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THE PREVALENCE OF FUNCTIONAL DYSPEPSIA IN PROTON PUMP INHIBITOR (PPI) USERS

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ABSTRACT

Background: With a global frequency of 21%, functional dyspepsia (FD) is a recurrent and remitting illness that affects the gastro-duodenal tract. Post-prandial discomfort (PDS) and epigastric pain syndrome (EPS) are its two subtypes. Gastric dysfunction, acid hypersensitivity, Helicobacter pylori infection, dysregulation of the gut-brain axis, and hereditary variables are some of the multimodal pathogenesis. **Aim of study:** To evaluate the effect of PPI overuse on gastric motility and functions. **Methodology:** A clinical trial study was conducted from January 2024 till May 2024 in endoscopic unit in Al-Mosul General Hospital, database surveyed 120 patients, who complain from upper GI symptoms (epigastric pain, bloating, early satiety, nausea, burning) who tried to used PPI for long period undergoing Oesophageo-Gastro-Duodenoscopy (OGD) and send stool for H.pylori and urea breath test. **Results:** The study compared 69 patients and 41 controls, with males being the predominant group. The most common age group was 20-25 years, while the least common was ≥75 years. There were no significant differences in age, sex, occupation, marital status, smoking, or family history. The duration of the disease was 2-5 years for 35 patients and 1-2 years for 5 controls. Symptoms included epigastric pain, retrosternal pain, and regurgitation. Most cases and controls showed Gastritis, while 10.1% and 2.4% showed Gastritis. Positive H. pylori tests were found in 39.1% of cases and 31.7% of controls. **Conclusion:** When compared to a placebo, there is proof that PPIs are beneficial in treating FD, regardless of dosage or length of treatment. With no or no short-term adverse effects, PPIs may have an analgesic impact in acute pain disorders such epigastric and non-chest thoracic discomfort of upper digestive system origins.

KEYWORDS: Proton Pump Inhibitor, Oesophageo-Gastro-Duodenoscopy, Functional Dyspepsia.

INTRODUCTION

Functional dyspepsia is a condition that is not life-threatening and has not been associated with any increase in mortality. The Rome III criteria for diagnosing functional dyspepsia include early satiety, fullness during or after a meal, or a combination of these symptoms, together with an epigastric burning or pain feeling. Early satiety, postprandial fullness, burning, epigastric discomfort, bloating, nausea, and belching are some of the symptoms of dyspepsia, which affects 20% to 40% of people.[1–3] The cause of functional dyspepsia is known to include peptic ulcer disease, gastro-esophageal reflux, and functional dyspepsia. Being a woman, taking over-the-counter painkillers, smoking, having anxiety or depression, having experienced physical or sexual abuse as a kid, and having Helicobacter pylori infection are risk factors for functional dyspepsia.[1,3]

Revised guidelines have placed endoscopy in the flow of functional dyspepsia diagnosis, requiring endoscopy in all cases where organic disease is suspected. Due to its vital functions in neutralizing the acidic chyme, preserving the mucousbicarbonate barrier, releasing gastric hormones, controlling pancreatic and gastric secretions, and controlling adaptive immune responses along the gastrointestinal mucosal surface, the duodenum is becoming more and more involved in the pathophysiology of functional dyspepsia.[4,5]

Prolong use of PPIs can cause upper gastrointestinal symptoms through two mechanisms: rebound acid

hypersecretion (RAHS) and delayed gastric emptying. After quitting PPI therapy, RAHS is the reappearance of symptoms brought on by an increase in stomach acid output above pre-treatment levels. In the treatment of functional dyspepsia, diabetes, and gastroesophageal reflux disease, delayed stomach emptying may have therapeutic consequences.[6]

Twenty to twenty-five percent of patients who receive long-term PPI medication have mild hypergastrinemia, and thirty to forty percent of patients who abruptly stop using PPI develop rebound acid hypersecretion (RAHS). Heartburn and a burning feeling in the esophagus are the most typical symptoms of gastroesophageal reflux and dyspepsia that most patients who stop using PPIs suddenly experience.[7]

PATIENTS AND METHODS

A clinical trial study was conducted from January 2024 till May 2024 in Endoscopic unit in Al-Mosul General Hospital, database surveyed 110 patients, who complain from upper GI symptoms (epigastric pain, bloating, early satiety, nausea, burning) who tried to used PPI for long period. The studied groups was subdivided into two groups; 69 as cases who were taking the PPI in overdose and 41 as controls who were not taking PPI. The participants had to be adults (at least 15 years old) with a valid diagnosis of FD that met Rome III criteria. According to these criteria, patients had to have experienced postprandial fullness, early satiety, and epigastric burning for at least three months, with the onset of symptoms occurring at least six months before the diagnosis, and they had to show no signs of a structural disease that could account for their symptoms, including any condition found by upper endoscopy. The criteria for postprandial distress syndrome include: early satiation that keeps one from finishing a typical meal, at least multiple times per week; and unpleasant postprandial fullness, which occurs after regular-sized meals, at least multiple times per week.

Additional symptoms might be postprandial nausea, frequent belching, or bloating in the upper abdomen. Epigastric pain syndrome could also be present. The following are all included in the epigastric pain syndrome: At least thrice a week, experience moderately severe epigastrium-specific discomfort or burning. The discomfort does not meet the criteria for biliary pain, is intermittent, not localized or generalized to various areas of the chest or abdomen, and is not alleviated by flatus or feces. Postprandial distress syndrome may coincide with other symptoms, such as searing epigastric pain without a retrosternal component, discomfort that is brought on or soothed by eating but can also happen during fasting.

All the participants undergoing Oesophageo-Gastro-Duodenoscopy (OGD) and send stool for H.pylori and urea breath test. The statistical analysis was done by using SPSS-IBM version 26; Chi square test, Fisher Exact test, and freeman-Halton Exact test were conducted to estimate the difference between the studied groups. p-value ≤0.05 considered as significant.

RESULTS

The current study included 69 patients and 41 controls, the socio-demographic distribution was evaluated the distribution according to the sex shown in figure (1). The males predominant in both groups.

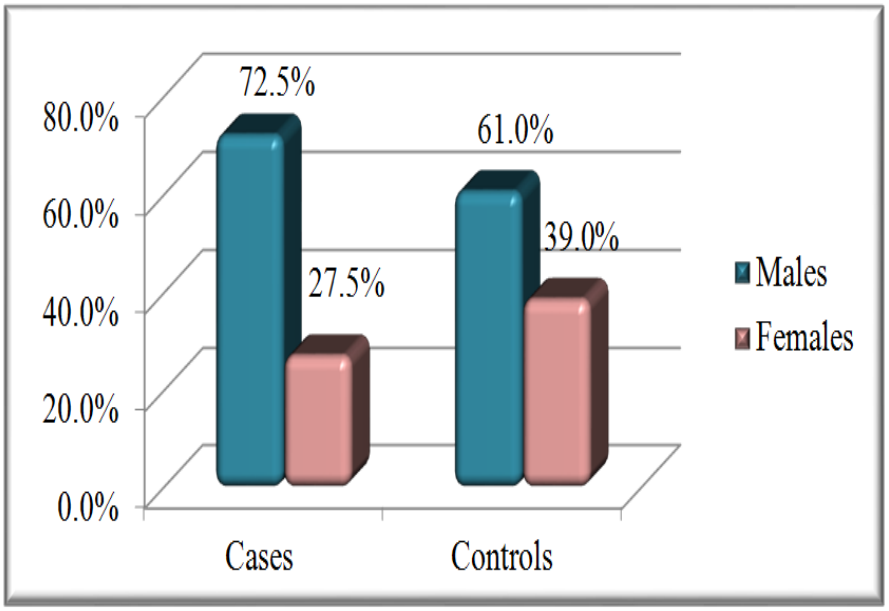

Figure (1): Distribution of the studied groups according to the sex.

The distribution of the studied groups according to the age groups was demonstrated in figure (2). This figure elicited that the most frequent age group was 20-25 years in both studied groups while the age group ≥75 years was the least frequent.

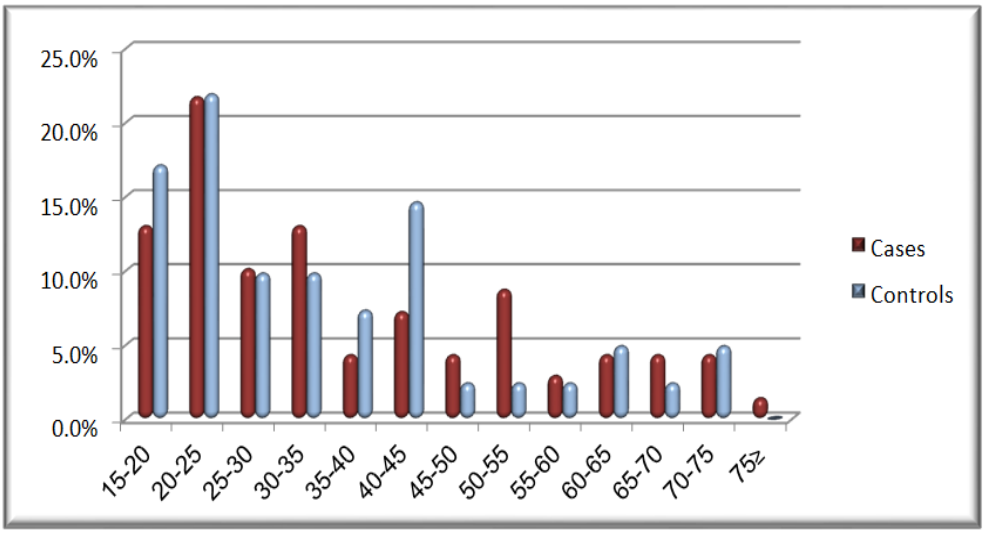

Figure (2): Distribution of studied groups according to age groups.

The comparison between the studied groups in relation to socio-demographic characteristics was demonstrated in table (1) which revealed that there were no significant differences concerning age groups, sex, occupation, marital status, smoking, and family history.

Table (1): Comparison between the studied groups in relation to sociodemographic characteristics.

Socio-demographic characteristics		Cases (n=69)	Controls (n=41)	p-value
		No. (%)	No. (%)	
Age groups	15-20	9(13.0)	6(17.1)	0.983*
	20-25	15(21.7)	9(21.9)	
	25-30	7(10.1)	4(9.8)	
	30-35	9(13.0)	4(9.8)	
	35-40	3(4.3)	3(7.3)	
	40-45	5(7.2)	6(14.6)	
	45-50	3(4.3)	1(2.4)	
	50-55	6(8.7)	1(2.4)	
	55-60	2(2.9)	1(2.4)	
	60-65	3(4.3)	2(4.9)	
	65-70	3(4.3)	1(2.4)	
	70-75	3(4.3)	2(4.9)	
	≥75	1(1.4)	0(0.0)	
Sex	Males	50(72.5)	25(61.0)	0.211**
	Females	19(27.5)	16(39.0)	
Occupations	Housewife	37(53.6)	16(39.0)	0.062*
	Worker	11(15.9)	6(14.6)	
	Retired	3(4.3)	0(0.0)	
	Students	18(26.1)	16(39.0)	
	Employee	0(0.0)	3(7.3)	
Marital status	Single	25(36.2)	18(43.9)	0.715*
	Married	43(62.3)	23(56.1)	
	Widow	1(1.4)	0(0.0)	
Smoking	Yes	8(11.6)	5(12.2)	1.000***
	No	61(88.4)	36(87.8)	
Family history	Yes	27(39.1)	9(21.9)	0.063**
	No	42(60.9)	32(78.1)	

*Freeman-Halton Exact test;**Chi square test;***Fisher Exact test. The distribution of the studied cases according to the duration of the disease was shown in figure (3). Out of the 69 cases, 35 patients had duration for 2-5 years, while only 5 patients had duration of the diseases <1 year.

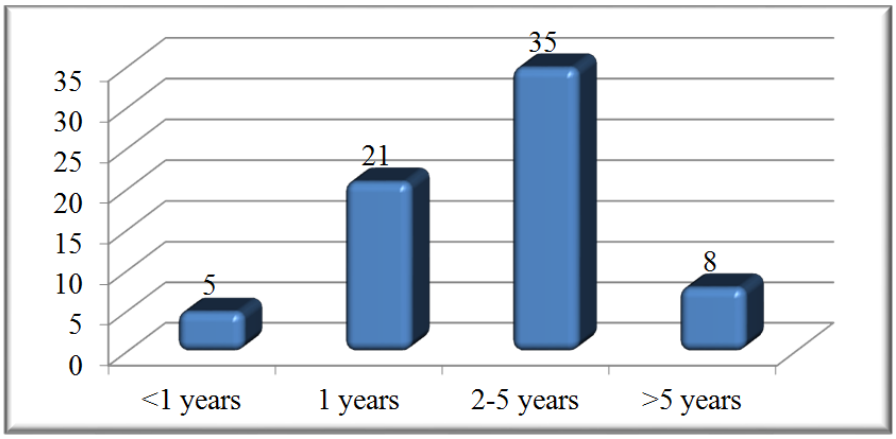

Figure (3): Duration of the disease.

The comparison between the studied groups in relation to symptoms revealed that 82.6% and 97.6% of cases and controls respectively had epigastric pain; the difference was statistically significant (p=0.029). The retrosternal pain was found among 56.5% of cases and 78.1% of the controls with a statistically significant difference (p=0.025). Regurgitation among cases was 37.7% which was significantly higher (p=0.016) than that among the controls 14.6%. The differences regarding nausea, postprandial fullness, bloating, early satiety, and dysphagia were statistically not significant.

Table (2): Comparison between the studied groups in relation to symptoms.

Symptoms		Cases (n=69)	Controls (n=41)	p-value*
		No. (%)	No. (%)	
Nausea	Yes	62(89.9)	39(95.1)	0.480*
	No	7(10.1)	2(4.9)	
Postprandial fullness	Yes	50(72.5)	32(78.1)	0.516**
	No	19(27.5)	9(21.9)	
Bloating	Yes	15(21.7)	14(34.1)	0.182**
	No	54(78.3)	27(65.9)	
Early Satiety	Yes	28(40.6)	24(58.5)	0.078**
	No	41(59.4)	17(41.5)	
Epigastric Pain	Yes	57(82.6)	40(97.6)	**0.029***
	No	12(17.4)	1(2.4)	
Retrosternal Pain	Yes	39(56.5)	32(78.1)	**0.025****
	No	30(43.5)	9(21.9)	
Dysphagia	Yes	4(5.8)	8(19.5)	0.053*
	No	65(94.2)	33(80.5)	
Regurgitation	Yes	26(37.7)	6(14.6)	**0.016****
	No	43(62.3)	35(85.4)	

*Fisher Exact test; **Chi square test.

The comparison between the studied groups in relation to symptoms score over the last 3 months was demonstrated in table (3) which depicted that there were significant difference for indigestion (p=0.000) and heartburn (p=0.001) had higher scores at 5 for both groups, in the other side, the nausea, and stomach upset or pain were had no significant differences while the regurgitation had score of 3 with significant statistical difference (p=0.016). Concerning the total score, 86.9%, 73.2% of the cases and control respectively had score of 20-25 with a statistically significant difference (p=0.001) as shown in table (3) and figure (4).

Table (3): Comparison between the studied groups in relation to symptoms score over the last 3 months.

Symptom score over last 3 months		Cases (n=69)	Controls (n=41)	p-value*
		No. (%)	No. (%)	
Indigestion	1	0(0.0)	2(4.9)	**0.000**
	2	0(0.0)	3(7.3)	
	3	0(0.0)	4(9.8)	
	4	0(0.0)	0(0.0)	

	5	69(100.0)	32(78.1)	
Heartburn	1	1(1.4)	5(12.2)	**0.001**
	2	2(2.9)	2(4.9)	
	3	6(8.7)	9(21.9)	
	4	12(17.4)	12(29.3)	
	5	48(69.6)	13(31.7)	
Regurgitation	1	2(2.9)	8(19.5)	**0.016**
	2	16(23.2)	11(26.8)	
	3	21(30.4)	14(34.1)	
	4	20(28.9)	5(12.2)	
	5	10(14.5)	3(7.3)	
Nausea	1	0(0.0)	0(0.0)	0.349
	2	0(0.0)	1(2.4)	
	3	11(15.9)	5(12.2)	
	4	9(13.0)	9(21.9)	
	5	49(71.0)	26(63.4)	
Stomach upset or pain	1	0(0.0)	0(0.0)	0.218
	2	2(2.9)	0(0.0)	
	3	4(5.8)	2(4.9)	
	4	3(4.3)	6(14.6)	
	5	60(86.9)	33(80.5)	
Score	<15	0(0.0)	7(17.1)	**0.001**
	15-20	5(7.2)	4(9.8)	

*Freeman-Halton Exact test.

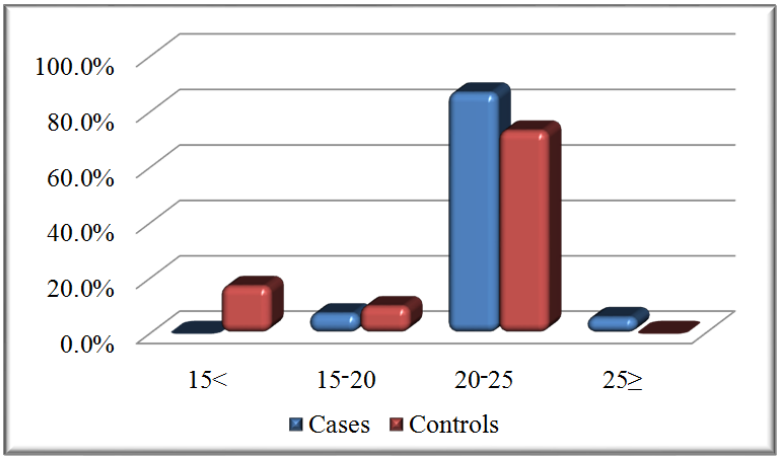

Figure (4): Distribution of studied groups according to total score.

The comparison between the studied groups in relation to Endoscopy was shown in table (4). It found that most of the cases and all the controls showed features of Gastropathy, while 10.1% of cases and 2.4% of controls showed findings of gastritis. Other features demonstrated in both groups in lower frequencies; the difference was statistically not significant (p=0.277).

Table (4): Comparison between the studied groups in relation to Endoscopy.

Endoscopy*	**Cases (n=69)**	**Controls (n=41)**	**p-value****
	No. (%)	**No. (%)**	
Gastropathy	66(95.7)	41(100.0)	0.277
Gastritis	7(10.1)	1(2.4)	
Other conditions***	4(5.8)	4(9.8)	

*studied sample had more than one finding; **Freeman-Halton Exact test; *** other conditions included GERD, Lazy stomach, hiatal hernia.

The comparison between the studied groups in relation to H. pylori test was demonstrated in table (5) and figure (5). These elicited that the total positive H. pylori test was found among 39.1% of cases and among 31.7% of

the controls with a statistically significant difference (p=0.025). Biopsy found positive in 63.0% of cases and 53.8% of controls. positive stool test was positive in 29.6% of cases and 30.8% of controls. Urea breath test was positive in 7.4% of cases and 15.4% of controls.

Table (5): Comparison between the studied groups in relation to H. pylori test.

H. pylori test		Cases (n=69) No. (%)	Controls (n=41) No. (%)	p-value*
Total	Positive	27(39.1)	13(31.7)	**0.025***
	Negative	49(60.9)	28(68.3)	
Biopsy	Positive	17(63.0)	7(53.8)	1.000*
	Negative	38(77.6)	15(53.8)	
Stool	Positive	8(29.6)	4(30.8))	**0.029****
	Negative	4(22.4)	13(46.2)	
Urea breath test	Positive	2(7.4)	2(15.4)	-----
	Negative	0(0.0)	0(0.0	

*Chi square test; ** Fisher Exact test.

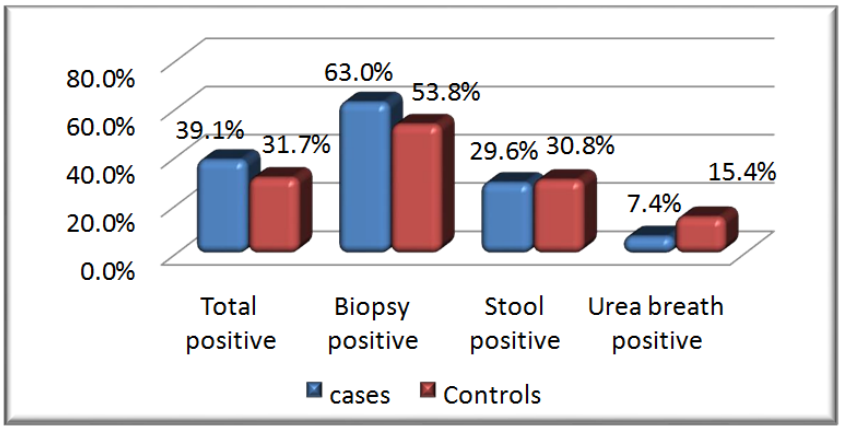

Figure (5): Distribution of studied groups according to H.pylori test.

DISCUSSION

A family of drugs known as proton pump inhibitors (PPIs) is frequently used to treat peptic ulcers, stomach acid-related disorders, and gastroesophageal reflux disease (GERD).[8] These drugs work by suppressing the production of gastric acid in the stomach, thereby reducing symptoms of acid reflux and promoting healing of ulcers. However, recent studies have suggested that overuse of PPIs may have negative effects on gastric motility and functions.[9]

The current study demonstrated the effect of PPI on the clinical symptoms of the functional dyspepsia, mainly the epigastric pain. The study indicated that taking PPI was effectively reduced the pain whether epigastric or retrosternal pain. This may have to do with the fact that PPIs, which prevent the production of acid, are unlikely to result in an instant alleviation of acute discomfort associated with problems of the upper gastrointestinal tract. This result was consistent with the findings of the three RCTs that examined the effectiveness of PPIs as pain relievers in the emergency department for suspected upper gastrointestinal tract diseases within 24 hours of admission.[10–12] The impact of PPIs in primary care was examined in one observational research.[13] Senay et al.[11] used a Visual Analogue Scale (VAS) of ≥20 mm to examine the efficacy of ranitidine and pantoprazole in individuals with dyspeptic symptoms. 33 patients got an intravenous infusion of 50 mg of ranitidine and 33 patients received an intravenous infusion of 40 mg of pantoprazole for 2–4 minutes. In both groups, the pain was successfully decreased after 30 and 60 minutes, although there was no discernible difference between the groups. Nevertheless, despite pain reduction, 24.2 to 39.4% of rescue rates were noted, suggesting further treatments at 60 minutes, which were greater in the Pantoprazole group but did not differ statistically. There was no mention of rescue medications. Khatir et al.[12] concentrated on patients with VAS > 20 mm and symptoms of epigastric discomfort in the setting of an early dyspepsia diagnosis. 50 patients received a 2–4 hour intravenous infusion of 50 mg of ranitidine, and 50 patients received a 2–4 hour intravenous infusion of 40 mg of pantoprazole. At 30 and 60 minutes, the pain score was considerably reduced by both treatments. The effectiveness of ranitidine was much higher (P<0.001). In addition to "the conventional gastrointestinal cocktail" (30 mL of open-labeled antacid containing 1.32 g of aluminum hydroxide, 0.72 g of magnesium hydroxide, and 20 mg of hyoscine butylbromide), Musikatavorn et al.[10] assessed the immediate effects of intravenous Pantoprazole in patients with severe dyspeptic pain

(either heartburn or epigastric pain as VAS ≥ 50). 44 participants got 10 mL of a placebo, whereas 43 patients received 80 mg of intravenous pantoprazole. The two groups' mean 60minute VAS scores were comparable. Regarding the rate of "responders," extra drug use, side effects, and patient satisfaction, there was no statistically significant difference.

Data from six placebo-controlled studies examining the impact of PPI medication on quality-of-life indicators did not consistently show a difference, despite the shown reduction in dyspepsia symptoms, notably pain. As the pathophysiology of functional dyspepsia is still poorly understood and guidelines have evolved, the study found significant variation in the definitions of the condition among research.[14]

Concerning the regurgitation and reflux, the current study showed that the patients taking PPI group were more prone in comparing to placebo group. According to a population-based survey by Delshad et al.[15], GERD symptoms are highly prevalent in the general population. Nearly one in three Americans reported having heartburn or regurgitation during the recent week, and over two out of five reported having similar symptoms in the past. Additionally, among those managing their symptoms with a daily PPI, it was found that more than half still have persistent, troublesome GERD symptoms. Several studies have reported that longterm use of PPIs can lead to changes in gastric motility and functions. For instance, a systematic review and meta-analysis[16–18] found that PPI use was associated with an increased risk of developing delayed gastric emptying, a condition characterized by slow movement of food from the stomach to the small intestine. This effect was more pronounced in patients with diabetes, suggesting that PPIs may exacerbate existing motility disorders[16] Gastric motility refers to the coordinated contractions and relaxations of the muscles in the stomach that help mix and propel food through the digestive tract. It is regulated by a complex interplay of hormonal, neural, and mechanical factors, and any disruption in this process can lead to gastrointestinal (GI) symptoms such as bloating, abdominal pain, and constipation (Foster et al., 2014). Similarly, a study by Lombardo et al. (2019) found that PPI use was associated with decreased antral motility, a region of the stomach responsible for mixing and propelling food into the small intestine. This effect was observed after just one week of PPI use, suggesting that even short-term use of PPIs can have a significant impact on gastric motility (Lombardo et al., 2019). There has been discussion of the underlying processes by which PPIs may impact stomach emptying, the majority of which are still theoretical. Peptic hydrolysis is a process involved in the gastric emptying of solids. PPIs prolong the solid emptying by decreasing acid-dependent peptic activity, which hinders hydrolytic digestion. The volume and energy density of the intragastric contents have a major influence on the gastric emptying of liquids.[19, 20]

There has long been debate over the connection between H pylori infection and functional dyspepsia.[21] According to the current study, patients on PPI had a greater rate of positive H. Pylori tests than those receiving a placebo. This may be connected to the fact that proton pump inhibitor medication is a stronger inhibitor for those with H pylori than for those without, which led to a reduction in symptoms.[22] In patients with H pylori infection, omeprazole 20 mg raises the 24hour median intragastric pH to 5.5; however, when H pylori is eradicated, this drops to 3.0. Out of 530 gastric biopsies examined in the study by Siavoshi et al.,[23] 80 biopsies were positive for culture and RUT despite PPI consumption, suggesting that PPI consumption may not have an impact on culture and RUT in certain patients. However, the number of patients with negative culture and RUT results who took PPI (184, 34.7%) was 2.8 times higher than those who did not (65, 12.3%) (P value = 0.000). PPI use and negative culture or RUT findings were significantly correlated, according to statistical studies on patients with at least one positive test (P value <0.05). The investigation of smear examination findings did not reveal this link, indicating that PPI use may negatively affect H. pylori culture and RUT outcomes but not smear examination results.

CONCLUSION

When compared to a placebo, there is proof that PPIs are beneficial in treating FD, regardless of dosage or length of treatment. With no or no short-term adverse effects, PPIs may have an analgesic impact in acute pain disorders such epigastric and non-chest thoracic discomfort of upper digestive system origins.

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