META-ANALYSIS

Histological changes of gastric mucosa after *Helicobacter pylori* eradication: A systematic review and meta-analysis

Yan-Jun Kong, Hong-Gang Yi, Jun-Cheng Dai, Mu-Xin Wei

Yan-Jun Kong, Division of Traditional Chinese Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China
Hong-Gang Yi, Jun-Cheng Dai, Division of Epidemiology, Nanjing Medical University School of Public Health, Nanjing 210029, Jiangsu Province, China
Mu-Xin Wei, Division of Traditional Chinese Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China
Mu-Xin Wei, National Institute for Physiological Sciences, Okazaki, Aichi 444-8585, Japan
Mu-Xin Wei, HiPep Laboratories, Kyoto 602-8158, Japan

Author contributions: Kong YJ collected the data and performed the meta-analysis; Dai JC and Yi HG participated in the retrieval of articles suitable for analysis; Wei MX provided guidance and proofread the manuscript.

Correspondence to: Mu-Xin Wei, Professor, Division of Traditional Chinese Medicine, the First Affiliated Hospital of Nanjing Medical University, Guangzhou Road 300, Nanjing 210029, Jiangsu Province, China. weimuxin@njmu.edu.cn

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Abstract

AIM: To systematically review pathological changes of gastric mucosa in gastric atrophy (GA) and intestinal metaplasia (IM) after *Helicobacter pylori* (*H. pylori*) eradication.

METHODS: A systematic search was made of PubMed, Web of Science, EMBASE, ClinicalTrials.gov, OVID and the Cochran Library databases for articles published before March 2013 pertaining to *H. pylori* and gastric premalignant lesions. Relevant outcomes from articles included in the meta-analysis were combined using Review Manager 5.2 software. A Begg’s test was applied to test for publication bias using STATA 11 software. *I*² and *I*² analyses were used to assess heterogeneity. Analysis of data with no heterogeneity (*P* > 0.1, *I*² < 25%) was carried out with a fixed effects model, otherwise the causes of heterogeneity were first analyzed and then a random effects model was applied.

RESULTS: The results of the meta-analysis showed that the pooled weighted mean difference (WMD) with 95%CI was 0.23 (0.18-0.29) between eradication and non-eradication of *H. pylori* infection in antral IM with a significant overall effect (*Z* = 8.19; *P* < 0.00001) and no significant heterogeneity (*I*² = 27.54, *I*² = 16%). The pooled WMD with 95%CI was -0.01 (-0.04-0.02) for IM in the corpus with no overall effect (*Z* = 0.66) or heterogeneity (*I*² = 14.87, *I*² = 0%) (fixed effects model). In antral GA, the pooled WMD with 95% CI was 0.25 (0.15-0.35) with a significant overall effect (*Z* = 4.78; *P* < 0.00001) and significant heterogeneity (*I*² = 86.12, *I*² = 71%; *P* < 0.00001). The pooled WMD with 95% CI for GA of the corpus was 0.14 (0.04-0.24) with a significant overall effect (*Z* = 2.67; *P* = 0.008) and significant heterogeneity (*I*² = 44.79, *I*² = 62%; *P* = 0.0003) (random effects model).

CONCLUSION: *H. pylori* eradication strongly correlates with improvement in IM in the antrum and GA in the corpus and antrum of the stomach.

Key words: Helicobacter pylori eradication; Gastric atrophy; Intestinal metaplasia; Pathological changes; Gastric mucosa; Meta-analysis

Core tip: This study reports the results of a meta-analysis conducted on a large number of articles using an extensive and thorough method. The inclusion of only high-quality relevant articles resulted in the identification of a very strong correlation between the eradication of *Helicobacter pylori* infection and intestinal metaplasia of the antrum, and a strong correlation with gastric atrophy in both the antrum and the corpus of the stomach.
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INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer in the world and the second leading cause of cancer-related deaths, accounting for 10.4% of all. The incidence and mortality of GC have fallen dramatically over the past 7 decades as a result of improved socioeconomic situations, sanitation, food preservation, as well as a decline in the incidence of Helicobacter pylori (H. pylori) infection[2-4]. Despite these declines, however, GC cure rates have not changed[8,10]. H. pylori infection has been known as a gastric carcinogen for over 10 years[11], and is the main cause of GC[2-4,12]. Infection triggers a multistep progression from chronic gastritis to gastric atrophy (GA), intestinal metaplasia (IM), dysplasia, and finally invasive cancer. H. pylori is a spiral-shaped, microaerophilic, Gram-negative bacterium measuring approximately 3.5 × 0.5 microns that is the cause for the most common chronic bacterial infection in humans, infecting 50% of the world population[13].

H. pylori, which causes active chronic gastritis in all infected patients, leads to clinically relevant diseases, such as gastric and duodenal ulcers, mucosa associated lymphoid tissue lymphoma and GC, in 20% of infected carriers[12-17]. Furthermore, meta-analyses have indicated that the infection confers a 2- to 3-fold increased risk of GC development[18,19]. While the course of the infection depends on microbial virulence, host genetic factors and environmental factors, the clinical outcomes are determined by the type and intensity of gastritis, which can be categorized as either a simple benign gastritis, a duodenal ulcer phenotype, or a GC phenotype.

As H. pylori infection plays a causal role in the formation of GC, eradication of infection may play a role in GC prevention[13,14]. After H. pylori eradication, neutrophils disappear and mononuclear cells slowly return to normal[12]. However, the improvement in gastric mucosal lesions following eradication of H. pylori is not entirely clear. While the majority of studies have reported a reversal of atrophy, no reversal of IM has been shown. To further examine and resolve these discrepancies, a systematic review and meta-analysis was conducted to determine if the eradication of H. pylori infection eliminates the precancerous lesions of GA and IM.

MATERIALS AND METHODS

Search strategy

A systematic search of PubMed, Web of Science, EMBASE, ClinicalTrials.Gov, OVID and the Cochrane Library databases was made to identify relevant review articles, editorials, and original studies published through March 2013 using the following key words: H. pylori OR Helicobacter pylori (H. pylori) OR HP, eradication OR treatment OR cure OR therapy, gastric atrophy OR atrophic OR GA OR intestinal metaplasia, clinical test, English-language. Data were independently extracted from each study by two of the authors working independently and using a predefined form; disagreements were resolved by discussion with a third investigator.

Inclusion and exclusion criteria

Published reports were selected for inclusion in the meta-analysis according to the following criteria: (1) English language publication; (2) prospective and randomized controlled trials on H. pylori eradication; (3) studies of adults testing positive for the presence of H. pylori prior to treatment and eradication of the infection documented both by histology and carbon (C) 14 urea breath test (UBT) or 13 C-UBT (sensitivity, 100%; specificity, 96%-99%); (4) H. pylori eradication as the only treatment; and (5) gastric histology from at least three pathological specimens per sample processed for hematoxylin-eosin and modified Giemsa staining. Specimens were required to have been taken at baseline and at least 6 mo after treatment, evaluated separately for the antrum and corpus, and scored using the Sydney system[20] or the updated Sydney system[21]. Studies not meeting these criteria, those without data for retrieval, and duplicate publications were excluded from the meta-analysis.

Study quality and data extraction

The quality of included studies was assessed using the Risk of Bias table outlined in the Cochrane Reviewer’s Handbook 5.0.1[24]. This method evaluates biases originating from sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), Blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). Every facet was judged as either yes, no, or unclear. A judgment of “yes” indicated that the method described was clear and correct, the information was complete, and indicated a low likelihood of bias. A judgment of “no” indicated a high likelihood of bias due to improper use of methods, unused allocation concealment, incomplete information, or selective reporting bias. An “unclear” judgment indicated that an assessment of bias could not be obtained due to insufficient descriptions. Judgments were assigned by two of the authors working independently, and discrepancies were remedied through discussions with a third investigator to obtain a consensus.

The data extracted from each study included the following: general article information (author, publication date, journal name, etc.); data to calculate the value of the total effect (treatment number, effective number, etc.); clinical heterogeneity of the study (sex, age, concurrent disease, treatment regimen, etc.); methodological heterogeneity of the study (design type, randomized, blinded, follow-up, quantity of and processing methods.
for pathological specimens, and methodology for histology scoring). Assessment of the degree of gastritis was performed according to the Sydney system[22] or the updated Sydney system[23]. For each graded variable, the following scores were assigned: 0 for absence and 1, 2 or 3 for mild, moderate or severe presence, respectively. The ultimate histology scores were used to weigh the severity of glandular atrophy or IM graded from 0 (normal) to 3 (markedly abnormal). Studies were reviewed and data extracted by two independent reviewers with knowledge of clinical medicine, epidemiology, and medical statistics, with discrepancies resolved through discussion. This process for data extraction was repeated to ensure accuracy.

### Statistical analysis

Agreement on the selection of studies between the two reviewers was evaluated by the $\kappa$ coefficient. Review Manager 5.2 and Begg’s test with STATA 11 were used to perform the meta-analysis to compare continuous variables, such as histological scores before and after H. pylori eradication. The inverse variance of the weighted mean difference (WMD) and 95% CIs for gastric mucosal histology scores was estimated for each study. The chi-square test and $P$-value analysis were used to indicate the presence of heterogeneity, and the size of the heterogeneity was tested with $I^2$. If there was no heterogeneity, a fixed effects model was applied. In cases where heterogeneity was indicated ($P < 0.1$, $I^2 > 25\%$), causes for the heterogeneity were first analyzed; a random effects model was applied when the clinical and methodological heterogeneity could not be identified[25] and subgroup analysis or sensitivity analysis was performed when the clinical or methodological heterogeneity was identified. In the presence of significant statistical heterogeneity, sensitivity analyses were performed to examine sample size, follow-up duration, number of biopsy samples, etc. To perform these analyses, meta-analyses were repeated following the exclusion of each individual study one at a time, in order to assess the overall effect of each study on the pooled WMD[26]. Overall effects were considered as statistically significant with a $P$-value < 0.05. Funnel plots were constructed to assess the likelihood of publication bias[27].

### RESULTS

#### Search results

The selection of studies included in the meta-analysis is described in a flow chart shown in Figure 1. The initial search strategy yielded 2925 citations. Of these, 1034
were rejected as duplicates or the title suggested that the articles were not appropriate, and a further 1604 were excluded after initial review (editorials, review articles, animal experiments, non-English language, etc.). Of the remaining 287 candidate articles, 245 did not fully meet the inclusion criteria and were excluded. A quality assessment of the 42 remaining papers led to elimination of a further 26 articles, leaving 16 studies eligible for the meta-analysis\([28-43]\). Initial agreement between the reviewers for the selection of relevant articles was high (\(\kappa = 0.96\)).

### Characteristics of included studies

The main characteristics of the 16 articles included in the meta-analysis are shown in Table 1. With the exception of one randomized control study\([30]\), all studies were single-center observational studies conducted in different parts of the world, mostly Japan and Italy. All the papers gave data for the four histological parameters evaluated (GA and IM separately for gastric corpus and antrum). \(H.\) pylori eradication in these studies consisted of a standard therapy with proton pump inhibitors, bismuth-based triple regimens, or dual regimens for 1-2 wk. Two studies enrolled patients with early gastric cancer who underwent endoscopic mucosal resection without recurrence\([33,34]\). Histological scores were calculated twice in one study, as \(H.\) pylori eradication occurred at different time points in two different groups\([35]\). Another study calculated the histological scores of both the lesser and greater parts of the antrum and corpus before and after \(H.\) pylori eradication\([36]\). Initial agreement between the reviewers for the data extraction was high (\(\kappa = 0.95\)).

### Intestinal metaplasia

Results of the analyses indicated no publication bias for reports on the effects of \(H.\) pylori eradication on IM in the antrum and corpus. The pooled WMD in the gastric antrum before and after \(H.\) pylori eradication with 95%CI was 0.23 (0.18-0.29) with a significant overall effect (\(P < 0.05\)) (Figure 2A). For IM in the corpus, the pooled WMD with 95%CI was -0.01 (-0.04-0.02) with no significant overall effect (Figure 2B). There was no significant heterogeneity among any of these trials, therefore fixed effects models were used.

### Gastric atrophy

Results of the analyses indicated no publication bias for reports on the effects of \(H.\) pylori eradication on GA in the antrum and corpus. The pooled WMD in the gastric antrum before and after \(H.\) pylori eradication with 95%CI was 0.25 (0.15-0.35) with a significant overall effect (\(P < 0.05\)) (Figure 3A). For GA in the corpus, the pooled WMD with 95%CI was 0.23 (0.18-0.29) with a significant overall effect (\(P < 0.05\)) (Figure 3B). There was significant heterogeneity among these trials, therefore random effects models were applied and multiple sensitivity analyses were performed. These analyses showed that the pooled WMD was not influenced by individual trials, thus no studies were excluded from the meta-analysis. These results indicate that the eradication of \(H.\) pylori aids in the reversal of both GA and IM in the antrum, but only reversal of GA, and not IM, was
observed in the corpus.

**DISCUSSION**

Despite the numerous reports on the improvement of gastric mucosal lesions following *H. pylori* eradication [48-51,56], some inconsistencies still remain [49-51,58]. Thus, it is still disputed whether the pathology of gastric mucosa, particularly GA and IM, improves after curing of the *H. pylori* infection. In this meta-analysis, data from relevant published studies were pooled with an effort to determine if GA and IM of the stomach are reversible after *H. pylori* eradication, and therefore whether therapeutic intervention is possible, or if efforts should be more appropriately directed at prevention.

The results of this study indicated that *H. pylori* eradi-
**Table:**

A | Before eradication | After eradication | Mean difference | Mean difference
--- | --- | --- | --- | ---
Annibale B 2000-1 | 0.56 | 1.2 | 0.64 | 2.5|
Annibale B 2000-2 | 1.19 | 1.13 | 0.9 | 25|
Annibale B 2000-3 | 1.19 | 1.13 | 15 | 25|
Annibale B 2000-1 | 0.25 | 0.71 | 0.25 | 25|
Annibale B 2000-2 | 0.6 | 0.96 | 0.6 | 25|
Iacopini F, 2003 (Italy) | 1.2 | 0.63 | 10 | 25|
Ito M 2002 | 2.14 | 0.81 | 22 | 22|
Kamada T 2005-1 | 1.9 | 0.7 | 20 | 20|
Kamada T 2005-2 | 1.9 | 21.02 | 1767 | 2|
Kamada T 2005-3 | 1.4 | 1.34 | 37 | 7|
Lahner E 2005 | 0.41 | 0.61 | 38 | 38|
Lu B, 2005 (China) | 1.25 | 0.44 | 92 | 92|
Oda Y, 2004 (Japan) | 0.95 | 0.68 | 59 | 59|
Ohkusa T 2001 | 0.9 | 115 | 0.8 | 141|
Ruiz B, 2001 (Colombia) | 0.28 | 0.16 | 29 | 29|
Sung JJ 2000 | 0.64 | 0.78 | 226 | 226|
Tokokawa T 2009 | 2.1 | 0.7 | 241 | 241|
Tucc A 1988-1 | 0.9 | 0.9 | 10 | 10|
Tucc A 1988-2 | 0.6 | 0.7 | 10 | 10|
Wamhura C 2004-1 | 1.35 | 1.23 | 107 | 107|
Wamhura C 2004-2 | 1.35 | 1.23 | 107 | 107|
Wamhura C 2004-3 | 1.35 | 1.03 | 107 | 107|
Wamhura C 2004-4 | 1.64 | 1.04 | 107 | 107|
Wamhura C 2004-5 | 1.64 | 1.04 | 107 | 107|
Wamhura C 2004-6 | 1.64 | 0.97 | 107 | 107|
Yamada T 2003 | 1.67 | 0.99 | 87 | 87|

Total (95%CI) | 3500 | 3500 | 100.0% | 0.25 [0.15, 0.35]

**Figure 3:** Forest plot comparing gastric atrophy in the antrum (A) and the corpus (B).

**Caption:**

Gastric corpus. The interpretation of this finding is not clear, but histological changes occurring after H. pylori eradication may play a role.

The results reported here differ from similar previously published meta-analyses. There are several reasons that may explain this discrepancy. First of all, the previous analyses included a limited number of studies, whereas our analysis included 16 comparatively high-quality scor-
Comments

Background
Gastric cancer (GC) is the fourth most common cancer in the world and the second leading cause of cancer-related deaths. Overall GC incidence and mortality have fallen dramatically over the past 7 decades, but despite that decline, the cure rates for GC have not changed. Therapeutic eradication of Helicobacter pylori (H. pylori) infection is one factor contributing to these declines; however, this association is still debated.

Research frontiers
Although H. pylori eradication has been reported to improve gastric mucosal lesions, there are many studies with contradictory results. A clear understanding of the role of H. pylori eradication plays in the incidence and progression of GC will help guide therapies towards effective treatment or prevention.

Innovations and breakthroughs
The results of this meta-analysis indicate that there is a very strong correlation between H. pylori infection and improvement in intestinal metaplasia in the antrum, but not the corpus, of the stomach. Furthermore, a strong correlation between H. pylori infection and improvement in gastric atrophy in the antrum and corpus was identified.

Applications
The results of this study confirm the association between H. pylori eradication and improvements in gastric pathologies. Although additional high quality clinical studies with longer follow-up periods are necessary to assess the long-term benefit of treatments, the findings implicate a viable treatment option for patients with intestinal metaplasia and gastric atrophy.

Terminology
Intestinal metaplasia is the transformation (metaplasia) of epithelium, usually of the stomach or the esophagus, to a type that bears some resemblance to the intestine, as seen in Barrett’s esophagus. Chronic H. pylori infection in the stomach and gastroesophageal reflux disease are seen as the primary instigators of metaplasia and subsequent adenocarcinoma formation.

Peer review
This article presents a well-designed meta-analysis of high quality studies evaluating the effect of H. pylori eradication on intestinal pathologies, namely intestinal metaplasia and gastric atrophy in the antrum and corpus of the stomach. The analyses show a strong correlation with improvement of intestinal metaplasia in the antrum, and gastric atrophy in the antrum and corpus, following eradication of H. pylori infection.

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**P-Reviewers:** Shehata MMM, Sijens PE

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