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Original Article

Long-term Effects of the Eradication of *Helicobacter pylori* on Metabolic Parameters, Depending on Sex, in South Korea

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Background/Aims: *Helicobacter pylori* (HP) infection is positively associated with metabolic syndrome (MS). However, the long-term effects of eradication therapy on MS and sex differences have not been thoroughly studied. We aimed to investigate the long-term effects of HP eradication on MS and sex differences.

Methods: This study included 2,267 subjects who visited a tertiary referral center between May 2003 and May 2019. HP was diagnosed by histology, a *Campylobacter*-like organism test, and culture, and the subjects were prospectively followed up. The participants were categorized into three groups: HP uninfected, HP infected but non-eradicated, and HP eradicated. The baseline characteristics and changes in metabolic parameters after HP eradication were compared over a 5-year follow-up period.

Results: Among 1,521 subjects, there was no difference in baseline metabolic parameters between the HP-uninfected (n=509) and HP-infected (n=1,012) groups, regardless of sex. Analysis of the metabolic parameters during follow-up among HP-uninfected (n=509), HP-non-eradicated (n=346), and HP-eradicated (n=666) groups showed that high-density lipoprotein (HDL) and the body mass index (BMI) increased after eradication, with a significant difference at 1-year of follow-up. In females, HDL increased after eradication (p=0.023), and the BMI increased after eradication in male subjects (p=0.010). After propensity score matching, the HDL change in female remained significant, but the statistical significance of the change in BMI in the male group became marginally significant (p=0.089).

Conclusions: HP eradication affected metabolic parameters differently depending on sex. HDL significantly increased only in females over time, especially at 1-year of follow-up. In contrast, BMI showed an increasing tendency over time in males, especially at the 1-year follow-up. **(Gut Liver 2023;17:58-68)**

Key Words: *Helicobacter pylori*; Eradication; Metabolic syndrome; Sex

INTRODUCTION

Helicobacter pylori (HP) infection is one of the most common chronic bacterial infections, with a prevalence of more than 50% worldwide.[1-3] HP is a type I carcinogen that causes chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.[3] In addition to gastrointestinal diseases, HP has been reported to be associated with many extragastric manifestations such as endocrine,[4,5] cardiovascular,[6] hematologic, neurologic,[7] and autoimmune diseases.[8,9]

Metabolic syndrome (MS) is a constellation of metabolic disturbances, including hypertension, hyperglycemia, dyslipidemia, and central obesity, which has been reported to increase the risk of cardiovascular or cerebrovascular diseases.[10] Furthermore, because the number of people with MS has been increasing worldwide[11-13] and in South Korea[13,14] for several decades, the importance of MS is also striking.

In recent years, a positive association between MS and HP has been reported worldwide.[15-18] However, the effect of HP eradication on MS remains controversial, despite a number of emerging studies. Several investigations have reported that eradication decreases the risk of dyslipidemia[19] or improved MS.[20-22] However, other studies have reported conflicting results. A recent study conducted in Taiwan showed improvements in metabolic parameters, with a decrease in insulin resistance, triglycerides (TGs), and low-density lipoprotein (LDL) and an increase in high-density lipoprotein (HDL), but no significant change in the prevalence of MS after eradication.[23] The effect of HP eradication on MS might differ depending on sex, ethnicity, diet, exercise, or body mass index (BMI). In addition, the effect could be different over long-term follow-up. Few studies have investigated the long-term outcomes or sex differences in the effects of eradication therapy on MS. As MS differs depending on sex, we hypothesized that the long-term effect of HP eradication on MS could be different between males and females. Therefore, we aimed to investigate the long-term effects of HP eradication on MS and identify the differences by sex.

MATERIALS AND METHODS

1. Study population

This was a prospective observational cohort study. After strictly excluding any kind of malignancy, we enrolled a total of 2,267 patients among those who underwent esophagogastroduodenoscopy at Seoul National University Bundang Hospital in South Korea from May 2003 to May 2019. Most patients underwent endoscopy due to mild dyspepsia symptoms or to check the possibility of gastric adenoma or gastric cancer. We excluded subjects from this study based on the following criteria: (1) previous history of HP eradication; (2) unknown previous eradication history; (3) unknown HP status; (4) positive anti-HP IgG in the absence of current HP infection; and (5) unknown post-treatment HP status. In addition, patients with a history of gastric surgery and/or gastric cancer, esophageal cancer, type 1 diabetes mellitus, and other major diseases, including systemic inflammation or advanced malignant diseases, were excluded. Finally, 1,521 subjects were analyzed, including 509 HP-negative and 1,012 HP-positive subjects. Among the HP-positive patients, 666 received successful eradication therapy, and 346 did not receive or failed eradication therapy due to patient preference, adverse effects, non-compliance, or antibiotic resistance (Fig. 1).

2. Anthropometric and laboratory data collection

Baseline demographic data, such as total cholesterol (TC), HDL cholesterol, LDL cholesterol, TG, fasting plasma glucose (FPG), systolic blood pressure (SBP), diastolic blood pressure (DBP), and BMI were recorded at enrollment. We followed up each parameter at 2 months and after 1, 3, and 5 years.

3. Behavioral factors and previous medical history

Past medical history and behavioral factors such as smoking and drinking habits were based on questionnaires that were completed by subjects at enrollment and were also collected from medical records. The subjects were diagnosed with hypertension if pretreatment blood pressure was >140/90 mm Hg or on antihypertensive treatment. Diabetes mellitus was diagnosed by FPG (>126 mg/dL), a 2-hour oral glucose tolerance test (higher than 200 mg/dL), random glucose test (higher than 200 mg/dL) with symptoms or a glycosylated hemoglobin level (hemoglobin A1C, higher than 6.5%), or diabetes medication. Dyslipidemia was defined as elevated TC (>240 mg/dL), LDL (>160 mg/dL) or TG (>200 mg/dL), or low HDL levels (<40 mg/dL).

4. Confirmation of HP infection

HP infection was diagnosed by esophagogastroduodenoscopy with biopsies for histology, culture, or the *Campylobacter*-like organism test. The mid antrum and mid corpus were the sites of mucosal biopsies, and a single endoscopist (N.K.) performed biopsies for consistency.

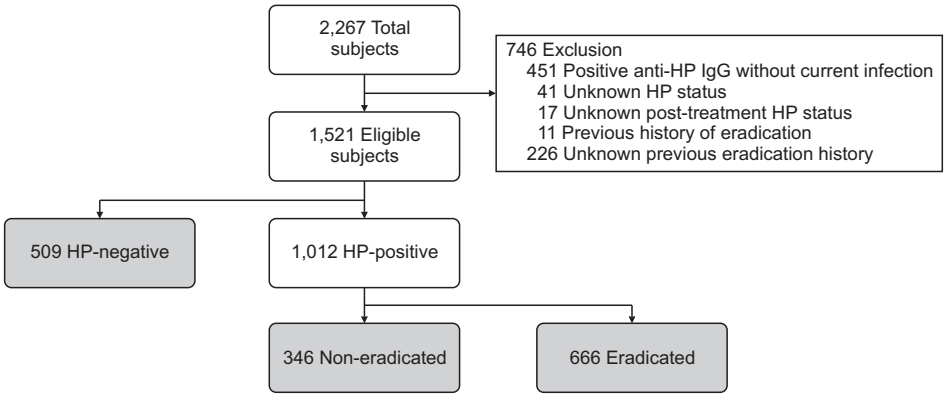

Fig. 1. Study flowchart. Schematic flow of the study.
HP, *Helicobacter pylori*.

5. HP eradication therapy and follow-up

Current HP infection was defined as when any of the three tests (histology, culture, and rapid urease test) was positive. If the subjects wanted eradication therapy, they received first-line triple therapy prior to 2012 and a 10-day sequential therapy after that. The triple therapy regimen consisted of 40 mg esomeprazole twice a day (b.i.d.), 1,000 mg amoxicillin b.i.d., and 500 mg clarithromycin b.i.d. for 7 days. The 10-day sequential therapy was a combination of 40 mg of esomeprazole, 1,000 mg of amoxicillin b.i.d. for 5 days followed by 40 mg of esomeprazole b.i.d., 500 mg of clarithromycin b.i.d., and 500 mg of metronidazole twice daily for the next 5 days. The ^{13}C-urea breath test was performed 4 to 6 weeks after completion of eradication therapy to evaluate the results. In patients with treatment failure after the first-line regimen, we prescribed a 14-day quadruple therapy including 40 mg esomeprazole b.i.d., 300 mg tripotassium dicitrate bismuthate (Denol; Green-cross Co., Seoul, Korea) four times a day (q.i.d.), 500 mg of metronidazole three times a day, and 500 mg of tetracycline q.i.d., or a 14-day moxifloxacin-based triple therapy containing 400 mg of moxifloxacin (Avelox; Bayer Health Care, AG, Wuppertal, Germany) q.i.d., 40 mg of esomeprazole b.i.d., and 1,000 mg of amoxicillin b.i.d. HP status was evaluated by histology and/or *Campylobacter*-like organism test at each follow-up visit for endoscopic surveillance.

6. Statistical analysis

Continuous data are shown as the mean±standard deviation, and categorical data are shown as numbers and percentages. The Student t-test and analysis of variance for continuous variables and the chi-square test for categorical variables were used to compare the baseline characteristics and metabolic parameters between groups. A linear mixed model (LMM) was applied to compare the changes in metabolic parameters over time among HP-negative, HP-non-eradicated, and HP-eradicated groups. We used 1:1 propensity score matching (PSM) to minimize the effects of potential confounding variables affecting metabolic parameters. Statistical significance was set at $p<0.05$. All statistical analyses were conducted using IBM SPSS Statistics version 25.0 software (IBM Corp., Armonk, NY, USA), and in cooperation with the Medical Research Collaborating Center.

7. Ethics statement

All subjects provided written informed consent in accordance with the ethical principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB number: B-1904/532-110).

RESULTS

1. Baseline characteristics

Baseline characteristics of the subjects are presented in Table 1. Among the 1,521 subjects who were finally analyzed, 509 (33.5%) were HP-negative and 1,012 (66.5%) were HP-positive. The mean age was 55.6 years, and 759 (49.9%) were male. The proportion of male was significantly higher in the HP-positive group than in the -negative group (53.2% vs 43.4%, $p<0.001$). There were no significant differences in age, number of alcohol drinkers, smokers, and subjects with hypertension, diabetes mellitus, or dyslipidemia, and the levels of TC, HDL, LDL, TG, FPG, SBP, DBP, and BMI between the groups (Table 1). Likewise, there was no significant difference in the baseline characteristics depending on HP infection between male and female subjects (Table 2).

The results showed differences in the baseline characteristics between the male and female subjects (Table 2). The proportion of current drinkers and smokers was significantly higher in males than in females. The level of TC, HDL, and LDL was significantly higher in female than male subjects, and the level of TG, SBP, and DBP was significantly higher in male than female subjects. FPG and BMI showed no significant differences according to sex. The number of patients with hypertension and diabetes mellitus was higher in males, and the number of patients with dyslipidemia was similar between males and females.

2. Effects of HP infection and eradication on metabolic parameters

The numbers of patients who were followed at 2-month, 1-year, 3-year, and 5-year were 985, 918, 827, and 637, respectively. The LMM analysis showed that there was an interaction between time and HP status in the BMI level, which implies that a significant difference was observed in the trend of BMI levels throughout the 5 years of follow-up between the HP-uninfected, HP-infected but non-eradicated, and HP-eradicated groups ($p=0.006$). The level of HDL also showed a marginally significant difference ($p=0.088$), but the levels of TC, LDL, TG, FPG, SBP, and DBP were not significantly different between the groups (Table 3).

We also compared the changes in metabolic parameters from baseline to each time point of follow-up among the three groups. The results showed that the BMI level increased at 1 year post-eradication with statistical significance ($p=0.002$) and the difference decreased at three and 5 years ($p=0.088$ and $p=0.203$, respectively). HDL also increased after eradication, while it decreased in the HP-non-eradicated groups. The difference among groups was greatest at 1 year ($p=0.027$), and it decreased afterwards

Table 1. Baseline Characteristics of the Subjects According to HP Status

Variable	Total (n=1,521, 100%)	HP-negative (n=509, 33.5%)	HP-positive (n=1,012, 66.5%)	p-value
Age, yr	55.6±13.8	54.8±15.5	56.0±12.8	0.127
Male sex	759 (49.9)	221 (43.4)	538 (53.2)	<0.001*
Alcohol (current)	807 (53.1)	255 (50.1)	552 (54.5)	0.101
Smoking (current)	250 (16.4)	72 (14.1)	178 (17.6)	0.087
Total cholesterol, mg/dL	183.7±40.8	183.0±43.6	184.1±39.4	0.733
HDL, mg/dL	51.8±14.4	51.9±13.9	51.7±14.7	0.912
LDL, mg/dL	108.1±32.6	110.0±34.7	107.2±31.6	0.532
TG, mg/dL	134.5±82.5	141.7±95.0	130.8±75.0	0.271
FPG, mg/dL	129.2±35.0	140.0±43.5	124.7±30.2	0.123
SBP, mm Hg	122.9±13.2	123.9±14.4	122.4±12.7	0.369
DBP, mm Hg	73.3±8.8	74.2±9.1	72.9±8.7	0.212
BMI, kg/m^2	23.8±3.5	24.1±3.9	23.7±3.4	0.397
HTN	409 (26.8)	130 (25.5)	279 (27.5)	0.400
DM	160 (10.5)	53 (10.4)	107 (10.6)	0.923
Dyslipidemia	294 (19.3)	106 (20.8)	188 (18.6)	0.295
Antihypertensive medication	444 (29.2)	140 (27.5)	304 (30.0)	0.305
Antidiabetic medication	156 (10.3)	52 (10.2)	104 (10.3)	0.971
Lipid-lowering medication	278 (18.3)	105 (20.6)	173 (17.1)	0.092

Data are presented as mean±SD or number (%).
HP, *Helicobacter pylori*; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus.
*Statistical significance.

Table 2. Baseline Characteristics and the Influence of HP Infection in Metabolic Parameters by Sex

Variable	Male (n=759)				Female (n=762)				p-value
	Total (n=759, 100%)	HP (–) (n=221, 29.1%)	HP (+) (n=538, 70.9%)	p-value	Total (n=762, 100%)	HP (–) (n=288, 37.8%)	HP (+) (n=474, 62.2%)	p-value	
Age, yr	56.2±14.2	56.2±16.2	56.3±13.3	0.934	54.9±13.3	53.8±14.9	55.6±12.2	0.064	0.067
Alcohol	509 (67.1)	148 (67.0)	361 (67.1)	0.972	298 (39.1)	107 (37.2)	191 (40.3)	0.389	<0.001*
Smoking	227 (30.0)	67 (30.3)	160 (29.7)	0.875	23 (3.0)	5 (1.7)	18 (3.8)	0.107	<0.001*
TC, mg/dL	176.1±39.3	175.2±41.0	176.5±38.8	0.764	193.1± 40.6	189.8±44.8	195.1±37.8	0.219	<0.001*
HDL, mg/dL	48.2±13.4	47.4±11.5	48.5±14.1	0.671	55.5±14.5	55.2±14.6	55.7±14.6	0.844	<0.001*
LDL, mg/dL	102.7±32.4	104.9±30.6	101.9±33.1	0.647	113.5±32.2	113.8±37.4	113.4±28.8	0.939	0.009*
TG, mg/dL	143.7±86.8	149.4±96.9	141.4±82.7	0.603	125.0±76.8	136.0±93.9	117.6±62.2	0.153	0.047*
FPG, mg/dL	126.0±36.1	133.7±60.0	124.5±30.7	0.578	133.8±33.5	143.1±35.5	125.3±30.3	0.190	0.396
SBP, mm Hg	125.7±12.6	128.5±13.5	124.4±12.0	0.074	120.4±13.3	120.1±14.0	120.5±13.0	0.873	0.001*
DBP, mm Hg	75.5±8.6	77.0±8.1	74.8±8.7	0.162	71.4±8.6	72.0±9.3	71.0±8.2	0.508	<0.001*
BMI, kg/m^2	23.7±3.2	23.9±3.6	23.7±3.1	0.641	23.9±4.0	24.2±4.3	23.8±3.8	0.511	0.343
HTN	230 (30.3)	66 (29.9)	164 (30.5)	0.866	179 (23.5)	64 (22.2)	115 (24.3)	0.520	0.003*
DM	96 (12.6)	28 (12.7)	68 (12.6)	0.991	64 (8.4)	25 (8.7)	39 (8.2)	0.827	0.007*
Dyslipidemia	145 (19.1)	44 (19.9)	101 (18.8)	0.718	149 (19.6)	62 (21.5)	87 (18.4)	0.284	0.824

Data are presented as mean±SD or number (%).
HP, *Helicobacter pylori*; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus.
*Statistical significance.

(p=0.095 at 3 years and p=0.691 at 5 years) (Table 4). *Post hoc* analysis showed that HDL was different between the HP-non-eradicated and HP-eradicated groups with marginal significance (p=0.053 after Bonferroni correction), and BMI was different between the HP-uninfected and HP-eradicated groups (p=0.003) and between the HP-non-eradicated and HP-eradicated groups (p=0.041) (Supplementary Table 1). The values of each parameter over the 5-year follow-up period are shown in Fig. 2.

Table 3. Effects of HP Infection and HP Eradication on Metabolic Parameters: Results from Linear Mixed Model in HP-Uninfected, HP-Non-Eradicated and HP-Eradicated Groups

Parameter	Overall effect (p-value)*	2 Months		1 Year		3 Years		5 Years	
		β (95% CI)	Adjusted p-value	β (95% CI)	Adjusted p-value	β (95% CI)	Adjusted p-value	β (95% CI)	Adjusted p-value
TC	0.835	−0.85 (−4.65 to 2.97)	0.661	2.50 (−1.02 to 6.06)	0.165	−1.36 (−4.59 to 1.89)	0.409	−0.52 (−3.82 to 2.82)	0.761
HDL	0.088	0.72 (−0.69 to 2.14)	0.321	1.15 (−0.09 to 2.41)	0.072	0.85 (−0.32 to 2.02)	0.158	0.78 (−0.41 to 1.98)	0.204
LDL	0.870	−7.24 (−12.41 to −2.04)	0.006	−4.32 (−8.90 to 0.22)	0.064	−3.37 (−7.56 to 0.81)	0.115	−5.49 (−9.70 to −1.25)	0.011
TG	0.480	−5.46 (−15.47 to 4.65)	0.288	−0.98 (−9.95 to 8.03)	0.832	−4.69 (−13.06 to 3.67)	0.273	−4.57 (−13.07 to 3.92)	0.293
FPG	0.209	−3.44 (−13.23 to 6.07)	0.490	−6.73 (−16.07 to 2.49)	0.162	−3.63 (−12.48 to 5.42)	0.434	−4.60 (−14.14 to 4.89)	0.352
SBP	0.926	1.67 (−0.82 to 4.15)	0.188	−0.13 (−2.11 to 1.84)	0.896	−0.97 (−2.66 to 0.71)	0.261	0.93 (−0.78 to 2.63)	0.285
DBP	0.297	1.33 (−0.26 to 2.92)	0.101	0.43 (−0.84 to 1.69)	0.510	0.55 (−0.53 to 1.62)	0.318	0.82 (−0.27 to 1.91)	0.139
BMI	0.006†	−0.41 (−0.90 to 0.08)	0.102	−0.44 (−0.90 to 0.03)	0.069	−0.37 (−0.76 to 0.02)	0.067	−0.70 (−1.11 to −0.29)	0.001†

HP, *Helicobacter pylori*; β, estimate; CI, confidence interval; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.
*Significance of the differences in metabolic parameters over time among the HP-infected, HP-non-eradicated and HP-eradicated groups; †Statistical significance.

3. Effects of HP eradication on metabolic parameters depending on sex

In male subjects, BMI increased after eradication, while it decreased in the HP-uninfected and non-eradicated groups. The difference between groups was significant at 1 year (p=0.010), but was not significant at three and 5 years of follow-up (p=0.156 at 3 years and p=0.243 at 5 years). *Post hoc* analysis showed that the difference in BMI in males was significant between the HP-eradicated and HP-uninfected groups and between the HP-eradicated and non-eradicated groups (Supplementary Table 2). Other metabolic parameters, including HDL, revealed no significant difference between the groups at each time point (Table 5).

In females, unlike in male subjects, there was no significant difference in the amount of BMI change from baseline to each time point among three groups. Instead, HDL showed a significant difference between the groups. HDL level increased after eradication, while it decreased in the non-eradicated group. The difference in HDL change was greatest at 1 year (p=0.023), and gradually decreased thereafter (p=0.090 at 3 years and p=0.116 at 5 years). LDL decreased post-eradication, and the difference among groups was significant at 3 years of follow-up (p=0.038) (Table 5). *Post hoc* analysis showed that the difference in HDL and LDL changes in females was significant between the HP-non-eradicated and HP-eradicated groups (Supplementary Table 2). The changes in HDL and BMI over 5 years in male and female subjects are shown in Supplementary Fig. 1.

4. Effects of HP eradication on metabolic parameters after PSM

After 1:1 PSM, the number of subjects was 346 in the HP-non-eradicated and eradicated groups. All standard mean differences of each variant were under 0.2, and the baseline characteristics of the subjects before and after PSM are shown in Supplementary Table 3. The LMM analysis after PSM showed that there was an interaction between time and HP eradication therapy at the HDL level (p=0.048). The levels of TC, LDL, TG, FPG, SBP, DBP, and BMI showed no interaction between time and HP eradication therapy (Supplementary Table 4).

The comparison of metabolic parameters at each time point showed that HDL increased after eradication while it decreased in the non-eradicated group. The difference between groups was significant at 1 year (p=0.025) (Supplementary Table 5). In the subgroup analysis, the difference in HDL between groups in female subjects remained significant even after PSM (p=0.006 at 1 year, p=0.031 at 3 years, and p=0.014 at 5 years). The difference in BMI in male subjects became marginally significant after PSM

Table 4. Changes in Metabolic Parameters in HP-Uninfected, HP-Non-Eradicated and HP-Eradicated Patients at Each Time Point of Follow-up Compared to Baseline

Parameter	2 Months				1 Year				3 Years				5 Years			
	HP-negative	Non-eradicated	Eradicated	p-value*	HP-negative	Non-eradicated	Eradicated	p-value*	HP-negative	Non-eradicated	Eradicated	p-value*	HP-negative	Non-eradicated	Eradicated	p-value*
TC	−3.11±42.89	−3.84± 35.75	−8.63±42.09	0.570	−0.17±44.69	−4.41±33.11	−1.14±38.32	0.779	−1.90±39.41	−8.89±43.11	−4.56±40.49	0.469	−0.28±44.42	−4.43±40.66	−5.85±39.80	0.515
HDL	0.20±7.71	−1.09± 7.68	2.77±8.67	0.150	−0.87±10.52	−2.38±10.47	3.05±9.61	0.027*	1.95±9.51	−2.24±9.28	1.08±8.59	0.095	−1.13±9.57	−0.73±11.10	0.59±8.74	0.691
LDL	−4.62±30.05	−6.10±33.66	−17.26±38.92	0.275	−0.85±38.50	−3.37±36.25	−7.94±30.38	0.600	0.05±34.52	4.47±28.37	−7.37±37.19	0.255	−6.02±28.70	−0.63±40.06	−8.68±32.63	0.584
TG	−7.09±98.46	14.38±80.93	−29.45±77.31	0.127	−3.82±88.59	12.26±87.63	−8.73±89.10	0.568	−12.91±88.02	10.77±60.51	−7.73±53.39	0.275	−9.79±78.09	6.82±81.24	−9.94±56.45	0.501
FPG	1.70±33.97	9.17±34.93	9.08±22.67	0.821	−18.09±46.11	−19.67±15.92	5.21±36.60	0.233	−25.60±30.78	4.50±33.65	−6.42±27.43	0.140	−18.13±43.73	3.75±36.37	−6.33±10.03	0.577
SBP	2.93±10.07	−0.63±17.36	4.07±12.12	0.605	−4.51±19.67	−3.75±13.30	0.34±13.42	0.401	−0.48±13.97	−2.34±10.38	0.36±10.37	0.623	2.25±13.52	−0.21±11.92	1.78±10.99	0.745
DBP	2.91±6.20	−0.36±10.54	2.31±5.59	0.477	−0.12±10.71	−1.12±8.65	1.57±8.40	0.555	−0.76±7.53	−0.39±5.43	2.05±6.71	0.080	−0.56±9.44	0.71±8.11	3.07±9.12	0.174
BMI	−1.11±1.33	−0.71±1.58	−0.51±0.82	0.562	−2.19±2.19	−1.23±2.67	0.87±1.43	0.002*	−0.81±2.35	−0.85±2.79	0.52±1.59	0.088	−0.22±2.44	−1.33±2.88	0.38±1.87	0.203

Data are presented as mean±SD.

HP, *Helicobacter pylori*; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

*p<0.05 were considered significant.

(p=0.089 at 1 year, p=0.123 at 3 years, and p=0.643 at 5 years). The LDL difference between groups in females also remained significant after PSM at 3 years (p=0.038) (Supplementary Table 6).

DISCUSSION

Our results revealed that the BMI and HDL levels increased after eradication, and HDL levels increased even after PSM. In comparing the effects of eradication therapy among the three groups, significant differences were present mostly between the HP-non-eradicated and eradicated groups. In addition, subgroup analysis demonstrated that HP eradication affected male and female subjects differently. The HDL levels increased, and LDL levels decreased after eradication in females, whereas BMI, but not HDL, increased in male subjects. The effects of eradication therapy on the levels of HDL and LDL in females remained significant, and post-eradication BMI increase in males was marginally significant after PSM. To our knowledge, this is the first report regarding the long-term effect of HP eradication therapy on metabolic parameters, especially focusing on sex differences.

Previous studies have reported that HP eradication increased HDL and BMI levels, although few have shown long-term outcomes. A recent meta-analysis of 24 studies with 5,270 participants, including four randomized controlled trials and 20 non-randomized controlled trials, showed an increase in HDL and TG levels after eradication and in the subgroup analysis of only randomized controlled trials, HDL elevation, but not TG, remained significant.[21] However, among the 24 studies, only two had follow-up periods of longer than a year. Meanwhile, in a study of 496 patients with HP-positive dyspepsia and/or peptic ulcer in Italy in 2009, Pellicano *et al.*[24] reported that HDL, BMI, and DBP increased significantly at 5 years after HP eradication compared to baseline. However, HP-negative subjects were not analyzed in their study.

A few studies have shown that eradication therapy decreases the LDL levels. Mokhtare *et al.*[25] from Iran reported that HP eradication decreased TC, LDL, FPG, hemoglobin A1c, and waist circumference in 2017. On the other hand, in a study Iwai *et al.*[20] from Japan reported that LDL level was not altered significantly after HP eradication in 2019 although there were significant increase in post-eradication HDL level, and resulting significant decrease in LDL/HDL ratio which is considered a predictive parameter for the assessment of the severity of coronary or carotid atherosclerosis.

Several other studies have reported that BMI increases

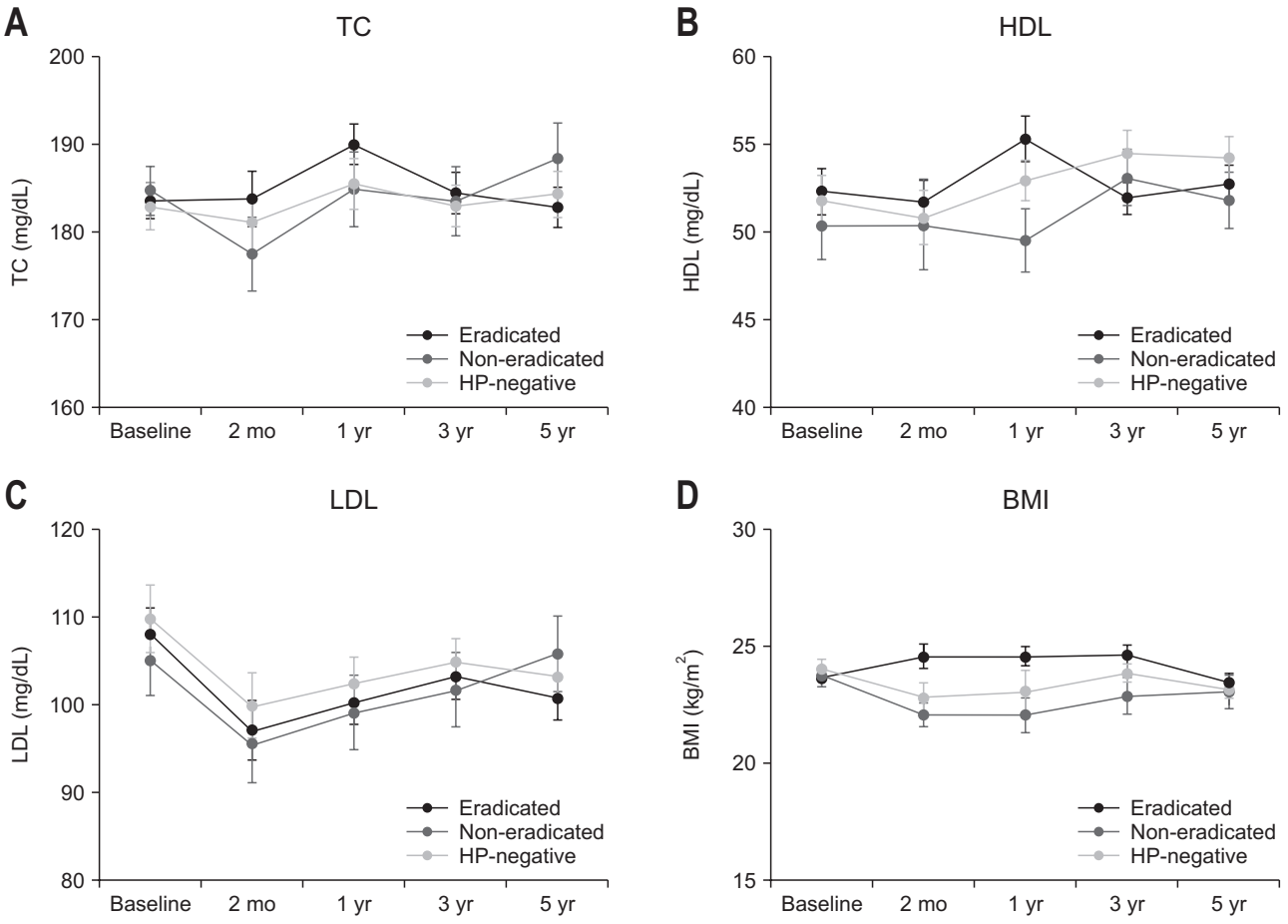

Fig. 2. Changes in the metabolic parameters over time in patients in the *Helicobacter pylori* (HP)-uninfected, HP-non-eradicated, and HP-eradicated groups. Serial changes in TC (A), HDL (B), LDL (C), and BMI (D) at baseline and after 2 months and 1 year, 3 years, and 5 years of follow-up in the HP-negative, HP-non-eradicated, and HP-eradicated groups. The overall trends of HDL levels were different among the three groups throughout the 5 years of follow-up with marginal significance, and the difference was greatest at 1 year (B). The overall trends of BMI were significantly different among groups, and the difference was greatest at 1 year as well (D). There was no significant difference in the TC and LDL change over 5 years among the HP-uninfected, HP-non-eradicated, and HP-eradicated groups (A, C).
TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; BMI, body mass index.

after HP eradication.[20,26-28] A randomized controlled study with 1,558 participants in the United Kingdom in 2011 revealed that BMI increased significantly at 6 months of follow-up in the HP eradication group compared with the placebo group. In contrast, Kim *et al.*[29] showed no significant difference in body weight change over 2 years between HP-eradicated and non-eradicated subjects in a Korean study in 2011. Our data showed similar results when analyzing both male and female subjects together, in which the BMI change over 5 years after HP eradication was not significantly different from that of the HP-non-eradicated group. However, our subgroup analysis showed interesting results. In females, the HP-eradicated group showed significantly higher HDL and decreased LDL levels than the non-eradicated group. On the other hand, BMI increased after eradication in male subjects, while there was no significant difference in the HDL or LDL levels between the eradicated and non-eradicated groups. There are only a few studies that have examined the sex differences in metabolic parameters in relation to HP eradication. Recently, in a retrospective cohort study with 2,626 healthy subjects in Korea, Park *et al.*[19] revealed that successful eradication demonstrated a protective effect for developing low HDL levels in females, but not in male subjects. Instead, HP eradication had a protective effect against the development of abnormal LDL levels in males.

The effects of HP eradication on metabolic parameters could be associated with the normalization of cytokines after eradication. Previous studies have shown that HP infection altered lipid metabolism by inducing the production of proinflammatory cytokines such as interleukin (IL)-1 and IL-6, interferon-alpha, and tumor necrosis factor-alpha, which decreased the activation of adipose tissue lipoprotein lipase, stimulated hepatic fatty acid synthesis, influenced

Table 5. Changes in Metabolic Parameters in the HP-Uninfected, HP-Non-Eradicated and HP-Eradicated Groups by Sex at Each Time Point of Follow-up Compared to Baseline

Parameter	2 Months				1 Year				3 Years				5 Years			
	HP-uninfected	Non-eradicated	Eradicated	p-value*	HP-uninfected	Non-eradicated	Eradicated	p-value*	HP-uninfected	Non-eradicated	Eradicated	p-value*	HP-uninfected	Non-eradicated	Eradicated	p-value*
Male																
TC	−2.43±40.34	−5.05±36.51	−1.64±41.96	0.900	4.88±39.64	−7.69±36.42	0.88±36.15	0.253	0.12±40.01	−11.79±41.06	1.68±40.43	0.144	2.58±45.21	−5.16±46.43	−6.58±41.00	0.440
HDL	0.53±8.55	−0.13±6.91	3.80±10.22	0.355	−0.70±12.40	−0.85±10.85	3.05±10.70	0.356	2.90±7.60	−0.70±10.93	0.98±9.21	0.464	2.89±6.82	0.95±12.27	−1.36±8.67	0.281
LDL	−3.22±22.62	−5.87±36.83	−8.27±31.34	0.893	7.10±41.49	−4.11±40.42	−8.92±30.19	0.343	12.29±29.74	−6.11±28.00	−5.38±36.32	0.112	0.71±24.24	−5.00±47.21	−4.50±31.03	0.858
BMI	−1.06±1.44	−0.78±1.61	−0.46±0.97	0.715	−1.94±2.35	−1.42±2.79	0.98±1.51	0.010*	−0.51±2.32	−1.26±3.37	0.65±1.69	0.156	0.56±1.98	−0.82±1.33	0.53±1.93	0.243
Female																
TC	−3.92±46.14	−0.79±34.52	−17.85±40.90	0.178	−4.49±48.49	1.46±25.82	−3.50±40.86	0.839	−3.49±39.10	−4.17±46.59	−13.40±39.17	0.278	−2.50±43.99	−3.13±28.53	−4.79±38.28	0.941
HDL	−0.11±7.07	−3.67±9.67	1.92±7.25	0.253	−1.00±9.09	−5.78±9.22	3.06±8.55	0.023*	1.46±10.41	−4.62±5.52	1.21±7.88	0.090	0.25±10.67	−4.10±7.77	3.11±8.31	0.116
LDL	−6.19±37.43	−6.80±25.14	−24.00±43.30	0.368	−7.04±35.55	−1.63±25.95	−6.96±31.16	0.911	−7.29±35.49	20.33±21.26	−9.69±38.70	0.038*	−10.11±30.79	8.11±18.72	−14.25±34.51	0.186
BMI	−1.28±1.13	−0.11±0.77	−0.65±0.39	0.313	−2.92±2.11	−0.24±0.75	0.29±0.99	0.117	−1.26±2.49	−0.40±1.51	0.03±1.28	0.351	−1.09±2.72	−1.06±4.97	−0.35±1.99	0.441

Data are presented as mean±SD

HP, *Helicobacter pylori*; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; BMI, body mass index.

*p-value was achieved from analysis of variance; p<0.05 were considered significant.

lipolysis, and increased hepatic HMG-CoA reductase activity.[5,15] HP eradication reversed these cytokine changes and induced insulin sensitivity, which led to a favorable effect on lipid profiles. On the other hand, weight gain and BMI are originated from the improvement in dyspepsia symptoms after HP eradication.[20,28] It may also be mediated by hormones such as leptin and ghrelin. In some studies, gastric leptin levels were elevated in HP-infected patients and decreased after eradication.[27,30] On the other hand, plasma ghrelin levels were lower in HP-infected patients and increased after eradication in some studies[31] although there are conflicting data on the effect of eradication on ghrelin levels.[32,33]

In addition to the changes of metabolic parameters in HP-eradicated group, metabolic parameters such as HDL, LDL, and BMI also changed in the HP-uninfected and HP-non-eradicated groups in this study. Although it is difficult to elucidate the exact reason for this, one possibility is the effect of education for decrease of the LDL and the importance of exercise. Subjects tend to be motivated to keep themselves healthy after education, which leads to start to lose weight or diet control. Our data showed that the LDL levels decreased at 2-month and increased again afterwards in all three groups: HP-uninfected, non-eradicated and eradicated, which could be explainable with this short-term effect of education for diet and exercise after blood tests.

In terms of the sex differences highlighted, sex hormones could be related to this mechanism. It is well known that sex hormones have a substantial influence on lipid metabolism. Premenopausal females have higher HDL and lower LDL levels than males. Lipid profile changes in females after menopause can be partially reversed by exogenous hormone replacement therapy.[34] Furthermore, Godsland[35] reported that hormone replacement therapy in healthy postmenopausal females raised HDL cholesterol and lowered LDL and TC, although these effects differed by estrogen route and progesterone type. A recent meta-analysis showed that the TG, TC, LDL, and TC to HDL ratio levels were significantly higher in postmenopausal females than in premenopausal females.[36] Thus, sex hormones could induce sex difference of HP eradication effect on lipid profiles although sex hormones may not be solely responsible for sex differences in terms of BMI or obesity. According to previous studies, obesity was more prevalent among males in some countries such as Japan, Korea, China, Germany, France, the United Kingdom, and the United States, in contrast to the worldwide average data.[13,37] Khang and Yun[38] suggested that the sex difference in obesity in East Asian countries may be attributed to social factors such as increased interest in leanness in Asian females.[13]

Our results demonstrated that the influence of eradi-

cation on HDL and BMI was maximized at 1 year and decreased after that. This may be a result of the gradual normalization of cytokines after eradication. Ando *et al.*[39] reported that IL-6 activity showed 6 months of gradual normalization compared to the 1-month rapid normalization of IL-8 after HP eradication. In addition, HDL may be affected by various factors, including lifestyle changes and body weight. In our study, BMI increased post-eradication although HDL increased, which is contradictory considering that increased body weight generally has a negative effect on lipid profile. Thus, we hypothesized that cytokines normalized gradually after eradication, and its positive effect on metabolic parameters was strong enough to overcome the negative effect of body weight increase until 1 year of follow-up.

There are also several limitations to this study. First, this was an observational study, although we prospectively enrolled the subjects. Second, although the effects of medications are important, we included 278 subjects who were taking lipid-lowering drugs in the analysis and it was very difficult to track all of the medication change over the follow-up period because many subjects (98 out of 278 subjects) took medications outside our center. However, of the 180 patients who were prescribed in our hospital, 129 had no medication change during the follow-up period. It changed in 51 subjects, but still the ratio was not significantly different among HP-uninfected, non-eradicated and eradicated groups, and neither was the ratio of subjects with dose increase or decrease. Moreover, we collected medication information at enrollment by survey, reviewed medical records, and used PSM for medication history at baseline to reduce the influence of possible confounding factors. Third, some participants were not able to undergo tests at all four follow-up times. Thus, some were included in the LMM analysis but excluded in the t-test used in the subgroup analysis, resulting in some differences between analyses. Fourth, the incidence and prevalence of MS could not be compared between groups because abdominal circumference could not be measured due to clinical surroundings. In spite of these limitations, our study has several strengths, especially in terms of the follow-up period and the clear and strict method. We analyzed the long-term data of a relatively large number of subjects, and we also investigated the effects of HP eradication on metabolic parameters focused on sex differences. In addition, we used PSM to overcome these limitations and ensure accuracy. PSM is a statistical method that can effectively adjust for confounders and thus facilitate comparability between groups in an observational study.[40-42]

In conclusion, HP eradication increased the BMI and HDL levels, with the greatest effect at 1 year of follow-up. There was a sex difference in the effect of HP eradication. In females, the HDL increased, and LDL decreased after eradication, while in males, the BMI level increase was prominent.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: N.K. Data acquisition: N.K. Data analysis and interpretation: W.S.K., S.H.L., Y.C., H.H.J. Drafting of the manuscript; critical revision of the manuscript for important intellectual content: J.P. Statistical analysis: E.J. Obtained funding: N.K. Administrative, technical, or material support; study supervision: H.Y., C.M.S., Y.S.P., D.H.L. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

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