Original Article

Atrophic gastritis is associated with coronary artery disease

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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**

Atrophic 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,[6–8] while others have shown no significant association.[9–11] 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 anamnesis 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 $\geq$ 25 kg/m^2. Hypertension was defined as systolic blood pressure/diastolic blood pressure $\geq$ 140/90 mmHg or pharmacological treatment for hypertension. Diabetes

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Table 1. Characteristics of this study subjects

	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/m^2)	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 ± 1409	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.

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 χ^2 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 influence of variables 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 those 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).

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

	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.

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, hyperuricemis, 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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and thus the T-helper 1 response results in epithelial cell damage rather than in the removal of *H. pylori*. The ongoing infection with *H. pylori* thus causes a lifelong proinflammatory response coupled to cellular damage and initiates the cancer cascade.[14] Epidemiologic studies have shown a positive association between *H. pylori* infection and CAD.[6–8] The underlying hypothetical mechanisms include chronic low-grade activation of the coagulation cascade and accelerating atherosclerosis due to the vascular endothelial damage resembling the gastric epithelial damage through the induction of inflammatory response.[15,16] On the other hand, several studies demonstrated that *H. pylori* infection was associated with atherogenic lipid profiles including increased serum triglyceride and total cholesterol concentrations,[17] and decreased HDL cholesterol concentrations.[18] However, some studies have shown no significant association between *H. pylori* infection and CAD.[9–11] This issue is still controversial, thus further studies are needed to confirm the relationship between *H. pylori* infection and CAD.

The mechanism by which AG influences the prevalence of CAD is not clear. Torisu *et al*.[13] 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,[19–22] were significantly lower in AG-positive subjects than in AG-negative subjects. Kutluana *et al*.[12] reported that AG diagnosed by histologic method might cause hyperhomocysteinemia, 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 *H. 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 *H. pylori* infection, because the serum immunoglobulin G antibody to *H. pylori* was not measured. Subjects with autoimmune gastritis and *H. 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 *H. 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.

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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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