Helicobacter pylori Infection and High-density Lipoprotein Cholesterol in Japanese Women: the JMS Cohort Study

Reiko Yamamoto, MD\textsuperscript{1) } Shizukiyo Ishikawa, MD, PhD\textsuperscript{1) }
Masafumi Mizooka, MD, PhD\textsuperscript{2) } Eiji Kajii, MD, PhD\textsuperscript{1) }
and the Jichi Medical School (JMS) Cohort Study

\textsuperscript{1)} Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University, Shimotsuke, Tochigi, Japan
\textsuperscript{2)} Department of General Medicine, Hiroshima University Hospital, Hiroshima, Japan

Background: \textit{Helicobacter pylori} (\textit{H. pylori}) infection has been reported to be associated with cardiovascular risk factors by inducing chronic low-grade inflammation and by influencing endocrine and metabolic systems, as well as the immunological response evoked by the host. This study investigated the association between \textit{H. pylori} infection and high-density lipoprotein cholesterol (HDL-C) in Japanese subjects.

Methods: The study subjects were 2,632 (1,061 men and 1,571 women) living in rural areas in Japan. We checked \textit{H. pylori} serum immunoglobulin G (IgG), HDL-C and other cardiovascular risk factors in 1999.

Results: The overall prevalence of \textit{H. pylori} seropositivity was 53.5% and increased with age. The prevalence was higher among men (58.3%) than women (50.3%). \textit{H. pylori} seropositive women were more associated with decreased HDL-C than seronegative subjects (58.1±13.6 vs. 60.5±14.7, \textit{p}<0.01). Multiple linear regression analysis with \textit{H. pylori} seropositivity, age, body mass index (BMI), fibrinogen, blood glucose, and smoking and alcohol habits demonstrated that \textit{H. pylori} seropositivity was a significant predictor of decreased HDL-C in women. In addition, there was a linear decrease in HDL-C with increments in the value of \textit{H. pylori} antibody titer as a continuous variable in women. This association remained in \textit{H. pylori} seropositive women aged ≥50 years. Moreover, \textit{H. pylori} seropositive women with BMI <22 were associated with decreased HDL-C, whereas the association was not significant in women with BMI ≥22.

Conclusions: We show that \textit{H. pylori} seropositivity is associated with decreased HDL-C, especially in women with a lower BMI in rural areas of Japan.

Key words: cohort studies, \textit{Helicobacter pylori}, cardiovascular risk factors

Author for correspondence: Shizukiyo Ishikawa MD, PhD
Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University
3311-1, Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan
E-mail: i-shizu@jichi.ac.jp
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INTRODUCTION

*H. pylori* infection is well known to be associated with chronic gastritis, peptic ulcers, and gastric cancer. Recently, associations with extragastric manifestations have been reported.\(^1,2\) *H. pylori* infection may cause gastric mucosal damage and, at the same time, elude the immunological response evoked by the host. The immunological response is not only locally-oriented but also systemic and may cause local damage, as well as influence the clinical course of other diseases beyond the stomach. For example, since *H. pylori* infection is probably associated with idiopathic thrombocytopenic purpura (ITP),\(^3\) eradication therapy for ITP started in 2009\(^4\) after eradication therapy for peptic ulcers started in 2000 in Japan.\(^2\)

Associations between *H. pylori* infection and cardiovascular risk factors\(^6,7\) such as hyperlipidemia,\(^8-11\) obesity,\(^12,13\) atherosclerosis,\(^14-16\) either type 1\(^17\) or 2\(^18\) diabetes mellitus and hypertension\(^10,19,20\) have been suggested by both observational and interventional studies. Notably, the inverse associations between *H. pylori* seropositivity and high density lipoprotein cholesterol (HDL-C) have been reported in some articles.\(^7,8,10,14,21,22\) Moreover, *H. pylori* expressing cytotoxin–associated gene A (CagA), a more virulent *H. pylori* strain that is widespread in Japan,\(^23\) has been indicated to show a strong association with cardiovascular disease.\(^24\) However, these hypotheses are still controversial.

The concentration of HDL-C is inversely correlated with the risk of cardiovascular disease.\(^25,26\) In Japan, the concentration of HDL-C has been found to be higher and the prevalence of cardiovascular disease much lower\(^27\) than in Western countries, but the association between HDL-C level and the incidence of cardiovascular disease is greatly affected by the serum total cholesterol and triglyceride levels in Japanese.\(^28\) Moreover, obesity is also a cardiovascular risk factor and the definition of obesity in Japan (body mass index (BMI)> 25 kg/m\(^2\)) is different from that of Western countries (BMI>30 kg/m\(^2\)).\(^29\)

The prevalence of *H. pylori* infection is much higher in the Japanese population than in Western countries.\(^30\) An examination of the association between *H. pylori* and cardiovascular disease and cardiovascular risk factors may have more practical value in Japan, as is the case with the association between *H. pylori* infection and gastric cancer. In this study, we show the association between *H. pylori* seropositivity and other cardiovascular risk factors, especially HDL-C and BMI, respectively by sex.

METHODS

Study Population

In 1999 we performed a large-scale cross-sectional survey in Japan as part of the Jichi Medical School (JMS) Cohort Study, which was a mass-screening examination to investigate cardiovascular risk factors.\(^31,32\) The subjects were invited to undergo a health check and agreed to participate in the study. All 2,632 subjects were healthy residents of 2 towns (Wara in Gifu Prefecture, Akaike in Fukuoka), 3 villages (Takasu and Kuze in Gifu, Sakuki in Hiroshima) and 1 island (Aino-shima in Fukuoka).

We obtained information using a standardized collection method detailed elsewhere.\(^31\)

BMI was calculated as weight (kg)/height (m\(^2\)). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a fully automated sphygmomanometer (BP203RV-Ⅱ, Nippon Colin, Komaki, Japan) placed on the right arm of subjects, who had been in a sitting position for 5 minutes before measurement. Smoking habits and alcohol consumption were assessed by a questionnaire developed by the committee. The smoking status was categorized as active-smoker or not. A drinker was defined as a person who regularly consumed alcohol more than 3 days a week. Drinking status was categorized as drinker or not.

Data Collection

We obtained blood samples before noon after an overnight fast. Blood samples were drawn from the antecubital vein of a seated subject with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing 1/10 volume of 3.8% trisodium citrate (fibrinogen), sodium fluoride (blood glucose (BG)) or no additives (lipids). The tubes were centrifuged at 3,000 × g for 15 minutes at room temperature. After separation, the serum and plasma samples were stored at 4°C in refrigerated...
containers and analysis was performed within a few days. The serum IgG antibody to \( H. \text{pylori} \) was measured by enzyme linked immunosorbent assay (ELISA) (HM-CAP, Enteric Products, INC, (EPI), USA). IgG to \( H. \text{pylori} \) \( \geq \) 2.3 was considered positive, 1.8 to 2.2 as pseudopositive and <1.8 as negative; therefore, we designated results of \( \geq \) 2.3 as positive and <2.3 as negative. Fibrinogen levels were determined with a one-stage clotting assay kit (Data-Fi, Dade, Miami, FL, USA; inter-assay coefficient of variation (CV) : 2.5%). Total cholesterol was measured by an enzymatic method (Wako, Osaka, Japan; inter-assay CV: 1.5%). HDL-C was measured using a homogeneous assay kit (Cholestest HDL, Daichi Pure Chemical, Co., Ltd, Tokyo, Japan). BG was measured by an enzymatic method (Kanto Chemistry, Tokyo, Japan; inter-assay CV: 1.9%). Blood variables were measured at the central laboratory of the Special References Laboratory (SRL, Tokyo, Japan).

The present study was approved by the institutional review board as the central committee of the JMS Cohort Study. The study participants gave their informed consent at entry. All procedures were performed in accordance with the guidelines of the institutional committee.

**Statistical analysis**

All data were reported as mean \( \pm \) standard deviation, or where indicated, median (interquartile range) and percentages. Values in two groups according to \( H. \text{pylori} \) status were compared by unpaired t-test for consecutive valuables and the chi-squared test or Fisher exact test for categorical data. To identify the association between \( H. \text{pylori} \) status and HDL-C levels we conducted multiple linear regression analysis by sex because our colleagues reported previously that the prevalence of \( H. \text{pylori} \) was higher among men than women.\(^{25}\) The model included known risk factors (age, BMI, fibrinogen, BG, and smoking and alcohol habits). Next, we categorized the subjects into two age groups (\( \geq \)50 years and <50 years, because our colleagues reported previously that the prevalence of \( H. \text{pylori} \) increased under the age of 50 and reached a plateau at 50 years\(^{35}\)). We further conducted the same analyses to assess a linear association between \( H. \text{pylori} \) antibody value and HDL-C levels. In order to investigate the interaction between \( H. \text{pylori} \) status and BMI on HDL-C levels, the subjects were divided into four categories (Group A: \( H. \text{pylori} \) negative (HP (−)) and BMI <22; Group B: \( H. \text{pylori} \) positive (HP (+)) and BMI <22; Group C: HP (−) and BMI \( \geq \)22; and, Group D: HP (+) and BMI \( \geq \)22). Differences in HDL-C levels among these groups were assessed by post hoc multiple comparisons testing using the Bonferroni method following one-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA). The covariates considered in the analyses were age, fibrinogen, BG, and smoking and alcohol habits. A P value of less than 0.05 was considered significant. All statistical analysis were performed using SPSS 19.0 J for Windows (SPSS Inc., Tokyo, Japan).

**RESULTS**

The characteristics of \( H. \text{pylori} \) seropositive and seronegative subjects are shown in Table 1. A total of 1,061 men and 1,571 women participated in these mass screening examinations. The prevalence of \( H. \text{pylori} \) among men (58.3%) was significantly higher than that among women (50.2%); \( H. \text{pylori} \) seropositive women were more associated with decreased HDL-C than seronegative subjects (58.1±13.6 vs. 60.5±14.7, P<0.01); and, \( H. \text{pylori} \) seropositivity was associated with age in both sexes and HDL-C and fibrinogen in women.

Multiple linear regression analysis of \( H. \text{pylori} \) seropositivity, age, BMI, fibrinogen, BG, and smoking and alcohol habits demonstrated that \( H. \text{pylori} \) seropositivity was a significant predictor of decreased HDL-C in women (Table 2). This association remained in women aged \( \geq \)50 years. In addition, there was a linear decrease in HDL-C with increments in the value of \( H. \text{pylori} \) antibody as a continuous variable in women (Table 3). This association remained in women aged \( \geq \)50 years.

To investigate the interaction between \( H. \text{pylori} \) status and BMI on HDL-C levels, the subjects were divided into four categories (Table 4). In men with neither lower (BMI <22) or higher (BMI \( \geq \)22) BMI, \( H. \text{pylori} \) seropositivity was associated with HDL-C. In women, \( H. \text{pylori} \) seropositive subjects with BMI
were associated with decreased HDL-C, whereas the association was not significant in women with BMI ≥ 22. These differences remained after adjustment for age, BG, fibrinogen, and smoking and alcohol habits (Group A: 62.4 ± 1.0 (mean ± standard error) mg/dL; Group B: 58.3 ± 0.9 mg/dL; Group C: 58.8 ± 0.8; Group D: 57.7 ± 0.8 mg/dL; Group A vs. Group B, P = 0.002; Group C vs. Group D, P = 1.000) (Fig. 1).

**DISCUSSION**
In the present study we made two major findings regarding the association between *H. pylori* and HDL-C. First, *H. pylori* seropositivity is associated with decreased HDL-C in women. Moreover, there was a
linear increase in HDL-C with increments in the \textit{Helicobacter pylori} antibody titer as a continuous variable in women. This association remained in women aged $\geq 50$ years. Second, in women with lower BMI (BMI < 22), \textit{Helicobacter pylori} seropositivity was more closely associated with decreased HDL-C than seronegatives, whereas there was no difference in women with higher BMI (BMI $\geq 22$).

\textit{Helicobacter pylori} infection has been reported to be associated with extragastric manifestations, especially serum lipid profile. Some previous reports showed an association between \textit{Helicobacter pylori} seropositivity and decreased HDL-C \cite{7, 8, 10, 14, 21, 22} and our study results proved similar. The role of \textit{Helicobacter pylori} infection in HDL-C levels is still a matter of debate and the underlying process responsible for any association also remains unclear. Polyzos et al. postulated that chronic \textit{Helicobacter pylori} infection may shift the lipid profile toward an atherogenic direction via the action of pro-inflammatory cytokines. These cytokine are capable of affecting the lipid metabolism.\cite{34}

Also, the role of \textit{Helicobacter pylori} IgG antibody titer in the pathogenesis of atherosclerosis has not yet been clarified. Franceschi et al. reported that \textit{Helicobacter pylori} anti-

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**Table 2. Multiple linear regression analysis of HDL-C and \textit{Helicobacter pylori} seropositivity plus conventional risk factors* by sex and age**

<table>
<thead>
<tr>
<th>Determinants</th>
<th>men (n = 837)</th>
<th>women (n = 1308)</th>
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<tbody>
<tr>
<td></td>
<td>Standardized coefficient</td>
<td>P value</td>
</tr>
<tr>
<td>all*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textit{Helicobacter pylori} seropositivity</td>
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<td>age</td>
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<td>blood glucose</td>
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</tr>
<tr>
<td>smoking</td>
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<tr>
<td>alcohol</td>
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<th>age $\geq 50$'</th>
<th>men (n = 692)</th>
<th>women (n = 1048)</th>
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</thead>
<tbody>
<tr>
<td>\textit{Helicobacter pylori} seropositivity</td>
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<td>0.29</td>
</tr>
<tr>
<td>BMI</td>
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<td>&lt;0.001</td>
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<tr>
<td>fibrinogen</td>
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<td>&lt;0.001</td>
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<td>blood glucose</td>
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<td>smoking</td>
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<td>alcohol</td>
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<th>women (n = 260)</th>
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<td>BMI</td>
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<tr>
<td>alcohol</td>
<td>0.24</td>
<td>&lt;0.01</td>
</tr>
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</table>

* age, body mass index, fibrinogen, blood glucose, and smoking and alcohol habits

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\textit{Helicobacter pylori}: \textit{Helicobacter pylori}. HDL-C: high density lipoprotein cholesterol.
CagA antibodies cross-react with antigens of both normal and atherosclerotic blood vessels. They speculated that anti-CagA antibodies could bind the exposed vascular antigens and further contribute to the activation of inflammatory cells within lesions. Production of cytokines and other inflammatory mediators by activated macrophages and fibroblasts could then lead to the destabilization of atherosclerotic plaques, possibly triggering ischemic events. Women, especially those aged \(<50\) years, showed a linear increase in HDL-C with an increment of the \(H.\) pylori antibody titer as a continuous variable in our study. The association remained significant after adjustment for fibrinogen. Our study results suggested that the association between \(H.\) pylori infection and HDL-C was at least in part independent of chronic inflammation.

Our study also showed that \(H.\) pylori seropositive women with lower BMI (BMI <22) were associated with decreased HDL-C, whereas the association was not significant in women with a higher BMI (BMI \(\geq\) 22). This appears to be a paradoxical phenomenon, because decreased serum HDL-C level is a strong inverse predictor of cardiovascular events and is usually caused by obesity.\(^3\) The association between \(H.\) pylori infection and BMI is controversial.\(^12,13,37,38\) The key mechanism might involve disturbances in gastric hormones, such as ghrelin, a body weight-regulating peptide. Figura et al. hypothesized that in countries with an intense circulation of CagA-positive \(H.\) pylori, such as Asia, Japan and Central Africa, corpus atrophy that occurs frequently and early in life destroys ghrelin-producing cells, contributing to a decrease in appetite: thus, infected people remained slim.\(^1\) Chen et al. reported that \(H.\) pylori infection enhances atherosclerosis in C57BL/6 mice fed a high-cholesterol diet.\(^39\) Therefore, the association between \(H.\) pylori seropositivity and lipid profile may be affected by diet and nutrition. These effects may be a key to resolving the association of \(H.\) pylori seropositivity and lower BMI with a decreased HDL-C level found in our study. There are also conflicting data regarding the effect of \(H.\) pylori eradication on serum lipids. Ando et al. followed patients for 3 years after eradication of \(H.\) pylori. They showed that body weight, BMI, and triglyceride levels increased gradually each year and that there were no significant changes in plasma levels of total cholesterol, IL-6 or IL-8, whereas those of HDL-C increased significantly, and those of C reactive protein, fibrinogen, and low density lipoprotein cholesterol decreased in patients demonstrating

| Table 3. Multiple linear regression analysis of HDL-C and value of \(H.\) pylori IgG antibody titer plus conventional risk factors\(^*\) by sex and age |
|---------------------------------|-----------------|-----------------|
| value of IgG to \(H.\) pylori | Standardized coefficient | P value |
| all men \((n = 837)\) | -0.04 | 0.18** |
| women \((n = 1308)\) | -0.10 | <0.001** |

| age\(\geq\)50 |
|-----------------|-----------------|-----------------|
| men \((n = 692)\) | -0.04 | 0.27 |
| women \((n = 1048)\) | -0.11 | <0.001 |

| age<50 |
|-----------------|-----------------|-----------------|
| men \((n = 145)\) | -0.08 | 0.32 |
| women \((n = 260)\) | -0.06 | 0.33 |

\* Adjusted for age, body mass index, fibrinogen, blood glucose, and smoking and alcohol habits

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\(H.\) pylori: \textit{Helicobacter pylori}. HDL-C: high density lipoprotein cholesterol.

\(H.\) pylori antibodies cross-react with antigens of both normal and atherosclerotic blood vessels.\(^35\) They speculated that anti-CagA antibodies could bind the exposed vascular antigens and further contribute to the activation of inflammatory cells within lesions. Production of cytokines and other inflammatory mediators by activated macrophages and fibroblasts could then lead to the destabilization of atherosclerotic plaques, possibly triggering ischemic events. Women, especially those aged \(\geq\)50 years, showed a linear increase in HDL-C with an increment of the \(H.\) pylori antibody titer as a continuous variable in our study. The association remained significant after adjustment for fibrinogen. Our study results suggested that the association between \(H.\) pylori infection and HDL-C was at least in part independent of chronic inflammation.

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| Table 4. Values of HDL-C in subgroups according to the status of \(H.\) pylori and BMI |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Group A \(HP(−)\) | Group B \(HP(+)\) | Group C \(HP(−)\) | Group D \(HP(+)\) |
| BMI<22          | 139 | 188 | 203 | 329 |
| HDL cholesterol | 60.9±15.7 | 58.9±15.6 | 51.4±14.3 | 50.3±13.9 | <0.001* |
| men (number)    | 280 | 287 | 392 | 376 |
| HDL cholesterol | 65.6±143 | 61.0±138 | 56.6±137 | 55.7±131 | <0.001* |

Variables are presented as means±standard deviation.

\* Statistical analyses were performed by one-way analysis of variance (ANOVA).

\(HP(+)\): \textit{Helicobacter pylori} seropositive subjects. \(HP(−)\): \textit{Helicobacter pylori} seronegative subjects. HDL-C: high density lipoprotein cholesterol. SD: standard deviation.

Variables are presented as means±standard deviation.

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\(HP(+)\): \textit{Helicobacter pylori} seropositive subjects. \(HP(−)\): \textit{Helicobacter pylori} seronegative subjects. HDL-C: high density lipoprotein cholesterol. SD: standard deviation.
Their study results suggested that *Helicobacter pylori* infection induced the level of HDL-C change; this strengthens our results, which could not show associations between causes and effects because of the cross-sectional study design.

**Study limitations**

The present study had some limitations. First, *H. pylori* serology was used to determine *H. pylori* infection status and could not indicate direct evidence of *H. pylori* infection. Since the specificity and sensitivity of the ELISA used in this study are more
than 95%, a minority of false-positive or false-negative subjects might have been included among the study subjects. Second, we did not check *H. pylori* Cag-A status. Since the prevalence of *H. pylori* Cag-A positive infection is high in Japan, our study of *H. pylori* seropositive subjects might also have included Cag-A positive status. Third, we did not check *H. pylori* eradication status. *H. pylori* eradication therapy typically decreases the value of *H. pylori* IgG titers. However, our data were collected in 1999, before eradication therapy for *H. pylori* had become widely available in Japan, so it was unlikely to have affected IgG values in our study. Fourth, in our study, *H. pylori* seropositive women with lower BMI (BMI <22) were more closely associated with decreased HDL-C than seronegative women, but the level of HDL-C was not as low as the level confirmed as a major cardiovascular risk factor by guidelines in the National Cholesterol Education Program Adult Treatment Panel III (HDL-C <40 mg/dL). Moreover, recently the functionalities of HDL-C have been pointed out. It is difficult to judge from the level of HDL-C whether HDL-C sub-fractions might affect risk of cardiovascular disease. Finally, we did not collect information about subject's gastric symptoms such as anorexia, or about their nutrition.

Since the relationship between *H. pylori* infection and cardiovascular disease is limited and various kinds of inflammatory processes are involved, the link remains unclear. Further large scale, prospective, epidemiologic studies and intervention studies are needed to elucidate whether *H. pylori* infection could be a contributing pathogenic factor in cardiovascular disease.

CONCLUSIONS

In conclusion, in a large scale Japanese study, we demonstrated that *H. pylori* seropositivity is associated with decreased HDL-C, especially in women with lower BMI living in rural areas of Japan in 1999. Further studies are needed to clarify whether *H. pylori* infection promotes the development of atherosclerosis and cardiovascular disease and whether eradication reduces these risks.

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