

Helicobacter pylori eradication improves glycemic control in type 2 diabetes patients with asymptomatic active *Helicobacter pylori* infection

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Keywords

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ABSTRACT

Aims/Introduction: *Helicobacter pylori* infection is associated with insulin resistance and glycemia in non-diabetes. However, the relationship between *H. pylori* infection and glycemia in diabetes remains inconclusive. Therefore, we explored the effect of *H. pylori* infection status and its eradication on glycemic control and antidiabetic therapy in type 2 diabetes patients.

Materials and Methods: A total of 549 diabetes patients were recruited for sequential two-step approach (immunoglobulin G [IgG] serology followed by ¹³C-urea breath test [UBT]) to discriminate “active” (IgG+ and UBT+) from “non-active” (UBT– or IgG–) *H. pylori* infection, and “past” (IgG+ but UBT–) from “never/remote” (IgG–) infection. The differences in hemoglobin A1c (A1C) and antidiabetic regimens between groups were compared. In the “active” infection group, the differences in A1C changes between participants with and without 10-day eradication therapy were compared after 3 months.

Results: Despite no between-group difference in A1C, the “active” infection group ($n = 208$) had significantly more prescriptions of oral antidiabetic drug classes (2.1 ± 1.1 vs 1.8 ± 1.1 , $P = 0.004$) and higher percentages of sulfonylurea use (67.3% vs 50.4%, $P < 0.001$) than the “non-active” infection group ($n = 341$). There were no differences in A1C and oral antidiabetic drug classes between “past” ($n = 111$) and “never/remote” infection groups ($n = 230$). Compared with the non-eradication group ($n = 99$), the eradication group ($n = 98$) had significant within-group ($-0.17 \pm 0.80\%$, $P = 0.036$) and between-group ($-0.23 \pm 0.10\%$, $P = 0.024$) improvements in A1C.

Conclusions: Diabetes patients with active *H. pylori* infection need higher glycemic treatment intensity to achieve comparable glycemia. Furthermore, *H. pylori* eradication decreases A1C, and thus improves glycemic control.

INTRODUCTION

Type 2 diabetes mellitus is a growing problem worldwide¹. The global number of people with diabetes is projected to rise from 415 million in 2015 to 642 million by 2040¹. Uncontrolled hyperglycemia causes microvascular and macrovascular

complications, which causes adverse effects on the quality of life of patients² and is an economic burden on healthcare systems³. The pathogenesis of type 2 diabetes is complex and multifaceted, but centered around insulin resistance and impaired pancreatic β -cell function⁴. Although some factors associated with insulin resistance are related to genetic mutations, many others are not inherited and probably modifiable⁵.

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These modifiable factors include physiological conditions and environmental factors, such as obesity, sedentary lifestyle, chronic inflammation and infections^{6–9}, and are potential targets to improve glycemic control in type 2 diabetes.

Helicobacter pylori infection is one of the most common chronic infections, and affects approximately 50% of the world's population¹⁰. *H. pylori* infection is associated with increased markers of chronic inflammation, such as tumor necrosis factor- α ¹¹ and C-reactive protein^{12,13}, and thus a positive association between *H. pylori* infection and insulin resistance has been observed in many studies on non-diabetic individuals¹⁴. Therefore, it is plausible that chronic *H. pylori* infection might predispose individuals to hyperglycemia. Consistent with this notion, several studies on non-diabetic individuals showed positive associations between *H. pylori* infection and glycemia^{15–18} or metabolic syndrome¹⁹, with only a few exceptions^{20,21}. However, in patients with type 2 diabetes, the association between *H. pylori* infection and hyperglycemia remains inconclusive. Some studies report higher hemoglobin A1c (A1C) levels in the *H. pylori*-infected individuals^{22,23}, but some others do not^{24–29}. Such an apparent discrepancy between diabetes and non-diabetes might be due to the methodological differences in diagnosing *H. pylori* infection, and thus fail to differentiate active from past *H. pylori* infection^{30,31}. Furthermore, currently available studies lack consideration of the effects of background antidiabetic medications, which might mitigate the consequences of *H. pylori* infection with regard to glycemia. Therefore, to investigate the glycemic impact of *H. pylori* infection on diabetes, the present study used a two-step diagnostic approach with the aim of investigating the effects of active *H. pylori* infection and background antidiabetic therapy on glycemic control in a cross-sectional diabetes cohort. Furthermore, the changes in A1C level after eradication of active *H. pylori* infection were examined in an interventional subcohort.

METHODS

Participants

This study was approved by the institutional review board of National Cheng Kung University Hospital (NCKUH B-ER-102-081), and all eligible participants signed informed consent forms before participation. All patients with type 2 diabetes aged 20–80 years visiting the endocrinology outpatient clinic of NCKUH from June 2013 to January 2014 were screened. The diagnosis of type 2 diabetes was based on the 2010 American Diabetes Association criteria³². Individuals with the following conditions or diseases were excluded: (i) type 1 diabetes mellitus; (ii) having a previous history of *H. pylori* eradication or major gastrointestinal surgery, or any symptoms suggestive of active peptic ulcer disease; (iii) acute ischemic heart event, cerebrovascular accident or pancreatitis; (iv) acute infection, such as pneumonia, urinary tract infection, soft tissue infection or cellulitis, or sepsis; (v) current use of drugs that affect the carbohydrate metabolism, such as corticosteroids, thiazides,

sympathomimetic agents and atypical antipsychotic drugs; (vi) receiving proton pump inhibitor treatment; (vii) pregnancy; and (viii) any other major diseases, including generalized inflammation or advanced malignant diseases contraindicating this study.

Cross-Sectional Study Design

A two-step diagnostic approach was used to diagnose active *H. pylori* infection. First, all patients recruited were screened for *H. pylori* infection by the serology test for *H. pylori* immunoglobulin (IgG) antibody (HEL-p TEST™ II; AMRAD Biotech, Perth, WA, Australia; with sensitivity and specificity as 96.9% and 90.4%, respectively³³). A serum level of *H. pylori* IgG antibody ≥ 8 (U/mL) was defined as a positive result and < 8 as a negative result. Next, those who had positive serology results had their current infection status further confirmed using the ¹³C-urea breath test (UBT) applied in our previous study³⁴. A UBT value of $> 3.5\%$ was defined as active *H. pylori* infection (UBT+), and $\leq 3.5\%$ as past *H. pylori* infection (UBT–). The schematic flow chart of the present study's design is shown in Figure 1.

After an overnight 12-h fast, all participants received a blood test including fasting plasma glucose, A1C, renal function (creatinine), liver enzyme (alanine aminotransferase) and lipid profiles (including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglyceride).

Wearing light indoor clothes, each participant's anthropometric data, including body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) were measured. Body mass index (in kg/m²) was calculated as weight (in kg) divided by height (in m) squared. For the blood pressure measurement, participants were resting in a supine position in a quiet ambience, and measurements were then obtained. Hypertension is defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg or being treated with antihypertensive agents. In addition, a comprehensive medication history of antihypertensive drugs, antidiabetic regimens and lipid-lowering agents were reviewed and recorded by an investigator who was blind to the patients' past history or biochemical results to reduce potential bias. For antidiabetic regimens, the use of insulin and different classes of oral antidiabetic agents, including metformin, sulfonylurea, glinide, thiazolidinedione, α -glucosidase inhibitor and dipeptidyl peptidase-4 inhibitor, were recorded.

Interventional Study Design

All patients with UBT+ were invited to receive a 10-day treatment for *H. pylori* eradication. Before eradication therapy, we carried out an esophagogastroduodenoscopy examination to rule out the possibility of gastric cancer, because *H. pylori* infection increases the risk of developing gastric cancer³⁵. The final decision of receiving examination and treatment ("*H. pylori* eradication" group) or not ("non-eradication" group) was up to the patients themselves after a comprehensive explanation of

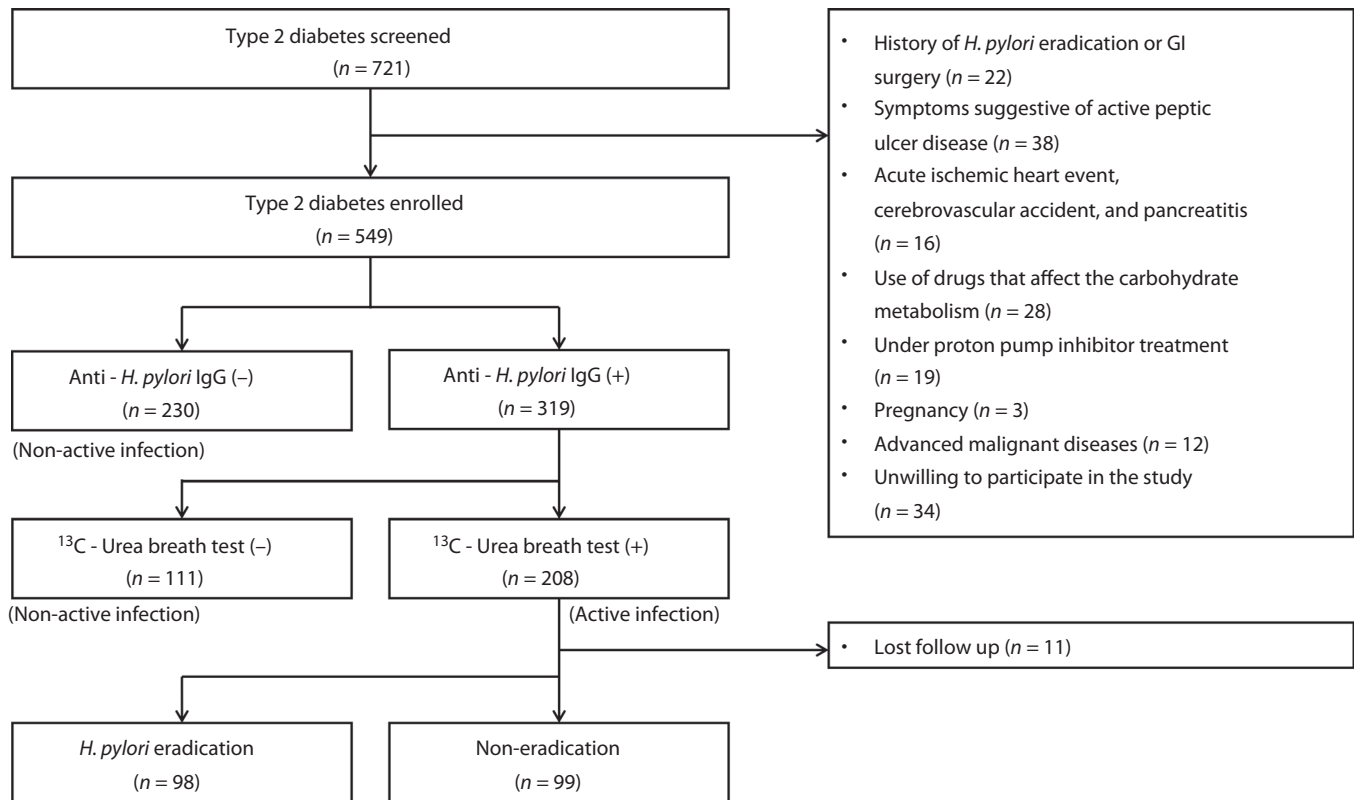


Figure 1 | Study flow chart. GI, gastrointestinal; IgG, immunoglobulin G.

the procedures. Patients in the eradication group were prospectively randomized into two therapeutic groups, namely, a clarithromycin-based sequential group and a levofloxacin-based concomitant group. The former group received a 10-day regimen, including pantoprazole 40 mg and amoxicillin 1000 mg twice daily for the first 5 days, followed by pantoprazole 40 mg, clarithromycin 500 mg and metronidazole 500 mg twice daily for another 5 days. In the latter group, the 10-day regimen included pantoprazole 40 mg, and amoxicillin 1000 mg, metronidazole 500 mg twice daily, as well as levofloxacin 500 mg once daily³⁶. All patients receiving 10-day treatment for *H. pylori* eradication repeated UBT 6–8 weeks after therapy. A change from UBT+ to UBT– after therapy was defined as successful *H. pylori* eradication. Furthermore, A1C levels of all participants with UBT+ were followed up 3 months later without change of the antidiabetic regimens during this 3-month period.

Statistical Analysis

Data were analyzed with the Windows version of the Statistical Package for the Social Sciences (SPSS version 21.0; SPSS, Chicago, IL, USA). Continuous variables were expressed as the means \pm standard deviation and categorical variables as percentages. Participants with a negative *H. pylori* IgG antibody were defined as “never/remote infection,” and those with a

positive *H. pylori* IgG antibody, but negative UBT, were designated as “past infection.” Furthermore, “never/remote infection” and “past infection” were collectively classified as “non-active infection,” and “active infection” indicated individuals with their *H. pylori* IgG antibody and UBT both positive. The differences of continuous variables between “non-active infection” and “active infection” groups, “never/remote infection” and “past infection” groups, as well as between “*H. pylori* eradication” and “non-eradication” groups, were compared using Student’s *t*-tests. The χ^2 -tests were used to analyze the differences of categorical variables between groups. All statistical tests were two-sided, and a *P*-value <0.05 was considered statistically significant.

RESULTS

A total of 549 type 2 diabetes patients, including 269 women and 280 men, were enrolled in the present study. The prevalence rates of *H. pylori* infection defined by anti-*H. pylori* IgG and UBT were 58.1% and 37.9%, respectively.

Cross-Sectional Comparisons Between “Active” and “Non-Active” Infection Groups

The clinical variables for “active” infection participants ($n = 208$) and “non-active” infection participants ($n = 341$) were compared, as shown in Table 1. There were no

differences in A1C (7.68 ± 1.38 vs $7.65 \pm 1.49\%$, $P = 0.829$) and fasting plasma glucose (7.8 ± 2.5 vs 7.8 ± 2.6 mmol/L, $P = 0.935$) between the “active” and “non-active” infection groups.

The percentages of insulin users between “active” infection and “non-active” infection participants were similar (33.2 vs 35.5%, $P = 0.644$). Among the insulin users, there were no differences between “active” and “non-active” infection groups in daily insulin dose (37.0 ± 28.1 vs 38.7 ± 24.4 units, $P = 0.659$) or insulin dose per kilogram per day (0.52 ± 0.39 vs

0.56 ± 0.32 units, $P = 0.497$). However, the “active” infection participants were treated with more classes of oral antidiabetic drugs (OADs) than the “non-active” infection participants (2.1 ± 1.1 vs 1.8 ± 1.1 , $P = 0.004$). A higher percentage of patients in the “active” infection group took two or more, and three or more classes of OAD than in the “non-active” infection group (71.2 vs 58.9%, $P = 0.005$; 38.9 vs 27.6%, $P = 0.006$, respectively). Specifically, there was a significantly higher percentage of sulfonylureas use in the “active” infection group than “non-active” infection group (67.3 vs 50.4%, $P < 0.001$). The

Table 1 | Comparisons of baseline characteristics between participants with “active” and “non-active” *Helicobacter pylori* infection

	Non-active infection	Active infection	P-value
<i>n</i>	341	208	
Age (years)	60.2 ± 11.7	61.9 ± 9.6	0.054
Male (%)	50.4	51.9	0.792
BMI (kg/m ²)	26.5 ± 4.7	27.1 ± 4.7	0.128
Diabetes duration (years)	11.4 ± 8.0	11.2 ± 7.4	0.754
Hypertension (%)	62.1	61.4	0.928
Statins (%)	70.4	70.7	1.000
eGFR (mL/min/1.73 m ²)	70.8 ± 21.7	70.0 ± 20.9	0.642
ALT (U/L)	33.2 ± 39.3	31.6 ± 31.4	0.562
Total cholesterol (mmol/L)	4.0 ± 0.9	4.1 ± 0.9	0.197
HDL-C (mmol/L)	1.4 ± 0.4	1.3 ± 0.4	0.144
LDL-C (mmol/L)	2.4 ± 0.8	2.5 ± 0.8	0.120
Triglyceride (mmol/L)	1.5 ± 1.1	1.6 ± 0.9	0.483
Fasting plasma glucose (mmol/L)	7.8 ± 2.6	7.8 ± 2.5	0.935
A1C (%)	7.65 ± 1.49	7.68 ± 1.38	0.829
A1C (mmol/mol)	60.1 ± 16.3	60.4 ± 15.1	0.826
Antidiabetic medications			
Insulin (%)	35.5	33.2	0.644
Insulin dose/day (Unit)	38.7 ± 24.4	37.0 ± 28.1	0.659
Insulin dose/kg/day (Unit)	0.56 ± 0.32	0.52 ± 0.39	0.497
OAD classes	1.8 ± 1.1	2.1 ± 1.1	0.004
No. participants (percentage)			
0 class of OAD	32 (9.4)	18 (8.7)	*
1 class of OAD	108 (31.7)	42 (20.2)	*
2 classes of OAD	107 (31.4)	67 (32.2)	*
3 classes of OAD	75 (22.0)	65 (31.3)	*
4 classes of OAD	19 (5.6)	15 (7.2)	*
5 classes of OAD	0 (0)	1 (0.5)	*
OAD (%)	90.6	91.3	0.879
Metformin (%)	79.4	83.7	0.262
Sulfonylureas (%)	50.4	67.3	<0.001
Glinides (%)	1.8	0.5	0.259
Thiazolidinediones (%)	18.5	24.0	0.129
AGIs (%)	10.3	11.1	0.776
DPP-4is (%)	22.6	23.1	0.917

Data are expressed as the mean ± standard deviation or percentage. * P -value by $2 \times 6 \chi^2$ -test <0.05 . Active infection: participants with both positive *Helicobacter pylori* immunoglobulin G antibody and UBT. Non-active infection: participants with a negative *H. pylori* immunoglobulin G antibody or “a positive *H. pylori* immunoglobulin G antibody, but negative urea breath test.” A1C, hemoglobin A1c; AGIs, alpha-glucosidase inhibitors; ALT, alanine transaminase; BMI, body mass index; DPP-4is, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OAD, oral antidiabetic drug.

use of other classes of OAD showed similar percentages between groups.

Cross-Sectional Comparisons Between “Never/Remote Infection” and “Past Infection” Groups

There were no differences between “never/remote infection” patients ($n = 230$) and “past infection” patients ($n = 111$), in A1C level (7.64 ± 1.49 vs $7.66 \pm 1.50\%$, $P = 0.890$), percentage of insulin users (36.5 vs 33.3% , $P = 0.629$), classes of OAD use (1.8 ± 1.0 vs 1.9 ± 1.1 , $P = 0.430$) and percentage of sulfonylureas use (48.7 vs 54.1% , $P = 0.358$; Table 2).

Interventional Study with *H. pylori* Eradication

Among the 208 patients of “active” infection group, we prospectively followed 197 patients successfully, including 98 with and 99 without *H. pylori* eradication. Each enrolled patient, either with or without *H. pylori* eradication, was followed up with regard to the paired A1C levels, one at enrollment and the other 3 months later. The baseline characteristics between “*H. pylori* eradication” and “non-eradication” groups were comparable, including age, sex, body mass index, diabetes duration, percentage of hypertension and statin use, renal function, alanine transaminase, and lipid profiles (Table 3). The

Table 2 | Comparisons of baseline characteristics between “never/remote infection” and “past infection” groups

	Never/remote infection	Past infection	P-value
<i>n</i>	230	111	
Age (years)	59.0 ± 12.2	62.5 ± 10.1	0.005
Male (%)	52.2	46.8	0.419
BMI (kg/m ²)	26.4 ± 4.6	26.5 ± 4.9	0.904
Diabetes duration (years)	11.0 ± 7.8	12.2 ± 8.3	0.217
Hypertension (%)	61.6	63.1	0.813
Statins (%)	68.3	74.8	0.255
eGFR (mL/min/1.73 m ²)	71.7 ± 22.0	69.1 ± 21.1	0.296
ALT (U/L)	31.7 ± 26.1	38.5 ± 58.8	0.137
Total cholesterol (mmol/L)	4.1 ± 0.9	3.9 ± 0.8	0.210
HDL-C (mmol/L)	1.4 ± 0.4	1.4 ± 0.3	0.989
LDL-C (mmol/L)	2.4 ± 0.8	2.4 ± 0.8	0.741
Triglyceride (mmol/L)	1.6 ± 1.2	1.4 ± 0.8	0.094
Fasting plasma glucose (mmol/L)	7.8 ± 2.7	8.0 ± 2.4	0.475
A1C (%)	7.64 ± 1.49	7.66 ± 1.50	0.890
A1C (mmol/mol)	60.0 ± 16.4	60.2 ± 16.3	0.905
Antidiabetic medications			
Insulin (%)	36.5	33.3	0.629
Insulin dose/day (Unit)	39.9 ± 25.2	36.0 ± 22.5	0.411
Insulin dose/kg/day (Unit)	0.58 ± 0.34	0.51 ± 0.27	0.265
OAD classes	1.8 ± 1.0	1.9 ± 1.1	0.430
No. participants (percentage)			
0 class of OAD	20 (8.7)	12 (10.8)	*
1 class of OAD	78 (33.9)	30 (27.0)	*
2 classes of OAD	75 (32.6)	32 (28.8)	*
3 classes of OAD	43 (18.7)	32 (28.8)	*
4 classes of OAD	14 (6.1)	5 (4.5)	*
5 classes of OAD	0 (0)	0 (0)	*
OAD (%)	91.3	89.2	0.555
Metformin (%)	81.7	74.8	0.154
Sulfonylureas (%)	48.7	54.1	0.358
Glinides (%)	1.3	2.7	0.403
Thiazolidinediones (%)	17.8	20.0	0.656
AGIs (%)	10.4	9.9	1.000
DPP-4is (%)	20.0	27.9	0.128

Data are expressed as the mean ± standard deviation or percentage. * P -value by $2 \times 6 \chi^2$ -test: not significant. Never/remote infection: participants with a negative *Helicobacter pylori* immunoglobulin G antibody. Past infection: participants with a positive *H. pylori* immunoglobulin G antibody, but negative urea breath test. A1C, hemoglobin A1c; AGIs, alpha-glucosidase inhibitors; ALT, alanine transaminase; BMI, body mass index; DPP-4is, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OAD, oral antidiabetic drug.

Table 3 | Comparisons of baseline characteristics between the “*Helicobacter pylori* eradication” and “non-eradication” groups

	Eradication	Non-eradication	P-value
<i>n</i>	98	99	
Age (years)	61.9 ± 9.7	62.5 ± 9.6	0.649
Male (%)	54.1	49.5	0.569
BMI (kg/m ²)	27.0 ± 5.3	27.1 ± 4.3	0.933
Diabetes duration (years)	11.0 ± 6.9	11.2 ± 7.7	0.879
Hypertension (%)	68.4	57.1	0.139
Statins (%)	72.4	67.7	0.534
eGFR (mL/min/1.73 m ²)	70.7 ± 21.9	68.7 ± 20.2	0.509
ALT (U/L)	34.6 ± 43.1	28.0 ± 13.8	0.147
Total cholesterol (mmol/L)	4.1 ± 0.9	4.1 ± 0.8	0.853
HDL-C (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	0.967
LDL-C (mmol/L)	2.5 ± 0.8	2.5 ± 0.8	0.602
Triglyceride (mmol/L)	1.6 ± 0.8	1.7 ± 1.1	0.404
Fasting plasma glucose (mmol/L)	8.0 ± 2.2	7.3 ± 2.2	0.019
A1C (%)	7.50 ± 1.24	7.54 ± 1.40	0.844
A1C (mmol/mol)	58.5 ± 13.6	58.9 ± 15.4	0.817
Antidiabetic medications			
Insulin (%)	33.7	31.3	0.763
Insulin dose/day (Unit)	37.0 ± 27.5	36.7 ± 29.3	0.974
Insulin dose/kg/day (Unit)	0.51 ± 0.42	0.54 ± 0.37	0.780
OAD classes	2.0 ± 1.2	2.2 ± 1.0	0.327
No. participants (percentage)			
0 class of OAD	12 (12.2)	4 (4.0)	*
1 class of OAD	21 (21.4)	20 (20.2)	*
2 classes of OAD	26 (26.5)	38 (38.4)	*
3 classes of OAD	32 (32.7)	29 (29.3)	*
4 classes of OAD	6 (6.1)	8 (8.1)	*
5 classes of OAD	1 (1.0)	0 (0)	*
OAD (%)	87.8	96.0	0.040
Metformin (%)	79.6	87.9	0.126
Sulfonylureas (%)	63.3	71.7	0.226
Glinides (%)	1.0	0	0.497
Thiazolidinediones (%)	24.5	24.2	1.000
AGIs (%)	10.2	11.1	1.000
DPP4is (%)	24.5	22.2	0.739

Data are expressed as the mean ± standard deviation or percentage. **P*-value by 2 × 6 χ^2 -test: not significant. A1C, hemoglobin A1c; AGIs, alpha-glucosidase inhibitors; ALT, alanine transaminase; BMI, body mass index; DPP-4is, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OAD, oral anti-diabetes drug.

fasting plasma glucose at baseline (8.0 ± 2.2 vs 7.3 ± 2.2 mmol/L, *P* = 0.019) was higher in the “*H. pylori* eradication” group than the “non-eradication” group. However, there was no difference in A1C between the “*H. pylori* eradication” and “non-eradication” groups (7.50 ± 1.24 vs 7.54 ± 1.40%, *P* = 0.844).

As for antidiabetic regimens, at baseline, there was a lower percentage (87.8 vs 96.0%, *P* = 0.04) of patients receiving one or more class of OAD in the “*H. pylori* eradication” group than in the “non-eradication” group. Otherwise, no differences in antidiabetic regimens were noted between groups, including the percentage of insulin users, insulin dose, the number of OAD classes used and the percentages of use for each class of OAD (Table 3).

After 3 months of follow up, without changing antidiabetic regimens during this period, the A1C level decreased in the “*H. pylori* eradication” group (from 7.50 ± 1.24 to 7.33 ± 1.14%, *P* = 0.036), but remained unchanged in the “non-eradication” group (from 7.54 ± 1.40 to 7.60 ± 1.38%, *P* = 0.345). The between-group difference of changes in A1C level was statistically significant (−0.23 ± 0.10%, *P* = 0.024; Figure 2). It is noted that the change in A1C level is independently associated with *H. pylori* eradication therapy after adjustment for age, sex, body mass index, diabetic duration, blood biochemistry and statin use (*P* = 0.019). Furthermore, we did not adjust the lipid-lowering agents and antihypertensive drugs during this 3-month period. The bodyweight, lipid profile and blood

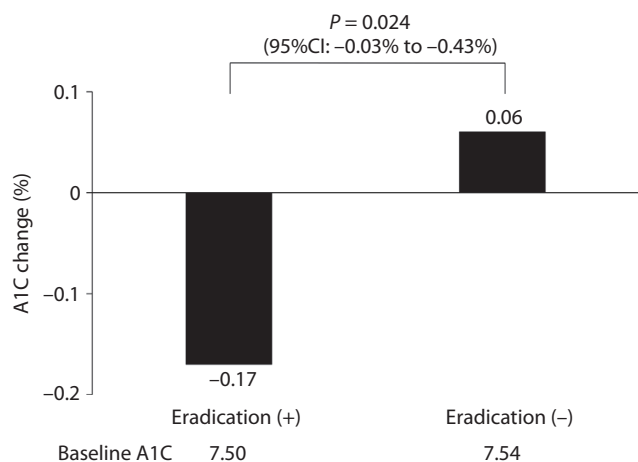


Figure 2 | The comparisons of hemoglobin A1c (A1C) changes from baseline to 3 months after between the “*Helicobacter pylori* eradication” and “non-eradication” groups. CI, confidence interval.

pressure data of all participants with UBT+ were collected and compared. There were no differences in bodyweight, lipid profiles and blood pressure at baseline and after 3 months in either the “*H. pylori* eradication” or “non-eradication” group. The between-group differences of changes in bodyweight, lipid profiles and blood pressure during 3 months were statistically insignificant (Table S1).

In the “*H. pylori* eradication” group, 92 patients had successful *H. pylori* eradication, while six patients still had positive UBT result 3 months later. The eradication rate was thus 93.9%, which was comparable with that in previous studies^{37–39}.

DISCUSSION

To the best of our knowledge, this is the first study to comprehensively evaluate the glycemic effect of *H. pylori* infection in real-world patients with diabetes. We found that diabetes patients with asymptomatic active *H. pylori* infection had a comparable level of glycemia to those without active infection, but at the expense of a higher intensity of antidiabetic therapy, particularly sulfonylureas. In addition, eradication of active *H. pylori* infection resulted in a significant improvement in glycemic control in diabetes patients.

In assessing the relationship between *H. pylori* infection and glycemia, the method used for diagnosing *H. pylori* infection status is critical. Current diagnostic methods of *H. pylori* infection can be divided into two types: invasive tests (histology examination, rapid urease test, and culture) and non-invasive tests (UBT, stool antigen test and serum or urine anti-*H. pylori* IgG)³¹. With the aid of gastrointestinal endoscopy, a positive result from the invasive tests confirms the presence of active *H. pylori* infection. As for non-invasive tests, while positive UBT and stool antigen tests also indicate an active infection status, serum or urine anti-*H. pylori* IgG are just markers of

exposure to *H. pylori*. Therefore, an IgG test alone cannot exactly indicate whether active infection is present. It is thus not surprising that when using serum²⁰ or urine²¹ IgG assay as the diagnostic method, no relationship between *H. pylori* infection and glycemia exists in studies of non-diabetic individuals^{20,21}. In contrast, a positive relationship between *H. pylori* infection and glycemia^{15–18} or metabolic syndrome¹⁹ is noted in mainly^{15–18} or exclusively¹⁹ non-diabetic individuals, when applying diagnostic tests that verify active *H. pylori* infection. Thus, it is evident that active or inactive infection affects the relationship between *H. pylori* infection and glycemia. Accordingly, tests with high diagnostic accuracy should be used to define the active infection of *H. pylori*, and thus its exact impact on glycemia control can be more clearly assessed. The IgG kit used in the present study has been confirmed to have high diagnostic accuracy (96.9% sensitivity and 90.4% specificity; positive/negative predictive value: 94.9%/94.0%) in a Taiwanese population³³. Therefore, we believe the impact of false positive or false negative IgG results on the findings of the present study is quite small. Meanwhile, although UBT+ might result from the existence of other urease-producing bacteria in the oral cavity or in the stomach, the clinical relevance is also very slight⁴⁰. Thus, the present study design confidently ensured the active *H. pylori* infection status using a two-step diagnostic approach. After large-scale screening by the serum anti-*H. pylori* IgG, all the patients with positive results had their active infection status further confirmed by UBT.

Despite the clear positive relationship between active *H. pylori* infection and glycemia in non-diabetic individuals, the effect of *H. pylori* infection on the A1C level in the diabetic patients remains inconclusive^{22–29}. Most studies using diagnostic methods other than IgG testing report no relationship^{26–29}, except for some that show higher A1C levels in the infected diabetes patients^{22,23}. Similarly, we also found no differences in glycemic control (in terms of A1C) between diabetes patients with “active” infection and “non-active” infection. We postulate that the discrepancy between non-diabetic and diabetic individuals might be due to the lack of consideration of the effects of background antidiabetic medications. In fact, in a glycemic targeted diabetes care system, the intensity of glycemic therapy significantly influences the adequacy and consequence of glycemic control. However, none of the previous studies of type 2 diabetes patients analyzed the regimen of antidiabetic medications, and then took their effects on A1C into consideration while interpreting the glycemic effects of *H. pylori* infection. Therefore, we analyzed the background antidiabetic regimens in the current study.

We found that the “active” infection group had a significantly higher intensity of glycemic treatment than the “non-active” infection group. This suggests that the comparable A1C level in type 2 diabetes patients with active *H. pylori* infection was actually achieved by a higher intensity of glycemic treatment. Specifically, there was a significantly higher percentage of sulfonylureas use in the “active” infection group than “non-

active" infection group. In both groups, a similar percentage (~80%) of patients were prescribed with metformin as the first-line therapy. After that, it is highly recommended that the second-line therapy should be selected based on patient-specific considerations. In real-world practice, sulfonylureas are the most commonly considered add-on therapy for patients whose glycemia cannot be adequately controlled by metformin^{41,42}. This might be why sulfonylurea was the only class of OAD that had a higher percentage of use in the "active" infection group than in the "non-active" infection group.

Our finding that active *H. pylori* infection was associated with a higher intensity of glycemic treatment was further supported by the interventional study. Without changing the antidiabetic regimens, the A1C level decreased in the "*H. pylori* eradication" group. These data supported the view that *H. pylori* eradication can provide additional glycemic benefit to current antidiabetic therapy.

In the present study, approximately 70% of the participants were taking statin. Although statin therapy has been found to be associated with new-onset diabetes in non-diabetic patients⁴³, whether statin therapy affects A1C levels in diabetes patients remains inconclusive⁴⁴. Additionally, we further carried out a multiple regression analysis and found that the change in A1C level is independently associated with *H. pylori* eradication therapy, even after adjustment for statin use ($P = 0.019$). Therefore, we believe that statin therapy did not affect the findings of the present study.

Interestingly, we also found no differences in classes of OAD and percentages of sulfonylureas use between the "never/remote infection" and "past infection" groups. This again showed that it is only the "active" infection, not "past" infection, that is associated with worse glycemic control in diabetes patients.

The findings of the present study raise an important issue with regard to whether to treat asymptomatic active *H. pylori* infection in diabetes patients or not. During the past few years, more prescriptions and thus higher expenditures of antidiabetic drugs have been required for diabetes patients⁴⁵, which places a huge economic burden on healthcare systems³. Given the beneficial effects of improving glycemia, thus reducing microvascular/macrovacular complications and medical costs of antidiabetic agents, as well as the very high response rate of *H. pylori* eradication³⁶ and its low-cost treatment, it is promising to advocate the eradication of *H. pylori* from the viewpoint of medical economics. However, more long-term large-scale studies are required to validate the exact costs and benefits.

There were some limitations in this work, as follows. First, the initial part of this work was a cross-sectional design, which thus does not allow for causal inference between the higher intensity of glycemic treatment and active *H. pylori* infection. However, the subsequent interventional study to eradicate active *H. pylori* infection resulted in improved glycemic control, which provides strong support to our speculation. Second, as patients with a negative serum IgG result did not receive further UBT, a false negative result might thereby lead to a

misclassification bias, although the possibility seems slight. Third, the design of our interventional study, although prospective, was not randomized. According to medical ethics, all patients with active *H. pylori* infection were invited to receive an esophagogastroduodenoscopy examination followed by medical treatment for *H. pylori* eradication. Ultimately, 98 patients decided to receive esophagogastroduodenoscopy examination followed by *H. pylori* eradication ("*H. pylori* eradication" group), whereas 99 patients refused ("non-eradication" group). Despite non-randomization, the baseline characteristics between "*H. pylori* eradication" and "non-eradication" groups were still comparable, which adds strength to the results.

Taken together, we found no difference in glycemic level between type 2 diabetes patients with and without active *H. pylori* infection. However, the comparable glycemia in patients with active *H. pylori* infection was actually achieved at the cost of a higher intensity of glycemic treatment. Meanwhile, eradication of active *H. pylori* infection in these patients resulted in improvement of glycemic control. Further validation of this *H. pylori* test-and-treat strategy will be promising to improve the glycemic control in asymptomatic active *H. pylori*-infected diabetes patients.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Between-group differences of changes in bodyweight, lipid levels and blood pressure over 3 months.