Endoscopic gastric mucosal atrophy as a predictor of colorectal polyps: a large scale case-control study

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Although some studies have indicated a correlation between Helicobacter pylori infection and the risk of colorectal neoplasms, these findings have not been consistent and are controversial. This case-control study aimed to investigate the association between endoscopic gastric mucosal atrophy and colorectal polyp occurrence. Records of 7,394 participants who underwent colonoscopy examinations from August 2008 to July 2018 were reviewed retrospectively. A total of 2,404 subjects were registered; 1,565 (65.1%) were in the gastric mucosal atrophy-positive group and 1,138 (47.3%) had colorectal polyps. The multivariate analysis adjusted by age, sex, smoking habits, alcohol habits, hemoglobin A1c, and systolic blood pressure indicated that patients in the gastric mucosal atrophy-positive group more frequently had colorectal polyps compared with patients in the gastric mucosal atrophy-negative group (odds ratio, 3.27; 95% confidence interval, 2.68–4.01; p < 0.001). An analysis of the association between gastric mucosal atrophy degree and colorectal polypl suggests that compared with mild gastric mucosal atrophy, severe gastric mucosal atrophy was associated with a higher risk of proximal colon polyps (odds ratio, 1.47; 95% confidence interval, 1.05–2.07; p = 0.024) and two or more colorectal polyps (odds ratio, 1.80; 95% confidence interval, 1.30–2.49; p < 0.001). In conclusion, gastric mucosal atrophy found during esophagogastroduodenoscopy may be an indication for complete colon screening.

Key Words: gastric mucosal atrophy, Helicobacter pylori, colorectal polyp, proximal colon, case-control study

Persistent Helicobacter pylori (H. pylori) infection begins during childhood and can cause peptic ulcers and gastric cancer.1-4 Chronic infection of the stomach mucosa induces gastric mucosal atrophy (GMA), which is found during esophagogastroduodenoscopy (EGD), usually during adulthood.5-7 H. pylori infections and GMA are associated with extra-gastric organ disease, including coronary artery disease and idiopathic thrombocytopenic purpura.8,9 Moreover, several investigations have reported an association between H. pylori infection and colorectal neoplasms.10-13 In general, risk of colorectal neoplasms increases because of some risk factors, such as lifestyle characteristics, anthropometric parameters, and metabolic syndrome.14,15 Most colorectal neoplasms found during endoscopic examinations are adenomas that possess the potential for cancer in the adenoma-carcinoma sequences.16,17 Therefore, recognizing risk factors for colorectal polyps is an immediate concern.

Although some investigations have suggested a positive correlation between H. pylori infection and the occurrence of colorectal polyps, including adenoma and adenocarcinoma,18-20 others have shown no significant relationship between them.18-20 Moreover, several studies have demonstrated an association between atrophic gastritis and colorectal polyps.21-23 In these studies, atrophic gastritis was diagnosed by a serological pepsinogen test or pathological examination and the updated Sydney System.22 A limited number of studies have investigated the association between endoscopic GMA and colorectal polyps. One cross-sectional study demonstrated that H. pylori infection and severe GMA diagnosed by endoscopy increased the risk of colorectal neoplasms.24 However, the relationship between GMA extent and the occurrence of colorectal polyps is unclear.

EGD examinations have been performed frequently during clinical consultations or medical examinations because of the widespread use of electronic endoscopy.23 Colonoscopy is also useful for discovering colorectal disease, including polyps; however, the examination is more burdensome than EGD for patients because of the required preparation and invasiveness. Recognizing the relationship between EGD findings and colorectal polyps is useful and important because it allows physicians to recommend colonoscopy examinations for specific patients.

This case-control study investigated the correlation between endoscopic GMA and the occurrence of colorectal polyps, and how the GMA extent is associated with the position, number, shape, and histological findings of polyps.

Materials and Methods

Study design and patients. This case-control study was conducted after collecting clinical data of 7,394 patients who underwent colonoscopy examinations at Oita University Hospital from August 2008 to July 2018. All clinical information required for the analyses including personal medical history, endoscopy examination findings, physical parameters, preferences, and blood examination results were recorded in a data file in the electronic medical record system. Figure 1 shows the study flow diagram, which includes the exclusion criteria of the subjects. A total of 3,362 subjects were excluded for the following reasons: younger than 20 years, history of inflammatory bowel disease or intestinal Behçet’s disease, incomplete colonoscopy examination due to poor colonic lavage or difficult scope insertion, history of endoscopic mucosal resection, surgery or chemotherapy for colon disease, no EGD examination, and difficulty recognizing the GMA extent. Another 1,628 subjects were excluded because of missing clinical data such as smoking and alcohol drinking habits.

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blood examination results, body height, and weight, which were needed as confounding factors in the analyses. Finally, 2,404 subjects were included in the study. This study was approved by the research ethics committee of Oita University Hospital (approval number 1486).

Clinical data collection. Age, sex, smoking habits, alcohol drinking habits, systolic blood pressure (SBP), diastolic blood pressure (DBP), body height, and weight were recorded in the electronic medical record system at the time of the first medical examination. Body mass index (BMI) was calculated using body height and weight. Additionally, blood examination data, including levels of low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), triglyceride (TG) levels, and hemoglobin A1c (HbA1c), which were measured before or on the day of the colonoscopy examination, were collected. The smoking habit was defined as positive if the participant was a current or former smoker; it was defined as negative for never smokers. The alcohol drinking habit was defined as positive if the participant reported drinking alcohol more than three times per week; it was defined as negative for social or never drinkers. Obesity, chronic hyperglycemia, dyslipidemia, and hypertension, which were used to determine the clinical status of lifestyle disease, were defined by the following criteria: obesity (BMI ≥25 kg/m²); chronic hyperglycemia (HbA1c ≥6.5%); dyslipidemia (LDLC ≥140 mg/dl, HDLC <40 mg/dl, or TG ≥150 mg/dl); and hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg).

Assessment of endoscopic findings. All endoscopic images used in this study were checked and diagnosed by two or more experienced endoscopists. The shape of the colorectal polyps was determined according to the Japanese classification of colorectal, appendiceal, and anal carcinoma. The histological diagnosis of the polyp was categorized into three types: adenoma, adenocarcinoma, or other.

The extent of GMA was determined according to the Kimura-Takemoto classification. This classification divided the extent of mucosal atrophy into closed type and open type. Closed type, which is further classified as three grades (C1 to C3), meant that the atrophic region was limited to the lesser curvature of the stomach. Open type meant that the atrophic region extended to the greater curvature side including the cardia; this was divided into three grades (O1 to O3). Endoscopic diagnosis of C1, which meant that mucosal atrophy was localized only to the
antrum, may not be easy because the mucosal surface patterns of fundic and pyloric gland regions are different.\(^{(26)}\) Therefore, a total of 185 subjects whose GMA extent was C1 were excluded from this study.

During the analyses of the correlation between GMA extent and the occurrence of colorectal polyps or polypl status, such as location, number, shape, and histological diagnosis, two types of GMA grades were defined as mild atrophy and severe atrophy. C2 and C3 were categorized as mild atrophy, and O2 and O3 were categorized as severe atrophy. To clearly distinguish these two types of atrophy, 261 subjects with O1 were excluded from these analyses.

**Statistical analysis.** Demographic data of study subjects are presented as means with standard deviations for continuous variables, and as the number of subjects with percentages for categorical variables. Chi-square tests were used for categorical variables and Student’s \(t\) tests were used for continuous variables to calculate \(p\) values. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for predictors of all colorectal polyps were computed by using the multiple logistic regression model. Twelve confounding factors (age, sex, smoking habits, alcohol drinking habits, HbA1c, LDLC, HDLC, TG, SBP, DBP, BMI, and GMA) were used as variables in the model. Based on the results of the univariate analysis, non-significant variables were excluded before executing the multivariate analysis. \(P<0.05\) was considered statistically significant.

During the analysis performed to compare the two grades of GMA and colorectal polyp occurrence, univariate and multivariate logistic regression analyses were performed only for subjects whose GMA findings were C2, C3, O2, and O3. Confounding factors were the same as previously mentioned. During the analysis performed to determine the association between GMA grade and colorectal polyp status, the data of subjects who had colorectal polyps in addition to GMA grade C2, C3, O2, and O3 were used. Because there were fewer subjects in this analysis, seven confounding factors (age, sex, smoking habits, alcohol drinking habits, HbA1c, SBP, and severe GMA) were used. Univariate and multivariate logistic regression analyses were also performed. Statistical analyses were performed using R (ver. 3.5.0, 2018; The R Foundation for Statistical Computing; Vienna, Austria).

**Results**

**Demographics of study patients.** Table 1 presents the clinical characteristics of 2,404 patients. GMA-positive subjects with C1 comprised 65.1% of subjects. A total of 1,138 subjects (47.3%) had colorectal polyps. Study subjects were divided into two groups; colorectal polyp-negative group and colorectal polyp-positive group. There were significant differences in the mean age, sex, smoking habits, alcohol drinking habits, HbA1c, systolic blood pressure, and GMA between these two groups.

| Variable | Overall (n = 2,404) | Colorectal polyp (-) (n = 1,266) | Colorectal polyp (+) (n = 1,138) | \(p\) value |
|----------|---------------------|---------------------------------|---------------------------------|-----------|
| Age (years)* | 64.2 (13.7) | 61.2 (15.0) | 67.6 (11.1) | <0.001 |
| Sex: male\(b\) | 1,360 (56.6) | 622 (49.1) | 738 (64.9) | <0.001 |
| Smoking habits\(c\) | 1,059 (44.1) | 489 (38.6) | 570 (50.1) | <0.001 |
| Alcohol drinking habits\(d\) | 845 (35.1) | 366 (28.9) | 479 (42.1) | <0.001 |
| HbA1c (\%)\(e\) | 6.1 (1.2) | 6.1 (1.2) | 6.2 (1.2) | 0.039 |
| LDLC (mg/dl)* | 108.6 (38.0) | 108.4 (35.8) | 108.7 (40.2) | 0.829 |
| HDLC (mg/dl)* | 52.4 (18.4) | 52.8 (18.3) | 52.1 (18.5) | 0.359 |
| Triglycerides (mg/dl)* | 129.5 (87.4) | 128.8 (94.4) | 130.3 (78.9) | 0.671 |
| Systolic BP (mmHg)* | 129.0 (20.2) | 127.8 (19.9) | 130.5 (20.4) | 0.001 |
| Diastolic BP (mmHg)* | 75.5 (13.9) | 75.4 (13.7) | 75.7 (14.2) | 0.624 |
| BMI (kg/m\(^2\)) | 24.1 (5.5) | 24.1 (6.2) | 24.0 (4.6) | 0.497 |
| Gastric mucosal atrophy\(h\) | 1,565 (65.1) | 647 (51.1) | 918 (80.7) | <0.001 |
| C\(^1\) | 185 (7.7) | 97 (7.7) | 88 (7.7) | 0.015 |
| C\(^2\) | 290 (12.1) | 121 (9.6) | 169 (14.9) | 0.001 |
| C\(^3\) | 343 (14.3) | 152 (12.0) | 191 (16.8) | 0.001 |
| O\(^1\) | 261 (10.9) | 82 (6.5) | 179 (15.7) | 0.001 |
| O\(^2\) | 241 (10.0) | 93 (7.3) | 148 (13.0) | 0.001 |
| O\(^3\) | 245 (10.2) | 102 (8.1) | 143 (12.6) | 0.001 |

\(a\)Data are presented as mean (SD). \(b\)Data are presented as number of positive case (percentage). HbA1c, hemoglobin A1c; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; BP, blood pressure; BMI, body mass index. The extent of gastric mucosal atrophy is denoted according to Kimura-Takemoto classification.\(^{(25)}\)

**Table 1.** Demographics of study patients.
Table 2. Univariate and multivariate logistic regression analyses of predictors of colorectal polyps

|                | Overall (n=2,219) | Colorectal polyp | Univariate analysis | Multivariate analysis |
|----------------|-------------------|------------------|--------------------|----------------------|
|                |                   | no. (%)          | OR (95% CI)        | p value              |
| Age ≥50 (years)| 1,878             | 978 (52.1)       | 4.06 (3.10–5.38)   | <0.001               |
| Male, sex      | 1,240             | 677 (54.6)       | 1.95 (1.65–2.32)   | <0.001               |
| Smoking habits | 967               | 521 (53.9)       | 1.60 (1.35–1.89)   | <0.001               |
| Alcohol drinking habits | 775          | 442 (57.0)       | 1.83 (1.53–2.18)   | <0.001               |
| HbA1c ≥6.5 (%) | 488               | 262 (53.7)       | 1.39 (1.13–1.70)   | 0.001                |
| LDLc ≥140 (mg/dl) | 362           | 170 (47.0)       | 0.98 (0.78–1.23)   | 0.882                |
| HDLC <40 (mg/dl) | 552            | 278 (50.4)       | 1.18 (0.97–1.43)   | 0.099                |
| TG ≥150 (mg/dl) | 580             | 282 (48.6)       | 1.07 (0.89–1.30)   | 0.465                |
| Systolic BP ≥140 (mmHg) | 635          | 323 (50.9)       | 1.22 (1.02–1.47)   | 0.034                |
| Diastolic BP ≥90 (mmHg) | 354          | 171 (48.3)       | 1.05 (0.84–1.32)   | 0.685                |
| BMI ≥25 (kg/m²) | 731             | 367 (50.2)       | 1.19 (1.00–1.42)   | 0.056                |

Table 3. The extent of gastric mucosal atrophy is denoted according to Kimura-Takemoto classification. OR, odds ratio; CI, confidence interval; no., number.

|                | Overall (n=1,119) | Colorectal polyp | Univariate analysis | Multivariate analysis |
|----------------|-------------------|------------------|--------------------|----------------------|
|                |                   | no. (%)          | OR (95% CI)        | p value              |
| Mild gastric mucosal atrophy (C2 and C3) | 633 | 360 (56.9) | 1 | 1 |
| Severe gastric mucosal atrophy (O2 and O3) | 486 | 291 (59.9) | 1.13 (0.89–1.44) | 0.313 |

Table 4. The extent of gastric mucosal atrophy is denoted according to Kimura-Takemoto classification. OR, odds ratio; CI, confidence interval; no., number.

|                | Overall (n=651) | Mild (C2 and C3) n=360 | Severe (O2 and O3) n=291 |
|----------------|-----------------|------------------------|--------------------------|
|                | no. (%)         | OR (95% CI)            | p value                  |
| Proximal colon | 424             | 219 (60.8)             | 1                        |
| Two or more polyps | 300         | 140 (38.9)             | 1                        |
| Superficial type polyp | 81          | 39 (10.8)              | 1                        |
| Adenocarcinoma | 79              | 41 (11.4)              | 1                        |

Table 5. The extent of gastric mucosal atrophy is denoted according to Kimura-Takemoto classification. OR, odds ratio; CI, confidence interval; no., number.

|                | Overall (n=300) | Two or more proximal colon polyps | Univariate analysis | Multivariate analysis |
|----------------|-----------------|----------------------------------|--------------------|----------------------|
|                | no. (%)         | OR (95% CI)                      | p value            |
| Mild gastric mucosal atrophy (C2 and C3) | 140 | 61 (43.6) | 1 | 1 |
| Severe gastric mucosal atrophy (O2 and O3) | 160 | 91 (56.9) | 1.71 (1.08–2.71) | 0.022 |

[^1]: Gastric mucosal atrophy is defined as positive when its extent is C2, C3, O1, O2, or O3 according to Kimura-Takemoto classification. A total of 185 subjects with C1 were excluded. OR, odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c; LDLc, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; TG, triglycerides; BP, blood pressure; BMI, body mass index; no., number.
Discussion

The present case-control study demonstrated that GMA found during endoscopy may be an independent risk factor for colorectal polyp occurrence. After GMA was defined as mild or severe, an analysis of the polyp status indicated that the severe GMA group showed a significantly higher risk of colorectal neoplasms. Additionally, the association between GMA and colorectal polyp occurrence in this study was consistent with that of several previous studies focused on atrophic gastritis and colorectal neoplasms.11,12,23 Furthermore, our study focused on GMA found during endoscopy as a predictor of colorectal polyps. Several previous studies investigated the relationship between H. pylori infection or atrophic gastritis diagnosed by the serological pepsinogen test and colorectal polyps.11,23 The extent of GMA can be easily diagnosed by trained endoscopists. Trained endoscopists can also easily recognize the difference between mild and severe GMA; however, the diagnosis of the GMA extent determined using the Kimura-Takemoto classification may involve the subjective judgment of the tester. Therefore, the results of this study provide useful knowledge regarding colorectal polyp prediction during daily clinical practice.

The physiological mechanisms involved in the relationship between GMA and the occurrence of colorectal polyps are not clear. Most cases of atrophic gastritis found by EGD are induced by H. pylori infection, and some GMA cases are caused by non-H. pylori or autoimmune mechanisms.30–32 Bacterial infections and autoimmune mechanisms cause chronic inflammation in the stomach mucosa, leading to the development of mucosal atrophy. However, colorectal polyps develop because of other risk factors, such as lifestyle characteristics, during the long-term.13,33 Nevertheless, both gastrointestinal disorders are chronic.

Several previous investigations have indicated that H. pylori infection causes increased levels of serum gastrin, thus stimulating mucosal proliferation of colon.34,35 However, some other studies were not able to show any association between them.36,37 Other studies showed that H. pylori could affect the colon mucosa directly, which might cause mucosal dysplasia. H. pylori virulence factor CagA encoded by cytotoxin-associated gene A, which is a gastric cancer risk factor, is contained in exosomes during systemic delivery and can reach any other organ.40 This may occur in colorectal neoplasms as extra-gastric lesions related to H. pylori. GMA may cause hypochlorhydria, which leads to intestinal dysbiosis.41 Eradication therapy for H. pylori infection could improve nutrition status of hemodialysis patients, whereas plasma ghrelin level had no significant difference.42 This outcome supports the idea that H. pylori infection or GMA might affect the intestinal microbiota. Other authors have suggested that intestinal bacterial overgrowth may increase secondary bile acid, which can be a risk factor for colorectal neoplasms.43 Multiple publications have indicated the relationship between intestinal microbiota and colorectal carcinogenesis.44–45 Gavage of fecal samples from patients with colorectal cancer have shown the occurrence of colorectal polyps with proinflammatory gene expressions and oncogenic factors in germ-free and conventional mice.46 These outcomes support the hypothesis that intestinal dysbiosis derived from the hypochlorhydria in the stomach can cause colorectal neoplasms.

An analysis of the association between colorectal polyp occurrence and GMA extent showed no significant difference between mild and severe GMA. The results suggested that the risk of colorectal polyps mainly depends on current or past H. pylori infections. Furthermore, during the analysis of colorectal polyp status and GMA grade, severe GMA was not a predictor of adenocarcinoma tissue in colorectal polyps. This supports the idea that systemic influences on pathogenic factors derived from H. pylori, such as CagA contained in exosomes,46 may be involved in the development of colorectal polyps and cancer. However, an analysis of the colorectal polyp status and GMA grade showed that those in the severe GMA group were at higher risk for multiple polyps in the proximal colon. This result implied that GMA does not have as much systemic influence as localized effects on the gastrointestinal tract. Hypochlorhydria induced by severe mucosal atrophy of the stomach presumably causes dysbiosis in the intestine, which might have greater effects on the proximal intestine than on the distal intestine. Alternatively, live H. pylori, which can be isolated from human feces,47 might attack the intestinal mucosa directly. Moreover, pathogenic factors released from the bacteria may cause the development of mucosal lesions. Additional biological studies are necessary to demonstrate their mechanisms.

The current study had several limitations. First, this was a retrospective observational study performed at a single center. It only included patients who underwent endoscopic examinations. Endoscopic examinations were performed for screening purposes and also because patients reported abdominal symptoms or other medical problems. Most participants had primary disease; therefore, bias may have occurred. Second, the diagnoses of GMA and colorectal polyps, except for pathologic diagnoses, were based only on the endoscopic findings. Although two or more experienced endoscopists diagnosed GMA and colorectal polyps according to the classification criteria, subjective judgment could not be excluded completely. Third, because this study focused on endoscopically discovered GMA, patient histories of H. pylori eradication therapy were not collected. Therefore, how the history of eradication therapy influenced the occurrence of colorectal polyps was unclear. Fourth, polyp size was not measured because of the retrospective study design. An analysis of the association between the extent of GMA and polyp size was not performed.

In conclusion, the present study indicated that endoscopically discovered GMA could indicate the existence of colorectal polyps. Furthermore, severe GMA may indicate the existence of multiple polyps in the proximal colon. These results may indicate that patients who have been diagnosed with atrophic gastritis, especially with severe mucosal atrophy, should undergo complete colon screening.

Author Contributions

YK: study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis and drafting of the manuscript; MK, KM and TO: study concept and design and acquisition of data; TS: acquisition of data and statistical analysis; YH, AS, KM, KO and RO: acquisition of data; TS: acquisition of data and statistical analysis; MK, KM and TO: study concept and design and interpretation of data, statistical analysis and drafting of the manuscript; YK: study concept and design; TS: acquisition of data, administrative, technical, or material support and study supervision.

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Abbreviations

BMI body mass index
DBP diastolic blood pressure
EGD esophagogastroduodenoscopy
GMA gastric mucosal atrophy
HbA1c hemoglobin A1c
HDLC high-density lipoprotein cholesterol

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Conflict of Interest

No potential conflicts of interest were disclosed.
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