




## The frequency of gastrointestinal parasitosis and the effect of proton pump inhibitor use on gastrointestinal parasitosis and histopathological findings in patients with dyspepsia

*Dispepsili hastalarda gastrointestinal parazitöz sıklığı ve proton pompa inhibitörü kullanımının gastrointestinal parazitöz ve histopatolojik bulgular üzerinde etkisi*

Elvina Almuradova<sup>1</sup> 

Elvan Erdogan<sup>2</sup> 

Rashad Ismayilov<sup>3</sup> 

Sebnem Oktem Ustun<sup>4</sup> 

Rukiye Vardar<sup>2</sup> 

<sup>1</sup> Ege University Faculty of Medicine, Department of Internal Medicine, Izmir, Turkiye

<sup>2</sup> Ege University Faculty of Medicine, Department of Gastroenterology, Izmir, Turkiye

<sup>3</sup> Ege University Faculty of Medicine, Izmir, Turkiye

<sup>4</sup> Ege University Faculty of Medicine, Department of Medical Microbiology and Parasitology, Izmir, Turkiye

### ABSTRACT

**Aim:** The main purpose of this study was to investigate the frequency of gastrointestinal parasites in patients with upper gastrointestinal system (GIS) complaints. The secondary aim was to evaluate the effect of proton pump inhibitors (PPI) on gastrointestinal parasite frequency and histopathological findings.

**Materials and Methods:** Adult patients who underwent endoscopy for upper GIS symptoms were included in the study. Biopsy specimen for histopathological evaluation, gastric and duodenal aspiration fluid, and stool specimen for parasitological evaluation were also obtained from the patients.

**Results:** A total of 40 patients (29 female and 11 male) were included in the study. The mean age of women was  $54 \pm 14.6$  and men was  $38.4 \pm 18.7$  years ( $p = 0.008$ ). The patients were divided into two groups as not using PPI [14 patients (35%)] and using PPI [26 patients (65%)]. Parasites were detected in 3 patients (7.5%). Two of them were from the group using PPI, and one from the group not using PPI ( $p = 0.95$ ). It was also observed that the effect of PPI on histopathological findings was not statistically significant. Helicobacter pylori positivity was associated with inflammation ( $p = 0.002$ ) and intestinal metaplasia ( $p < 0.001$ ).

**Conclusion:** It was determined that dyspeptic complaints were more common in women. The effect of PPI on histopathological findings or the frequency of parasites were not statistically significant. Inflammation and intestinal metaplasia were found to be statistically higher in Helicobacter pylori positive cases than negatives.

**Keywords:** Proton pump inhibitors, parasites, dyspepsia.

### ÖZ

**Amaç:** Bu çalışmanın esas amacı üst gastrointestinal sistem (GIS) semptomları olan hastalarda gastrointestinal parazitöz sıklığını araştırmaktır. İkincil amaç ise proton pompa inhibitörleri (PPI) kullanımının gastrointestinal parazit sıklığı ve histopatolojik bulgular üzerine etkisini değerlendirmektir.

**Gereç ve Yöntem:** Üst GIS semptomları nedeniyle endoskopi yapılan erişkin hastalar çalışmaya dahil edildi. Hastalardan histopatolojik değerlendirme için biyopsi örneği, parazitolojik inceleme için ise gastrik ve duodenal aspirasyon sıvısı ve gaita örneği alındı.

**Bulgular:** Çalışmaya toplamda 40 hasta (29 kadın ve 11 erkek) alındı. Kadınların ortalama yaşı  $54 \pm 14,6$ , erkeklerin ise  $38,4 \pm 18,7$  yıldır ( $p = 0,008$ ). Hastalar PPI kullanmayan [14 hasta (35%)] ve kullanan [26 hasta (65%)] olarak iki gruba ayrıldı. Toplam 3 hastada (7,5%) parazitoz saptandı. Bunlardan ikisi PPI kullanan grupta, biri ise kullanmayan grupta idi ( $p = 0,95$ ). Bunun yanı sıra, PPI kullanımı ile histopatolojik bulgular arasında istatistiksel olarak anlamlı ilişki gözlemlenmedi. *Helicobacter pylori* pozitifliği ile inflamasyon ( $p = 0,002$ ) ve intestinal metaplazi ( $p < 0,001$ ) ilişkili bulundu.

**Sonuç:** Çalışmamıza alınan hastalar arasında dispeptik şikayetlerin kadınlarda daha fazla olduğu saptandı. PPI kullanımının gastrointestinal parazit sıklığı ve histopatolojik bulgular üzerinde istatistiksel olarak anlamlı etkisinin olmadığı görüldü. Ek olarak, *Helicobacter pylori* pozitif hastalarda negatif olanlara göre inflamasyon ve intestinal metaplazi sıklığı anlamlı düzeyde yüksek izlendi.

**Anahtar Sözcükler:** Proton pompa inhibitörleri, parazitler, dispepsi.

## INTRODUCTION

Upper GIS symptoms are dyspepsia, epigastric pain, heartburn, regurgitation, nausea, and vomiting. It is reported that 25% of the world population has dyspeptic complaints every year. Although 25% of these patients have an organic cause, no underlying disease can be found in the remaining (1, 2). Organic causes include peptic ulcer, gastroesophageal reflux, gastric malignancy, nonsteroidal anti-inflammatory drug (NSAID) use, celiac disease, chronic pancreatitis, eosinophilic gastritis, Crohn's disease, metabolic diseases, or intestinal parasitosis (3). Intestinal parasitosis may cause diarrhea, constipation, steatorrhea, and malabsorption, as well as presenting with upper GIS symptoms (4).

PPIs inhibit hydrochloric acid secretion in the stomach and increase the gastric pH (5). Under normal conditions, bacteria taken orally cannot be colonized in the stomach and small intestine due to the pH 1-1.5 level in the stomach lumen. Increasing pH above 4 with the use of PPI may disable the protection of stomach acid and cause enteric infections. Achlorhydria may pose a risk infections such as *Clostridium difficile*, *Vibrio cholera*, *Shigella*, *Campylobacter*, *Listeria*, or *Salmonella* (6). Studies investigating the effect of PPI use on the presence of parasites in the gastrointestinal tract are very limited (7). It has been proven that PPIs cause vitamin and mineral malabsorption, especially vitamin B12 deficiency. Investigating the effect of PPI on parasitic infestations and especially determining the frequency of giardiasis can help us understand the source of absorption problems in patients using long-term PPIs.

The main purpose of this study was to determine the frequency of parasites in patients presenting with upper gastrointestinal system complaints.

The secondary objectives of the study are to evaluate the association between PPI use and the frequency of gastrointestinal parasites and histopathological findings.

## MATERIALS and METHODS

### Patient selection

Adult patients diagnosed with dyspepsia according to Rome IV criteria and who requested upper GIS endoscopy by the gastroenterologist were included in the study. Ethics committee approval for this study was obtained from the Ege University Faculty of Medicine Medical Research Ethics Committee (28.09.2011/05). The patients were informed in writing and verbally, and the "Informed Consent Form" was signed. Patients with a diagnosis of bleeding diathesis, underwent gastric or duodenal surgery, using antiparasitic drugs in the last month, and disease affecting the immune system were excluded from the study. Patients were evaluated according to gender, age, smoking, alcohol use, drug use (NSAID and aspirin), and admission complaints.

### Evaluation

Upper GIS endoscopy was performed with a fiberoptic video endoscope (Olympus Evis Exera III). The endoscopic view was divided into normal, antral gastritis, or pangastritis. Biopsies were taken from the antrum and corpus for histopathological examination. Histopathological evaluation of biopsy specimens was performed blindly from endoscopic diagnosis and symptom score. According to Sydney criteria (8); chronic inflammation, atrophy, intestinal metaplasia, and *Helicobacter pylori* (HP) parameters were used in the evaluation. During endoscopy, gastric and duodenum aspiration fluid and additional stool samples were taken from the patients and

examined in the parasitology laboratory. After centrifugation, the aspirated fluid was examined under the microscope with native-lugol and trichrome staining methods. Stool samples were also evaluated microscopically by native-lugol, modified formol-ether sedimentation and trichrome staining methods.

#### Statistical Analysis

NCSS 2007&PASS 2008 Statistical Software (Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency) were used for evaluating the study data. The Oneway Anova test for comparing normally distributed parameters between groups and the Tukey HSD test to identify the group that caused the difference were performed. Chi-Square test and Fisher's Exact Chi-Square test were used to compare qualitative data. The results were evaluated at the 95% confidence interval and the level of 0.05 was defined as statistically significant.

## RESULTS

A total of 40 patients (29 female and 11 male) with dyspepsia were included in the study. The mean age of women was  $54 \pm 14.6$  and men was  $38.4 \pm 18.7$  years ( $p = 0.008$ ). Ten patients (25%) were over and 30 patients (75%) were under 65

years old. Seven (17.5%) of the patients were smokers and 4 (10%) were consuming alcohol.

Gastrointestinal parasites were detected in a total of 7.5% ( $n=3$ ) patients. The parasites detected were *Enterobius vermicularis* (in stool), *Entamoeba histolytica* (in stool), and *Giardia intestinalis* (in stool and duodenal fluid). Thirty-five percent ( $n=14$ ) of patients were in the group of not using PPI and 65% ( $n=26$ ) in the group of using PPI. The median time of PPI use was 6.1 months (range, 2 to 16). Parasites were detected in 7.7% ( $n=2$ ) of patients using PPI and 7.1% ( $n=1$ ) of patients who did not. No significant difference was found between PPI use and parasite frequency ( $p = 0.95$ ).

The histopathological staging parameters according to the Sydney system were grouped separately for the corpus and antrum, and for the general gastric mucosa. Chronic and active inflammation was recorded as inflammation together (Table-1). There was no statistically significant relationship between PPI use and histopathological findings (Table-2).

HP was positive in 50% ( $n=20$ ) of the cases. Inflammation was seen in 60% ( $n=12$ ) of HP negative and in 100% ( $n=20$ ) of positive patients ( $p = 0.002$ ). Intestinal metaplasia was found in 10% of the HP negative ( $n=2$ ) and 100% ( $n=20$ ) of the positive cases ( $p < 0.001$ ).

**Table-1.** Histopathological findings of the gastric mucosa.

Pathological diagnosis	Antrum	Corpus	Total gastric mucosa
Normal	6 (15%)	14 (35%)	5 (12.5%)
Inflammation	32 (80%)	24 (60%)	32 (80%)
Chronic atrophic gastritis	2 (5%)	2 (5%)	3 (7.5%)
Intestinal metaplasia	3 (7.5%)	1 (2.5%)	4 (10%)
Helicobacter pylori	16 (40%)	17 (42%)	20 (50%)
Total	40 (100%)	40 (100%)	40 (100%)

**Table-2.** Relationship between proton pump inhibitor use and histopathological findings.

Pathological diagnosis	Using PPI group (n=26)	Not using PPI group (n=14)	p values*
Normal	0 (0%)	1 (7.1%)	<b>0.35</b>
Inflammation	21 (80.7%)	11 (78.5%)	<b>0.86</b>
Chronic atrophic gastritis	2 (7.7%)	1 (7.1%)	<b>0.95</b>
Intestinal metaplasia	3 (11.5%)	1 (7.1%)	<b>0.65</b>
Helicobacter pylori	13 (50%)	7 (50%)	<b>1.00</b>

\* Fisher's exact test. PPI, proton pump inhibitor.

## DISCUSSION

Endoscopy is the main method in the diagnosis of patients with dyspepsia. With an endoscopic biopsy, it is possible to detect the presence of gastric inflammation, metaplasia, atrophy, and dysplasia, and to diagnose pathologies such as giardiasis, amyloidosis, Crohn's disease, sarcoidosis, eosinophilic and lymphocytic gastritis, and malignancy (9, 10). However, in 60% of patients presenting with dyspeptic complaints, the endoscopic cause cannot be determined (11). In addition to all these, it should be kept in mind that upper gastrointestinal system complaints can be the harbinger of many diseases ranging from inflammation to cancer, from autoimmune diseases to parasitic infections.

Studies on the prevalence of intestinal parasites in our country have generally been conducted in university hospitals, and different results have been found. It was found 10.8% and 15% in Izmir, 8.1% in Bursa, 5.9% in Istanbul, 4.2% in Ankara, 21% in Hatay, 13.1% in Manisa, 24% in Kayseri, 17.2% in Elazığ, 4.9% in Malatya, and 28.5% in Van (12-14). In these studies, the frequency of *G. intestinalis* differed according to the regions. Demirçeken et al (12) detected giardiasis in 8.7% of patients with dyspepsia in the duodenal aspirate fluid examination. In our study, we detected *G. intestinalis* in 2.5% (n=1) patients in both duodenal aspirate fluid and stool. In our country, *E. vermicularis* has been detected with the cellophane tape method at a frequency varying between 0.16% and 42.9%, and it has been found to be more common in the eastern regions (14). In a study conducted at Dumlupınar University, *E. histolytica* was detected at a rate of 5.99% in 617 patients (15). In studies conducted in universities to determine the prevalence of intestinal parasites, the lowest parasite rate was reported from Uludağ University Hospital with 3.5%, and the highest from Harran University Hospital with 34.8% (16, 17). When the studies are evaluated, it is seen that the difference in positivity rate is closely related to the study group and geographical regions.

In vitro studies shows that PPI impairs neutrophil functions, thus causing a decrease in the adhesion and bactericidal ability of endothelial cells. Although there are mostly reports of *Clostridium difficile* associated disease and *Salmonella* infection in the literature, there are cases of increased parasitic infections such as giardiasis (18, 19). In a study conducted in Italy,

0.27% (41 of 15,023 patients) of patients with atrophic gastritis were found to have giardiasis (20). In another study conducted in Egypt, it was shown that *G. lamblia* colonization occurs in the stomach and duodenum in the case of hypochlorhydria (21). However, especially in recent studies, it has been shown that PPIs do not increase the frequency of parasitosis (22). In our study, gastric and duodenal fluid aspirates and stool samples were examined and no significant relationship was found between the use of PPI and the frequency of parasites.

Recent studies generally suggest that the use of PPI does not increase the risk of neoplastic changes (23). In our study, no significant relationship was found between the use of PPI and mucosal atrophy or intestinal metaplasia.

In a study, conducted in the south-east of Turkey, the incidence of precursor lesions were observed as normal mucosa in 2.7%, chronic gastritis in 78.6%, gastric atrophy in 3.4%, intestinal metaplasia in 11.5%, and dysplasia in 3.8% in patients with dyspeptic symptoms (24). In our study, the results of antrum and corpus biopsy were considered together as general gastric mucosa in order to evaluate the patients in general and to compare the findings. It was observed that 12.5% of patients had normal mucosa, 80% had inflammation, 7.5% had chronic atrophic gastritis, 10% had intestinal metaplasia and 50% of the patients had HP infection. In the extensive prevalence study conducted in our country, the HP positivity rate was reported as 61.5% (25). In our study, Sydney findings were observed more in HP positive patients, although it was not statistically significant. The role of HP infection in the etiology of peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer is well known. In this respect, detecting and treating HP infection in patients with dyspeptic complaints is important for the prevention of a wide range of diseases from atrophic gastritis to gastric cancer.

The limitation of this study is that it was conducted with a small number of patient groups. Due to the small number of patients, the frequency of parasites and other findings were found to be proportionately less, and therefore the statistics were not significant. In addition, the low frequency of parasites in the Aegean region may have also affected the study data and the frequency of parasites were found to be low.

## CONCLUSION

As a conclusion, in the patients we evaluated with dyspepsia, pathological findings such as intestinal metaplasia, peptic ulcer, atrophy, and parasitosis were also encountered. Therefore, it would be a cost-effective approach to resort to diagnostic methods such as endoscopy in patients with severe and resistant upper gastrointestinal system complaints or who do not respond to treatment.

**Declaration of conflicting interests:** The authors declare that there are not conflicts of interest.

**Financial support:** This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

**Conflict of interest:** The authors declare no conflict of interest.

## References

1. Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004; 127: 1239-55.
2. Ford A.C, Moayyedi P. Current guidelines for dyspepsia management. *Dig Dis* 2008; 26: 225-30.
3. Richter J.E. Dyspepsia: organic causes and differential characteristics from functional dyspepsia. *Scand J Gastroenterol Suppl* 1991;182: 11-6.
4. Mandell, Douglas, and Bennet's Principles and Practice of Infectious Diseases. Eight Edition. Volume 2, Section II. ISBN: 978-1-4557-4801-3.
5. Lew E.A. Review Article: Pharmacokinetic concerns in the selection of anti-ulcer therapy. *Aliment Pharmacol Ther* 1999; 13: 11-6.
6. François M, Lévy-Bohbot N, Caron J, et al. Chronic use of proton-pump inhibitors associated with giardiasis: A rare cause of hypomagnesemic hypoparathyroidism? *Ann Endocrinol* 2008; 69: 446-8.
7. Leonard J, Marshall J.K, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007; 102: 2047-56.
8. Dixon M.F, Genta R.M, Yardley J.H, et al. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996; 20: 1161-81.
9. Carpenter H.A, Talley N.J. Gastroscopy is incomplete without biopsy: clinical relevance of distinguishing gastropathy from gastritis. *Gastroenterology* 1995; 108: 917-24.
10. Sipponen P, Stolte M. Clinical impact of routine biopsies of the gastric antrum and body. *Endoscopy* 1997; 29: 671-8.
11. Kagevi I, Löfstedt S, Persson L.G. Endoscopic findings and diagnoses in unselected dyspeptic patients at a primary health care center. *Scand J Gastroenterol* 1989; 24: 145-50.
12. Demirceken F.G, Soykan I, Kuloglu Z, et al. Dispepsili hastalarda Giardiazis sıklığı. *Akademik Gastroenteroloji Dergisi* 2007; 6: 132-6.
13. Alver O, Özakin C, Yilmaz E, et al. Uludağ Üniversitesi Tıp Fakültesinde farklı yıllarda bağırsak parazit dağılımlarının değerlendirilmesi. *Türkiye Parazitoloji Dergisi* 2005; 29: 193-9.
14. Degirmenci A, Sevil N, Gunes K, et al. Ege Üniversitesi Tıp Fakültesi Hastanesi Parazitoloji Laboratuvarında 2005 Yılı Boyunca Saptanan Bağırsak Parazitlerinin Dağılımı. *Türkiye Parazit Derg* 2007; 31: 133-5.
15. Aydın A, Akdemir C. Dumlupınar Üniversitesi Tıp Fakültesi Hastalarında Entamoeba histolytica Prevalansı. *Kafkas Univ Vet Fak Derg* 2012; 18: A53-A56.
16. Alver O, Tore O. Uludağ Üniversitesi Tıp Fakültesindeki bağırsak paraziti olgularının prevalansı ve dağılımı. *Türkiye Parazit Derg* 2006; 30: 296-301.
17. Zeyrek F.Y, Özbilge H, Zeyrek C.D, et al. Harran Üniversitesi Tıp Fakültesi Mikrobiyoloji Laboratuvarına başvuran hastalarda bağırsak parazitlerinin dağılımı. *Türkiye Parazit Derg* 2002; 26: 278-81.
18. François M, Lévy-Bohbot N, Caron J, et al. Chronic use of proton-pump inhibitors associated with giardiasis: A rare cause of hypomagnesemic hypoparathyroidism? *Ann Endocrinol (Paris)* 2008; 69: 446-8.
19. Kwok C.S, Arthur A.K, Anibueze C.I, et al. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012; 107: 1011-9.
20. Doglioni C, Boni M.D, Cielo R, et al. Gastric giardiasis. *J Clin Pathol* 1992; 45: 964-7.

21. Sanad M.M, Darwish R.A, Nasr M.E, et al. Giardia lamblia and chronic gastritis. J Egypt Soc Parasitol 1996; 26: 481-95.
22. Pépin J, Saheb N, Coulombe M.A, et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis 2005; 41: 1254-60.
23. Ahn J.S, Park S.M, Eom C.S, et al. Use of Proton Pump Inhibitor and Risk of Colorectal Cancer: A Meta-analysis of Observational Studies. Korean J Fam Med 2012; 33: 272-9.
24. Aygün C, Demirci E, Çayırıcı M. Prevalence of gastric cancer precursor lesions in patients with dyspepsia. Dicle Med J 2010; 37: 25-9.
25. Sari Y.S, Sander E, Erkan E, et al. Endoscopic diagnoses and CLO test results in 9239 cases, prevalence of Helicobacter pylori in Istanbul, Turkey. J Gastroenterol Hepatol 2007; 22: 1706-11.