*Original Article*

**SAGE Open Medicine**

SAGE Open Medicine
Volume 7: 1–7

DOI: 10.1177/2050312119832093
journals.sagepub.com/home/smo
SAGE

# *Helicobacter pylori* eradication in patients with type 2 diabetes mellitus: Multicenter prospective observational study

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## Abstract

**Objective:** To compare *Helicobacter pylori* (*H. pylori*) eradication rate of type 2 diabetic patients with non-diabetic subjects.

**Methods:** In this multicenter prospective observational study, *H. pylori*-infected subjects were enrolled from three university-affiliated hospitals. Eradication regimen was triple therapy with standard dose of proton pump inhibitors (b.i.d), amoxicillin (1.0 g b.i.d), and clarithromycin (500 mg b.i.d) for 7 days. Urea breath test was performed 4 weeks after treatment. Various clinical and laboratory data were collected for identification of factors associated with successful eradication.

**Results:** Totally, 144 subjects were enrolled and 119 (85 non-diabetic and 34 diabetic patients) were finally analyzed. Eradication rate was 75.6% and there was no difference between diabetic patients and non-diabetic subjects (73.5% vs 76.5%, *p* value: 0.814). Adverse drug reactions were reported in 44.5% of patients. In multivariate analysis for predicting *H. pylori* eradication in diabetic patients, HbA1c (⩾7.5%) was a significant factor affecting eradication rate (adjusted odds ratio: 0.100, 95% confidence interval: 0.011–0.909, *p* value: 0.041).

**Conclusion:** Diabetes itself is not a major factor affecting *H. pylori* eradication. However, poor glucose control may harmfully affect *H. pylori* eradication.

## Keywords

*Helicobacter pylori*, diabetes mellitus type 2, glycated hemoglobin A

Date received: 16 August 2018; accepted: 29 January 2019

## Introduction

*Helicobacter pylori* infections are common, globally affecting approximately 50% of world's population.[1] Many studies investigated the relationship between *H. pylori* infection and diabetes mellitus. Some studies reported higher prevalence of *H. pylori* infection in type 2 diabetic patients.[2–4] Some investigated effect of *H. pylori* infection on the glycemic control of diabetes such as fasting plasma glucose, glycosylated hemoglobin (HbA1c), and insulin resistance.[3,5,6] However, there are limited study on the eradication rate of *H. pylori* infection in type 2 diabetic patients, and controversy still persists.

In this study, we aimed to study the efficacy of *H. pylori* eradication of standard triple therapy in type 2 diabetic patients and comparing its eradication rate with non-diabetic subjects.

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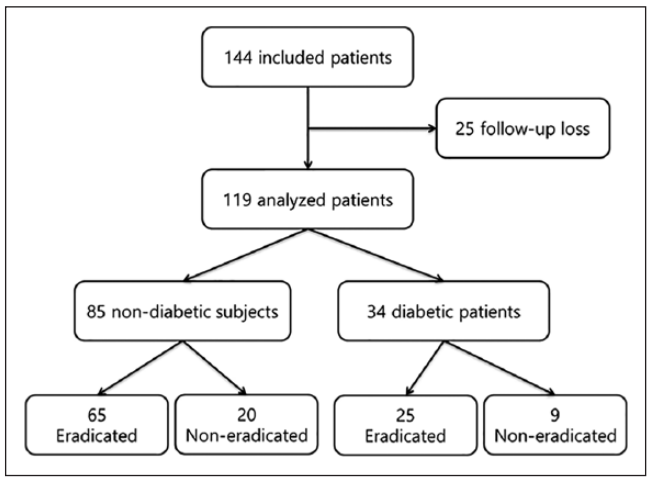


**Figure 1.** Flowchart of patients.

## Patients and methods

### Subjects

We conducted multicenter prospective observational study. Patients were recruited from three affiliated hospitals in Gangwon province, South Korea, from April 2014 to September 2016. Patients more than 18 years old who underwent esophagogastroduodenoscopy (EGD) for gastrointestinal symptoms or for participating national cancer screening program were evaluated for *H. pylori* infection and enrolled when they are positive for *H. pylori* infection. Exclusion criteria were current malignancy of gastrointestinal tract, history of previous *H. pylori* eradication, history of antibiotics administration within 3 months prior to the enrollment, history of gastric operation, and history of allergy or adverse events to antibiotics and pregnancy. Among eligible subjects, 144 patients were included, 25 patients were lost during follow-up period, and finally 119 patients were analyzed in this study (Figure 1). All patients provided written informed consent. This study was approved by the institutional review board (IRB; no. KWNUH 2014-01-009-001).

### Diagnosis, treatment, and follow-up

*H. pylori* infection was diagnosed by rapid urease test (campylobacter-like organism (CLO) test) or endoscopic biopsy of gastric mucosa (histologic assessment). The diagnosis of diabetes mellitus in this study was established according to the American Diabetes Association criteria as meeting any of the following criteria: (1) HbA1c $\geqslant$6.5% or fasting plasma glucose $\geqslant$126 mg/dL or 2-h plasma glucose $\geqslant$200 mg/dL during oral glucose tolerance test or random plasma glucose $\geqslant$200 mg/dL in a patient with classic symptoms of hyperglycemia and (2) self-reporting of physician's diagnosis of diabetes.[7]

*H. pylori* eradication regimen was triple therapy with standard dose of proton pump inhibitor (PPI, b.i.d), amoxicillin (1.0 g b.i.d), and clarithromycin (500 mg b.i.d) for 7 days. Eradication was confirmed by $^{13}$C-urea breath test performed 4 weeks after the treatment. Good compliance was defined as consumption of $>$80% of the prescribed drugs. Also, clinical and laboratory data were collected (age, sex, body mass index (BMI), alcohol, smoking, comorbidities, medications, duration of diabetes, diabetic microvascular complications, HbA1c, fasting blood glucose, and EGD findings).

### Statistical analysis

For sample size calculation, we presumed the eradication rate of diabetic patients to be 50%–60% and of non-diabetic subjects to be 70%–80% based on previous studies.[8,9] With the expected eradication rate of 55% and 75% for each group, significance level of 5% (one-sided), power of 80%, and allocation ratio of 1:2 for diabetic patients and non-diabetic subjects, we calculated the study sample size as 59:118 for each group. We could not achieve planned size of study sample and discontinued our study prematurely (Figure 1). At the time of study enrollment, Korean guideline recommended triple therapy of PPI, amoxicillin, and clarithromycin for 7–14 days as standard eradication regimen. The duration of eradication (7 days vs 14 days) has been the subject of controversy. But with the establishment of Maastricht V guideline in 2016, 14 days regimen is strongly recommended currently. So, we had to terminate our study enrollment prematurely due to the ethical issue of the 7-day treatment.

Statistical analysis in this study was based on the "full analysis set" (FAS), which is as complete as possible and as close as possible to the intention-to-treat population.[10] In the FAS analysis, patients who were lost during follow-up without clinical and eradication information were excluded. The *H. pylori* eradication rate of diabetic and non-diabetic subjects, which is the primary endpoint of the study, was evaluated with both FAS and per protocol set (Table 2).

The results were summarized as percentages or means $\pm$ standard deviations. Statistical significance of the difference between two groups was analyzed using Student's *t*-test or Fisher's exact test. Multivariable analysis was performed using multiple logistic regression analysis; *p* values less than 0.05 were considered statistically significant in all analyses. Data were analyzed using SPSS version 21.

## Results

### Clinical characteristics of the study groups

A total of 144 patients were included in this study; 25 patients were lost during follow-up period, so *H. pylori* eradication status and adverse events of eradication regimen could not be evaluated, and finally, 119 patients were analyzed. Table 1 shows clinical characteristics of the study population. Of the 119 subjects, 85 were non-diabetic and 34 were diabetic patients. Mean duration of diabetes was 10.16 years. Diabetic

**Table 1.** Clinical characteristics of the study groups.

| Characteristics | Total ($n=119$) | Non-DM ($n=85$) | DM ($n=34$) | $p$ value |
|---|---|---|---|---|
| Sex | | | | |
| Male | 68 (57.1) | 47 (55.3) | 21 (61.8) | 0.546 |
| Female | 51 (42.9) | 38 (44.7) | 13 (38.2) | |
| Age (years) | 59.05 ± 11.91 | 57.19 ± 11.87 | 63.71 ± 10.81 | 0.006 |
| BMI (kg/m$^2$) | 24.73 ± 4.07 | 24.35 ± 3.02 | 25.68 ± 5.92 | 0.229 |
| Alcohol | 58 (48.7%) | 41 (48.2%) | 17 (50.0%) | 1.000 |
| Smoking | 37 (31.1%) | 26 (30.6%) | 11 (32.4%) | 0.831 |
| Comorbidity[a] | 37 (31.1%) | 17 (20.0%) | 20 (58.8%) | <0.001 |
| Compliance (>80%) | 114 (95.8%) | 80 (94.1%) | 34 (100%) | 0.320 |
| Diabetes duration (years) | N/A | N/A | 10.16 ± 9.13 | N/A |

DM: diabetes mellitus; non-DM: non-diabetic control subjects; BMI: body mass index; N/A: not applicable.
Categorical values are presented as *N* (%) and continuous values are presented as mean ± standard deviation.
[a]Comorbidity: hypertension, cardiovascular disease, chronic kidney disease, chronic liver disease, and chronic lung disease.

**Table 2.** *Helicobacter pylori* eradication rate based on the full analysis set and per protocol set.

| | Total | Non-DM | DM | $p$ value[a] |
|---|---|---|---|---|
| Full analysis set | | | | |
| Number of patients (eradicated/total) | 90/119 | 65/85 | 25/34 | 0.814 |
| Eradication rate (%) | 75.6 | 76.5 | 73.5 | |
| Per protocol set | | | | |
| Number of patients (eradicated/total) | 87/114 | 62/80 | 25/34 | 0.638 |
| Eradication rate (%) | 76.3 | 77.5 | 73.5 | |

DM: diabetes mellitus; non-DM: non-diabetic control subjects.
[a]Fisher's exact test for comparison of eradication rate between diabetic patients and non-diabetic subjects.

patients were older and had more comorbid diseases (such as hypertension, cardiovascular disease, chronic kidney disease, chronic liver disease, and chronic lung disease) compared to non-diabetic subjects. Otherwise, there was no significant difference between non-diabetic and diabetic patients in sex ratio, BMI, alcohol and smoking consumption, and drug compliance (Table 1).

## *Comparison of* H. pylori *eradication rate between diabetic and non-diabetic subjects*

*H. pylori* eradication rate was 75.6% in our study population. For non-diabetic patients, eradication rate was 76.5%. For diabetic patients, eradication rate was 73.5%. There was no statistically significant difference between two groups (Table 2). Eradication rate calculated by per protocol analysis also showed no significant difference (Table 2, 77.5% vs 73.5%). In multiple logistic regression analysis, diabetes was not a significant factor when we control other various factors assessed in this study (Table 3). Although not statistically significant, eradication rates tended to be low in women and older age ($p$ value 0.053 and 0.059 for each).

We also compared clinical characteristics between *H. pylori* eradicated group ($n=90$) and non-eradicated groups ($n=29$). Age was older in non-eradicated group compared to eradicated group. Other factors did not show significant difference between two groups (Supplementary Table 1).

## *Adverse events during eradication therapy*

We investigated various adverse reactions during eradication treatment period. Adverse drug reactions (ADRs) were recorded by Likert-type scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Most patients showed no or mild ADR, but 10 patients showed severe ADR, which are severe nausea for 2 patients, severe abdominal pain for 1 patient, severe diarrhea for 1 patient, and severe metallic taste for 8 patients. Most severe ADRs were reported in non-diabetic subjects (8 subjects) except 2 diabetic patients who complained severe metallic taste. All patients who reported severe nausea, abdominal pain, or diarrhea showed poor compliance of eradication treatment. However, for metallic taste, only 1 of 8 patients showed poor compliance. Because most patients showed no or mild ADRs, we reanalyzed the results as none or any (i.e. we recorded response categories 1, 2, and 3 as 1 and recoded 0 as 0). Total reported ADRs were significantly lower in diabetic patients compared to non-diabetic patients (29.4% vs 50.6%, Table 4). Abdominal pain and metallic taste were frequently reported adverse events for both groups. Compliance of the treatment was

**Table 3.** Multiple logistic regression results for predicting *Helicobacter pylori* eradication.

| Model variables | Adjusted odds ratio[a] (95% CI) | *p* value |
|---|---|---|
| DM | 0.741 (0.252–2.181) | 0.586 |
| Female | 0.357 (0.126–1.014) | 0.053 |
| Age | 0.960 (0.920–1.002) | 0.059 |
| BMI | 0.984 (0.871–1.112) | 0.797 |
| Alcohol | 1.168 (0.372–3.668) | 0.791 |
| Smoking | 0.691 (0.188–2.540) | 0.577 |
| Comorbidity[b] | 1.623 (0.561–4.695) | 0.371 |
| Compliance | 2.990 (0.409–21.861) | 0.281 |

CI: confidence interval; DM: diabetes mellitus; BMI: body mass index.
[a]Odds ratios from logistic regression were adjusted for diabetes, sex, age, BMI, alcohol and smoking status, comorbidity, and compliance.
[b]Comorbidity: hypertension, cardiovascular disease, chronic kidney disease, chronic liver disease, and chronic lung disease.

**Table 4.** ADRs of eradication regimen.

| | Non-DM ($n=85$) | DM ($n=34$) | *p* value* |
|---|---|---|---|
| Total (%) | 43 (50.6%) | 10 (29.4%) | 0.042 |
| Nausea/vomiting (%) | 10 (11.8%) | 2 (5.9%) | 0.505 |
| Abdominal pain (%) | 10 (11.8%) | 5 (14.7%) | 0.761 |
| Diarrhea (%) | 11 (12.9%) | 1 (2.9%) | 0.175 |
| Constipation (%) | 4 (4.7%) | 2 (5.9%) | 1.00 |
| Rash (%) | 3 (3.5%) | 0 (0%) | 0.557 |
| Metallic taste (%) | 26 (30.6%) | 4 (11.8%) | 0.037 |

DM: diabetes mellitus; ADR: adverse drug reaction.
ADR was recorded by Likert-type scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).
*$p$ value for each components of ADR coded by 0 or 1 (none: 0 or any: 1).

significantly lower in group with any ADRs compared to group without any ADRs (90.6% vs 100%, $p$ value = 0.016 by Fisher's exact test).

### *Factors associated with* H. pylori *eradication in diabetic patients*

We performed subgroup analysis about factors associated with *H. pylori* eradication in diabetic patients, even though the number of diabetic patients was small ($n=34$; Supplementary Table 2). There was no significant difference between eradicated and non-eradicated groups in age, sex, BMI, diabetic duration, fasting glucose level, and treatment modalities. In addition, there was no relationship between the kinds of diabetic drugs and eradication outcome (data not shown). However, the proportion of well-controlled diabetes (HbA1c $<$ 7.5%) was significantly higher in eradicated group compared to non-eradicated group (81.0% vs 37.5%), suggesting that control of blood sugar is a significant factor for *H. pylori* eradication in type 2 diabetic patients. Multivariate analysis also showed that HbA1c ($\geqslant$7.5%) was a significant factor predicting *H. pylori* eradication in diabetic patients (adjusted odds ratio: 0.100, 95% confidence interval: 0.011–0.909, $p$ value: 0.041; Table 5).

## Discussion

Many studies have been published on the relationship of *H. pylori* and type 2 diabetes, but still there are controversies in many aspects. Some studies reported high prevalence of *H. pylori* infection in type 2 diabetic patients,[11–14] while others reported no difference of the prevalence between type 2 diabetic patients and non-diabetic control subjects.[15–17] In addition, some studies reported significant effect of *H. pylori* infection on the glucose control of diabetes such as HbA1c and insulin resistance,[18–20] while others showed no relationship between *H. pylori* infection and glucose control.[9,21,22] Studies for the effect of type 2 diabetes on the eradication rate of *H. pylori* treatment are limited,[2,8,9,23–25] but they showed similar results of lower eradication rate compared to non-diabetic controls with standard triple antibiotics for 7–14 days, except one study showing similar eradication rate between two groups treated with bismuth-based quadruple regimen for 14 days.[26] Recently, one retrospective study reported similar eradication rate between type 2 diabetic patients and non-diabetic subjects with standard triple antibiotics for 7–14 days.[27] The proposed mechanism of lower eradication rate in diabetic patients is impaired gastric mucosal microvasculature leading to reduced antibiotics absorption, frequent antibiotic usage in diabetic patient group due to recurrent bacterial infections, and immunosuppressive condition of diabetes.[2,23]

**Table 5.** Multiple logistic regression results for predicting *Helicobacter pylori* eradication in diabetic patients.

| Model variables | Adjusted odds ratio[a] (95% CI) | *p* value |
|---|---|---|
| Age (years) | 0.946 (0.842–1.063) | 0.349 |
| Female | 0.781 (0.120–5.069) | 0.795 |
| BMI | 1.015 (0.804–1.281) | 0.899 |
| HbA1c (⩾7.5%) | 0.100 (0.011–0.909) | 0.041 |

CI: confidence interval; BMI: body mass index.
[a]Odds ratios from logistic regression were adjusted for age, sex, BMI, and HbA1c.

In this study, we performed multicenter prospective observational study treating *H. pylori*-infected type 2 diabetic patients with standard triple therapy (PPI, amoxicillin, and clarithromycin) for 7 days and showed no significant difference in eradication rate between diabetic patients and non-diabetic control subjects (eradication rate 73.5% vs 76.5% for each). The eradication rate in this study was similar to previous studies for non-diabetic controls (75.9%–87.7%), but eradication rate of diabetic patients was significantly higher compared to other studies (42.9%–63%), resulting in no significant difference between two groups.[2,8,9,23,24] It is difficult to define the factors causing this difference, but glucose control may be one factor because HbA1c level of diabetic patients in our study was relatively well controlled ($7.4 \pm 1.5$), and BMI was lower ($25.7 \pm 5.9$) compared to previous studies. In addition, considering several Korean studies showing eradication rate of 73.9% and 75.8% in diabetic patients,[27,28] some factors such as previous antibiotics exposure of diabetic patients in Korea or other ethical differences which are difficult to clarify from the previous data can have an effect on the eradication rate.

The rate of ADRs in this study was 50.6% for non-diabetic subjects and 29.4% for diabetic patients, which are higher compared to previous results of 10%–20%.[8] We recorded ADRs by Likert-type scale as none, mild, moderate, and severe. Most ADRs were mild and the rate of moderate-to-severe ADRs was 16.8%, which is similar to previous data, so we believe that the different method of ADR investigation results in difference in the rate of ADRs. Diabetic patients reported lower ADRs compared to non-diabetic subjects, which was inconsistent to previous report showing no difference.[8] We could not identify the exact reason but assume that detailed investigation of symptoms may obtain more subtle discomfort from non-diabetic subjects than diabetic patients who are already suffering from the similar discomfort due to diabetes itself or several medications.

This prospective study has an advantage in that it can determine the compliance of patients, the duration of diabetes, and the diabetic controls enabling to analyze the effect of these factors on the eradication rate. In subgroup analysis for diabetic patients, the only significant factor affecting eradication rate was HbA1c (Supplementary Table 2 and Table 5). One of the possible mechanisms of low eradication rate in hyperglycemic state is its impact on immune system, especially on innate immune systems.[29–31] Also, hyperglycemia affects endothelial function acutely and chronically leading to impaired gastric mucosal microvasculature resulting in reduced antibiotics absorption.[30,32,33] There is few study analyzing factors associated with *H. pylori* eradication rates in type 2 diabetic patients,[2] so our result needs to be validated by more large number of patients of clinical trials, but good glucose control may be an important measure to improve the rate of *H. pylori* eradication in type 2 diabetic patients.

Our study has several limitations. First, the number of diabetic patients ($N=34$) was not enough to analyze significant factors associated with *H. pylori* eradication rate in type 2 diabetic patients. Second, we treated patients with standard triple regimen for 7 days resulting in unsatisfactory eradication rate. Recently, clarithromycin resistance rates of Korea are high (>15%), so other approach needs to be addressed even though Korean guideline still recommends standard triple therapy for 7–14 days.[34] In addition, recent Maastricht V consensus recommends 14 days of treatment duration of PPI-clarithromycin-based triple therapy rather than 7 days.[35] Third, we did not check the state of clarithromycin resistance (e.g. detection of point mutations by polymerase chain reaction) for each individual. Different state of antibiotics resistance can affect the eradication rate, confounding the effect of diabetes on the eradication. Fourth, we did not check the state of PPI usage within 1 month prior to eradication treatment, which is possibly associated with *H. pylori* eradication rate. Several previous studies showed controversial effect of PPI pretreatment on the *H. pylori* eradication which is beneficial or harmful,[36,37] but recent data showed no significant effect of PPI pretreatment on eradication rate, so this subject still needs to be verified.[38] We consider relatively small number of diabetic patients and short course of eradication regimen which was standard regimen at the time of study design but are not popular nowadays are the main limitations in this study. But this study clearly shows and compares the eradication rate of diabetic patients and non-diabetic subjects.

In contrast to previous studies, this multicenter prospective observational study to compare *H. pylori* eradication rate between type 2 diabetic patients and non-diabetic subjects with PPI-clarithromycin-based triple therapy for 7 days shows no significant difference in eradication success rate between two groups. Multivariable analysis also shows that diabetes is not a significant factor affecting eradication. ADRs of treatment are more prevalent in non-diabetic subjects. In subgroup analysis for diabetic patients, HbA1c was the only significant factor associated with eradication success in type 2 diabetic patients. From our study, we conclude that diabetes itself is not a major factor affecting *H. pylori* eradication, but poor glucose control may harmfully affect *H. pylori* eradication. Further study with more number of diabetic subjects will help optimize *H. pylori* eradication therapy in diabetic patients.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Ethical approval for this study was obtained from * INSTITUTIONAL REVIEW BOARD (KWNUH 2014-01-009-001)*.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by 2016 Research Grant from Kangwon National University (No. 520160433) and a grant of the Kangwon Branch of the Korean Society of Gastrointestinal Endoscopy (KSGE_KW_04).

## Informed consent

Written informed consent was obtained from all subjects before the study.

## Supplemental material

Supplemental material for this article is available online.

## Trial registration

Clinical Research Information Service (CRIS): KCT0001062.

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