Chapter 7
Symptom Generation

Juntaro Matsuzaki and Hidekazu Suzuki

Abstract Patients whose dyspepsia symptoms had disappeared after 12 months from *Helicobacter pylori* (*H. pylori*) eradication therapy were decided to be called *H. pylori*-associated dyspepsia (HpD), and were clearly distinguished from functional dyspepsia. *H. pylori* eradication is more effective than placebo with a number needed to treat (NNT) of 14 for *H. pylori*-positive dyspepsia. *H. pylori* is likely to be associated with the presence of postprandial distress symptoms rather than epigastric pain symptoms, although the evidence whether therapeutic responses to *H. pylori* eradication differ between subgroups of dyspepsia is still limited. The altered ghrelin secretion from the stomach, the presence or severity of microscopic duodenitis, and altered expression of muscle-specific microRNAs in the gastric smooth muscle layer would be possible mechanisms of HpD.

Keywords Dyspepsia • The Rome criteria • Ghrelin

7.1 *Helicobacter pylori*-Associated Dyspepsia

Most individuals infected with *Helicobacter pylori* (*H. pylori*) have few or no symptoms. However some may experience chronic dyspepsia symptoms even though they do not have peptic ulcer or gastric cancer. Dyspepsia is a term which includes a group of symptoms, such as epigastric pain, epigastric burning, uncomfortable postprandial fullness, and early satiation, which are thought to originate in the gastroduodenal region. By the Rome III definition, functional dyspepsia (FD) is diagnosed when no structural or biochemical explanation for a patient's symptoms is identified after appropriate investigations, regardless of the existence of *H. pylori* infection [1]. FD is one of the most common gastrointestinal diseases, which greatly impacts the quality of life. Since recent studies including systematic reviews and

J. Matsuzaki
Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, 5-1-1 Tsukiji, Chuo-ku 104-0045, Tokyo, Japan

H. Suzuki (✉)
Medical Education Center, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582 Tokyo, Japan
e-mail: hsuzuki.a6@keio.jp

© Springer Japan 2016

H. Suzuki et al. (eds.), *Helicobacter pylori*, DOI 10.1007/978-4-431-55705-0_7

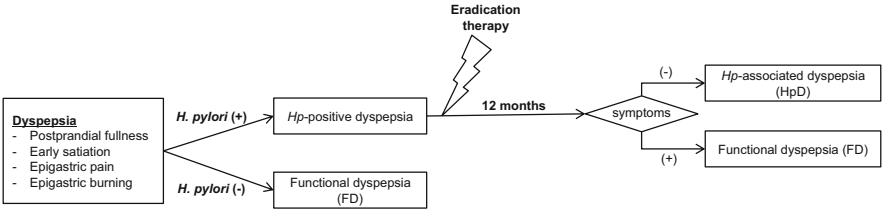

Fig. 7.1 *Helicobacter pylori*-associated dyspepsia (HpD) is defined as chronic dyspepsia which is improved for more than 12 months after *H. pylori* eradication. HpD should be separated from functional dyspepsia (FD)

meta-analysis showed the significant association between *H. pylori* infection and dyspepsia symptoms [2, 3], chronic dyspepsia symptoms which are thought to be caused by *H. pylori* infection are decided to be separated from FD and defined as *H. pylori*-associated dyspepsia (HpD) in the Kyoto Global Consensus Conference held on Jan. 30–Feb. 1, 2014 [4]. In this meeting, patients who remain symptom-free 12 months after eradication are considered to be cases of HpD, while patients who continue to experience dyspepsia even after *H. pylori* eradication will be considered as FD [5] (Fig. 7.1). In this section, we reviewed the epidemiology and the pathophysiology of HpD.

7.2 Epidemiology

An old meta-analysis showed that the prevalence of dyspepsia symptoms was greater in patients with *H. pylori* infection than in those without *H. pylori* infection, with an OR [odds ratio] of 2.3 (95 % CI [confidence interval] 1.9–2.7) [6]. More recent meta-analysis of 103 reports containing 312415 individuals showed that the prevalence of uninvestigated dyspepsia was higher in *H. pylori*-positive individuals (OR 1.18; 95 % CI 1.04–1.33) [7].

According to the Rome III criteria, FD patients were categorized into epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). Fang et al. reported the prevalence of *H. pylori* infection in FD patients diagnosed by the Rome III criteria in Taiwan [8]. In this study, 491 fulfilled the diagnostic criteria of FD among 2378 individuals. 298 (60.7 %) and 353 (71.9 %) individuals were diagnosed with EPS and PDS respectively, whereas 169 (34.4 %) had the overlap syndrome. *H. pylori* infection was positively associated with FD (OR 1.60; 99.5 % CI 1.03–2.48). *H. pylori* were associated with PDS alone (OR 1.86; 99.5 % CI 1.01–3.45), but not with EPS alone (OR 1.43; 99.5 % CI 0.72–2.84) or overlap syndrome (OR 1.12; 99.5 % CI 0.55–2.28). The density of *H. pylori*, severity of intestinal metaplasia, and infiltration of neutrophils and monocytes were not significantly different among the three subgroups. However, there was a trend of more moderate and marked gastric atrophy at the antrum in the subgroup of PDS alone. Among *H. pylori*-infected patients, a trend ($p = 0.044$) of more CagA-positive

strains was observed in PDS alone (98.4 %), as compared with EPS alone (89.1 %) and the overlap syndrome (85.7 %). Piriyapong et al. also investigated the prevalence and impact of *H. pylori* infection on 300 patients with FD in Thailand and showed that *H. pylori* infection was significantly higher in PDS than EPS patients (27.1 % vs 16.7 %; OR 1.86; 95 % CI, 1.01–3.53) [9].

There is evidence of a small but statistically significant benefit in eradicating *H. pylori* in *H. pylori*-positive dyspepsia. In a Cochrane review of 21 placebo-controlled trials, the NNT (number needed to treat) for improvement in symptoms after eradicating *H. pylori* was 14, with no heterogeneity between studies and no evidence of funnel plot asymmetry [10]. Therefore, the eradication therapy is recommended as first-line therapy for *H. pylori*-positive dyspepsia. Zhao et al. reviewed 14 randomized controlled trials which contained information on the long-term (12 months or more) effects of *H. pylori* eradication on dyspeptic symptoms, and a subgroup analysis on geographical regions was conducted [11]. The improvements of dyspepsia symptoms in patients of eradication group were similarly better than in patients of control group in the European (OR 1.49; 95 % CI, 1.10–2.02), Asian (OR 1.54; 95 % CI, 1.07–2.21), and American populations (OR 1.43; 95 % CI, 1.12–1.83). Kim et al. reported that among the successfully eradicated dyspepsia patients ($n = 67$), male ($p = 0.013$) and higher initial BMI ($p = 0.016$) were associated with the improvement of dyspepsia at 1 year in Korean population [12]. Lan et al. reported that *H. pylori* eradication tended to be effective only in the EPS subgroup in China [13], although the other reports did not show the beneficial differences between subgroups of dyspepsia [14, 15].

7.3 Pathophysiology

Several hypotheses for the cause of HpD are considered [16], but pathophysiological conditions which were reported to be associated with dyspepsia symptoms have been limited (Fig. 7.2).

Ghrelin, which is produced and secreted by the A-like cells of the oxyntic glands of the stomach, has a well-established role in increasing appetite and food intake and in stimulating gastric emptying and acid secretion [17]. *H. pylori*-infected patients were shown to have lower gastric ghrelin mRNA expression than uninfected subjects [18]. Furthermore, the suppression of ghrelin expression is correlated with severity of glandular atrophy and chronic inflammation in the gastric corpus. Plasma ghrelin levels also decrease in *H. pylori*-infected patients [19, 20]. *H. pylori* infection may induce gastric motor dysfunction and reduce appetite with suppressed ghrelin secretion. Moreover, Lee et al. reported that preprandial ghrelin levels are significantly lower in PDS patients [21]. Shindo et al. also revealed that the maximum gastric emptying time for PDS is significantly higher with significant lower acyl-ghrelin levels in these patients [22]. Moreover, recent study showed that repeated ghrelin administrations have stimulatory effects

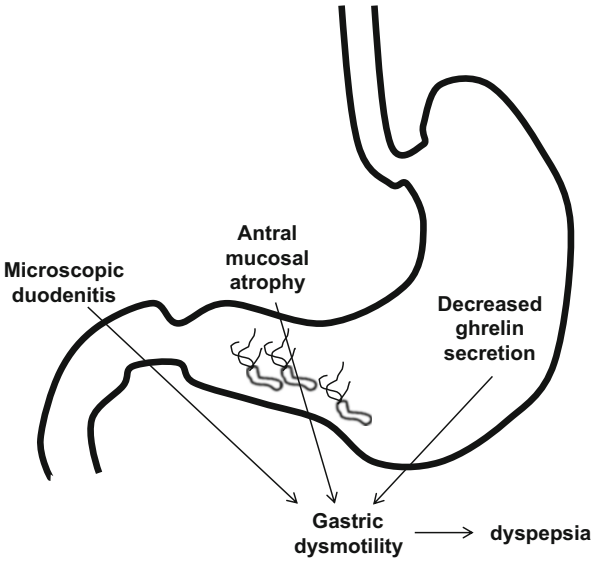

Fig. 7.2 Pathophysiological conditions associated with dyspepsia symptoms

on food intake in FD patients [23]. Taken together, *H. pylori* infection may reduce appetite with suppressed ghrelin secretion.

Inflammatory cell infiltration in the duodenal mucosa would be another possible cause of HpD. Mirbagheri et al. reported that *H. pylori* infection was significantly associated with presence and severity of microscopic duodenitis [24]. Although severity of dyspepsia symptoms was not higher in *H. pylori*-infected patients than *H. pylori*-noninfected patients, microscopic duodenitis significantly worsened the dyspepsia symptoms in the presence of *H. pylori* infection. Moreover, they also compared the symptom response to *H. pylori* eradication in dyspepsia patients in presence or absence of microscopic duodenitis [25]. Among 37 dyspepsia patients with *H. pylori*, microscopic duodenitis was observed in 16 (43.2 %). The improvement in severity of dyspepsia symptoms in the presence of microscopic duodenitis was significantly greater than when it was absent.

We previously reported the importance of muscle-specific microRNAs (miRNAs), such as *miR-1* and *miR-133*, in gastric motility disorders associated with *H. pylori* infection in mice [26]. These miRNAs were downregulated in the stomach, while the expression levels of histone deacetylase 4 (HDAC4) and serum response factor (SRF), which are target genes of *miR-1* and *miR-133*, were increased. Aberrant expression of HDAC4 and SRF induced gastric muscular hyperproliferation, thereby the gastric emptying was impaired.

7.4 Future Prospects

As described above, the evidence of the association between *H. pylori* infection and dyspepsia has been increasing. However, it is still unknown why most of individuals with *H. pylori* infection have no symptoms, while some of them have chronic dyspepsia symptoms. This point would be explained by distinct host-microbe interactions, but the evidence is insufficient for them. Tahara et al. reported the p22PHOX C242T polymorphism in host was inversely related to the risk of dyspepsia just in *H. pylori*-infected patients, but not in *H. pylori*-noninfected patients [27], although the reason for this difference is unknown. We therefore need to conduct further investigations about the complex interactions between *H. pylori* and the host to reveal mechanisms of HpD.

References

1. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, et al. Functional gastroduodenal disorders. Gastroenterology. 2006;130(5):1466–79. doi:10.1053/j.gastro.2005.11.059. S0016-5085(06)00508-7 [pii].
2. Suzuki H, Matsuzaki J, Hibi T. What is the difference between *Helicobacter pylori*-associated dyspepsia and functional dyspepsia? J Neurogastroenterol Motil. 2011;17(2):124–30. doi:10.5056/jnm.2011.17.2.124.
3. Suzuki H, Moayyedi P. *Helicobacter pylori* infection in functional dyspepsia. Nat Rev Gastroenterol Hepatol. 2013;10(3):168–74. doi:10.1038/nrgastro.2013.9.
4. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut. 2015;64(9):1353–67. doi:10.1136/gutjnl-2015-309252.
5. Miwa H, Kusano M, Arisawa T, Oshima T, Kato M, Joh T, et al. Evidence-based clinical practice guidelines for functional dyspepsia. J Gastroenterol. 2015;50(2):125–39. doi:10.1007/s00535-014-1022-3.
6. Armstrong D. *Helicobacter pylori* infection and dyspepsia. Scand J Gastroenterol Suppl. 1996;215:38–47.
7. Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. Gut. 2014. doi:10.1136/gutjnl-2014-307843.
8. Fang YJ, Liou JM, Chen CC, Lee JY, Hsu YC, Chen MJ, et al. Distinct aetiopathogenesis in subgroups of functional dyspepsia according to the Rome III criteria. Gut. 2014. doi:10.1136/gutjnl-2014-308114.
9. Piriyapong K, Tangaroonsanti A, Mahachai V, Vilaichone RK. *Helicobacter pylori* infection impacts on functional dyspepsia in Thailand. Asian Pac J Cancer Prev. 2014;15(24):10887–91.
10. Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. Cochrane Database of Syst Rev. 2006;2, CD002096. doi:10.1002/14651858.CD002096.pub4.
11. Zhao B, Zhao J, Cheng WF, Shi WJ, Liu W, Pan XL, et al. Efficacy of *Helicobacter pylori* eradication therapy on functional dyspepsia: a meta-analysis of randomized controlled studies with 12-month follow-up. J Clin Gastroenterol. 2014;48(3):241–7. doi:10.1097/MCG.0b013e31829f2e25.
12. Kim SE, Park YS, Kim N, Kim MS, Jo HJ, Shin CM, et al. Effect of *Helicobacter pylori* eradication on functional dyspepsia. J Neurogastroenterol Motil. 2013;19(2):233–43. doi:10.5056/jnm.2013.19.2.233.

13. Lan L, Yu J, Chen YL, Zhong YL, Zhang H, Jia CH, et al. Symptom-based tendencies of *Helicobacter pylori* eradication in patients with functional dyspepsia. World J Gastroenterol. 2011;17(27):3242–7. doi:10.3748/wjg.v17.i27.3242.
14. 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(4):417–24. doi:10.1097/MEG.0b013e328317b89e.
15. Mazzoleni LE, Sander GB, Francesconi CF, Mazzoleni F, Uchoa DM, De Bona LR, et al. *Helicobacter pylori* eradication in functional dyspepsia: HEROES trial. Arch Intern Med. 2011;171(21):1929–36. doi:10.1001/archinternmed.2011.533.
16. Suzuki H, Mori H. *Helicobacter pylori*: *Helicobacter pylori* gastritis-a novel distinct disease entity. Nat Rev Gastroenterol Hepatol. 2015;12(10):556–7. doi:10.1038/nrgastro.2015.158.
17. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402(6762):656–60. doi:10.1038/45230.
18. Tatsuguchi A, Miyake K, Gudis K, Futagami S, Tsukui T, Wada K, et al. Effect of *Helicobacter pylori* infection on ghrelin expression in human gastric mucosa. Am J Gastroenterol. 2004;99(11):2121–7. doi:10.1111/j.1572-0241.2004.30291.x.
19. Suzuki H, Masaoka T, Hosoda H, Nomura S, Ohara T, Kangawa K, et al. Plasma ghrelin concentration correlates with the levels of serum pepsinogen I and pepsinogen I/II ratio—a possible novel and non-invasive marker for gastric atrophy. Hepatogastroenterology. 2004;51(59):1249–54.
20. Isomoto H, Nakazato M, Ueno H, Date Y, Nishi Y, Mukae H, et al. Low plasma ghrelin levels in patients with *Helicobacter pylori*-associated gastritis. Am J Med. 2004;117(6):429–32. doi:10.1016/j.amjmed.2004.01.030.
21. Lee KJ, Cha DY, Cheon SJ, Yeo M, Cho SW. Plasma ghrelin levels and their relationship with gastric emptying in patients with dysmotility-like functional dyspepsia. Digestion. 2009;80(1):58–63. doi:10.1159/000215389.
22. Shindo T, Futagami S, Hiratsuka T, Horie A, Hamamoto T, Ueki N, et al. Comparison of gastric emptying and plasma ghrelin levels in patients with functional dyspepsia and non-erosive reflux disease. Digestion. 2009;79(2):65–72. doi:10.1159/000205740.
23. Akamizu T, Iwakura H, Ariyasu H, Hosoda H, Murayama T, Yokode M. Repeated administration of ghrelin to patients with functional dyspepsia: its effects on food intake and appetite. Eur J Endocrinol. 2008;158(4):491–8. doi:10.1530/EJE-07-0768. 158/4/491.
24. Mirbagheri SA, Khajavirad N, Rakhshani N, Ostovaneh MR, Hoseini SM, Hoseini V. Impact of *Helicobacter pylori* infection and microscopic duodenal histopathological changes on clinical symptoms of patients with functional dyspepsia. Dig Dis Sci. 2012;57(4):967–72. doi:10.1007/s10620-011-1960-z.
25. Mirbagheri SS, Mirbagheri SA, Nabavizadeh B, Entezari P, Ostovaneh MR, Hosseini SM, et al. Impact of microscopic duodenitis on symptomatic response to *Helicobacter pylori* eradication in functional dyspepsia. Dig Dis Sci. 2015;60(1):163–7. doi:10.1007/s10620-014-3285-1.
26. Saito Y, Suzuki H, Tsugawa H, Suzuki S, Matsuzaki J, Hirata K, et al. Dysfunctional gastric emptying with down-regulation of muscle-specific microRNAs in *Helicobacter pylori*-Infected mice. Gastroenterology. 2011;140:189–98. doi:10.1053/j.gastro.2010.08.044.
27. Tahara T, Shibata T, Wang F, Nakamura M, Sakata M, Nakano H, et al. A genetic variant of the p22PHOX component of NADPH oxidase C242T is associated with reduced risk of functional dyspepsia in *Helicobacter pylori*-infected Japanese individuals. Eur J Gastroenterol Hepatol. 2009;21(12):1363–8. doi:10.1097/MEG.0b013e32830e2871.