Dig Dis Sci (2011) 56:1743–1748
DOI 10.1007/s10620-010-1493-x

ORIGINAL ARTICLE

Fundic Gland Polyps and Association with Proton Pump Inhibitor Intake: A Prospective Study in 1,780 Endoscopies

Adriana Zelter · José Luis Fernández · Claudio Bilder · Pablo Rodríguez · Andrés Wonaga · Fernanda Dorado · Miriam Galich · Luis Alberto Viola

Received: 16 June 2010 / Accepted: 10 November 2010 / Published online: 3 December 2010

Abstract
Background and Aims Fundic gland polyps (FGPs) are incidentally found when an endoscopy is performed for a non-related indication. Some authors suggested a relationship with proton pump inhibitor (PPI) intake. We aimed to determine their prevalence and association with PPI intake.
Methods We prospectively studied 1,780 patients who underwent a gastroduodenal endoscopy at our ambulatory care center between June 2007 and August 2008. PPI intake during a period of at least 12 months, female gender and age were statistically evaluated as risk factors for the presence of FGPs. Then, a multiple logistic regression analysis was applied to these variables.
Results Gastric polyps were found in 129 patients (7.2%) and 77 (4.33%) were FGPs. Five patients with no available histology were excluded for the assessment of risk factors. PPI intake was detected in 49 patients with FGPs (63.6%) and 264 without FGPs (15.5%) ($P < 0.0001$). Fifty-nine patients with FGPs (76.7%) and 987 without FGPs (58.1%) were women ($P < 0.001$). The mean age was 58.91 ± 11.82 years in patients with FGPs and 50.34 ± 15.04 years in patients without FGPs ($P < 0.0001$). The three variables remained significant in the multiple model: PPI intake: $P < 0.0001$, OR 9.00 (95% CI 5.44–14.89); female gender: $P = 0.0001$, OR 2.95 (95% CI 1.69–5.15); age: $P = 0.001$, OR 1.03 (95% CI 1.01–1.05).
Conclusions In our population, the prevalence of FGPs was high. Although female gender and age were also significant, PPI intake was the strongest risk factor associated with the presence of FGPs.

Keywords Fundic gland polyps · Stomach neoplasms · Proton pump inhibitors · Endoscopy, gastrointestinal

A. Zelter · J. L. Fernández · C. Bilder · P. Rodríguez · A. Wonaga · F. Dorado · M. Galich · L. A. Viola (✉)
Centro Integral de Gastroenterología,
Ecuador 1481, Buenos Aires C1425EUG, Argentina
e-mail: violaluis@yahoo.com

Introduction

Fundic gland polyps (FGPs) are incidentally found when an upper gastroduodenal endoscopy is performed for a non-related indication. It has been reported that benign gastric polyps in patients undergoing upper endoscopy have a prevalence ranging from 0.5 to 14% [1–4]. The proportion of these gastric polyps that are FGPs also varies widely and ranges from 3 to 77% [4, 5]. The wide range of both prevalences has not been fully explained to date but FGPs prevalence seems to be increasing in recent years. A recent series based on a large pathology database of biopsy specimens from private endoscopy practice showed a 6.35% overall prevalence of gastric polyps, representing FGPs in 77% of them [2].

There are two different types of FGPs: sporadic FGPs and FGPs in patients with familial adenomatous polyposis (FAP) syndrome [6, 7]. There are not histological differences between the two types but dysplasia is frequent in FAP-associated FGPs (30–50%) and scarce in sporadic FGPs (1%) [8–10]. Regarding their etiology, FGPs were initially considered as hamartomatous but later mechanisms related to acid suppression were proposed by some authors and questioned by others [9–11]. Proton pump inhibitor (PPI) intake causes secretory changes of the corpus mucosa that could favour the development of FGPs, but animal experiments with omeprazole and some epidemiological observations have challenged this causal

relationship [11]. Genetic studies show that sporadic FGPs are linked to the somatic mutations in the β-catenin gene and FAP-associated FGPs to germ-line mutations in the APC tumour-suppressor gene, but this last mutation is also observed in sporadic FGPs with dysplasia. Although both mutations occur in the same genetic pathway, they show differing biological properties and may not be enough to clarify the pathogenesis of FGPs [12].

In 1992, Graham reported three cases of FGPs developed after one year of omeprazole intake [13]. Since that report, the association of FGPs with PPI intake has been considered by several authors but most assumptions were based on small or retrospective series and not all the authors confirmed it [8, 11, 14]. The hypothesis that the increasing and massive consumption of PPIs should be reflected by an increase in FGPs prevalence has also been addressed [2]. Middle-aged women have been considered to be prone to develop FGPs but it was not completely determined if age and gender are independent risk factors [2, 8]. *Helicobacter pylori* infection also plays a role in the development of FGPs. It has been postulated that the progressive eradication of *Helicobacter pylori* should favour a lower prevalence of polyps associated with chronic and atrophic gastritis, such as hyperplastic inflammatory polyps and adenomas, with a relative increase in the prevalence of FGPs [2]. This prevalence should also increase with the eradication because it has been observed that almost all FGPs grow in *Helicobacter pylori*-free gastric mucosa [2, 8].

In this prospective study we aimed to determine the prevalence of FGPs in our population and its association with PPI intake, considering gender and age as possible confounding factors. Although *Helicobacter pylori* infection was not a primary aim, it was also partially evaluated on the basis of available data.

Methods

We prospectively studied 1,780 consecutive patients who underwent an upper gastroduodenal endoscopy at our ambulatory care centre between June 2007 and August 2008. Our centre is devoted to clinical gastroenterology and endoscopy practice and virtually all patients who attend belong to private health insurance systems. Endoscopies were performed in the context of daily clinical practice by five experienced endoscopists (LAV, PR, AW, FD and CB). They used GIF-0140 and GIF-0150 video endoscopes (Olympus Medical Systems Corp, Tokyo, Japan). All the procedures were performed under propofol sedation (dose range, 150–220 mg) and concluded without major complications. No special protocol was designed related to endoscopy indication or biopsy obtention and international practice guidelines were followed. Polypoid lesions were systematically biopsied. Biopsies were taken using a standard biopsy forceps (Olympus Medical Systems Corp, Tokyo, Japan), fixed in a 10% formalin solution and sent to the pathology laboratory within the subsequent 24 h.

When patients attended the endoscopy unit they were asked about PPI consumption. The following data were recorded as possible risk factors for the presence of FGPs: female gender, age and continuous PPI intake during a period of at least 12 months. Consumption of PPIs in an intermittent way (at least 2 months of non-consumption) or during less than 12 months was considered as non-consumption. The dose and the type of PPI were asked but not recorded because patients changed PPI type and dose following self-indications and economic reasons.

Biopsy specimens were embedded in paraffin, stained with hematoxylin and eosin, and analyzed by a single and blinded pathologist (MG). Polyps were classified according to their histology [15] and FGPs were specially considered for the purpose of our study. Diagnostic criteria of FGPs were one or more cystically dilated oxyntic glands, composed of parietal and chief cells with a distorted glandular architecture composed of microcysts admixed with normal glands. In patients with PPI intake the associated hypertrophy and hyperplasia of parietal cells producing a serrate profile were also considered [9, 16–18]. Criteria for the diagnosis of dysplasia included nuclear enlargement or pleomorphism, stratification and hyperchromatism [19]. *Helicobacter pylori* prevalence was evaluated in patients with FGPs who underwent routine gastric biopsies to detect this infection, based on the histological diagnosis using a modified Giemsa stain.

The study was approved by the local ethical committee and written informed consent for endoscopy was obtained from all patients. The anonymous database was analyzed by two independent gastroenterologists who did not perform the endoscopies (AZ, JLF). PPI intake, gender and *Helicobacter pylori* infection were statistically evaluated as dichotomous variables by a χ^2 test and age as a continuous variable by an unpaired t test. Then, a multiple logistic regression analysis was applied to these variables. A P value lower than 0.05 was considered as significant and odds ratio (OR), with its 95% confidence interval (CI), was used as a measure of association. Statistical analysis was performed with the computer software program *R: A Language and Environment for Statistical Computing* (R Foundation for Statistical Computing, Vienna, Austria 2008).

Results

Gastric polyps were found in 129 patients, representing a prevalence of 7.25%. Histology was not available in five patients (0.28%) only. The study profile is shown in Fig. 1

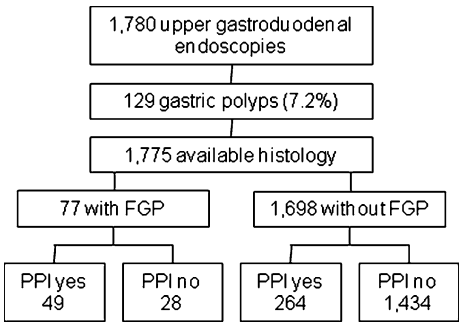

Fig. 1 Study profile. *FGP* fundic gland polyp, *PPI* proton pump inhibitor

Table 1 Gastric polyps in 1,780 upper gastrointestinal endoscopies

Histology	*n*	%
Fundic gland polyp	77	4.33
Pseudopolypoid foveolar hyperplasia	26	1.46
Chronic gastritis	12	0.67
Hyperplastic polyp	8	0.45
Carcinoid polyp	1	0.06
Non available histology	5	0.28

and the distribution of polyps according to their histological characteristics in Table 1.

FGPs were found in 77 patients, representing an overall prevalence of 4.33% and 62.1% of the 124 gastric polyps with histologically confirmed diagnosis. No known case of FAP was detected in these patients. There were no biopsies with dysplasia in the FGPs.

The five patients without histological diagnosis were excluded from the assessment of risk factors for the development of FGPs and a total population of 1,775 patients was considered for this purpose. PPI intake was detected in 49 of 77 patients with FGPs (63.6%) and in 264 of 1,698 without FGPs (15.5%) [$P < 0.0001$, OR 9.5 (95% CI 5.9–15.3)]. Fifty-nine patients with FGPs (76.7%) and 987 without FGPs (58.1%) were women [$P < 0.001$, OR 2.4 (CI 95% 1.4–4.0)]. Mean age was 58.91 $\pm$ 11.82 years in patients with FGPs and 50.34 $\pm$ 15.04 years in patients without FGPs, with a difference of 8.57 years (95% CI 5.13–12.00) ($P < 0.0001$).

As shown in Table 2, the three variables maintained their significance in the multiple model. The goodness of fit of the model, measured as the area under the curve, was 81.3%. According to the general rule given by Hosmer and Lemeshow, this figure indicates a very good discrimination [20].

Biopsies to detect *Helicobacter pylori* infection were available in 306 patients. Sixty-eight of them had FGPs (66 *Helicobacter pylori* negative and 2 *Helicobacter pylori* positive) and 238 did not have FGPs (188 *Helicobacter pylori* negative and 50 *Helicobacter pylori* positive). Thus, 97.06% of FGPs grew in *Helicobacter pylori*-free mucosa and the absence of *Helicobacter pylori* infection was a significant predictor of FGP development [$P < 0.0001$, OR 8.78 (CI 95% 2.29–33.49)]. In the 55 patients of this subgroup without PPI consumption, *Helicobacter pylori* infection was absent in 24 of 25 patients with FGPs and in 21 of 30 patients without FGPs [$P = 0.015$, OR 10.29 (CI 95% 1.51–66.81)].

Table 2 Proton pump inhibitor intake, age and gender as risk factors for the development of fundic gland polyps in the multiple logistic regression analysis

Risk factor	*P*	OR (95% CI)
PPI intake	<0.0001	9.00 (5.44–14.89)
Female gender	0.0001	2.95 (1.69–5.15)
Age	0.001	1.03 (1.01–1.05)

PPI proton pump inhibitor, *OR* odds ratio, *CI* confidence interval

Discussion

We demonstrated that the overall prevalence of FGPs in our population was 4.33% and that PPI intake was the strongest risk factor associated with their presence.

The prevalence of gastric polyps and FGPs varies widely in the different published series (Table 3). Many factors may account for this difference, including the demographic characteristics of the population, the accuracy of the histological diagnosis and the study methodology. Previous reports have several biases that may underestimate the true prevalence of these polyps, such as small sample size, pathology-based or retrospective studies.

Our method, including all consecutive patients undergoing upper endoscopy, as it has been previously pointed out [4], and obtaining systematic biopsies of virtually all polypoid lesions, is the best way to establish a true prevalence. However, the prevalence that we observed is valid for a particular segment of the population with a high socioeconomic level but does not necessarily reflect the overall prevalence in Argentina.

In our population, the prevalence of gastric polyps and the proportion of gastric polyps that are FGPs were higher than those in the vast majority of previous reports but agree with the figures published since 2009 [2, 4]. This suggests that it has augmented in recent years, probably due to the widespread PPI intake, as will be discussed later. Other authors found a prevalence of 0.09% for adenocarcinomas, 0.06% for lymphomas and 0.04% for carcinoids [2]. We only diagnosed one carcinoid polyp (0.06%). Neither did we observe dysplasia in FGPs as it was previously reported [8].

Table 3 Prevalence of gastric polyps, proportion of fundic gland polyps and prevalence of fundic gland polyps in the literature

Year	Author	Country	*n*	GPs prevalence (%)	FGPs proportion (% of GP)	FGPs prevalence (%)
1985	Niv and Bat [21]	Israel	13,500 pts	0.53	23.61	0.13
1989	Deppisch and Rona [22]	USA	121 GPs	NR	17.36	NR
1990	Roseau et al. [23]	France	13,000 pts	1.47	9.97	0.15
1993	Marcial et al. [3]	Puerto Rico	5,554 pts	NR	NR	0.79
1994	Stolte et al. [24]	Germany	5,515 GPs	NR	47	NR
1996	Archimandritis et al. [1]	Greece	12,974 pts	1.21	<18	NR
1998	Papa et al. [5]	Italy	121 GPs	NR	3.31	NR
2002	Ljubicic et al. [25]	Croatia	6,700 pts	0.46	9.68	0.04
2003	Gencosmanoglu et al. [26]	Turkey	150 GPs	NR	14.00	NR
2007	Morais et al. [27]	Brazil	26,000 pts	0.58	16.3	0.09
2009	Carmack et al. [2]	USA	121,564 pts	6.35	77	4.99
2009	Genta et al. [28]	USA	103,385 pts	NR	NR	5.88
2009	Ally et al. [4]	USA	385	14.3	78	11.1
2010	Our series	Argentina	1,780	7.25	62.1	4.33

GPs gastric polyps, *FGPs* fundic gland polyps, *pts* patients, *NR* not reported

The relationship between PPIs and FGPs was a central issue in our study. So, the information about PPI use was directly collected from each patient taking into account that there is a recall bias about the exact duration of consumption, the type of PPI and the dosage. We preferred a dichotomous variable to evaluate PPI intake and we arbitrarily chose a cutoff of 12 months with continuous intake, following previous observations suggesting that this may be the critical threshold of duration for the development of these polyps [4, 8].

Since PPIs were marketed in 1988, they are widely used worldwide [14] and the association between the acid suppression and the development of FGPs has been frequently reported with sparse and controversial results [8, 11, 13, 14, 29–31]. Choudry et al. observed that 3.9% of patients developed FGPs after 32 months of PPI therapy and suggested a link between PPIs and FGPs [31]. Vieth and Stolte challenged this idea because they observed that 5% of 30,347 patients developed FGPs either with or without PPI intake, but it should be considered that they included patients with only 4 weeks of therapy [11]. Jalving et al. published a study in 599 patients and concluded that PPI therapy longer than 1 year was associated with an increased risk of FGPs [8]. Recently, Ally et al. observed that PPI intake was an independent predictor of FGP development on logistic regression [4]. These four studies published as full papers have discordant results and some biases may account for the difference: three are retrospective [4, 11, 31] and patients were prospectively included in only one [8]. A different sample size and a recall bias regarding PPI intake could also account for these conflicting results. Our study aimed to avoid these biases with a prospective design analyzing all the upper endoscopies performed in our centre. A significant odds ratio of 9 in the multiple logistic regression clearly demonstrates that PPI consumption increases the risk of developing FGPs.

The mechanisms by which PPIs induce FGPs remain unknown and should be investigated in depth. The increase of gastrin production secondary to acid suppression could cause the enlargement of enterochromaffin-like and parietal cells and the decrease of the number of chief cells without affecting A-like cells [4, 32]. However, evidence of gastrin acting as a growth factor in the stomach are lacking [33] and it has been observed that gastrin FGPs induced by PPIs are not related to the level of hypergastrinemia [34]. Besides, an increased resistance to glandular outflow could cause retention of secretory products and parietal cell protrusions, with development of gland dilatation and cystic change as alterations preceding FGPs [35]. By contrast, other authors did not find an association of parietal cell protrusion with these features of FGPs [36].

Results about age and gender as risk factors for FGP development are also discordant. Some authors found that age was higher in patients with FGPs [8] but others did not [2, 4, 28]. FGPs were more frequently found in female patients by some authors [28] but not by others [4, 8]. We hypothesized that age and gender might be confounding factors related to PPI intake. However, the multiple logistic regression revealed that they maintained a weak but significant association as independent risk factors.

Biopsies for *Helicobacter pylori* were not available in most patients because ours was a real-life study and these biopsies were taken on the basis of clinical criteria. So, it

should have been misleading to include *Helicobacter pylori* as a risk factor in our multivariate analysis. Nevertheless, data obtained on the basis of available biopsies allow us to reach some conclusions. First, 97% of our patients who underwent a biopsy had *Helicobacter pylori*-free mucosa, in agreement with several previous observations [2, 28, 37]. Second, the absence of *Helicobacter pylori* had a strong association with the presence of FGPs in these patients. This association remained statistically valid in patients with no PPI consumption, although the confidence interval was wide due to the small size of the subgroup. Some mechanisms have been proposed for this protective effect of *Helicobacter pylori*. The parietal cell protrusion is the first step in the development of FGPs, probably related to trophic effect of high gastrin levels, to pharmacological blocking of acid secretion or to *Helicobacter pylori* gastritis. This protrusion may cause the obstruction of the glandular isthmus with outflow blocking, leading to the formation of fundic gland cysts. Finally, these cysts may enlarge and progress to FGPs. *Helicobacter pylori protease* could induce the enzymatic degradation of gastric mucus and facilitate the glandular outflow, thus protecting against retention and cystic dilation [35].

Considering that the prevalence of *Helicobacter pylori* infection in Argentina is 35.7% [38], a lower prevalence of FGPs should have been expected. However, both the inverse relationship between *Helicobacter pylori* infection and high socioeconomic level [38] and its massive eradication in the last decade [4] may attenuate this effect. In fact, *Helicobacter pylori* prevalence in our patients with available biopsy was lower than that in the Argentine general population (17.0%), probably due to the high socioeconomic status of most of them. Indirect evidence of the lower impact of this infection is the scant prevalence in our patients of hyperplastic polyps that were prevalent in older series [1, 5, 21, 25–27] and believed to be associated with *Helicobacter pylori.*

We conclude that PPI intake is the strongest risk factor for the development of FGPs and their prevalence has increased due to the massive use of these drugs. The natural history and long-term clinical implication of FGPs remain to be elucidated. Some cases of dysplasia in sporadic FGPs have been reported [8, 9, 12] and FGPs have been associated with colonic adenomas in women over 60 years of age [28]. However, there is no current evidence suggesting an increased risk of dysplasia or cancer in sporadic FGPs as it has been observed in FGPs associated with FAP [39, 40]. FGPs seem to have a benign course and limitation to prolonged PPI therapy or follow-up endoscopies are not guaranteed.

Acknowledgments We thank Lic. Laura Marangunich and Lic. Virginia López, for the logistic regression analysis; Mrs Liliana Noe, for the secretarial support; and Translator María Laura Devincenzi, for the revision of the English manuscript.

References

1. Archimandritis A, Spiliadis C, Tzivras M, et al. Gastric epithelial polyps: a retrospective endoscopic study of 12,974 symptomatic patients. *Ital J Gastroenterol*. 1996;28:387–390.
2. Carmack SW, Genta RM, Schuler CM, Saboorian MH. The current spectrum of gastric polyps: A 1-year national study of over 120,000 patients. *Am J Gastroenterol*. 2009;104:1524–1532.
3. Marcial MA, Villafaña M, Hernandez-Denton J, Colon-Pagan JR. Fundic gland polyps: Prevalence and clinicopathologic features. *Am J Gastroenterol*. 1993;88:1711–1713.
4. Ally MR, Verappan GR, Maydonovitch CL, et al. Chronic proton pump inhibitor therapy associated with increased development of fundic gland polyps. *Dig Dis Sci*. 2009;54:2617–2622.
5. Papa A, Cammarota G, Tursi A, et al. Histologic types and surveillance of gastric polyps: A 7 year clinico-pathological study. *Hepatogastroenterology*. 1998;45:579–582.
6. Bertoni G, Sassatelli R, Nigrisoli E, et al. Dysplastic changes in gastric fundic gland polyps of patients with familial adenomatous polyposis. *Ital J Gastroenterol Hepatol*. 1999;31:192–197.
7. Attard TM, Cuffari C, Tajouri T, et al. Multicenter experience with upper gastrointestinal polyps in pediatric patients with familial adenomatous polyposis. *Am J Gastroenterol*. 2004;99:681–686.
8. Jalving M, Koornstra JJ, Wesseling J, Boezen HM, de Jong S, Kleibeuker JH. increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. *Alim Pharmacol Ther*. 2006;24:1341–1348.
9. Carmack SW, Genta RM, Graham DY, Lauwers GY. Management of gastric polyps: A pathology-based guide for gastroenterologists. *Nat Rev Gastroenterol Hepatol*. 2009;6:331–341.
10. Jalving M, Koornstra JJ, Götz JM, et al. High-grade dysplasia in sporadic fundic gland polyps: A case report and review of the literature. *Eur J Gastroenterol Hepatol*. 2003;15:1229–1233.
11. Vieth M, Stolte M. Fundic gland polyps are not induced by proton pump inhibitor therapy. *Am J Clin Pathol*. 2001;116:716–720.
12. Abraham SC, Park SJ, Mugartegui L, Hamilton SR, Wu TT. Sporadic fundic gland polyps with epithelial dysplasia: evidence for preferential targeting for mutations in the adenomatous polyposis coli gene. *Am J Pathol*. 2002;161:1735–1742.
13. Graham JR. Gastric polyposis: Onset during long-term therapy with omeprazole. *Med J Austr*. 1992;157:287–288.
14. Freeman HJ. Proton pump inhibitors and an emerging epidemic of gastric fundic gland polyposis. *World J Gastroenterol*. 2008;14:1318–1320.
15. Turner JR, Odze RD. Polyps of the stomach. In: Odze RD, Goldblum JR, eds. *Surgical pathology of the GI tract, liver, biliary tract and pancreas*. Philadelphia, PA: Saunders Elsevier; 2009:415–445.
16. Lee RG, Burt RW. The histopathology of fundic gland polyps of the stomach. *Am J Clin Pathol*. 1986;86:498–503.
17. Burt RW. Gastric fundic gland polyps. *Gastroenterology*. 2003;125:1462–1469.
18. Park DY, Lauwers GY. Gastric polyps. Classification and management. *Arch Pathol Lab Med*. 2008;132:633–640.
19. Morson BC, Sobin LH, Grundmann E, Johansen A, Nagayo T, Serck-Hanssen A. Precancerous conditions and epithelial dysplasia in the stomach. *J Clin Pathol*. 1980;33:711–721.
20. Hosmer DW, Lemeshow S. *Applied logistic regression*. New York, NY: John Wiley & Sons, Inc; 2000.

21. Niv Y, Bat L. Gastric polyps—a clinical study. *Isr J Med Sci*. 1985;21:841–844.
22. Deppisch LM, Rona VT. Gastric ephitelial polyps. A 10-year study. *J Clin Gastroenterol*. 1989;11:110–115.
23. Roseau G, Ducreux M, Molas G, et al. Ephitelial gastric polyps in a series of 13,000 gastroscopies. *Presse Med*. 1990;19:650–654.
24. Stolte M, Sticht T, Eidt S, Ebert D, Finkenzeller G. Frequency, location, and age and sex distribution of various types of gastric polyp. *Endoscopy*. 1994;26:659–665.
25. Ljubicic N, Kujundzic M, Roic G, et al. Benign epithelial gastric polyps—frequency, location, and age and sex distribution. *Coll Antropol*. 2002;26:55–60.
26. Gencosmanoglu R, Sen-Oran E, Kurtkaya-Yapicier O, Avsar E, Sav A, Tozun N. Gastric polypoid lesions: analysis of 150 endoscopic polypectomy specimens from 91 patients. *World J Gastroenterol*. 2003;9:2236–2239.
27. Morais DJ, Yamanaka A, Zeitune JM, Andreollo NA. Gastric polyps: a retrospective analysis of 26,000 digestive endoscopies. *Arq Gastroenterol*. 2007;44:14–17.
28. Genta RM, Schuler CM, Robiou CI, Lash RH. No association between gastric fundic gland polyps and gastrointestinal neoplasia in a study of over 100,000 patients. *Clin Gastroenterol Hepatol*. 2009;7:849–854.
29. Van Vlierberghe H, De Vos M, De Cock G, Cuvelier C, Elewaut A. Fundic gland polyps: Three other case reports suggesting a possible association with acid suppressing therapy. *Acta Gastroenterol Belg*. 1997;60:240–242.
30. el-Zimaity HM, Jackson FW, Graham DY. Fundic gland polyps developing during omeprazole therapy. *Am J Gastroenterol*. 1997;92:1858–1860.
31. Choudry U, Boyce HW, Coppola D. Proton pump inhibitor-associated gastric polyps: A retrospective analysis of their frequency, and endoscopic, histologic, and ultrastructural characteristics. *Am J Clin Pathol*. 1998;110:615–621.
32. Masaoka T, Suzuki H, Hibi T. Gastric epithelial cell modality and proton pump inhibitor. *J Clin Biochem Nutr*. 2008;42:191–196.
33. Kh TJ, Chen D. Gastrin as a growth factor in the gastrointestinal tract. *Regul Pept*. 2000;93:37–44.
34. Fossmark R, Jianu CS, Martinsen TC, Qvigstad G, Syversen U, Waldum HL. Serum gastrin and chromogranin A levels in patients with fundic gland polyps caused by long-term proton-pump inhibition. *Scand J Gastroenterol*. 2008;43:20–24.
35. Cats A, Schenk BE, Bloemena E, et al. Parietal cell protrusions and fundic gland cysts during omeprazole maintenance treatment. *Hum Pathol*. 2000;31:684–690.
36. Krishnamurthy S, Dayal Y. Parietal cello protrusions in gastric ulcer disease. *Hum Pathol*. 1997;28:1126–1130.
37. Shand AG, Taylor AC, Banerjee M, et al. Gastric fundic gland polyps in south-east Scotland: Absence of adenomatous polyposis coli gene mutations and a strikingly low prevalence of *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2002;17:1161–1164.
38. Olmos JA, Ríos H, Higa R. Prevalence of *Helicobacter pylori* infection in Argentina: Results of a nationwide epidemiologic study. Argentinean Hp epidemiologic study group. *J Clin Gastroenterol*. 2000;31:33–37.
39. Hofgärtner WT, Thorp M, Ramus MW, et al. Gastric adenocarcinoma associated with fundic gland polyps in a patient with attenuated familial adenomatous polyposis. *Am J Gastroenterol*. 1999;94:2275–2281.
40. Zwick A, Munir M, Ryan CK, et al. Gastric adenocarcinoma and dysplasia in fundic gland polyps with attenuated adenomatous polyposis coli. *Gastroenterology*. 1997;113:659–663.