Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology

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SUMMARY

Background
Proton pump inhibitors (PPIs) have a well-established safety profile. However, concerns have been raised about a potential relationship between PPI-induced hypergastrinaemia and the development of enterochromaffin-like (ECL) cell hyperplasia, neuroendocrine tumours and gastric cancer during long-term therapy.

Aim
To review the effects of long-term PPI use on serum gastrin levels and gastric histopathology.

Methods
A systematic literature search was conducted in PubMed on 21 April 2015 to identify studies reporting the effects of long-term (defined as >3 years) PPI use on gastrin levels and gastric histopathology.

Results
A total of 16 studies (1920 patients) met the inclusion criteria. During long-term PPI therapy, mean gastrin levels rose to one to three times the upper limit of the normal range (~100 pg/mL), and an increased prevalence of ECL cell hyperplasia was observed (+7.8–52.0%). Helicobacter pylori-positive patients had a significantly increased risk of developing ECL linear/micronodular hyperplasia compared with H. pylori-negative patients [OR: 2.45 (95% CI: 1.47–4.10), P = 0.0006]; however, no evidence of neoplastic changes was found. The risk of corpus atrophy was markedly higher in H. pylori-positive patients than in H. pylori-negative patients [OR: 11.45 (95% CI: 6.25–20.99), P < 0.00001]. Not a single case of gastric adenocarcinoma was found.

Conclusions
Long-term PPI therapy induced moderate hypergastrinaemia in most patients and an increased prevalence of ECL cell hyperplasia. H. pylori-positive patients receiving long-term PPI therapy were exposed to a higher risk of corpus atrophy than H. pylori-negative patients. No neuroendocrine tumours or gastric cancers were found.
INTRODUCTION

First introduced in the late 1980s, proton pump inhibitors (PPIs) represent a class of drugs that were developed for the treatment of gastric acid-related disorders. PPIs are the most potent inhibitors of gastric acid secretion currently available and are well-tolerated, with an adverse event rate of 1–3%. The most commonly reported adverse drug reactions are headache, abdominal pain, diarrhea, flatulence, nausea/vomiting and constipation, the majority of which are of mild/moderate severity. In accordance with the evidence supporting the efficacy and safety of PPIs, clinical guidelines recommend PPIs as the treatment of choice for gastrointestinal reflux disease (GERD) and peptic ulcer disease. The high efficacy and low toxicity of PPIs, combined with the high prevalence of GERD in Western countries (10–20%), has led to PPIs becoming one of the most commonly prescribed classes of drugs worldwide. GERD is a chronic condition and the majority of patients experience relapse of symptoms if PPI therapy is discontinued. Thus, many patients with GERD require continuous maintenance therapy with PPIs.

One area of concern with long-term PPI use is that the gastric acid blockade induces elevated levels of the peptide hormone gastrin. This is a homoeostatic reaction by the G cells of the gastric antrum to the reduced acidity of the gastric juice. Gastrin has been shown to have trophic effects on tissues throughout the gastrointestinal tract, including the enterochromaffin-like (ECL) cells, which are distributed throughout the oxyntic mucosa. ECL cells play a key role in the regulation of gastric acid production via the release of histamine, which stimulates parietal cell acid secretion by binding to histamine-2 (H2) receptors. In female rats, hypergastrinaemia resulting from lifelong administration of high doses of PPIs or H2 receptor antagonists or from partial gastric corporectomy was associated with the development of ECL cell hyperplasia and neuroendocrine tumours (NETs). These findings raised the possibility of a relationship between PPI-induced hypergastrinaemia and the development of proliferative ECL cell lesions and NETs in humans. These concerns were reiterated in recent case reports that presented evidence on the potential risks of NET development during long-term PPI therapy.

A key modulatory factor in the development of hypergastrinaemia is infection with Helicobacter pylori. A high percentage of the population is infected with H. pylori, and PPI-induced hypergastrinaemia has been shown to be more severe in H. pylori-positive patients. H. pylori infection is the most common cause of gastritis, and an additional safety concern is that PPI use alters the pattern of gastritis from an antrum-predominant to a corpus-predominant gastritis in H. pylori-positive patients. This has been the subject of much attention because corpus-predominant atrophic gastritis is a risk factor for the development of gastric cancer. In the pivotal study by Uemura et al., H. pylori-positive Japanese patients with corpus-predominant atrophic gastritis were shown to have a significantly higher risk of developing gastric cancer than patients with antrum-predominant gastritis (relative risk 95% CI: 34.5 (7.1–166.7]). Corpus-predominant atrophy involves the loss of specialised glandular cell types, including parietal and chief cells, and as such, represents the first step in the pre-cancerous cascade proposed by Correa and colleagues. The first study that raised the question of whether prolonged treatment with PPIs accelerates the development of corpus atrophic gastritis in H. pylori-positive patients was presented by Kuipers et al. The results of this study sparked a vigorous debate in which the study was criticised for weaknesses in its design. A number of subsequent studies corroborated the observation that prolonged acid inhibition in the presence of H. pylori infection promotes a change in the pattern of gastritis from an antrum-predominant to a corpus-predominant gastritis, thereby accelerating atrophic changes in the fundus-corpus mucosa. However, other studies were unable to find evidence that supported such an effect of PPIs on the gastric mucosa.

Although PPIs have a well-established safety profile, the widespread, long-term exposure of patients to PPIs mandates the continuous monitoring of potential adverse safety effects. Here, we seek to update the body of scientific data on the safety of PPIs by providing a systematic review of the effects of long-term PPI use on serum gastrin levels and exocrine and endocrine gastric histopathology.

METHODS

A systematic literature search was conducted in PubMed on 21 April 2015 to identify studies that reported data on the effect of long-term PPI use on serum gastrin levels and gastric histopathology. Current clinical guidelines do not provide a definition of long-term PPI use; however, the US Food and Drug Administration has requested that manufacturers of PPIs supply 3-year...
safety data if available. Based on this, long-term PPI use in this study was defined as a duration of more than 3 years. The following search terms were used: (long-term OR year OR years OR safety) AND (proton pump OR acid inhibition OR acid suppressive OR omeprazole OR esomeprazole OR pantoprazole OR rabeprazole OR dexamethasone) AND (enterochromaffin OR ECL OR endocrine OR neuroendocrine OR gastrin levels OR hypergastrinemia OR mucosa OR carcinoids OR cancer OR atrophic gastritis OR corpus-predominant gastritis). Interventional or observational studies of adult patients with GERD or peptic ulcer disease receiving long-term PPI therapy were included in this study. Recent reviews were also examined for citations of relevant primary studies. Studies were excluded if they were not published in the English language. Also excluded were review articles, case studies, studies conducted in paediatric populations, and studies that contained fewer than 25 patients. Studies were initially screened on the basis of manual review of titles and abstracts. The full article was reviewed when its relevance to this study was not clear from the abstract. All authors independently reviewed the initial search results to ascertain their suitability for inclusion with disagreements resolved by consensus. Two authors independently performed assessment of trial quality, according to the GRADE system.

Statistical analysis
Relative risk estimates based on prevalence data were carried out using the Mantel–Haenszel test (fixed effect model).

RESULTS

Search results and study characteristics
A systematic review of the 232 initial search results identified a total of 16 studies that met the inclusion criteria, containing a total of 1920 patients (Figure 1). Table 1 summarises the study characteristics of the 16 studies included in this review. Six studies were observational in design (Bardhan, Brunner, Geboes, Hage, Hendel). The other 10 were clinical trials, comprising one randomised controlled, double-blind trial (Rindi), two randomised controlled, open-label trials (Lundell; Fiocca) and seven uncontrolled, open-label trials (Brunner, Brunner, Eissele, Freston, Klinkenberg-Knol, Lamberts, Lambert). Study sample size ranged from 25 patients (Hage, Hendel) to 266 patients (Fiocca). The distribution of PPIs and dose range across the studies were: pantoprazole 40–160 mg/day (two studies), omeprazole 20–120 mg/day (eight studies), lansoprazole 15–90 mg/day (four studies), esomeprazole 20–40 mg/day (one study) and rabeprazole 10 or 20 mg/day vs. omeprazole 20 mg/day (one study). PPI treatment duration ranged from 3.5 years (Brunner) to 15 years (Brunner). PPI use was examined in eight studies of patients with GERD or peptic ulcers resistant to H2-receptor antagonists, two studies of patients with systemic sclerosis and GERD, and six studies of treatment-naïve patients with GERD or peptic ulcer disease. Nine studies assessed H. pylori infection status. Histological assessment of the antral and oxyntic mucosa for inflammation, activity, atrophy and H. pylori infection was carried out according to the Sydney system or the
updated Sydney system.\textsuperscript{79} Oxyntic endocrine cell density was evaluated according to the morphological classification proposed by Solcia: hyperplasia (diffuse, linear, micronodular, adenomatous), dysplasia and neoplasia.

### Table 1 | Overview of studies included in this review

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Quality of study\textsuperscript{65}</th>
<th>Indication</th>
<th>Patients, n</th>
<th>PPI therapy</th>
<th>Duration of PPI therapy, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardhan\textsuperscript{66}</td>
<td>Observational</td>
<td>Very low</td>
<td>Peptic ulcers or GERD refractory to H2-receptor antagonists</td>
<td>150</td>
<td>Pantoprazole 40 mg/day</td>
<td>5</td>
</tr>
<tr>
<td>Brunner\textsuperscript{67}</td>
<td>Observational</td>
<td>Very low</td>
<td>Ranitidine-resistant peptic ulcers</td>
<td>143</td>
<td>Omeprazole 40 mg/day</td>
<td>Up to 5</td>
</tr>
<tr>
<td>Brunner\textsuperscript{68}</td>
<td>Uncontrolled, open-label</td>
<td>Low</td>
<td>Ranitidine-resistant peptic ulcers</td>
<td>42</td>
<td>Lansoprazole 30–60 mg/day</td>
<td>Up to 3.5</td>
</tr>
<tr>
<td>Brunner\textsuperscript{72}</td>
<td>Uncontrolled, open-label</td>
<td>Low</td>
<td>Peptic ulcers or GERD</td>
<td>142</td>
<td>Pantoprazole 40–160 mg/day</td>
<td>Up to 15</td>
</tr>
<tr>
<td>Eissele\textsuperscript{73}</td>
<td>Uncontrolled, open-label</td>
<td>Low</td>
<td>Ranitidine-resistant peptic ulcers</td>
<td>42</td>
<td>Lansoprazole 30–90 mg/day</td>
<td>5</td>
</tr>
<tr>
<td>Fiocca\textsuperscript{54}</td>
<td>RCT, open-label</td>
<td>Moderate</td>
<td>GERD</td>
<td>266</td>
<td>Esomeprazole 20–40 mg/day</td>
<td>5</td>
</tr>
<tr>
<td>Freston\textsuperscript{74}</td>
<td>Uncontrolled, open-label</td>
<td>Low</td>
<td>GERD</td>
<td>195</td>
<td>Lansoprazole 15–30 mg/day</td>
<td>6.8</td>
</tr>
<tr>
<td>Geboes\textsuperscript{56}</td>
<td>Observational</td>
<td>Very low</td>
<td>GERD</td>
<td>78</td>
<td>Lansoprazole 30 mg/day</td>
<td>5</td>
</tr>
<tr>
<td>Hage\textsuperscript{69}</td>
<td>Observational</td>
<td>Very low</td>
<td>Systemic sclerosis and GERD</td>
<td>25</td>
<td>Omeprazole 40–120 mg/day</td>
<td>7.5 (mean)</td>
</tr>
<tr>
<td>Hende\textsuperscript{70}</td>
<td>Observational</td>
<td>Very low</td>
<td>Systemic sclerosis and GERD</td>
<td>25</td>
<td>Omeprazole 20–80 mg/day</td>
<td>Up to 5</td>
</tr>
<tr>
<td>Klinkenberg-Knol\textsuperscript{75}</td>
<td>Uncontrolled, open-label</td>
<td>Low</td>
<td>Ranitidine-resistant GERD</td>
<td>91</td>
<td>Omeprazole 20–40 mg/day</td>
<td>4 (mean)</td>
</tr>
<tr>
<td>Klinkenberg-Knol\textsuperscript{51}</td>
<td>Observational</td>
<td>Very low</td>
<td>Ranitidine-resistant GERD</td>
<td>230</td>
<td>Omeprazole 20 mg/day</td>
<td>6.5 (mean)</td>
</tr>
<tr>
<td>Lamberts\textsuperscript{76}</td>
<td>Uncontrolled, open-label</td>
<td>Low</td>
<td>Ranitidine-resistant peptic ulcers</td>
<td>74</td>
<td>Omeprazole 40 mg/day</td>
<td>4 (median)</td>
</tr>
<tr>
<td>Lamberts\textsuperscript{77}</td>
<td>Uncontrolled, open-label</td>
<td>Low</td>
<td>Ranitidine-resistant peptic ulcers</td>
<td>61</td>
<td>Omeprazole 40–60 mg/day</td>
<td>Up to 10</td>
</tr>
<tr>
<td>Lundell\textsuperscript{52}</td>
<td>RCT, open-label</td>
<td>Moderate</td>
<td>GERD</td>
<td>113</td>
<td>Omeprazole 20–40 mg/day</td>
<td>7</td>
</tr>
<tr>
<td>Rindi\textsuperscript{71}</td>
<td>RCT, double-blind</td>
<td>High</td>
<td>GERD</td>
<td>243</td>
<td>Rabeprazole 10 or 20 mg/day; omeprazole 20 mg/day</td>
<td>5</td>
</tr>
</tbody>
</table>

GERD, gastro-oesophageal reflux disease; PPI, proton pump inhibitors; RCT, randomised controlled trial.

### Serum gastrin levels

Data on serum gastrin levels were reported in 11 studies (Table 2). Mean (or median) gastrin levels increased following long-term PPI therapy in all these studies; however, the magnitude of the increase was variable, ranging
from the 1.3-fold increase reported by Rindi\textsuperscript{71} to the 2.9-fold increase reported by Brunner.\textsuperscript{72} These increases are equivalent to mean gastrin levels 1–3 times the upper limit of the normal range (~100 pg/mL). Overall, the data reported in these studies show that there was considerable inter-patient variation in gastrin levels during long-term PPI therapy. Figure 2 shows mean (or median) serum gastrin data over time from four studies: Bardhan,\textsuperscript{66} Brunner,\textsuperscript{67} Eissele\textsuperscript{73} and Brunner.\textsuperscript{72} Bardhan\textsuperscript{66} (observational; \(n = 150\)) showed a gradual increase in median gastrin levels during years 1–5, whereas in Brunner\textsuperscript{67} (observational; \(n = 143\)) and Eissele\textsuperscript{73} (uncontrolled, open-label; \(n = 42\)), gastrin levels were relatively stable after years 1–2.

With regard to the influence of \textit{H. pylori} status, Bardhan\textsuperscript{66} showed that \textit{H. pylori}-positive patients had consistently higher gastrin levels than \textit{H. pylori}-negative patients at all timepoints but the difference was not significantly different. Fiocca\textsuperscript{54} also reported no significant difference in gastrin levels in the presence or absence of \textit{H. pylori} infection.

**ECL cell histology**

**ECL cell density.** Data on change in ECL cell density during long-term PPI treatment were reported in six studies (Table 3). Bardhan\textsuperscript{66} (observational; \(n = 150\)) reported little change in ECL cell density over time; while Brunner\textsuperscript{67} (observational, \(n = 143\)), Brunner\textsuperscript{72} (open-label, \(n = 142\)), Eissele\textsuperscript{73} (open-label, \(n = 74\)) all reported an increase in ECL cell density over time. Figure 3 shows ECL cell volume density data over time from Brunner,\textsuperscript{67} Brunner\textsuperscript{72} and Lamberts.\textsuperscript{76} In these studies, ECL cell density peaked at years 4–5 and then stabilised.

Eissele\textsuperscript{73} and Lamberts\textsuperscript{76} reported a significant correlation between ECL cell density and serum gastrin levels; Fiocca\textsuperscript{54} was unable to corroborate this finding. Bardhan\textsuperscript{66} and Brunner\textsuperscript{72} both reported no correlation of ECL cell density with \textit{H. pylori} infection status.

**ECL cell hyperplasia.** Ten studies reported data on changes in ECL cell hyperplasia during long-term PPI treatment (Table 3). All of these studies reported an increase in the prevalence of ECL cell hyperplasia, ranging from +7.8% (Lamberts\textsuperscript{76}) to +52.0% (Hendel\textsuperscript{70}). Representative data from three studies showing progressive changes in the prevalence of ECL cell hyperplasia from years 1–5 (Fiocca,\textsuperscript{54} Klinkenberg-Knol,\textsuperscript{75} Lamberts\textsuperscript{76}) are shown in Figure 4. A significant correlation between the prevalence of ECL cell hyperplasia and serum gastrin levels was reported by Eissele\textsuperscript{73} (open-label, \(n = 42\)), Lamberts (2001; open-label, \(n = 61\))\textsuperscript{77} and Rindi\textsuperscript{71} (ran-

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**Table 2 | Effect of long-term proton pump inhibitors (PPIs) therapy on serum gastrin levels**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Gastrin assay method</th>
<th>Gastrin levels at baseline, pg/mL</th>
<th>Gastrin levels at study end, pg/mL</th>
<th>Fold increase after PPI therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardhan\textsuperscript{66}</td>
<td>150</td>
<td>Radioimmunoassay</td>
<td>65*</td>
<td>175*</td>
<td>2.7</td>
</tr>
<tr>
<td>Brunner\textsuperscript{67}</td>
<td>143</td>
<td>N/D</td>
<td>110†</td>
<td>150†</td>
<td>-1.4</td>
</tr>
<tr>
<td>Brunner\textsuperscript{68}</td>
<td>42</td>
<td>Radioimmunoassay</td>
<td>125 ± 25</td>
<td>200 ± 50</td>
<td>1.6</td>
</tr>
<tr>
<td>Brunner\textsuperscript{72}</td>
<td>142</td>
<td>Radioimmunoassay</td>
<td>110 ± 129</td>
<td>320 ± 448</td>
<td>2.9</td>
</tr>
<tr>
<td>Eissele\textsuperscript{73}</td>
<td>42</td>
<td>Radioimmunoassay</td>
<td>124 ± 21</td>
<td>278 ± 56</td>
<td>2.2</td>
</tr>
<tr>
<td>Fiocca\textsuperscript{54}</td>
<td>266</td>
<td>Radioimmunoassay</td>
<td>66†</td>
<td>164†</td>
<td>2.5</td>
</tr>
<tr>
<td>Freston\textsuperscript{74}</td>
<td>195</td>
<td>N/D</td>
<td>62*</td>
<td>120*</td>
<td>1.9</td>
</tr>
<tr>
<td>Klinkenberg-Knol\textsuperscript{75}</td>
<td>91</td>
<td>Radioimmunoassay</td>
<td>60*</td>
<td>120*</td>
<td>2.0</td>
</tr>
<tr>
<td>Lamberts\textsuperscript{76}</td>
<td>74</td>
<td>Radioimmunoassay</td>
<td>74*</td>
<td>145*</td>
<td>2.0</td>
</tr>
<tr>
<td>Lamberts\textsuperscript{77}</td>
<td>61</td>
<td>Radioimmunoassay</td>
<td>137‡</td>
<td>293‡</td>
<td>2.1</td>
</tr>
<tr>
<td>Rindi\textsuperscript{71}</td>
<td>243</td>
<td>N/D</td>
<td>91 ± 62</td>
<td>126 ± 87</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Serum gastrin levels are mean ± s.d. unless indicated otherwise.

*Median value; †Mean value; ‡Extracted from Figure 1 in the publication; N/D, not disclosed.
randomised controlled trial, \( n = 243 \); whereas Hendel\(^70\) (observational; \( n = 25 \)) found no evidence of such a correlation.

Eissele (open-label, \( n = 42 \))\(^73\), Klinkenberg-Knol\(^51\) (observational; \( n = 230 \)), Lundell\(^52\) (randomised controlled trial, \( n = 113 \)) and Rindi\(^71\) (randomised controlled trial, \( n = 243 \)) all reported that the prevalence of ECL cell micronodular hyperplasia was higher in \( H. pylori \)-positive patients than in \( H. pylori \)-negative patients. The relative risk of developing ECL linear/micronodular hyperplasia was significantly increased in \( H. pylori \)-positive vs. \( H. pylori \)-negative patients [OR: 2.45 (95% CI: 1.47–4.10), \( P = 0.0006; \) Figure 5]. However, there was high inter-study heterogeneity (\( I^2 = 65\% \)); and a sensitivity analysis indicated that exclusion of the Klinkenberg-Knol\(^51\) study [the study with the highest weight (82.9%) but lowest effect size (OR: 1.58)] eliminated the heterogeneity (\( I^2 = 0\% \)) and increased the overall effect size [OR: 6.72 (95% CI: 2.36–19.11), \( P = 0.0004 \)]. Representative data from Eissele\(^73\) are shown in Figure 6. None of the studies that reported data on ECL cell hyperplasia found evidence of dysplastic or neoplastic changes (NETs) in the ECL cell population after long-term PPI treatment.

**Corpus inflammation and atrophy in \( H. pylori \)-positive patients**

Data on gastritis and atrophy of the corpus mucosa were reported in 11 studies, nine of which assessed the relationship of these variables with \( H. pylori \) infection (Table 3). Overall, these studies reported that corpus atrophy scores were substantially worse in \( H. pylori \)-positive patients than in \( H. pylori \)-negative patients. An analysis of prevalence data from six studies (Eissele\(^73\), Geboes\(^56\), Klinkenberg-Knol\(^51\), Lamberts\(^77\), Lundell\(^52\) and Rindi\(^71\)) confirmed that the risk of developing corpus atrophy was markedly higher in \( H. pylori \)-positive patients than in \( H. pylori \)-negative patients [OR: 11.45 (95% CI: 6.25–20.99), \( P < 0.00001; \) Figure 7]. Corpus atrophy scores over time from Bardhan\(^66\), Brunner\(^72\) and Eissele\(^73\) are shown in Figure 8. In Brunner\(^72\), corpus atrophy scores in \( H. pylori \)-positive patients peaked at years 3–4, and then followed a steady decline to year 15 (study end).

Rindi\(^71\) used logistic regression analysis to show that \( H. pylori \)-positive status was a highly significant (\( P < 0.001 \)) predictor of all gastritis variables except atrophy of the antral mucosa. Brunner\(^72\) showed that patients with successful \( H. pylori \) eradication exhibited long-term regression of both antral and corpus gastritis. Finally, not a single case of gastric adenocarcinoma was found in either \( H. pylori \)-positive or \( H. pylori \)-negative patients.

**DISCUSSION**

In this systematic review, we set out to examine two main areas of concern pertaining to the long-term safety of PPI therapy in patients with peptic ulcer disease or...
Table 3 | Key findings from studies reporting data on the effect of long-term proton pump inhibitors therapy on gastric histopathology

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>ECL cell density and hyperplasia</th>
<th>Corpus gastritis and atrophy</th>
<th>Neoplastic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardhan66</td>
<td>150</td>
<td>• Little change in ECL cell density over time in H. pylori-positive and H. pylori-negative patients</td>
<td>• Corpus gland atrophy scores rose five- to sixfold over time in H. pylori-positive patients compared with a 1.5-fold increase in H. pylori-negative patients</td>
<td>No</td>
</tr>
<tr>
<td>Brunner67</td>
<td>143</td>
<td>• Mean ECL cell density increased from 0.43% to 0.68%</td>
<td>N/D</td>
<td>No</td>
</tr>
<tr>
<td>Brunner72</td>
<td>142</td>
<td>• Mean ECL cell density increased from 0.34 ± 0.24% at baseline to a maximum of 0.62 ± 0.36% at year 5</td>
<td>• In H. pylori-positive patients, the maximum mean grade of corpus atrophy was 3.09 ± 1.70 at year 3, declining to 0.53 ± 0.69 by year 15. In H. pylori-negative patients, the mean grade of corpus atrophy remained consistently low (0–0.5)</td>
<td>No</td>
</tr>
<tr>
<td>Eissele73</td>
<td>42</td>
<td>• Mean ECL cell density increased from 86 ± 4 cells/mm² at baseline to 151 ± 8 cells/mm² in year 5 (P &lt; 0.05)</td>
<td>• Scores for chronic inflammation, gastritis activity and atrophy of the oxyntic mucosa worsened in the first 2 years then stabilised in H. pylori-positive patients</td>
<td>No</td>
</tr>
<tr>
<td>Fiocca54</td>
<td>266</td>
<td>• ECL cell density increased significantly (P &lt; 0.001)</td>
<td>• No consistent change in the severity of corpus inflammation was observed in H. pylori-positive patients</td>
<td>No</td>
</tr>
<tr>
<td>Geboes56</td>
<td>78</td>
<td>N/D</td>
<td>• Corpus gastritis was mildly or moderately active in 72% of H. pylori-positive patients compared with 9% of H. pylori-negative patients</td>
<td>No</td>
</tr>
<tr>
<td>Hage69</td>
<td>25</td>
<td>• An increase in the prevalence of diffuse and linear ECL cell hyperplasia was observed from 4% (n = 1) at baseline to 41% (n = 10) in patients with progressive systemic sclerosis</td>
<td>N/D</td>
<td>No</td>
</tr>
</tbody>
</table>
GERD. The first is that long-term PPI use induces elevated serum gastrin levels, which may cause proliferative changes in the gastric mucosa. Gastrin has a powerful trophic effect on ECL cells, and hypergastrinaemia is associated with the development of NETs in patients with Zollinger–Ellison syndrome (ZES) and multiple endocrine neoplasia type 1 (MEN1), end-stage corpus atrophic gastritis and other hypergastrinaemic states. The studies identified by this review indicate that most patients on long-term PPI therapy exhibit an immediate but modest hypergastrinaemia (100–500 pg/mL), with the caveat that there is considerable inter- and intra-individual variation in gastrin levels. Moreover, we observed that the majority of studies suggest that gastrin levels plateau after 1–2 years of PPI therapy.

Fiocca noted that the chronically elevated gastrin levels seen in PPI-treated patients seemed to exert a continuous proliferative drive on the endocrine cell population of the oxyntic gland area. The data presented here support this conclusion. Long-term PPI therapy resulted in an increase in the prevalence of ECL cell hyperplasia. Table 3 | (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>ECL cell density and hyperplasia</th>
<th>Corpus gastritis and atrophy</th>
<th>Neoplastic changes</th>
</tr>
</thead>
</table>
| Hendel      | 25          | • A total of 13/25 (52%) patients developed diffuse or linear ECL cell hyperplasia from 0% at baseline  
• No significant correlation between the grade of ECL cell hyperplasia and serum gastrin concentration | N/D                                                                                       | No                 |
| Klinkenberg-Knol | 91           | • Prevalence of ECL cell micronodular hyperplasia increased from 3% at baseline to 20% after treatment  
(P < 0.001)                                                                 | Prevalence of subatrophic or atrophic corpus gastritis increased from <1% to 25%  
(P < 0.001)                                                                 | No                 |
| Klinkenberg-Knol | 230         | • Prevalence of ECL cell micronodular hyperplasia increased from 3% to 29% in H. pylori-positive patients and 3% to 11% in H. pylori-negative patients | H. pylori-positive patients showed an increase in the severity of corpus atrophy over time, whereas there was little change in H. pylori-negative patients | No                 |
| Lamberts    | 74          | • Mean ECL cell density increased from 0.36% to 0.74% (P < 0.01)  
• Significant correlation between ECL cell density and mean serum gastrin concentrations up to 5 years (P < 0.05)  
• Prevalence of ECL micronodular hyperplasia increased from 9% to 17% | Prevalence of atrophic corpus gastritis increased from 1.8% to 20.8% (P < 0.05) | No                 |
| Lamberts    | 61          | • Prevalence of ECL cell hyperplasia increased from 19% to 54% (P < 0.02)  
• ECL cell hyperplasia was correlated with serum gastrin levels (P < 0.01) | Corpus atrophy increased from 11% to 30% in H. pylori-positive patients, and from 0% to 11% in H. pylori-negative patients | No                 |
| Lundell     | 113         | • In H. pylori-positive patients, there was a tendency to develop ECL cell micronodular hyperplasia over time  
(P = 0.03)                                                                 | In H. pylori-positive patients, there was a nonsignificant numerical increase in the corpus atrophy score | No                 |
| Rindi       | 243         | • Strong association between ECL cell hyperplasia and serum gastrin levels  
(P = 0.001)                                                                 | Atrophy of the corpus mucosa became more common in H. pylori-positive patients but not in H. pylori-negative patients | No                 |

ECL, enterochromaffin-like; N/D, not determined.
from 3–19% at baseline to 17–54% after PPI treatment. Two studies reported a significant correlation between serum gastrin levels and ECL cell density;73, 76 and two studies reported a significant correlation between gastrin levels and the prevalence of ECL cell hyperplasia.71, 77 These results are consistent with the known trophic effects of gastrin on the gastric mucosa30, 81, 82 and are comparable with a prevalence of ~28% reported by Solcia et al.,87 a histological study of 2120 biopsy samples from patients receiving omeprazole treatment for durations of several months to 4 years. In a meta-analysis of data from six randomised controlled trials, Song et al.88 reported that patients with PPI maintenance treatment (6 months or greater) were significantly more likely to experience diffuse (OR: 5.01; P = 0.007) or linear/micronodular (OR: 3.98; P = 0.02) ECL cell hyperplasia than controls. These results are comparable with the estimated relative risk of developing linear/micronodular ECL hyperplasia in H. pylori-positive vs. H. pylori-negative patients (OR: 2.45; P = 0.0006) reported in the current study. Lundell et al.52 postulated that the increased prevalence of ECL cell micronodular hyperplasia in H. pylori-positive patients is the result of an ECL proliferative effect driven by synergism between acid suppression and an undefined H. pylori-driven process.

None of the studies in this review reported evidence for the development of NETs in patients taking PPIs on a long-term basis, neither in H. pylori-positive nor in H. pylori-negative individuals. Case reports have documented the development of NETs in patients who had been taking PPIs for up to 15 years.33–36 In one of these reports, the patient was diagnosed with a malignant, poorly differentiated NET unusually localised within a

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**Figure 3 |** ECL cell density during long-term PPI therapy. Data were extracted from figure 2 of Brunner,67 figure 4 of Brunner,72 and figure 5 of Lamberts.76 ECL, enterochromaffin-like; PPI, proton pump inhibitor.

**Figure 4 |** ECL cell hyperplasia during long-term PPI therapy. Data shown are the total combined prevalence of diffuse, linear and micronodular ECL cell hyperplasia. Data were extracted from figure 2 of Fiocca,54 figure 4 of Klinkenberg-Knol,75 and table 3 of Lamberts.76 It should be noted that Fiocca54 did not report data for years 2 and 4. Data values for these timepoints were assumed to be the same as that for year 3 and year 5 respectively. ECL, enterochromaffin-like; PPI, proton pump inhibitor.
The problem in all of these cases is that it is difficult to exclude the possibility that the findings described are coincidental. Case reports have an important role to play in pharmacovigilance, in terms of reporting rare adverse drug reactions. However, it is universally acknowledged that data presented in case reports must be interpreted with caution given their small sample size, retrospective nature, and the absence of an appropriate control group.

The second safety concern we examined is that PPIs may accelerate the development of corpus-predominant gastritis with atrophy, a known risk factor for the development of gastric cancer. The rate of atrophy development in the oxyntic mucosa is dependent on multiple factors, including the type of gastric disease being treated, the genetic background of the patient population, the type of colonising *H. pylori* strains and the incidence of gastritis. Therefore, the increment of atrophy found in PPI-treated patients with GERD should be evaluated in comparison with non-PPI-treated control groups from the same population affected by the same disease. In practice, this is difficult to obtain and has been attempted in only a few studies, for example, by comparing PPI treatment with fundoplication. The Song *et al.* meta-analysis reported a nonsignificant OR of 1.50 (*P* = 0.39) for corpus atrophy development in long-term PPI users relative to non-PPI users.

*Helicobacter pylori* is an important aetiological factor in the development of corpus-predominant gastritis during long-term treatment with PPIs. Although the results from the studies in this review are not entirely consistent, the preponderance of the evidence indicates that patients on long-term PPI treatment who are *H. pylori*-positive are at a significantly higher risk for developing corpus gastritis than *H. pylori*-negative patients. These findings support the recommendations of the Maastricht IV/Flor-
ence consensus report, which recommend that *H. pylori* infections should be eradicated prior to the commencement of long-term PPI therapy.\(^6\) In addition to the open-label study of Brunner\(^7\) included in the present analysis, two further studies, including a randomised, controlled study, investigated the effect of *H. pylori* eradication in patients who continued PPI treatment.\(^9\) All three studies demonstrated that *H. pylori* eradication resulted in a marked improvement in gastric histological parameters, supporting the conclusion that *H. pylori* is a key aetiological factor in the development of corpus-predominant gastritis in the presence of PPI treatment.

A strength of this systematic review was the focus on studies with a PPI therapy duration of greater than 3 years, including one study that examined the impact of 15 years continuous PPI therapy (Brunner\(^7\)). By contrast, the Cochrane review of Song *et al.*\(^8\) defined long-term PPI use as 6 months or greater. Five of the seven studies analysed by Song had a PPI therapy duration of 6–12 months. We have shown that ECL changes develop over a timeframe far longer than 6–12 months: ECL cell density peaked at 4–5 years of PPI therapy (Figure 3), the prevalence of ECL cell hyperplasia showed a slow upward trend out to 5 years (Figure 4), and corpus atrophy scores in *H. pylori*-positive patients peaked at years 3–4. Thus, the available evidence suggests that the long-term effects of PPI therapy could not be adequately assessed by the Song review.

A limitation of our review was the heterogeneity of the studies, in terms of the duration and dose of PPI therapy. However, our analyses did not address the question of a potential relationship between PPI dose and gastrin levels and/or the degree of ECL cell hyperplasia. In eight of the 16 studies in this review, patients had been exposed to previous ranitidine therapy, which may have affected baseline levels of gastrin and ECL cell hyperplasia. This review did not aim to evaluate the potential association between long-term PPI use and the incidence of gastric cancer. A statistically rigorous examination of the risk of gastric cancer would require large epidemiological studies\(^9\)–\(^11\) or the meta-analysis of large-scale randomised controlled trials of PPIs vs. non-PPI therapy with gastric cancer as a predefined endpoint. Such analyses are clearly beyond the scope of the present study. Nevertheless, it should be noted that the total sample size of 1920 patients afforded very low power to detect gastric cancer.

Assuming an incidence of 7.5 per 100 000 individuals (US data)\(^9\) and \(\alpha = 5\%\), 1920 patients would have a
power of only 13.8% to detect a case of gastric cancer (a sample size of 20 505 patients would be needed for 80% power).

In conclusion, the studies identified in this systematic review indicate that long-term PPI therapy induced moderate hypergastrinaemia in most individuals. The prevalence of ECL cell hyperplasia increased progressively during long-term PPI therapy; however, none of the patients in these studies developed a NET. *H. pylori*-positive patients receiving long-term PPI therapy have a higher risk for developing a corpus-predominant gastritis than *H. pylori*-negative patients.

**AUTHORSHIP**

**Guarantor of the article:** Lars Lundell.

**Author contributions:** All authors contributed to the design of the study, analysis of the search results, and writing of the manuscript.

All authors approved the final version of the article, including the authorship list.
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