Fundic Gland Polyps Are Not Induced by Proton Pump Inhibitor Therapy

Michael Vieth, MD, PhD, and Manfred Stolte, MD, PhD

Key Words: Fundic gland polyp; Proton pump inhibitor; Gastric polyp

Abstract

It is still unclear whether proton pump inhibitors (PPIs) could cause fundic gland polyps (FGPs) in patients without Helicobacter pylori infection. The frequency of FGPs in patients during PPI therapy has not been compared, however, with a control group of patients who did not have H pylori infection and were not undergoing PPI treatment.

In a retrospective 12-month study, the frequency of FGPs in 2,251 patients without H pylori infection receiving PPI therapy (duration of treatment at least 4 weeks) was compared with a control group of 28,096 patients who did not have H pylori infection and were not receiving PPI therapy. FGPs were identified with an identical frequency in both groups (5.0% in the control and 5.2% in the PPI group). No significant differences were present between the groups with respect to the presence of gastritis or age or sex.

Our study shows that a causal pathogenetic relationship between PPI therapy and FGPs is unlikely.

Since the first description of 3 patients in whom fundic gland polyps (FGPs) developed during omeprazole therapy, an additional 135 cases have been described in the literature. Lansoprazole therapy and pantoprazole therapy (unpublished data) also are associated with the development of FGPs. Others, however, have stated that long-term therapy with omeprazole leads only to hypertrophy of parietal cells without the simultaneous development of FGPs.

The question of whether proton pump inhibitor (PPI) therapy could be the cause of gastric polyp development or whether there is no causal relationship between PPI therapy and the appearance of FGPs is a controversial point in the literature. While some authors consider such a relationship likely, others have the opinion that it is only a coincidental finding, since FGPs also can appear without PPI therapy and are the most common of all gastric polyps, constituting about 47%.

So far, most FGPs identified during PPI therapy have been described only in case reports, and their frequency has not been compared with control groups without PPI therapy. Only 1 publication describes the appearance of FGPs during PPI therapy in comparison with a large group of patients not receiving PPI therapy. In this study FGPs were identified in 9 (3.9%) of 231 patients during PPI therapy and in 6 (0.3%) of 2,072 patients in the control group without PPI therapy. This difference was statistically significant.

This study had, however, several weak points in its methodologic approach. FGPs are reported to develop during PPI therapy in corpus mucosa without Helicobacter pylori infection. But often, the H pylori status in the control group was not described precisely, ie, the frequency of FGPs in the H pylori-negative cases of the control group is unclear.
For this reason, the goal of the present study was to determine the frequency of FGPs in patients without \textit{H pylori} infection with and without long-term PPI therapy, in order to evaluate whether PPI therapy is really responsible for the development of FGPs.

**Materials and Methods**

For this retrospective study, gastric biopsy specimens of patients not receiving PPI therapy and patients receiving long-term PPI therapy that were examined during the year 1999 in the Institute of Pathology, Bayreuth, Germany, were evaluated for the frequency of FGPs. Only patients who had received PPI therapy for at least 4 weeks at the time of biopsy were included in the study. The data concerning the type, duration, and dose of the PPI therapy and the number of the endoscopically diagnosed gastric polyps were taken from the pathology request forms, the endoscopic findings, and the medical reports of the patients. Since FGPs were found only in gastric mucosa without \textit{H pylori} infection in both groups, we analyzed only patients who had no \textit{H pylori} infection in the 2 collectives with and without PPI therapy.

The study included 28,096 patients without PPI therapy and 2,251 patients receiving long-term PPI therapy for gastroesophageal reflux disease. All of these patients were free of \textit{H pylori} infection. For the group receiving PPI therapy, only patients who underwent an endoscopic examination with biopsies before the beginning of PPI therapy and who had no evidence of FGPs by endoscopy or by histologic examination were selected.

For the long-term PPI therapy, omeprazole usually was used at the standard dose of 20 mg/d. In a few cases, lansoprazole (30 mg/d) and pantoprazole (40 mg/d) were given. Since the frequency of FGPs was similar regardless of the type of PPI, its dose, or the duration of therapy, the results for all groups receiving PPI therapy were analyzed together.

**Histologic Methods**

At least 2 biopsy specimens from the normal mucosa of antrum and corpus (each consisting of at least 2 tissue fragments) as well as biopsy specimens from endoscopically identified small polyps of the corpus mucosa were analyzed. The biopsy specimens were fixed in a 4% formalin solution and then dehydrated and embedded in paraffin by a routine procedure. The 4-µm-thick sections were cut (at least 8 per paraffin block) and, after deparaffinization, were stained with H&E and Warthin-Starry (WS) stains. FGPs were diagnosed according to established histologic criteria.

**Statistical Methods**

The data for comparison were all mean values obtained from the corpus mucosal biopsy specimens of 30,347 consecutive patients without \textit{H pylori} infection examined at the Institute of Pathology, Bayreuth, during 1999. All analyses were performed using SPSS software (SPSS, Chicago, IL). The nominal data in the resulting tables were checked for uniformity using the Student \(t\) test. The significance level was .05.

**Results**

Among 28,096 patients without evidence of \textit{H pylori} infection by the WS stain and without PPI therapy, FGPs were found in 1,415 (5.0%). None of these patients had pari-etal cell hypertrophy, a finding that could be a histologic sign of PPI therapy that was not reported. Among 2,251 patients without evidence of \textit{H pylori} infection by the WS stain but who were receiving long-term PPI therapy, 116 (5.2%) had FGPs. In all of these patients, hypertrophy of parietal cells was identified in the surrounding corpus mucosa, a finding that is typical of PPI therapy. The FGP frequency showed no statistically significant difference between the patient groups.

**Table I**

<table>
<thead>
<tr>
<th>Normal Corpus Mucosa Without \textit{H pylori} Infection</th>
<th>No. of Patients</th>
<th>No. (%) of Patients With FGPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without PPI therapy</td>
<td>28,096</td>
<td>1,415 (5.0)</td>
</tr>
<tr>
<td>With PPI therapy</td>
<td>2,251</td>
<td>116  (5.2)</td>
</tr>
</tbody>
</table>

FGPs, fundic gland polyps; PPI, proton pump inhibitor.
Discussion

Our study unequivocally shows that there is no causal correlation between long-term PPI therapy and the appearance of FGPs. The frequency of FGPs in the patient group receiving PPI therapy was 5.2% vs 5.0% in the group not receiving long-term PPI therapy, not a statistically significant difference. These results confirm the previously published opinion that FGPs are a coincidental finding during PPI therapy and develop independent of this treatment.3

This result was to be expected, since the following points speak against a causal relationship between PPI therapy and the development of FGPs:

• In animal experiments, treatment with omeprazole fails to produce such FGPs.29,30

• Despite the fact that more than 100 million patients have been treated worldwide with PPIs, FGPs have been reported in only 138 patients since 1992.1-16

• In addition, FGPs are the most common type of gastric polyp, accounting for 47% of the polyps in a study by Stolte et al.22

Most published reports that were concerned with the possible correlation between long-term PPI therapy and the development of FGPs have described only a few cases with FGPs (1-35 cases per study) Table 3. Only Graham8 reported an unusually high frequency for FGPs of 36% (12/33) among patients receiving long-term PPI therapy. Since the total number of patients in Graham’s study was only 33, the high frequency of FGPs that he observed could have been coincidental. This seems to be confirmed by the study of Choudhry et al,10 which included 231 patients without Helicobacter pylori infection in whom newly developed FGPs could be identified in only 3.9% of the patients receiving long-term PPI therapy. Until now, these authors are the only ones who compared the frequency of FGPs with a large control group (2,072 patients). In this control group, FGPs were found in only 0.3% of patients, a significantly lower rate than in the group receiving PPI therapy. However, this control group was not defined with respect to Helicobacter pylori status. Since FGPs occur almost exclusively in normal corpus mucosa or after Helicobacter pylori eradication,3,23-25 only patients without Helicobacter pylori colonization of the gastric mucosa can be used as a control group, as we did in the present study.

![Table 2]

<table>
<thead>
<tr>
<th>Normal Corpus Mucosa Without Helicobacter pylori Infection</th>
<th>Mean Age (y)</th>
<th>Sex (M/F Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without FGPs</td>
<td>With FGPs</td>
</tr>
<tr>
<td>Without PPI therapy</td>
<td>52.6 ± 17.7</td>
<td>61.1 ± 14.5</td>
</tr>
<tr>
<td>With PPI therapy</td>
<td>52.6 ± 16.6</td>
<td>63.2 ± 11.5</td>
</tr>
</tbody>
</table>

FGPs, fundic gland polyps; PPI, proton pump inhibitor.

![Table 3]

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>FGPs</th>
<th>Helicobacter pylori Infection</th>
<th>PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham1/1992</td>
<td>3</td>
<td>0</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Weinstein et al2/1994</td>
<td>1</td>
<td>0</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Stolte et al3/1995</td>
<td>9</td>
<td>0</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Rodi et al4/1995</td>
<td>7</td>
<td>7</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Hirt et al5/1996</td>
<td>13</td>
<td>7</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Mogadam and Houk6/1996</td>
<td>9</td>
<td>0</td>
<td>Omeprazole (7 patients); ranitidine (2 patients)</td>
</tr>
<tr>
<td>Schenck et al7/1997</td>
<td>11</td>
<td>0</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>el-Zimaty et al8/1997</td>
<td>6</td>
<td>0</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Van Vlierberghe et al9/1997</td>
<td>3</td>
<td>0</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Dignan et al10/1998</td>
<td>35</td>
<td>Not reported</td>
<td>Omeprazole (5 patients)</td>
</tr>
<tr>
<td>Jackson and Gordon11/1998</td>
<td>1</td>
<td>Not reported</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Collins and Tydd12/1998</td>
<td>11</td>
<td>Not reported</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Graham13/1998</td>
<td>12</td>
<td>0</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Naegels and Urbain14/1998</td>
<td>4</td>
<td>0</td>
<td>Omeprazole (7 patients); ranitidine (2 patients)</td>
</tr>
<tr>
<td>Choudhry et al15/1998</td>
<td>9</td>
<td>0</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Stolte et al16/2000</td>
<td>4</td>
<td>0</td>
<td>Lansoprazole</td>
</tr>
</tbody>
</table>

FGPs, fundic gland polyps; PPI, proton pump inhibitor.
Our frequency rate of FGPs during PPI therapy of 5.2% is markedly higher than the 3.9% in the study by Choudhry et al. At first, the FGP frequency of 5.0% in our group without PPI therapy seems to be relatively high in comparison with the data in the literature, since such polyps are described to occur at a rate of 0.085% to 1.9% in patients without familial adenomatous polyposis coli and are identified in 2% of patients during routine gastroscopy. Our higher frequency probably can be best explained by the substantial improvement in the optical quality of gastroscopes during the last few years. In addition, previous studies did not take into account the fact that FGPs develop almost exclusively in mucosa without H pylori infection. If one considers that approximately 50% of patients examined by routine gastroscopy have an H pylori infection, one can assume that the incidence of FGPs in patients without H pylori infection may be twice as high as has been reported in previous studies.

Even if our study did not show a statistically significant increase in the development of FGPs during long-term PPI therapy, such a connection might still be possible, since the pathogenesis of FGPs is unknown. The originally published hamartoma hypothesis is not very likely, since FGPs appear predominantly in older women and can regress spontaneously. The hypothesis of the functional-secretory disturbance is more plausible. These polyps increase in size during pentagastrin stimulation. If one looks at the secretory changes of the corpus mucosa during PPI therapy, the development of FGPs is not difficult to imagine, since PPI therapy leads to a strong inhibition of acid secretion and thereby causes a reduction of the secretory volume. On the other hand, the mucus secretion of the foveolar epithelium remains normal. Reduced acid secretion in combination with continuous, normal secretion by the chief cells could result in reduced wash-out of the foveolar mucus, leading to relative obstruction that could cause the development of retention cysts in the fundic glands. The observations that, apart from hypertrophy and hyperplasia of parietal cells, a mild focal dilation of the fundic glands also can frequently be identified during PPI therapy and that the pressure in the fundic glands actually increases also argue in favor of this hypothesis.

But even if other studies eventually are able to prove that in a few cases FGPs develop as a result of PPI-induced changes in fundic gland secretion, the question arises as to whether these newly formed FGPs are clinically relevant. The answer is clearly no, since sporadic FGPs are clinically harmless. They are not associated with the development of dysplasia, adenoma, or even carcinoma. In fact, one might take the existence of sporadic FGPs as an indicator of a good prognosis, since FGPs develop almost exclusively in gastric mucosa without H pylori infection. This is supported by our own archive for the year 1999: 34,000 of 64,347 patients who underwent corpus biopsies during 1999 had an active H pylori gastritis. None of these patients had fundic gland cysts (data not shown). The possibility of developing additional adenomas or dysplasia on the surface of FGPs exists only for patients with familial adenomatous polyposis in whom it is seen in 11% to 25%. So far, the development of early cancer on the surface of FGPs has been described only twice in case reports, both in patients with familial adenomatous polyposis.

Our study shows the following:

- FGPs seldom develop during PPI therapy (5.2%) in patients without H pylori infection.
- Their frequency does not differ from sporadic FGPs in patients who have not received PPI therapy and do not have H pylori infection (5.0%).
- Therefore, a causal pathogenetic connection between long-term PPI therapy and the development of FGP is unlikely.
- In both groups, FGPs develop only in corpus mucosa without H pylori infection and are, therefore, a sign that the risk for peptic ulcers and gastric neoplasia is not increased.

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References


