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

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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.

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 have published in the literature over the past two decades have suggested potential associations for H. pylori and several extragastrointestinal 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, 13C-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 weighted mean differences (WMD) with 95% confidence intervals (CIs). Statistical heterogeneity was assessed by the Cochran Q test and the I² statistic. Heterogeneity was considered significant by the Cochran Q test for P < 0.05 or I² > 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 noneeradicated diabetic patients[41,42], and 4 trials that compared glycemic control before and after H. pylori eradication treatment in diabetics[23,24-45]), and two studies of the association between H. pylori reinfection and glycemic control[25,46].

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 ≥ 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[17,29,32,35-37] involving T2DM patients, and one study[35] 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 (I² = 72%; P < 0.01). But significant homogeneity was observed among the studies on children and adolescents with T1DM (I² = 25%; P = 0.26), whereas the studies on T2DM patients were heterogeneous (I² = 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 (I² = 70%; P < 0.01; Figure 2).

Two observational studies[36,40] assessed the association of H. pylori infection and plasma insulin...
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\textsuperscript{[40]} found that fasting and 1-h and 2-h postprandial insulin was significantly lower in the T1DM patients with \textit{H. pylori} positivity than in those with \textit{H. pylori} negativity (\(P < 0.05\)). The study by Zhou \textit{et al}\textsuperscript{[36]} found no significant difference in the fasting C-peptide levels of T2DM patients with \textit{H. pylori} positivity and \textit{H. pylori} negativity (\(P > 0.05\)).

| Ref. | Location | Study design and type of intervention | DM patients, n (HP+ vs HP-)\textsuperscript{1} | Diagnosis of \textit{H. pylori} | Parameter(s) measured | Glycemic control (HP+ vs HP-) | Quality score\textsuperscript{2} |
|------|----------|-------------------------------------|---------------------------------------------|-------------------------------|----------------------|-----------------------------|------------------------|
| de Luis \textit{et al}\textsuperscript{[34]}, 2000 | Spain | Observational; before and after eradication (6-mo-follow-up) | 13 (13/13) | UBT and serologic test | HbA1c | ND | 9 |
| Arslan \textit{et al}\textsuperscript{[35]}, 2000 | Turkey | Observational; HP+ vs HP- | 88 (49/39) | Serologic test | HbA1c | ND | 8 |
| Ko \textit{et al}\textsuperscript{[36]}, 2001 | Hong Kong, China | Observational; HP+ vs HP- | 63 (32/31) | RUT | HbA1c and FPG | ND | 9 |
| Jones \textit{et al}\textsuperscript{[37]}, 2002 | Australia | Observational; HP+ vs HP- | 63 (15/48) | Serologic test | HbA1c | ND | 9 |
| Ogetti \textit{et al}\textsuperscript{[38]}, 2002 | Italy | Observational; reinfected vs not reinfected (1-yr-follow-up) | 34 (13/21) | UBT and histology | HbA1c | Worse | 7 |
| Candelli \textit{et al}\textsuperscript{[39]}, 2003 | Italy | Observational; HP+ vs HP- | 121 (34/87) | UBT and serologic test | HbA1c | ND | 8 |
| Wang \textit{et al}\textsuperscript{[40]}, 2003 | China | Observational; HP+ vs HP- | 94 (75/19) | Serologic test | HbA1c and FPG | ND | 8 |
| Candelli \textit{et al}\textsuperscript{[41]}, 2004 | Italy | Observational; before and after eradication (6-mo-follow-up) | 58 (29/29) | UBT | HbA1c | ND | 8 |
| Agrawal \textit{et al}\textsuperscript{[42]}, 2005 | India | Observational; HP+ vs HP- | 80 (50/30) | RUT | FPG | Worse | 8 |
| Moghimi \textit{et al}\textsuperscript{[43]}, 2007 | Iran | RCT eradication vs non-eradication (3-mo-follow-up) | 41 (22/19) | UBT | HbA1c decrease and FPG decrease | ND | 3 (Jadad score) |
| Ogetti \textit{et al}\textsuperscript{[44]}, 2007 | Italy | Observational; reinfected vs not reinfected (5-yr-follow-up) | 40 (11/29) | UBT and histology | HbA1c | Worse | 7 |
| Toporowska-Kowalska \textit{et al}\textsuperscript{[45]}, 2007 | Poland | Observational; HP+ vs HP- | 198 (48/150) | UBT | HbA1c | Worse | 7 |
| Khalili \textit{et al}\textsuperscript{[46]}, 2007 | Belgium | Observational; before and after eradication (12-mo-follow-up) | 100 (49/51) | UBT | HbA1C | ND | 7 |
| Demir \textit{et al}\textsuperscript{[47]}, 2008 | Turkey | Observational; HP+ vs HP- | 141 (87/54) | RUT and histology | HbA1c and FPG | ND | 9 |
| Lu \textit{et al}\textsuperscript{[48]}, 2010 | China | Observational; HP+ vs HP- | 80 (49/31) | UBT and histology | Insulin and C-peptide | Worse | 8 |
| Candelli \textit{et al}\textsuperscript{[49]}, 2012 | Italy | Observational; HP+ vs HP- | 69 (17/52) | UBT | HbA1c | ND | 8 |
| Wei \textit{et al}\textsuperscript{[50]}, 2012 | China | Observational; HP+ vs HP- | 68 (38/30) | RUT | FPG | Worse | 7 |
| Zhou \textit{et al}\textsuperscript{[51]}, 2012 | China | Observational; HP+ vs HP- | 180 (84/96) | Serologic test | HbA1c, insulin and C-peptide | ND | 8 |
| Vafaeeimanesh \textit{et al}\textsuperscript{[52]}, 2013 | Iran | Observational; HP+ vs HP- | 93 (46/47) | UBT | HbA1c decrease and FPG decrease | ND | 3 (Jadad score) |
| Peng \textit{et al}\textsuperscript{[53]}, 2013 | China | Observational; HP+ vs HP- | 85 (43/42) | RUT and histology | HbA1c and FPG | Worse | 7 |
| Wada \textit{et al}\textsuperscript{[54]}, 2013 | Japan | Observational; before and after eradication (6-mo-follow-up) | 72 (72/72) | UBT and histology | HbA1c | ND | 7 |

\textsuperscript{1} HP+ includes those who did not receive/failed eradication treatment, and those who were reinfected; HP- includes those who received successful eradication treatment; \textsuperscript{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+: \textit{Helicobacter pylori}-positive; HP-: \textit{H. pylori}-negative; ND: No difference; RCT: Randomized controlled trial; RUT: Rapid urease test; UBT: \textit{C}-urea breath test.
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[34], 2000 | T1DM    | 44.9 ± 15.5 | 4/9          | 13.49 ± 7.0 (1-33) | Insulin                | 10 with dyspepsia |
| Arslan et al[35,36], 2000 | T1DM    | 12.6 ± 4.2 | 36/32        | HP+: 3.85 ± 3.62; HP-: 2.30 ± 2.12 (P = 0.02) | Insulin                | 5 had upper GI symptoms |
| Ko et al[37,38], 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[39], 2002  | T1DM and T2DM | 44.7 ± 2.99 | 25/38        | 16.6 ± 1.4 | Insulin; oral drugs | GI symptoms occurred frequently |
| Ojetti et al[40], 2002 | T1DM    | 42 ± 9    | 18/16        | NA               | Insulin                | None had GI symptoms |
| Candelli et al[41], 2003 | T1DM    | 15 ± 6    | 65/36        | 6.6 ± 4.6 | Insulin                | A proportion had GI symptoms |
| Wang et al[42], 2003   | T2DM    | (28-83)   | 44/50        | HP+: 5.8 ± 2.2; HP-: 9.3 ± 6.5 (P < 0.05) | Insulin and oral drugs | A proportion had GI symptoms |
| Candelli et al[43], 2004 | T1DM    | 13.35 ± 3.62 | 28/30        | NA               | Insulin                | 35 had GI symptoms |
| Agrawal et al[44], 2004 | T2DM    | 52.8 ± 11.1 | 62/18        | NA               | Insulin                | 36 had GI symptoms |
| Moghimi et al[45], 2004 | T2DM    | NA        | NA           | No difference in two | Insulin and oral drugs | NA |
| Ojetti et al[46], 2007 | T1DM    | 48 ± 9    | 23/17        | 27.5 ± 12.5 (0.5-16) | Insulin                | NA |
| Toporowska-Kowalska et al[47], 2007 | T1DM | 14.38 ± 3.75 | NA | NA | Insulin                | NA |
| Khalil et al[48], 2007 | T1DM    | 14.2 ± 2.8 | 56/44        | 6.2 ± 2.3 | Insulin                | 45 had vague abdominal pain |
| Demir et al[49], 2008  | T2DM    | 52.0 ± 8.2 | 44/97        | 6.1 ± 5.9 | Insulin, oral drugs or diet alone | All had GI symptoms |
| Lu et al[50], 2010     | T1DM    | 18.6 ± 10.6 | 45/35        | No difference in two | Insulin                | NA |
| Candelli et al[51], 2012 | T1DM    | 16.8 ± NA (9-21) | 41/28        | NA               | Insulin                | A proportion had GI symptoms |
| Wei[52], 2012          | T2DM    | 50.0 ± 11.2 | 36/32        | NA               | NA                     | NA |
| Zhou et al[53], 2012   | T2DM    | 59.22 ± 2.57 | 87/93        | NA               | NA                     | NA |
| Vafaeimanesh et al[54], 2013 | T2DM | 55.3 ± 10.4 | 50/43        | NA               | Non-insulin users       | A proportion had GI symptoms |
| Peng et al[55], 2013   | T2DM    | 50.1 ± 10.3 | 51/34        | No difference in two | NA                     | NA |
| Wada et al[56], 2013   | T2DM    | 63.7 ± 1.1 | 55/17        | NA               | NA                     | NA |

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: I² = 0%; P = 0.76; FPG decrease: I² = 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.

Reinfecion with *H. pylori* and glycemic control

Two cohort studies[18,10] 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
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| Study or subgroup | H. pylori (+) | H. pylori (-) | Mean difference | Mean difference |
|-------------------|---------------|---------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95%CI | IV, Random, 95%CI |
| 1.1.1 T1DM (children and adolescents) | Arslan, 2000 | 11.0 | 3.1 | 49 | 10.3 | 2.6 | 39 | 5.6% | 0.76 (-0.45, 1.97) |
|                   | Candelli, 2003 | 8.3 | 1.1 | 34 | 8.2 | 1.5 | 87 | 12.2% | 0.10 (-0.39, 0.59) |
|                   | Candelli, 2012 | 8.5 | 1.0 | 29 | 8.4 | 1.7 | 52 | 9.5% | -0.15 (-0.88, 0.58) |
|                   | Toporowska 2007 | 7.8 | 1.5 | 48 | 7.1 | 1.6 | 150 | 12.2% | 0.70 (0.21, 1.19) |
| Subtotal (95%CI)  | 177  | 357 | 52.3% | | | | | | |
| Heterogeneity: Tau2 = 0.03; \( \chi^2 = 5.31, df = 4 (P = 0.26); I^2 = 25\% |
| Test for overall effect: Z = 2.30 (P = 0.02) |

| Study or subgroup | H. pylori (+) | H. pylori (-) | Mean difference | Mean difference |
|-------------------|---------------|---------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95%CI | IV, Random, 95%CI |
| 1.1.2 T2DM        | Demir, 2008 | 7.9 | 1.8 | 87 | 8.7 | 7.1 | 54 | 2.8% | -0.80 (-2.73, 1.13) |
|                   | Ko, 2001    | 8.0 | 2.1 | 32 | 8.4 | 2.3 | 31 | 6.2% | -0.33 (-1.44, 0.78) |
|                   | Peng, 2013  | 9.3 | 1.9 | 43 | 7.0 | 1.5 | 42 | 9.3% | 2.27 (1.52, 3.02) |
|                   | Wang, 2003  | 11.6 | 2.2 | 75 | 11 | 3 | 19 | 4.4% | 0.60 (-0.84, 2.04) |
|                   | Zhou, 2012  | 8.4 | 2.4 | 84 | 8.1 | 2.1 | 96 | 10.0% | 0.27 (-0.41, 0.95) |
| Subtotal (95%CI)  | 321  | 242 | 32.8% | | | | | | |
| Heterogeneity: Tau2 = 1.32; \( \chi^2 = 23.95, df = 4 (P < 0.0001); I^2 = 83\% |
| Test for overall effect: Z = 0.88 (P = 0.38) |

| Study or subgroup | H. pylori (+) | H. pylori (-) | Mean difference | Mean difference |
|-------------------|---------------|---------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95%CI | IV, Random, 95%CI |
| 1.1.3 Undistinguished | Jones, 2002 | 8.8 | 0.4 | 15 | 8.6 | 0.2 | 48 | 14.9% | 0.20 (-0.01, 0.41) |
|                   | Subtotal (95%CI) | 15 | | 48 | | | | | |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 1.87 (P = 0.06) |

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.

| Study or subgroup | H. pylori (+) | H. pylori (-) | Mean difference | Mean difference |
|-------------------|---------------|---------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95%CI | IV, Random, 95%CI |
| Agrawal, 2005     | 9.73 | 2.03 | 50 | 7.7 | 2.19 | 30 | 20.2% | 2.03 (1.07, 2.99) |
| Demir, 2008      | 9.17 | 3.59 | 87 | 8.9 | 3.44 | 54 | 18.5% | 0.27 (-0.92, 1.46) |
| Ko, 2001         | 9.2 | 3.6 | 32 | 9.8 | 4.2 | 31 | 13.2% | -0.60 (-2.53, 1.33) |
| Peng, 2013       | 10.85 | 2.97 | 43 | 8.1 | 2.69 | 42 | 18.4% | 2.74 (1.54, 3.94) |
| Wang, 2003       | 10.6 | 3.8 | 75 | 10.5 | 3.2 | 19 | 14.9% | 0.10 (-1.58, 1.78) |
| Wei, 2012        | 12.12 | 3.74 | 38 | 10.1 | 3.31 | 30 | 14.9% | 2.02 (0.34, 3.70) |
| Total (95%CI)    | 325  | 206 | 100.0% | | | | | | |
| Heterogeneity: Tau2 = 1.12; \( \chi^2 = 16.81, df = 5 (P = 0.005); I^2 = 70\% |
| Test for overall effect: Z = 2.29 (P = 0.02) |

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...
**Table 3** Glycosylated hemoglobin levels in *H. 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 | NA | > 0.05 |
| Candelli et al[44], 2004 | < 14 yr: A: 50 mg/kg, C: 30 mg/kg, R: 2 mg/kg; 7 d | 8.2 ± 1.0 | NA | NA | > 0.05 |
|                 | > 14 yr: A: 2000 mg, C: 750 mg, R: 20 mg; 7 d | 7.4 ± 1.3 | NA | NA | > 0.05 |
| Khalil et al[45], 2007 | Two antibiotics among A, C or M; O: 7 d | 7.0 ± 0.1 | 7.0 ± 0.1 | 7.0 ± 0.1 | > 0.05 |
| Wada et al[46], 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 | > 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
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 \textit{H. pylori} eradication on glycemic control in both T1DM and T2DM patients. Furthermore, results from our meta-analysis showed that \textit{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 \textit{H. pylori} and glycemic control in diabetics showed that \textit{H. pylori} carriers did not have higher HbA1C levels than the noncarriers.\(^{461}\) The authors concluded that \textit{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 \textit{H. pylori} eradication treatment and reinfection with \textit{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 \textit{H. pylori} and glycemic control.

The mechanisms linking \textit{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. \textit{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 \textit{H. pylori} infection could delay gastric emptying, consequently favoring poor glucose control.\(^{13,43}\) Furthermore, Ibrahim \textit{et al.}\(^{49}\) demonstrated that infection with cytotoxin-associated gene A antigen-positive strains of \textit{H. pylori} is strongly associated with poor glycemic control in T2DM patients. This finding suggests that the more pathogenic type of \textit{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 \textit{H. pylori} seems to be a pathogenic factor for DM, eradication of \textit{H. pylori} does not benefit all diabetic patients. Khamaisi \textit{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 end-stage renal disease who developed 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 \textit{H. pylori} eradication therapy, so as to be careful to avoid adverse events.

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

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**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 \textit{Helicobacter pylori}-positive and \textit{Helicobacter pylori}-negative diabetics.
anti-inflammatory drug use, gastric cancer, iron-deficiency anemia and idiopathic thrombocytopenic purpura [31]. Since our study has suggested a positive association between \textit{H. pylori} and glycemic control in diabetics, there should be a debate about whether we need to extend the \textit{H. pylori} eradication indications for patients with DM. Since this systematic review does not allow for a conclusion about the long-term effect of \textit{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.

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