



OPEN Safety and effectiveness of dual therapy for *Helicobacter pylori* infection and the effect on the glycated hemoglobin level in type 2 diabetes

Jie Zhang^{2,3}, Xin Cao^{1,3}, Kai Ma¹, Yizhou Jiang¹, Xiangrong Qin¹ & Xiaoyong Wang¹✉

Patients with diabetes have a high risk of failure of *H. pylori* eradication therapy. The present study aims to evaluate the efficacy and safety of vonoprazan–amoxicillin (VA) dual therapy for the treatment of *H. pylori* infection in patients with type-2 diabetes mellitus (T2DM), and determine the influence of *H. pylori* eradication on the glycated hemoglobin A1C (A1C) level. The present prospective, single-center, single-arm, clinical trial enrolled 75 T2DM patients diagnosed with *H. pylori* infection. The patients were treated with the VA dual therapy regimen, which comprised of vonoprazan (20 mg, twice daily) and amoxicillin (750 mg, thrice daily), for 14 days (14-day VA dual therapy). The eradication rate in the intention-to-treat analysis and per-protocol analysis was 84.00% (63/75) and 87.14% (61/70), respectively. The multivariate analysis revealed that the independent risk factors for *H. pylori* eradication failure were smoking (OR: 4.59, 95% CI: 1.20–17.58, $p=0.026$) and elevated A1C level (OR: 1.65, 95% CI: 1.01–2.68, $p=0.044$). Patients in the successful eradication group presented with a significant decrease in the A1C level at 3 months, post-treatment, when compared to the pre-eradication level ($7.70 \pm 1.05\%$ vs. $7.23 \pm 1.00\%$, $p=0.006$). VA dual therapy is a safe and effective regimen for patients with T2DM.

Keywords *Helicobacter pylori*, Type 2 diabetes, Dual therapy, Glycemic control

Helicobacter pylori (*H. pylori*) is a highly prevalent chronic infection classified by the World Health Organization as a Group 1 carcinogen^{1–3}. The role of *H. pylori* in the causation of gastritis, gastroduodenal ulcers, and gastric cancer has been well-documented. In addition, *H. pylori* infection is associated to other systemic diseases, such as diabetes. For example, it was identified that patients with type-2 diabetes mellitus (T2DM) have a higher prevalence of *H. pylori* infection^{4,5}. In addition, *H. pylori* infection has been identified as a risk factor for the development of nephropathy and cardiovascular complications in patients with diabetes^{6–8}. Glycated hemoglobin A1C (A1C) is a serological marker of glycemic control, which is closely associated to outcomes in diabetic patients. In some studies, it was found that *H. pylori* eradication in T2DM patients can improve insulin resistance, and reduce A1C levels⁹. However, a research revealed that *H. pylori* eradication in patients with T2DM has no role in glycemic control¹⁰. At present, there is a lack of consensus on the effect of *H. pylori* eradication on A1C levels, and this relationship needs to be further explored.

The Maastricht VI/Florence Consensus reports, and the Sixth Chinese Consensus on *H. pylori* infection recommends the 14-day bismuth quadruple therapy as a first-line treatment in areas with a high prevalence of clarithromycin resistance ($>15\%$)^{11,12}. However, these quadruple therapy regimens have some disadvantages, including high cost, numerous side effects, and poor treatment compliance due to the use of numerous drugs. In addition, previous studies reported that bismuth-containing quadruple therapies achieved a low *H. pylori* eradication rate in T2DM patients (38.20–81.00%)^{13–15}. Diabetes patients are often prescribed multiple drugs to achieve glycemic control, and treat diabetes complications. The bismuth quadruple therapy regimen contains

¹Department of Gastroenterology, Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou Medical Center, Nanjing Medical University, 68 Gehu Middle Road, Wujing District, Changzhou 213000, Jiangsu, China. ²Department of Endocrinology, Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou Medical Center, Nanjing Medical University, Changzhou, China. ³Jie Zhang and Xin Cao have contributed equally to this work. ✉email: wxy20009@126.com

bismuth, a proton pump inhibitor (PPI), and two antibiotics. The intake of various drugs may lead to adverse reactions, reduce compliance, and may lead to confusion on the dose and timing of various drugs, resulting in poor compliance to the prescribed treatment. All these factors are liable to impact the efficacy of *H. pylori* eradication. According to a meta-analysis, T2DM patients have a higher risk of *H. pylori* eradication failure, when compared to non-diabetic patients (odds ratio [OR]: 2.59, 95% confidence interval [CI]: 1.82–3.70)⁹. Therefore, developing a safe and effective *H. pylori* eradication regimen for diabetic patients is of great clinical significance.

In recent clinical studies, the eradication rate for vonoprazan (VPZ)-amoxicillin (3 g/d) dual therapy (VA dual therapy), as the first-line treatment, was approximately 89.50–94.60%^{16–18}, showing acceptable efficacy and safety. In our previous study, the VPZ-based regimen (amoxicillin 750 mg, three times daily) was identified as a safe and effective rescue therapy (eradication rate: 92.60%)¹⁹. Thus, VA dual therapy is an extremely promising therapeutic strategy for *H. pylori* eradication, due to simplicity, good efficacy, fewer side effects, and reduced amount of medication used. Nevertheless, all VA dual therapies have been conducted in the general population, and no prospective trials have evaluated the efficacy of the VA dual regimen in diabetic patients.

The present study aimed to assess the effectiveness and safety of VA dual therapy in T2DM patients, and determine the potential factors that influence the eradication rates. Furthermore, subgroup analyses were conducted to determine the impact of *H. pylori* eradication on A1C levels.

Methods

Study design

The present prospective, single-center, single-arm clinical trial was conducted in Changzhou No. 2 People's Hospital, between April 2023 and December 2023. The ethics clearance for the present pilot study was obtained from Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University (No. [2022] YLJSA056). The present study adhered to the principles enshrined in the Declaration of Helsinki, and was registered in the Chinese Clinical Trial Registry (No. ChiCTR2300070231) in 06/04/2023.

Study population

T2DM patients diagnosed with *H. pylori* infection were eligible for inclusion in the present trial. The diagnosis of *H. pylori* infection was confirmed by rapid urease test or ¹³C-urea breath test (UBT). The exclusion criteria were, as follows: (1) patients who underwent prior *H. pylori* eradication therapy; (2) patients allergic to amoxicillin or VPZ; (3) patients who were treated with PPI, VPZ, bismuth, or antibiotics within four weeks preceding the study; (4) patients with acute upper gastrointestinal bleeding and history of gastric surgery; (5) pregnant or lactating women; (6) patients who did not provide an informed consent; (7) patients who changed their hypoglycemic regimen during the treatment and follow-up period; (8) patients with severe comorbid conditions, such as hepatic or renal dysfunction.

A written informed consent was obtained from all patients before enrollment. Data on the following demographic and clinical characteristics were obtained by face-to-face interviews, and electronic medical records: age, gender, height, weight, body mass index (BMI), body surface area (BSA), history of smoking and alcohol consumption, duration of diabetes, glycemic control regimen, A1C level, gastroscopy findings, and comorbidities.

Management of diabetes mellitus

The diagnosis of T2DM was based on the guidelines for the prevention and treatment of T2DM in China (2020 Edition). For newly diagnosed diabetes patients, lifestyle management (medical nutrition therapy and exercise therapy) was the primary treatment measure to achieve glycemic control. Patients who received any of the following oral hypoglycemic drugs (alone or in combination) were assigned to the oral hypoglycemic drug group: metformin, insulin secretomotor, α -glucosidase inhibitor, thiazolidinedione (TZD), dipeptidyl peptidase IV inhibitor (DPP-4i), sodium-glucose co-transporter 2 inhibitor (SGLT2i), or glucagon-like peptide-1 receptor agonist (GLP-1RA). Patients who received insulin injection in divided doses, or as a continuous subcutaneous insulin infusion were assigned to the insulin group. Patients who received a combination of oral hypoglycemic drugs and insulin were assigned to the combined group. The aforementioned treatment plans were individualized based on the condition of the patient. Blood glucose levels were monitored regularly during the treatment period to prevent hypoglycemia.

Intervention and follow-up

All subjects were treated with the VA dual regimen, which contained VPZ (20 mg, twice daily; Takeda Pharmaceutical, Tokyo, Japan) and amoxicillin (750 mg, thrice daily; Federal Pharmaceutical, Hong Kong, China), for 14 days (14-day VA dual therapy). VPZ was taken before meals, while amoxicillin was taken after meals. In case of any discomfort during treatment, these patients were instructed to immediately contact the investigators for further assistance. At least four weeks after treatment, the *H. pylori* status was confirmed using the ¹³C-UBT. An δ value that exceeded the baseline value of 4 was considered indicative of positive *H. pylori* status, while an δ value below the baseline value of 4 was considered indicative of negative *H. pylori* status. The A1C levels were again measured at approximately three months, post-treatment.

All patients were required to respond to a questionnaire within three days after completion of the eradication therapy. Adverse events (AEs) were assessed based on the questionnaire responses. Patient compliance was assessed based on the medication diaries maintained by the patients. The severity of AEs was classified, as follows: none, mild (causing discomfort, but not interfering with daily life), moderate (causing discomfort, and interfering with daily life), and severe (causing discomfort, necessitating treatment cessation). The intake of at least 80% of the prescribed medicine was defined as good compliance.

Outcomes

The primary outcome measure for the present study was the *H. pylori* eradication rate. All patients were included in the intention-to-treat (ITT) analysis. Patients who did not undergo the ¹³C-UBT during the follow-up period were classified as cases of treatment failure in the ITT analysis. Patients who were lost to follow-up, or patients with poor treatment compliance were excluded from the per-protocol (PP) analysis. The secondary endpoints were, as follows: rate of AEs, patient compliance, and factors associated to eradication. Lastly, the effect of *H. pylori* eradication on A1C levels was examined.

Sample-size calculation and statistical analysis

In the present study, the *H. pylori* eradication rate for T2DM patients treated with the VA dual regimen was taken as the main evaluation index to calculate the sample size. The calculation formula was, as follows (where: n refers to the sample size, P_0 refers to the reference eradication rate, and P_1 refers to the expected eradication rate):

$$N = \frac{(\mu_{\alpha} + \mu_{\beta})^2 P_0 (1 - P_0)}{(P_1 - P_0)^2}$$

According to our previous research¹⁹, the reference eradication rate was $P_0 = 93.0\%$ ($n = 68$), with a 95% CI of 86.60–98.80%. Furthermore, the expected upper limit eradication rate was $P_1 = 99.2\%$, the p -value (α) accepted as significant was 0.1, and the power ($1 - \beta$) was 0.8. According to the formula, the calculated sample size was 66 cases. Considering the dropout situation during the follow-up period, a 10% increase in sample size was needed. That is, at least 73 patients would be required. Categorical variables were presented in frequency (proportion), and between-group differences were assessed for statistical significance using Pearson's chi-square test or Fisher's exact test. Continuous variables were tested for normal distribution. If the data conformed to the normal distribution, the data was expressed in mean \pm standard deviation (SD), the differences between groups were determined by independent samples test, and the differences within groups were determined by paired samples t -test. If the data did not conform to the normal distribution, the data was expressed in $M (P_{25}, P_{75})$, between-group comparisons were conducted using the Mann–Whitney U -test, and within-group comparisons were conducted using the Wilcoxon signed-rank test. In order to assess the risk factors for *H. pylori* eradication failure, binary logistic regression analysis was used to estimate the ORs and 95% CIs. A p -value of < 0.05 were considered statistically significant. The statistical analysis was performed using the Statistical Package for the Social Sciences v26.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

A total of 89 patients were screened for eligibility. Among these patients, 14 patients did not meet the inclusion criteria. Finally, 75 patients (44 male patients and 31 female patients) were enrolled. Among these patients, 58 patients underwent endoscopy, 39 patients consented to follow-up for the A1C level, and 37 patients underwent pre- and post-treatment liver and kidney function tests. Five patients were excluded from the PP analysis due to poor compliance (Fig. 1).

The mean age of these patients was 61.91 ± 9.37 years old. Forty patients (53.30%) had comorbid hypertension. Furthermore, smoking habits were reported by 21 patients (28.0%), and alcohol consumption was reported by 13 patients (17.3%). The median duration of T2DM was seven years. The mean A1C level at baseline was $7.79 \pm 1.27\%$. Majority of the patients received oral hypoglycemic agents ($n = 52$, 69.3%). Among the 58 patients who underwent endoscopy, atrophic gastritis was diagnosed in 30 cases, peptic ulcer was diagnosed in 16 cases, and chronic non-atrophic gastritis was diagnosed in 12 cases (Table 1).

Eradication rate and factors that influence efficacy

The eradication rate in the ITT analysis and PP analysis was 84.0% (63/75) and 87.14% (61/70), respectively. Univariate and multivariate logistic regression were performed to identify the risk factors for *H. pylori* eradication (Table 2). The multivariate analysis revealed that the significant and independent risk factors for *H. pylori* eradication failure were smoking (OR: 4.59, 95% CI: 1.20–17.58, $p = 0.026$) and elevated A1C levels (OR: 1.65, 95% CI: 1.01–2.68, $p = 0.044$).

Adverse events, safety and compliance

The overall incidence of AEs in the present trial was 13.3% (10/75), and none of the patients developed any severe AEs. The main symptoms were, as follows: dry mouth (one case), nausea (two cases), rash (one case), abdominal pain (two cases), diarrhea (two cases), abdominal distension (one case), and fatigue (one case). Most of the AEs were mild and resolved, without additional intervention (Table 3). One patient experienced localized rash and pruritus on the upper limbs on day six, which subsequently improved with oral anti-allergic medication, and the treatment was not interrupted. Furthermore, one patient developed abdominal pain and one patient developed diarrhea on day two, and these patients refused to continue treatment. Their symptoms resolved after drug withdrawal. Moreover, 93.3% (70/75) of patients took at least 80% of all prescribed medications. None of the 37 patients who underwent liver and kidney function tests presented with any significant difference in pre- and post-treatment results (Table 4).

Effect of *H. pylori* eradication on the A1C level

After the three-month follow-up period, a significant decrease in A1C levels was observed (7.70 ± 1.05 vs. 7.23 ± 1.00 , $p = 0.006$). The subgroup analysis revealed a significant decrease in A1C levels in the successful

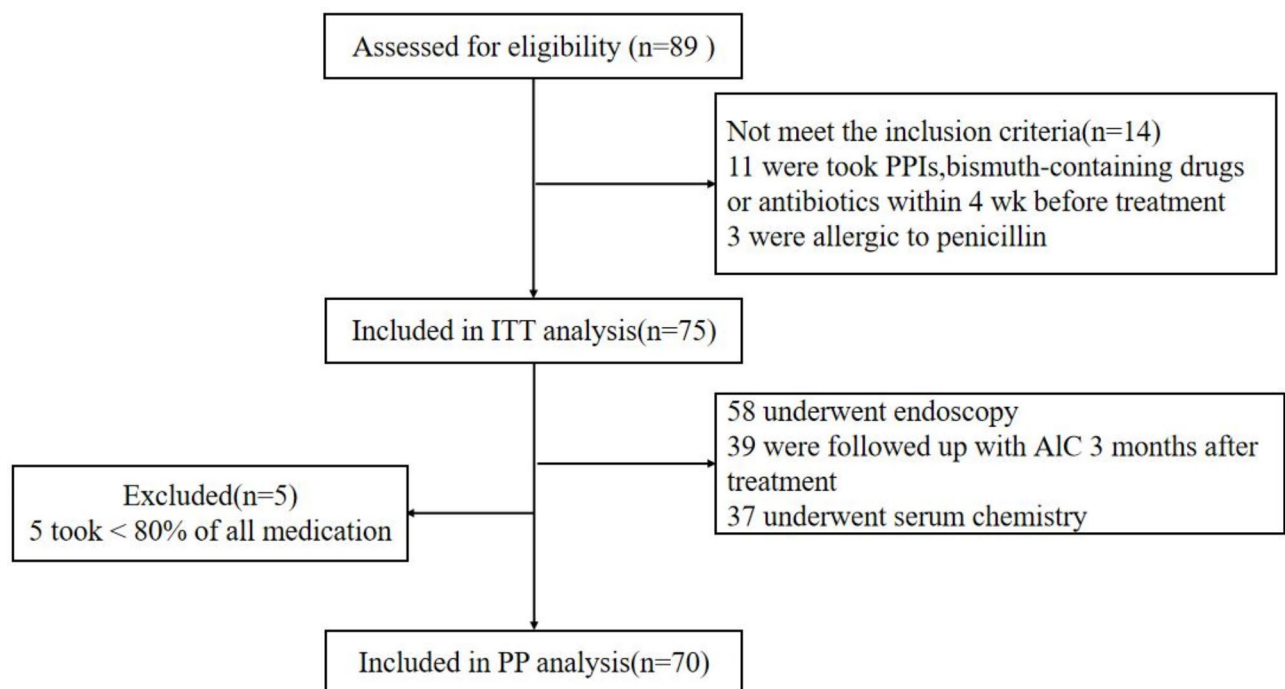


Fig. 1. Schematic diagram for the study design and patient selection criteria. PPI, proton pump inhibitor; ITT, intention-to-treat analysis; PP, per-protocol analysis; UBT, urea breath test; *H. pylori*, *Helicobacter pylori*.

Characteristic	Number of patients (n = 75)
Gender (male)	44 (58.70)
Age (years)	61.91 ± 9.37
Body mass index (kg/m ²)	23.59 ± 2.88
Body surface area (m ²)	1.81 ± 0.15
Hypertension	40 (53.30)
Smoking	21 (28.00)
Alcohol consumption	13 (17.30)
T2DM duration years, M (Q1,Q3)	7.00 (2.50, 11.50)
A1C (%)	7.79 ± 1.27
Diabetes treatment	
No treatment	5 (6.70)
Oral antihyperglycemic drug	52 (69.30)
Insulin monotherapy	4 (5.30)
Combination therapy	14 (18.70)
Symptoms	
Abdominal pain	11 (14.70)
Acid reflux	14 (18.70)
Bloating	6 (8.00)
Halitosis	3 (4.00)
Belching	9 (12.00)
Asymptomatic	32 (42.70)
Gastroscopy findings	
Non-atrophic gastritis	12 (16.00)
Peptic ulcer	16 (21.30)
Atrophic gastritis	30 (40.00)
No gastroscopy	17 (22.70)

Table 1. Clinical and demographic characteristics of the study population. T2DM, type-2 diabetes mellitus; A1C, glycated hemoglobin A1C.

Variables	Univariate analysis		Multivariate analysis	
	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)
Gender	0.220	0.42 (0.10–1.69)		
Hypertension	0.801	0.85 (0.25–2.93)		
Smoking	0.016	4.90 (1.35–17.84)	0.026	4.59 (1.20–17.58)
Alcohol	0.448	1.77 (0.41–7.69)		
Gastroscopy				
Non-atrophic gastritis	0.367	3.20 (0.26–40.06)		
Peptic ulcer	0.518	2.29 (0.19–27.99)		
Atrophic gastritis	0.157	4.87 (0.54–43.52)		
Diabetes				
Insulin monotherapy	0.992	42,544,812.61 (0.00–Inf)		
Oral antihyperglycemic drug	0.993	8,904,728.22 (0.00–Inf)		
Combination therapy	0.993	3,272,677.89 (0.00–Inf)		
Age	0.398	1.03 (0.96–1.11)		
BMI	0.819	1.03 (0.83–1.27)		
BSA	0.623	0.34 (0.00–24.86)		
T2DM (years)	0.156	1.06 (0.98–1.15)		
A1C	0.027	1.69 (1.06–2.70)	0.044	1.65 (1.01–2.68)

Table 2. Logistic regression analysis of factors associated to *Helicobacter pylori* eradication. OR, odds ratio; CI, confidence interval; BMI, body mass index; BSA, body surface area; T2DM, type-2 diabetes mellitus; A1C, glycated hemoglobin A1C. Significant values are in [bold].

Adverse events	%
Overall incidence	13.30% (10/75)
Dry mouth	1.30% (1/75)
Nausea	2.70% (2/75)
Rash	1.30% (1/75)
Abdominal pain	2.70% (2/75)
Diarrhea	2.70% (2/75)
Abdominal distension	1.30% (1/75)
Dizziness	0.00% (0/75)
Fatigue	1.30% (1/75)
Classification of adverse events	
Mild	9.30% (7/75)
Moderate	4.00% (3/75)
Severe	0.00% (0/75)
Patient compliance	
Good	93.30% (70/75)
Poor	6.70% (5/75)

Table 3. Incidence of adverse events and patient compliance. Intake of > 80% of all prescribed medications was rated as good compliance.

Variable	Pre-treatment (<i>n</i> = 37)	Post-treatment (<i>n</i> = 37)	<i>p</i> -value
Total bilirubin (μmol/L)	9.90 (6.90, 15.30)	12.10 (9.70, 14.60)	0.052
ALT (U/L)	19.10 (14.00, 23.80)	20.30 (16.00, 27.50)	0.245
AST (U/L)	19.00 (14.40, 24.00)	20.40 (17.00, 26.80)	0.478
Creatinine (μmol/L)	73.14 ± 13.80	74.02 ± 17.02	0.183

Table 4. Comparison of pre- and post-treatment liver and kidney function indices. AST, aspartate transaminase; ALT, Alanine aminotransferase.

eradication group, when compared to the pre-treatment level (7.63 ± 1.11 vs. 7.23 ± 0.98 , $p = 0.026$). The failed eradication group presented with no significant differences between the pre-treatment A1C levels and A1C level at three months after completion of treatment (8.06 ± 0.61 vs. 7.23 ± 1.16 , $p = 0.117$).

Discussion

To the best of our knowledge, the present study was the first prospective study to investigate the efficacy and safety of the 14-day VA dual therapy for eradicating *H. pylori* in T2DM patients. In the present study, the 14-d VA regimen achieved a high eradication rate (87.14% in the PP analysis and 84.0% in the ITT analysis). In recent studies, the efficacy of triple or quadruple regimens based on PPIs was significantly lower in diabetic patients, when compared to their non-diabetic counterparts^{15,20,21}. For instance, Vafaeimanesh et al.¹⁵ reported a low 63% eradication rate for diabetic patients who received the 14-day quadruple therapy regimen (20 mg of omeprazole, 500 mg of metronidazole, 1 g of amoxicillin, and 240 mg of bismuth citrate, twice daily). Similarly, Sargyn et al. reported a 50% eradication rate for diabetes patients who received the standard 10-day triple therapy regimen (500 mg of clarithromycin, 20 mg of omeprazole, 1 g of amoxicillin, twice a day)²⁰. Several factors may have contributed to the low eradication rate in diabetic patients. A key factor that contributed to the low eradication rate was the increase in prevalence of antibiotic resistance in diabetic patients²². Diabetes patients typically have compromised immune responses, rendering them more susceptible to infections, resulting in frequent antibiotic usage, and the subsequent emergence of drug-resistant strains. Furthermore, diabetic microvascular disease compromises the gastric microvasculature, impairing blood circulation in the gastric mucosa. This may reduce the absorption of drugs through the gastric mucosa²³. Moreover, the poor compliance of patients is a crucial factor that influences eradication. Most diabetic patients are prescribed multiple types of hypoglycemic drugs, which need to be adjusted based on glucose fluctuations. The concurrent use of multiple medications often leads to confusion on the dose and timing, affecting compliance. All these factors are liable to impact the efficacy of *H. pylori* eradication.

T2DM patients have significantly higher rates of clarithromycin resistance, when compared to non-diabetic patients¹³. Yao et al. reported a 50% prevalence rate of resistance for both clarithromycin and levofloxacin in diabetic patients, while the corresponding rate in non-diabetic patients was 17.10% and 22.90%, respectively. Clarithromycin resistance was identified as an independent risk factor for *H. pylori* eradication failure (OR: 25.472, $p = 0.023$)²¹. In contrast to the aforementioned antibiotics, amoxicillin has a consistent low primary and secondary resistance rate²⁴. The bactericidal effect of amoxicillin is both pH- and time-dependent.

Traditional PPIs have a short half-life (0.5–2.0 h), and the metabolism is influenced by *CYP2C19* gene polymorphism, resulting in a limited duration of acid inhibition. Compared to PPIs, VPZ (as the first potassium-competiting acid blocker employed in clinical practice) causes a more rapid and sustained acid inhibition²⁵. Therefore, VPZ-amoxicillin dual therapy is expected to be more effective in eradicating *H. pylori* in T2DM patients.

In the present study, the multivariate analysis revealed that elevated A1C level (OR: 1.65, 95% CI: 1.01–2.68, $p = 0.044$) is an independent risk factor for *H. pylori* eradication failure, suggesting that T2DM patients with poor glycemic control are more likely to fail in achieving eradication. In the study conducted by Nam et al.²⁶ the A1C level of $\geq 7.5\%$ was a risk factor for failure to achieve *H. pylori* eradication. This was likely attributable to the detrimental impact of hyperglycemia on innate immune responses to infection, immunoglobulin-mediated bacterial opsonization and complement fixation to bacteria, and phagocytosis²⁷. In addition, hyperglycemia can impair endothelial function, leading to damage to the gastric mucosal microvasculature, and the subsequently reduced absorption of antibiotics²³. Therefore, optimizing glycemic control is the key to achieve *H. pylori* eradication in T2DM patients.

In addition, smoking is a risk factor for failure of *H. pylori* eradication in T2DM patients. Smoking is known to decrease gastric blood flow and mucus secretion, which can reduce the delivery of antibiotics to the gastric mucosa²⁸. Furthermore, compared to non-smokers, long-term heavy smokers exhibit elevated pentapeptide secretion, leading to increased gastric acid secretion²⁹. Consequently, the effectiveness of amoxicillin, which is an acid-sensitive antibiotic, may be diminished in smokers.

In the present study, the three-month follow-up assessment of A1C levels after eradication revealed a significant reduction in A1C levels in patients who achieved successful eradication. Although all included patients did not change their hypoglycemic regimen during the treatment and follow-up period, merely 39 patients consented to follow-up for the A1C level, and merely six patients failed to be eradicated. In addition, the confounding influence of factors that could affect A1C levels (e.g. diet, exercise, and drug compliance) were not analyzed in the study. Thus, the presented data was not adequate to comment on the impact of *H. pylori* eradication on the change in A1C level.

Some limitations of the present study should be acknowledged. First, the present study was a prospective single-center, single-arm study. Larger, multicenter, randomized, controlled trials that include non-diabetic control subjects are required to obtain more robust evidence. Second, no antibiotic susceptibility tests were performed for the present study. Therefore, the influence of different antibiotic resistance on the eradication rate of the 14-day VA dual therapy could not be evaluated. Third, the bilirubin levels increased at post-treatment, when compared to pre-treatment, although the difference was not statistically significant. When using dual therapy for *H. pylori* infection in diabetes patients, more attention should be given in monitoring the bilirubin level. Fourth, no amoxicillin absorption test was performed to support the VA dual therapy. Amoxicillin is mainly absorbed by the gastrointestinal tract. Compared to non-diabetic patients, it remains unclear whether there are differences in amoxicillin absorption in diabetic patients. Research would be conducted with this regard in the future. Finally, the confounding influence of factors that can affect the A1C levels (e.g. diet, exercise, and medications) was not analyzed in the study. Thus, future large-scale, multicenter prospective studies should account for these confounding factors in the statistical analysis to confirm the present results.

Conclusion

In conclusion, the present study revealed the efficacy and safety of the 14-day VA dual therapy for eradicating *H. pylori* in T2DM patients. T2DM patients should abstain from smoking, and achieve optimal glycemic control to increase the eradication rate of *H. pylori*.

Data availability

The data sets supporting the results of the current research are available from the corresponding authors upon request.

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Author contributions

JZ and XC: acquisition of data, analysis and interpretation of data, and drafting of the manuscript; KM, YJ and

XQ: interpretation of data and revision of the manuscript; XW: conception and design of the study, critical revision, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. All authors had reviewed, edited and approved the final version of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to X.W.

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