Atrophic gastritis is associated with coronary artery disease

Takafumi Senmaru,1 Michiaki Fukui,1,* Muhei Tanaka,1 Masaaki Kuroda,2 Masahiro Yamazaki,1 Yohei Oda,3 Yuji Naito,4 Goji Hasegawa,1 Hitoshi Toda,5 Toshikazu Yoshikawa4 and Naoto Nakamura1

1Department of Endocrinology and Metabolism, 2Department of Immunology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan
2Department of Gastroenterology, Yamashiro Public Hospital, 74-1 Kizu, Kizugawa 619-0214, Japan
3Department of Internal Medicine, Oike Clinic, 11 Nishinokyoshimoai-cho, Nakagyo-ku, Kyoto 604-8436, Japan
4Department of Molecular Gastroenterology and Metabolism, 5Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

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Atrophic gastritis is characterized by chronic inflammation of gastric mucosa by Helicobacter pylori infection and other factors. Helicobacter pylori infection has been linked to coronary artery disease. To our knowledge, however, no reports are available on the relationship between atrophic gastritis and coronary artery disease. In this study, we investigated the relationship between atrophic gastritis, which is diagnosed based on serum pepsinogen levels (pepsinogen I ≤ 70 ng/mL and pepsinogen I/II ratio ≤ 3.0), and the prevalence of coronary artery disease in general Japanese population. Among 2,633 study subjects, 531 subjects (20.2%) were diagnosed as atrophic gastritis. The prevalence of coronary artery disease was higher in the atrophic gastritis-positive group than that in the atrophic gastritis-negative group (5.8% vs 2.8%, p = 0.0005). Multiple logistic regression analysis demonstrated that atrophic gastritis was independently associated with coronary artery disease (odds ratio, 1.67; 95% confidence interval, 1.03–2.72), after adjustment for age, sex, obesity, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, and habits of smoking and drinking. These results suggest that atrophic gastritis is an independent risk factor for coronary artery disease. Chronic inflammation of gastric mucosa may be associated with the prevalence of coronary artery disease.

Key Words: atrophic gastritis, pepsinogen, chronic inflammation, coronary artery disease

A trophic gastritis (AG) is a histopathologic entity characterized by chronic inflammation of the gastric mucosa with loss of gastric glandular cells and replacement by intestinal-type epithelium, pyloric-type glands, and fibrous tissue. Atrophy of the gastric mucosa is the endpoint of chronic processes, such as chronic gastritis associated with Helicobacter pylori (H. pylori) infection, other unidentified environmental factors, and autoimmunity directed against gastric glandular cells. Pepsinogen (PG) is precursors of pepsin, and consists of two biochemically and immunologically distinct types, namely, PG I and PG II. Serum PG levels are related to gastritis, gastric mucosal lesion, with a particular relationship to AG. Decreased serum PG I levels and the PG I/II ratio can be used to assess gastric atrophy.(1) Miki et al.(2) reported that the PG I/II ratio of more than 3 has a sensitivity of 93.3% and specificity of 87.7% for the diagnosis of normal fundic gland mucosa.

H. pylori infection is the most common cause of AG,(3) and at least 50% of the world’s population is infected with H. pylori.(4) H. pylori infection can lead to variety of upper gastrointestinal disorders, including peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. In addition, H. pylori infection has been linked to several extra-gastric disorders, such as atherosclerosis and coronary artery disease (CAD).(5,6) Some studies have shown a positive association between H. pylori infection and CAD,(7–9) while others have shown no significant association.(10–11) The results are still controversial. Recently, two studies have suggested that AG irrespective of H. pylori status was associated with atherosclerosis in general population.(12,13) To the best of our knowledge, however, no previous reports have investigated the effects of AG on the prevalence of CAD in general population. Therefore, we investigated the relationship between AG, which is diagnosed based on serum PG levels, and CAD in general Japanese individuals.

Materials and Methods

Study subjects. The “human dry dock”, is one of the most popular medical services in Japan, for the purpose of the medical health checkup promoting public health through early detection of chronic diseases and their risk factors. A standard human dry dock features amnesis and a survey of lifestyle, a physical examination, serum and urine examination, a chest X-ray, abdominal ultrasonography, and other tests. The fee is paid by participants or supported (fully or partially) by their employers or medical insurers. This study was designed to cross-sectionally evaluate the relationship between AG and CAD in Japanese population. The study included 1,758 male and 875 female subjects, aged 21–90 years, who attended the human dry dock of Oike clinic in Kyoto, Japan in 2009.

Study measurements. Medical history and lifestyle factors were obtained from a self-administered questionnaire completed by all the subjects, which included medication use, family history of diseases, and habits of smoking and drinking. In addition, all participants underwent physical examinations, routine biochemical screening tests obtained by venipuncture after an overnight fast. All participants gave their informed consent, and the study was approved by the ethics committee of Oike clinic.

Body mass index (BMI) was calculated as body weight in kilogram divided by the square of the participant’s height in meters. Systolic blood pressure and diastolic blood pressure were measured in the right upper arm of participants in a sedentary position using an automatic oscillometric blood pressure recorder. Obesity was defined as BMI ≥ 25 kg/m². Hypertension was defined as systolic blood pressure/diastolic blood pressure ≥ 140/90 mmHg or pharmacological treatment for hypertension. Diabetes

*To whom correspondence should be addressed. E-mail: sayarinapm@hotmail.com
mellitus was defined as fasting blood glucose ≥ 7.0 mmol/L or pharmacological treatment for diabetes mellitus. Dyslipidemia was defined as total cholesterol ≥ 5.7 mmol/L, triglyceride ≥ 1.7 mmol/L, or pharmacological treatment for hyperlipidemia. Hyperuricemia was defined as serum uric acid ≥ 416.3 μmol/L, or pharmacological treatment for hyperuricemia. Atrophic gastritis was defined as PG I ≤ 70 ng/mL and PG I/II ratio ≤ 3.0. Coronary artery disease was defined as a previous myocardial infarction based on the clinical history or electrocardiogram.

**Statistical analysis.** Means or frequencies of potential confounding variables were calculated. Triglyceride value was presented as median (interquartile range) due to skewed distribution, and other continuous variables were presented as mean ± standard deviation (SD). Unpaired Student’s t tests, Mann-Whitney’s U test, or χ² test were conducted as appropriate to assess statistical significance of differences between groups, using Stat View software (ver. 5.0; SAS Institute, Cary, NC). Multiple logistic regression analysis was performed to assess the combined effects of various factors on the prevalence of CAD. To examine the effects of various factors on the prevalence of CAD, the following factors were considered as independent variables: AG, age, sex, obesity, hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia, and habits of smoking and drinking. A p value <0.05 was considered statistically significant.

**Results**

Characteristics of the 2,633 subjects enrolled in this study are shown in Table 1. Among 2,633 study subjects, 531 subjects (20.2%) were diagnosed as AG. Mean age was significantly higher in the AG-positive group than that in the AG-negative group (64.5 ± 9.4 vs 56.2 ± 11.6 years, p<0.0001). Serum uric acid concentration was lower in AG-positive group than that in AG-negative group (327.1 ± 83.3 vs 345.0 ± 83.3 μmol/L, p<0.0001). Proportions of drinker were significantly fewer in the AG-positive group than that in the AG-negative group (64.5 ± 9.4 vs 82.1 ± 8.6%, p<0.0001). The prevalence of hyperuricemia was significantly lower in the AG-positive group than that in the AG-negative group (36.0% vs 40.9%, p<0.0001).

The prevalence of hyperuricemia was significantly lower in the AG-positive group than that in the AG-negative group (19.2% vs 25.0%, p = 0.0051). The prevalence of CAD was significantly higher in the AG-positive group than that in the AG-negative group (5.8% vs 2.8%, p = 0.0005) (Table 2).

Multiple logistic regression analysis demonstrated that age (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.04–1.09), hypertension (OR, 2.75; 95% CI, 1.67–4.53), habits of smoking (OR, 2.53; 95% CI, 1.54–4.15), and AG (OR, 1.67; 95% CI, 1.03–2.72) were significantly associated with CAD (Table 3).

**Discussion**

We have shown that AG determined by serum PG levels is significantly associated with CAD. This significant association remained unchanged even after adjustment for age, sex, obesity, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, and habits of smoking and drinking.

Atrophic gastritis represents the end stage of chronic inflammation of gastric mucosa, and H. pylori infection of the stomach is by far the most common cause of AG. H. pylori infection can eventually lead to loss of the normal gastric mucosal architecture, with destruction of gastric glands and replacement by fibrosis and intestinal-type epithelium. This process of AG and intestinal metaplasia are involved in the induction of an inflammatory response characterized by an influx of neutrophils, mononuclear cells, and T-helper 1 cells, typically aimed at clearing intracellular infections. However, H. pylori is not an intracellular pathogen,

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**Table 1. Characteristics of this study subjects**

| Characteristic                  | AG-positive | AG-negative | p value |
|--------------------------------|-------------|-------------|---------|
| Number                         | 531         | 2102        |         |
| Age (years)                    | 64.5 ± 9.4  | 56.2 ± 11.6 | <0.0001 |
| Sex (Male/Female)              | 339/192     | 141/685     | 0.1189  |
| Body mass index (kg/m²)        | 23.2 ± 3.2  | 23.4 ± 3.3  | 0.1894  |
| Systolic blood pressure (mmHg) | 126 ± 16    | 125 ± 16    | 0.1488  |
| Diastolic blood pressure (mmHg)| 78 ± 10     | 78 ± 11     | 0.8092  |
| Fasting plasma glucose (mmol/L)| 5.54 ± 1.09 | 5.58 ± 1.24 | 0.5155  |
| Total cholesterol (mmol/L)     | 5.36 ± 0.89 | 5.44 ± 0.91 | 0.0974  |
| Triglyceride (mmol/L)          | 1.11 (0.79–1.49) | 1.14 (0.81–1.66) | 0.2223  |
| HDL-cholesterol (mmol/L)       | 1.64 ± 0.44 | 1.66 ± 0.47 | 0.3153  |
| Uric acid (μmol/L)             | 327.1 ± 83.3| 345.0 ± 83.3| <0.0001 |
| Leukocyte (μl)                 | 5335 ± 1401 | 5390 ± 1588 | 0.3153  |
| Current smoking (–/+)          | 453/78      | 1645/457    | 0.4725  |
| Alcohol intake (–/+)           | 340/191     | 1243/859    | <0.0001 |

Data are number of patients, mean ± SD, or median (interquartile range). AG, atrophic gastritis; HDL, high-density lipoprotein.

**Table 2. Prevalence of obesity, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, and coronary artery disease in this study subjects**

| Characteristic               | AG-positive | AG-negative | p value |
|-----------------------------|-------------|-------------|---------|
| Obesity (%)                 | 25.6        | 28.7        | 0.1518  |
| Hypertension (%)            | 33.9        | 31.3        | 0.2566  |
| Diabetes mellitus (%)       | 10.4        | 10.7        | 0.8240  |
| Dyslipidemia (%)            | 55.0        | 55.8        | 0.7410  |
| Hyperuricemia (%)           | 19.2        | 25.0        | 0.0051  |
| Coronary artery disease (%) | 5.8         | 2.8         | 0.0005  |

AG, atrophic gastritis.

**Table 3. Multiple logistic regression analysis of risk factors associated with coronary artery disease in this study subjects**

| Risk factor | OR     | 95% CI   | p value |
|-------------|--------|----------|---------|
| Age         | 1.07   | 1.04–1.09| <0.0001 |
| Male sex    | 1.33   | 0.71–2.51| 0.3784  |
| Obesity     | 1.16   | 0.72–1.89| 0.5397  |
| Hypertension| 2.75   | 1.67–4.53| <0.0001 |
| Diabetes mellitus | 1.58 | 0.93–2.71 | 0.0942 |
| Dyslipidemia| 1.63   | 0.99–2.67| 0.0558  |
| Hyperuricemia| 0.99  | 0.59–1.65| 0.9626  |
| Current smoking | 2.53 | 1.54–4.15| 0.0002  |
| Drinking    | 1.24   | 0.76–2.05| 0.3913  |
| Atrophic gastritis | 1.67 | 1.03–2.72| 0.0383  |

OR, odds ratio; CI, confidence interval.
and thus the T-helper 1 response results in epithelial cell damage rather than in the removal of Helicobacter pylori. The ongoing infection with Helicobacter pylori thus causes a lifelong proinflammatory response coupled to cellular damage and initiates the cancer cascade. Epidemiologic studies have shown a positive association between Helicobacter pylori infection and CAD. The underlying hypothetical mechanisms include chronic low-grade activation of the coagulation cascade and atherosclerosis due to the vascular endothelial damage resembling the gastric epithelial damage through the induction of inflammatory response. On the other hand, several studies demonstrated that Helicobacter pylori infection was associated with atherogenic lipid profiles including increased serum triglyceride and total cholesterol concentrations, and decreased HDL cholesterol concentrations. However, some studies have shown no significant association between Helicobacter pylori infection and CAD. This issue is still controversial, thus further studies are needed to confirm the relationship between Helicobacter pylori infection and CAD.

The mechanism by which AG influences the prevalence of CAD is not clear. Torisu et al. reported that pulse wave velocity, which is an early preclinical marker of atherosclerosis, was significantly higher in healthy subjects with AG diagnosed by serum PG test method than in those without AG. They reported that serum ghrelin levels which might be protective against atherosclerosis, were significantly lower in AG-positive subjects than in AG-negative subjects. Kutluana et al. reported that AG diagnosed by histologic method might cause hyperhomocysteinaemia, which is an independent risk factor for atherosclerosis, in general population. In their report, carotid intima-media thickness in subjects with AG was found to be thicker than that in controls, although it did not reach statistically significant levels. Those two reports have suggested that AG irrespective of Helicobacter pylori status was associated with atherosclerosis. Our study based on a large number of subjects suggested that AG was an independent risk factor for CAD. Taken together these findings, it seems plausible that AG influences the development of atherosclerotic changes in coronary arteries.

Our study has several limitations. First, this study was cross-sectionally designed, but not prospectively. Second, it was not clear which extent of AG was related to Helicobacter pylori infection, because the serum immunoglobulin G antibody to Helicobacter pylori was not measured. Subjects with autoimmune gastritis and Helicobacter pylori-induced gastritis were included in AG-positive group. However, the prevalence of autoimmune gastritis is low in Japan, therefore the relationship between AG and CAD could be regarded as the relationship between Helicobacter pylori-induced AG and CAD. Third, we did not measure proinflammatory cytokines such as C-reactive protein, tumor necrosis factor-alpha, and interleukin-6, although they might not be markedly increased in the end stage of chronic inflammation. Finally, we did not measure homocysteine, ghrelin, and others, each of which has been reported to be related to atherosclerosis.

In conclusion, our study suggests that AG is an independent risk factor for CAD. Chronic inflammation of gastric mucosa may be associated with the prevalence of CAD.

Acknowledgments

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Abbreviations

AG atrophic gastritis
BMI body mass index
CAD coronary artery disease
CI confidence interval
HDL high-density lipoprotein
OR odds ratio
PG pepsinogen

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