Prevalence of Helicobacter Pylori Infection and Its Link to Coronary Risk Factors in Japanese Patients With Acute Myocardial Infarction

Kunihiro Kinjo, MD; Hiroshi Sato, MD; Hideyuki Sato, MD; Issei Shiotani, MD; Toshiya Kurotobi, MD⁎; Yozo Ohnishi, MD†; Eiji Hishida, MD; Daisaku Nakatani, MD; Hiroya Mizuno, MD; Tatsuya Sasaki, MD‡; Akio Kohama, MD§; Yukichi Abe, MD‡‡; Hisaki Morita, MD; Mitsuaki Kubo, MD⁎⁎; Hiroshi Takeda, MD; Masatsugu Hori, MD; on Behalf of The Osaka Acute Coronary Insufficiency Study (OACIS) Group

The association between Helicobacter pylori (H. pylori) infection and coronary artery disease, as well as the association between H. pylori infection and classic coronary risk factors, is controversial in patients from Western countries. The high prevalence of H. pylori infection in Japanese subjects enables an examination of these associations in a large population, especially in young patients, because coronary risk factors may be more strongly associated with younger individuals than with older individuals. The IgG seropositivity to H. pylori was assessed in 618 cases with acute myocardial infarction (AMI) and in 967 controls. The prevalence of seropositivity to H. pylori was similar between cases and controls, but in subjects younger than 55 years, the rate was significantly higher in cases than in controls (58.7% vs 43.3%, p=0.009). After adjustment for age, gender, diabetes mellitus, hypertension, smoking, body mass index, total cholesterol, and high density lipoprotein cholesterol, the odds ratio for acute myocardial infarction was 2.97 (95% confidence interval, 1.37–6.41; p=0.006). Worsening of classic coronary risk factors was not associated with H. pylori infection in subjects younger than 55 years. These results suggest that in younger individuals in Japan, H. pylori infection is significantly associated with AMI independent of the classic coronary risk factors. (Circ J 2002; 66: 805–810)

Key Words: Acute myocardial infarction; Helicobacter pylori; Japanese; Risk factors

Although several classic risk factors for the development of coronary artery disease have been identified (ie hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, marked obesity, and inactivity), they only explain half of all patients with coronary artery disease (CAD). In an effort to better identify patients with CAD, several markers of risk, including infectious agents, have been proposed for screening programs. Seroepidemiologic studies have shown an association between previous infection with Helicobacter pylori (H. pylori) and CAD, as well as increased risk for developing acute coronary events but other studies have not demonstrated such an association.

The role of infection in the pathogenesis of atherosclerosis is still a matter of debate and the underlying processes responsible for any association also remain unclear. Potential causative mechanisms that may play either an acute (ie precipitating plaque rupture) or chronic (ie promoting plaque growth) role have been proposed to explain the reported associations between infections and CAD. Some of these involve direct effects of H. pylori on the arterial wall, including smooth muscle cell proliferation, lipid accumulation, endothelial dysfunction, and local inflammation but most are indirect effects mediated in the circulation through chronic inflammation cross-reactive antibodies or alterations in the classic coronary risk factors (ie diabetes mellitus (DM)) hypertension (HT) body mass index (BMI) and lipid metabolism). However, correlations between H. pylori infection and coronary risk factors remain controversial.

Because the prevalence of H. pylori infection is much higher in the Japanese population than in Western countries, an examination of the association between H. pylori infection and CAD may have more practical value in Japan, as is the case with the association between H. pylori infection and gastric cancer. A registry of patients with acute myocardial infarction (AMI) in the Osaka area provided a unique opportunity to perform a stratified analysis of the association between AMI in Japanese patients and seroepidemiologic data. Because the association of coronary risk factors with CAD tends to be stronger in younger individuals than in older individuals, we performed subgroup analysis based on age. Furthermore, we examined the association between H. pylori infection and changes in the classic coronary risk factors.
Methods

Case and Control Subjects

Cases and controls were recruited between April 1999 and March 2000. The case subjects were 618 patients with AMI who had been enrolled in the Osaka Acute Coronary Insufficiency Study (OACIS; a detailed description of this study has been published elsewhere). Briefly, we conducted a prospective, multicenter observational study in which 25 collaborating hospitals in the Osaka area recorded demographic, procedural and outcome data on patients with AMI, beginning in April 1998. The diagnosis of acute myocardial infarction required the presence of 2 of 3 criteria: (1) a clinical history of central chest pressure, pain, or tightness lasting for 30 min or more, (2) ST segment elevation greater than 0.1 mV in at least 1 limb or 2 precordial leads, and (3) an increase in the serum creatine kinase concentration to greater than twice the normal laboratory value. All patients presenting within 1 week of the onset of infarction were registered prospectively. Research cardiologists and specialized research nurses recorded sociodemographic variables, medical history, therapeutic procedures and clinical events during the patient’s stay in the hospital. Information was obtained from hospital medical records, by direct interview with the patient, the family, and the treating physician. After written informed consent for entering the OACIS study was obtained from patients, all in-hospital data were transmitted to the OACIS office located in the Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine.

Control subjects included individuals undergoing medical examination in collaborating hospitals who were representative of the general population. All control subjects completed a standard questionnaire conducted by a trained interviewer on sociodemographic variables, medical history, current medications, and smoking habit. We enrolled 967 consecutive individuals who did not have a history of definite or suspected coronary heart disease and did not report infections or surgery within the previous 4 weeks. Written informed consented was obtained from all control subjects.

This study was approved by the ethics committee of the Osaka University.

Laboratory Methods

Cases and controls provided venous blood samples that were centrifuged and the serum then stored at –80°C until analysis. We measured IgG antibody to the high molecular weight cell-associated proteins of H. pylori using an (enzyme-linked immunosorbent assay ELISA) (HM-CAP, Kyowa Medex, Tokyo, Japan). The manufacturer’s recommended cut-off point is 2.3 ELISA units, which provides a sensitivity and specificity of ≥95%.

Measurements of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) concentrations were performed in the laboratory of each collaborating institution by routine enzymatic methods. All laboratory analyses were done in a blinded fashion.

Definition of Coronary Risk Factors

Obesity was defined as a body mass index ≥25 kg/m²; DM was defined as a fasting plasma glucose ≥126 mg/dl, or the use of antidiabetic therapy; HT was defined as a documented previous systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or the use of antihypertensive therapy; smoking was defined as currently or previously smoking.

Statistical Analysis

To investigate the association between H. pylori infec-

![Graph](image-url)
tion and AMI in younger individuals, we defined younger individuals as patients with an age below the 20th percentile cut-off point. Continuous variables were compared by t test and categorical variables by chi-square test. We compared the prevalence of seropositivity among age groups using a chi-square test. The odds ratio (OR) and 95% confidence intervals (95%CI) assessing the risk of onset of AMI associated with H. pylori infection were estimated by use of multivariate logistic regression analysis, adjusted for age, gender, DM, HT, smoking, BMI, TC, and HDL-C. For all analyses, significance was defined as p<0.05.

**Results**

**Characteristics of the Study Population (Table 1)**

As expected, cases were older, had a higher prevalence of DM, HT and smoking, had a higher BMI and lower HDL-C concentrations than controls. However, the TC concentrations were similar between cases and controls.

**Seropositivity to H. pylori IgG Antibody**

Fig 1 shows the prevalence of seropositivity to H. pylori IgG antibody based on age in the cases and controls. In controls, the prevalence significantly increased with age, from 29.2%, 46.2%, 60.4%, 62.6%, to 80.0% in subjects <44 years, 45–54 years, 55–64 years, 65–74 years, and 75–84 years, respectively. However, in cases, the prevalence showed a random distribution among the age groups: 54.2%, 61.1%, 63.7%, 55.8%, 60.0%, and 70.0%, respectively, in those <44 years, 45–54 years, 55–64 years, 65–74 years, and >84 years.

**H. pylori Infection and AMI**

Overall, the prevalence of seropositivity to H. pylori was not significantly different between cases and controls (60.0% vs 57.7%, p=0.359; Table 2). In subjects aged 55–64 years, ≥65 years, and in both sexes, the prevalence of seropositivity did not differ between cases and controls, but in subjects <55 years, the prevalence of seropositivity to H. pylori was significantly higher in cases than in controls (58.7% vs 43.3%, p=0.009; Table 3). Table 2 also shows the results of multivariate logistic regression analysis in which the association between H. pylori infection and AMI was adjusted for age, gender, and the other potential confounding factors (ie DM, HT, smoking, BMI, TC and HDL-C). IgG seropositivity to H. pylori was not associated with AMI by the fully adjusted model (OR 0.97; 95%CI 0.71–1.32; p=0.836). Subgroup analysis revealed that in
subjects aged 55–64 years, ≥65 years, and in both sexes, IgG seropositivity to H. pylori was not associated with AMI, but in subjects <55 years, it was significantly associated by the fully adjusted model (OR 2.97; 95% CI 1.37–6.41; p=0.006). These results suggest that the association between H. pylori infection and AMI is stronger in younger individuals than in older individuals in Japan.

**Comparison of Demographic and Classic Coronary Risk Factors by H. pylori Seropositivity in Cases and Controls**

Table 3 compares the demographic and classic coronary risk factors in cases and controls based on H. pylori seropositivity. In younger subjects, there was no significant association between H. pylori seropositivity and any of the classic coronary risk factors in either group. However, in cases aged <55 years, H. pylori IgG seropositive subjects had a significantly lower prevalence of DM and a lower BMI and TC concentration. In controls aged <55 years, H. pylori IgG seropositive subjects also had a significantly lower prevalence of DM. Therefore, in both the total study group and in subjects aged <55 years, H. pylori seropositive subjects did not have more coronary risk factors than H. pylori seronegative subjects, which suggests that indirect effects of H. pylori infection on the onset of AMI through alteration of classic coronary risk factors are minimally involved in the Japanese population.

**Discussion**

The present case–control study, which comprised 1,585 Japanese individuals, has 2 important findings. First, IgG seropositivity to H. pylori was not associated with AMI in the overall group, but the fully adjusted model found an association in younger individuals (<55 years). Second, we found no detrimental effects of H. pylori infection on the classic coronary risk factors (ie DM, HT, BMI and lipid metabolism).

It was important that the controls in our study were representative of the current Japanese population with respect to the prevalence of seropositivity to H. pylori. A recent large study consisting of 5,732 Japanese individuals showed that the overall prevalence of seropositivity to H. pylori was 47.0%.24 However, we found an overall prevalence of seropositivity to H. pylori of 57.7% in the controls. Because the present controls were older than the subjects in the previous study, it is reasonable to expect a higher overall prevalence of seropositivity to H. pylori in our study. Indeed, the age distribution of the prevalence to H. pylori in our controls was consistent with the distribution in the previous study, which demonstrated that the prevalence to H. pylori increased from 30% in the 40s to 60% in the 60s. Therefore, our controls can be considered representative.

Although it has been reported that the prevalence of H. pylori infection was much higher in Japan than in Western countries in the early 1990s19 that prevalence may have decreased with the Westernization of Japan.25 Recent large sample surveys in Western countries have shown that the prevalence of H. pylori infection is 15–43%.26–29 but our study results confirm a higher prevalence in Japan.

The evidence for a causal relationship between H. pylori infection and CAD is controversial.2–7 In the present study, IgG seropositivity to H. pylori was not associated with the incidence of AMI in the total study group, but was significantly associated in younger individuals by the fully adjusted model. Finding that the association of the risk of AMI with IgG seropositivity is age-dependent is not entirely unexpected because the association of most coronary risk factors with CAD tends to be stronger in younger than older individuals.30,31 Indeed, our finding is consistent with a previous study showing that the risk of myocardial infarction is about twice as great in young patients seropositive for antibodies to H. pylori.2 Therefore, the association between H. pylori infection and AMI is also likely to be stronger in younger individuals than in older individuals in Japan. To demonstrate a causal relationship between H. pylori infection and AMI in younger individuals, further prospective studies and antibiotic treatment studies are needed.

Previous studies have shown an association between previous infection with Chlamydia pneumoniae32,33 or H. pylori2–7 and the presence of CAD or the risk for an acute coronary event. However, the underlying processes responsible for the association between infectious agents and atherosclerotic diseases remain unclear. Various potential mechanisms that may act through direct effects, including smooth muscle cell proliferation, lipid accumulation, endothelial dysfunction, and local inflammation4 or indirect effects mediated in the circulation through chronic inflammation9 cross-reactive antibodies,10 or alterations of the classic coronary risk factors (ie DM11 HT12,13 BMI14 and lipid metabolism15–17) have been proposed, so we also examined the association between H. pylori infection and changes in the classic coronary risk factors. We did not find any detrimental effect of H. pylori infection on the classic coronary risk factors in Japanese individuals, which is consistent with a meta-analysis of 18 studies that involved 10,000 people and which also did not find a strong correlation between H. pylori seropositivity and coronary risk factors.18 That meta-analysis suggests that the existence of such correlations reported in previous smaller studies were largely or wholly the result of chance or to the preferential publication of positive results.

The underlying processes that might explain the lack of a detrimental effect of H. pylori infection on the classic coronary risk factors in Japanese patients are unclear. Hishiki et al studied the effect of eradication of H. pylori on coronary risk factors in patients with peptic ulcer disease34 Patients in whom H. pylori was eradicated showed significant increases in their BMI and TC concentration during the first and second years after eradication, and the authors hypothesized that the recovery of appetite through the improvement of dyspepsia may exaggerate the metabolic syndrome. Because Japanese individuals with seropositivity to H. pylori frequently have atrophic gastritis35 the effects of H. pylori infection on the metabolic syndrome may be attenuated.

A causal role for H. pylori infection in the pathogenesis of AMI could not be confirmed in this study. In subjects aged <55 years there was no detrimental effect of H. pylori infection on coronary risk factors, but by the fully adjusted model IgG seropositivity to H. pylori was significantly associated with the onset of AMI. Therefore, direct effects and/or indirect effects may be important causative factors. First, it has been suggested that chronic direct infection of arteries with H. pylori contributes to the development of atherosclerosis36,37 H. pylori has been detected not only in gastric mucosa but also in human atherosclerotic plaques36,37 and the expression of intercellular adhesion molecule-1 is higher in plaques containing H. pylori than in
those which do not. Therefore, local vessel inflammation caused by the presence of H. pylori in plaques may be associated with the development of atherosclerosis.

Second, it has been suggested that H. pylori increases the risk of myocardial infarction through the promotion of an enhanced systemic inflammatory response. H. pylori seropositivity is associated with increased concentrations of systemic markers of inflammation (ie fibrinogen and C-reactive protein) and inflammatory cytokines (ie IL-6 and tumor necrosis factor). Systemic markers of inflammation are associated with the onset of myocardial infarction and inflammatory cytokines are believed to activate or injure vascular smooth muscle cells and endothelial cells. Therefore, systemic inflammation from H. pylori infection may be associated with the development of atherosclerosis. Recent studies have shown that the H. pylori cytotoxin-associated gene product A (Cag A) is a marker of enhanced virulence and increased inflammatory response, and is more commonly found in strains of H. pylori causing more severe gastritis, peptic ulcer disease, and gastric cancer.

Most of the H. pylori strains in Japan possess Cag A and therefore the local and systemic inflammatory responses to H. pylori infection may be enhanced in Japanese patients. If that is the case, the association between H. pylori infection and AMI may have practical value for young Japanese individuals and further studies are needed to determine the effects of H. pylori infection on the onset of AMI.

Study Limitations
Our study has several limitations common to case–control studies. In particular, we cannot exclude the possibility that unrecognized population stratification of relevant factors influenced the findings. Specifically, socioeconomic status is known to affect both the prevalence of H. pylori infection and the risk of CAD. Although our controls were recruited from individuals undergoing medical examination, information concerning socioeconomic status was not obtained. However, it has been reported that occupational or educational level is not associated with H. pylori infection in Japan, probably because of the homogeneous population. Therefore, we believe that the effect of socioeconomic status on the association between H. pylori infection and the onset of acute myocardial infarction was negligible in our study population.

Because the present study examined IgG antibody to H. pylori, which can reflect a previous infection, IgG seropositivity to H. pylori may not reflect an active infection. However, IgG antibody to the high molecular weight cell-associated proteins of H. pylori detected by ELISA correlates well with the presence of active infection when compared with the results of urea breath testing using 13C-labeled urea or histological examination of the gastric mucosa. Urea breath testing has been shown to reliably detect active H. pylori infection, but the cost, time involved in testing, and the risk of exposure to radioactive materials make this method less practical for routine clinical use. Many studies of the epidemiology of infectious diseases have relied on serologic assays to detect the presence of antibodies to antigens contained in the infecting organism and we believe that detection of IgG antibody using an ELISA should be the method of choice for screening large populations.

Another limitation is that this study does not provide direct mechanistic information concerning the role of H. pylori infection in CAD, so the association of IgG seropositivity to H. pylori and the risk of AMI needs to be confirmed in further prospective studies, and in antibiotic treatment studies, especially in younger individuals.

Conclusion
This study shows that IgG seropositivity to H. pylori is significantly associated with AMI in younger individuals in Japan and therefore measuring IgG antibody to H. pylori may have a practical value in identifying high-risk individuals for AMI.

Acknowledgments
We thank Kumiko Miyoshi, Chizuru Hamaguchi, Hiroko Machida, Mariko Yoneda, Ayako Okamoto, and Kana Sakatani for their excellent assistance with data collection.

This work was supported by a Grant-in-Aid for University and Society Collaboration (#11794035) from the Ministry of Education, Culture, Sports, Science, and Technology.

References
16. Laurila A, Bloigu A, Nayha S, Hassi J, Leinonen M, Saikku P.


