A Cross-Sectional Study on the Risk Factors for Erosive Esophagitis in Young Adults

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Abstract

Objective  To investigate the impact of metabolic and lifestyle factors on erosive esophagitis in young adults.

Methods  A total of 5,069 people under the age of 40 years old were enrolled in a medical survey at our institute. People with a previous history of upper gastrointestinal tract surgery were excluded, as were individuals taking medication for reflux symptoms, peptic ulcers, or malignancies. Independent and significant predictors affecting the presence of erosive esophagitis were determined by multivariate analysis.

Results  A total of 4,990 participants (male/female; 3,871/1,119, age; 33.9±3.9 years) were eligible. A total of 728 participants (14.6%) had erosive esophagitis. Male gender and increasing age were independent predictors for increased prevalence of erosive esophagitis (odds ratio=2.242 and 1.045. 95% confidence interval=1.613-3.117 and 1.019-1.072; p<0.001 and 0.001, respectively). Moderate-to-heavy alcohol consumption, light-to-moderate-to-heavy smoking, hypertension, hyperglycemia, and hiatal hernia each significantly and independently increased the risk for erosive esophagitis (odds ratio=1.499, 1.398, 1.353, 1.570, 1.884, 1.297, 1.562, and 3.213. 95% confidence interval=1.181-1.903, 1.040-1.880, 1.094-1.675, 1.250-1.971, 1.307-2.716, 1.074-1.566, 1.063-2.295, and 2.712-3.807; p=0.001, 0.027, 0.005, <0.001, 0.001, <0.001, <0.001, and <0.001 respectively). Helicobacter pylori infection decreased the risk for erosive esophagitis (odds ratio=0.575, 95% confidence interval =0.436-0.759 p<0.001). Neither body mass index nor waist girth conferred increased risk of erosive esophagitis after adjusting for potential confounding factors.

Conclusion  Risk of erosive esophagitis in Japanese young adults was not increased by obesity, but it was increased by hiatal hernia and metabolic and lifestyle profiles including hypertension, hyperglycemia, alcohol consumption and smoking.

Key words: erosive esophagitis, gastroesophageal reflux disease, obesity, metabolic syndrome, hiatal hernia

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Introduction

Gastroesophageal reflux disease (GERD) is defined as the backward flow of acidic gastric contents into the esophagus, causing heartburn or acid regurgitation at least once a week (1). GERD can cause esophageal mucosal damage that may lead to esophageal bleeding or stricture, and can provoke long-term complications including Barrett’s esophagus or esophageal adenocarcinoma (2, 3). GERD often requires costly treatments, and prevalence has increased worldwide over recent decades (4-8). Considering the clinical impact of GERD, investigation of GERD risk factors in an asymptomatic general population may provide insight into how to prevent or treat this affliction. Recently, the incidence of GERD has increased in Japan (9), but the majority of these cases are mild GERD. The natural history of mild GERD, however, is still unclear. Manabe et al. showed that among
patients with mild GERD, 10.5% progressed to more severe forms in a long-term follow-up study (10). From this point, we need to observe the courses in these patients carefully, regardless of the grade of GERD.

The main pathogenetic mechanism of GERD is considered to be transient lower esophageal sphincter (LES) relaxation, which may account for the majority of reflux episodes (11). Elevation of intragastric pressure, gastric acid production levels, and esophageal acid exposure are important factors contributing to GERD (12-15). While there have been many reports on the relationship between obesity and GERD (16-24), other studies contradict such a connection (25, 26).

Our recent cross-sectional study involving 9,840 Japanese asymptomatic males demonstrated central obesity, as determined by waist girth and visceral adipose tissue, did not increase the risk for endoscopic erosive esophagitis (27). In addition, studies of Asian populations have identified several risk factors for GERD, including age, male sex, race, family history, higher socioeconomic status, increased body mass index (BMI), and smoking (28). The precise pathogenicity for these factors is still under debate.

No risk factors for GERD in young adults have been described. We pursued a cross-sectional study focused on the impact of physical, physiological, and lifestyle factors on endoscopic erosive esophagitis (EE) in a large Japanese non-patient population with individuals younger aged than 40 years old.

Materials and Methods

Study population

Between May 2007 and April 2010, 5,069 healthy Japanese people aged younger than 40 years old underwent a comprehensive medical survey at the Center for Preventive Medicine in our hospital as part of a survey study. In this connection, this study’s subjects included Japanese males and females under age 40 years old, and therefore they were not a subgroup of the previous our report involving asymptomatic males of all ages (27). Most participants were professional workers in higher socioeconomic category from around the Tokyo metropolitan area. All participants underwent a voluntary self-paid screening program, including physical check-up, abdominal ultrasonography, upper gastrointestinal endoscopy, blood tests, and a doctor’s interview. Participant clinical information was retrospectively extracted from our center’s database for analysis. All participants were informed that clinical data might be retrospectively analyzed and published. All examinations were done as a routine part of the health check-up program, and none were intended to collect their data specifically for this study. Therefore, written informed consent was not required. The study protocol was approved by the ethical committee of Kanto Medical Center (No. 10-329).

Exclusion criteria

The following individuals were excluded from our study: people taking medication for gastroesophageal reflux symptoms, gastric/duodenal ulcers, or malignant diseases; people with a history of Helicobacter pylori (H. pylori) eradication, gastro-esophageal tumors, or upper gastrointestinal surgery. Individuals with gastric or esophageal cancer detected at the time of endoscopic screening were also excluded.

Data collection

BMI was defined as weight divided by height squared (kg/m²). Abdominal circumference in the standing position was measured midway between the lowest rib and the iliac crest. Blood tests were performed by common enzymatic methods using an auto-analyzer (Hitachi Corp., Hitachi, Japan). Based on the report from Japan Society for the Study of Obesity (29), subjects were classified by BMI as follows: underweight; BMI<18.4 kg/m², normal; 18.5-24.9 kg/m², and obese; ≥25.0 kg/m². In addition, waist-girth-defined obesity was defined as waist girth ≥85 cm. According to Japanese criteria of metabolic syndrome (30), the following criteria were adopted: hypertension [systolic blood pressure (SBP)≥130 mmHg and/or diastolic blood pressure (DBP)≥ 85 mmHg], hyperlipidemia [triglyceride (TG)≥150 mg/dL and/or high density lipoprotein cholesterol (HDL-C)<40 mg/dL], hyperglycemia [fasting blood glucose (FBG)≥110 mg/dL], and hyper low density lipoprotein cholesterol (LDL-C) ≥140 mg/dL. Determination of H. pylori infection was based on H. pylori-specific antibody detection in patient serum. Participants with antibody titers higher than 10 U/mL were considered seropositive for H. pylori infection. A trained team of professional interviewers conducted face-to-face interviews with all participants using a questionnaire standardized for our unit. Information obtained via the questionnaire included alcohol consumption, smoking status, and physical activity (walking duration per day, sleeping hours per day, and strength of exercise per week). The reliability of information on alcohol consumption and smoking habits was confirmed independently by interviews with a doctor and a nurse for each participant. Total alcohol consumed per week (volume per day multiplied by drinking days per week) was converted into grams, and then categorized into four grades: non-drinker, <40 g/week; light drinker, 40 g to 140 g/week; moderate drinker, 140 g to 280 g/week; and heavy drinker, >280 g/week. The alcohol content for each beverage was as follows: beer (5% alcohol by volume), Japanese sake (brewed from rice, 15% alcohol by volume), and Japanese shochu (distilled from sweet potatoes, rice, or buckwheat; 25% alcohol by volume) (31). Enrollee smoking status was classified into 4 groups according to the Brinkman index (cigarettes per day multiplied by years of smoking); non-smoker, 0; light smoker, 1 to 200; moderate smoker, 200 to 400; and heavy smoker, >400 (32). In the questionnaire, participants were also asked about lifestyle aspects, including walking duration per day (<10 minutes,
Table 1. Differences in Biological Parameters Related to Erosive Esophagitis (EE)

<table>
<thead>
<tr>
<th></th>
<th>EE (-) n=4,262</th>
<th>EE (+) n=728</th>
<th>Difference p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female (%male)</td>
<td>3,193/1,069 (74.9%)</td>
<td>678/50 (93.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>33.8 ± 3.9</td>
<td>34.9 ± 3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (% of U/N/O category)</td>
<td>1.0/17.6/81.4</td>
<td>1.1/35.7/63.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist girth (% of N/O category)</td>
<td>74.9/25.1</td>
<td>54.5/45.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (+/-, %positive)</td>
<td>1,300/2,962 (69.5%)</td>
<td>119/609 (83.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia (+/-, %positive)</td>
<td>3,037/1,225 (28.7%)</td>
<td>386/342 (47.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperglycemia (+/-, %positive)</td>
<td>4,145/117 (2.7%)</td>
<td>678/50 (6.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyper LDL-C (+/-, %positive)</td>
<td>3,651/611 (14.3%)</td>
<td>568/160(22.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol consumption (% of N/L/M/H category)</td>
<td>54.4/25.2/13.3/7.1</td>
<td>43.0/24.9/19.9/12.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking habits (% of N/L/M/H category)</td>
<td>55.1/25.6/15.9/3.3</td>
<td>37.1/26.8/27.6/8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hiatal hernia (+/-, %positive)</td>
<td>3,241/1,021 (24.0%)</td>
<td>327/401 (55.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Helicobacter pylori(+/-, %positive)</td>
<td>3,620/635 (14.9%)</td>
<td>659/68 (9.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Obesity: Subjects were classified by BMI as follows; BMI <18.4 kg/m² was underweight (U), 18.5-24.9 kg/m² was normal (N), and ≥25.0 kg/m² was obese (O).

Waist girth: Subjects were classified by waist girth (WG) as follows; WG <84.9 cm was normal (N) and WG ≥85.0 cm was over WG (O).

Hypertension: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg

Hyperlipidemia: triglyceride ≥150 mg/dL and/or high density lipoproteins < 40 mg/dL

Hyperglycemia: fasting blood glucose ≥110 mg/dL

Hyper low density lipoprotein cholesterol (LDL-C): LDL-C ≥140 mg/dL

N/L/M/H: non/light/moderate/heavy

p values are based on t-tests, except for categorical parameters on chi² tests.

Classification of endoscopic findings

Esophagogastroduodenoscopy screening was performed by experienced endoscopists at the Gastroenterology Department in our hospital. All examiners had more than 5 years of endoscopy experience. Examiners had no knowledge of the results of blood-test screening, physical and physiological examinations, or the questionnaire. The endoscopists graded the reflux esophagitis using the Los Angeles (LA) classification system with Japanese modification (33). In addition, hiatal hernia was diagnosed by endoscopy when the distance between the gastroesophageal junction and the diaphragmatic hiatus was 2 cm or more.

Statistical analysis

Results are presented as mean ± standard deviation (SD) or as percentages for quantitative data. First, we used univariate analysis to evaluate the association of metabolic and lifestyle parameters with the presence of EE (continuous and categorical parameters were analyzed using Student’s t-test and Pearson’s χ² test, respectively). We then further confirmed associations by multiple logistic regression analyses. The covariates used for the multivariate analysis were: gender, age, BMI, waist girth, SBP, DBP, HDL-C, TG, FBG, LDL-C, alcohol consumption, smoking status, H. pylori serostatus, and hiatal hernia. The odds ratio (OR) and 95% confidence interval (95% CI) were given for each variable. All analyses were performed using Stata software (Intercooled Version 10.1 for Windows, College Station, TX). All statistical analyses were two-sided. A p-value <0.05 was considered statistically significant.

Results

Participant description

Among the 5,069 participants (3,923 men and 1,146 women), 79 (1.6%) were excluded based on the criteria listed above. No excluded individuals were diagnosed with gastric or esophageal cancer at the time of endoscopy screening in this program. A total of 4,990 participants (3,871 men and 1,119 women, mean age 33.9±3.9; age range 20-39 years) were eligible for the study. There were 728 (14.6%) cases with EE and the numbers of cases of LA grades A, B, C, and D were 653, 63, 11, and 1, respectively. H. pylori was seropositive in 14.1%, and the prevalence of hiatal hernia was 28.5%. Table 1 shows the differences in biological parameters between participants with EE and
those without EE. The mean age of participants with EE was 34.9±3.4 years, which was significantly higher than those without EE (p <0.001). Compared to participants without EE, the seropositivity rate of H. pylori was significantly lower in those with EE (9.4% vs. 14.9%, p<0.001) and the proportion of participants with hiatal hernia was statistically higher in the EE group (55.1% vs. 24.0%, p< 0.001). In addition, the value of metabolic parameters, including BMI, over waist girth, hypertension, hyperlipidemia, hyperglycemia, hyper LDL-C, and the consumption of smoking and alcohol were significantly higher in participants with EE (p<0.001, respectively).

**Multivariate regression analysis**

As indicated in Table 2, some independent risk factors for EE in healthy young adults were identified using a multiple logistic regression mode. These include male sex, increasing age, moderate-to-heavy alcohol consumption, light-to-moderate-to-heavy smoking, hypertension, hyperglycemia and the presence of hiatal hernia (OR=2.144, 1.044, 1.472, 1.401, 1.330, 1.566, 1.916, 1.297, 1.562 and 3.179; 95%CI= 1.550-2.967, 1.018-1.070, 1.164-1.862, 1.048-1.871, 1.076-1.643, 1.253-1.957, 1.338-2.743, 1.074-1.566, 1.063-2.295 and 2.685-3.763; p<0.001, respectively). In contrast, seropositivity for H. pylori contributed significantly and independently to a decreased prevalence of endoscopic EE (OR= 0.575, 95%CI=0.436-0.759, p<0.001). Notably, our study demonstrated that there was no significant association between the prevalence of endoscopic EE and metabolic factors including BMI, waist girth and hyperlipidemia in young adults.

**Discussion**

To our knowledge, the present study is the first to demonstrate risk factors of EE in healthy young adults. The prevalence and onset of EE in the general population is not clear since asymptomatic healthy individuals usually do not undergo endoscopic examination. It is rare for healthy young adults to undergo endoscopic examinations. Individuals in this study were healthy individuals who underwent endoscopy screening as part of a routine health check-up. Considering the large sample size, and adjusting for various potential confounders, we believe that the results of this study accurately represent the impact of physical and physiological parameters on EE in young Japanese people.

An important question faced in the primary care setting is whether weight reduction can be a measure to prevent EE. The impact of obesity on endoscopic EE has remained controversial in the literature. Hampel et al. demonstrated an association between a BMI ≥25 kg/m² and EE (34). This association was verified in a report using a symptomatic questionnaire paired with upper endoscopy in 6,215 participants in Germany (35). A recent cross-sectional case-control study involving 7,078 participants demonstrated an association between metabolic syndrome and EE (36); this study showed that obesity (in particular visceral fat) and elevated triglycerides represented independent factors for EE. However, a link between BMI and EE was not confirmed in a recent Japanese prospective study (36) or in a multicenter Italian observational study (37). A large population-based study in Sweden revealed that there was no association between BMI and the severity or duration of GERD symptoms (24). Similarly, the present results with a larger sample and adjusting for various confounding variables showed that none of the hallmarks of the metabolic syndrome, including obesity (BMI or waist girth) and hyperlipidemia, are significant risk factors of EE in young Japanese. However, it should also be noted that EE in the Japanese is generally mild (LA grade M, A or B) (36) and that the mean BMI in this study was 22.6 kg/m² and that the number of severe obesity cases (BMI ≥30.0 kg/m²) was 160 cases (3.2%) (data not shown).

| Table 2. Predictors of Erosive Esophagitis (EE) |
|---|---|
| Variables | OR (95% CI) | p value |
| Gender | 2.242(1.613-3.117) | <0.001 |
| Age | 1.045(1.019-1.072) | 0.001 |
| Obesity | | |
| Underweight | 1 | |
| Normal | 1.146(0.700-1.875) | 0.587 |
| Obese | 1.395(0.799-2.434) | 0.241 |
| Waist girth | | |
| Normal | 1 | |
| Over | 1.276 (1.000-1.628) | 0.050 |
| Hypertension | 1.297(1.074-1.566) | 0.007 |
| Hyperlipidemia | 1.194(0.970-1.471) | 0.095 |
| Hyperglycemia | 1.562(1.063-2.295) | 0.023 |
| Hyper LDL-C | 1.097(0.881-1.366) | 0.407 |
| Alcohol consumption | | |
| Non-drinker | 1 | |
| Light drinker | 1.126(0.911-1.391) | 0.272 |
| Moderate drinker | 1.499(1.181-1.903) | 0.001 |
| Heavy drinker | 1.398(1.040-1.880) | 0.027 |
| Smoking habits | | |
| Non-smoker | 1 | |
| Light smoker | 1.353(1.094-1.675) | 0.005 |
| Moderate smoker | 1.570(1.250-1.971) | <0.001 |
| Heavy smoker | 1.884(1.307-2.716) | 0.001 |
| Hiatal hernia | 3.213(2.712-3.807) | <0.001 |
| Helicobacter pylori | 0.575(0.436-0.759) | <0.001 |

Obesity: Subjects were classified by BMI as follows; BMI<18.4 kg/m² was underweight, 18.5-24.9 kg/m² was normal, and ≥25.0 kg/m² was obese.

Waist girth: Subjects were classified by waist girth (WG) as follows; WG <84.9 cm was normal and WG ≥85.0 cm was over WG.

Hypertension: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg.

Hyperlipidemia: triglyceride ≥150 mg/dL and/or high density lipoproteins < 40 mg/dL.

Hyperglycemia: fasting blood glucose ≥110 mg/dL.

Hyper LDL-C: LDL-C ≥140 mg/dL.

Results of multiple logistic regression analysis.

Statistical significance is based on p value <0.005.
which was suggestive of a low proportion in the general Japanese population. Relevance with EE and obesity or metabolic factors might differ depending on the severity of EE (38). The precise reason for such conflicting results from different studies is still unclear. The present results indicated that the impact of waist girth on EE was only at the marginal level (p=0.050). To gain better insight into the biological link between obesity and GERD, further studies are needed to compare the role of obesity and cytokine kinetics among different grades of EE.

The relationship between age and GERD is also unclear (39). Some cross-sectional studies found no association, but other reports showed that the prevalence of EE increased with age (40). We observed an association between age and endoscopic EE in people younger than 40. This association remained significant after adjustment for various metabolic factors, physical and dietary habits, and hiatal hernia (Table 2). A previous study in Japan showed that gastric acid secretion increased due to unknown factors, and that these factors did not include a decrease in *H. pylori* infection (41). Increased acid contents may be associated with the development of EE among Japanese young people. On the other hand, the prevalence of *H. pylori* infection is higher in Japan compared to western countries. Sugiyama et al. reported that the seropositivity rate of *H. pylori* was 74.9% in participants born before 1950 and the rate was as low as 20.7% in those born after 1950 (42). *H. pylori* infection has an inverse association with GERD (15, 33, 43-45), so a decrease in the infection rate may lead to an increased prevalence of GERD in the Japanese population (9). The present study indicated that the protective link between *H. pylori* and EE was independent of BMI or waist girth. To gain better insight into the biological link between *H. pylori* and EE, further studies are needed to compare the role of cytokine kinetics, chronic inflammatory conditions, and oxidative stress between individuals with and without EE.

In accordance with previous reports (46, 47), we showed that lifestyle profiles, including alcohol consumption and smoking habits were significant and independent risk factors for EE. A recent population-based retrospective cohort study of Japanese men revealed an association between alcohol consumption and the risk of EE (48). Consumption of large amounts of alcohol, regardless of the type of alcoholic beverage, has been reported to promote acid regurgitation by reducing the pressure of the LES and slowing both esophageal motility and gastric emptying (49-51). Unexpectedly, GERD risk in heavy drinkers was lower than that in moderate drinkers. The precise mechanism of our results remains unclear. Details of preferred alcohol beverage such as wine, beer, or other kind of liquor was not specified among light, moderate, and heavy drinkers in this study. The effect of alcohol on GERD might be different among these different types of beverage. It is therefore important to specify the type of alcohol beverage preferred among each drinking group, and determine the type of beverages actually associated with GERD risk.

Some studies suggested that smoking may represent a risk factor for GERD (52). Cigarette smoking is suggested to reduce LES pressure (53) and decrease salivary bicarbonate secretion, reducing the physiological neutralizing effect of saliva on intraesophageal acid, thereby prolonging acid clearance (54). Some studies have suggested that dietary fat intake reduces LES pressure and affects postprandial reflux. Since contributing factors for EE found in this study were evaluated by multivariate analysis after adjusting for various dietary habits, including high fat intake and high calorie intake, the impact of alcohol consumption and smoking habits on EE are considered independent of excessive dietary component intake. The present study also found that hypertension or sugar metabolism had a significant and independent association with the prevalence of EE. Our results showed that hypertension was a risk factor for EE. Calcium antagonists are used to treat hypertension, but these drugs decrease the lower LES pressure (55). However, we did not investigate drug therapy in these candidates. In Japan, calcium antagonists are widely used to treat hypertension, so antihypertensive therapy may impact our results. Concerning sugar metabolism, a recent Japanese study demonstrated that hyperglycemia was a significant risk factor of EE (56). The pathophysiological role of sugar metabolism in EE remains unclear, but profile in blood sugar might affect the antireflux barrier mechanism through modulation of transient LES relaxation.

The completeness of the clinical data and the large number of participants constitute the power of the present study. Nevertheless, our study has limitations. First, all participants in this study were voluntary attendees of a self-paid health check-up, and most were of a middle- and high-socioeconomic demographic. To study the prevalence of EE in the general population, one would have to define and enroll a random population sample. Second, GERD is a multifactorial disease in which anatomical and functional factors play a pathogenetic role (46, 47). Therefore, it would be important to further investigate other factors including the use of nonsteroidal anti-inflammatory drugs (57), nitrates, or calcium channel blockers, as well as esophageal/gastric motility. Third, there was an imbalance in gender among study participants, with men outnumbering women (ratio of 3 : 1). Fourth, we were not able to evaluate the detailed status of gastric mucosal atrophy in all cases. The present study showed that the presence of gastric mucosal atrophy caused by *H. pylori* infection was negatively correlated with erosive esophagitis (58). This may imply that suppression of gastric acid production caused by *H. pylori* infection has a negative impact on erosive esophagitis. Fifth, the design of this study was a cross-sectional study, so a prospective study may be needed to evaluate a true risk factor for erosive esophagitis.

In conclusion, our study showed that the prevalence of endoscopic EE in Japanese adults younger than 40 years was 14.6%. Risk of EE in this group was increased by alcohol or smoking habits, hypertension, hyperglycemia, and hiatal hernia. A longitudinal follow-up study in a large co-
hort may be needed to further evaluate the relationship between physical, physiological, or lifestyle factors and EE.

The authors state that they have no Conflict of Interest (COI).

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