Helicobacter Pylori Infection is a Significant Risk for Modified Lipid Profile in Japanese Male Subjects

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Aim: Helicobacter pylori infection was associated with the risk of cardiovascular disease; however, the relation between Helicobacter pylori infection and the lipid profile has not been fully established.

Methods: We measured anti-Helicobacter Pylori antibody concentration and lipid profiles in 6,289 Japanese subjects aged 21−64 years (5,077 male and 1,212 female).

Results: The prevalence of Helicobacter pylori-seropositive subjects was 46.8% and 39.6% in men and women, respectively. Adjusted mean values of low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol in men were significantly higher and lower in Helicobacter pylori-seropositive than-negative subjects, respectively, (LDL-cholesterol: 129.0 ± 0.8 vs. 125.3 ± 0.7 mg/dL, p<0.001, HDL-cholesterol: 54.6 ± 0.3 vs. 56.6 ± 0.3 mg/dL, p<0.01), whereas these associations were not significant in female subjects. Moreover, the odds ratio of Helicobacter pylori infection for high LDL-cholesteremia and low HDL-cholesteremia in male subjects was 1.23 (95% CI: 1.08−1.40, p<0.05) and 1.29 (95% CI: 1.03−1.59, p<0.05), respectively. Female subjects did not have such associations.

Conclusions: The present study demonstrates that Helicobacter pylori infection is significantly associated with high LDL-cholesteremia and low HDL-cholesteremia in Japanese male subjects.

Key words; Helicobacter pylori, Low-density lipoprotein cholesterol, High-density lipoprotein cholesterol, Japanese population

Introduction

Helicobacter pylori, the etiologic agent of peptic ulcers, can cause persistent infections of the gastrointestinal tract and induce persistent low-grade inflammation process. A number of previous studies have demonstrated a significant relation between Helicobacter pylori and metabolic risk factors, atherosclerosis, and cardiovascular diseases. Although, other studies could not confirm this association. Thus, the interrelation between Helicobacter pylori infection and metabolic risk factors of atherosclerosis and cardiovascular diseases remains controversial. Among metabolic risk factors, modified lipid profiles, such as high low density lipoprotein (LDL) cholesterol and low high density lipoprotein (HDL) cholesterol have been well established as major risks for cardiovascular diseases. Several studies have indicated that chronic infection was closely associated with alterations of lipid metabolism. This is of critical importance because the prevalence of Helicobacter pylori is relatively high in the Japanese population among developed countries; however, the relation between the lipid profile and Helicobacter pylori infection has not been fully established.

The aim of the present study was to examine the association between Helicobacter pylori infection and the lipid profile in the Japanese population.
Methods

Study Subjects

The present study included 6,599 Japanese subjects without *Helicobacter pylori* eradication therapy and a past history of cardiovascular disease, employed in local government in Hokkaido, aged from 21 to 64 years old (48 ± 7 years, mean ± standard deviation (SD)), and who had annual health check from April 2003 to March 2004. Overall, 106 subjects (85 male and 21 female) who had triglyceride values greater than 400 mg/dL were excluded from the present study, and 204 subjects (146 male and 58 female) were excluded because they had already received anti-hyperlipidemic therapy. Thus, 6,289 subjects remained in the present analysis. The study was conducted after obtaining written informed consent from all subjects and was approved by the institutional ethics committee for epidemiological studies of Hokkaido University Graduate School of Medicine.

Data Collection

We used a self-administered questionnaire including items on medical history, smoking, alcohol consumption, frequency of exercise, menopausal status, and hormone-replacement therapy. The questionnaire was distributed to study subjects and was collected at the time of the annual health checkup. The smoking status was classified as current, ex-smoker, and non-smokers. The total average amount of alcohol consumed was calculated in grams per day, after taking account of the frequency, amount, and alcohol content of specific beverages. Alcohol consumption was categorized into never, less than 25 g/day, and greater than 25 g/day. Exercise was classified as none, once or twice per week, and greater than three times per week. Height and weight were measured in the morning in the fasting state. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²).

Blood samples were obtained from the antecubital vein in the morning after overnight fasting and serum samples were separated after centrifugation. HDL-cholesterol was measured after precipitation of apo B-containing lipoproteins with a commercial reagent containing phosphotungstate and magnesium chloride (Daiichi Pure Chemicals, Tokyo, Japan). Triglyceride was measured enzymatically (Kyowa Medex, Tokyo, Japan). Fasting plasma glucose was enzymatically determined by the hexokinase method (Shino-Test, Tokyo, Japan). LDL-cholesterol values were calculated using the Friedewald formula. C-reactive protein (CRP) was measured by nephelometry, with a latex particle-enhanced immunoassay (N Latex CRP II; Date Behring, Tokyo). The assay could detect 0.004 mg/dL CRP. Undetectable CRP values were recorded as 0.002 mg/dL. Blood pressure was measured by a trained nurse using a standard mercury sphygmomanometer with the study subjects in the sitting position after at least a 5-minute rest.

The anti- *Helicobacter pylori* antibody concentration was measured using an enzyme immunoassay (E plate; Eiken Chemical, Tokyo)33; an assay value < 10 U/mL was considered negative and ≥ 10 U/mL was considered positive.

Statistical Analysis

All analyses were performed separately according to sex. The clinical and biochemical data of the study subjects are expressed as means ± SD, the median (and interquartile range) for variables with skewed distribution, and percentages. Differences between two groups were examined by Students unpaired t test for variables distributed normally, by the Wilcoxon rank-sum test for triglyceride and CRP, and by the χ²-test for categorical variables. The adjusted means of LDL-cholesterol and HDL-cholesterol were compared between *Helicobacter pylori* positive and negative in both genders using general linear model univariate analyses adjusted for age, body mass index, systolic blood pressure, LDL-cholesterol, log triglyceride, HDL-cholesterol, fasting plasma glucose, CRP, smoking, alcohol intake, exercise, hypertension, and diabetes mellitus were entered in the model as covariates for men; and all variables and the menopausal status were used for women. Multiple logistic regression analysis was used to examine the odds ratios of *Helicobacter pylori* positive for low HDL-cholesterol and high LDL-cholesterol, adjusted for age, BMI, systolic blood pressure, LDL-cholesterol, log triglyceride, HDL-cholesterol, fasting plasma glucose, CRP, smoking, alcohol intake, exercise, hypertension, and diabetes mellitus for men; and all variables and the menopausal status for women. Low HDL-cholesterol and high LDL-cholesterol were identified as values less than 40 mg/dL and greater than 140 mg/dL, respectively. A p-value 0.05 was considered significant. All statistical analyses were performed using the Statistical Package for Social Science (version 11.0).

Results

Table 1 shows the comparison of the characteristics of male and female subjects. Male subjects were older and had greater BMI, higher systolic and diastolic blood pressure, LDL-cholesterol, triglyceride,
fasting plasma glucose, CRP, and lower HDL-cholesterol than female subjects. The prevalence of smoking, alcohol, exercise, hypertension, and diabetes mellitus was significantly greater in male than in female subjects.

Table 2 shows the comparison of the characteristics between Helicobacter pylori-seropositive and-seronegative subjects in the male subgroup, of which 2,375 (46.8%) had greater anti-Helicobacter pylori antibodies. The median (interquartile) value of Helicobacter pylori antibodies in Helicobacter pylori-seropositive male subjects was 68 (42–120) U/mL. Positive subjects were older and had greater BMI, LDL-cholesterol, triglyceride, and lower HDL-cholesterol in positive subjects than in negative subjects. The prevalence of hypertension, postmenopausal, current use of hormone-replacement therapy, and high LDL-cholesterol was significantly greater in positive than in negative subjects. Variables such as systolic and diastolic blood pressure, fasting plasma glucose, CRP, and the prevalence of smoking, alcohol, exercise, diabetes mellitus, and low HDL-cholesterol did not differ between the two groups.

Table 3 shows the comparison of characteristics between Helicobacter pylori-seropositive and-seronegative subjects in the female subgroup, of which 480 (39.6%) had greater anti-Helicobacter pylori antibodies. The median (interquartile) value of Helicobacter pylori antibodies in Helicobacter pylori-seropositive female subjects was 65 (35–111) U/mL. Positive subjects were older and had greater BMI, LDL-cholesterol, triglyceride, and lower HDL-cholesterol in positive subjects than in negative subjects. The prevalence of hypertension, postmenopausal, current use of hormone-replacement therapy, and high LDL-cholesterol was significantly greater in positive than in negative subjects. Variables such as systolic and diastolic blood pressure, fasting plasma glucose, CRP, and the prevalence of smoking, alcohol, exercise, diabetes mellitus, and low HDL-cholesterol did not differ between the two groups.
variate analyses. LDL-cholesterol was significantly higher in *Helicobacter pylori*-positive male subjects than in negative. In female subjects, LDL-cholesterol values did not differ between *Helicobacter pylori*-positive and-negative subjects. HDL-cholesterol values were significantly lower in *Helicobacter pylori*-positive male subjects than in negative. In female subjects, HDL-cholesterol values did not differ between *Helicobacter pylori*-positive and-negative subjects.

Table 4 shows that the odds ratio of *Helicobacter pylori* positive for high LDL-cholesterol defined as values greater than 140 mg/dL. In male subjects, *Helicobacter pylori* positive was a significant risk for high LDL-cholesterol, whereas it was not significant in female subjects.

Table 5 shows that the odds ratio of *Helicobacter pylori* positive for low HDL-cholesterol defined as values less than 40 mg/dL. In male subjects, *Helicobacter pylori* positive was significantly related to low HDL-cholesterol, whereas it was not significant in female subjects.

**Discussion**

The present study demonstrated that *Helicobacter pylori* infection was a significant and independent risk for a modified lipid profile, including high LDL-cholesterol and low HDL-cholesterol in Japanese male subjects.

The prevalence of *Helicobacter pylori* infection significantly increased with age in both genders. Asaka et al. showed that the prevalence of *Helicobacter pylori* infection significantly increased with age in both genders.
pylori infection in subjects older than 40 years was 74.9% in Japan, higher than in Caucasians. In the present study, it was 45.4% and in subjects older than 40 years, it was 50.3%, which was lower than that reported in the Japanese general population. Several studies have suggested that the spread of Helicobacter pylori infection was affected by a socially deprived environment and socioeconomic class. Our study subjects were employed in local government and were in the middle-high socioeconomic class, which might be relevant to the low prevalence of Helicobacter pylori infection.

Experimental and clinical studies have demonstrated that the acute phase response induced by infections may modify metabolism and increase CRP values. HDL-cholesterol had a role of removing free cholesterol from vessels to the liver and also possessed antioxidant and anti-inflammatory properties. In the present study, CRP values did not differ between Helicobacter pylori-positive and-negative subjects. Thus, HDL-cholesterol values in Helicobacter pylori-positive subjects might be lower than in negative subjects due to the use of anti-inflammatory functions found with HDL-cholesterol. Moreover, the decrease of HDL-cholesterol values weakened the function of LDL-cholesterol extraction from vessels, and LDL-

| Table 3. Comparison of characteristics between Helicobacter pylori-seropositive and -seronegative subjects within female subgroup |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Positive (n = 480) | Negative (n = 732) | p value          |
| Age (years)                    | 48 ± 7           | 44 ± 8           | <0.001          |
| Body mass index (kg/m²)        | 22.2 ± 3.3       | 21.5 ± 3.1       | <0.001          |
| Systolic blood pressure (mmHg) | 110 ± 16         | 109 ± 33         | n.s.            |
| Diastolic blood pressure (mmHg)| 67 ± 11          | 65 ± 11          | n.s.            |
| LDL-cholesterol (mg/dL)        | 127 ± 29         | 117 ± 29         | <0.001          |
| Triglyceride (mg/dL)           | 51–95 (71)       | 47–86 (61)       | <0.001          |
| HDL-cholesterol (mg/dL)        | 68 ± 15          | 71 ± 15          | <0.01           |
| Fasting plasma glucose (mg/dL) | 89 ± 12          | 88 ± 13          | n.s.            |
| CRP (mg/dL)                    | 0.025 (0.013–0.053) | 0.024 (0.011–0.048) | n.s. |
| High LDL-cholesterol (%)       | 32.8             | 21.2             | <0.001          |
| Low HDL-cholesterol (%)        | 2.3              | 1.8              | n.s.            |
| Smoking status (%)             |                  |                  |                 |
| Never                          | 66.5             | 70.5             | n.s.            |
| Ex-smoker                      | 23.5             | 20.6             |                 |
| Current smoker                 | 10.0             | 8.9              |                 |
| Alcohol consumption (%)        |                  |                  |                 |
| Never                          | 49.1             | 45.3             | n.s.            |
| ≤ 25 g/day                     | 34.0             | 35.1             |                 |
| > 25 g/day                     | 16.9             | 19.6             |                 |
| Frequency of exercise (%)      |                  |                  |                 |
| Never                          | 68.5             | 67.9             | n.s.            |
| 1-2/week                       | 21.5             | 23.6             |                 |
| ≥ 3/week                       | 10.0             | 8.5              |                 |
| Medical history                |                  |                  |                 |
| Hypertension (%)               | 5.4              | 3.1              | <0.05           |
| Diabetes mellitus (%)          | 0.4              | 0.4              | n.s.            |
| Menopausal status (%)          |                  |                  |                 |
| Postmenopausal                 | 45.9             | 29.9             | <0.001          |
| Under hormone-replacement therapy | 3.1             | 2.0              | <0.01           |

Variables are presented as the mean ± SD, median (interquartile range) for skewed variables, or percentage. LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein.

High LDL-cholesterol was defined as values > 140 mg/dL. Low HDL-cholesterol was defined as values < 40 mg/dL.
cholesterol values might be greater in *Helicobacter pylori* positive than-negative subjects. These mechanisms need further examination.

Longo-Mbenza et al. indicated that men infected with *Helicobacter pylori* eliminated infection antibodies more slowly than infected women \(^{32}\). Thus, infection with strains of *Helicobacter pylori* with a longer inflammatory period might vary the difference in metabolic risk factors between genders. In the present study, a modified lipid profile could not be found in female subjects, which confirmed this previous study.

Previous studies have demonstrated that *Helicobacter pylori* infection was associated with low HDL-cholesterol in Caucasians \(^{10, 33}\); however, the number of subjects enrolled in previous studies was relatively small compared to the present study. Laurila et al. indicated that *Helicobacter pylori*-seropositive men had high triglyceride, high total cholesterol, and low HDL-cholesterol in a large epidemiological study \(^{20}\); however, they did not adjust for variables such as alcohol intake and exercise, which may affect the lipid profile. In addition, the present study also examined the relation between *Helicobacter pylori* infection and LDL-cholesterol levels. *Helicobacter pylori* eradication...
therapy may be expected to prevent or ameliorate a modified lipid profile, particularly in the Japanese population with Helicobacter pylori infection, which needs to be tested by conducting well-designed and large-scale clinical trials.

There are several limitations which should be acknowledged in the present study. First, the status of Helicobacter pylori infection was diagnosed solely based on the Helicobacter pylori-specific IgG antibody; however, a positive Helicobacter pylori antibody does not indicate current Helicobacter pylori infection. Second, the prevalence of Helicobacter pylori-positive subjects in the present study was relatively lower than in the Japanese population. Thus, we need to be cautious when applying the present findings to the general population. Third, because the present study was cross-sectional, the relationship between Helicobacter pylori infection and the modified lipid profile could not be proved conclusively. Further longitudinal study is required to clarify the cause-effect relation.

In conclusion, the present study demonstrated that Helicobacter pylori infection was significantly associated with a modified lipid profile and was significantly and independently related to high LDL-cholesteremia and low HDL-cholesteremia.

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