this subdivision remain to be clarified.

EPIDEMIOLOGY AND ISSUES OF OVERLAPPING DISORDERS

The prevalence of uninvestigated dyspepsia varies from 7% to 45% worldwide, and many epidemiological studies globally support the Rome III classification of EPS and PDS subtypes based on a better-than-expected separation of these subgroups in the general population [15,16]. However, a recent report on primary care patients found that EPS and PDS subtypes overlap in the majority of patients with FD, indicating that the value of dividing FD into EPS and PDS subgroups is ineffective [17].

In Korea, the prevalence of FD as assessed by the Rome I criteria in a rural community was reportedly 15.5%, and the prevalence determined from a population-based study using the Rome II criteria was 9.5% [18,19]. In ad-

Table 1. Diagnosis of functional dyspepsia using the Rome III criteria

Functional dyspepsia	Postprandial distress syndrome	Epigastric pain syndrome
Must include: 1. One or more of: a. Bothersome postprandial fullness; uncomfortably full after regular sized meal, more than 1 day/wk b. Early satiation; unable to finish regular sized meal, more than 1 day/wk c. Epigastric pain; pain or burning in middle of abdomen at least 1 day/wk d. Epigastric burning; this criterion is incorporated in the same question as epigastric pain *AND* 2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms	Must include all of the following: 1. Bothersome postprandial fullness; uncomfortably full after regular sized meal, more than 1 day/wk 2. Early satiation that prevents finishing a regular meal, more than 1 day/wk	Must include all of the following: 1. Pain or burning localized to the epigastrium, of at least moderate severity at least once per week 2. The pain is intermittent 3. Not generalized or localized to other abdominal or chest regions 4. Chest pain occurs once a month or less often 5. Not relieved by defecation or passage of flatus 6. Not fulfilling criteria for biliary pain All criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

dition, the prevalence of FD in patients undergoing health check-ups in Korea was estimated as 13.4% according to the Rome II criteria. In this analysis, the most common subtype of FD was dysmotility-like dyspepsia (69.5%) [20]. Two tertiary hospital-based studies revealed prevalences of 37.0% and 24.8%, respectively [21,22]. In another point-prevalence study of FD using the Rome III criteria, 46.5% and 45.8% of respondents who visited primary clinics and tertiary hospitals, respectively, were diagnosed with FD [23]. This report showed that 74.4% of all cases were defined as PDS, 5.0% as EPS, 2.2% as mixed, and 18.3% as an undetermined subtype. The prevalences of FD from various Korean studies are presented in Table 2. The mixed subgroup percentage in this report was much lower than those reported in Western studies [13,17]. A recent Korean nationwide, multicenter report on the prevalence of FD in patients undergoing health check-ups (FD not determined using the Rome criteria) revealed a 20.4% prevalence of FD symptoms among seven healthcare screening centers in Korea. In this study, atrophic gastritis and positive serology for *H. pylori* infection were not associated with the prevalence of FD, suggesting that FD is a multifactorial disease [24].

Upper and lower GI symptoms commonly overlap, and psychological disorders (e.g., anxiety, neuroticism, and somatization) have been reported in both patients with FD and in those with IBS [25,26]. Overlap between functional GI disorders may be a manifestation of generalized motor disturbances, altered visceral sensitivity, and/or brain-gut dysfunction [27,28]. In a population cross-sectional survey of Korean subjects, overlaps between FD and gastroesophageal reflux disease (GERD) and between FD and IBS were observed in 2.3% and 1.3% of the population, respectively. In addition, 24% and 14% of dyspeptic subjects had GERD and IBS, respectively [28]. These overlaps occurred predominantly in individuals with anxiety. In particular, a depressive mood was significantly related to FD-IBS overlap based on the Rome III criteria. Patients with FD-IBS overlap appeared to have poorer quality of life than did patients with FD or IBS alone [29]. A report regarding the overlap of FD and GERD in patients undergoing health screening revealed that FD occurred more frequently in patients with nonerosive reflux disease than in patients with reflux esophagitis (74.3% vs. 10.5%, respectively). In addition, the EPS and PDS subtypes overlapped more commonly with nonerosive reflux disease than with reflux esophagitis, and EPS was more prevalent than PDS in patients with nonerosive reflux dis-

Table 2. Prevalence of functional dyspepsia in Korea

Study	Setting	No. of subjects	Definition	Prevalence of FD (%)	Subtype (%)
Choo et al. [18]	Population-based	420	Rome I	65/420 (15.5)	Dysmotility-like (33.8) Ulcer-like (72.0)
Lee et al. [19]	Population-based	1,443	Rome II	137/1,443 (9.5)	NA
Rhie et al. [20]	Health check-up center	708	Rome II	95/708 (13.4)	Dysmotility-like (69.5) Ulcer-like (24.2) Unspecified (6.3)
Kim et al. [21]	Tertiary hospital-based	476	Rome II	178/476 (37.0)	Dysmotility-like (59.0) Ulcer-like (41.0)
Ji et al. [22]	Tertiary hospital-based	274	Rome II	68/274 (24.8)	Dysmotility-like (63.2) Ulcer-like (10.3) Unspecified (26.5)
Park et al. [23]	Primary clinics and tertiary hospital-based	391	Rome III	180/391 (46.0)	PDS (74.4) EPS (5.0) Mixed (2.2)
Kim et al. [24]	Health check-up multicenter	3,399	Symptom questionnaire	694/3,399 (20.4)	PDS (53.6) EPS (31.8) Mixed (14.6)
Noh et al. [30]	Health check-up center	2,388	Rome III	193/2,388 (8.1)	NA

NA, not available; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome.

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ease (68.9% vs. 48.6%, respectively) [30].

Several genetic studies have suggested that serotonin transporter gene polymorphisms and G-protein β3 C825T gene polymorphisms are associated with functional GI disorders [31,32]. However, in a few Korean studies, no relationship was found between these genetic polymorphisms and FD, including overlap [33,34]. In contrast, a pediatric study showed that the CC genotype of G-protein β3 C825T may be associated with FD in Korean children [35].

VALIDATION OF THE ROME III CRITERIA AND DIAGNOSTIC QUESTIONNAIRE

In a validation study in a Western population, the Rome III criteria were not sufficiently sensitive to differentiate functional GI disorders from organic disease [36]. However, the criteria for subgroups of FD had good specificity [37]. An early validation study of the Rome III criteria in Korean subjects revealed that their sensitivity and specificity for discriminating functional GI disorders from organic diseases of the upper GI tract were 60% and 53%, respectively [38]. This finding supports the use of the Rome III criteria in Korea. A Korean version of the Rome III questionnaire was developed recently through structural translational processes; its good reliability and convergent validity suggested it to be useful for clinical and research assessments in the Korean population [39]. In addition, the Functional Dyspepsia-Related Quality of Life scale and a Korean version of the Bowel Disease Questionnaire have been validated in Korean patients with FD [40,41].

SYMPTOMS

A study that correlated dyspeptic symptoms with endoscopic findings showed that dyspeptic symptoms alone did not predict the presence or absence of organic disease [42]. According to a systematic review that evaluated whether clinical symptoms or socioeconomic factors can differentiate organic disease from FD before endoscopy, symptoms or socioeconomic factors have limited power in discerning organic disease from FD [43]. Another meta-analysis was conducted to determine whether alarm symptoms discern organic dyspepsia; alarm symptoms had a suboptimal sensitivity of 67% and specificity of 66% for detecting malignancy [44].

A Korean study that enrolled subjects who underwent upper GI endoscopy in a hospital or health screening setting showed that dyspepsia was not significantly associated with the presence of organic disease. However, male subjects with alarm symptoms had a statistically significant twofold increase in the relative risk of organic disease [45]. In this study, despite the increase in the relative risk of organic disease with age, a significant proportion of organic disease could have been missed. Together, these results show that organic disease in patients with dyspepsia is difficult to predict on the basis of sex, the presence or absence of alarm symptoms, and age. In a large-scale analysis at a health promotion center, ~40% of subjects with dyspepsia had abnormal endoscopic findings. In addition, the Rome III diagnostic criteria were useful in predicting the absence of significant upper endoscopic findings [46]. An investigation to verify whether endoscopic findings differ according to the symptoms of patients with FD showed that erythema and raised erosions were observed more frequently in the antrum of patients with EPS while atrophy was observed more frequently in the fundus of patients with PDS [47].

EARLY ENDOSCOPIC EVALUATION

According to the clinical guidelines of the American Gastroenterological Association, immediate endoscopy is recommended if alarm symptoms exist or the patient is > 55 years of age. If *H. pylori* eradication or protein pump inhibitor administration fails or a relapse occurs in patients ≤ 55 years of age, endoscopy is recommended [48]. The British guidelines are similar to the American guidelines [49]. The Canadian guidelines recommend immediate endoscopy for patients aged ≥ 55 years [50]. Such guidelines arose from comparative studies of early endoscopic evaluation and the *H. pylori* test-and-treat strategy [51,52].

Previous meta-analysis results indicated that there was no significant difference in symptom improvement between an early endoscopic evaluation strategy

and the *H. pylori* test-and-treat strategy [49,53]. Age is the most important factor in determining the indications for the use of early endoscopic evaluation. Organic disease, particularly malignant disease, commonly occurs in older people; thus, the most effective age for endoscopy to detect organic disease differs based on epidemiological characteristics such as location or ethnicity [10,54]. The prevalence of gastric cancer is high (0.9% to 3.4%) in Asia, including Korea [55]. Because cancer occurs in both young and old people, the Asian guidelines regarding FD have a younger standard age for implementation of endoscopy than do the Western guidelines [56-59].

In Korea, studies on the cutoff age for immediate endoscopic evaluation are scant. Evaluation of alarm symptoms, performance of the *H. pylori* serum test, and performance of endoscopy for patients with dyspepsia revealed no malignancy in patients < 35 years of age; in contrast, malignancy was found in four patients aged ≥ 35 years [59]. However, because this study was limited by the small sample size and was conducted only in a tertiary hospital, additional studies are needed to determine the optimal cutoff age for implementation of early endoscopic evaluation in Korean patients with dyspepsia.

HELICOBACTER PYLORI TEST-AND-TREAT STRATEGY

The prevalence of *H. pylori* infection is currently decreasing in the West, and the incidences of peptic ulcers and gastric cancer are decreasing proportionately [60]. Given that gastric cancer was found in < 1% of patients who underwent upper GI endoscopy, the majority of cases of organic diseases associated with dyspepsia are regarded to involve peptic ulcers [10].

In a study of dyspeptic patients in primary care facilities in Canada, 30% of patients were positive for *H. pylori* infection, and organic disease was found in 58% of patients undergoing upper GI endoscopy [61]. In a study conducted in Europe, upon the completion of a urea breath test as an initial test for dyspepsia, the *H. pylori* status showed high diagnostic value in detecting peptic ulcers in patients suspected to have dyspepsia [62]. In addition to these findings, the worldwide clinical guidelines recommend the *H. pylori* test-and-treat strategy if the result of the *H. pylori* test as an initial test for dyspepsia is positive [63-66]. The national survey of *H. pylori* prevalence in Korea showed a trend toward reduction; the *H. pylori* prevalence rate in those aged ≥ 16 years was 66.9% in 1998, but 59.6% in 2005. Whereas 80.0% of patients with peptic ulcer disease who were referred to a tertiary institution for evaluation of dyspepsia were *H. pylori*-positive, only 20.2% among those diagnosed with FD were *H. pylori*-positive [67]. There was also a report that only 28.4% of those diagnosed with FD after undergoing comprehensive health screening were *H. pylori*-positive. However, this report was not representative because of the very low *H. pylori* prevalence [20]. Among patients who underwent endoscopy for evaluation of dyspepsia in tertiary medical facilities, the *H. pylori* prevalences were 86.7%, 77.8%, and 54.2% in those with peptic ulcer disease, gastric cancer, and nonulcer dyspepsia, respectively [68-70]. No observational study or randomized controlled study on whether an *H. pylori* test should be performed to diagnose FD in Korea has been performed. A study of use of a serum *H. pylori* test before endoscopy on Korean patients with FD revealed that among subjects younger than 40 years, sensitivity to organic disease was 76.7% and the negative predictive value was 85.8% when the *H. pylori* test was positive [71]. In subjects ≥ 40 years of age, the sensitivity was 61.9% and the negative predictive value was 64.0%. Therefore, the *H. pylori* test-and-treat strategy is expected to have low diagnostic value for dyspepsia in Korea. This issue played a critical role in the recently developed Korean clinical guidelines for *H. pylori* infection and FD in Korea [9,72].

HELICOBACTER PYLORI ERADICATION

In more than one study, *H. pylori* eradication resulted in longer-term symptom improvement in the FD patient group than in the placebo group [73,74]. A Cochrane review showed that the risk of symptom persistence was reduced significantly by 9% in the *H. pylori* eradication group compared with the placebo group [75]. In addition, a prospective study conducted in a primary medi-

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cal facility showed that *H. pylori* eradication had a significant effect on symptom improvement in patients with FD [76]. In Asia, whether *H. pylori* eradication can improve FD is unclear because of insufficient evidence from studies with small sample sizes or nonrandomized protocols. Although a meta-analysis showed 3.6-fold symptom improvement in the *H. pylori* eradication group, evaluation of cost-effectiveness was limited due to the different costs of *H. pylori* eradication among the various regions [77]. Another analysis of 12 randomized studies showed that *H. pylori* eradication had good cost-effectiveness for FD [78]. Most guidelines worldwide recommend *H. pylori* eradication in some patients with FD, and all guidelines based on evidence regarding eradication in FD suggest that the data are of the highest quality [63-66].

There are no results from any randomized controlled studies on the effect of *H. pylori* eradication on FD in Korea [79]. A nonrandomized prospective study showed no difference in symptom improvement between the successful *H. pylori* eradication group and the failed group [80]. However, another study reported significant symptom improvement upon the completion of *H. pylori* eradication [81]. Other observational studies that evaluated parameters of gastric emptying or hypersensitivity did not show significant differences in symptoms, emptying, or hypersensitivity in patients with *H. pylori* infection [82-84]. The effect of *H. pylori* eradication on FD and the relationship between the changes in histological gastritis and FD symptom responses in Korea were evaluated recently, but the results suffered from a number of limitations, including the low sample size and the nonrandomized, non-double-blind design [85]. That study showed that *H. pylori* eradication (odds ratio [OR], 5.81) and symptom improvement at 3 months (OR, 28.90) were associated with improvement in dyspepsia at 1 year. Because the *H. pylori* infection rate is high in Korea, *H. pylori* eradication for all patients with FD might result in adverse events or development of antibiotic resistance. Furthermore, the benefits and risks of the treatment should be considered based on the cost-effectiveness [86]. From this viewpoint, the Korean clinical guidelines weakly recommend that *H. pylori* eradication may be helpful in long-term symptom improvement in only a proportion of patients with FD [9,72].

CONCLUSIONS

FD is a common disease that imparts a high socioeconomic burden. A few prevalence studies of FD using the Rome III criteria revealed that the PDS subtype was more prevalent than the EPS subtype in Korea. In addition, a cross-sectional population survey revealed considerable overlap between FD and other functional GI disorders, including GERD (particularly nonerosive reflux disease) and IBS. The recently developed Korean version of the Rome III questionnaire may be useful for diagnosing FD and performing clinical and research assessments in the Korean population. In contrast to results from Western trials, there is insufficient evidence that the *H. pylori* test-and-treat strategy is superior as an initial approach to FD in Korea. The results do, however, suggest the benefit of early endoscopic evaluation in Korea. However, additional studies are necessary to adjust the cutoff age for implementing immediate endoscopic evaluation of patients without alarm symptoms. When the benefits and risks, together with the cost-effectiveness, are taken into consideration, *H. pylori* eradication may be a therapeutic option for FD in Korea.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Nyren O, Lindberg G, Lindstrom E, Marke LA, Seensalu R. Economic costs of functional dyspepsia. Pharmacoeconomics 1992;1:312-324.
2. Hulisz D. The burden of illness of irritable bowel syndrome: current challenges and hope for the future. J Manag Care Pharm 2004;10:299-309.
3. Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. J Manag Care Pharm 2013;19:755-764.
4. Talley NJ. Functional gastrointestinal disorders as a public health problem. Neurogastroenterol Motil 2008;20 Suppl 1:121-129.
5. Jung HK, Jang B, Kim YH, et al. Health care costs of

digestive diseases in Korea. Korean J Gastroenterol 2011;58:323-331.
6. Tack J, Talley NJ. Functional dyspepsia: symptoms, definitions and validity of the Rome III criteria. Nat Rev Gastroenterol Hepatol 2013;10:134-141.
7. Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. Gastroenterology 2006;130:1466-1479.
8. Suzuki H, Moayyedi P. Helicobacter pylori infection in functional dyspepsia. Nat Rev Gastroenterol Hepatol 2013;10:168-174.
9. Jee SR, Jung HK, Min BH, et al. Guidelines for the treatment of functional dyspepsia. Korean J Gastroenterol 2011;57:67-81.
10. Jung HK, Keum BR, Jo YJ, et al. Diagnosis of functional dyspepsia: a systematic review. Korean J Gastroenterol 2010;55:296-307.
11. Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Talley NJ. Do distinct dyspepsia subgroups exist in the community? A population-based study. Am J Gastroenterol 2007;102:1983-1989.
12. Aro P, Talley NJ, Ronkainen J, et al. Anxiety is associated with uninvestigated and functional dyspepsia (Rome III criteria) in a Swedish population-based study. Gastroenterology 2009;137:94-100.
13. Zagari RM, Law GR, Fuccio L, et al. Epidemiology of functional dyspepsia and subgroups in the Italian general population: an endoscopic study. Gastroenterology 2010;138:1302-1311.
14. Shin CM. Overlap between postprandial distress and epigastric pain syndromes in functional dyspepsia: its implications for research and clinical practice (Am J Gastroenterol 2013;108:767-774). J Neurogastroenterol Motil 2013;19:409-411.
15. Mahadeva S, Goh KL. Epidemiology of functional dyspepsia: a global perspective. World J Gastroenterol 2006;12:2661-2666.
16. Ghoshal UC, Singh R, Chang FY, et al. Epidemiology of uninvestigated and functional dyspepsia in Asia: facts and fiction. J Neurogastroenterol Motil 2011;17:235-244.
17. Vakil N, Halling K, Ohlsson L, Wernersson B. Symptom overlap between postprandial distress and epigastric pain syndromes of the Rome III dyspepsia classification. Am J Gastroenterol 2013;108:767-774.
18. Choo KY, Choi MG, Choi H, et al. The prevalences of gastrointestinal symptoms in a rural community in Korea. Korean J Gastrointest Motil 2000;6:31-43.
19. Lee SY, Lee KJ, Kim SJ, Cho SW. Prevalence and risk factors for overlaps between gastroesophageal reflux disease, dyspepsia, and irritable bowel syndrome: a population-based study. Digestion 2009;79:196-201.
20. Rhie SY, Choi CH, Lee HW, et al. The frequency of functional dyspepsia subtypes and its related factors for health check up subjects. Korean J Neurogastroenterol Motil 2007;13:31-37.
21. Kim JS, Lee KJ, Kim JH, Hahm KB, Cho SW. Functional gastrointestinal disorders in patients referred to specialist gastroenterologists in a tertiary hospital. Korean J Neurogastroenterol Motil 2004;10:111-117.
22. Ji SW, Park HJ, Choi JP, Lee TH, Lee DY, Lee SI. Validation of Rome II criteria for functional gastrointestinal disorders in Korean patients. Korean J Gastroenterol 2003;41:183-189.
23. Park JM, Choi MG, Cho YK, et al. Functional gastrointestinal disorders diagnosed by Rome III questionnaire in Korea. J Neurogastroenterol Motil 2011;17:279-286.
24. Kim SE, Park HK, Kim N, et al. Prevalence and risk factors of functional dyspepsia: a nationwide multicenter prospective study in Korea. J Clin Gastroenterol 2014;48:e12-e18.
25. Barry S, Dinan TG. Functional dyspepsia: are psychosocial factors of relevance? World J Gastroenterol 2006;12:2701-2707.
26. Locke GR 3rd, Zinsmeister AR, Fett SL, Melton LJ 3rd, Talley NJ. Overlap of gastrointestinal symptom complexes in a US community. Neurogastroenterol Motil 2005;17:29-34.
27. Cremonini F, Talley NJ. Review article: the overlap between functional dyspepsia and irritable bowel syndrome: a tale of one or two disorders? Aliment Pharmacol Ther 2004;20 Suppl 7:40-49.
28. Kim SE, Chang L. Overlap between functional GI disorders and other functional syndromes: what are the underlying mechanisms? Neurogastroenterol Motil 2012;24:895-913.
29. Lee HJ, Lee SY, Kim JH, et al. Depressive mood and quality of life in functional gastrointestinal disorders: differences between functional dyspepsia, irritable bowel syndrome and overlap syndrome. Gen Hosp Psychiatry 2010;32:499-502.
30. Noh YW, Jung HK, Kim SE, Jung SA. Overlap of erosive

http://dx.doi.org/10.3904/kjim.2014.29.2.156

and non-erosive reflux diseases with functional gastrointestinal disorders according to Rome III criteria. J Neurogastroenterol Motil 2010;16:148-156.
31. Camilleri CE, Carlson PJ, Camilleri M, et al. A study of candidate genotypes associated with dyspepsia in a U.S. community. Am J Gastroenterol 2006;101:581-592.
32. van Lelyveld N, Linde JT, Schipper M, Samsom M. Candidate genotypes associated with functional dyspepsia. Neurogastroenterol Motil 2008;20:767-773.
33. Park HY, Jahng JH, Lee YJ, Park H, Lee SI. Serotonin transporter gene and G-protein beta3 C825T gene polymorphism in patients with functional dyspepsia and irritable bowel syndrome. Korean J Neurogastroenterol Motil 2009;15:58-64.
34. Kim HG, Lee KJ, Lim SG, Jung JY, Cho SW. G-protein beta3 subunit C825T polymorphism in patients with overlap syndrome of functional dyspepsia and irritable bowel syndrome. J Neurogastroenterol Motil 2012;18:205-210.
35. Park CS, Uhm JH. Polymorphisms of the serotonin transporter gene and G-protein beta3 subunit gene in Korean children with irritable bowel syndrome and functional dyspepsia. Gut Liver 2012;6:223-228.
36. Choung RS, Talley NJ, Crowell MD, et al. Validation of Rome III criteria for functional GI disorders. Gastroenterology 2007;132 Suppl 2:A676.
37. Park H. Functional gastrointestinal disorders and overlap syndrome in Korea. J Gastroenterol Hepatol 2011;26 Suppl 3:12-14.
38. Kim ES, Lee BJ, Kim YS, Lee SI, Park H. Validation of Rome III criteria in the diagnosis of functional gastrointestinal disorders in Korean patients. Korean J Neurogastroenterol Motil 2008;14:39-44.
39. Song KH, Jung HK, Min BH, et al. Development and validation of the Korean Rome III questionnaire for diagnosis of functional gastrointestinal disorders. J Neurogastroenterol Motil 2013;19:509-515.
40. Lee EH, Hahm KB, Lee JH, et al. Development and validation of a functional dyspepsia-related quality of life (FD-QOL) scale in South Korea. J Gastroenterol Hepatol 2006;21:268-274.
41. Song HJ, Jung HK. Reliability and validity of Korean bowel disease questionnaire for functional gastrointestinal disorders. Ewha Med J 2011;34:39-46.
42. Zagari RM, Law GR, Fuccio L, Pozzato P, Forman D, Bazzoli F. Dyspeptic symptoms and endoscopic findings in the community: the Loiano-Monghidoro study. Am J Gastroenterol 2010;105:565-571.
43. Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia? JAMA 2006;295:1566-1576.
44. Bowrey DJ, Griffin SM, Wayman J, Karat D, Hayes N, Raimes SA. Use of alarm symptoms to select dyspeptics for endoscopy causes patients with curable esophagogastric cancer to be overlooked. Surg Endosc 2006;20:1725-1728.
45. Han CH, Lee JS, Ahn JO, et al. The meaning of warning symptoms in the patients with dyspepsia. Korean J Med 2007;73:25-33.
46. Jung HK, Kim SE, Shim KN, Jung SA. Association between dyspepsia and upper endoscopic findings. Korean J Gastroenterol 2012;59:275-281.
47. Kim JI, Jun EJ, Kim TH, et al. Endoscopic finding according to symptoms in patients with functional dyspepsia. Korean J Helicobacter Up Gastrointest Res 2011;11:124-128.
48. Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. Gastroenterology 2005;129:1756-1780.
49. North of England Dyspepsia Guideline Development Group. Dyspepsia: Managing Dyspepsia in Adults in Primary Care. Newcastle upon Tyne: University of Newcastle upon Tyne, 2004.
50. Veldhuyzen van Zanten SJ, Bradette M, Chiba N, et al. Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: an update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool. Can J Gastroenterol 2005;19:285-303.
51. Duggan AE, Elliott CA, Miller P, Hawkey CJ, Logan RF. Clinical trial: a randomized trial of early endoscopy, Helicobacter pylori testing and empirical therapy for the management of dyspepsia in primary care. Aliment Pharmacol Ther 2009;29:55-68.
52. Heaney A, Collins JS, Watson RG, McFarland RJ, Bamford KB, Tham TC. A prospective randomised trial of a "test and treat" policy versus endoscopy based management in young Helicobacter pylori positive patients with ulcer-like dyspepsia, referred to a hospital clinic. Gut 1999;45:186-190.
53. Ford AC, Qume M, Moayyedi P, et al. Helicobacter pylori "test and treat" or endoscopy for managing dyspepsia:

an individual patient data meta-analysis. Gastroenterology 2005;128:1838-1844.
54. Schmidt N, Peitz U, Lippert H, Malfertheiner P. Missing gastric cancer in dyspepsia. Aliment Pharmacol Ther 2005;21:813-820.
55. Shin MH, Oh HK, Ahn YO. Ten year trend of cancer incidence in Seoul, Korea: 1993-2002. J Prev Med Public Health 2008;41:92-99.
56. Liou JM, Lin JT, Wang HP, et al. The optimal age threshold for screening upper endoscopy for uninvestigated dyspepsia in Taiwan, an area with a higher prevalence of gastric cancer in young adults. Gastrointest Endosc 2005;61:819-825.
57. Kim JH, Kim HY, Kim NY, et al. Seroepidemiological study of Helicobacter pylori infection in asymptomatic people in South Korea. J Gastroenterol Hepatol 2001;16:969-975.
58. Salkic NN, Zildzic M, Zerem E, et al. Simple uninvestigated dyspepsia: age threshold for early endoscopy in Bosnia and Herzegovina. Eur J Gastroenterol Hepatol 2009;21:39-44.
59. Lee JH, Kim HY, Rho SH, et al. Dyspepsia in Korean population: who needs endoscopy? Korean J Gastrointest Endosc 2001;22:1-7.
60. Blaser MJ. Hypothesis: the changing relationships of Helicobacter pylori and humans: implications for health and disease. J Infect Dis 1999;179:1523-1530.
61. Thomson AB, Barkun AN, Armstrong D, et al. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: the Canadian Adult Dyspepsia Empiric Treatment-Prompt Endoscopy (CADET-PE) study. Aliment Pharmacol Ther 2003;17:1481-1491.
62. McColl KE, el-Nujumi A, Murray L, et al. The Helicobacter pylori breath test: a surrogate marker for peptic ulcer disease in dyspeptic patients. Gut 1997;40:302-306.
63. Asaka M, Kato M, Takahashi S, et al. Guidelines for the management of Helicobacter pylori infection in Japan: 2009 revised edition. Helicobacter 2010;15:1-20.
64. Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific consensus guidelines for Helicobacter pylori infection. J Gastroenterol Hepatol 2009;24:1587-1600.
65. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection: the Maastricht IV/ Florence Consensus Report. Gut 2012;61:646-664.
66. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol 2007;102:1808-1825.
67. Suh SO, Lee DH, Park YS, et al. Difference in Helicobacter pylori eradication rates in patients with peptic ulcer and non-ulcer dyspepsia. Korean J Med 2006;70:505-510.
68. Jung HK, Na YJ, Moon IH. Changes of Helicobacter pylori-positive peptic ulcer disease: based on data from a general hospital. Korean J Gastrointest Endosc 2006;32:1-8.
69. Kim KC, Park HJ, Lee HW, et al. Relation of serum gastrin and pepsinogen levels to serologic recognition of CagA and VacA in Helicobacter pylori infection. Korean J Gastroenterol 1997;29:25-34.
70. Park IS, Lee YC, Park HJ, et al. Helicobacter pylori infection in Korea. Yonsei Med J 2001;42:457-470.
71. Hwang IR, Kim JH, Lee KJ, Cho SW. Can Helicobacter pylori serology predict non-ulcer dyspepsia in young dyspeptic patients? Korean J Gastrointest Endosc 2000;21:696-703.
72. Kim SG, Jung HK, Lee HL, et al. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. Korean J Gastroenterol 2013;62:3-26.
73. Harvey RF, Lane JA, Nair P, et al. Clinical trial: prolonged beneficial effect of Helicobacter pylori eradication on dyspepsia consultations: the Bristol Helicobacter Project. Aliment Pharmacol Ther 2010;32:394-400.
74. McColl K, Murray L, El-Omar E, et al. Symptomatic benefit from eradicating Helicobacter pylori infection in patients with nonulcer dyspepsia. N Engl J Med 1998;339:1869-1874.
75. Moayyedi P, Soo S, Deeks J, et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. Cochrane Database Syst Rev 2006;(2):CD002096.
76. Mazzoleni LE, Sander GB, Francesconi CF, et al. Helicobacter pylori eradication in functional dyspepsia: HEROES trial. Arch Intern Med 2011;171:1929-1936.
77. Gwee KA, Teng L, Wong RK, Ho KY, Sutedja DS, Yeoh KG. The response of Asian patients with functional dyspepsia to eradication of Helicobacter pylori infection. Eur J Gastroenterol Hepatol 2009;21:417-424.

http://dx.doi.org/10.3904/kjim.2014.29.2.156

78. Moayyedi P, Soo S, Deeks J, et al. Systematic review and economic evaluation of Helicobacter pylori eradication treatment for non-ulcer dyspepsia. Dyspepsia Review Group. BMJ 2000;321:659-664.
79. Hong SJ, Sung IK, Kim JG, et al. Failure of a randomized, double-blind, placebo-controlled study to evaluate the efficacy of H. pylori eradication in H. pylori-infected patients with functional dyspepsia. Gut Liver 2011;5:468-471.
80. Kim SH, Hong DY, Kang PS, et al. Community-based Helicobacter pylori screening and its effects on eradication in patients with dyspepsia. Korean J Prev Med 2000;33:285-298.
81. Lee EJ, Gham CW, Park TW, et al. The effect of Helicobacter pylori eradication on the improvement of the symptoms in patients with functional dyspepsia and peptic ulcer disease. Korean J Med 2006;71:141-148.
82. Rhee PL, Kim YH, Son HJ, et al. Lack of association of Helicobacter pylori infection with gastric hypersensitivity or delayed gastric emptying in functional dyspepsia. Am J Gastroenterol 1999;94:3165-3169.
83. Shim SG, Rhee PL, Kim YH, et al. Influence of Helicobacter pylori infection on proximal gastric motor function in functional dyspepsia. Korean J Gastroenterol 1999;34:143-150.
84. Lee SY, Lee YD, Jeon SW, et al. The effect of Helicobacter pylori infection on gastric emptying in patients with functional dyspepsia. Korean J Gastroenterol 2000;35:677-686.
85. Kim SE, Park YS, Kim N, et al. Effect of Helicobacter pylori eradication on functional dyspepsia. J Neurogastroenterol Motil 2013;19:233-243.
86. Yoon BC. Treatment of Helicobacter pylori infection in functional dyspepsia. Korean J Med 2008;75:492-495.