

Effect of long-term proton pump inhibitor administration on gastric mucosal atrophy: A meta-analysis

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Abstract

Background/Aims: Proton pump inhibitors (PPIs) are widely used for the treatment of acid-related gastrointestinal diseases. Recently, some studies have reported that PPIs can alter the gastric mucosal architecture; however, the relationship remains controversial. This meta-analysis study was designed to quantify the association between long-term PPI administration and gastric atrophy.

Materials and Methods: A PubMed search was conducted to identify studies using the keywords proton pump inhibitors or PPI and gastric atrophy or atrophic gastritis; the timeframe of publication searched was up to May 2016. Heterogeneity among studies was tested with the Q test; odds ratios (OR) and 95% confidence intervals (CI) were calculated. *P* values were calculated by *I*² tests and regarded as statistically significant when <0.05.

Results: We identified 13 studies that included 1465 patients under long-term PPI therapy and 1603 controls, with a total gastric atrophy rate of 14.50%. There was a higher presence of gastric atrophy (15.84%; statistically significant) in PPI group compared to the control group (13.29%) (OR: 1.55, 95% CI: 1.00–2.41).

Conclusions: The pooled data suggest that long-term PPI use is associated with increased rates of gastric atrophy. Large-scale multicenter studies should be conducted to further investigate the relationship between acid suppressants and precancerous diseases.

Keywords: Gastric atrophy, meta-analysis, proton pump inhibitors


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INTRODUCTION

Proton pump inhibitors (PPIs) are widely used for the treatment of acid-related gastrointestinal diseases because they reduce the gastric acid secretion by blocking the H⁺/K⁺-ATPase. PPIs include omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. The recognition of the role of *Helicobacter pylori* in the pathogenesis of gastric and duodenal ulcer disease as well as the development of *H. pylori* eradication therapies

with high success rates has strongly reduced the need for long-term treatment with anti-secretory drugs. However, maintenance therapy with PPIs is still required for patients with gastroesophageal reflux disease (GERD) and Zollinger–Ellison syndrome.^{1-2]}

Recent studies have suggested that long-term treatment with PPIs may accelerate the development of atrophic changes of the gastric mucosa, especially in *H. pylori*-infected

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individuals.^[3] Those taking PPIs without *H. pylori* tend to have normal gastric mucosa, whereas those infected with the organism show changes ranging from mild to severe corpus atrophy. Thus, the histological effects are not a result of treatment with the drug itself but rather a consequence of infection. Nowadays, the long-term safety of these drugs has been extensively evaluated but not entirely established.

Previously, there have been several studies addressing the relationship between long-term PPI use and gastric atrophy. Interest in this phenomenon has been boosted by the possibility that the widespread and indiscriminate use of PPIs may expand the infected population at risk of developing gastric cancer. Some studies have reported positive associations,^[4-6] while other studies have produced null results,^[7-16] and none have suggested an inverse relationship. Moreover, increased corpus gastritis and a decrease in the activity of antral gastritis have been suggested as a consequence of long-term treatment.

To gain a better understanding of whether maintenance treatment of PPIs results in a different gastric mucosal atrophy compared to controls, we systematically reviewed the published studies and conducted a meta-analysis.

MATERIALS AND METHODS

Search strategy

The PRISMA guidelines for conducting meta-analysis were followed. A comprehensive search was conducted by two investigators (LZ and WC), using a combination of MeSH and free text terms incorporating the population, intervention and outcome, and the third investigator (FJ) confirmed and agreed with the result. The three investigators worked independently, at different times, and at different medical science information centers affiliated to the third affiliated hospital of Soochow University. The search strategy was as follows: PubMed search using the key words proton pump inhibitors or PPIs and atrophic gastritis or mucosal atrophy. The search was repeated several times. The last search was conducted on May 1, 2016. The relevant articles texts and reference lists were manually searched to broaden the scope of our findings. We evaluated the full-texts of papers published in English. No language restrictions were used. If the papers were in an other language, English abstracts were used. When further information was required from a potentially relevant manuscript, the corresponding authors were contacted by the reviewers.

Inclusion criteria

Articles resulting from these searches and relevant references cited in those articles were screened and assessed

independently by two reviewers (LZ and WC) for eligibility. The following inclusion criteria were used:

- Study design: published case-control and cross-sectional studies
- Studies that provide raw data dealing with gastric mucosal atrophy in both PPI group and control group
- Studies in which gastric mucosal atrophy was confirmed by endoscopic assessment or mucosal biopsy.

Exclusion criteria

- Subset of a published article by the same authors
- Studies limited to animals.

Data extraction

The three investigators who performed the literature search also independently performed data extraction. The first authors, year, and country of publication, study type, type of specimen, sample size were recorded for each included study. The numbers of patients with mucosal atrophy in the PPI group and the control group were collected. When data from one study was reported in more than one manuscript, only one was selected for the meta-analysis, according to the following criteria (applied consecutively): (1) availability of adjusted odds ratio (OR) estimates for diabetics and non-diabetics; (2) longer follow-up period (applicable to nested case-control and cross-sectional analyses); and (3) larger sample size. When the relationship between PPI use and gastric mucosal atrophy was reported in different articles referring to the same study, both were considered eligible, but only one was included in the meta-analysis.

Statistical analysis

Our meta-analysis consisted of three parts. The first part was an epidemiological description of gastric atrophy rate in the PPI treatment group and the second part was a subgroup of *H. pylori* status in each study. The third part was a statistical pooling of the PPI treatment and gastric atrophy risk estimates. The incidence rate and the OR were the two main parameters for these studies.

An unconditional logistic regression model was adopted to compare and adjust the gastric atrophy rate by two parameters: the duration of PPIs use and medicine used in each study (omeprazole, lansoprazole, esomeprazole). A McNemar test and Kappa test were adopted to estimate the diversity and consistency of the outcomes among the paired data extracted from available studies.

In this study, the random effects model or fixed effects model was used for meta-analysis, according to the heterogeneity between studies. Heterogeneity was tested by the Q test ($P < 0.10$ was considered indicative of statistically

significant heterogeneity) and the I^2 statistic (values of 25%, 50% and 75% were considered to represent low, medium, and high heterogeneity, respectively). The fixed effect model was used when there was no significant heterogeneity ($I^2 < 50\%$); otherwise the random effect model was used.^[17] P values were calculated by I^2 tests. All the reported P values are two-sided, and P values < 0.05 were regarded as statistically significant for all included studies.

Calculation of dichotomous variables was carried out using the OR with the 95% confidence interval (CI) as the summary statistic. The Mantel–Haenszel method was used to combine ORs for the outcome parameters. Yate's correction was performed for studies containing a 'zero' value in one cell for the number of positive cases in one of the two groups.^[18]

Publication bias was examined by a funnel plot of log OR against its standard error using Begg's test. The degree of asymmetry was tested statistically using Egger's unweighed regression asymmetry test. Publication bias was considered to exist if the rank correlation coefficient from Begg's test was close to 1, or the slope parameter from Egger's regression was high.^[19]

Data manipulation and statistical analyses were undertaken using the Statistical Software Package (STATA) version 12.0 (STATA Corporation, College Station, TX, USA, 2011).

RESULTS

Description of studies

A total of 102 potentially relevant publications up to May 1, 2016, were systematically identified through PubMed. Of these, 68 (66.67%) were excluded because they did not satisfy the inclusion criteria, or they failed to provide sufficient information to determine whether the criteria were satisfactory. An additional 21 articles were excluded because of a lack of full text, while two other articles were added after being identified from the reference lists of relevant articles [Figure 1]. There were a total of 13 studies included in the final analysis that were published between 1996 and 2010^[4-16] and met our inclusion criteria [Table 1]. As for the detection methods, all studies used only biopsy.

The 13 studies included 1465 patients under long-term PPI therapy and 1603 controls, with a total gastric atrophy rate of 14.50%. We observed a statistically significant higher presence of gastric atrophy in the PPI group (15.84%) compared to the control group (13.29%); control group OR: 1.55, 95% CI: 1.00–2.41 [Figure 2].

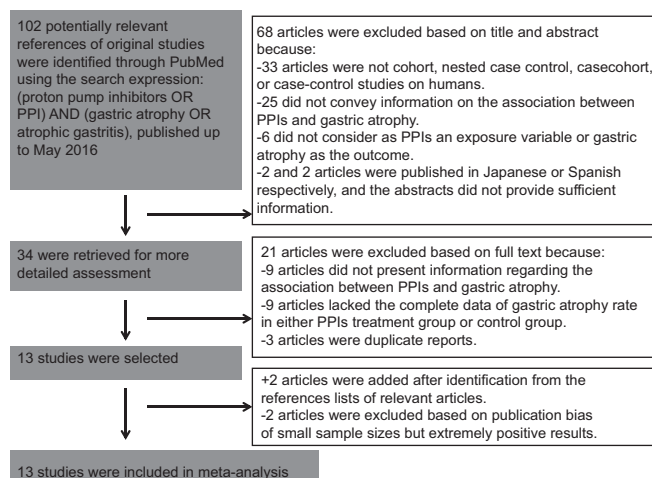


Figure 1: Flow chart of the study design

Type of proton pump inhibitors

Different types of PPIs including omeprazole,^[4-8,10,13,15] lansoprazole,^[5,11,12,14] esoprazole,^[16] and others^[7,9] were utilized in the included studies.

The pooled data showed that the gastric atrophy rate was different between the maintenance therapy group and control group possibly due to differences in the various pharmacokinetics or dosages used [Figure 3].

The subgroup analysis indicated higher gastric atrophy rates both in the omeprazole and lansoprazole groups when compared to the control groups (16.15% vs. 11.05%, $P = 0.001$; 22.03% vs. 20.33%, $P = 0.012$). Conversely, for esoprazole there was a lower rate of gastric atrophy in treatment group than control group (6.93% versus 9.48%).

H. pylori status

A subgroup analysis of nine studies that assessed *H. pylori* status was also undertaken [Table 2 and Figure 4].

Among the 509 *H. pylori*-positive patients, atrophy of any degree was diagnosed in 155 (30.45%) patients at follow-up. Among the 628 *H. pylori*-negative patients, atrophy of the gastric mucosa of any degree was diagnosed in 39 (6.21%) patients at the last visit (mild to severe). The development of any degree of atrophy was strongly associated with *H. pylori* infection (OR = 8.96, 95% CI = 3.11–25.83).

In addition, our analysis suggests a significant relationship between the presence of gastric atrophy in *H. pylori*-infected patients after long-term PPI use (OR = 1.72, 95% CI = 1.30–2.27). Moreover, there was a lower rate of gastric atrophy in *H. pylori*-negative patients after PPI maintenance therapy (OR = 0.60, 95% CI = 0.40–0.91).

Corpus and antrum gastric atrophy

In patients treated with PPI maintenance therapy, biopsy specimens were obtained both from the antrum and corpus in six studies [Table 3]. The gastric atrophy rate in the antrum was slightly higher (18.63%) than in corpus (14.68%) (OR = 1.52, 95% CI = 0.49–4.70), gastric atrophy in the antrum had decreased (OR = 0.79, 95%CI = 0.38–1.62), but had increased in the corpus (OR = 1.14, 95%CI = 0.55–2.37).

Description of atrophy incidence at baseline and after different periods of time

In our meta-analysis, we analyzed atrophy at different time periods of PPI therapy, although the information was insufficient to analyze [Table 4]. In the future, large-scale and multicenter studies are still needed to clarify whether

more severe morphological changes occur with time under PPI use.

Publication bias

To measure publication bias, a funnel plot and Harbord's weighted linear regression test [Figures 5 and 6] were used. It suggested there was no publication bias ($P = 0.008$). A sensitivity analysis calculating the pooled ORs for the remainder of the studies showed that there was no heterogeneity.

DISCUSSION

Clinically, the most common indications for long-term PPI use are for the management of symptomatic GERD and for prevention of non-steroidal anti-inflammatory drugs (NSAID)-associated upper gastrointestinal complications. Like several other prolonged treatments, concern has arisen regarding possible long-term effects, especially of neoplastic nature. We analyzed the published data

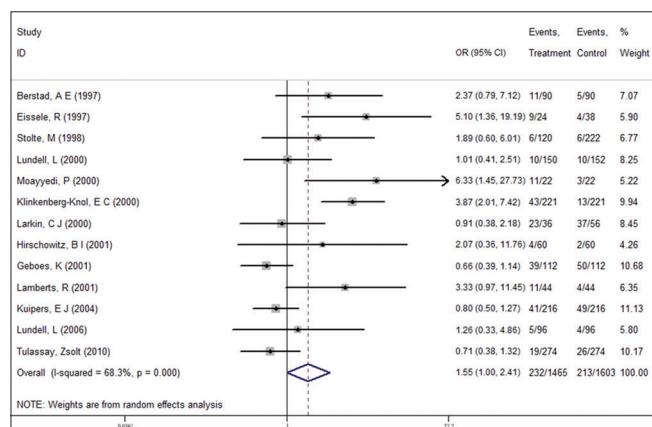


Figure 2: Association between proton pump inhibitors (PPIs) use and gastric atrophy risk (Odds Ratio; ORs). A total of 13 studies were selected for the analysis. Random-effects model was chosen to estimate the ORs after pooling due to the high heterogeneity among these studies ($I^2 = 68.3\%$, $P = 0.000$). A significant, 1.55-fold (95% CI = 1.00–2.41) increased atrophy risk in patients under PPIs therapy was shown

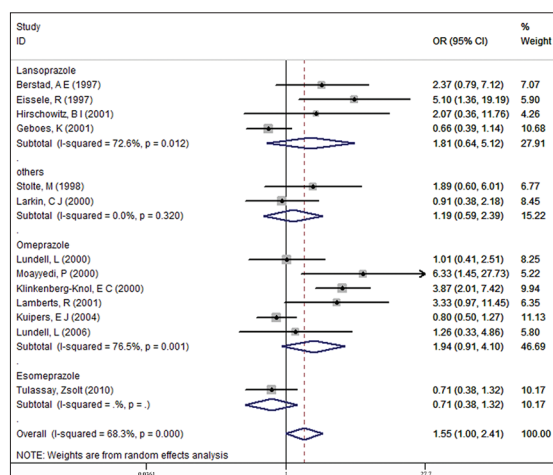


Figure 3: Subgroup analysis of different kinds of PPIs therapy

Table 1: Descriptive characteristics of included studies on gastric atrophy in long-term PPIs use group and control group

Reference	Year	Follow up years	Country	PPI (dose and treatment time)	Atrophy in PPI ^a group	Atrophy in control group	OR (95% CI)
A E. Berstad	1997	3 months	Norway	Lansoprazole (30 mg, 3 month)	11/90	5/90	2.37 (0.79,7.12)
R. Eissele	1997	5 years	Italy	Lansoprazole (90 mg, 5 years)	9/24	4/38	5.10 (1.36,19.19)
M. Stolte	1998	1 year	Germany	Omeprazole (20 mg, 1 year), Lansoprazole (15/30 mg, 1 year)	6/120	6/222	1.89 (0.60,6.01)
L. Lundell	2000	3 years	Sweden	Omeprazole (20/40 mg, 3 years)	10/150	10/152	1.01 (0.41,2.51)
P. Moayyedi	2000	1 year	UK	Omeprazole (20mg, 1 year)	11/22	3/22	6.33 (1.45,27.73)
C. J. Larkin	2000	2 years	Ireland	others ^b	23/36	37/56	0.91 (0.38,2.18)
E. C. Klinkenberg-Knol	2000	6.5 years	Sweden	Omeprazole (40 mg, 3 months)	43/221	13/221	3.87 (2.01,7.42)
B. I. Hirschowitz	2001	1 year	USA	Lansoprazole (60 mg, 1 years)	4/60	2/60	2.07 (0.36,11.76)
R. Lamberts	2001	10 years	Italy	Omeprazole (40/60 mg, 9 years)	11/44	4/44	3.33 (0.97,11.45)
K. Geboes	2001	5 years	Netherlands	Lansoprazole (30 mg, 5 years)	39/112	50/112	0.66 (0.39,1.14)
E. J. Kuipers	2004	2 years	Netherlands	Omeprazole (20 mg, >12 months)	41/216	49/216	0.80 (0.50,1.27)
L. Lundell	2006	7 years	Sweden	Omeprazole (20/40 mg, 7 years)	5/96	4/96	1.26 (0.33,4.86)
Zsolt Tulassay	2010	1 year	Sweden	Esomeprazole (20 mg, 4 weeks)	19/274	26/274	0.71 (0.38,1.32)

a: PPI proton pump inhibitors, b: Others - the medicine names were not given in the article, USA: The United States of America; UK: the United Kingdom, 95% CI: confidence interval, OR: Odds ratio

investigating the association between PPI administration and gastric mucosal atrophy. Meta-analysis of 13 studies from across the globe suggested that the rate of gastric mucosal atrophy was higher in PPI use group than that in their counterparts.

PPIs are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production. Millions of individuals have been using these medications on a continuous or long-term basis.^[20]

In the early days of PPI therapy, there was particular concern about hypergastrinaemia in response to profound acid inhibition and resultant endocrine cell hyperplasia with possible tumor formation.^[21] Indeed, it was just such a consideration that led to the temporary halt of the clinical development of omeprazole, the first PPI, and the delay of its widespread introduction.^[22] It is perhaps due to the difficulty in conducting such studies that to date only

limited data are available on changes in gastric levels or gastric mucosal endocrine cell numbers after prolonged PPI administration.^[4,13] It may also lead to the bias of the results.

The question of whether long-term PPI treatment in *H. pylori*-infected patients accelerates the development of GA has been raised.^[5,23-25] By comparing *H. pylori*-infected persons taking PPIs with uninfected persons of a similar age receiving the same treatment, we found that there was a significant increase of gastric atrophy incidence in *H. pylori*-positive patients. Our results suggest that patients with GERD and *H. pylori* infection who are treated with PPIs are at an increased risk of severe gastric atrophy. Moreover, our data found a higher prevalence of gastric atrophy in *H. pylori*-positive patients after long-term PPI use but a lower prevalence of gastric atrophy in *H. pylori*-negative patients.

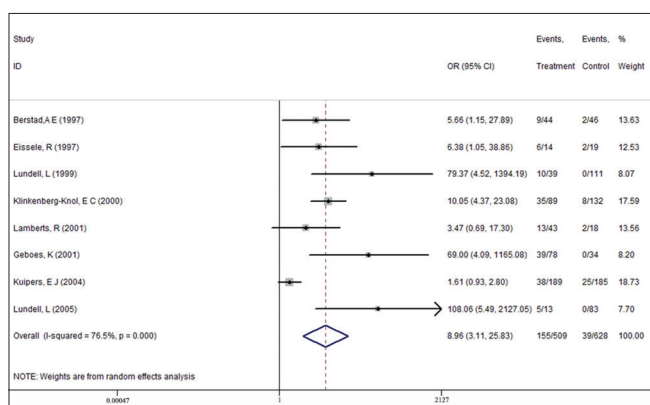


Figure 4: Subgroup analysis according to *Helicobacter pylori* infection status

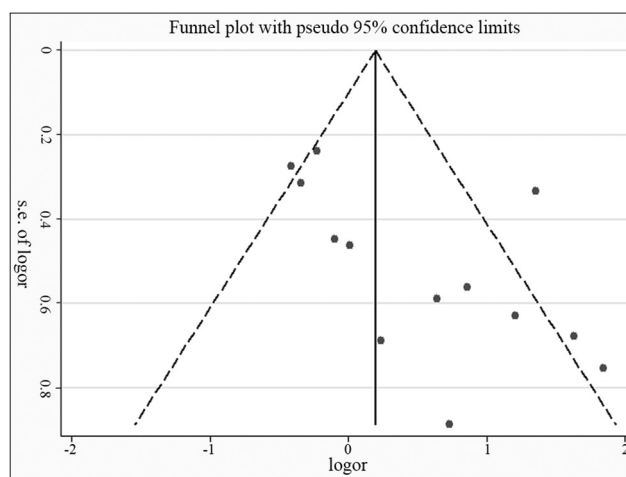


Figure 5: Estimating publication bias by funnel plot

Table 2: Subgroup analysis of gastric atrophy in *H. pylori*-negative vs. *H. pylori*-positive patients under PPI therapy

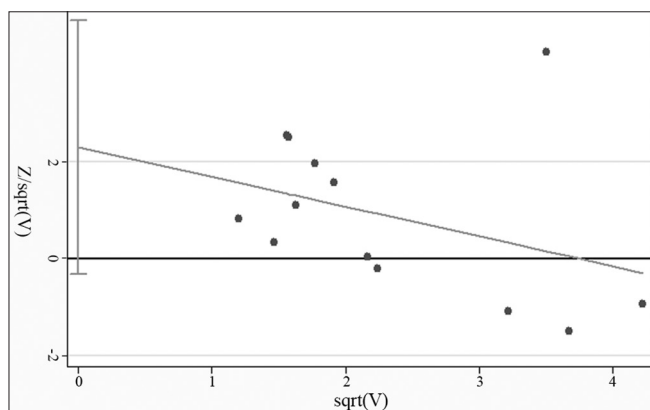
Study	Year	Atrophy in <i>H. pylori</i> positive group	Atrophy in <i>H. pylori</i> negative group	OR (95% CI)
A. E. Berstad	1997	9/44	2/46	5.66 (1.15,27.89)
R. Eissele	1997	6/14	2/19	6.38 (1.05,38.86)
L. Lundell	1999	10/39	0/111	79.37 (4.52,1394.19)
E. C. Klinkenberg-Knol	2000	35/89	8/132	10.05 (4.37,23.08)
R. Lamberts	2001	13/43	2/18	3.47 (0.89,17.30)
K. Geboes	2001	39/78	0/34	69.00 (4.09,1165.08)
E. J. Kuipers	2004	38/189	25/185	1.61 (0.93,2.80)
L. Lundell	2006	5/13	0/83	108.06 (5.49,2127.05)

Table 3: Distribution of atrophy in the gastric antrum and corpus in patients receiving treatment with proton pump inhibitors

Reference	Year	Antrum atrophy at baseline visit	Antrum atrophy at PPI use follow-up visit	Corpus atrophy at baseline visit	Corpus atrophy at PPI use follow-up visit
M. Stolte	1998	3/111	6/60	3/111	0/60
P. Moayyedi	2000	2/11	5/11	1/11	6/11
C. J. Larkin	2000	20/56	5/36	17/56	18/36
E. J. Kuipers	2004	22/107	16/107	27/109	25/109
Zsolt Tulassay	2010	20/137	19/137	6/137	0/137
K. Geboes	2001	41/56	25/56	8/56	14/56

Table 4: Atrophy in the oxyntic mucosa under long-term PPI therapy at last-line visit

Study	Year	Duration	0 month	2 month	3 month	6 month	12 month	2 year	3 year	5 year	6.5 year	7 year	10 year
A. E. Berstad	1997	3 months	5/90	-	11/90	-	-	-	-	-	-	-	-
R. Eissele	1997	5 years	4/38	-	-	-	-	10/33	-	9/24	-	-	-
M. Stolte	1998	1 year	6/222	6/178	-	5/148	6/120	-	-	-	-	-	-
P. Moayyedi	2000	1 year	3/22	-	-	-	11/22	-	-	-	-	-	-
C. J. Larkin	2000	2 years	-	-	-	-	-	23/36	-	-	-	-	-
E. C. Klinkenberg-Knol	2000	6.5 years	13/221	-	-	-	-	-	-	-	43/221	-	-
L. Lundell	2000	3 years	10/152	-	-	-	-	-	10/150	-	-	-	-
B. I. Hirschowitz	2001	1 year	2/60	-	-	-	4/60	-	-	-	-	-	-
R. Lamberts	2001	10 years	4/44	-	-	6/37	3/42	-	-	8/33	-	-	11/44
K. Geboes	2001	5 years	50/112	-	-	-	-	-	-	39/112	-	-	-
E. J. Kuipers	2004	2 years	49/216	-	-	-	-	41/216	-	-	-	-	-
L. Lundell	2006	7 years	4/96	-	-	-	-	-	-	-	-	5/96	-
Zsolt Tulassay	2010	1 year	26/274	-	-	-	19/274	-	-	-	-	-	-

**Figure 6:** Harbord's weighted linear regression indicated a non-significant publication bias ($P = 0.008$)

The role of *H. pylori* in chronic gastritis and peptic ulcer disease is well recognized, and further research revealed that chronic *H. pylori*-associated gastritis predisposed to gastric atrophy and gastric cancer. This usually affects the antrum. But some patients may develop corpus atrophy. These subjects are thought to have a reduced parietal cell mass, that is, they are natural hyposecretors of acid, and so the *H. pylori* can find a suitable environment in the corpus, which is normally too acidic to enable survival of the bacterium.

PPI treatment can lead to *H. pylori* colonization reduction. However, recent studies have found that corpus inflammation was significantly intensified despite stable bacterial counts.^[26] The number of neutrophils increased significantly in the lamina propria and epithelium. It has been shown *in vitro* that epithelial cells infected with live *H. pylori* secrete large amounts of interleukin-8, which has a strong chemoattractant effect on neutrophils.^[27] Continuous neutrophil activation may lead to tissue destruction.^[28] Moreover, removal of acid from the *H. pylori* colonized luminal surface of the oxyntic mucosa could affect penetration of bacterial toxins, especially unprotonated ammonia, through the gastric

barrier, which may result in enhanced mucosal damage.^[29] Chemical modifications of bacterial toxins in a less acidic environment or deeper location of *H. pylori* in the foveolae could exaggerate mucosal damage.

Importantly, those without known active *H. pylori* also may develop gastric atrophy while taking PPIs, suggesting that in some patients either *H. pylori* was not detected or overgrowth by non-*H. pylori* organisms may on occasion lead to the same outcome.^[30]

It is well known that concurrent PPI treatment can cause an apparent change in the distribution of the organism with a corpus predominant colonization and result in active chronic corpus gastritis with atrophy. So we analyzed the combined results from two biopsy sites (antrum and corpus).

In our study, the follow-up visit of gastric atrophy in the antrum was decreased, while it increased in the corpus. In addition, gastric atrophy incidence in antrum was (insignificantly) slightly higher than in corpus under PPIs maintenance therapy, possibly due to the small sample size and sampling error, as atrophy can be only focal. So, multiple punch biopsies of each person's stomach should be performed to improve the atrophy scores in future studies.

Study limitations

First, the selection of the controls varied between studies, some studies involve patients who had *H. pylori*, while others may include patients with GERD. Second, since the papers included in the present meta-analysis were limited to those published and listed on PubMed through May 2016, it is possible that some relevant published or unpublished studies, which may have met the inclusion criteria, were missed. These overlooked studies may have corrected some inherent biases due to the study design. Third, a few of the studies used in the present meta-analysis had a small sample size that may affect the final results.

In conclusion, this meta-analysis revealed an association between the presences of gastric atrophy in long-term PPI treatment patients. These findings support the notion that *H pylori* eradication should be seriously considered before initiating long-term treatment with PPIs. Due to the limited number of studies and their small sample sizes, further research should be conducted to investigate the possible relation between long-term PPIs use and gastric atrophy.

Competing interests

The authors declare that they have no competing interests.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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