Influence of Proton Pump Inhibitor Use in Gastrointestinal Polyps

Wen-Hung Hsu,[1] I-Chen Wu,[2] Chao-Hung Kuo,[1,3] Yu-Chung Su,[2,3] Chien-Yu Lu,[2,3] Fu-Chen Kuo,[4] Chang-Ming Jan,[2,3] Wen-Ming Wang,[1,3] Deng-Chyang Wu,[2,3,5] and Fang-Jung Yu[2]

[1]Division of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, [2]Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, [4]Department of Gynecology and Obstetrics, E-Da Hospital, I-Shou University; and [3]Department of Medicine, Faculty of Medicine, College of Medicine, and [5]Center of Excellence for Environmental Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

Proton pump inhibitors (PPIs) are the most potent anti-acid agents and are extensively used worldwide. PPI-induced hypergastrinemia is one of the very few side effects associated with these drugs. However, because hypergastrinemia is related to the occurrence of colonic adenomatous polyps, the purpose of this study was to analyze the relationship between the occurrence of gastrointestinal polyps and hypergastrinemia induced by PPIs. This study included 259 patients who underwent colonoscopy and esophagogastroduodenoscopy between January and August 2007. Chart records, including medication history and fasting plasma gastrin level, were reviewed and analyzed. Any subtle polypoid lesions in the stomach and colon were sampled by biopsy for histological examination. *Helicobacter pylori* infection status was examined by a rapid urea test during esophagogastroduodenoscopy. All patients underwent endoscopy examinations. A total of 122 patients were receiving PPI treatment for either peptic ulcer disease or reflux esophagitis and were included as the study group. The remaining 137 patients were not treated with PPIs and served as the non-PPI group. The mean fasting gastrin level in PPI users versus non-PPI users was 121.8 ng/L versus 56.8 ng/L, respectively ($p < 0.001$). Although the prevalence of gastric gland polyps was higher in the PPI group (65.6% *vs*. 37.2%, $p < 0.001$), there was no difference in the prevalence of colonic adenomatous polyps observed (22.13% *vs*. 22.62%, $p = 0.928$). In conclusion, the prevalence of gastric polyps, particularly fundic gland polyps, was higher among PPI users. However, the prevalence of colonic polyps was not affected by PPI use, regardless of past history of colonic adenomatous polyps.

Key Words: colon polyps, gastric polyps, gastrin, proton pump inhibitor
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Gastrin is a pleiotropic peptide synthesized and secreted by G cells in the stomach, duodenum, and pancreas. It has been shown to exert growth-promoting effects on the mucosa of gastrointestinal tract, in addition to its major physiological function to stimulate gastric acid secretion from parietal cells in the stomach [1]. Proton pump inhibitors (PPIs), launched more than 20 years ago, were designed to irreversibly block proton pumps of parietal cells and are the most effective drug for treating acid-related diseases. PPIs are also used to treat peptic ulcer disease and acid reflux-associated esophagus disease. Moreover, PPIs are relatively safe, with very few side effects; hypergastrinemia is one of the most common side effects. Long-term use of PPIs was reported to increase the

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Address correspondence and reprint requests to: Dr Fang-Jung Yu, Visiting Staff of Gastroenterology, Kaohsiung Medical University Hospital, 100 Tz-You 1st Road, Kaohsiung 807, Taiwan.
E-mail: yufj@kmu.edu.tw or gi@kmu.edu.tw

serum gastrin level by 1.5–2-fold, which has raised concerns over whether hypergastrinemia resulting from long-term use of PPI may have adverse effects on the gastrointestinal tract [2]. Although no obvious neoplastic change was found in the gastric mucosa, an increase in enterochromaffin-like cells and fundic gland polyps was reported [3]. Numerous studies have suggested that the proliferative effect of hypergastrinemia may also affect the mucosa of the small intestine and colon [1,3–5]. Patients with hypergastrinemia as a result of Zollinger-Ellison syndrome have a higher colonic proliferation index [1]. Interestingly, in some case-control studies, the prevalence of hypergastrinemia was higher in patients with colon cancer than in the control subjects. Because of the possible link between hypergastrinemia and colonic adenomatous polyps or colon cancer, it is likely that hypergastrinemia is mitogenic to human colon mucosa, and promote colonic carcinogenesis [6–11]. Conversely, gastrin gene expression was observed in most colon cancer cell lines and in primary colorectal carcinoma [7,8,12]. In animal models, exogenous gastrin or hypergastrinemia induced by high-dose PPI increased the proliferation of normal colonic mucosa [13]. Although the US Food and Drug Administration has approved the long-term use of PPI in patients with reflux esophagitis, few studies have investigated the effect of PPI-induced hypergastrinemia on the colonic mucosa or the incidence of colonic adenomatous polyps. The aim of this study was to investigate whether PPI-induced hypergastrinemia was associated with gastrointestinal tract polyps, particularly colonic adenomatous polyps.

Methods

This cross-sectional study was carried out at Kaohsiung Medical University Hospital, Taiwan. All patients and controls were recruited from our Digestive Endoscopy Center. This study was approved by the ethics committees of our institutional review board.

Patients

Between January 2007 and August 2007, a total of 259 subjects were enrolled in this study. These subjects underwent esophagogastroduodenoscopy (EGD) and colonoscopy. Exclusion criteria included incomplete colonoscopy examination, inadequate bowel preparation, inflammatory bowel disease, newly diagnosed gastrointestinal malignancy, and familial colon polyposis. Subjects with hypergastrinemia induced by conditions other than PPI use were excluded, including previous gastric surgery, pernicious anemia, Zollinger-Ellison syndrome, acromegaly, and pheochromocytoma. Medical records were reviewed, including history of chronic diseases and medication history including PPIs, non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors. An uninterrupted period of PPI prescription of 2 months and 6 months was defined as continuous and long-term PPI use, respectively.

Serological test

Five milliliters of fasting blood was taken for plasma gastrin examination. The gastrin level was estimated by a radioimmunoassay.

Endoscopy

EGD was performed to evaluate gastric lesions. *Helicobacter pylori* infection status was examined by a rapid urease test. Gastric polyps were sampled by biopsy for histological examination. Pan-colonoscopy was performed after a complete bowel preparation with sodium phosphate. Detailed information was recorded for all polypoid lesions, including size and location (cecum, ascending colon, transverse colon, descending colon, and rectosigmoid colon). Biopsy was obtained for histological examination.

Statistical analysis

Qualitative parameters were analyzed using the χ^2 test and Fisher's exact two-sided tests. Analysis of variance was performed to compare the variations between the patient and control groups. A p value of <0.05 was considered statistically significant. Data were analyzed with SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 259 subjects were included in this study, and all of them underwent EGD and colonoscopy. A total of 122 patients used PPIs for an average duration of 21.89 months (range, 1–97 months) and 91.8% used PPIs for more than 6 months. The control group who had no history of PPI or H2-blocker use comprised

137 patients. The demographic data for patients in both groups are shown in Table 1. The PPI users were older than the non-PPI users, because older patients often show more co-morbidities, including peptic ulcer disease, reflux esophagitis, arthropathy, and cardiovascular disease.

The prevalence of *H. pylori* infection was lower in both groups compared with general population because most of these patients had previously received *H. pylori* eradication therapy for peptic ulcer disease, particularly in the PPI user group. Furthermore, most of the patients in the PPI user group had received continuous PPI treatment, which affected the accuracy of the rapid urease test for *H. pylori* infection and provided some false-negative results.

The average gastrin level was 121.8 ρg/mL and 56.8 ρg/mL in the PPI group and the non-PPI group, respectively ($p < 0.001$) (Figure 1). The prevalence of gastric polyps was higher in the PPI group than in the non-PPI group (65.6% *vs*. 37.2%; $p < 0.001$) (Table 2). By contrast, the prevalence of colon polyps was comparable in both groups (57.4% *vs*. 51.8%) (Table 3).

Although female sex, gastrin level, PPI use, and negative *H. pylori* infection were associated with gastric polyps, only female sex and PPI use were significant risk factors in multivariate analysis (Table 2). We also found that longer duration of PPI use was associated with higher incidence of gastric polyps (Figure 2). By contrast, male sex, age, and history of colonic adenomas were associated with colon polyps, and age was the only significant risk factor in multivariate analysis (Table 3).

We further analyzed the histological type of gastric polyps and colon polyps (Table 4). Fundic gland polyps were the most prevalent gastric polyps and

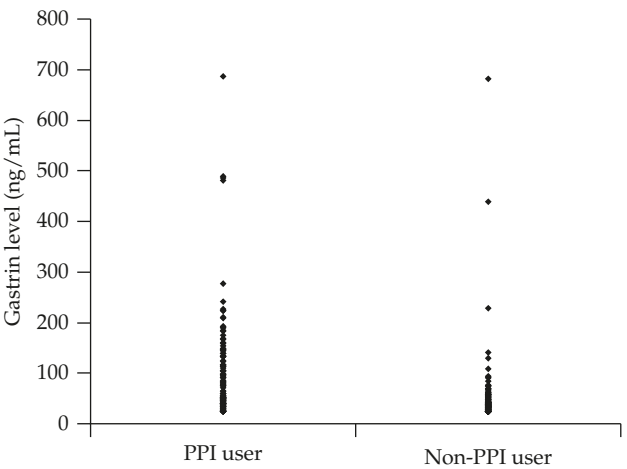

Figure 1. *Gastrin levels of patients using proton pump inhibitors and control patients. The mean gastrin level was 112.8 ng/mL in the proton pump inhibitor group and 56.8 ng/mL in the control group (independent t test, p < 0.001). PPI = proton pump inhibitor.*

Table 1. Characteristics of patients in this study*

Characteristics	PPI user ($n = 122$)	Non-PPI user ($n = 137$)	p
Age	61.3 ± 11.2	52.5 ± 12.9	< 0.001
Sex			0.78
Male	54 (44.3)	63 (45.6)	
Female	68 (55.7)	74 (54.4)	
H. pylori infection			0.001
Negative	114 (93.4)	108 (78.8)	
Positive	8 (6.6)	29 (21.2)	
NSAID or COX-2 inhibitor use			0.020
Yes	9 (7.4)	2 (1.5)	
No	113 (92.6)	135 (98.5)	
Gastrin level (ρg/mL)	121.8 ± 154.2	56.8 ± 100.7	< 0.001
Gastric polyps†			< 0.001
Present	80 (65.6)	51 (37.2)	
Absent	42 (34.4)	86 (62.8)	
Colon polyps‡			0.440
Present	70 (57.4)	72 (51.8)	
Absent	52 (42.6)	65 (48.2)	

*Data presented as mean ± standard deviation or *n* (%). †Included inflammatory polyps, hyperplasia polyps, and fundic gland polyps; ‡included inflammatory polyps, hyperplasia polyps, adenomatous polyps; PPI = proton pump inhibitor; NSAID = non-steroidal anti-inflammatory drugs; COX = cyclooxygenase.

were significantly associated with PPI use (PPI group *vs*. non-PPI group: 49.2% *vs*. 27.7%; $p < 0.001$). PPI use was not associated with a carcinogenic effect on the stomach. Furthermore, PPI use was not associated with the prevalence of inflammatory polyps and hyperplastic polyps. No significant difference was observed between the two groups in terms of the prevalence, histological type and size of colonic polyps.

Table 2. Characteristics of patients with and without gastric polyps*

	With gastric polyps ($n = 131$)	Without gastric polyps ($n = 128$)	*p*	Adjusted OR† (95% CI)
Sex			0.011	
Female	82	60		1
Male	49	68		0.51 (0.297–0.863)
Age	57.73 ± 11.96	55.55 ± 13.80	0.176	1.00 (0.980–1.024)
Gastrin level (ρg/mL)			0.005	
< 90	89	106		1
≥ 90	42	22		1.36 (0.690–2.684)
H. pylori			0.043	
No	118	104		1
Yes	13	24		0.60 (0.276–1.300)
History of PPI use			< 0.001	
No	51	86		1
Yes	80	42		2.70 (1.488–4.928)

*Data presented as *n*, mean ± standard deviation; Gastric polyps included inflammatory polyps, hyperplasia polyps and fundic gland polyps; †multivariate analysis with adjusted OR for age (continuous), gastrin level (< 90 *vs*. ≥ 90 ρg/mL), sex (male *vs*. female), *H. pylori* infection (yes *vs*. no) and PPI use (yes *vs*. no). OR = odds ratio; CI = confidence interval; PPI = proton pump inhibitor.

Table 3. Characteristics of patients with and without colon polyps*

	Patients with colon polyps ($n = 142$)	Patients without colon polyps ($n = 117$)	*p*	Adjusted OR† (95% CI)
Sex			0.013	
Female	68	74		1
Male	74	43		1.56 (0.925–2.630)
Age	59.48 ± 11.60	53.23 ± 13.60	< 0.001	1.03 (1.012–1.056)
Gastrin level (ρg/mL)			0.399	
< 90	104	91		–
≥ 90	38	26		
H. pylori			0.540	
No	120	102		–
Yes	22	15		
PPI use			0.438	
No	74	65		–
Yes	70	52		
NSAID or COX-2 inhibitor user			0.544	
Yes	7	4		–
No	135	113		
History of colonic adenoma			0.012	
No	90	89		1
Yes	52	28		1.46 (0.816–2.616)

*Data presented as *n* or mean ± standard deviation; Colon polyps included inflammatory polyps, hyperplasia polyps and adenomatous polyp; †multivariate analysis with adjusted OR for sex (male *vs*. female), age (continuous) and history of colon adenoma (yes *vs*. no). OR = odds ratio; CI = confidence interval; PPI = proton pump inhibitor; NSAID = non-steroidal anti-inflammatory drugs; COX = cyclooxygenase.

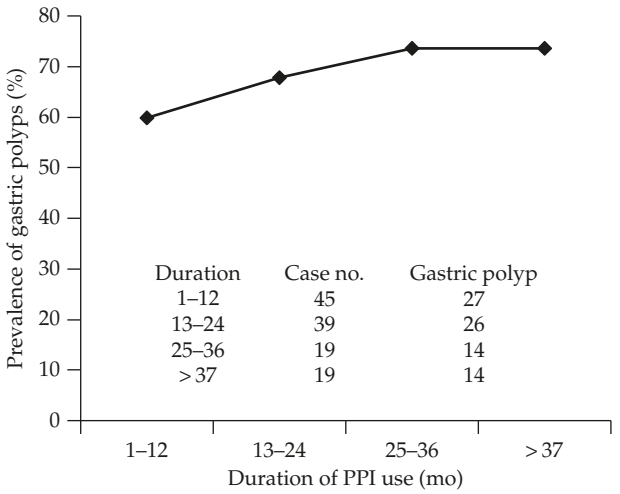

Figure 2. *The prevalence of gastric polyps increased with longer duration of proton pump inhibitor use (χ^2 test, $p=0.951$). PPI = proton pump inhibitor.*

Table 4. Histological features and location of gastric polyps and colon polyps in patient treated with proton pump inhibitors

	PPI user ($n=122$)	Non-PPI user ($n=137$)	p
Gastric polyps	80	51	<0.001
Fundic gland polyps	60	38	<0.001
Inflammatory polyps	17	13	0.266
Hyperplasia polyps	3	0	0.997
Colonic polyps	70	72	0.440
Non-adenoma*	43	41	0.365
Adenoma	27	31	0.928
Mean size (cm)	0.351	0.358	

*Non-adenoma polyps include hyperplastic polyps and inflammatory polyps. PPI = proton pump inhibitors.

To exclude the possibility of underestimation, we found that, of the 259 patients included in this study, 165 patients had undergone colonoscopy in our hospital at least once, including 97 patients in the PPI group and 68 patients in the non-PPI group (Table 5). The average number of previous colonoscopy examinations was 2.36 in the PPI group and 2.09 in the control group. There was no difference in the prevalence of colonic adenomas between the two groups, even in patients with history of colonic adenoma.

Table 5. Association between proton pump inhibitor treatment in patients with versus without history of colonic adenomas

	PPI user ($n=97$)	Non-PPI user ($n=68$)	p
New adenomas	26	11	0.111
History of colonic adenomas	48	32	
Colonic adenomas	17	9	0.495
Negative finding	31	23	
No history of colonic adenomas	49	36	
New colonic adenomas	9	2	0.082
Negative finding	40	34	

PPI = proton pump inhibitor.

Discussion

PPIs are powerful inhibitors of acid secretion and induce hypergastrinemia [2,14]. Although the safety concerns over PPI-induced hypergastrinemia have been demonstrated in many studies, and are well reviewed [3,15], few studies have investigated the long-term effect of hypergastrinemia on colon mucosa. Meanwhile, the effect of hypergastrinemia on the incidence of colorectal adenomatous polyps remains controversial [10,11,16,17].

In animal models, hypergastrinemia has been implicated as a risk factor for colon cancer. Gastrin may induce proliferation during intestinal crypt regeneration following chemical or radiation injury [4]. Omeprazole-induced hypergastrinemia was shown to increase the number of small intestinal adenomas in $APC^{min-/+}$ mice [13]. However, in this study, the gastrin level was 6–10-fold higher than that in the normal population and the effect of hypergastrinemia may be amplified. In humans, relatively few studies have examined the effect of hypergastrinemia on colon mucosa, particularly PPI-related hypergastrinemia. Two studies based on patients with Zollinger-Ellison syndrome showed that hypergastrinemia increased the rate of colonic proliferation but not the prevalence of adenomas [1,18]. However, these studies did not describe the distribution of colonic adenomas and or provide longitudinal follow-up with colonoscopy. Another study analyzed 10 patients with autoimmune gastritis and six patients with Zollinger-Ellison syndrome, and all of them had undergone

proctoscopy. This study showed that endogenous hypergastrinemia enhanced the proliferation of colorectal mucosa. However, it is unwise to over-interpret the results obtained in the rectum [5]. Two large population-based studies in Europe revealed that long-term PPI therapy (>5 years) was not associated with increased risk of colon cancer. Unfortunately, these studies did not report the results of the colonoscopy examination, precancerous evaluation or the gastrin level [19,20].

In our study, hypergastrinemia was two-fold higher in the PPI group than in the non-PPI group. The prevalence of gastric polyps was higher, particularly fundic gland polyps, in the PPI group. Our results are consistent with those of previous studies [21–23]. Moreover, we evaluated the long-term effect of PPI on colon mucosa in patients who had used PPIs for over 6 months. Overall, the prevalence of adenoma was similar in both groups. Our results are consistent with the results from population-based studies, suggesting that 20–40% of patients have prevalent colonic adenomas. We also found that neoplastic changes (tubulovillus adenoma, large adenoma, and high-grade dysplasia) were not associated with hypergastrinemia, regardless of the history of colonic adenoma. More importantly, our results reveal an important implication, that follow-up colonoscopy for colonic adenomas may be adequate for PPI users [24,25].

However, there are several weaknesses of our study. Selection bias may present in the patients who visited our hospital for their first colonoscopy. Patients who had undergone colonoscopy more than twice may be more relevant for evaluating the effect of hypergastrinemia between PPI users and non-PPI users. A huge variation in fasting gastrin level was noted among the PPI users. Many reasons may be attributed for this, including age, atrophic gastritis, blood sampling time and individual differences. One of the limitations of our study was the lack of longitudinal analysis of the gastrin level and assessment of gastrointestinal polyps before and after PPI use. These problems were also encountered in other studies. More studies are needed to clarify the association between long-term PPI use and effects on colonic mucosa.

In conclusion, our study showed that PPI users are prone to have gastric polyps, including fundic gland polyps. However, long-term use of PPIs was not associated with increased prevalence of colon polyps, irrespective of history of colonic adenoma. We also showed no carcinogenic effect of PPI use on the stomach and colon.

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氫離子阻斷劑使用對腸胃道息肉之影響

許文鴻[1] 吳宜珍[2] 郭昭宏[1,3] 蘇育正[2,3] 盧建宇[2,3] 郭富珍[4] 詹昌明[2,3]
王文明[1,3] 吳登強[2,3,5] 余方榮[2]
[1]高雄市立小港醫院 內科
[2]高雄醫學大學附設醫院 胃腸內科
高雄醫學大學 [3]醫學系 [5]環境頂尖醫學中心
[4]義守大學義大醫院 婦產部

氫離子阻斷劑已廣泛使用於消化性潰瘍及逆流性食道炎，然而會造成胃泌素 2–3 倍之上升，刺激胃粘膜 enteochromaffin-like cell 增生，此外也有刺激小腸及大腸黏膜增生之作用。本研究針對自 2007 年 1 月至 2007 年 8 月在本院接受內視鏡檢查之病患，分析血中胃泌素值。回溯分析病患過去用藥的病史及用藥時間。本研究共分析 122 位使用氫離子阻斷劑患者，以 137 位同期接受內視鏡檢查而未使用氫離子阻斷劑患者作為對照組。其血中胃泌素值分別為 121.8 ng/L 及 56.8 ng/L（$p = 0.034$），具統計學差異。使用氫離子阻斷劑患者平均使用氫離子阻斷劑的時間為 21.89 個月（1–76 個月）。胃鏡檢查發現，胃癌肉在兩組的發生率分別為 PPI user: 65.6％；non-PPI user: 37.2%（$p < 0.001$）。使用氫離子阻斷劑患者可能有較高的胃息肉發生率，但以良性小型 fundic gland polyps 居多，無增加 adenomatous polyps 之影響。大腸癌肉的發生率分別為 PPI user: 22.13％；non-PPI user: 22.62%（$p = 0.928$），兩組無統計學之差異。本研究的觀察，氫離子阻斷劑未增加消化道癌症或腺瘤之發生率。

關鍵詞：大腸癌肉，胃癌肉，胃泌素，氫離子阻斷劑
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通訊作者：余方榮醫師
高雄醫學大學附設醫院胃腸內科
高雄市 807 三民區自由一路 100 號