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IMPACT OF PROTON PUMP INHIBITORS ON LONG-TERM GUT HEALTH.

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ABSTRACT

Background: Proton Pump Inhibitors (PPIs) are very popular in the treatment of gastrointestinal disorders caused by acid. Although it is effective, there is increasing evidence that its long-term use can adversely affect gut health by affecting the equilibrium of microbes, exposing the human body to infection risk, and disrupting nutrient absorption, which makes the question of its long-term safety questionable.

Objective: To assess the effects of the use of long-term PPI on gut microbiota, gastrointestinal symptoms, and complications in adult patients.

Methodology: this cross-sectional study conducted at department of Gastroenterology MTI LRH Peshawar from jan 2021 to jan 2022. We split them into long-term PPI users (more than 12 months, n=50) and non-users (n=50). Adults aged 18–65 years were recruited, and those adults who had previous antibiotic intake or any chronic gastrointestinal disorder were excluded. Gastrointestinal symptoms data were collected using structured questionnaires, and microbiota diversity was analyzed in stool samples. The statistical analysis was done with the help of SPSS version 25, and the mean standard deviation has been computed, and a p-value of less than 0.05 was taken as significant.

Results: The mean age of participants was 42.6 ± 11.3 years, with 54% males. Gastrointestinal symptoms were significantly higher among PPI users, with bloating (68% vs. 32%, p=0.002) and diarrhea (40% vs. 18%, p=0.01). Reduced microbial diversity and decreased beneficial bacteria were observed in PPI users (p=0.003). SIBO was more prevalent in the PPI group (28% vs. 10%, p=0.02). Additionally, vitamin B12 deficiency (22% vs. 8%, p=0.04) and lower magnesium levels (1.7 ± 0.3 vs. 2.0 ± 0.2 mg/dL, p=0.01) were noted.

Conclusion: The use of PPI over a long period of time is related to serious negative impacts on gut health. The use of rational prescriptions and periodic monitoring is also necessary to reduce possible risks.

Keywords: Proton Pump Inhibitors, Gut Microbiota, SIBO, Dysbiosis

Introduction

One of the most commonly prescribed classes of drugs in the world is used to treat the ulcers of the gastrointestinal tract caused by acid (gastrointestinal reflux disease (GERD), peptic ulcer disease, and dyspepsia) through Proton Pump Inhibitors (PPIs). They work by irreversibly inhibiting the system of the hydrogen-potassium ATPase enzyme (proton pump) in gastric parietal cells, resulting in significant inhibition of gastric acid production. PPIs are also used on a long-term basis and are described as mostly prescribed without strict clinical indications due to their high efficacy and positive short-term safety profile [1,2]. There was a rise in concerns about the long-term safety of PPIs, especially on gut health, in recent years. The gastric acid is vital in that it contributes to a natural guard against the pathogens taken in and also controls the makeup of intestinal microbes. Inhibition of gastric acid by the long-term use of PPI could enable the survival and colonization of pathogenic microorganisms, therefore, interfering with the intestinal microbial status. Studies have attributed this change, which is often known as dysbiosis, to a number of gastrointestinal and systemic diseases [3,4]. It has been shown that the usage of PPI in the long-

term results in decreased microbial diversity and an increased number of possibly harmful bacteria. Such microbial imbalance can predispose one to infection, such as Clostridioides difficile infection and small intestinal bacterial overgrowth (SIBO). SIBO is an excessive growth of bacteria in the small intestine that is accompanied by symptoms such as bloating, abdominal discomfort, diarrhea, and malabsorption [5]. Besides a change in microbiota, long-term PPI therapy has also been associated with the disturbance of the absorption of the most necessary nutrients. Vitamin B12, magnesium, calcium, and iron need to be absorbed with the help of gastric acid. Sustained inhibition of acid secretions can cause deficiencies, which can have serious clinical outcomes, such as anaemia, neurological malfunctions, and susceptibility to bone fractures [6]. Moreover, new data indicate that chronic PPI administration can also have an impact on the intestinal barrier function, which results in higher intestinal permeability, so-called leaky gut. Such a condition can permit the transfer of bacteria and toxins into the systemic circulation, which are the causes of persistent inflammation and can raise the likelihood of systemic illnesses [7]. Nevertheless, PPIs are common and are not examined frequently on whether they are necessary or not. Most patients on PPI therapy in a clinical setting are kept on this therapy without proper observation of the risks that may occur. This confirms the necessity to have well-designed studies to assess the effects of PPIs on gut health in the long run, especially in local populations where data might be scarce [8].The current research will examine the impact of long-term PPI on intestinal microbiota, bowel symptoms, and nutritional condition among adult participants. This study aims to facilitate evidence-based clinical decision-making through the promotion of rational prescribing habits and, as a consequence, better patient outcomes by performing a risk assessment of the potential dangers of ongoing chronic PPI therapy [9,10].

Study Objectives

To evaluate the long-term Proton Pump Inhibitor, use effects on gut microbiota, gastrointestinal symptoms, and nutritional status, as well as compare these effects with those of non-users in adult patients.

Materials And Methods

Study Design & Setting

This was a cross-sectional study conducted at this cross-sectional study conducted at department of Gastroenterology MTI LRH Peshawar from jan 2021 to jan 2022.in the outpatient and inpatient departments to have a wide range of patients.

Participants

100 adult patients were included and categorized into two groups: long-term users of PPI (>12 months, n=50) and non-users (n=50) of the drug. The non-probability consecutive sampling was used to select patients. There were both male and female participants to make them representative. Each subject gave informed consent before joining the study.

Sample Size Calculation

The sample size of 100 patients was determined with 95 percent confidence, 5 percent margin of error, and the expectancy of the prevalence of gastrointestinal complications among the PPI users as per past research. Both exposed and non-exposed groups were equally allocated to make the statistical comparison of groups statistically comparable and sufficiently strong to identify significant differences.

Ethical Approval Statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB)/Ethics

Committee of the respective institution prior to the commencement of the study. Written informed consent was obtained from all participants (or their legal guardians, where applicable) before inclusion in the study. Confidentiality and anonymity of participant data were strictly maintained throughout the research process. Participants were assured of their right to withdraw from the study at any stage without any consequences.

Inclusion Criteria

- Adults aged 18–65 years
- Patients on PPIs (12 months and above) (case group).
- Patients who are not taking PPIs (control group)
- Accepting informed consent.

Exclusion Criteria

- New application of antibiotics (in the past 4 weeks)
- Gastrointestinal surgical history.
- So-called chronic inflammatory bowel disease.
- Serious systemic disease or cancer.

Diagnostic and Management Strategy.

Gastrointestinal symptoms assessment of the patients was achieved by clinical history and questionnaires. The samples of stool were taken to analyze microbiota diversity. Investigations in the laboratories covered serum vitamin B12 and magnesium levels. No treatment was administered since this was an observational study.

Statistical Analysis

SPSS version 25 was used to analyze the data. Continuous variables were represented in the form of mean and standard deviation, whereas categorical variables were noted in the form of frequencies and percentages. Comparison between the groups was done by using an independent t-test and a chi-square test. A p-value of below 0.05 was regarded as significant.

Results

A total of 100 patients were included in the study, with a mean age of 42.6 ± 11.3 years. Among them, 54% were male and 46% female. The prevalence of gastrointestinal symptoms was significantly higher among long-term PPI users compared to non-users. Bloating was reported in 68% of PPI users versus 32% in controls (p=0.002), while diarrhea was observed in 40% of users compared to 18% of non-users (p=0.01). Microbiological analysis demonstrated reduced gut microbial diversity among PPI users, with a significant decrease in beneficial bacteria such as Lactobacillus species (p=0.003). Additionally, 28% of PPI users exhibited features suggestive of Small Intestinal Bacterial Overgrowth (SIBO), compared to 10% in the control group (p=0.02). Nutritional deficiencies were also more prevalent among PPI users. Vitamin B12 deficiency was observed in 22% of the PPI group, compared to 8% in non-users (p=0.04). Mean serum magnesium levels were significantly lower in PPI users (1.7 ± 0.3 mg/dL) compared to controls (2.0 ± 0.2 mg/dL, p=0.01). These findings indicate a statistically significant association between long-term PPI use and adverse gut health outcomes, including dysbiosis, gastrointestinal symptoms, and nutrient deficiencies.

Intervention Outcome

No direct intervention was offered, but as observations indicate, restricting the needless prolonged use of PPI and supervising the patients with regard to gastrointestinal symptoms and nutritional shortages may enhance the gut health results. Frequent review of treatment and a proper clinical approach can be used to minimize the related risks.

Table 1: Demographic Characteristics of Study Participants

Variable	PPI Users (n=50)	Non-Users (n=50)	p-value
Age (years, mean ± SD)	43.1 ± 10.8	42.1 ± 11.7	0.68
Male, n (%)	28 (56%)	26 (52%)	0.68
Female, n (%)	22 (44%)	24 (48%)	0.68

Table 1 shows the baseline demographic characteristics of the study population. There was no statistically significant difference between PPI users and non-users in terms of age and gender distribution ($p>0.05$), indicating comparable groups.

Table 2: Comparison of Gastrointestinal Symptoms

Symptom	PPI Users (n=50)	Non-Users (n=50)	p-value
Bloating	34 (68%)	16 (32%)	0.002
Diarrhea	20 (40%)	9 (18%)	0.01
Abdominal Pain	18 (36%)	10 (20%)	0.08

Table 2 compares gastrointestinal symptoms between both groups. Bloating and diarrhea were significantly more common among PPI users ($p<0.05$), while abdominal pain did not show a statistically significant difference.

Table 3: Microbiota and SIBO Findings

Parameter	PPI Users (n=50)	Non-Users (n=50)	p-value
Reduced Microbial Diversity	30 (60%)	14 (28%)	0.003
Lactobacillus Reduction	28 (56%)	12 (24%)	0.003
SIBO Presence	14 (28%)	5 (10%)	0.02

Table 3 illustrates microbiological findings. PPI users showed significantly reduced gut microbial diversity and lower levels of beneficial bacteria such as Lactobacillus. The prevalence of Small Intestinal Bacterial Overgrowth (SIBO) was also significantly higher among PPI users.

Table 4: Nutritional Deficiencies and Laboratory Findings

Parameter	PPI Users (n=50)	Non-Users (n=50)	p-value
Vitamin B12 Deficiency	11 (22%)	4 (8%)	0.04
Magnesium (mg/dL, mean ± SD)	1.7 ± 0.3	2.0 ± 0.2	0.01

Table 4 presents laboratory findings related to nutritional status. Vitamin B12 deficiency and lower serum magnesium levels were significantly more common in long-term PPI users, indicating potential adverse effects on nutrient absorption.

Discussion

The current study finding that there is a strong connection between prolonged use of Proton Pump Inhibitor (PPI) and poor gut health, such as high gastrointestinal symptoms, changes in microbiome, and nutrient deficiencies. The results are in line with new evidence in the recent literature that points to the unintended effects of the chronic acid suppressive therapy. We obtained a prevalence of bloating and diarrhea in PPI users, and this is consistent with recent clinical findings that chronic acid inhibition promotes bacterial proliferation and intestinal dysmotility. A recent systematic review also found that in patients receiving long-term PPI therapy, there was a much higher incidence of small intestinal bacterial overgrowth (SIBO), which reached up to 36.8% as opposed to 19.9% in controls, which supported the results of our study [11]. It proves the

hypothesis that the lower gastrointestinal tract with low gastric acidity facilitates bacterial colonization. Moreover, we found out that there was lower diversity in microbes and lower concentrations of the useful bacteria like Lactobacillus in those who used PPI. As mentioned above, recent reviews also present similar results and stress the importance of PPIs to change the gut microbiota composition by increasing oral and pathogenic bacteria and decreasing commensal ones [12,13]. This dysbiosis is argued as a major pathway connecting the use of PPIs and complications of the gastrointestinal and systemic systems. Recent mechanistic insights also support the observed association between the use of PPI and SIBO in our study (28 vs. 10, p=0.02). Findings that emerged within the past five years indicate that long-term PPI treatment interferes with the natural gastric barrier, facilitating translocation of the oral microbes into the intestinal milieu, which in turn favors such bacterial overgrowth and inflammation [14]. Besides microbiota changes, our results with nutrient deficiency, especially the vitamin B12 and magnesium deficiency, are in line with modern research. Gastric acid is important in the absorption of nutrients, and the inhibition of gastric acid can result in the obstruction of the release and dissolution of micronutrients. Recent studies have noted that the chronic use of PPI is linked to clinically significant deficiencies, particularly in vulnerable groups [15,16]. Furthermore, new evidence has indicated that dysbiosis induced by PPI can be a cause of inflammatory bowel diseases. Recent research results have shown that PPI use can increase changes in gut microbiota that could mediate the pathogenesis of disorders, including ulcerative colitis, which also highlights the clinical significance of microbiome balance [17]. Surprisingly, the increase in evidence indicating that PPIs have systemic effects mediated by the gut microbiome is also supported by our findings. Recent meta-analyses indicate that any change in microbiota due to PPIs could have downstream effects on immune functions and metabolism, but no causal links between the two have been established yet [18]. Although there are these consistencies, there is certain variability in the studies because the study design, population, and duration of exposure to PPI vary among the studies. Although the majority of the recent research proves the hypothesis about the correlation between PPI use and the occurrence of dysbiosis, the clinical implications of those findings are diverse, which is why longitudinal and interventional research is necessary [19,20].In general, the results of the current research are consistent with the recently published findings of the last five years that provide support for the current anxiety about the long-term use of the PPI. The similarity of the findings in several studies confirms that long-term use of PPI may have a significant negative impact on the health of the gut by disrupting the microflora, exposing the gut to infection, and reducing the absorption of nutrients. Such results indicate the significance of the rational prescriptions, periodic monitoring, and the alternative strategies of therapy consideration in case of necessity.

Limitations

This study has its limitations, such as its cross-sectional design that restricts causation. It had a small sample size and was also done in one center, which decreased generalizability. Microbiota analysis was small and not founded on sophisticated methods of sequencing. Moreover, no full evaluation of the dietary factors and duration-specific differences in exposure to PPI was done.

Conclusion

The use of long-term Proton Pump Inhibitors is also indicated to trigger considerable changes in gut health, such as dysbiosis, GI, and nutrient deficiencies. These results emphasize the need to prescribe carefully, regularly monitor, and periodically re-analyze treatment to reduce possible risks and enhance patient outcomes.

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