injury.[14] Gastric ischaemia–reperfusion injury induces delayed gastric emptying through the inactivation of interstitial cells of Cajal and neuronal nitric oxide synthase (nNOS)-positive nerves.[15] Under such a state of ischaemia–reperfusion, gastric mucosal ghrelin-positive X/A-like cells and the levels of plasma ghrelin and ghrelin production in the stomach decrease, resulting in anorexia in rats.[16] These alterations are predicted to trigger dyspeptic symptoms, such as postprandial fullness and early satiation, in humans.

Acid secretion

Acid secretion, which is affected by infection with *H. pylori*, is also associated with dyspepsia.[17] Indeed, patients with functional dyspepsia and *H. pylori* infection had a fourfold increase in acid secretion after intravenous infusion of gastrin-releasing peptide (GRP)—a neuropeptide that induces responses that mimic the physiological responses to food ingestion.[18] By contrast, asymptomatic *H. pylori*-positive individuals had only a 2.5-fold increase in stimulated acid secretion. Acid secretion during *H. pylori* infection depends on the spread of gastric mucosal atrophy and the local inflammatory states, which are determined by host–bacterial interactions and environmental factors.[19] In a subset of *H. pylori*-infected patients with antral predominant gastritis without corpus atrophy, acid secretion might be enhanced compared with those with normal uninfected mucosa, and is a potential cause of dyspeptic symptoms, such as epigastric pain or burning.[20,21] Conversely, when atrophy extends to the corpus mucosa (fundic gland), diminished acid secretion caused by the direct damage to parietal cells in the corpus has been shown to be associated with gastric ulcers and gastric cancer; interestingly, this atrophy does provide protection from gastro-oesophageal reflux.[22]

Gastric endocrinology

Gastrin and somatostatin

H. pylori colonized in the antral mucosa have been hypothesized to lead to the injury of somatostatin-producing D cells, leading to a decrease in the secretion of somatostatin. As somatostatin is a negative regulator of gastrin secretion, the reduction in somatostatin levels would, in turn, lead to an increase in gastrin levels.[23–26] Support for this hypothesis comes from the observation that fasting and postprandial serum gastrin levels are increased in patients infected with *H. pylori*, with an equivalent decrease in gastric mucosal concentrations of somatostatin.[27,28] Interestingly, these abnormalities are corrected by *H. pylori* eradication therapy.[23,29] These findings suggest that the eradication of *H. pylori* in patients with symptomatic antral gastritis would be beneficial for symptom relief.

Ghrelin

Given the gastric location of ghrelin production, it is perhaps not surprising that an insult to the gastric mucosa affects circulating ghrelin levels in humans, which has a subsequent affect on appetite. Indeed, infection with *H. pylori* is associated with chronic gastritis, gastric atrophy and ulceration as well as reduced appetite and a reduced BMI. *H. pylori* also damages the ghrelin-producing gastric X/A-like cells[30] and decreases ghrelin secretion.[31–33] Ghrelin is predominantly produced by the gastric enteroendocrine cell compartment and is octanoylated by ghrelin *o*-acyltransferase (GOAT) before secretion into the bloodstream. This octanoylation is essential for many of the biological properties of ghrelin including appetite stimulation and anti-inflammatory properties, as only the acylated form of ghrelin binds to the ghrelin receptor, the growth hormone secretagogue receptor.[34] Ghrelin is involved in hunger sensations, acid secretion[35] and gastrointestinal motility; the alteration of ghrelin production in the stomach by *H. pylori* could contribute to upper gastrointestinal symptoms in patients with functional dyspepsia. This idea is supported by the observation that ghrelin levels fluctuate in some patients with functional dyspepsia,[36] although whether this fluctuation is the cause or a consequence of upper gastrointestinal symptoms remains to be elucidated. Both enhanced acid and ghrelin secretion can be reversed to some extent by eradication therapy,[37–39] and restoration of these physiological changes might explain the beneficial effect of eradication therapy on dyspeptic symptoms in patients with *H. pylori* infection. In *H. pylori*-positive patients with chronic atrophic gastritis, the plasma level of total and active ghrelin is

Key points

- *Helicobacter pylori* infection is a major cause of gastritis and is associated with a variety of motility, endocrine and acid-secretory abnormalities that could drive the symptoms of functional dyspepsia
- In a meta-analysis of randomized controlled trials, *H. pylori* eradication had a small but statistically significant effect in controlling the symptoms of functional dyspepsia
- *H. pylori* eradication improves symptoms in patients with epigastric-pain-predominant and postprandial-distress-predominant functional dyspepsia
- The majority of guidelines recommend *H. pylori* eradication in at least a subset of patients with functional dyspepsia

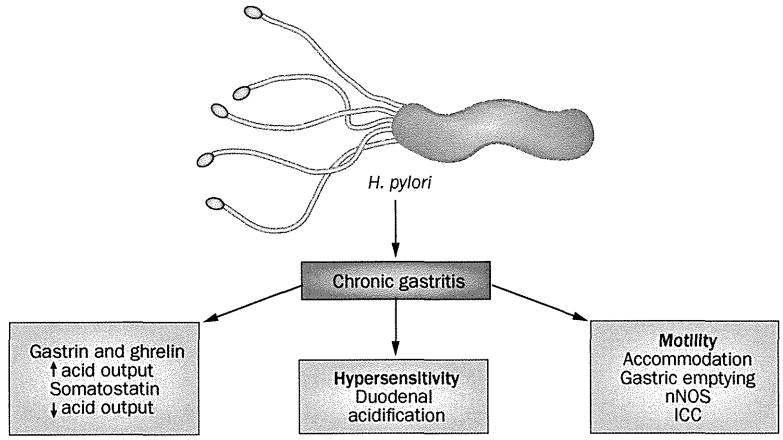

Figure 1 | Symptoms of chronic gastritis caused by *Helicobacter pylori* infection. Duodenal acidification leads to duodenal hypersensitivity. Deregulation of accommodation and gastric emptying is thought to be caused by inactivation of nNOS and ICC. Acid output is predicted to be promoted by gastrin and ghrelin, and suppressed by somatostatin. Abbreviations: ICC, interstitial cells of Cajal; nNOS, neuronal nitric oxide synthase.

significantly lower than in uninfected individuals.[37–39] However, after eradication of this pathogen, results are mixed;[39,40] some researchers report restoration of ghrelin levels,[41,42] whereas others report no significant changes in ghrelin levels after eradication.[32,43]

As ghrelin—especially the active acylated form of ghrelin—has an appetite-promoting action through neuropeptide Y (NPY) in the hypothalamus, the change in ghrelin dynamics could affect the gastroduodenal symptoms of early satiety and appetite loss. Indeed, activation of ghrelin receptors leads to increased levels of NPY and agouti-related peptide.[44] Such enhancement of the NPY pathway would promote appetite and so could be beneficial for the treatment of early satiety or anorexic symptoms.

MicroRNAs

Gastroduodenal motility might be linked to *H. pylori* infection in a subset of infected individuals, such as those with delayed gastric emptying.[45,46] However, a correlation between gastric emptying and eradication therapy has not been observed in all studies.[47] In 2011, we found that gastric emptying was significantly accelerated in mice with chronic *H. pylori* infection, as well as those infected with another *Helicobacter* species, *H. felis*.[48] The muscular layer of the stomach of the *H. pylori*-infected mice was considerably thickened; moreover, infected mice had hyperplasia of myocytes in the stomach and downregulation of the muscle-specific microRNAs *miR-1*, *miR-133a* and *miR-133b*. However, the expression of histone deacetylase 4 and serum response factor (reported to be target genes of *miR-1* and *miR-133* and known to enhance muscular hyperproliferation) were increased. Chronic *H. pylori* infection with downregulated expression of muscle-specific miRNAs might cause hyperplasia of the muscular layer of the stomach and dysfunction of gastric emptying, especially accelerated gastric emptying, possibly through disturbed gastric accommodation. These findings provide a novel insight into the molecular pathogenesis of gastric dysmotility, specifically associated with *H. pylori* infection.[48]

In idiopathic gastroparesis, administration of ghrelin enhances gastric emptying and improves meal-related symptoms.[49] Therefore, analogues of ghrelin are expected to represent a new class of prokinetic agents that could be useful in gastric dysmotility.[50] TZP-101, a synthetic, selective ghrelin agonist, is now being tested in clinical trials.[51]

Mast cells

Mast cells are considered as another cause of dyspeptic symptoms. However, mast cells are found in patients with *H. pylori*-negative dyspepsia but not in *H. pylori*-positive patients, suggesting a different mechanism underlying the development of symptoms in patients with *H. pylori*-negative dyspepsia.[52]

Detection of *H. pylori*-positive gastritis

Nodular gastritis, a unique type of gastritis caused by *H. pylori* infection, is detectable by routine endoscopy.[53,54] Patients with this type of gastritis often have dyspeptic symptoms, which remit after *H. pylori* eradication, with the disappearance of goose-flesh gastritis.[53,54] In addition, enlarged fold gastritis with hypochlorhydria is reversed by the eradication of *H. pylori*,[55] although no specific dyspeptic symptoms have been reported. Macroscopic or endoscopic changes (including gastric mucosal atrophy and intestinal metaplasia) are frequently observed in patients from North Eastern Asia, such as Japan and Korea, where highly virulent *H. pylori* strains, such as those that express the vacuolating cytotoxin (for example, m1VacA-positive strains), are predominant.[56] Endoscopy has revealed that *H. pylori* infection causes definite structural changes, possibly fulfilling the definition for organic disease.[57–59] Since 2005, reports from both Japan and Western countries have shown that high-resolution endoscopy equipped with magnification apparatus can be used to identify *H. pylori* infection status with high accuracy.[60,61] Therefore, if clinicians are well-trained, the presence of *H. pylori* infection could be diagnosed endoscopically by checking the absence of the regular arrangement of collecting venules. On the other hand, the diagnosis of *H. pylori* infection could be performed without endoscopy by using urea breath test, stool antigen test, serological testing or urine test.[12,62]

Eradication in functional dyspepsia

In an era of evidence-based medicine, the key question is whether any evidence from randomized controlled trials (RCTs) supports the proposal that eradication of *H. pylori* leads to resolution of functional dyspepsia symptoms. Initial RCT evidence was conflicting,[63,64] as were the main systematic reviews that addressed this question.[65,66] As data have emerged,[67] however, it has become clear that *H. pylori* eradication has a small but statistically significant effect on functional dyspepsia symptoms. This conclusion was confirmed by a large South American RCT[68] and by the latest Cochrane review on *H. pylori* eradication, which is in the process of being updated.[69,70] In the published Cochrane review, 21 trials involving 4,331 patients with functional dyspepsia who had undergone *H. pylori* eradication therapy or received placebo were analysed.[70] All trials used either improvement in overall dyspepsia symptoms or complete absence of symptoms as an outcome. When more than one outcome was given in the paper, the most stringent outcome was chosen for the meta-analysis (that is, the outcome that was closest to describing complete absence of dyspepsia symptoms). No statistically significant variation was observed between RCT results, and most studies evaluated participants at 12 months. Overall, the number needed to treat to cure one case of dyspepsia that would not be cured by placebo was 14 (95% CI 10–20).[70] This estimate does not include studies identified in a further systematic review[71] that also found a significant effect of *H. pylori* eradication on functional dyspepsia, although six of the seven studies only evaluated patients at 1 month.

Overall, the effect of *H. pylori* eradication on functional dyspepsia is modest and it could be argued

Table 1 | Summary of guidelines that evaluate use of *H. pylori* eradication in functional dyspepsia

Country	Focus of guideline	*H. pylori* eradication in functional dyspepsia	Recommendation	Level of evidence	Comments	Study
Denmark	*H. pylori*	Yes	Strong	Highest	"Effect modest at best"	Bytzer *et al.* (2011)[89]
Korea	Functional dyspepsia	Yes	N/A	N/A	"*H. pylori* eradication can be one of the therapeutic options in functional dyspepsia"	Jee *et al.* (2011)[90]
Germany	*H. pylori*	Yes	Strong	Highest	N/A	Fischbach (2009)[91]
Asia	Functional dyspepsia	Yes	Strong	Highest	"Eradicate *H. pylori* if socioeconomic conditions allow"	Miwa *et al.* (2012)[94]
Asia	*H. pylori*	Yes	Strong	Highest	N/A	Fock *et al.* (2009)[93]
Japan	*H. pylori*	Yes	Strong	Highest	"Eradication therapy is strongly recommended for patients with *H. pylori*-positive functional dyspepsia. However, further investigation will be required to determine the actual value of eradication therapy for Japanese patients"	Asaka *et al.* (2010)[95]
Europe	*H. pylori*	Yes	Strong	Highest	"*H. pylori* eradication produces long-term relief of dyspepsia in one of 12 patients with *H. pylori* and functional dyspepsia; this is better than any other treatment"	Malfertheiner *et al.* (2012)[96]
USA	*H. pylori*	Controversial	N/A	N/A	"A subset of patients with functional dyspepsia derives benefit from *H. pylori* eradication"	Chey *et al.* (2007)[92]

Abbreviation: N/A, not applicable.

that acid suppression[72,73] or prokinetic therapy[73] have a greater effect on functional dyspepsia symptoms. However, the sizes of the effect reported in these studies are driven by lower quality studies than those for eradication treatment.[74] Moreover, in the case of prokinetic therapy, there is evidence of publication bias or other small study effects[73] that could have led to an overestimation of the treatment effect. Furthermore, an economic analysis suggested that *H. pylori* eradication is the most cost-effective treatment approach for infected patients with functional dyspepsia,[66] as long-term effects are seen with just 1 week of therapy. By contrast, alternative medical therapies need to be taken long-term as the majority of patients with functional dyspepsia continue to have symptoms over a number of years.[75] Long-term acid suppressive therapy might also be related to serious adverse events, such as risk of hip fracture, pneumonia and enteric infection, although this area is still controversial.[76] New eradication protocols[77,78] have been developed with increased eradication rates, which might increase the efficacy of *H. pylori* eradication therapy in individuals with functional dyspepsia.

Some trials in the Cochrane systematic review[70] supported eradication therapy, although most found no benefit. One possibility is that these different conclusions are a result of variations in trial design; indeed, this hypothesis is likely to be the case for some of the Chinese studies,[71] which had unclear methods of randomization and only a 1-month follow-up period. Another possibility is that positive studies had different approaches to patient selection, treated control patients differently or used different *H. pylori* eradication therapies. However, when these possibilities were explored in subgroup analyses, they did not seem to be the explanation.[70] Indeed, no statistically significant heterogeneity was found between studies and so it is most likely that any variation in individual trial results was simply owing to chance. The beneficial effect of *H. pylori* eradication in functional dyspepsia is modest and all trials were underpowered to detect this difference. It would therefore be expected that most trials would show no benefit but a few, by chance, would find a statistically significant effect and indeed this trend was observed in the meta-analysis.[70]

Symptom subgroups in functional dyspepsia

Patients with functional dyspepsia have various upper gastrointestinal symptoms that have been grouped together in different ways.[79] Current concepts have focused on epigastric pain predominant and postprandial distress related symptoms.[80] Acid suppressive therapy can improve symptoms in patients with reflux-predominant symptoms and epigastric-pain-predominant symptoms, but is ineffective in patients with dysmotility-type symptoms.[72] It is currently unclear whether *H. pylori* eradication therapy has a different efficacy depending on the symptom subgroup of functional dyspepsia. Three RCTs,[68,81,82] involving a total of 468 patients with functional dyspepsia categorized into either epigastric pain or dysmotility subgroups, have investigated the effect of *H. pylori* eradication. Overall, *H. pylori* eradication seemed to be effective in both epigastric-pain-predominant dyspepsia and dysmotility-type dyspepsia, with no heterogeneity in effect between the subgroups. This trend is supported by three other trials[83–85] that evaluated the effect of *H. pylori* eradication in 470 patients with epigastric pain; *H. pylori* eradication was significantly more efficacious than placebo at relieving this symptom. This symptom relief was also

seen in the 200 patients in these three studies who had bloating but not in the 252 patients with early satiety. A potential explanation for these observations is related to ghrelin levels. As ghrelin enhances gastric emptying, a decrease in ghrelin levels could delay gastric emptying, resulting in postprandial fullness, whereas an increase in ghrelin levels could lead to early gastric emptying, early duodenal acidification,[86] hypersensitivity and epigastric pain.[87]

Overall, *H. pylori* eradication therapy has an effect on a wide variety of upper gastrointestinal symptoms, which suggests that although the effect is modest it does seem to apply to the general functional dyspepsia population rather than specific patient subgroups. This observation is in contrast to acid suppressive therapies or prokinetic therapies, which are only effective for certain functional dyspepsia symptoms.[88]

Eradication in Asia

The prevalence of *H. pylori* infection and gastric cancer is extremely high in the East, especially in East Asia including Japan, Korea and the northern part of China. Symptom relief from eradication of *H. pylori* in functional dyspepsia might, therefore, be different, as a much larger proportion of the population in these regions is infected with *H. pylori* than in the West. Furthermore, genetic profiles, socioeconomic conditions and dietary habits are different in Asian populations than in European and American populations. A comparison of data from Chinese,[71] South American[68] and Western[69,70] studies revealed that *H. pylori* eradication therapy has a statistically significant effect on functional dyspepsia symptoms in all populations; overall, however, the effect of *H. pylori* eradication seems to be more pronounced in Asian populations, which could relate to the factors specific to Asian populations as described above. However, much greater variation in trial results was observed in Asian populations and most of this was unexplained. Moreover, the majority of the Asian studies only evaluated patients for 1 month compared to 1 year in non-Asian studies. Therefore, other differences in these studies might explain the greater effects rather than just the population that was studied.

Guidelines

Two types of guidelines have addressed *H. pylori* eradication in functional dyspepsia: guidelines aimed at managing *H. pylori* infection and those related to functional dyspepsia. We have searched for both types of guidelines published over the past 5 years and identified eight papers from Asian, European and US societies[89–96] (Table 1). Most guidelines were from the perspective of *H. pylori* management and the majority also formally evaluated the quality of the evidence and gave a strength of recommendation (Table 1). All guidelines recommended *H. pylori* eradication in some patients with functional dyspepsia and all of those that graded the evidence suggested that the data were of the highest quality (Table 1). These recommendations reflect the high number of RCTs that have evaluated *H. pylori* eradication in functional dyspepsia and the consistency of the effect seen in the meta-analyses described above. The weakest recommendation was seen in the oldest guideline to be included in our search, namely the American College of Gastroenterology guideline.[92] It will be interesting to see what the update of this guideline will show and whether it will soon agree with the guidelines that have been published since. On the other hand, many guidelines also noted that the effect was modest and the data are also consistent in this regard. Guidelines strongly recommended *H. pylori* eradication despite the small benefit as no therapy has been shown to be particularly effective in functional dyspepsia,[94] and some guidelines noted that the effect is long-term and eradication has other benefits such as the prevention of peptic ulcer disease,[97] including bleeding ulcers[98] and the possible reduction in the risk of gastric cancer.[99]

Conclusions

High quality evidence indicates that *H. pylori* infection is the cause of dyspeptic symptoms in a small proportion of the infected population with functional dyspepsia. Patients with dyspepsia undergoing endoscopy should have a test for this infection and if positive should be offered treatment. The pathophysiology underlying symptom generation in *H. pylori*-positive individuals is clearly different from those who are uninfected. *H. pylori*-positive and *H. pylori*-negative cohorts should therefore be independently assessed in clinical trials investigating the efficacy of medication.

Review criteria

A search for original articles published between 1966 and September 2012 was conducted using MEDLINE. The search terms used were "pylori" combined with "dyspepsia". The reference lists of identified articles were also searched for further relevant papers.

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Author contributions

Both authors contributed to all aspects of this article.

Original Article

Improvement of reflux symptom related quality of life after *Helicobacter pylori* eradication therapy

Kenro Hirata,[1] Hidekazu Suzuki,[1,*] Juntaro Matsuzaki,[1] Tatsuhiro Masaoka,[1,2] Yoshimasa Saito,[1] Toshihiro Nishizawa,[3] Eisuke Iwasaki,[4] Seiichiro Fukuhara,[1] Sawako Okada[1] and Toshifumi Hibi[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
[2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Eiju General Hospital, 2-23-16 Higashiueno, Taito-ku, Tokyo 110-0015, Japan
[3]Division of Gastroenterology, National Hospital Organization Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-0021, Japan
[4]Department of Internal Medicine, Saiseikai Central Hospital, 1-4-17 Mita, Minato-ku, Tokyo 108-0073, Japan

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The relationship between *Helicobacter pylori* (*H. pylori*) eradication therapy and the risk of developing gastroesophageal reflux disease (GERD) is controversial. We investigated the influence of *H. pylori* eradication on the risk of GERD by focusing on the quality of life (QOL) and evaluating reflux symptoms. Patients with *H. pylori* infection were administered triple therapy for *H. pylori* eradication. At 3 months and 1 year after the eradication therapy, surveys were conducted to determine the health-related QOL by quality of life in reflux and dyspepsia-Japanese version, (QOLRAD-J) and the severity of GERD symptoms by Carlsson-Dent questionnaire (CDQ). Forty patients were included in the analysis. Although no significant changes of these scores were apparent 3 months after *H. pylori* eradication, the QOLRAD-J and CDQ scores were significantly improved after 1 year. The degree of improvement was even more marked in cases with initially low scores. In conclusion, improved GERD-related QOL and reflux symptoms were noted 1 year after *H. pylori* eradication therapy. In addition, the degree of improvement was more marked in cases with severe reflux symptoms.

***Key Words*: *Helicobacter pylori*, eradication therapy, reflux symptoms, quality of life, questionnaire**

Helicobacter pylori (*H. pylori*) eradication therapy has been reported as an effective strategy in the treatment of peptic ulcers and gastric mucosa-associated lymphoid tissue lymphoma, in addition to the prevention of recurrence of gastric cancer after endoscopic resection.[1,2] On the other hand, the influence of *H. pylori* eradication in the management of gastroesophageal reflux disease (GERD) is controversial. Some researchers have suggested that *H. pylori* eradication leads to a more resilient GERD.[3–5] Decreased acid secretion in patients with *H. pylori* infection occurs as a result of progressive gastric mucosal atrophy.[6] Thus, reflux symptoms were thought to be exacerbated after *H. pylori* eradication therapy because of the recovery of acid secretion. Meanwhile, other researchers have reported that *H. pylori* eradication does not exacerbate GERD symptoms.[7–9] Sasaki *et al.*[10] reported that it was rare for reflux esophagitis that develops after *H. pylori* eradication therapy to become severe or cause long-term GERD symptoms.

Quality-of-life (QOL) is an important determinant of symptom generation in GERD patients. The endoscopic severity of GERD is not always correlated with heartburn severity.[11,12] Regardless of the endoscopic findings, QOL may be greatly reduced by the presence of strong symptoms. It has been reported that GERD-related QOL may be worse than that of mild heart failure or angina.[13] Laine *et al.*[14] reported no significant change in QOL 6 months after *H. pylori* eradication therapy, and concluded that *H. pylori* eradication did not worsen the GERD-related QOL. However, how the GERD-related QOL might change on long-term follow-up has not yet been explored.

Talking medical history is one of the most useful means of diagnosing GERD. The presence of GERD can be diagnosed only by history taking in many cases, although endoscopy, 24 h pH monitoring, etc., have been developed to assist in diagnosis. The heartburn version of QOLRAD[15] (quality of life in reflux and dyspepsia) is a self-administered questionnaire. QOLRAD was created with an emphasis on the GERD-related QOL. QOLRAD is a disease-specific instrument, including 25 items classified into 5 domains: emotional distress, sleep disturbance, food/drink problems, physical/social functioning, and vitality. The scores for each QOLRAD domain are expressed on a scale of +1 to +7: the lower the QOLRAD score, the more severe the effect on daily QOL. The QOLRAD has been extensively documented in international studies in patients with heartburn for its reliability, validity, and responsiveness, and in the assessment of GERD-related QOL.[15,16] The Japanese version of QOLRAD (QOLRAD-J) has demonstrated utility in the evaluation of GERD-related QOL in Japanese patients.[17]

The Carlsson-Dent questionnaire (CDQ) is a self-administered questionnaire designed for screening GERD.[18] CDQ contains 7 kinds of questions about regurgitation, stomach discomfort and chest discomfort. The response to each question is chosen from among 3 or 4 alternatives. A score ranging from −7 to +18 is calculated by adding the individual positive and negative scores for the items in the questionnaire: the higher the CDQ score, the stronger the reflux symptoms. Dent *et al.*[19] reported that the CDQ is useful for the diagnosis of GERD and a cut-off level of 4 points is frequently used for a clinical diagnosis of GERD. In addition, the Japanese version of the CDQ is useful as a diagnostic tool for GERD in Japan.[20]

The serum pepsinogen (PG) test is sensitive for atrophic gastritis.[21–23] Serum PG consists of 2 biochemically and immunologically distinct types, pepsinogen I (PGI) and pepsinogen II (PGII).[24] The levels of PGI and the PG I/II ratio are useful sero-

*To whom correspondence should be addressed.
E-mail: hsuzuki@a6.keio.jp

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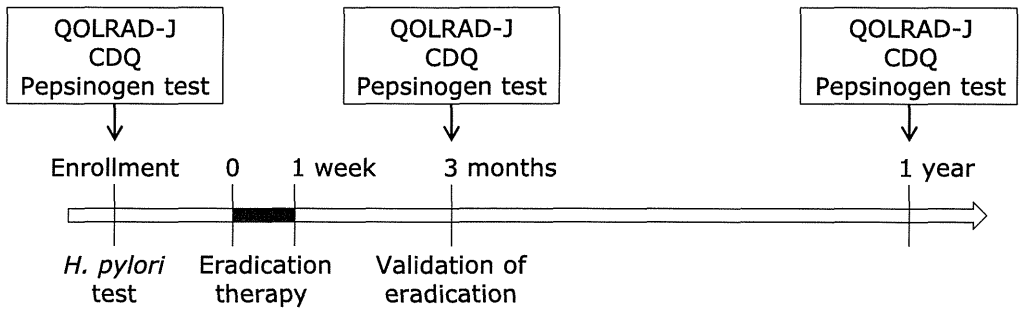

Fig. 1. Study design. All patients were given *H. pylori* eradication therapy (omeprazole 20 mg b.i.d., clarithromycin 400 mg b.i.d., and amoxicillin 750 mg b.i.d.) for 1 week, and eradication status was validated 3 months later. The QOLRAD-J questionnaire survey, the CDQ questionnaire surveys, and serum pepsinogen test were performed before, and at 3 months and 1 year after eradication therapy.

logical markers for chronic atrophic gastritis.[25–27] Kitahara *et al.*[28] reported that it is possible to detect gastric cancer by serum PG screening, using a PGI concentration of less than 70 ng/mL and a PG I/II ratio of less than 3.0 as the cut-off point for diagnosing severe atrophic gastritis.

This study was designed to identify the time course of changes in the GERD-related QOL and GERD symptoms using the QOLRAD-J and CDQ self-administered questionnaires after *H. pylori* eradication therapy.

Materials and Methods

Study design. This was a 2-center prospective cohort study. Outpatients with *H. pylori* infection at Keio University Hospital (Tokyo, Japan) and Eiju General Hospital (Tokyo, Japan) were enrolled from September 2008 to March 2009. *H. pylori* infection status was determined by the ^{13}C urea breath test, microaerobic bacterial cultivation, or histopathological examination of endoscopic biopsy specimens. All patients were given eradication therapy for 1 week with omeprazole 20 mg b.i.d., clarithromycin 400 mg b.i.d., and amoxicillin 750 mg b.i.d. Eradication status was validated 3 months after eradication therapy. The QOLRAD-J and CDQ surveys were conducted and PG levels were measured before eradication (BE) therapy, and at 3 months (3M) and 1 y (1Y) after (Fig. 1). Using QOLRAD-J, the scores for the following 5 domains were determined: emotional distress, sleep disturbance, food/drink problems, physical/social functioning, and vitality. The questionnaires were mailed to the patients who did not come to the outpatient clinic. Patients who did not receive eradication therapy, dropped out during treatment because of side effects from the eradication therapy, did not undergo evaluation of the effect of eradication therapy, or showed eradication failure were excluded from the study. The study protocol was approved by the ethics committees of Keio University School of Medicine and Eiju General Hospital, and written informed consent was obtained prior to subject enrollment. The UMIN Clinical Trials Registry number for this study is UMIN000001399 [http://www.umin.ac.jp/ctr/]. The study was performed in accordance with the principles of the Declaration of Helsinki.

Patient background. Height, weight, body mass index (BMI), alcohol consumption status, smoking status, presence/absence of dyspepsia, and previous history of peptic ulcer before eradication therapy were obtained from a review of medical records and medical interview sheets. Alcohol consumption status was defined as a positive/negative history of daily alcohol consumption. Smoking status was defined as a positive/negative history of smoking cigarettes. The presence/absence of dyspepsia was defined as a positive/negative history of epigastralgia, discomfort, or feeling of fullness in the epigastrium. Patients' prescription histories of antisecretory agents (histamine type-2 receptor antagonist or proton pump inhibitor) at 1 week (1W), 3M, 6 months (6M), and 1Y after eradication therapy were also reviewed.

Statistical analysis. The average QOLRAD-J and CDQ scores and PG expression were compared using one-way repeated-measures analysis of variance and the Bonferroni post-hoc test. Associations between the clinical background factors—age, height, weight, and BMI—and changes in the QOLRAD-J and CDQ scores were compared using the Student's t test, and the associations between clinical background factors—sex, the presence/absence of dyspepsia, previous history of peptic ulcer, alcohol consumption status, smoking status, and PG—and changes in the QOLRAD-J and CDQ scores were compared using the chi-square test. The correlation between changes in QOLRAD-J and CDQ scores were evaluated by a linear regression model. Statistical significance was defined as a p value of less than 0.05. All statistical analyses were performed using PASW Statistics (SPSS Inc., Chicago, IL).

Results

Patient characteristics. Fifty-seven patients were enrolled with informed consent. From these 57, 17 patients were excluded: 3 did not receive eradication therapy, 2 dropped out halfway owing to the appearance of side effects (nausea and hemorrhagic colitis), 6 did not undergo evaluation of the effect of eradication therapy, and 6 showed eradication failure (Fig. 2). Finally, data from 40 patients (55.7 ± 11.3 years old, range 22–76 y; 21 men and 19 women) were included. Patient characteristics are shown in Table 1. The number and percentage of subjects for whom data were collected was 40 (100.0%) at BE, 39 (97.5%) at 3M, and 35 (87.5%) at 1Y for estimation of the QOLRAD-J scores, and 37 (92.5%) at BE, 38 (95.0%) at 3M, and 34 (85.0%) at 1Y for the CDQ scores.

Changes in the QOLRAD-J and CDQ scores after *H. pylori* eradication therapy. Improvement in both the QOLRAD-J and CDQ scores was observed at 1Y, although no significant differences were noted between the levels at BE and at 3M. With regard to the sub-domains of QOLRAD-J, significant improvements were observed in emotional distress, sleep disturbance, and food/drink problems at 1Y. On the other hand, improvement in PG score was identified not only in 1Y but in 3M (Table 2.).

A positive history of gastric antisecretory agent prescription during the follow-up period was identified in 32 of 40 patients. The number of patients prescribed antisecretory agents at 1W was 9 (28.1%), at 3M was 4 (12.5%), at 6M was 3 (9.4%), and at 1Y was 3 (9.4%). Improvement in both the QOLRAD-J and CDQ scores was observed at 1Y, even when the 3 patients who were taking antisecretory agents from 6M to 1Y were excluded from the analysis.

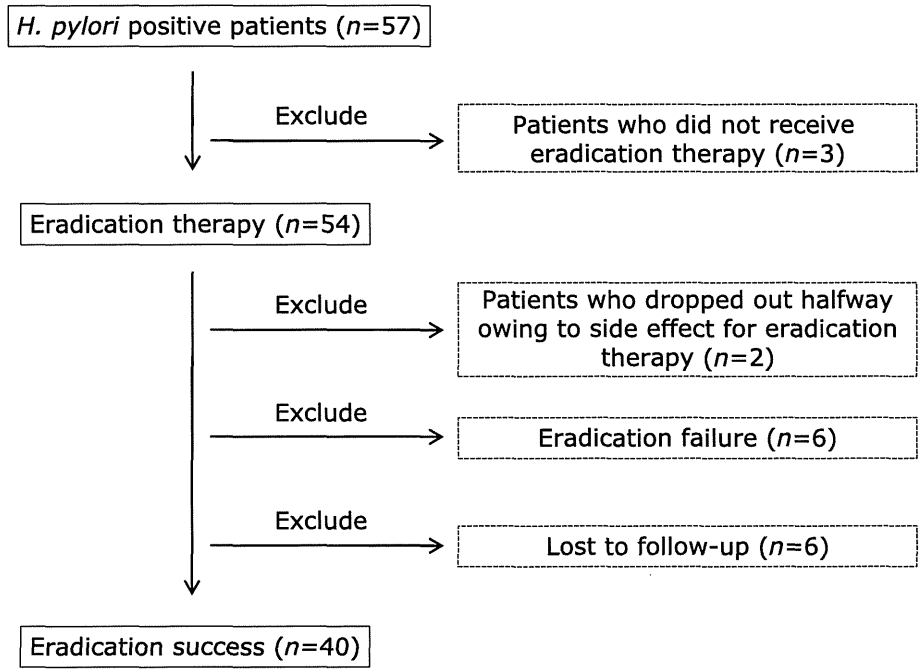

Fig. 2. Exclusion criteria. Fifty-seven outpatients with *H. pylori* infection were enrolled after obtaining their written informed consent. Patients who did not receive the eradication therapy, dropped out halfway due to side effects, did not undergo evaluation of the effect of the eradication therapy, or showed eradication failure were excluded from the study.

Table 1. Characteristics of subjects (n = 40)

Sex, No.	
Male (%)	21 (52.5)
Female (%)	19 (47.5)
Age, years	
Mean ± SD (range)	55.7 ± 11.3 (22–76)
Body Height, cm	
Mean ± SD (range)	163.9 ± 10.3 (150.0–184.0)
Body Weight, kg	
Mean ± SD (range)	58.7 ± 12.6 (41.0–110.0)
Body Mass Index, %	
Mean ± SD (range)	21.9 ± 3.3 (17.1–32.5)
Dyspepsia, No.	
Presence (%)	19 (47.5)
Absence (%)	13 (32.5)
Unknown (%)	8 (20.0)
Peptic ulcer, No.	
Presence (%)	15 (37.5)
Absence (%)	18 (45.0)
Unknown (%)	7 (17.5)
Alcohol Habit, No.	
Everyday (%)	13 (32.5)
Social drinker or nothing (%)	22 (55.0)
Unknown (%)	5 (12.5)
Smoking Habit, No.	
Presence (%)	6 (15.0)
Absence (%)	29 (72.5)
Unknown (%)	5 (12.5)

The proportions of patients in which no worsening of the QOLRAD-J scores was observed were 82.1% (32 of 39 patients) at 3M and 85.7% (30 of 35 patients) at 1Y, whereas those in which no worsening of the CDQ scores was observed were 73.0% (27 of 37 patients) at 3M and 88.2% (30 of 34 patients) at 1Y. In addition, worsening of the QOLRAD-J and CDQ scores was observed in 18.0% (7 of 39 patients) and 27.0% (10 of 37 patients) of the patients, respectively, at 3M, although score improvement was observed in 57.1% (4 of 7 patients) and 80.0% (8 of 10 patients) of the patients, respectively, at 1Y (Table 3).

Changes from the initial scores. Fig. 3A shows the changes in the QOLRAD-J score and Fig. 3B shows the changes in the CDQ score relative to the initial score. The CDQ scores were divided into groups with initial scores of <4 and ≥4, which represents the clinical cutoff. QOLRAD-J does not have a cut-off level because of digitizing of the QOL, whereas CDQ was developed for screening GERD. In this study, the average QOLRAD-J score at BE was 6.51 ± 0.15. Therefore, for the QOLRAD-J score, we set a cut-off level of 6 points for descriptive purposes to analyze the group with lower QOL scores. In this study, 7 of the 40 patients had QOLRAD-J scores <6 points at BE and 17 of 37 patients had CDQ scores ≥4 points at BE. In the group of patients (n = 7) with QOLRAD-J scores of <6, 5 patients showed improvement, while 2 became worse at 3M. However, at 1Y, all 7 patients showed significant improvement. In addition, the group with QOLRAD-J scores ≥6 hovered around the same high scores throughout the study period. Meanwhile, the group of patients with CDQ scores <4 points at BE showed significant improvement even at 3M. In particular, 29.4% (5 of 17 patients) of the patients with scores <4 became completely asymptomatic within 3M. On the other hand, among the patients in whom the CDQ scores were <4 at BE, the scores became worse at 3M, even though the average score was better than 4 at that time. However, no significant changes were noted between BE and 1Y.

Correlations between the QOLRAD-J and CDQ scores. Fig. 4A shows the correlations between the changes in QOLRAD-

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Table 2. Alteration of QOLRAD-J and CDQ score after *H. pylori* eradication therapy

	BE	3M†	1Y†
QOLRAD-J score			
Overall average	6.51 ± 0.15	6.71 ± 0.12	6.85 ± 0.06*
Emotional distress	6.55 ± 0.13	6.75 ± 0.10	6.86 ± 0.06*
Sleep disturbance	6.57 ± 0.16	6.78 ± 0.12	6.91 ± 0.05*
Food/Drink problems	6.29 ± 0.20	6.54 ± 0.17	6.77 ± 0.08*
Physical/Social functioning	6.72 ± 0.13	6.87 ± 0.66	6.97 ± 0.03
Vitality	6.58 ± 0.15	6.59 ± 0.16	6.72 ± 0.11
CDQ score	4.00 ± 0.69	4.43 ± 0.68	3.03 ± 0.72*
Serum pepsinogen level			
Pepsinogen I (ng/ml)	100.97 ± 22.91	51.94 ± 12.99*	48.54 ± 3.62*
Pepsinogen II (ng/ml)	32.97 ± 5.85	8.80 ± 1.70**	8.72 ± 0.44**
Pepsinogen I/II ratio	2.94 ± 0.36	5.55 ± 0.45**	5.60 ± 0.38**

Each value represents the mean ± SE. BE: before the eradication therapy, 3M: 3 months after the eradication therapy, 1Y: 1 year after the eradication therapy. †one-way repeated-measures analysis of variance and the Bonferroni post-hoc test compared to BE. *$p<0.05$, **$p<0.01$.

Table 3. The proportions of change in patients' scores

	BE-3M	BE-1Y
QOLRAD-J score		
Improvement	13/39 (33.3%)	13/35 (37.1%)
No change	19/39 (48.7%)	17/35 (48.6%)
Aggravation	7/39 (18.0%)	5/35 (14.3%)
CDQ score		
Improvement	13/37 (35.1%)	16/34 (47.1%)
No change	14/37 (37.8%)	14/34 (41.2%)
Aggravation	10/37 (27.0%)	4/34 (11.8%)

Values are *n* (%). BE: before the eradication therapy, 3M: 3 months after the eradication therapy, 1Y: 1 year after the eradication therapy.

J and CDQ scores at BE and 3M, and Fig. 4B shows the correlations between 3M and 1Y. Significant correlations were identified between the scores at 3M and 1Y, although no such correlation was identified between the scores at BE and 3M.

Association between clinical background factors and the QOLRAD-J and CDQ scores. Table 4 shows the association between clinical background factors and changes in the QOLRAD-J and CDQ scores. In order to identify the difference between the groups in which the scores worsened or did not worsen, the associations with clinical background factors were analyzed; however, no significant correlation was identified. When the association between clinical background factors and the baseline QOLRAD-J and CDQ scores were analyzed, no significant correlations were identified.

Changes of CDQ scores in initial positive/negative PG test group. In addition, we evaluated the degree of atrophic gastritis by performing the PG test at BE. The number and percentage of subjects for whom data were collected at BE was 31 of 40 (77.5%). Eight patients were positive for the PG test (PGI >70 and PG I/II ratio <3), and 23 were negative. Changes of CDQ scores in positive/negative PG test groups were shown in Fig. 5. The CDQ score varied from 2.88 ± 1.55 to 3.25 ± 1.76 (from BE to 1Y) in the positive-PG test group. On the other hand, the CDQ score varied from 4.65 ± 0.85 to 3.40 ± 0.95 (from BE to 1Y) in the negative-PG test group. Therefore, CDQ score tended to improve in the negative-PG test group than in the positive-PG test group ($p = 0.065$). No significant differences were observed in the QOLRAD-J score.

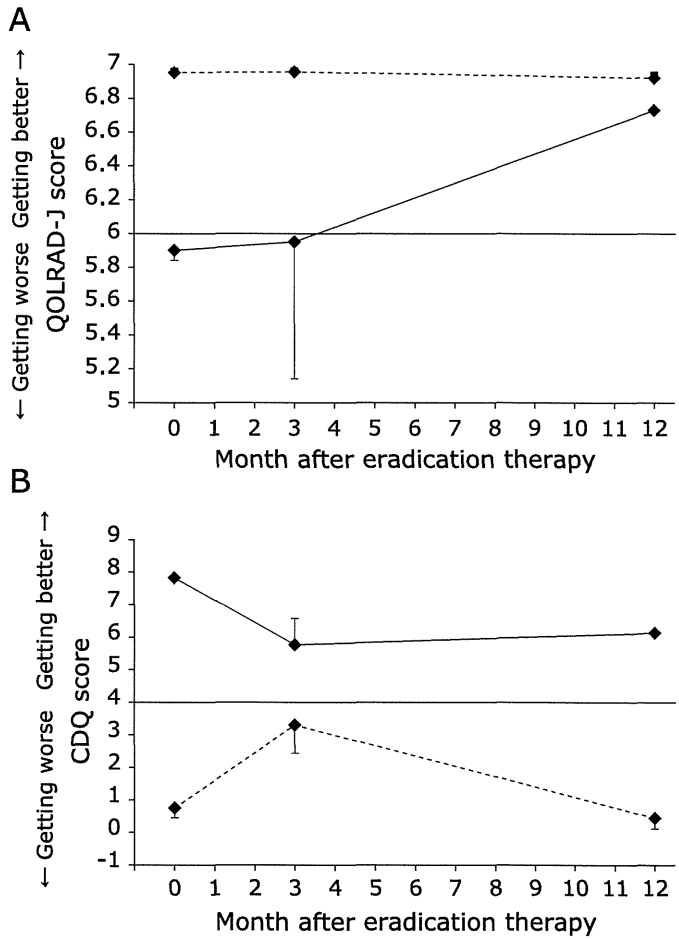

Fig. 3. Changes in QOLRAD-J and CDQ scores with low or high initial scores. The solid lines represent the low-score group and the dashed lines the high-score group. Changes in the QOLRAD-J score according to the initial score dichotomized at a cut-off of 6 [≥6 ($n = 33$); <6 ($n = 7$)] (A). Changes in the CDQ score according to initial score dichotomized at a cut-off of 4 [≥4 ($n = 17$); <4 ($n = 20$)] (B). *$p<0.05$ compared to BE using one-way repeated-measures analysis of variance and the Bonferroni post-hoc test.

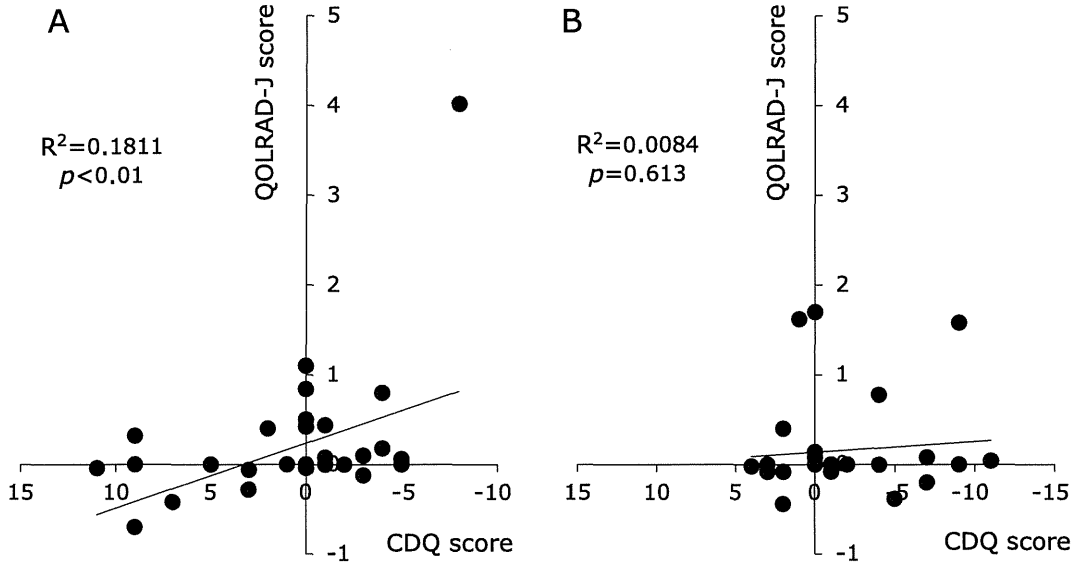

Fig. 4. Correlations between the changes in the QOLRAD-J and CDQ scores. The changes in the QOLRAD-J score are plotted on the y axis, and those in the CDQ score are plotted on the x axis. Correlation between the changes in the 2 scores from BE to 3M. (A) Correlation between the changes in the 2 scores from 3M to 1Y. (B) Significant correlation was identified between the changes in QOLRAD-J and CDQ scores from BE to 3M; however, no such significant correlation was identified from 3M to 1Y.

Table 4. Association between clinical background factors and change of QOLRAD-J and CDQ score

Clinical background factor	*p* value			
	QOLRAD-J score		CDQ score	
	BE-3M	BE-1Y	BE-3M	BE-1Y
Sex[1)]	0.671	0.682	0.863	0.052
Age[2)]	0.342	0.424	0.435	0.859
Body height[2)]	0.873	0.914	0.729	0.419
Body weight[2)]	0.511	0.501	0.872	0.814
Body Mass Index[2)]	0.748	0.551	0.693	0.223
Dyspepsia[1)]	0.132	0.971	0.976	0.606
Peptic ulcer[1)]	0.732	0.286	0.400	0.128
Alcohol habit[1)]	0.192	0.686	0.491	0.901
Smoking habit[1)]	0.218	0.424	0.882	0.464

BE: before the eradication therapy, 3M: 3 months after the eradication therapy, 1Y: 1 year after the eradication therapy. [1)]chi-square test, [2)]Student's *t* test.

Discussion

This study showed significant improvement in both the QOLRAD-J and CDQ scores at 1Y after *H. pylori* eradication therapy, even though no significant changes were observed at 3M after therapy. In a previous study, no significant change in QOL was identified at 6M after *H. pylori* eradication therapy.[14] However, our data showed improvement in the GERD-related QOL at 1Y after *H. pylori* eradication therapy, the period of follow-up being longer in this than in the previous report. On the other hand, no change in the GERD-related QOL was observed at 3M after *H. pylori* eradication therapy.

The degree of improvement was even more marked in cases with low initial scores. On the other hand, in patients with high initial scores, the scores remained high even after eradication therapy. On the basis of these results, we conclude that *H. pylori* eradication therapy may be more effective in patients with severe reflux symptoms or low QOL scores. Furthermore, strong reflux symptoms or reduction in the QOL may not occur after *H. pylori* eradication therapy.

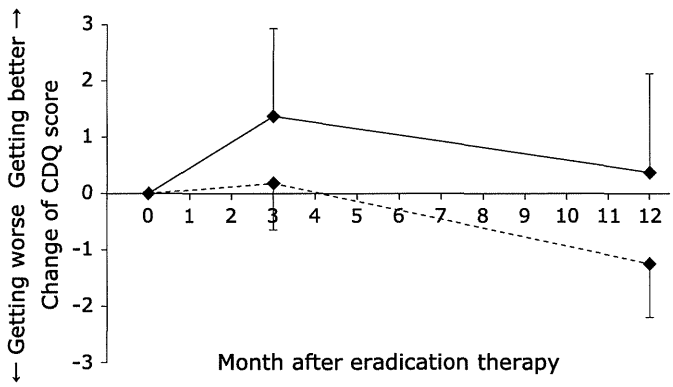

Fig. 5. Changes in CDQ scores with initial PG positive/negative test group. The solid lines represent the PG positive test group (n = 8) and the dashed lines the PG negative test group (n = 23). CDQ score tended to improve in the PG-negative test group than in the PG-positive test group (p = 0.065).

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Antisecretory agents, such as histamine type-2 receptor antagonist or proton pump inhibitor, are thought to primarily protect gastric mucosa by inhibiting gastric acid secretion.[29] Therefore, the effect of antisecretory agents should be considered as a confounding factor, because antisecretory agents might improve the QOL and/or the symptoms of reflux. Yoshida *et al.*[30] reported that omeprazole improved symptoms and QOL in patients with reflux esophagitis. In this study, significant improvement in the QOLRAD-J and CDQ scores were noted at 1Y, even among patients who did not take antisecretory agents from 6M to 1Y. Furthermore, the number of patients who were prescribed antisecretory agents at their own request decreased in a time-dependent fashion after the eradication therapy. This result also suggests that the symptoms of reflux and GERD-related QOL improved gradually after *H. pylori* eradication therapy.

This study also showed that the changes in the QOLRAD-J and CDQ scores were not correlated during the period from 3M to 1Y, whereas a significant correlation was identified during the period from BE to 3M. This result suggests that exacerbation of symptoms might not always imply decreased QOL after 3M. GERD-related QOL might improve following recovery from *H. pylori* infection, even if the reflux symptoms worsen after 3M. The announcement of eradication success at 3M might possibly influence the improvement in the QOL.

In this study, no significant correlation was identified between clinical background factors and the QOLRAD-J and CDQ scores. Hunt *et al.*[31] reported that there was no association between *H. pylori* eradication and the risk of GERD in a population of dyspeptic patients, while a 2-fold higher risk of erosive GERD was observed in patients with peptic ulcer disease. No significant association was identified between dyspepsia and the development of reflux symptoms or GERD-related QOL in our study as well; however, no association between the presence of peptic ulcer disease and the risk of developing reflux symptoms or GERD-related QOL was observed, although our study population included 15 patients with a previous history of peptic ulcer and 18 patients without a history of peptic ulcer. Patients with peptic ulcer might develop erosive GERD following *H. pylori* eradication therapy; however, the GERD-related QOL and severity of reflux symptoms may remain unchanged.

Our data show that the CDQ score tended to improve in the negative-PG group than in the positive-PG group. This means that milder atrophic gastritis may indicate improval of reflux symptoms by *H. pylori* eradication therapy. Atrophic gastritis spreads from an antral-predominant phenotype to a pangastritis phenotype as it progresses. Because of *H. pylori* eradication therapy, recovery of acid secretion may strongly affect reflux symptoms in patients with severe atrophic gastritis.

The limitation of this study is that we could not analyze the groups with *H. pylori* eradication failure. There were only 6 patients with eradication failure in our study. We performed a second eradication as soon as eradication failure was identified. Therefore, we did not follow the eradication failure group.

In summary, improvement in GERD-related QOL and reflux symptoms was observed at 1Y after *H. pylori* eradication therapy. While some patients showed worsening of GERD-related QOL and reflux symptoms 3M after eradication therapy, all patients showed improvement at 1Y. In addition, the degree of improvement was even more pronounced in cases with severe symptoms. Thus, *H. pylori* eradication therapy may be a valid therapeutic option for improving the GERD-related QOL and reflux symptoms.

Acknowledgments

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Conflict of Interest

No potential conflicts of interest were disclosed.

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PANCREAS, BILIARY TRACT, AND LIVER

Biliary Findings Assist in Predicting Enlargement of Intraductal Papillary Mucinous Neoplasms of the Pancreas

JUNTARO MATSUZAKI,* HIDEKAZU SUZUKI,* SHIGEO OKUDA,‡ AKIHIRO TANIMOTO,‡ KEIKO ASAKURA,§ SEIICHIRO FUKUHARA,* SAWAKO OKADA,* KENRO HIRATA,* HIDEKI MORI,* TATSUHIRO MASAOKA,* HAJIME HIGUCHI,* SHIGENARI HOZAWA,* SACHIO KURIBAYASHI,‡ TORU TAKEBAYASHI,§ and TOSHIFUMI HIBI*

Division of Gastroenterology and Hepatology, Department of Internal Medicine, ‡Department of Diagnostic Radiology, and §Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, Japan

BACKGROUND & AIMS: **There is controversy over the optimal management strategy for patients with branch-duct type intraductal papillary mucinous neoplasms of the pancreas (BD-IPMNs), precursors to pancreatic cancer. We aimed to identify factors associated with the presence of BD-IPMNs and changes in their diameter.**

METHODS: **Two separate analyses were conducted in a cohort of patients who underwent magnetic resonance cholangiopancreatography (MRCP) in a single year (2006). MRCP findings and clinical outcomes of these patients were followed for a maximum of 6 years. We evaluated initial MRCP findings and demographics associated with the presence of BD-IPMNs at baseline and increase in BD-IPMN diameter over time.**

RESULTS: **During the follow-up period, 154 patients developed BD-IPMN and 322 patients did not. Older age, diabetes mellitus, gallbladder adenomyomatosis, and absence of gallstones were associated with the presence of BD-IPMNs at baseline. Increases in diameter of BD-IPMNs were associated with 3 baseline factors: BD-IPMN diameter greater than 17 mm, gallbladder adenomyomatosis, and a common bile duct diameter less than 5.5 mm. Patients with BD-IPMNs could be stratified into 4 groups with varying risk for the enlargement of BD-IPMNs over time: those with 3 risk factors (hazard ratio [HR], 11.4; 95% confidence interval [CI], 3.4–37.8), 2 risk factors (HR, 4.7; 95% CI, 1.7–12.8), or 1 risk factor (HR, 3.1; 95% CI, 1.2–8.2) compared with those without risk factors.**

CONCLUSIONS: **For patients with BD-IPMNs, careful follow-up evaluation is particularly important for those with BD-IPMN >17 mm in size, common bile duct diameter <5.5 mm, or gallbladder adenomyomatosis.**

Keywords: Prognostic Factors; Tumor Development; Imaging Results; Progression.

See editorial on page 555.

Intraductal papillary mucinous neoplasms (IPMNs) are characterized by tall columnar mucin-producing epithelium with or without papillary projections. IPMNs are precursor lesions from which neoplastic progression along an adenoma-carcinoma sequence occurs. The incidence of IPMN has increased rapidly, representing 1% of all pancreatic adenocarcinomas, mainly because of an increase in diagnostic scrutiny.[1] IPMNs involve the main duct (MD), branch ducts (BD), or both (mixed IPMNs). Because MD-IPMNs and mixed IPMNs have a significant risk of malignancy, resection is recommended.[2] In comparison, the natural history of BD-IPMN suggests slower progression to cancer.[3] For patients with BD-IPMNs, the decision to recommend surgery or surveillance is based on factors that predict malignant behavior. Previous studies showed that invasive malignancy was more common in patients with symptoms, larger diameter of BD-IPMN, mural nodules, dilated main pancreatic duct (MPD), and positive cytology, although the specificity was low (23%–31%).[2,4] Increased specificity of

Abbreviations used in this paper: BD, branch-duct; CBD, common bile duct; CI, confidence interval; HR, hazard ratio; IPMC, intraductal papillary mucinous carcinoma; IPMN, intraductal papillary mucinous neoplasms; MD, main-duct; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PBM, pancreaticobiliary maljunction; ROC, receiver operator characteristic; SSFSE, single shot fast spin-echo.

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clinical prognostic markers could lead to a more tailored approach to patients with BD-IPMNs.

Enlargement of diameter of BD-IPMN is one of the most reliable predictors of malignant transformation of BD-IPMN.[5,6] A recent study showed that growth rate of BD-IPMN could be used to predict malignancy in patients with BD-IPMNs.[7] Therefore, factors associated with increased IPMN diameter might also be risk factors for the development of pancreatic malignancy. The aim of this study was to identify clinical factors that predict the presence of or increase in diameter of BD-IPMNs.

Methods

Study Population

The protocol for this study was approved by the ethics committee of the Keio University School of Medicine (no. 2012-035). Patients who received care from the Division of Gastroenterology and Hepatology at Keio University Hospital and who had undergone abdominal magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) in 2006 were retrospectively enrolled in this study, and an imaging diagnosis of BD-IPMN was made. MRCP was considered diagnostic when a cystic pancreatic mass communicating with MPD through a small channel was identified. On the basis of initial MRI and MRCP findings, patients diagnosed with MD-IPMN, mixed IPMN, pancreatic cancer, which included pancreatic ductal adenocarcinoma and pancreatic neuroendocrine tumor, and chronic pancreatitis were excluded from the analyses. Patients with BD-IPMN were followed according to the international consensus guidelines for the management of IPMN/mucinous cystic neoplasm published in 2006.

Magnetic Resonance Imaging and Image Analysis

MR examinations were performed with a 1.5 Tesla clinical scanner (Signa Excite HD or Signa Advantage LX; GE Healthcare, Waukesha, WI) by using an 8-channel body coil as a receiver. To reduce the signals in the stomach and bowel, oral negative contrast material was administered approximately 10 minutes before the start of MR examination (ferric ammonium [FerriSeltz; Otsuka Pharmaceutical, Tokyo, Japan] in 2006 or manganese chloride tetrahydrate [Bothdel oral solution 10; Kyowa Hakko Kirin, Tokyo, Japan] after 2006). Transverse and coronal heavy T2-weighted images were obtained by using single shot fast spin-echo (SSFSE) with following parameters to cover the whole pancreas: repetition time, infinite; effective echo time, 90–180 milliseconds; field of view, 32–38 cm; section thickness, 5–7 mm with slice gap of 1 mm; and matrix size, 288 × 192. MRCP images were obtained by using a thick-slab, single-slice SSFSE sequence in rotating coronal oblique orientations with the following parameters: repetition time, infinite; effective echo time, 1200 milliseconds; field of view, 32–36 cm; slice thickness, 50 mm; and matrix size, 512 × 320. Additional sequences were obtained including breath-hold fat-suppressed T2-weighted images, 2-dimensional or 3-dimensional T1-weighted images with fat suppression, diffusion-weighted images, and steady state coherent imaging; however, only transverse and coronal SSFSE and MRCP images were served for the evaluation in the current study. Images were reviewed and evaluated retrospectively on a PACS system (Centricity; GE Healthcare) by 2 independent investigator teams each consisting of 1 radiologist and 1 gastroenterologist. The images were interpreted by 2 radiologists who had 24 and 30 years of experiences in hepatobiliary imaging. The κ coefficient was calculated to assess interobserver agreement.

Study Design and Measurement of Variables

We conducted 2 analyses by using this population, a cross-sectional study and a retrospective cohort study. In the cross-sectional study, analyzed patients were divided into patients with and without BD-IPMN in 2006. By using initial MRI and MRCP findings, the presence/absence of gallbladder adenomyomatosis, gallstones, chronic pancreatitis, and malignant pancreaticobiliary diseases were assessed. Demographic information including age, gender, smoking habits, height, weight, and presence/absence of diabetes mellitus was collected in 2006 by using medical records. Body mass index (weight/height^2) was calculated. MRI findings and demographics of patients were compared between these 2 groups.

Patients were followed by using MRCP for a maximum of 6 years. In a retrospective cohort study, alteration of BD-IPMN diameter was serially examined among patients with BD-IPMN. To identify possible risk factors for enlargement of BD-IPMN, characteristics were compared between patients in whom BD-IPMN diameter had increased and had not increased. For this analysis, the diameters of largest BD-IPMN, common bile duct (CBD), and MPD were used as predictors. In addition, the presence/absence of mural nodule was assessed by using initial MRCP images among patients with BD-IPMN. Follow-up MRCP films of patients without BD-IPMN were reviewed to identify development of BD-IPMN or pancreatic cancer and increasing diameter of BD-IPMN.

Statistical Analysis

To identify risk factors for the presence of BD-IPMN at the baseline, univariate and multivariate regression models were constructed. All variables that were significant ($P < .05$) in the univariate analysis were included in a multivariate model. In the retrospective cohort study, baseline characteristics were compared between patients who did or did not experience increasing diameter of BD-IPMN by using the Fisher exact test for categorical variables or Student t test for continuous variables. Receiver operator characteristic (ROC) analyses were constructed to determine the optimal cutoff values of extracted risk factors. Hazard ratios (HRs) for increasing diameter of BD-IPMN were calculated for each risk factor by using Cox proportional hazards model. Possible risk factors that were worthwhile to include in the risk prediction model for the enlargement of BD-IPMN were determined by using ROC analysis. Finally, patients with BD-IPMN were stratified into risk groups by counting the number of risks. The cumulative proportion of BD-IPMN that enlarged during follow-up in each risk group was computed by Kaplan–Meier method. HRs in each risk group were calculated by using Cox proportional hazards model.

All statistical analyses were performed by using SPSS version 18.0 for Windows (SPSS Inc, Chicago, IL). The data were expressed as mean ± standard deviation. Two-sided P values were considered to be statistically significant at a level of less than .05.

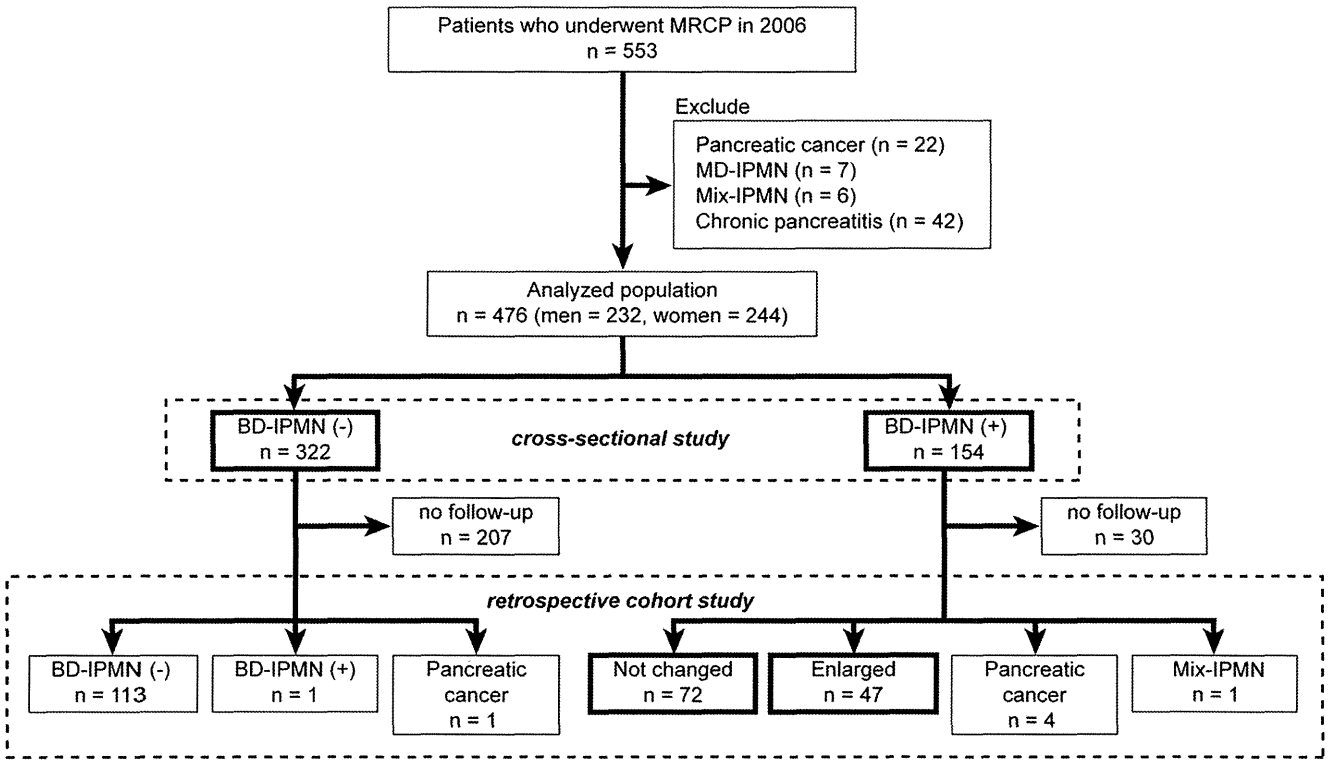

Figure 1. The study population. Two separate analyses were conducted in a cohort of patients who underwent MRCP in a single year (2006). In the cross-sectional study, MRCP findings and demographics were compared between patients with and without BD-IPMN in 2006. In the retrospective cohort study, baseline characteristics were compared between patients who did or did not experience the enlargement of BD-IPMN. Mix-IPMN, mixed type intraductal papillary mucinous neoplasm.

Results

Participant Characteristics

Of 553 patients who underwent MRCP in 2006, 22 with pancreatic cancer, 7 with MD-IPMN, 6 with mixed IPMN, and 43 with chronic pancreatitis were excluded. A total of 476 patients were included in this analysis, which was divided into 154 patients with BD-IPMN and 322 patients without BD-IPMN (Figure 1). Among patients with BD-IPMN at baseline, 3 developed pancreatic ductal adenocarcinoma, 1 developed intraductal papillary mucinous carcinoma (IPMC), 1 developed mixed IPMN, 47 showed an increased diameter of BD-IPMN, 72 did not show any change, and 30 were not followed up. Among patients without BD-IPMN at baseline, 1 developed pancreatic ductal adenocarcinoma, 1 developed BD-IPMN, 113 did not show any change in terms of BD-IPMN, and 207 were not followed up. The incidence of pancreatic cancer, which included pancreatic ductal adenocarcinoma and IPMC, was numerically higher among patients with BD-IPMN compared with patients without BD-IPMN, although the difference did not reach statistical significance (P = .37, Fisher exact test). Interobserver agreement between the 2 MRCP reviewer teams was κ = 0.63, which indicates substantial agreement.

Among 154 patients with BD-IPMN, BD-IPMN had already been identified in 135 patients (87.7%), all of whom underwent MRCP in 2006 as part of their regular checkups. BD-IPMNs were incidentally identified in the other 19 patients; 9 patients were required to undergo MRCP as a further examination based on the results of general health checkup, 8 patients underwent MRCP for the evaluation of biliary tract diseases such as CBD stones and cholangitis; and 2 patients underwent MRCP for the evaluation of liver diseases such as chronic hepatitis and metastatic liver tumor. None of the patients with BD-IPMN had any symptoms that were thought to be of pancreatic origin.

Among patients with BD-IPMN, 93 patients (60.4%) also underwent abdominal ultrasound or computed tomography scanning in addition to MRCP, and pancreatic cysts having an appearance compatible with BD-IPMN were identified, although abdominal ultrasound and computed tomography often could not detect a ductal connection, estimate main duct involvement, or identify small branch duct cysts.[8] Twenty-three of 154 patients with BD-IPMN underwent endoscopic retrograde cholangiopancreatography or endoscopic ultrasound, and all diagnoses of BD-IPMN were confirmed, which showed that MRCP has excellent accuracy in diagnosing BD-IPMN.

Results of Cross-sectional Analysis

The presence of BD-IPMN was associated with older age, diabetes mellitus, gallbladder adenomyomatosis, and absence of gallstones (Table 1). All patients with biliary cancer or gallbladder cancer did not have BD-IPMN. Results of multivariate logistic regression model with adjustment for age, diabetes mellitus, adenomyomatosis, and gallstones showed that these 4 factors were independently associated with the presence of BD-IPMN. The association between adenomyomatosis or gallstones and BD-IPMN suggests that some altered condition in the biliary tract would contribute to the development of BD-IPMN.

Table 1. Initial Clinical Characteristics of Patients and Association for Presence of BD-IPMN

			Univariate analysis	Multivariate analysis[a]
	BD-IPMN (–) (n = 322)	BD-IPMN (+) (n = 154)	Odds ratio (95% CI)	Odds ratio (95% CI)
Age (*y*), mean ± SD	59.0 ± 16.8	68.9 ± 10.0	1.05 (1.03–1.07)[b]	1.05 (1.04–1.07)[b]
Sex (male)	173 (53.7%)	71 (46.1%)	0.74 (0.50–1.08)	
Smoking				
Current smokers	47 (14.6%)	16 (10.4%)	0.61 (0.33–1.13)	
Ex-smokers	59 (18.3%)	20 (13.0%)	0.61 (0.35–1.07)	
BMI (kg/m^2), mean ± SD	21.7 ± 3.7	21.8 ± 2.9	1.01 (0.95–1.07)	
Diabetes mellitus	30 (9.3%)	27 (17.5%)	2.07 (1.18–3.62)[b]	1.92 (1.05–3.51)[b]
Adenomyomatosis	27 (8.4%)	22 (14.3%)	1.82 (1.00–3.32)[b]	02.21 (1.14–4.31)[b]
Gallstones	96 (29.8%)	30 (19.5%)	0.57 (0.36–0.91)[b]	0.38 (0.23–0.63)[b]
Biliary cancer	15 (4.7%)	0 (0%)	NA	
Gallbladder cancer	3 (0.9%)	0 (0%)	NA	
Chronic hepatitis	28 (8.7%)	16 (10.4%)	1.22 (0.64–2.32)	
Primary sclerosing cholangitis	10 (3.0%)	0 (0%)	NA	

BMI, body mass index; NA, could not be analyzed.
[a]Analyzed by multivariate logistic regression model with adjustment for age, diabetes mellitus, adenomyomatosis, and gallstones.
[b]Significant difference.

Results of Retrospective Cohort Analysis

Median follow-up duration was 4.76 years among patients in whom BD-IPMN diameter increased and 5.13 years among patients in whom BD-IPMN diameter did not increase. The mean follow-up interval was 0.79 ± 0.44 years among patients in whom BD-IPMN diameter increased and 0.94 ± 0.59 years among patients in whom BD-IPMN diameter did not increase. There was no significant difference between the intervals. Compared with patients in whom BD-IPMN diameter did not increase during the follow-up period, there was a higher prevalence of diabetes mellitus, gallbladder adenomyomatosis, baseline larger diameter of BD-IPMN, and smaller diameter of CBD among patients in whom BD-IPMN diameter increased during the follow-up period (Table 2). A priori, the optimal cutoff values of diameter of IPMN and CBD were hypothesized to be 17 and 5.5 mm, respectively, for the prediction of increasing diameter of BD-IPMN (Figure 2). Univariate Cox regression analysis revealed that the enlargement of BD-IPMN could be predicted by the following 3 factors: diameter of IPMN greater than 17 mm, adenomyomatosis, and diameter of CBD less than 5.5 mm (Table 3). A multivariate Cox regression model showed that a baseline diameter of BD-IPMN greater than 17 mm was the strongest predictive factor for the enlargement of BD-IPMN. In addition, presence of adenomyomatosis and diameter of CBD less than 5.5 mm trended with the enlargement of BD-IPMN, although these 2 factors lost significance in the multivariate model ($P < .1$). Therefore, ROC analysis was performed to identify the optimal prediction model for the enlargement of BD-IPMN. Area under the curves were 0.641 (95% confidence interval [CI], 0.538–0.744) for the model that used only a baseline diameter of BD-IPMN greater than 17 mm, 0.685 (95% CI, 0.585–0.785) for the model that used both a baseline diameter of BD-IPMN greater than 17 mm and presence of adenomyomatosis, 0.690 (95% CI, 0.594–0.787) for the model that used both a baseline diameter of BD-IPMN greater than 17 mm and diameter of CBD less than 5.5 mm, and 0.723 (95% CI, 0.630–0.816) for the model that used all 3 factors. This showed that a model that incorporated all 3 factors yielded the best prediction of increasing diameter of BD-IPMN.

Patients with BD-IPMN could be stratified into 4 risk groups: those who had none of these factors, those who had 1 factor, those who had 2 factors, and those who had all 3 factors. Patients were also categorized according to the latest international guidelines of IPMN[2] into 4 groups by using only the size of BD-IPMN (<1, 1–2, 2–3, and >3 cm). The cumulative proportion of patients in whom BD-IPMN diameter increased is shown in Figure 3. Although both risk stratification models predicted enlargement of BD-IPMN (log rank test, $P < .05$), risk stratification including adenomyomatosis and the diameter of

Table 2. Characteristics of Patients in 2006 Stratified by Enlargement of BD-IPMN

	Not changed (n = 72)	Enlarged (n = 47)	*P* value
Median follow-up period (*y*)	4.76	5.13	
Age (*y*)	67.7 ± 10.3	69.9 ± 9.4	.26[a]
Sex (male)	33 (45.8%)	19 (40.4%)	.58[b]
Smoking			
Current smokers	6 (8.3%)	3 (6.4%)	1.00[b]
Ex-smokers	11 (16.2%)	4 (9.3%)	.40[b]
BMI (kg/m^2)	21.7 ± 3.0	22.4 ± 2.9	.28[a]
Diabetes mellitus	8 (11.1%)	12 (25.5%)	.048[b,c]
Diameter of IPMN (*mm*)	14.8 ± 11.3	22.1 ± 11.8	.001[a,c]
Diameter of CBD (*mm*)	6.6 ± 2.9	5.6 ± 2.0	.027[a,c]
Diameter of MPD (*mm*)	2.4 ± 0.9	2.3 ± 1.0	.90[a]
Mural nodule	2 (2.8%)	4 (8.5%)	.21[b]
Adenomyomatosis	5 (6.9%)	13 (27.7%)	.003[b,c]
Gallstones	14 (19.4%)	8 (17.0%)	.81[b]
IPMN location			
Head	43 (59.7%)	32 (68.1%)	.44[b]
Body	41 (56.9%)	33 (70.2%)	.18[b]
Tail	21 (29.2%)	14 (29.8%)	1.00[b]

BMI, body mass index.
[a]Student *t* test.
[b]Fisher exact test.
[c]Significant difference.

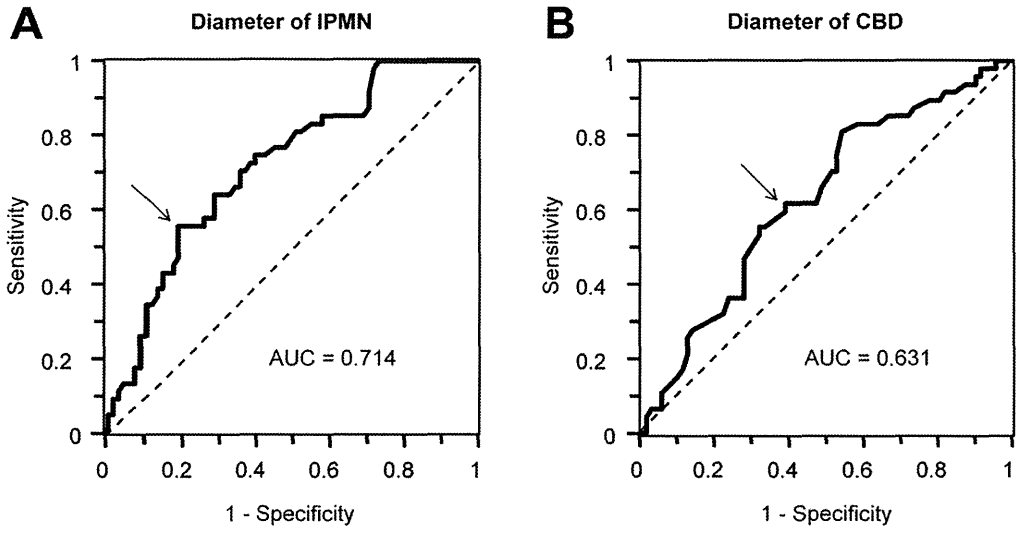

Figure 2. ROC curves illustrating optimal cutoff points of BD-IPMN diameter (*A*) and of CBD diameter (*B*) to predict the enlargement of BD-IPMN. *Arrows* indicate optimal cutoff points.

CBD in addition to baseline diameter of BD-IPMN illustrated superior separation of the Kaplan–Meier curves (Figure 3).

Characteristics of Patients Who Developed Pancreatic Cancer During Follow-up

Four patients developed pancreatic cancer among patients with BD-IPMN during follow-up (Figure 1). None were included in the lowest risk group; however, 2 of 3 patients who developed pancreatic ductal adenocarcinoma had a baseline BD-IPMN diameter greater than 17 mm, and 1 had gallbladder adenomyomatosis. One patient who developed IPMC had a baseline BD-IPMN diameter greater than 17 mm. One patient who developed mixed IPMN had 3 risk factors such as baseline BD-IPMN diameter greater than 17 mm, gallbladder adenomyomatosis, and CBD diameter less than 5.5 mm.

Discussion

In a cross-sectional analysis, we identified an association of older age, diabetes mellitus, gallbladder adenomyomatosis, and absence of gallstones with the presence of BD-IPMN. Moreover, this study provides evidence that adenomyomatosis and baseline narrow CBD (<5.5 mm) in addition to large diameter BD-IPMN (>17 mm) are risk factors for increased diameter of BD-IPMN. Categorizing patients with BD-IPMN into risk groups on the basis of the number of risk factors improved prediction for BD-IPMN diameter increase over current guidelines. Because the presence/absence of these factors can be evaluated with not only MRCP but also abdominal ultrasound, the results of the present study can improve the detection and management of BD-IPMN.

Large diameter of BD-IPMN is a known risk factor for malignant IPMN and concomitant ductal carcinoma.[9] Although presence of mural nodules and dilated MPD are reliable findings for the prediction of malignancy,[2] these 2 factors were not identified as risk factors for the enlargement of BD-IPMN in the present study. This may be because MPD dilatation and mural nodules are not the "cause" of malignancy but are the "result" of malignancy. On the other hand, the association of adenomyomatosis and narrow CBD with enlargement of BD-IPMN is novel. Although the mechanism of this association could not be elucidated in the present study, reflux of biliary or duodenal contents into the pancreatic duct might be a possible cause to explain these findings. The CBD and the MPD frequently form a common channel. In patients with a pancreaticobiliary maljunction (PBM), the sphincter of Oddi does not function properly, and two-way regurgitation (pancreaticobiliary and biliopancreatic refluxes) occurs. Some clinical reports have demonstrated the occurrence of IPMC in patients with PBM.[10,11] Animal experiments also confirmed that bile reflux into the pancreatic ducts is a significant factor predisposing to the development of IPMC.[10] Furthermore, it has become obvious that pancreaticobiliary reflux can occur in individuals without PBM,[12] suggesting that biliopancreatic reflux might also occur and lead to the development of IPMN in those without PBM.[13] On

Table 3. Regression Coefficients for Enlargement of BD-IPMN From a Cox Hazard Regression Model

	Univariate analysis				Multivariate analysis[a]			
	B	SE	HR (95% CI)	*P* value	B	SE	HR (95% CI)	*P* value
IPMN >17 mm	0.954	0.30	2.60 (1.45–4.64)	.001[b]	0.859	0.31	2.39 (1.29–4.42)	.006[b]
Adenomyomatosis (+)	0.824	0.33	2.28 (1.20–4.33)	.012[b]	0.608	0.33	1.84 (0.96–3.53)	.069
CBD <5.5 mm	0.599	0.30	1.82 (1.01–3.29)	.047[b]	0.556	0.31	1.74 (0.96–3.18)	.070
Diabetes mellitus (+)	0.582	0.34	1.79 (0.93–3.45)	.082	0.159	0.36	1.17 (0.58–2.37)	.580

B, unstandardized regression coefficient; SE, standard error.
[a]Analyzed by multivariate logistic regression model with adjustment for diameter of IPMN >17 mm, adenomyomatosis, diameter of CBD <5.5 mm, and diabetes mellitus.
[b]Significant difference.

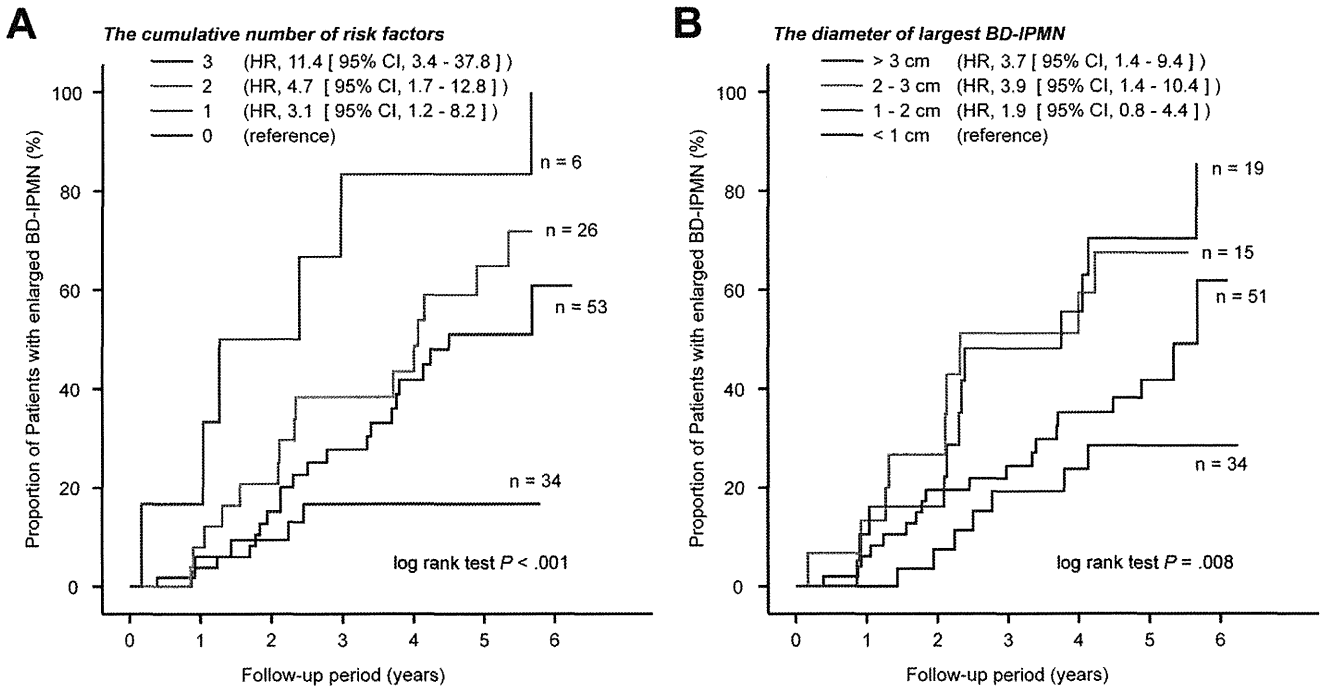

Figure 3. Kaplan–Meier curves of patients with enlarging BD-IPMN and HRs of the enlargement. (*A*) Patients with BD-IPMN were divided into 4 groups according to the number of risk factors consisting of diameter of IPMN more than 17 mm, gallbladder adenomyomatosis, and diameter of CBD less than 5.5 mm. (*B*) Patients with BD-IPMN were divided into 4 groups according to the size of BD-IPMN.

the other hand, gallbladder adenomyomatosis is frequently observed in patients with PBM. Tanno et al[14] reported that adenomyomatosis is more common among patients with undilated type PBM. Even among patients without PBM, the association between occult pancreaticobiliary reflux and adenomyomatosis has been demonstrated.[12] Thus, two-way regurgitation between CBD and MPD could explain the association between BD-IPMN and adenomyomatosis. In addition, among individuals in whom two-way regurgitation occurs, a narrow CBD might contribute to divert the direction of flow (pancreaticobiliary reflux to biliopancreatic reflux), because the flow volume in narrow tubes is decreased as the diameter of the tubes decreases. If occult pancreaticobiliary and biliopancreatic refluxes would contribute to the enlargement of BD-IPMN, endoscopic biliary sphincterotomy to abolish the common channel might prevent enlargement of BD-IPMN. In fact, 3 patients with BD-IPMN underwent endoscopic sphincterotomy before 2006, and none of their BD-IPMNs were enlarged.

Limitations of our study include generalizability; our patients without BD-IPMN may not be representative of the general population because this is a hospital-based study. Another criticism is that the duration of time required for enlargement of BD-IPMN might be longer than the duration that subjects were observed in this study. Time-to-event data were calculated by using the date of MRCP examination in which the enlargement of BD-IPMN was observed; however, follow-up intervals were different among participants. To establish a proper follow-up strategy for BD-IPMN, further prospective studies should be performed, and the results of the present study can contribute to the design of such studies.

In conclusion, this study demonstrates that BD-IPMN >17 mm in diameter, presence of gallbladder adenomyomatosis, and CBD <5.5 mm in diameter predict the enlargement of BD-IPMN. These factors might be able to improve specificity in prediction of pancreatic cancer. Careful follow-up is particularly necessary among patients with these risk factors.

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Reprint requests

Address requests for reprints to: Hidekazu Suzuki, MD, PhD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. e-mail: hsuzuki@a6.keio.jp; fax: 81-3-5363-3967.

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Conflicts of interest

The authors disclose no conflicts.

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