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ORIGINAL RESEARCH

First-line *Helicobacter pylori* eradication rates are significantly lower in patients with than those without type 2 diabetes mellitus

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Purpose: To assess the difference of the first-line therapy for *Helicobacter pylori* in patients with or without type 2 diabetes (DM) and to investigate the clinical factors influencing treatment outcomes.

Patients and methods: In total, 719 patients with *H. pylori* infection were treated with 7-day standard first-line triple therapy, of whom 182 did and 537 did not have DM. Propensity score matched at a 1:2 ratio – for age, sex and body mass index was performed for the two groups, yielding a DM group with 147 patients and a non-DM group with 249 matched controls for analysis. Urea breath test was performed 6–8 weeks after treatment. Clinical and laboratory parameters were collected for identifying factors associated with failed eradication.

Results: *H. Pylori* was eradicated in 74.1% (95% confidence interval [CI] =66.2–81.0) of the DM group and 85.3% (95% CI =80.8–89.4) of the non-DM group (p=0.005). Of 51 gastric biopsy samples cultured for *H. pylori*, 41 were positive. In the DM group, the rates of resistance to amoxicillin, clarithromycin, levofloxacin, and tetracycline were 0%, 50.0%, 50.0% and 0%, respectively. In the non-DM group, the comparable proportions were 2.9%, 17.1%, 22.9%, and 0%, respectively. Univariate analysis revealed that DM (Odds ratio [OR], 1.771, 95% CI, 1.167–2.668, p=0.006), clarithromycin resistance (OR, 15.273; 95% CI, 1.687–138.269; p=0.015), and amoxicillin resistance (OR, 4.672; 95% CI, 2.431–8.979; p<0.001) were independently associated with failure to eradicate *H. pylori*. Multivariate analysis showed that clarithromycin resistance was the major factor independently associated with failure of eradication (OR, 25.472; 95% CI, 1.549–418.956; p=0.023).

Conclusions: First-line *H. pylori* eradication rates in patients with DM were significantly lower than in those without DM, although neither group achieved >90% eradication.

Keywords: *Helicobacter pylori* infection, standard triple therapy

Introduction

Helicobacter pylori infection affects approximately 50% of the world's population.[1–4] The World Health Organization classified *H. pylori* as a grade I carcinogen, and the major risk factor of peptic ulcer diseases. Chronic gastritis attributed to the organism can progress through the pre malignant stages of atrophic gastritis, intestinal metaplasia, and dysplasia, and then gastric cancer.[5–8] Hence, successful eradication is a major issue with the potential to influence patient outcomes.

Recent studies have explored significant association between *H. pylori* infection and extragastric diseases such as cardiovascular disease, metabolic syndrome and certain liver diseases, such as non-alcoholic fatty liver disease, non-alcoholic steatohepatitis,

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liver fibrosis and cirrhosis.[9] The involved pathogenesis is chronic inflammation and immune responses on the local and systemic level.[10] Since more convincing evidences are still an unmet need on this issue, it is therefore worth further investigation.

A higher prevalence of *H. pylori* infection in patients with type 2 diabetes mellitus (DM) has been reported in previous studies.[11–14] In addition, some have investigated the influence of *H. pylori* infection on the glucose control in a diabetic cohort of patients with DM.[15,16] However, there are limited studies regarding eradication rates of *H. pylori* in patients with DM, and the findings have been inconsistent.[17–19] Therefore, we aimed to assess the difference of the first line *H. pylori* in patients with or without type 2 DM and to investigate the clinical factors influencing treatment outcomes.

Patients and methods

Patients

We assessed records of 719 patients who were treated for *H. pylori* infection with standard first-line triple therapy (Proton-pump inhibitor twice daily, 500 mg clarithromycin twice daily, and 1 g amoxicillin twice daily for 7 days) between January 1, 2013 and December 31, 2014 at outpatient clinics in Kaohsiung Chang Gung Memorial Hospital, Taiwan. All patients were at least 18 years of age and had undergone endoscopy that showed either peptic ulcers or gastritis. *H. pylori* infection was diagnosed by histological assessment of endoscopic biopsy specimens of gastric mucosa. Records of patients with a history of previous *H. Pylori* eradication, antibiotics administration within 3 months prior to endoscopy, gastric malignancy, who were lost to follow-up or had incomplete records, or who were treated by 7-day non-bismuth containing quadruple therapy were also excluded.

Of the 719 patients for whom records were available, 182 had DM and 537 did not. To minimize potential selection bias between the two groups, we employed propensity score matching (PSM) with the covariates age, gender, and body mass index (BMI). Using a greedy matching algorithm, the groups were matched in a 1:2 ratio, resulting in 147 patients in the DM group and 279 in the non-DM control group.

The criteria for the diagnosis of DM were 1) a fasting blood glucose level greater than or equal to 126 mg/dl on two occasions; 2) a hemoglobin A1c level greater than or equal to 6.5% on two occasions; 3) a random blood glucose level greater than or equal to 200 mg/dl with classic symptoms of hyperglycemia.

Outcomes and follow-up

The primary outcome of interest was the successful eradication of *H. pylori*. Failure of eradication by first-line therapy was confirmed after treatment by either one positive 13C-urea breath test or any two positive results of the rapid urease test, histology or culture when repeating the testing twice. According to our hospital requirements, all patients were followed to assess drug compliance and adverse effects as soon as they finished their medications. Then, they underwent either an endoscopy or a urea breath test 6–8 weeks later. Failure to finish 80% of all medication due to adverse effects was considered poor compliance.[20,21]

Demographic information recorded from the electronic medical records included age, gender, BMI, history of smoking, alcohol consumption, previous peptic ulcer history, duration of DM, medications, and laboratory data (fasting glucose sugar, HbA1c, lipid profile).

Culture and antimicrobial resistance

One antral gastric and one corpus biopsy specimen were obtained from 51 patients for *H. pylori* isolation using previously described culture methods.[20] The biopsy specimens were cultured on plates containing Brucella chocolate agar with 7% sheep blood and incubated for 4–5 days under micro-aerobic conditions. The minimal inhibitory concentration (MIC) was determined by the agar dilution test. *H. pylori* strains with MIC values ≥0.5, ≥1, ≥1, ≥4 and ≥8 mg/L were considered to be resistant to amoxicillin, clarithromycin, levofloxacin, tetracycline and metronidazole , respectively.[21]

Statistical analysis

The primary outcome variables were the eradication rate, occurrence of adverse events, and level of patient compliance. Using the SPSS program (Statistical Package for the Social Sciences version 20, IBM Corporation, Armonk, NY, USA), Chi-square tests with or without Yates' correction for continuity and Fisher's exact tests were used when appropriate to compare the outcomes between groups. Eradication rates were analyzed for all included patients. We also excluded patients with unknown *H. pylori* status following therapy and those with major protocol violations. A p-value <0.05 was considered statistically significant. To determine the independent factors that affected treatment response, clinical and laboratory parameters were analyzed after PSM for age, gender, and BMI by univariate and multivariate analysis.

Results

The demographic data of the two groups before and after PSM are summarized in Table 1. Before PSM, the mean age of patients in the DM group was higher than in the non-DM group, but there was no significant difference among any covariates in the groups after PSM. The duration of DM was 8.1±5.9 years and 80.8% (147/182) of the patients were taking oral antihyperglycemic drugs. Only three patients (1.6%) needed Insulin monotherapy, while six took both an oral antihyperglycemic drug and insulin. The eradication rates attained in the DM and non-DM groups before PSM were 75.3% (95% confidence interval (CI) =68.4–81.4) and 84.4% (95% CI =81.1–87.4) (p=0.006) and 74.1% (95% confidence interval (CI) =66.2–81.0) and 85.3% (95% CI =80.8.8–89.4) (p=0.005) (Table 2). Samples from 51 patients were cultured for *H. pylori*, yielding 41 positive cultures. In the DM group, the rates of resistance to the antibiotics were amoxicillin, 0% (0/6); clarithromycin, 50.0% (3/6); levofloxacin, 50.0% (3/6); and tetracycline, 0% (0/6). In the non-DM group, the rates of resistance were amoxicillin, 2.9% (1/35); clarithromycin, 17.1% (6/35); levofloxacin, 22.9% (8/35); and tetracycline, 0 % (0/35).

Adverse events

The incidence of adverse events did not differ significantly between the two groups (DM 4.1% vs non-DM 6.5%, p=0.313) (Table 3). The adverse events included abdominal pain, constipation, diarrhea, dizziness, headache, nausea or vomiting, and skin rash. In the DM group, two patients had abdominal pain (1.4%), two (1.4%) had constipation, two had loose stool passage (1.4%) and one (0.7%) had nausea; In the non-DM group, four patients (1.4%) had abdominal pain, five patients (1.8%) had constipation, seven patients (2.5%) had loose stool passage, three (1.1%) had dizziness, one (0.4%) had headache and two (0.7%) had nausea. These adverse events were mild and did not disturb the patients' daily activities.

Factors influencing the efficacy of anti-*H. pylori*therapy

On univariate analysis, factors independently associated with failure to eradicate *H. pylori* included DM (Odds ratio [OR], 1.771, 95% CI, 1.167–2.668, p=0.006), clarithromycin resistance (OR, 15.273; 95% CI, 1.687–-138.269; p=0.015 and amoxicillin resistance (OR, 4.672; 95% CI, 2.431–8.979; p<0.001) (Table 4).

Table 1 Baseline characteristics of patients with and without DM

	Before PSM			After PSM for age, sex, BMI		
	DM group N=182 (%)	Control N=537 (%)	*P*-value	DM group N=147 (%)	Matched control N=279 (%)	*p*-value
Age (years)	64.1±9.0	58.3±12.2	<0.001	63.2±8.9	63.9±10.3	0.401
Sex (male); n (%)	87 (47.8)	270 (50.3)	0.564	68 (46.3)	126 (45.2)	0.829
Body weight (kg)	68.9±12.6	64.4±13.1	<0.001	69.3±12.9	67.3±12.7	0.119
BMI; mean ± SD	26.0±3.9	24.3±4.2	<0.001	26.0±3.9	25.5±3.9	0.203
Previous history of peptic ulcer	39 (21.4)	101 (18.8)	0.440	31 (21.1)	60 (21.5)	0.920
Alcohol; n (%)	23 (12.6)	83 (15.5)	0.354	21 (14.3)	49 (17.6)	0.386
Smoking; n (%)	24 (13.2)	76 (14.2)	0.745	22 (15.0)	41(14.7)	0.940
Diabetes duration (years)	8.1±5.9	NA		7.9±5.9	NA	
Diabetes treatment; n (%)						
No treatment	26 (14.3)	NA		25 (17.0)	NA	
Oral antihyperglycemic drug	147 (80.8)			116 (78.9)		
Insulin monotherapy	3 (1.6)			2 (1.4)		
Combination therapy	6 (3.3)			4 (2.7)		
Low-density lipoprotein (mg/dL)	101.7±31.7	108.7±31.7	0.032	103.6±32.9	106.8±31.8	0.416
Triglycerides (mg/dL)	148.4±83.8	124.8±75.4	0.003	153.5±88.5	135.3±8 4.0	0.077
GFR (ml/min/1.73 m^2)	77.6±29.0	84.8±24.6	0.003	78.2±27.6	81.0±24.4	0.330

Abbreviations: PSM, propensity score matching; DM, diabetes mellitus; SD, standard deviation; BMI, body mass index; GFR, glomerular filtration rate; NA, no analysis.

Table 2 Major outcomes of *H. pylori* eradication therapy

Eradication rate	DM group	Control	*p*-value
Patients, % (n) Before matching	75.3% (137/182)	84.4% (453/537)	0.006
Patients, % (n) After matching	74.1% (109/147)	85.3% (238/279)	0.005

Abbreviation: DM, diabetes mellitus.

Table 3 Adverse events of the *H. pylori* treatment regimen after matching

	DM group N=147 (%)	Matched control N=279 (%)	*p*-value
Skin rash	0	0	-
Abdominal pain	2 (1.4)	4 (1.4)	0.951
Constipation	2 (1.4)	5 (1.8)	0.739
Loose stool	2 (1.4)	7 (2.5)	0.433
Dizziness	0	3 (1.1)	0.207
Headache	0	1 (0.4)	0.467
Nausea	1 (0.7)	2 (0.7)	0.966

Abbreviation: DM, diabetes mellitus.

Multivariate analysis showed that clarithromycin resistance was the major factor independently associated with failure of *H. pylori* eradication (OR, 25.472; 95% CI, 1.549–418.956; p=0.023) (Table 5).

Discussion

H. pylori infection is the major risk factor in peptic ulcer disease. Successful eradication of *H. pylori* has greatly reduced the recurrence of peptic ulcers as well as the incidence of atrophic gastritis and gastric cancer. Reports on *H. pylori* infection in DM have had conflicting findings. Some studies have shown a higher prevalence of *H. pylori* infection in patients with DM, while others have found no difference.[11,14,22,23] In a large, well-designed study by Xia et al,[24] there was no difference in *H. pylori* seroprevalence between patients with DM and non-DM controls.[24] Reports on the effect of *H. pylori* infection on the glucose control of diabetes measured by HbA1c or insulin resistance have also yielded inconsistent findings,[15,25,26] as have studies of the success rate of first line eradication in patients with DM.[12,18,19] In the present study, the eradication rate with standard triple therapy in the non-DM group was 84.4%

Table 4 Univariate analysis of factors associated with failure of *H. pylori* eradication

Variants	Comparison	Univariate OR (95% CI)	*p*-value
Age	Per 1-year increment	0.999 (0.983–1.015)	0.877
Sex	Male vs female	1.301 (0.887–1.908)	0.177
BMI	Per 1 kg/m^2 increment	0.997 (0.951–1.045)	0.894
Previous history of ulcer	Yes vs no	0.949 (0.589–1.528)	0.829
Alcohol	Yes vs no	1.202 (0.663–2.177)	0.545
Smoking	Yes vs no	1.065 (0.575–1.971)	0.841
Comorbidity			
Diabetes	Yes vs no	1.771 (1.167–2.668)	0.006
Hypertension	Yes vs no	1.151 (0.769–1.724)	0.496
Coronary artery disease	Yes vs no	0.730 (0.321–1.661)	0.453
Cerebrovascular accident	Yes vs no	1.870 (0.711–4.916)	0.204
Chronic kidney disease	Yes vs no	0.985 (0.576–1.686)	0.957
Dyslipidemia	Yes vs no	1.489 (0.962–2.307)	0.074
***H. pylori* culture (n=41)**			
Clarithromycin resistance	Yes vs no	15.273 (1.687–138.269)	0.015
Amoxicillin resistance	Yes vs no	4.672 (2.431–8.979)	<0.001

Note: Factors with a *P*-value less than 0.3 were entered into logistic regression analysis.
Abbreviation: BMI, body mass index.

Table 5 Multivariate analysis of the clinical factors associated with failure of *H. pylori* eradication

Clinical factor	Coefficient	Standard error	Odds ratio (95% CI)	*p*-value
Clarithromycin resistance	3.238	1.429	25.472 (1.549–418.956)	0.023

Abbreviation: CI, confidence interval.

before and 85.3% after PSM, results which are compatible with results in Taiwan 5 years previously.[27]

Some investigations have found that eradication rates of *H pylori* in patients with type I diabetes were lower than in non-DM patients.[26,28,29] For instance, Gasbarrini et al[26] showed that the *H. pylori* eradication rate with 7-day standard triple therapy comprising amoxicillin, clarithromycin, and pantoprazole was 65% in patients with type I diabetes compared with 92% in non-DM controls in 1999.[26] They suggested that patients with insulin-dependent DM often had chronic infections which might lead to poor antibiotic absorption. However, reports on factors influencing *H. pylori* eradication in type 2 DM have been inconsistent. In our study after PSM, patients with DM treated with 7-day standard triple therapy had significantly lower eradication rates than the non-DM control group (74.1% vs 85.3%, p=0.005). This is consistent with previous reports that standard triple therapy conferred lower eradication rates in patients with DM.[17,18,30,31,32] For example, Sargýn et al[30] reported eradication in 50% of patients with diabetes versus 85% in the control group by prescribing a 10-day standard triple therapy (p<0.001).[30] In another study by Vafaeimanesh et al,[17] the 14-day regimens yielded *H. pylori* eradication rate of 63% in the DM group and 87.7% in the control group (p=0.017).[17]

Several proposed mechanisms may explain the low eradication rate of *H. pylori* eradication in DM patients. First, DM impairs the immune system to a variable extent.[33,34]Second, patients with DM are more susceptible to bacterial and mycotic infections, leading to frequent use of antibiotics, which may in turn contribute to the development of resistance.[35,36] Third, diabetes may impair gastric mucosal microvasculature, leading to reduction in antibiotics absorption.[37] Fourth, it is very likely that the more frequent use of multiple antibiotics in these patients may ultimately lead to *H. pylori*-resistant strains, like the high rate of clarithromycin resistance in this study. Finally, re-infection after bacterial eradication, although rarely observed in the general population, seems to be more frequent in patients with diabetes than in controls.[38] Nevertheless, we were unable to assess the actual re-infection rate in this study due to its retrospective nature.

We performed univariate and multivariate analysis to assess factors independently associated with *H. pylori* eradication. On univariate analysis, a diagnosis of DM, and clarithromycin or amoxicillin resistance were factors associated with failure of *H. pylori* eradication. On multivariate analysis, clarithromycin resistance was the only significant factor associated with lack of *H. pylori* eradication. The clarithromycin resistance rate in the DM patients was very high compared with non-DM group. It was also higher than in the general population in Taiwan, reported by Liou et al [39]only 7.9%.[39] It was probably one of the main causes for the lower *H. pylori* eradication rate in our DM group, which was consistent with that in the report by Demir et al.[32]As noted above, it is likely that poor eradication rates among patients with DM may be attributed to factors such as decreased immunocompetence, increased antibiotic resistance because of frequent antibiotic use, and poor gastric absorption. Another study by Demir et al[19] from Turkey reported that the eradication rate with triple therapy was only 51% in patients with DM, which was very likely associated with the high clarithromycin resistance rate of 40%.[19] They had much better results with a 14-day clarithromycin-free regimen including pantoprazole (40 mg b.i.d.), bismuth citrate (400 mg b.i.d.), tetracycline (500 mg q.i.d.), and metronidazole (500 mg b.i.d.), which succeeded in eradicating *H. pylori* in 85% of the DM group and 87% of the non-DM group.

This study encountered some limitations. First, this was a retrospective study in a single medical center. Second, 7-day standard triple therapy was used in this study during our study period from January 2013 to December 2014. This was because first-line clarithromycin triple therapy was reimbursable for only 7 days under the Taiwan National Health Insurance System even until now. However, 10–14 day reports with standard triple therapies reported in the literature showed that this regimen was also suboptimal in this DM patient cohort. However, very high clarithromycin resistance was observed in the patients with DM and was the major factor independently associated with failure of *H. pylori* eradication. It is an important message that there are still unmet needs in the treatment of *H. Pylori* infection in patients with DM, given the limited number of studies focusing on this population. Ataseven et al[40]

reported a disappointing <60% eradication rate for 14-day sequential therapy in patients with type 2 DM.[40] Demir et al showed that the bismuth-based quadruple eradication regimen as first-line therapy attained 85% eradication.[19]Clearly more evidences are required to clarify the best treatment in these patients.

Conclusions

This study found that first-line *H. pylori* eradication rates in patients with DM were significantly lower than in those without DM, although neither group achieved >90% eradication. Studies seeking for optimal novel first line *H. pylori* regimens for diabetic patients are mandatory.

Ethics approval and informed consent

The data in this study were collected from computerized medical charts. This study was approved by both the Institutional Review Board and Ethics Committee of Chang Gung Memorial Hospital, Taiwan (IRB 201801207B0). The Ethics Committee waived the requirement for informed consent, and each patient's medical records were anonymized and deidentified prior to access. None of the patients were minors. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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