

Helicobacter pylori Infection is Associated with Elevated Low Density Lipoprotein Cholesterol Levels in Elderly Koreans

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Received: 12 January 2011
Accepted: 28 February 2011

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This study was conducted to investigate the association between *Helicobacter pylori* (*H. pylori*) infection and the lipid profile among elderly Koreans. A total of 462 subjects (mean age 66.2 ± 7.6 yr, 84% males) who underwent health check-up were investigated. Each subject underwent gastroduodenoscopy with gastric mucosal biopsy, and *H. pylori* infection was determined by histopathological examination using the updated Sydney System score. The presence of *H. pylori* infection was significantly associated with the elevated serum levels of total cholesterol and low density lipoprotein (LDL) cholesterol ($P < 0.05$ for each) in univariate analysis. *H. pylori* infection was not associated with triglyceride and high density lipoprotein (HDL) cholesterol levels ($P > 0.05$ for each). After controlling confounders, multiple logistic regression analysis showed that the odds ratio of *H. pylori* infection for high LDL cholesterol level (> 140 mg/dL) was 3.113 (95% confidence interval, 1.364-7.018; $P = 0.007$). There were no significant associations between the presence of *H. pylori* infection and elevated total cholesterol levels (> 200 mg/dL) in this model ($P = 0.586$). The results of this study demonstrate that *H. pylori* infection is associated with the elevated serum LDL cholesterol levels in elderly Koreans, supporting the hypothesis that *H. pylori* plays a role in promoting atherosclerosis by modifying lipid metabolism.

Key Words: *Helicobacter pylori*; Cholesterol, LDL

INTRODUCTION

Helicobacter pylori (*H. pylori*) induces chronic inflammation of underlying mucosa of the human stomach causing gastritis and peptic ulceration (1). A number of previous studies have suggested that mild systemic inflammation provoked by *H. pylori* infection is associated with metabolic syndrome and atherosclerotic cardiovascular disease (2-6). However, some studies could not confirm this association (7-9). The underlying mechanisms of how *H. pylori* infection promotes the development of such diseases still remain unclear.

Modified blood cholesterol levels, such as elevated low density lipoprotein (LDL) and decreased high density lipoprotein (HDL), are major risk factors for cardiovascular disease and metabolic syndrome (10). The effect of *H. pylori* infection on the serum lipid profile is still a matter of debate. Several studies have demonstrated that *H. pylori* infection might modify serum lipid concentrations through increase the risk of atherosclerosis (10-13), while others have not confirmed these findings (14, 15).

The purpose of this study was to investigate the association between *H. pylori* infection and the serum lipid profile in elderly Koreans.

MATERIALS AND METHODS

Study subjects

We recruited 775 subjects who underwent upper gastrointestinal (GI) endoscopic examination during routine health check-up at the Armed Forces Seoul Hospital (Seoul, Korea) from January 1, 2005 to December 31, 2009. Gastric mucosal biopsy specimens were obtained from 558 of these subjects. In total, 103 subjects were excluded according to the following criteria: 1) subjects who had a history of *H. pylori* eradication or gastric surgery, 2) those who had already received anti-hyperlipidemic therapy, 3) those suffering from acute or chronic inflammatory conditions, severe liver or renal dysfunction, or malignancy, and 4) those who had not information available for the study variables. Finally, a total of 454 subjects were included in the study.

Data collection

Information regarding the underlying diseases, medication history, alcohol drinking, and exercise habits was recorded by a trained family medicine doctor using a standardized questionnaire. Systolic/diastolic blood pressures (SBP/DBP), body weight and height were measured by a trained nurse. The body mass index (BMI) was calculated by the ratio of weight (kg)/squared

height (m²). Hypertension was physician-reported for an SBP of ≥ 140 mmHg, a DBP of ≥ 90 mmHg, or a history of the use of anti-hypertensive medications. Diabetes was determined by physician reports based on a fasting blood sugar level of ≥ 126 mg/dL or a history of the use of medications for diabetes. After an overnight fast (≥ 12 hr), 10 mL of venous blood was obtained from the antecubital vein of each subject. The hemoglobin level was analyzed by an automated blood cell counter (ADVIA 120, Bayer, NY, USA). Total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, alanine aminotransferase, fasting blood sugar and creatinine levels were measured by enzymatic methods using an automated chemistry analyzer (Toshiba TBA-120 FR, Toshiba Medical Systems, Tokyo, Japan).

Histology

Endoscopic gastric mucosal biopsies were performed by skilled endoscopists. Two or three biopsy specimens were taken from either the gastric body (n = 237, 52.2%), antrum (n = 196, 43.2%) or cardia (n = 21, 4.6%). The specimens were fixed in 10% formalin, embedded in paraffin block on the oriented edge, and cut into 4 μ m-thick sections. All sections were stained with hematoxylin-eosin and Giemsa for histological evaluation. The pres-

ence and intensity of *H. pylori* were microscopically examined. Each stained slide was interpreted semiquantitatively as none, mild, moderate and severe, according to the updated Sydney System (16) (Fig. 1). The density of *H. pylori* was evaluated by 2 independent pathologists using a light microscope in a blinded fashion. Discordant cases were reviewed on a multi-headed microscope to achieve a consensus.

Statistical analysis

Data are presented as mean values with standard deviation or percentage. For univariate analysis, continuous variables were compared using the Student's t-test and categorical variables were compared using the chi-square test. The crude odds ratios (cORs) and adjusted odds ratios (aOR) of *H. pylori* infection for elevated total cholesterol and LDL cholesterol were tested with the chi-square test and multiple logistic regression analysis, respectively. Age, sex, BMI, cigarette smoking, alcohol drinking, regular exercise, hypertension, diabetes, SBP, DBP, fasting blood sugar and creatinine were adjusted during the logistic regression analysis. LDL cholesterol levels according to the *H. pylori* severity were analyzed by using analysis of variance (ANOVA). Elevated total cholesterol and LDL cholesterol levels were iden-

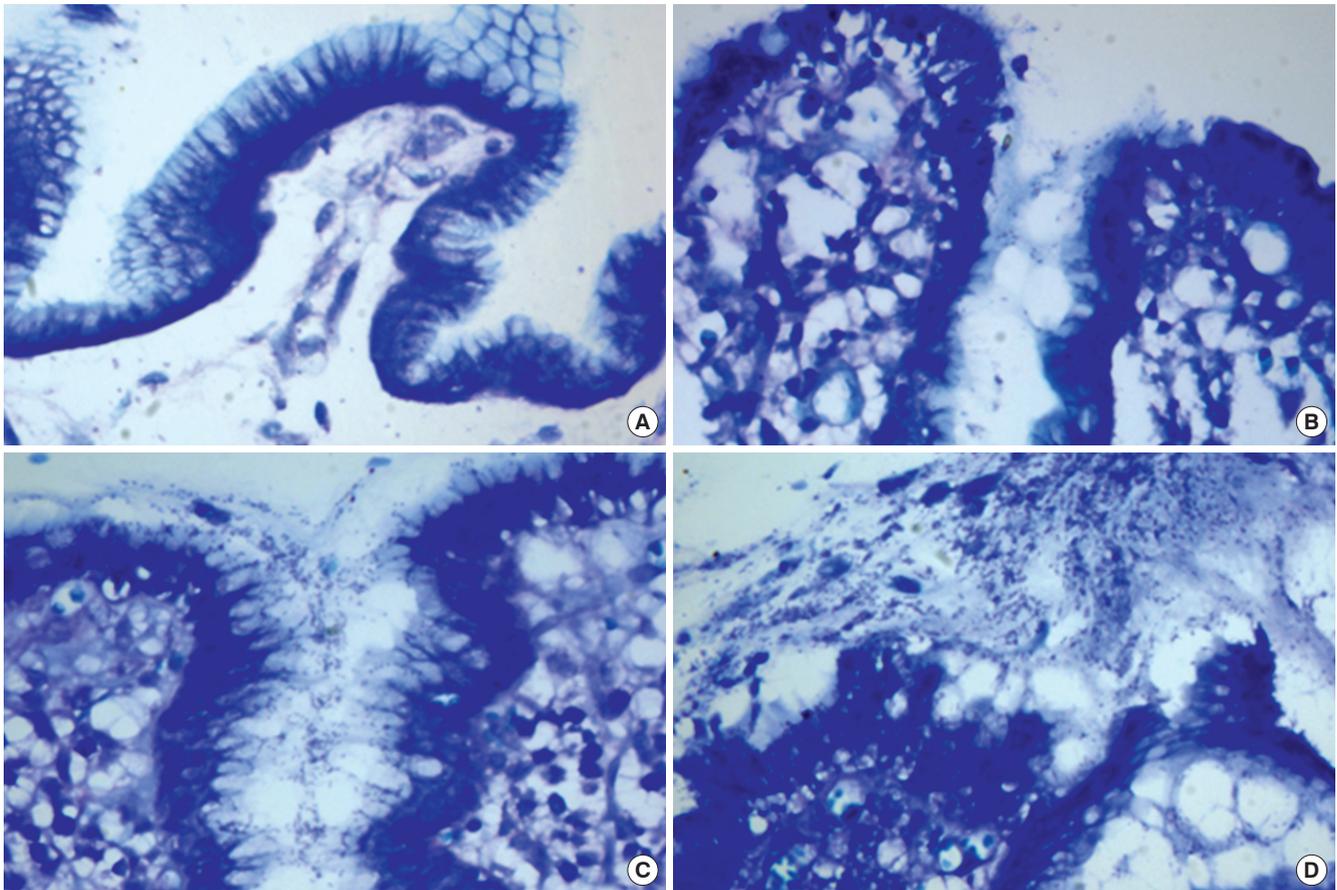


Fig. 1. *Helicobacter pylori* gastritis in endoscopic biopsy. The degree of *H. pylori* infection is shown according to the updated Sydney classification; none (A), mild (B), moderate (C), and severe (D) (Giemsa staining, $\times 400$).

tified as values greater than 200 and 140 mg/dL, respectively. A two-tailed P value of < 0.05 was considered statistically significant. All data were analyzed using SPSS for Windows v.13.0 (SPSS Inc, Chicago, IL, USA).

Ethics statement

The study protocol was approved by the institutional review board of the Armed Forces Medical Command (Seongnam, Korea, research number AFMC-10-IRB-018). Written informed consent was obtained from each participant before endoscopy.

RESULTS

Among 454 study subjects (mean age 66.2 ± 7.6 yr, 84% males), 45 had normal upper GI endoscopic findings, 385 had gastritis, and 24 had peptic ulcer disease. Gastric mucosal biopsy showed that 193 subjects (42.5%) were positive for *H. pylori*. Table 1 compared clinical characteristics between *H. pylori* (+) and *H. pylori* (-) subjects. Subjects with *H. pylori* (+) were younger (65.1 ± 7.7 vs 67.0 ± 7.4 yr, $P = 0.008$) and had a lower incidence of diabetes (4.2% vs 7.8%, $P = 0.010$) compared to those with *H. pylori* (-). The other clinical and laboratory parameters including BMI, smoking, alcohol consumption, regular exercise, blood pressure, hemoglobin, alanine aminotransferase, albumin, fasting blood sugar and creatinine, were not different between the 2 groups ($P > 0.05$).

Total cholesterol (184.6 ± 29.6 vs 177.4 ± 31.0 mg/dL, $P = 0.014$)

Table 1. Characteristics of study participants

Characteristics	Total (n = 454)	HP (+) (n = 193)	HP (-) (n = 261)	P value*
Age (yr)	66.2 ± 7.6	65.1 ± 7.7	67.0 ± 7.4	0.008
Male sex (%)	83.9	81.3	85.8	0.199
BMI (kg/m ²)	24.1 ± 2.2	24.1 ± 2.2	24.0 ± 2.2	0.800
Cigarette smoking (%)	55.1	52.8	56.8	0.661
Alcohol drinking (%)	66.9	71.7	66.2	0.512
Regular exercise (%)	76.2	71.7	79.5	0.313
Hypertension (%)	15.3	16.1	14.7	0.667
Diabetes (%)	8.0	4.2	7.8	0.010
SBP (mmHg)	126.3 ± 14.0	125.7 ± 13.7	126.7 ± 14.1	0.438
DBP (mmHg)	78.2 ± 8.3	78.2 ± 8.0	78.2 ± 8.6	0.917
Hb (g/dL)	14.1 ± 1.1	14.1 ± 1.1	14.1 ± 1.2	0.992
ALT (IU/L)	22.9 ± 13.6	23.4 ± 16.2	22.5 ± 11.3	0.469
Albumin (g/dL)	4.06 ± 0.18	4.05 ± 0.18	4.06 ± 0.18	0.675
FBS (mg/dL)	99.8 ± 16.1	99.4 ± 13.8	100.1 ± 17.7	0.599
Creatinine (mg/dL)	0.84 ± 0.15	0.83 ± 0.15	0.84 ± 0.15	0.539
Total cholesterol (mg/dL)	180.5 ± 30.6	184.6 ± 29.6	177.4 ± 31.0	0.014
HDL cholesterol (mg/dL)	51.8 ± 11.8	51.7 ± 11.3	51.9 ± 12.1	0.892
LDL cholesterol (mg/dL)	128.6 ± 32.7	138.5 ± 33.0	121.3 ± 30.6	< 0.001
Triglyceride (mg/dL)	106.1 ± 63.6	110.9 ± 68.3	102.4 ± 59.8	0.161

Values are expressed as mean \pm standard deviation or number. * P values were obtained by comparison between HP (+) and HP (-) groups. HP, *Helicobacter pylori*; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; ALT, alanine aminotransferase; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein.

and LDL cholesterol (138.5 ± 33.0 vs 121.3 ± 30.6 mg/dL, $P < 0.001$) were significantly elevated in the subjects with *H. pylori* (+) compared to those with *H. pylori* (-). There were no significant differences in other lipid profile, including HDL cholesterol and triglyceride, between the 2 groups ($P > 0.05$).

Table 2 shows that the ORs of *H. pylori* (+) for elevated total cholesterol (> 200 mg/dL) and LDL cholesterol (> 140 mg/dL). *H. pylori* (+) was significantly associated with elevated total cholesterol (cOR 1.476, 95% CI 1.015-2.145, $P = 0.041$), however, this significance disappeared after adjustment for confounders including age, sex, BMI, cigarette smoking, alcohol drinking, regular exercise, hypertension, diabetes, SBP, DBP, fasting blood sugar and creatinine (aOR 1.241, 95% CI 0.571-2.698, $P = 0.586$). In contrast, *H. pylori* (+) was significantly associated with elevated LDL cholesterol even after adjustment for potential confounders (cOR 2.709, 95% CI 1.845-3.980, $P < 0.001$; aOR 3.113, 95% CI 1.364-7.108, $P = 0.007$).

Among 193 subjects with *H. pylori* (+), 100 (51.8%) had a mild degree of *H. pylori* infection, 38 (19.6%) had a moderate degree of *H. pylori* infection, and 55 (28.6%) had a severe degree of *H. pylori* infection on histological examination. Fig. 2 shows LDL cholesterol levels according to the severity of *H. pylori* infection. As *H. pylori* severity increased, the blood LDL cholesterol level increased gradually. LDL cholesterol levels were 121.3 ± 30.6 ,

Table 2. Odds ratios of *Helicobacter pylori* infection for high total cholesterol and LDL cholesterol

	Odds ratio	95% CI	P value
High total cholesterol (≥ 180 mg/dL)			
Crude	1.476	1.015-2.145	0.041
Adjusted*	1.241	0.571-2.698	0.586
High LDL cholesterol (≥ 130 mg/dL)			
Crude	2.709	1.845-3.980	< 0.001
Adjusted*	3.113	1.364-7.108	0.007

*Adjusted for age, sex, body mass index, cigarette smoking, alcohol drinking, regular exercise, hypertension, diabetes, systolic and diastolic blood pressure, fasting blood sugar and creatinine. LDL, low density lipoprotein; CI, confidence interval.

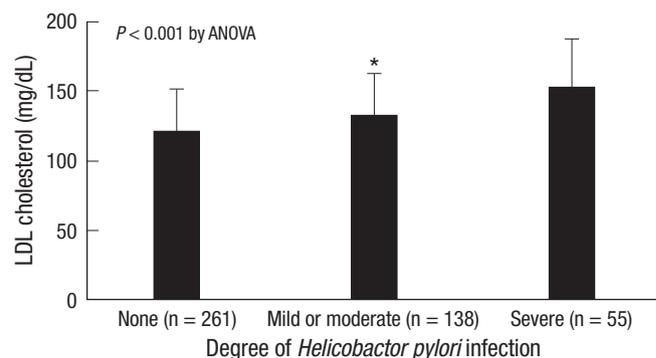


Fig. 2. Blood LDL cholesterol levels according to the degree of *Helicobacter pylori* infection. As *H. pylori* severity increases, blood LDL cholesterol levels also increase gradually. LDL cholesterol levels were 121.3 ± 30.6 , 132.7 ± 30.5 and 153.0 ± 35.1 mg/dL in the absence of *H. pylori* infection, and mild or moderate and severe degrees of *H. pylori* infection, respectively. * $P < 0.01$ versus other two groups by Bonferroni post-hoc analysis. LDL, low density lipoprotein; ANOVA, analysis of variance.

132.7 ± 30.5 and 153.0 ± 35.1 mg/dL in the none, mild or moderate and severe degrees of *H. pylori* infection, respectively ($P < 0.001$).

DISCUSSION

The results of this study showed that *H. pylori* infection was independently associated with elevated LDL cholesterol levels in elderly Koreans. LDL cholesterol levels were higher in subjects with *H. pylori* infection, and LDL cholesterol levels increased with increasing *H. pylori* severity. The odds ratio *H. pylori* infection for elevated LDL cholesterol (LDL > 140 mg/dL) was 3.113. These findings suggest that *H. pylori* infection may cause lipid alteration and, at least partially contribute to the atherosclerotic process.

The prevalence of *H. pylori* infection was 42.5% in our study, which is similar to that in a previous study of the Korean population demonstrating younger age and smoking history as risk factors of *H. pylori* infection (17). In our study, *H. pylori* infection was associated with younger age by univariate analysis, but not with smoking.

Systemic inflammatory response to the bacterium induces changes in lipid and lipoprotein metabolism (18). Although previous studies on the association between *H. pylori* infection and lipid profiles showed contradictory results, there is a general agreement that *H. pylori* infection itself modifies serum lipid profiles (3, 4, 11-13, 19, 20). Patients infected with *H. pylori* showed an atherogenic lipid profile characterized by an increase in LDL cholesterol or decreased HDL cholesterol compared to uninfected patients (5, 11, 12, 19-22). Our result also provided additional evidence supporting the hypothesis that *H. pylori* played a role in inducing atherosclerosis with lipid metabolism by elevating LDL cholesterol levels. Based on these results, it is conceivable that *H. pylori* infection is a predisposing factor for the atherosclerotic process and can be a reliable indicator for the assessment of cardiovascular disease risk.

H. pylori infection was confirmed by the presence of serum *H. pylori*-specific antibody in most of the previous studies on the relationship between *H. pylori* infection and lipid profile (2, 3, 5, 20). Although the serologic diagnosis of *H. pylori* infection has a high diagnostic accuracy, it is an indirect method. Thus, histological detection remains the standard for the diagnosis of *H. pylori* infection (23). A few studies have investigated the association between *H. pylori* infection and lipid profiles by histopathological examination (4). In our study, *H. pylori* infection was confirmed with the histopathological examination of the biopsied specimens. We graded the severity of *H. pylori* infection based on the updated Sydney System score (16) and showed that serum LDL cholesterol levels gradually increased along with *H. pylori* severity. The updated Sydney System has been widely employed to assess the severity and activity of gastric in-

flammation (16). Kucukazman et al. (4) also used the Sydney System score and demonstrated the correlation between histological evaluation of *H. pylori* and LDL cholesterol levels; however, they did not adjust for confounders.

There are some limitations that should be acknowledged in this study. Because of cross-sectional design of this study, the relationship between *H. pylori* infection and LDL cholesterol levels could not be conclusively proven. Longitudinal studies are required to confirm our results. Assessing serum LDL cholesterol levels before and after *H. pylori* eradication may be a good example (19, 24). Also, there would be a possibility of underestimating the number of subjects infected with *H. pylori* because *H. pylori* infection was diagnosed solely based on the histological detection of biopsied specimens from focal lesions.

In our conclusion, the results of this study suggest that *H. pylori* infection can be associated with elevated LDL cholesterol levels, the most important risk factor for atherosclerosis, and that eradication of *H. pylori* may play a role in preventing atherosclerosis by decreasing LDL cholesterol levels, particularly in elderly Koreans.

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AUTHOR SUMMARY

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