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INTRODUCTION

Gastroesophageal reflux disease (GERD) includes not only reflux esophagitis (RE) confirmed by upper gastrointestinal endoscopy, but also non-erosive reflux disease (NERD) characterized only by subjective symptoms, such as heartburn without RE. The Montreal definition was presented as the worldwide consensus on GERD in 2006[1] and is based mostly on subjective symptoms: "GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications". According to this definition, GERD is further classified into esophageal syndrome and extraesophageal syndrome, and a wide variety of symptoms are present. Thus, closer examination of subjective symptoms is required in differentiating GERD from other organic digestive tract diseases.

Questionnaires are effective in ascertaining the subjective symptoms of GERD patients. Many GERD-specific questionnaires have been developed[2], including the questionnaire for the diagnosis of reflux diseases[3], which is the most widely used of these questionnaires around the world. In Japan, Kusano *et al* developed the frequency scale for symptoms of GERD (FSSG)[4], a scale that has been used for early diagnosis and therapy assessment. Of the 12 FSSG questions, 7 questions deal with acid reflux symptoms, and the remaining 5 questions deal with gastrointestinal dysmotility symptoms, allowing GERD to be assessed by symptom group[5]. Assessing upper gastrointestinal symptoms by broadly dividing them into two groups is not only useful for planning treatment strategy for GERD[6], but it is also important for objectively analyzing the disease state.

By measuring two serum parameters, the *Helicobacter pylori* (*H.pylori*) antibody (Ab) titer and the serum pepsinogen (PG) level as a screening test for extensive chronic atrophic gastritis (CAG)[7], we have graded *H.pylori*-related chronic gastritis into four stages from A to D: Group A, *H.pylori*-negative/PG-negative; Group B, *H.pylori*-positive/PG-negative; Group C, *H.pylori*-positive/PG-positive; and Group D, *H.pylori*-negative/PG-positive. Group A included *H.pylori* non-infected healthy subjects. Group B showed established *H.pylori* infection, but without CAG. Group C had CAG. Group D had severe intestinal metaplasia due to progression of CAG, but *H.pylori* had been spontaneously eliminated, representing so-called metaplastic gastritis. CAG advances from A to B to C, and then to D. We have documented that the incidence of gastric cancer gradually increases with chronic gastritis progression[8,9,10]. This has enabled screening of high-risk patients for gastric cancer based on serodiagnosis. An inverse relationship has been reported between CAG and RE onset[11], and many studies have found that the incidence of *H.pylori* infection is lower in Japanese RE patients than in healthy individuals (control group)[12-14]. A study found that NERD is closely related to *H.pylori* infection and progression in gastric mucosal atrophy[15]. Moreover, one study found a negative correlation between GERD and the anti-*H.pylori*-Ab positive rate[16], while another study documented that *H.pylori* infection was unrelated to GERD and was neither an exacerbating factor nor a preventive factor[17]. To the best of our knowledge, no studies have used GERD-specific questionnaires to quantify acid reflux and gastrointestinal dysmotility symptoms and to closely examine the relationships between *H.pylori*-related chronic gastritis progression and upper gastrointestinal symptoms.

In routine clinical care, performing endoscopy on all patients complaining of upper gastrointestinal symptoms is difficult, and some supplementary parameters would be useful to gather more information to make the diagnosis of GERD. The aim of this study was to examine the relationship of *H.pylori* and PG status with GERD.

MATERIALS AND METHODS

Study subjects

In Japan, health checkup programs are performed to identify selected diseases (e.g., gastric cancer) in their early stages of development. Both symptom-free subjects and subjects showing specific symptoms took part in upper gastrointestinal endoscopic examinations at our institution. Between January 2006 and March 2008, a total of 1165 factory workers (1147 males, 18 females) ranging in age from 40 to 70 years who underwent upper gastrointestinal endoscopy and completed the FSSG questionnaire were enrolled. In addition, all enrolled subjects underwent serological testing and their *H.pylori*-Ab titers and serum PG levels were measured. Subjects who had a previous history of surgical resection of the stomach, *H.pylori* eradication, or those who had been prescribed a proton pump inhibitor (PPI), which might affect gastrointestinal function, were excluded from the study. Furthermore, subjects with and without *H.pylori* infection were selected for the study using serum-specific antibody titers as described in the following section. Thus, 825 subjects (812 males, 13 females) were eligible for this study. The ethics committee of Wakayama Medical University approved the study protocols.

Diagnosis of H.pylori infection and extensive CAG by serological tests

H.pylori-Ab titers were measured using an enzyme-linked immunosorbent assay (ELISA) (MBL, Nagoya, Japan)[18]. In the present study, *H.pylori*-Ab titers $\geq$ 50 U/mL were taken to be *H.pylori*-positive, and $<$ 30 U/mL indicated *H.pylori*-negative. *H.pylori*-Ab titers $\geq$ 30 but $<$ 50 U/mL were considered unclassifiable, and subjects showing titers within this range were excluded from *H.pylori* infection

Table 1 Relationship between *H.pylori* infection or serum PG test and upper abdominal symb to ms erosive reflux esophagitis

	H.pylori infection		*P* value	Serum PG test		*P* value
	-	+		-	+	
n	236	589		529	296	
FSSG						
-total score (mean ± SD)	3.58 ± 4.00	3.17 ± 3.90	0.175	3.45 ± 3.96	2.99 ± 3.87	0.104
-acid reflux score (mean ± SD)	1.78 ± 2.21	1.62 ± 2.32	0.350	1.79 ± 2.33	1.45 ± 2.20	0.038
-dysmotility score (mean ± SD)	1.80 ± 2.32	1.55 ± 1.99	0.127	1.66 ± 2.14	1.54 ± 2.02	0.432
Erosive esophagitis (LA grade A-D)	28.4% (67/236)	10.7% (63/589)	0.000	21.2% (112/529)	6.1% (18/296)	0.000
FSSG total score ≥ 8 (= GERD)	13.6% (32/236)	11.7% (69/589)	0.465	13.8% (73/529)	9.5% (28/296)	0.076
FSSG total score ≥ 8 and non-erosive esophagitis (= NERD)	8.1% (19/236)	9.5% (56/589)	0.510	9.8% (52/529)	7.8% (23/296)	0.377
NERD/GERD	59.4% (19/32)	81.2% (56/69)	0.027	71.2% (52/73)	82.1% (23/28)	0.317

H.pylori: *Helicobacter pylori*; PG: pepsinogen; CAG: chronic atrophic gastritis; FSSG: frequency scale for symptoms of gastroesophageal reflux disease; SD: standard deviation; LA: Los Angeles classification; GERD: gastroesophageal reflux disease; NERD: non-erosive reflux disease.

assessment. The sensitivity and specificity of the ELISA test used in this study were 93.5% and 92.5%, respectively[18]. Serum PG levels were measured by radioimmunoassay (Dainabot, Tokyo, Japan)[19]. PG, a measure of gastric atrophy, was considered positive for values of PG Ⅰ ≤ 70 μg/L with a PG Ⅰ / Ⅱ ratio of ≤ 3[20,21]. These criteria offer a sensitivity of 70.5% and a specificity of 97% for the diagnosis of extensive CAG, using pathological diagnosis as the gold standard[20]. Subjects for whom both *H.pylori* infection and PG level could be determined were divided into the following four groups in terms of *H.pylori*-related chronic gastritis stage: Group A, *H.pylori*-negative/PG-negative; Group B, *H.pylori*-positive/PG-negative; Group C, *H.pylori*-positive/PG-positive; and Group D, *H.pylori*-negative/PG-positive[8].

Endoscopic findings of RE

RE was diagnosed by upper gastrointestinal endoscopy. According to the Los Angeles classification system[22], Grades A through D indicate erosive esophagitis. In the present study, only patients with erosive esophagitis were diagnosed with RE, and subjects with Grade M (minimal change)[23]or Grade N were not diagnosed with RE. Hiatal hernia was diagnosed endoscopically when the distance between the crural impression and the gastroesophageal junction was 2 cm or more.

Assessment of FSSG questionnaire and determination of GERD

Using the FSSG questionnaire, subjective symptoms of GERD were quantified, and total, acid reflux, and gastrointestinal dysmotility scores were calculated. GERD was defined as a total score ≥ 8, which is the recommended cut-off FSSG value for GERD[4]. Furthermore, NERD was defined as total score ≥ 8 without endoscopic erosive esophagitis.

Statistical analysis

All data analyses were performed using SPSS version 11.0 software (SPSS, Chicago, IL, USA). Pair-wise differences in the FSSG score were analyzed using the unpaired Student's *t*-test, and overall differences in age and FSSG score were analyzed using the Kruskal-Wallis test. Pair-wise and overall differences in categorical variables were analyzed by Fisher's exact test. All tests were 2-sided, and values of $P < 0.05$ were considered significant. Data are expressed as means ± standard deviation.

RESULTS

Clinical characteristics of study subjects

As mentioned above, of the 1165 subjects in whom *H.pylori*-Ab titers and serum PG levels were measured, those meeting the exclusion criteria were removed. Most of the remaining 825 subjects were men (98.4%) and drinkers (74.9%). Reflecting the high incidence of *H.pylori* infection among middle-aged and elderly individuals in Japan, the incidence of *H.pylori* infection was high (71.4%). With regard to RE, Grade D (the most severe LA grade) was not seen in any subjects, and Grades A and B (mild grades) accounted for 94.6% of cases.

Comparison of upper gastrointestinal symptoms and RE between H.pylori-positive and H.pylori-negative subjects and between PG-positive and PG-negative subjects

The analysis was conducted between *H.pylori*-positive (n = 589) and *H.pylori*-negative (n = 236) subjects and between PG-positive (n = 296) and PG-negative (n = 529) subjects (Table 1). The prevalence of RE was significantly higher for PG- and *H.pylori*-negative subjects than for their positive counterparts ($P < 0.001$). The acid reflux score was significantly higher for PG-negative subjects than for PG-positive subjects ($P < 0.05$), but no significant difference existed between *H.pylori*-positive and -negative subjects. No significant differences in gastrointestinal dysmotility scores between *H.pylori*-positive and -negative subjects or between PG-positive and -negative subjects were present. The prevalence of GERD patients with total FSSG scores ≥ 8 tended to be high for PG-negative subjects ($P = 0.076$), but no significant difference existed between *H.pylori*-positive and -negative subjects. While no significant difference in the prevalence of NERD patients was evident between *H.pylori*-positive and -negative subjects or between PG-positive and -negative subjects, the prevalence of NERD among GERD patients was significantly higher for *H.pylori*-positive subjects ($P = 0.027$).

Table 2 Relationship between the stage of *H.pylori*-related chronic gasrtritis ang upper abdominal symptoms or erosive reflux esophagitis

Stages of *H.pylori*-related chronic gastritis	Group A	Group B	Group C	Group D	Overall
H.pylori infection	-	+	+	-	*P* value
Serum PG test (extensive CAG)	-	-	+	+	
n	219	310	279	17	
Age (years: mean ± SD)	55.23 ± 4.23	55.84 ± 4.08	56.79 ± 3.91	53.94 ± 5.01	0.001
Sex (male/female)	214/5	308/2	273/6	17/0	0.306
Smokers	44.29%	35.16%	41.58%	41.18%	0.164
Drinkers	75.34%	75.48%	74.19%	70.59%	0.939
Serum PG Ⅰ (ng/mL mean ± SD)	59.82 ± 26.52	81.76 ± 48.16	36.59 ± 18.42	21.98 ± 15.99	-
Serum PG Ⅱ (ng/mL mean ± SD)	10.80 ± 5.81	25.89 ± 18.42	20.70 ± 8.60	12.89 ± 4.84	-
PG Ⅰ / Ⅱ	5.70 ± 1.13	3.74 ± 1.31	1.76 ± 0.69	1.53 ± 0.95	-
H.pylori Ig G Ab titer (U/mL mean ± SD)	13.54 ± 5.26	475.31 ± 632.73	441.07 ± 50.94	16.71 ± 6.44	-
FSSG					
-total score (mean ± SD)	3.69 ± 4.01	3.33 ± 3.87	3.00 ± 3.94	2.88 ± 2.55	0.183
-acid reflux score (mean ± SD)	1.83 ± 2.26	1.77 ± 2.39	1.46 ± 2.25	1.29 ± 1.26	0.038
-dysmotility score (mean ± SD)	1.81 ± 2.37	1.56 ± 1.96	1.54 ± 2.03	1.59 ± 1.77	0.800
Erosive esophagitis (LA grade A-D)	30.6% (67/219)	14.5% (45/310)	6.5% (18/279)	0% (0/17)	0.000
LA grade A/B/C/D	45/18/4/0	30/13/2/0	11/6/1/0	0/0/0/0	-
Hiatal hernia	3.2% (7/219)	5.8% (18/310)	7.2% (20/279)	5.9% (1/17)	0.231
FSSG total score ≥ 8 (=GERD)	14.6% (32/219)	13.2% (41/310)	9.7% (28/279)	0% (0/17)	0.177
FSSG total score ≥ 8 and non-erosive esophagitis (=NERD)	8.7% (19/219)	10.6% (33/310)	8.2% (23/279)	0% (0/17)	0.496
NERD/GERD	59.4% (19/32)	80.5% (33/41)	82.1% (23/28)	-	0.081

H.pylori: *Helicobacter pylori*; PG: pepsinogen; CAG: chronic atrophic gastritis; FSSG: frequency scale for symptoms of gastroesophageal reflux disease; SD: standard deviation; LA: Los Angeles classification; GERD: gastroesophageal reflux disease; NERD: non-erosive reflux disease.

Relationship of the stage of H.pylori-related chronic gastritis to upper gastrointestinal symptoms and RE

The stage of *H.pylori*-related chronic gastritis was assessed in the 825 subjects (Table 2). With regard to background factors, significant differences were seen in age. The prevalence of RE showed significant decreases with the stage of the chronic gastritis (from Group A to D) ($P < 0.001$). Acid reflux scores showed a significant decrease with the chronic gastritis stage ($P < 0.05$). The gastrointestinal dysmotility score showed no significant differences between stages ($P = 0.800$). The ratios of GERD patients with total FSSG scores ⩾ 8 showed no significant differences related to the chronic gastritis stage. No significant differences existed in the prevalence of NERD patients among Groups A, B, and C. However, the prevalence of NERD among GERD patients for Groups A, B, and C tended to increase with the chronic gastritis stage ($P = 0.081$).

DISCUSSION

Previously, we have investigated the risk of gastric cancer based on *H.pylori*-related chronic gastritis stage as assessed by a combination of *H.pylori*-Ab titer and serum PG level[8]. The present results suggest that the disease states of GERD and NERD can also be assessed by evaluating the risk for RE and upper gastrointestinal symptoms accompanying gastric acid reflux and gastrointestinal dysmotility. As reported previously[11], the prevalence of RE was low for subjects with CAG. The FSSG was used to closely examine upper gastrointestinal symptoms, and acid reflux scores were low for the group in the advanced stages of *H.pylori*-related chronic gastritis, but no marked difference in gastrointestinal dysmotility scores was seen in relation to the chronic gastritis stage. The prevalence of NERD patients among GERD patients was lowest for Group A and highest for Group C, clarifying the relationship between NERD and the stage of *H.pylori*-related chronic astritis.

Compared to Western countries, the number of GERD patients is lower in Japan, and the prevalence of NERD among GERD patients is higher[24]. Differences exist in the extent of CAG and in its associated reduction in gastric acid secretion that strongly correlate to *H.pylori* infection differences between Japan and Western countries[25], and the present study also showed that they most closely reflected the disease state of GERD in Japan. The prevalence of CagA+ *H.pylori*[26], which correlates pathologically to atrophic gastritis, is particularly high in Japan[27]. This is believed to contribute to differences in the relationship between GERD and *H.pylori* infection[28] in Japan and Western countries[29].

The present study also assessed the difference between *H.pylori*-positive and *H.pylori*-negative subjects and between PG-positive and PG-negative subjects. No significant differences existed in acid reflux and dysmotility scores between *H.pylori*-positive and *H.pylori*-negative subjects. Upper gastrointestinal symptom scores, particularly acid reflux scores, were significantly higher for PG-positive subjects than for PG-negative subjects. No significant differences existed in the prevalence of GERD patients with total FSSG scores ⩾ 8 between *H.pylori*-positive and *H.pylori*-negative subjects, but the prevalence was greater for PG-negative subjects than for PG-positive subjects. GERD-related upper gastrointestinal symptoms are thus more closely influenced by extensive CAG than *H.pylori* infection. However, the finding that the incidence of endoscopy-diagnosed RE for *H.pylori*-negative subjects and PG-negative subjects was higher compared to their

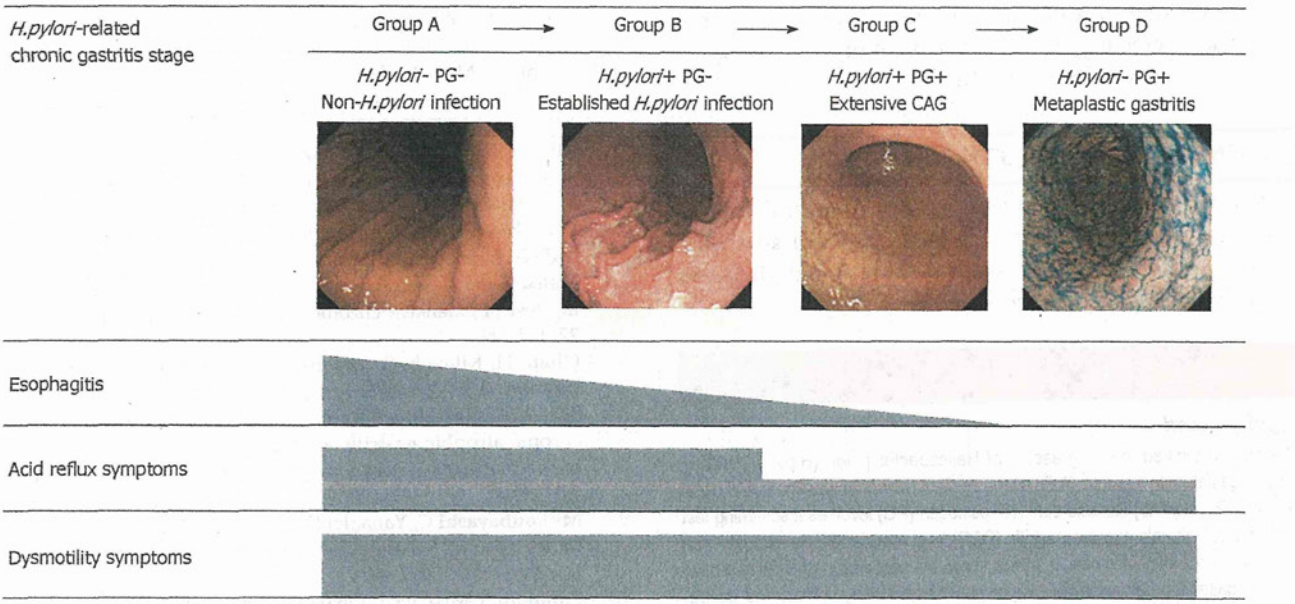

Figure 1 Schematic of the results of this study. *H.pylori: Helicobacter pylori* infection; PG: serum pepsinogen test; CAG: chronic atrophic gastritis.

positive counterparts was very interesting. In other words, reduced acid secretion due to CAG has a great effect on the suppression of esophageal mucosal erosion, and, of the various subjective symptoms, acid reflux symptoms are suppressed because gastric acid secretion is markedly low. This might be the reason why the prevalence of NERD among GERD patients changes according to the *H.pylori*-related chronic gastritis groups.

The prevalence of NERD among subjects with total FSSG scores $\geqslant 8$ was higher for *H.pylori*-positive subjects than for their negative counterparts. Groups A-D showed no marked differences in gastrointestinal dysmotility scores, and no marked differences were apparent between *H.pylori*-positive and *H.pylori*-negative subjects or between PG-positive and PG-negative subjects. These findings are extremely important when studying the disease state of GERD. In other words, in Groups C and D, where gastric mucosal atrophy is severely advanced, the symptoms and onset of NERD are influenced by gastrointestinal dysmotility rather than acid reflux, thus affecting therapy planning[6].

At present, the incidence of *H.pylori* infection is decreasing in Japan, and the number of patients with chronic atrophic gastritis or gastric cancer is expected to decrease in the future. However, the number of Group A subjects (*H.pylori*-negative and PG-negative) is likely to increase. Therefore, RE in Group A subjects who may experience both acid reflux and dysmotility symptoms must be managed. In Groups C and D, with a higher risk of gastric cancer[8,30], treatments are provided less frequently for RE, but because acid reflux symptoms are lacking, these subjects are less likely to visit a medical center on their own and undergo thorough testing, such as upper gastrointestinal endoscopy.

Instead of prospectively observing the onset rate of GERD over a long period of time, the present study analyzed GERD-related symptoms and the prevalence of endoscopic RE, based on the stage of *H.pylori*-related chronic gastritis at a single time point when endoscopy and history-taking were performed. A prospective study based on long-term follow-up observation is needed to more accurately assess GERD risks. However, acid reducers, including PPIs, are often prescribed to patients with upper abdominal symptoms, and various therapeutic modifications make such studies difficult to implement. The present study involved a group of workers, consisting of almost all males, who underwent endoscopy as part of regular checkup programs of gastric cancer screening. Thus, since most study subjects were men, this must be taken into account when interpreting the results. The present study clarified that *H.pylori* infection and CAG stage correlate closely with acid reflux and dysmotility symptoms. However, because GERD is a disease that is closely related to diet and lifestyle diseases such as obesity and diabetes[31-33], thorough investigation of the correlations of these factors to upper gastrointestinal symptoms is necessary using a GERD-specific questionnaire. Furthermore, ambulatory esophageal pH (with/without impedance) monitoring was not done in this study, and the term "NERD" might not be appropriate. NERD cases include functional heartburn cases in this study, and this should be taken into consideration when interpreting the data.

In conclusion, the present results suggest that the disease state of GERD was related to the stage of *H.pylori*-related chronic gastritis based on measurements of *H.pylori*-Ab titers and serum PG levels (Figure 1). These two serum markers can be measured conveniently, noninvasively, and relatively inexpensively. The reproducibility of test results is high, and many specimens can be measured at the same time. Like Japan, the prevalence of *H.pylori* infection is high and the development of CAG is closely involved with gastric cancer in East Asian countries, such as China and Korea and in Eastern Europe, and Middle and South America. Conducting serum tests along with

routine endoscopic examination is useful not only for gastric cancer screening, but also to obtain more information about patients with reflux disease.

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COMMENTS

Background

We have classified the progression of Helicobacter pylori (H.pylori)-related chronic gastritis into 4 groups (A-D) on the basis of two serum parameters, H.pylori antibody (H.pylori-Ab) titer and serum pepsinogen (PG) level, as a screening test for extensive chronic atrophic gastritis (CAG), and reported a stepwise increase in the incidence of gastric cancer. In this study, the association of H.pylori-related chronic gastritis progression with upper gastrointestinal symptoms and gastroesophageal reflux disease (GERD) was evaluated, because there are only a few previous studies in which this association has been examined.

Research frontiers

This study can help us to understand the natural history of GERD, as well as other illnesses including gastric cancer.

Innovations and breakthroughs

Conducting serum tests along with routine endoscopic examination is useful for not only gastric cancer screening, but also to obtain more information about patients with GERD.

Applications

A prospective study based on long-term follow-up observation is needed to more accurately assess GERD risks.

Terminology

H.pylori-related chronic gastritis stage: The groups were determined by the results of the 2 serologic tests (H.pylori-Ab and PG). This classification reflects each stage of the serial changes in stomach mucosa induced by chronic H.pylori infection. The H.pylori-free healthy condition corresponds to 2 negative tests (Group A). With the establishment of H.pylori infection, the antibody test becomes positive (Group B). As the infection spreads, the PG test also turns positive (Group C). Group C has extensive CAG. Intestinal metaplasia develops and spreads in the presence of CAG, leading to reduction of the bacterial load in the stomach. This results in a negative specific antibody test (Group D). Thus, Group D comprises those subjects with metaplastic gastritis.

Peer review

This article provides interesting data about H.pylori-Ab and serum PG levels in subjects with GERD. These data are of epidemiological interest and provide some insight into theoretical aspects.

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ORIGINAL ARTICLE

Transnasal and standard transoral endoscopies in the screening of gastric mucosal neoplasias

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Abstract

AIM: To compare the diagnostic performances of transnasal and standard transoral esophagogastroduodenoscopy (EGD) in gastric cancer screening of asymptomatic healthy subjects.

METHODS: Between January 2006 and March 2010, a total of 3324 subjects underwent examination of the upper gastrointestinal tract by EGD for cancer screening, with 1382 subjects (41.6%) screened by transnasal EGD and the remaining 1942 subjects (58.4%) by standard transoral EGD. Clinical profiles of the screened subjects, detection rates of gastric neoplasia and histopathology of the detected neoplasias were compared between groups according to the stage of *Helicobacter pylori* (*H. pylori*)-related chronic gastritis.

RESULTS: Clinical profiles of subjects did not differ significantly between the two EGD groups, except that there were significantly more men in the transnasal EGD group. During the study period, 55 cases of gastric mucosal neoplasias were detected. Of these, 23 cases were detected by transnasal EGD and 32 cases by standard transoral EGD. The detection rate for gastric mucosal neoplasia in the transnasal EGD group was thus 1.66%, compared to 1.65% in the standard transoral EGD group, with no significant difference between the two groups. Detection rates using the two endoscopies were likewise comparable, regardless of *H. pylori* infection. However, detection rates when screening subjects without extensive chronic atrophic gastritis (CAG) were significantly higher with standard transoral EGD (0.70%) than with transnasal EGD (0.12%, $P < 0.05$). In particular, standard transoral EGD was far better for detecting neoplasia in subjects with *H. pylori*-related non-atrophic gastritis, with a detection rate of 3.11% compared to 0.53% using transnasal EGD ($P < 0.05$). In the screening of subjects with extensive CAG, no significant differences in detection of neoplasia were evident between the two endoscopies, although the mean size of detected cancers was significantly smaller and the percentage of early cancers was significantly higher with standard transoral EGD.

CONCLUSION: These results strongly suggest that the diagnostic performance of transnasal endoscopy is

suboptimal for cancer screening, particularly in subjects with *H. pylori*-related non-atrophic gastritis.

Key words: Transnasal endoscopy; Gastric cancer; Gastric adenoma; Atrophic gastritis; *Helicobacter pylori*; Cancer screening

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INTRODUCTION

To address the high mortality rate associated with gastric cancer, a nationwide program of gastric cancer screening has been introduced throughout Japan as a public service sponsored by local governments. In 2007, a total of 6 385 118 individuals underwent these screenings, resulting in the detection of 5606 cases of gastric cancer[1]. This screening program utilizes barium x-ray with photofluorography as a standard screening test and is considered effective in reducing the cancer mortality rate[2-5]. However, the sensitivity of barium X-ray is by no means high, reaching only 39% for early cancer[6]. To cope with this problem and improve the quality of screening, esophagogastroduodenoscopy (EGD) has gradually been adopted in several workplaces, local communities for organized screening and in health check-up institutions, including private health assessment clinics for opportunistic screening. A total of 211 821 subjects underwent cancer screening using EGD in 2007, according to the annual report of the Japanese Society of Gastroenterological Screening[1]. Since EGD is an unpleasant examination for subjects, evoking anxiety, pharyngeal discomfort, nausea, the gag-reflex and choking, and has been associated with adverse effects such as cardiovascular accidents[7-9], this screening method is highly dependent on the skill of the endoscopist. The limited number of highly experienced endoscopists thus represents a major limitation to the feasibility of widespread cancer screening using EGD. Transnasal EGD using a small-diameter endoscope is more patient-friendly than standard transoral EGD, is safer, with little impact on the cardiopulmonary and autonomic nerve systems[10-13], and provides good operability. Transnasal EGD is thus more acceptable for patients and appears to be better suited to endoscopic cancer screening. However, because the luminous intensity and quality of endoscopic images varies greatly depending on differences in endoscope diameter, the screening performance of transnasal EGD for gastric cancer, particularly with regard to early cancer, must be determined carefully in the setting of cancer screening. The present study compared screening performance for gastric mucosal neoplasia (adenoma or cancer) between transnasal EGD and standard transoral EGD. In addition, the morphological and biological characteristics of gastric mucosal neoplasia are influenced by the stage of *Helicobacter pylori* (*H. pylori*)-related chronic gastritis[14-18], which thus seems likely to influence the diagnostic ability of these two EGDs. We therefore compared screening by transnasal and standard transoral EGDs according to the stage of *H. pylori*-related chronic gastritis.

MATERIALS AND METHODS

Subjects comprised 3324 patients [1442 men, 1882 women; mean (SD) age, 53.4 (15.4) years] who underwent EGD for screening of the upper gastrointestinal tract in our health assessment clinic between January 2006 and March 2010. All subjects were essentially symptom-free and each was free to choose between transnasal and standard transoral EGD. The transnasal EGD group included 1382 subjects [684 men, 698 women; mean (SD) age, 53.4 (15.4) years] and the standard transoral EGD group included 1942 subjects [758 men, 1184 women; mean (SD) age, 53.5 (15.4) years]. Standard transoral EGD was performed using a GIF-Q260 or prototype GIF-Y0004 endoscope (Olympus, Tokyo, Japan), whereas transnasal EGD was performed using a GIF-N260 or prototype GIF-Y0022 endoscope (Olympus) or an EG-530N2 endoscope (Fuji Film Medical, Tokyo, Japan). Outer diameters of the standard endoscopes were larger than those of transnasal endoscopes: GIF-Q260, 9.2 mm; GIF-Y0004, 7.7 mm; GIF-N260, 4.9 mm; GIF-Y0022, 5.4 mm; and EG-530N2, 5.9 mm. Sizes of the charge-coupled device for the two standard endoscopes were the same and about 30% larger than those of the GIF-N260 and GIF-Y0022 transnasal endoscopes. The optical system in EG-530N2 differs from those of the other endoscopes but image quality for the EG-530N2 was equivalent to that with the other two transnasal endoscopes. Standard endoscopes were equipped with two light guides, while transnasal endoscopes were equipped with either single (GIF-N260) or double light guides (GIF-Y0022 and EG-530N2); the visual field of the transnasal endoscopes were dark compared with the standard endoscopes, due to the smaller number of light guide fibers. Viewing angles of all standard and transnasal EGDs were 140° and 120°, respectively. The tip flexion capability of en-

Table 1 Clinical profiles of the subjects screened by transnasal or transoral endoscopy and clinicopathological characteristics of detected gastric mucosal neoplasia (mean ± SD) *n* (%)

	Total subjects	Subject screened	
		By transnasal EGD	By transoral EGD
No. of screened subjects	3324	1382	1942
Age (yr)	53.4 ± 15.4	53.4 ± 15.4	53.5 ± 15.4
Males	1442 (43.4)	684 (49.4)*	758 (39.0)
Smokers	678 (20.4)	267 (19.3)	411 (21.1)
Helicobacter pylori-infected subjects	1202 (40.2)	510 (39.8)	692 (40.5)
CAG-positive subjects	1360 (40.9)	560 (40.5)	800 (41.2)
No. of subjects with gastric neoplasia/DR	55/0.0165	23/0.0166	32/0.0165
Location of neoplasia (U/M/L)	20/15/20	8/7/8	12/8/12
Adenoma cases/DR	12/0.0036	3/0.0022	9/0.0046
Location of adenoma (U/M/L)	2/4/6	0/2/1	2/2/5
Size of adenoma (mm)	10.5 ± 7.0	9.7 ± 4.0	10.8 ± 7.9
Cancer cases/DR	43/0.0129	20/0.0145	23/0.0118
Location of cancer (U/M/L)	18/11/14	8/5/7	10/6/7
Ssize of cancer (mm)	27.3 ± 16.7	32.6 ± 19.5*	22.3 ± 12.8
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	12/1/15/13	6/1/5/8	6/0/12/5
With intestinal-type cancer	33 (76.7)	18 (90.0)*	15 (65.2)
Depth of invasion (m/sm/pm-)	20/10/13	5/7/8	15/3/5
With early cancer	30 (69.7)	12 (60.0)	18 (78.3)

*$P < 0.05$ *vs* transoral esophagogastroduodenoscopy (EGD). CAG: Chronic atrophic gastritis; DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach.

doscopes was 210° up, 90° down and 100° right and left, with the exception of GIF N260, a two-way angulation transnasal endoscope, which showed flexion capability of 210° up and 120° down in a single plane. All endoscopes used in the present study were equipped with a forceps channel (diameter, 2 mm).

In both groups, a sedative (midazolam, 2.5-5 mg/body) was provided for subjects who desired it. All endoscopic examinations were performed by a single endoscopist with 20 years' experience in gastrointestinal endoscopy. Narrow-band imaging, flexible spectral imaging color enhancement or indigo carmine spraying was applied for full observation when considered necessary. Chronic atrophic gastritis (CAG), defined as chronic gastritis with open-type atrophy in the background gastric mucosa according to the definitions of Kimura *et al*[19], was diagnosed by endoscopic observation, whereas *H. pylori* infection was diagnosed by histopathological analysis using Giemsa staining of endoscopically biopsied mucosal samples obtained from the greater curvature of the gastric body and antrum. Furthermore, on the basis of previous reports[20,21], subjects with *H. pylori*-related chronic gastritis were examined after being divided into the following 4 groups according to the stage of *H. pylori*-related chronic gastritis: Group A, *H. pylori*-negative and CAG-negative; Group B, *H. pylori*-positive and CAG-negative; Group C, *H. pylori*-positive and CAG-positive; and Group D, *H. pylori*-negative and CAG-positive. Among the subjects screened, the status of *H. pylori*-related chronic gastritis in the background stomach was able to be analyzed in 2987 subjects.

Histopathological assessment of gastric mucosal neoplasias, adenoma and cancer was performed on resected specimens obtained by endoscopy or surgery. Early gastric cancers were defined as those confined to the mucosa or submucosa. Advanced cancers were defined as those invading into the muscularis propria or beyond. Pathologically, gastric cancer cases were classified into intestinal type or diffuse type, according to Lauren's classification[22]. The ethics committee of Wakayama Medical University approved the protocol of the present study and informed consent was obtained from all subjects prior to participation.

Statistical analysis

Data were analyzed using SPSS version 11.0 (SPSS, Chicago, IL, USA) and STATA (STATA, College Station, TX, USA). Differences were tested for significance using analysis of variance for comparisons between groups and Scheffe's LSD test for comparisons between pairs of groups. The χ^2 test and Fisher's exact test were used to compare categorical variables. For all comparisons, values of $P < 0.05$ were considered statistically significant.

RESULTS

Between January 2006 and March 2010, a total of 3324 subjects underwent examination of the upper gastrointestinal tract by EGD for cancer screening, with 1382 subjects (41.6%) screened by transnasal EGD and the remaining 1942 subjects (58.4%) by standard transoral EGD. Clinical profiles of subjects in the two endoscopy groups are shown in Table 1. Although significantly more men were included in the transnasal EGD group than in the standard transoral EGD group, no significant differences in age, smoking habits, *H. pylori* infection or extent of concomitant CAG were seen between groups. Endoscopy screening identified 55 cases of gastric mucosal

Table 2 Screening performance of the two esophagogastroduodenoscopies in subjects with or without *Helicobacter pylori* infection (mean ± SD) *n* (%)

	Total subjects (*H. pylori* analyzed)	*H. pylori*	
		Positive	Negative
Screened by transnasal EGD			
Screened subjects	1280	510	770
Age (yr)	53.4 ± 15.4	56.8 ± 13.6[c]	50.2 ± 14.3
Males	623 (48.7)[a]	268 (52.5)[a]	355 (46.1)[a]
Smokers	247 (19.3)	118 (23.1)[c]	129 (16.7)[a]
Subjects with gastric neoplasia/DR	21/0.0164	16/0.0314[c]	5/0.00649
Location of neoplasia (U/M/L)	7/6/8	4/6/6	3/0/2
Adenoma cases/DR	3/0.0023	3/0.00589	0/0
Size of adenoma (mm)	9.7 ± 4.0	9.7 ± 4.0	0
Cancer cases/DR	18/0.0141	13/0.0255[c]	5/0.00649
Size of cancer (mm)	31.2 ± 19.5	25.5 ± 13.3	46.0 ± 28.2
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	6/1/4/7	5/0/4/4	1/1/0/3
With intestinal-type cancer	16 (88.9)	12 (92.3)	4 (80)
Depth of invasion (m/sm/pm-)	5/6/7	4/5/4	1/1/3
With early cancer	12 (66.7)	10 (76.9)	2 (40)
Screened by transoral EGD			
Screened subjects	1707	692	1015
Age (yr)	53.5 ± 15.4	56.3 ± 14.7[c]	51.8 ± 14.8
Males	655 (38.4)	298 (43.1)	357 (35.2)
Smokers	354 (20.7)	141 (20.3)	213 (21.0)
Subjects with gastric neoplasia/DR	33/0.0193	26/0.0376[c]	6/0.00591
Location of neoplasia (U/M/L)	12/8/12	10/8/9	2/0/3
Adenoma cases/DR	9/0.0052	5/0.00722	4/0.00394
Size of adenoma (mm)	10.8 ± 7.9	13 ± 11.5	10 ± 4.08
Cancer cases/DR	23/0.0135	21/0.0303[c]	2/0.00197
Size of cancer (mm)	22.3 ± 12.8	23.2 ± 13.4	20 ± 0
Morphological cancer type (Ⅰ-Ⅱa/Ⅱb/Ⅱc-Ⅲ/Ad)	6/0/12/5	6/0/10/5	0/0/2/0
With intestinal-type cancer	15 (65.2)	14 (66.7)	1 (50)
Depth of invasion (m/sm/pm-)	15/3/5	13/3/5	2/0/0
With early cancer	18 (78.3)	14 (76.2)	2 (100)

[a]$P < 0.05$ *vs* transoral, [c]$P < 0.05$ *vs Helicobacter pylori* (*H. pylori*)-negative. DR: Detection rate; U: Upper third of the stomach; M: Middle third of the stomach; L: Lower third of the stomach; EGD: Esophagogastroduodenoscopy.

neoplasia (detection rate, 1.65%), with gastric cancers in 43 subjects (detection rate, 1.29%) and adenomas in 12 subjects (detection rate, 0.36%). Of these, 23 cases were detected by transnasal EGD (detection rate, 1.66%) and 32 cases by standard transoral EGD (detection rate, 1.65%). Detection rates for screening using the two different types of endoscopes were thus almost equivalent (Table 1). The detection rate of adenoma was higher in the standard transoral EGD group (0.46%) than in the transnasal EGD group (0.22%), but no significant differences in detection rate, size or location of adenoma were evident between groups. The detection rate of gastric cancer likewise did not differ significantly between groups, at 1.45% for transnasal EGD and 1.18% for standard transoral EGD. However, mean size of detected lesions was significantly smaller with standard transoral EGD. The percentage of early cancers tended to be higher for standard transoral EGD (78.3%) than for transnasal EGD (60%), although no significant difference was apparent. Locations and morphological types of detected cancers did not differ significantly between groups, although standard transoral EGD detected depressed-type cancers located in the upper third of the stomach more frequently. With regard to the histopathological type of detected cancers, standard transoral EGD detected significantly more non-intestinal-type cancers (i.e. diffuse-type cancers) than transnasal EGD.

Next, we compared detection rates of gastric mucosal neoplasia using the two different EGDs according to the status of *H. pylori* infection (Table 2) and the extent of CAG (Table 3). Mean age of screened subjects was significantly higher in the *H. pylori*-positive group and in the CAG-positive group than in their respective negative counterparts, and no significant differences in mean age of screened subjects were seen between the two EGD groups when stratified into subgroups according to positivity for *H. pylori* infection or the extent of CAG. However, the percentage of men was significantly higher in the transnasal EGD group irrespective of *H. pylori* status or the extent of CAG. In the *H. pylori*-negative group, the percentage of smokers was significantly higher among subjects screened by standard transoral EGD than by transnasal EGD, while the *H. pylori*-positive group showed no significant difference in the percentage of smokers between EGD groups. No significant difference in the percentage of smokers was seen between EGD groups, regardless of CAG status.

Detection rates of gastric mucosal neoplasia using