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META-ANALYSIS

Is *Helicobacter pylori* infection associated with glycemic control in diabetics?

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Abstract

AIM: To investigate whether *Helicobacter pylori* (*H. pylori*) infection is associated with glycemic control and whether hyperglycemia is modified by eradication therapy.

METHODS: The databases of PubMed, Cochrane Library, Chinese BioMedicine Web Base and Chinese Science and Technology Journals were searched from inception to June 2014. Studies examining the association between *H. pylori* infection and glycemic control and/or the effect of eradication treatment on glycemic control in diabetic humans were eligible for inclusion. Meta-analyses were conducted using the Review Manager software version 5.2. The outcome measures are presented as weighed mean differences (WMDs) with 95% confidence intervals (CIs). Statistical heterogeneity was assessed by the Cochran Q test and the I^2 statistic.

RESULTS: A total of 21 relevant publications were identified. A meta-analysis of 11 studies with 513 patients with diabetes mellitus (DM) showed significantly lower glycosylated hemoglobin (HbA1c) levels in the *H. pylori*-negative than *H. pylori*-positive DM participants (WMD = 0.43, 95%CI: 0.07-0.79; P = 0.02). In children and adolescents with type 1 DM (T1DM), there was a positive association between *H. pylori* infection and HbA1c level (WMD = 0.35, 95%CI: 0.05-0.64; P = 0.02), but there was no difference in those with type 2 DM (T2DM, WMD = 0.51, 95%CI: -0.63-1.65; P = 0.38). A meta-analysis of six studies with 325 T2DM participants showed a significant difference in the fasting plasma glucose levels between *H. pylori*-positive and *H. pylori*-negative participants (WMD = 1.20, 95%CI: 0.17-2.23; P = 0.02). Eradication of *H. pylori* did not improve glycemic control in the T2DM participants in a three-month follow-up period (HbA1c decrease: WMD = -0.03, 95%CI = -0.14-0.08; P = 0.57; fasting plasma glucose decrease: WMD = -0.06, 95%CI: -0.36-0.23; P = 0.68). Glycemic control was significantly better in T1DM participants who were not reinfected than in those who were reinfected (HbA1c: WMD = 0.72, 95%CI: 0.32-1.13: P = 0.00).

CONCLUSION: *H. pylori* infection is associated with poorer glycemic control in T1DM patients, but eradication may not improve glycemic control in DM in a short-term

follow-up period.

Key words: Diabetes mellitus; Eradication; Glycemic control; *Helicobacter pylori*; Meta-analysis; Reinfection

Core tip: Infection with *Helicobacter pylori* (*H. pylori*) has been suggested to play a pathogenic role in diabetes mellitus. The association between *H. pylori* and glycemic control in diabetics remains controversial. Our systematic review suggests a positive association between *H. pylori* and glycemic control in diabetics, especially in patients with type 1. While a short-term follow-up analysis demonstrated that *H. pylori* eradication does not improve glycemic control in diabetics, the long-term effects of eradication treatment remain unknown. Thus, the question remains as to whether the indication for *H. pylori* eradication in diabetic patients should be extended.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped, microaerophilic bacterium that plays a major pathogenic role in gastric diseases, including, but not limited to, chronic gastritis, peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue-associated lymphoma[1-3]. Studies published in the literature over the past two decades have suggested potential associations for *H. pylori* and several extragastric manifestations, such as idiopathic thrombocytopenic purpura, iron deficiency anemia, and atherosclerotic disease[4,5], as well as cardiovascular disease, diabetes mellitus (DM), nonalcoholic fatty liver disease, and other metabolic syndromes[6-9].

It has been suggested that infection with *H. pylori* is potentially linked to DM in many aspects. Various studies have reported a higher prevalence of *H. pylori* infection[10-13], a lower eradication rate[12-16] and a more frequent reinfection prevalence[12,13,17-19] in diabetic patients *vs* controls. Moreover, *H. pylori* infection is considered to be associated with metabolic control in diabetics[6,7,20]. Chen *et al*[20] found that *H. pylori* seropositivity was positively associated with glycosylated hemoglobin (HbA1c) levels through a large-scale cross-sectional analysis, which indicated a role of *H. pylori* in impaired glucose tolerance in adults. However, the questions of whether *H. pylori* infection is associated with poorer glycemic control in diabetic patients and whether eradication of *H. pylori* can improve their glycemic control remain controversial. Thus, we performed a systematic review with the aim of assessing whether *H. pylori* infection is associated with glycemic control in patients with DM and whether hyperglycemia in diabetics is modified by eradication of *H. pylori*.

MATERIALS AND METHODS

Search strategy

The PubMed, Cochrane Library, Chinese BioMedicine Web Base and Chinese Science and Technology Journals databases were systematically searched from inception to June 2014 for relevant studies. No language restriction was used. The search terms included: "*Helicobacter pylori*"[Mesh] or "*Helicobacter pylori*" or "*H. pylori*" and "Diabetes mellitus"[Mesh] or "diabetes mellitus" or "diabetes" or "diabetic" or "hyperglycemia" and "glucose" or "sugar" or "glucose control" or "glycemic control" or "glycaemic control" or "insulin" or "insulin sensitivity." We also performed manual searches and screenings of the reference lists of each article identified by the electronic search.

Selection criteria

Cross-sectional studies, case-control studies, cohort studies and randomized controlled trials (RCTs) examining the association between *H. pylori* infection and glycemic control and/or the effect of eradication treatment on glycemic control in diabetic humans were considered eligible for study inclusion. Letters were also selected for use in our systematic review and meta-analysis. Two reviewers independently judged the eligibility of each study identified by the electronic and manual searches, and disagreements were resolved by consulting a third reviewer.

To be accepted for study inclusion, articles had to meet the following criteria: (1) study of subjects that had received previous diagnosis of DM [either type 1 (T1) or type 2 (T2)]; (2) measurement of fasting plasma glucose (FPG), HbA1c, insulin or C-peptide, and/or other parameters reflecting glycemic control in *H. pylori*-positive *vs H. pylori*-negative patients, in patients with *H. pylori* reinfection *vs* those who were not reinfected after successful eradication, in patients with successful *H. pylori* eradication treatment *vs* patients with *H. pylori* infection that was not eradicated, or in patients before and after an *H. pylori* eradication treatment; (3) *H. pylori* infection was confirmed by methods that were either invasive (histology, culture, or rapid urease test) or noninvasive (serologic test, ^{13}C-urea breath test, stool antigen test). Age and gastrointestinal symptoms of the subjects at the time of enrollment were not considered as inclusive/exclusive criteria for study inclusion.

Articles were excluded if they provided no sufficient information of *H. pylori* infection or parameters reflecting glycemic control. Case series were also excluded.

Data extraction and quality assessment

A data extraction sheet was developed and pilot-tested using randomly selected studies, the results of which were used to refine the sheet accordingly. Data were extracted by two reviewers working independently. The following information was extracted from each included paper: (1) study characteristics, including author and year of publication, location of the study, sample size, study design, and type of intervention; (2) population information, including age, sex, type of DM, *H. pylori* status, duration of DM, presence or absence of dyspeptic symptoms, type of therapy for DM; (3) outcome data, including mean change and standard deviation in FPG, HbA1c, insulin or C-peptide, and other parameters reflecting glycemic control; (4) diagnosis of *H. pylori* infection; and (5) eradication treatment schedules and follow-up time. Disagreements were resolved by discussion.

The quality of included studies was also assessed by two reviewers working independently. Observational studies were assessed using standards by reference to Quality Assessment Forms[21] that ranged from 0 to 11 points, concerning the selection and representativeness of subjects, the diagnosis of DM and *H. pylori* infection, the comparability of the experimental group and the control group, the measurement of parameters, the loss of follow-up, and many other factors. RCTs were assessed by the Jadad scale[22], which ranged from 0 to 5 points, with higher scores indicating better quality.

Statistical analysis

The outcome measures were continuous and are presented as weighed mean differences (WMD) with 95% confidence intervals (CIs). Statistical heterogeneity was assessed by the Cochran *Q* test and the I^2 statistic. Heterogeneity was considered significant by the Cochran *Q* test for $P < 0.05$ or $I^2 > 50\%$[23,24]. A fixed or random effects model was adopted, depending on the absence or presence of heterogeneity. Funnel plots[25] were generated to initially assess publication bias, after which publication bias was confirmed using Egger's[26] and Begg's[27] tests. The meta-analyses were conducted using Review Manager software, version 5.2, while the Egger's and Begg's tests were carried out using Stata software, version 12.0.

In cases when the study design and population characteristics varied markedly, we decided not to combine studies but instead to show outcome data of each study in a table form or to describe the conclusion of each study.

RESULTS

Study selection, quality, and characteristics

The electronic searches yielded 193 publications with potential relevancy. After each publication was reviewed, only 21 met our inclusion criteria and were selected for study[17-19,28-45], including 14 studies that investigated the association between *H. pylori* and glycemic control in diabetics (11 examined HbA1c level[17,28-37], 6 examined FPG[29,32,35,37-39], and 2 examined the levels of insulin and C-peptide[36,40] in *H. pylori*-positive and *H. pylori*-negative diabetic patients), 6 studies of the effect of eradication treatment (2 trials that compared glycemic control in *H. pylori*-eradicated and noneradicated diabetic patients[41,42], and 4 trials that compared glycemic control before and after *H. pylori* eradication treatment in diabetics[33,43-45]), and two studies of the association between *H. pylori* reinfection and glycemic control[18,19].

The principal characteristics of the selected trials, as well as the quality score of each study, are shown in Table 1. All observational studies scored $\geqslant 7$, and the Jadad scores of the two RCTs were both 3, which represented moderate to high quality. The basic information of the population is shown in Table 2. There were no significant differences in diabetes duration or gastrointestinal symptoms between the subjects in the experimental and control groups of each study, except for those denoted in the table, or those studies with data that were unavailable.

H. pylori infection and glycemic control

Eleven of the included publications[17,28-37] measured plasma HbA1c level in *H. pylori*-positive and *H. pylori*-negative patients with DM, including five studies[17,28,31,33,34] involving children and adolescents with T1DM, five studies[29,32,35-37] involving T2DM patients, and one study[30] in which the T1DM and T2DM patients were not distinguished. Overall, the pooled mean difference in HbA1c level showed a positive association with *H. pylori* infection (WMD = 0.43, 95%CI: 0.07-0.79; $P = 0.02$). Through the subgroup analysis, we found that the HbA1c level was significantly higher in the *H. pylori*-positive children and adolescents with T1DM than in their *H. pylori*-negative counterparts (WMD = 0.35, 95%CI: 0.05-0.64; $P = 0.02$). However, there was no significant difference in the HbA1c levels between *H. pylori*-positive and *H. pylori*-negative patients with T2DM (WMD = 0.51, 95%CI: -0.63-1.65; $P = 0.38$). Overall, the studies included were heterogeneous ($I^2 = 72\%$: $P < 0.01$). But significant homogeneity was observed among the studies on children and adolescents with T1DM ($I^2 = 25\%$; $P = 0.26$), whereas the studies on T2DM patients were heterogeneous ($I^2 = 83\%$; $P < 0.01$; Figure 1).

Six observational studies[29,32,35,37-39] assessed FPG in *H. pylori*-positive and *H. pylori*-negative T2DM patients, the meta-analysis of which showed a positive association between *H. pylori* infection and FPG (WMD = 1.20, 95%CI: 0.17-2.23; $P = 0.02$). The included studies did not show homogeneity ($I^2 = 70\%$; $P < 0.01$; Figure 2).

Two observational studies[36,40] assessed the association of *H. pylori* infection and plasma insulin

Table 1 Characteristics of the selected studies in our systematic review

Ref.	Location	Study design and type of intervention	DM patients, *n* (HP+/HP-)[1]	Diagnosis of *H. pylori*	Parameter(s) measured	Glycemic control (HP+ *vs* HP-)	Quality score[2]
de Luis *et al*[43], 2000	Spain	Observational; before and after eradication (6-mo-follow-up)	13 (13/13)	UBT and serologic test	HbA1c	ND	9
Arslan *et al*[28], 2000	Turkey	Observational; HP+ *vs* HP-	88 (49/39)	Serologic test	HbA1c	ND	8
Ko *et al*[29], 2001	Hong Kong, China	Observational; HP+ *vs* HP-	63 (32/31)	RUT	HbA1c and FPG	ND	9
Jones *et al*[30], 2002	Australia	Observational; HP+ *vs* HP-	63 (15/48)	Serologic test	HbA1c	ND	9
Ojetti *et al*[18], 2002	Italy	Observational; reinfected *vs* not reinfected (1-yr-follow-up)	34 (13/21)	UBT and histology	HbA1c	Worse	7
Candelli *et al*[31], 2003	Italy	Observational; HP+ *vs* HP-	121 (34/87)	UBT and serologic test	HbA1c	ND	8
Wang *et al*[32], 2003	China	Observational; HP+ *vs* HP-	94 (75/19)	Serologic test	HbA1c and FPG	ND	8
Candelli *et al*[33], 2004	Italy	Observational; HP+ *vs* HP- before and after eradication (6-mo-follow-up)	58 (29/29)	UBT	HbA1c	ND	8
Agrawal *et al*[38], 2005	India	Observational; HP+ *vs* HP-	80 (50/30)	RUT	FPG	Worse	8
Moghimi *et al*[41], 2007	Iran	RCT eradication *vs* non-eradication (3-mo-follow-up)	41 (22/19)	UBT	HbA1c decrease and FPG decrease	ND	3 (Jadad score)
Ojetti *et al*[19], 2007	Italy	Observational; reinfected *vs* not reinfected (5-yr-follow-up)	40 (11/29)	UBT and histology	HbA1c	Worse	7
Toporowska-Kowalska *et al*[34], 2007	Poland	Observational; HP+ *vs* HP-	198 (48/150)	UBT	HbA1c	Worse	7
Khalil *et al*[44], 2007	Belgium	Observational; before and after eradication (12-mo-follow-up)	100 (49/51)	UBT	HbA1C	ND	7
Demir *et al*[35], 2008	Turkey	Observational; HP+ *vs* HP-	141 (87/54)	RUT and histology	HbA1c and FPG	ND	9
Lu *et al*[40], 2010	China	Observational; HP+ *vs* HP-	80 (49/31)	UBT and histology	Insulin and C-peptide	Worse	8
Candelli *et al*[17], 2012	Italy	Observational; HP+ *vs* HP-	69 (17/52)	UBT	HbA1c	ND	8
Wei[39], 2012	China	Observational; HP+ *vs* HP-	68 (38/30)	RUT	FPG	Worse	7
Zhou *et al*[36], 2012	China	Observational; HP+ *vs* HP-	180 (84/96)	Serologic test	HbA1c, insulin and C-peptide	ND	8
Vafaeimanesh *et al*[42], 2013	Iran	RCT; eradication *vs* noneradication (6-mo-follow-up)	93 (46/47)	UBT	HbA1c decrease and FPG decrease	ND	3 (Jadad score)
Peng *et al*[37], 2013	China	Observational; HP+ *vs* HP-	85 (43/42)	RUT and histology	HbA1c and FPG	Worse	7
Wada *et al*[45], 2013	Japan	Observational; before and after eradication (6-mo-follow-up)	72 (72/72)	UBT and histology	HbA1c	ND	7

[1]HP+ includes those who did not receive/failed eradication treatment, and those who were reinfected; HP- includes those who received successful eradication treatment; [2]Quality score is presented in each study by reference to Quality Assessment Forms, except for the two RCTs assessed using the Jadad Scale. DM: Diabetes mellitus; FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; HP+: *Helicobacter pylori*-positive; HP-: *H. pylori*-negative; ND: No difference; RCT: Randomized controlled trial; RUT: Rapid urease test; UBT: ^{13}C-urea breath test.

and C-peptide levels in patients with DM. We did not perform a meta-analysis for these parameters due to insufficient data and varied population characteristics. The study by Lu *et al*[40] found that fasting and 1-h and 2-h postprandial insulin was significantly lower in the T1DM patients with *H. pylori* positivity than in those with *H. pylori* negativity ($P < 0.05$). The study by Zhou *et al*[36] found no significant difference in the fasting C-peptide levels of T2DM patients with *H. pylori* positivity and *H. pylori* negativity ($P > 0.05$).

Table 2 Population information of the selected studies

Ref.	DM type	Age (yr)	Sex (M/F, *n*)	DM duration (yr)	Type of therapy for DM	GI symptoms, *n*
de Luis *et al*[43], 2000	T1DM	44.9 ± 15.5	4/9	13.49 ± 7.0 (1-33)	Insulin	10 with dyspepsia
Arslan *et al*[28], 2000	T1DM	12.6 ± 4.2	36/52	HP+: 3.85 ± 3.62; HP-: 2.30 ± 2.12 (P = 0.02)[1] (0-13)	Insulin	5 had upper GI symptoms
Ko *et al*[29], 2001	T2DM	49.9 ± 12.0	29/34	HP+: 5.2 ± 5.7; HP-: 7.3 ± 6.6 (NS) (1-26; median: 3)	Irrespective	29 had upper GI symptoms
Jones *et al*[30], 2002	T1DM and T2DM	44.7 ± 2.99	25/38	16.6 ± 1.4	Insulin; oral drugs	GI symptoms occurred frequently
Ojetti *et al*[18], 2002	T1DM	42 ± 9	18/16	NA	Insulin	None had GI symptoms
Candelli *et al*[31], 2003	T1DM	15 ± 6	65/56	6.6 ± 4.6	Insulin	A proportion had GI symptoms
Wang *et al*[32], 2003	T2DM	(28-83)	44/50	HP+: 5.8 ± 2.2; HP-: 9.3 ± 6.5 (P < 0.05)[1]	Insulin and oral drugs	A proportion had GI symptoms[2]
Candelli *et al*[33], 2004	T1DM	13.35 ± 3.62	28/30	NA	Insulin	35 had GI symptoms
Agrawal *et al*[38], 2005	T2DM	52.8 ± 11.1	62/18	NA	NA	36 had GI symptoms
Moghimi *et al*[41], 2007	T2DM	NA	NA	No difference in two groups	Insulin and oral drugs	NA
Ojetti *et al*[19], 2007	T1DM	48 ± 9	23/17	27.5 ± 12.5	Insulin	NA
Toporowska-Kowalska *et al*[34], 2007	T1DM	14.38 ± 3.75	NA	(0.5-16)	Insulin	NA
Khalil *et al*[44], 2007	T1DM	14.2 ± 2.8	56/44	6.2 ± 2.3	Insulin	45 had vague abdominal pain
Demir *et al*[35], 2008	T2DM	52.0 ± 8.2	44/97	6.1 ± 5.9 HP+: 5.9 ± 6.1; HP-: 6.28 ± 5.9 (NS)	Insulin, oral drugs or diet alone	All had GI symptoms
Lu *et al*[40], 2010	T1DM	18.6 ± 10.6	45/35	No difference in two groups	Insulin	NA
Candelli *et al*[17], 2012	T1DM	16.8 ± NA (9-21)	41/28	NA	Insulin	A proportion had GI symptoms
Wei[39], 2012	T2DM	50.0 ± 11.2	36/32	NA	NA	NA
Zhou *et al*[36], 2012	T2DM	59.22 ± 2.57	87/93	NA	NA	NA
Vafaeimanesh *et al*[42], 2013	T2DM	55.3 ± 10.4	50/43	NA	Non-insulin users	A proportion had GI symptoms
Peng *et al*[37], 2013	T2DM	50.1 ± 10.3	51/34	No difference in two groups	NA	NA
Wada *et al*[45], 2013	T2DM	63.7 ± 1.1	55/17	NA	NA	NA

[1]Significant difference in the duration of diabetes for the HP+ *vs* HP-; [2]Prevalence of GI symptoms was higher in the HP+ group than in the HP- group. Data are presented as mean ± SD (range). DM: Diabetes mellitus; HP+: *Helicobacter pylori*–positive; HP-: *H. pylori*–negative; GI: Gastrointestinal; NA: Not available; NS: Not significant; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Effect of eradication

Two RCTs[41,42] assessed the effect of *H. pylori* eradication on HbA1c and FPG decreases in T2DM patients, after 3 or 6 mo of follow-up. Moghimi *et al*[41] compared *H. pylori*-positive patients with or without eradication [achieved by omeprazole (40 mg), azithromycin (500 mg), bismuth subcitrate (480 mg), and metronidazole (1000 mg) for 10 d]. Vafaeimanesh *et al*[42] compared *H. pylori*-positive patients with successful eradication to those who failed to achieve eradication treatment [by omeprazole (40 mg), metronidazole (1000 mg), amoxicillin (2000 mg) and bismuth subcitrate (480 mg), or by omeprazole (40 mg), clarithromycin (1000 mg), and amoxicillin (2000 mg) for 14 d]. Meta-analysis of these studies indicated no significant difference of glycemic control in the eradication group *vs* the noneradication group at 3 mo after treatment (HbA1c decrease: WMD = -0.03, 95%CI: -0.14-0.08, P = 0.57; FPG decrease: WMD = -0.06, 95%CI: -0.36-0.23; P = 0.68). The included studies were homogeneous (HbA1c decrease: I^2 = 0%; P = 0.76; FPG decrease: I^2 = 0%; P = 0.52; Figure 3).

Four observational studies[33,43-45] compared plasma HbA1c levels in *H. pylori*-positive diabetic patients before and after eradication treatment. Because the populations were heterogeneous in age, type of DM, gastrointestinal symptoms and so on, we did not perform meta-analysis and instead listed the results of each study in Table 3. All four studies suggested that eradication therapy for *H. pylori* does not affect glycemic control according to short-term follow-up (3-12 mo) in diabetic subjects.

Reinfection with H. pylori and glycemic control

Two cohort studies[18,19] assessed plasma HbA1c levels in *H. pylori* reinfected T1DM patients after *H. pylori* eradication compared to those who were not reinfected. Glycemic control was significantly better in

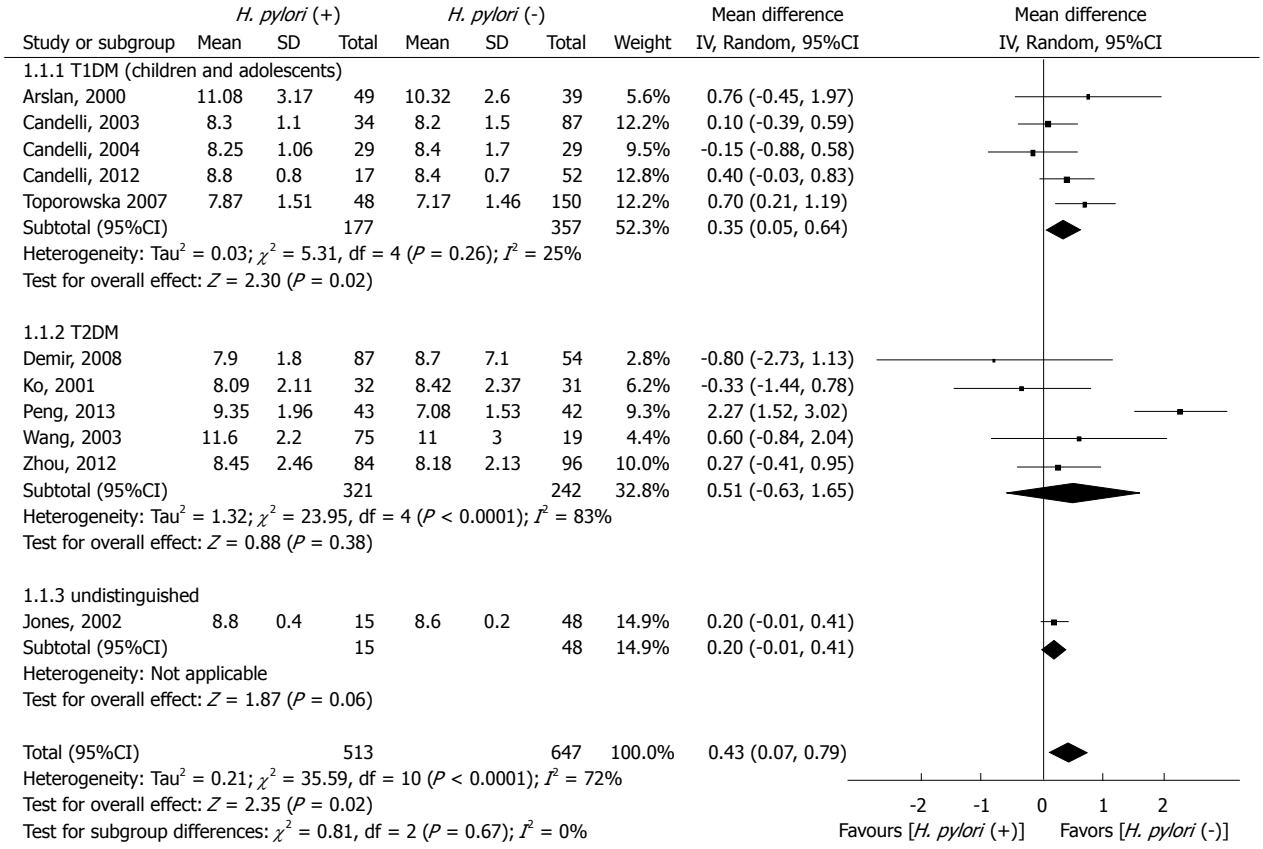

Figure 1 ***Helicobacter pylori*** **infection and glycosylated hemoglobin levels in diabetic patients.** The forest plot demonstrates the positive association between *Helicobacter pylori* infection and HbA1c levels in children and adolescents with type 1 diabetes mellitus (T1DM) but not type 2 diabetes mellitus (T2DM). IV: Inverse variance.

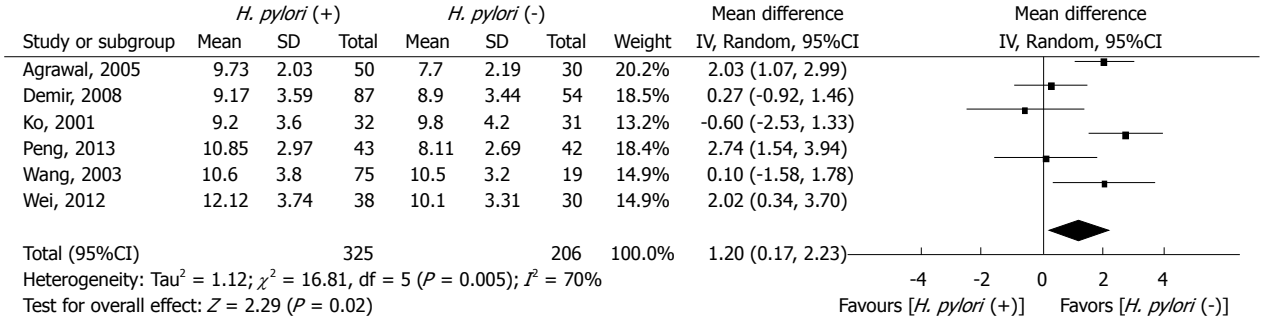

Figure 2 ***Helicobacter pylori*** **infection and fasting plasma glucose levels in type 2 diabetes mellitus patients.** The forest plot demonstrates the positive association between *Helicobacter pylori* infection and fasting plasma glucose levels in type 2 diabetes mellitus patients. The studies included were not homogeneous. IV: Inverse variance.

those who were not reinfected (WMD = 0.72, 95%CI: 0.32-1.13; $P < 0.01$). Significant homogeneity was observed among the studies ($I^2 = 15\%$; $P = 0.28$; Figure 4).

Publication bias

Examination of the funnel plots (Figure 5) suggested some publication bias, but the results of Egger's and Begg's tests showed no evidence of significant bias in the studies considered. For studies on HbA1c level in *H. pylori*-positive and *H. pylori*-negative patients, the *P*-values of Egger's and Begg's tests were 0.365 and 0.350, respectively. For studies on FPG in *H. pylori*-positive *vs H. pylori*-negative patients, the *P*-values of Egger's and Begg's tests were 0.631 and 0.452, respectively.

DISCUSSION

The results of the systematic review and meta-analyses suggest that *H. pylori* infection is associated with higher HbA1c levels in T1DM children and adolescents, which indicates poorer glycemic control. However, further studies are needed to prove whether

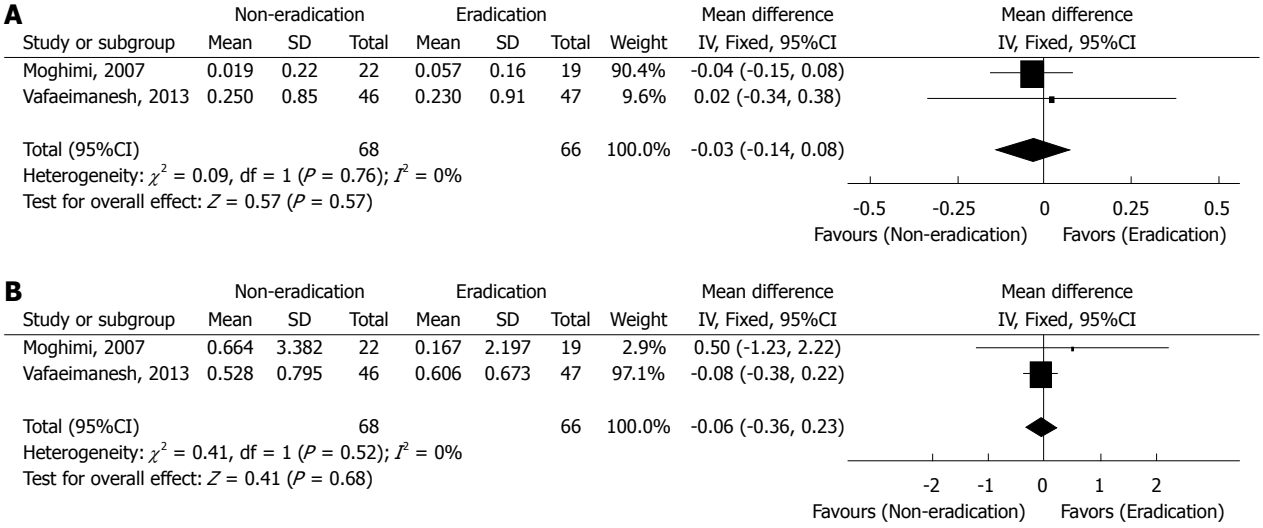

Figure 3 Effect of *Helicobacter pylori* eradication on glycemic control in type 2 diabetes mellitus patients. A: Glycosylated hemoglobin decrease (%); B: Fasting plasma glucose decrease (mmol/L). The forest plot demonstrates that eradication of *Helicobacter pylori* did not improve glycemic control in type 2 diabetes mellitus patients in a 3-mo follow-up period. IV: Inverse variance.

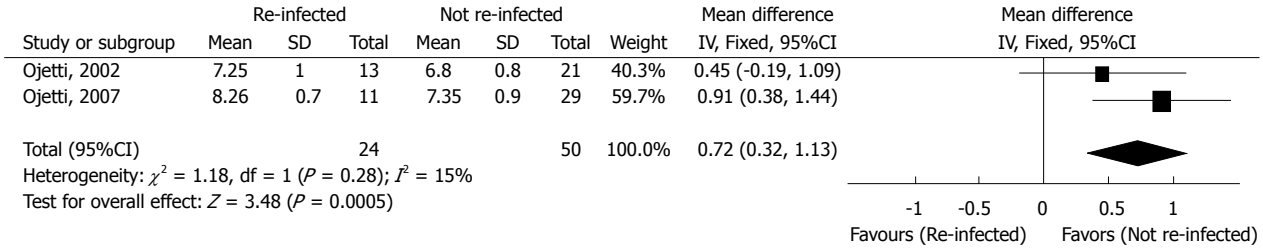

Figure 4 *Helicobacter pylori* reinfection and glycosylated hemoglobin levels in type 1 diabetes mellitus patients. The forest plot demonstrates the positive association between *Helicobacter pylori* re-infection and glycosylated hemoglobin levels in type 1 diabetes mellitus patients. IV: Inverse variance.

Table 3 Glycosylated hemoglobin levels in *Helicobacter pylori*-positive diabetics before and after eradication treatment

Ref.	Eradication regimen	Before treatment	After treatment			*P* value
			3 mo	6 mo	12 mo	
de Luis *et al*[43], 2000	A: 2000 mg, C: 1000 mg, O: 40 mg; 10 d	7.7 ± 1.4	NA	7.3 ± 1.0	NA	> 0.05
Candelli *et al*[33], 2004	< 14 yr: A: 50 mg/kg, C: 30 mg/kg, R: 2 mg/kg; 7 d > 14 yr: A: 2000 mg, C: 750 mg, R: 20 mg; 7 d	8.2 ± 1.0	NA	8.3 ± 1.0	NA	> 0.05
Khalil *et al*[44], 2007	Two antibiotics among A, C or M; O; 7 d	7.4 ± 1.3	NA	NA	7.9 ± 1.1	> 0.05
Wada *et al*[45], 2013	A: 1500 mg, C: 800 mg, L: 60 mg or O: 40 mg or R: 40 mg; 7 d	6.9 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	NA	> 0.05

Data are presented as mean ± SE. A: Amoxicillin; C: Clarithromycin; L: Lansoprazole; M: Metronidazole; NA: Not available; O: Omeprazole; R: Rabeprazole.

H. pylori infection is associated with glycemic control in patients with T2DM because significant heterogeneity exists among the studies that have assessed HbA1c level and the studies that have assessed FPG level in *H. pylori*-positive and *H. pylori*-negative T2DM patients. We found that the subjects with T2DM in our selected studies may differ in several ways that affect glycemic control, including type of therapy for diabetes, diabetes duration, dyspeptic symptoms, and the compliance for glycemic control. These inconsistencies result in heterogeneity among the studies assessing glycemic control in T2DM patients. In contrast, the subjects with T1DM in our selected studies were all dependent upon insulin therapy, and as a result, no significant heterogeneity was seen in these studies.

Lu *et al*[40] reported that fasting and postprandial insulin secretions were significantly higher in *H. pylori*-negative T1DM patients than in their *H. pylori*-positive counterparts. Although there was a limitation of small sample size in that study, the previous finding is consistent with our current finding of better glycemic control occurring in *H. pylori*-negative T1DM patients compared to the *H. pylori*-positive patients with T1DM.

The results from the current systematic review also support the conclusion that eradication of *H. pylori* may not improve glycemic control in diabetic

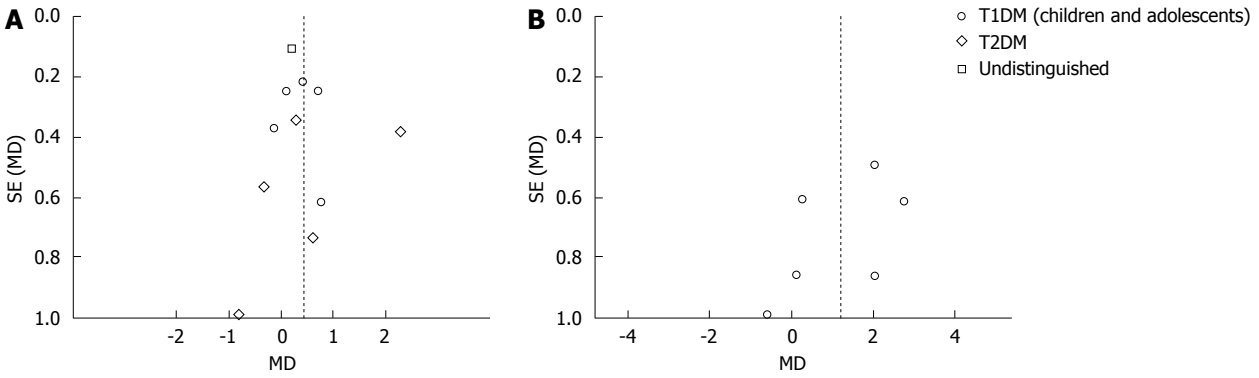

Figure 5 Funnel plots for publication bias. Each dot represents the mean difference for glycosylated hemoglobin level (A) or fasting plasma glucose level (B) in *Helicobacter pylori*-positive and *Helicobacter pylori*-negative diabetics.

patients in a short-term follow-up period. Because the number of studies was limited and the follow-up time of the studies was short, further studies are needed to confirm the effect of *H. pylori* eradication on glycemic control in both T1DM and T2DM patients. Furthermore, results from our meta-analysis showed that *H. pylori* reinfection is associated with poorer glycemic control in T1DM patients.

A recent meta-analysis performed by another group that assessed the association of *H. pylori* and glycemic control in diabetics showed that *H. pylori* carriers did not have higher HbA1C levels than the noncarriers[46]. The authors concluded that *H. pylori* infection did not worsen glycemic control in patients with DM. Nevertheless, their meta-analysis did not estimate the quality of each included study. Moreover, the authors only examined a single parameter (HbA1C level) to estimate glycemic control of the subjects. The different search strategy used in our current meta-analysis, as well as the different databases that were searched and the different inclusion criteria that were applied, may have led to different conclusions. However, considering the relatively limited population in the current meta-analysis, we appeal for further large-scale observational studies to verify this association. On the other hand, our systematic review further assessed the effects of *H. pylori* eradication treatment and reinfection with *H. pylori* on glycemic control in diabetic humans, which may have some value for clinical practice.

The overall quality of the selected articles is moderate to high. Many of the studies evaluated confounding factors that may affect glycemic control, such as age, sex, duration of DM and gastrointestinal symptoms; in those studies, however, the cases and controls were comparable based upon the consistent measures of the potential confounders. Nevertheless, a few studies observed differences among the confounders in their comparative analyses, without any adjustments. The sample sizes of the selected studies were also small, which represents a major limitation. Furthermore, most of the selected articles were descriptive studies, which precluded their ability to determine the causal relationship between *H. pylori* and glycemic control.

The mechanisms linking *H. pylori* and glycemic control in diabetics are complicated. It is well known that T1DM occurs because of the autoimmune destruction of pancreatic islets (the micro-organ in which insulin production and secretion occur), whereas insulin resistance is a central pathogenic factor in T2DM. *H. pylori* might condition the pathophysiology of autoimmune response and insulin resistance syndrome by pathologic consequences through chronic inflammation outside the stomach, by which the bacterium affects glycemic control in diabetic patients[9,13,47,48]. In another aspect, gastrointestinal conditions related to *H. pylori* infection could delay gastric emptying, consequently favoring poor glucose control[13,43]. Furthermore, Ibrahim *et al*[49] demonstrated that infection with cytotoxin-associated gene A antigen-positive strains of *H. pylori* is strongly associated with poor glycemic control in T2DM patients. This finding suggests that the more pathogenic type of *H. pylori*, which expresses the cytotoxin-associated gene A antigen and the vacuolating cytotoxin-associated gene antigen, may play a major pathogenic role in DM through its interactions with factors related to the host inflammatory response.

Although *H. pylori* seems to be a pathogenic factor for DM, eradication of *H. pylori* does not benefit all diabetic patients. Khamaisi *et al*[50] reported a case of an 80-year-old man with end-stage renal disease and well-controlled T2DM, who developed severe hypoglycemia after administration of clarithromycin due to a clarithromycin-repaglinide drug interaction. Otsuka[51] reported the case of an 82-year-old man with insulin-controlled T2DM who experienced severe hypoglycemia during triple drug therapy. These collective findings remind us that clinicians should be aware of possible drug interactions that may occur in diabetics while undergoing *H. pylori* eradication therapy, so as to be careful to avoid adverse events.

Nowadays, the indications for treatment of *H. pylori* include peptic ulcer, mucosa-associated lymphoid tissue, functional dyspepsia, long-term nonsteroidal

anti-inflammatory drug use, gastric cancer, iron-deficiency anemia and idiopathic thrombocytopenic purpura[4]. Since our study has suggested a positive association between *H. pylori* and glycemic control in diabetics, there should be a debate about whether we need to extend the *H. pylori* eradication indications for patients with DM. Since this systematic review does not allow for a conclusion about the long-term effect of *H. pylori* eradication on glycemic control in diabetics, further studies with large populations are needed to observe glycemic control in diabetics after eradication therapy in a longer follow-up period.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) is potentially related to a series of extragastric diseases, including diabetes mellitus (DM). DM is a major health burden worldwide, and glycemic control in DM is an issue of great public concern. The findings regarding the association between *H. pylori* and glycemic control in diabetics have been largely inconsistent. Therefore, the authors conducted a systematic review to explore the relationship between *H. pylori* and glycemic control in DM.

Research frontiers

H. pylori is known to play a role in autoimmune disease and insulin resistance through complex processes. A large-scale survey has suggested an association between *H. pylori* and impaired glucose tolerance in adults. Consequently, a current hotspot in DM research is the association between *H. pylori* infection and glycemic control, as well as the effect of eradication treatment on glycemic control.

Innovations and breakthroughs

Previous studies have indicated that DM is linked to a higher prevalence of *H. pylori*, a lower eradication rate, and a higher incidence of reinfection. In addition, it is believed that *H. pylori* is associated with metabolic control in DM. However, the association between *H. pylori* and glycemic control in diabetics remains controversial. This systematic review has evaluated this potential association from a comprehensive perspective, including infection, eradication, reinfection with *H. pylori* and glycemic control. Meta-analyses were performed to examine the overall effect.

Applications

The results of this study indicate that *H. pylori* infection is associated with poorer glycemic control in type 1 DM patients and that eradication of *H. pylori* may not improve glycemic control in the short-term (3-12 mo). These findings may provide insights into clinical therapy and promote discussions as to whether the *H. pylori* eradication indications should be extended for DM patients.

Terminology

H. pylori is a gram-negative, spiral-shaped, microaerophilic bacterium that is related to gastric diseases in humans. Infection with *H. pylori* remains a worldwide threat to human health. DM is a common metabolic disease, which is characterized by high plasma glucose levels for a prolonged period. Type 1 DM results from the insufficient secretion of insulin, while type 2 DM is due to insulin resistance.

Peer-review

This is an interesting meta-analysis about the relation between *H. pylori* and glycemic control in diabetics. The title clearly states the purpose of the study. The study selection criteria were broad and included letters. The results section is clearly presented. The authors concluded that *H. pylori* infection is associated with poorer glycemic control in type 1 DM patients and that eradication of *H. pylori* may not improve glycemic control in diabetic patients over a short-term period. The fact that the authors found no improvement in HbA1c before and after eradication confirms the uncertainty of the relationship.

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