

The Impact of Long-Term Proton Pump Inhibitor (PPI) Use on Gut Microbiota Composition and Diversity in Patients with Peptic Ulcer Disease: A Literature Review

Remaz El-Tahir¹, Sadiya Qureshi², Nida Ashfaq³, Sadia Sikandar², Syed Omar⁴, Pankti Shah⁵, Ezzat Bitar³

¹Faculty of Medicine, The University of Georgia, Tbilisi, Georgia

²Faculty of Medicine, Tbilisi State University, Tbilisi, Georgia

³Faculty of Medicine, Caucasus International University, Tbilisi, Georgia

⁴Faculty of Medicine, Tbilisi State Medical University, Tbilisi, Georgia

⁵Faculty of Medicine, David Tvildiani Medical University, Tbilisi, Georgia

Email: remazmahdii@email.com

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Abstract

Proton pump inhibitors (PPIs) are a key component of treatment for peptic ulcer disease (PUD) and ulcer healing, as demonstrated by their highly effective acid-suppressing effects. However, their continued use has shown that they can indirectly affect the gut microbiota, a system vital to both digestive and overall health. Evidence suggests that proton pump inhibitors (PPIs) can alter microbial composition and function. The extent of the clinical impact of these changes remains uncertain, especially when patients with PUD often require extended therapy. In this context, the paper examines existing evidence on PPI use and its relationship with the gut microbiome, with particular attention to whether certain microbes emerge more prominently under prolonged use. Across studies, several trends emerge. Microbial diversity declines, oral-origin taxa become increasingly prevalent in the intestine, and protective commensals decline. Such alterations could contribute to dysbiosis-related complications. These findings highlight an important clinical dilemma. While PPIs are highly effective in the treatment and management of PUD, their associated effects on the microbiome are raising concerns about long-term safety. Thus, larger, more targeted studies in PUD groups are needed to address existing knowledge gaps. In addition, strategies for microbial balance protection, therapeutic benefits, and acid suppression are required to preserve microbial homeostasis while maintaining the therapeutic benefits of acid suppression.

Keywords

Proton Pump Inhibitors, Dysbiosis, Gut Microbiota, Peptic Ulcer Disease, Long-Term Therapy, Microbial Diversity

1. Background

Peptic ulcer disease (PUD) is a worldwide health concern, affecting millions of people. *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drug use are the main risk factors for its development [1]. Both increase the risk of recurrence and complications such as bleeding and perforation. The treatment of PUD has changed with the arrival of newer drugs, such as PPIs. Proton pump inhibitors suppress gastric acid secretion by promoting mucosal healing and reducing the risk of recurrence [2] [3]. As a result, PPIs have remained the primary drug for both acute treatment and long-term prophylaxis of PUD [4] [5].

Besides their effectiveness, PPIs are frequently prescribed for longer than the recommended duration (4 - 8 weeks). Long-term exposure to the drug is increased by the fact that the majority of PUD patients require ongoing medication or PPI-based *H. pylori* eradication treatment [6]. Long-term Proton Pump Inhibitor (PPI) use is commonly defined in clinical practice and research as any duration longer than eight weeks. Peptic ulcer treatment, on the other hand, usually lasts four to eight weeks. Thus, due to possible safety issues, prolonged use (6 to 12 months or longer) necessitates a thorough medical examination [7]. Researchers have linked the long-term use of (>12 months) to infections, kidney illness, bone fractures, and nutrient malabsorption as well. which in turn raises many safety concerns [5] [8].

The impact of PPIs on gut flora has also gained more attention. Immune system modulation, nutritional absorption, host metabolism, and pathogen defense all rely on the gut microbiome [9] [10].

Long-term PPI use has been associated with reduced microbial diversity and shifts in gut microbiota composition, including increased oral taxa and decreased beneficial commensals [11] [12], which may increase the risk of gastrointestinal infections. In patients with PUD, these alterations in microbiota are significant, as many undergo eradication therapy consisting of PPIs and antibiotics, which can further cause significant or permanent changes that persist for more than a year [13]. Dysbiosis may influence ulcer regrowth, alter normal responses to therapy, and increase the future vulnerability to infections.

Although peptic ulcer disease (PUD) is the main focus of this study, most of the microbiome information currently available comes from other groups, including patients with dyspepsia, GERD, and other acid-related illnesses. This review summarizes the current evidence on the effects of long-term PPI use (>12 months) on gut microbiota composition and diversity and discusses the relevance of these findings to patients with PUD, particularly regarding microbial alterations and

infection risk.

2. Methodology

The purpose of the literature review was to compile data on how long-term use of PPIs (>12 months) affects the composition and diversity of the gut microbiota in individuals with peptic ulcer disease (PUD).

Several electronic databases, including PubMed, ScienceDirect, and Google Scholar, were used to conduct a thorough literature search. Combinations of terms including “proton pump inhibitors”, “PPIs”, “peptic ulcer disease”, “gut microbiota”, “microbiome”, “dysbiosis”, and “long-term use” were used in the search. Boolean operators (AND, OR) were used to improve relevance and narrow the search.

Studies that satisfied the inclusion criteria included those involving adult patients (≥ 18 years) with a diagnosis of peptic ulcer disease or on long-term PPI therapy, and examined the impact of PPIs on the composition or diversity of gut microbiota. Studies that employed validated microbiological assessment techniques, such as metagenomic analysis, 16S rRNA sequencing, or culture techniques. Randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and pertinent systematic reviews and meta-analyses published in peer-reviewed journals were all acceptable study designs.

Included were only English-language articles published between 2010 and the present. Studies that examined acid-suppressive treatments other than PPIs, included pediatric or animal populations, concentrated on short-term PPI usage (less than four weeks), or failed to provide gut microbiota-related outcomes were all removed. Non-peer-reviewed literature, editorials, opinion pieces, and case reports were also not included.

The chosen studies underwent a full-text review for eligibility after being assessed for relevance based on their titles and abstracts. Because study designs, demographics, and outcome measures varied, data were synthesized qualitatively. To give a summary of PPI-associated changes in gut microbiota and their clinical significance in peptic ulcer disease, the results were arranged thematically.

3. Results

3.1. Mechanism and Long-Term Use of PPIs

Proton pump inhibitors (PPIs) are prodrugs that require activation in the parietal cell canaliculi, where the pH is highly acidic. They become reactive and convert to sulfenamide or sulfenic acid intermediates upon protonation, which then covalently bind to sulfhydryl (thiol) groups on cysteine residues of the stomach to suppress acid secretion irreversibly. Instead of the medication being eliminated, recovery of acid secretion happens only after new proton pumps are created [14].

The average duration of PPI therapy for peptic ulcer disease (PUD) is four to eight weeks. Gastric ulcers require 6 to 8 weeks, whereas duodenal ulcers take 4

weeks. PPIs are primarily used in triple or quadruple therapy regimens for typically 14 days for treating *Helicobacter pylori*-induced ulcers. After this period, acid suppression is continued until mucosal healing occurs. Research has also shown that PPI use frequently lasts longer than these time frames. Approximately 35% of PUD patients take PPIs for longer than the advised time frame [14].

Furthermore, long-term PPI medication significantly alters the composition of the gut microbiota. Long-term PPI users, therefore, show lower Shannon diversity indices and fewer beneficial short-chain fatty acid-producing bacteria, such as Ruminococcaceae and Lachnospiraceae. This may affect the intestinal barrier and metabolic function. These changes in microbiota have been associated in some studies with increased risk of *Clostridioides difficile* infection, small intestinal bacterial overgrowth, and altered gastrointestinal barrier function, though most studies infer rather than directly measure clinical outcomes. In addition, long-term PPI use has been linked to systemic adverse effects, such as deficiencies in magnesium and vitamin B12, as well as increased risks of bone fractures, *Clostridium difficile* infections, and chronic kidney disease [14]-[16].

3.2. Gut Microbiota Structure and Function

The human gut microbiota is closely linked to the host's general health and the stability of the ecosystem. The normal gut microbiota composition requires the recognition of a stable symbiosis, characterized predominantly by an abundance of the Phyla Firmicutes and Bacteroidetes [10]. While Actinobacteria and Proteobacteria are typically present, their relative rarity often serves as an early indicator of microbial balance.

The measure of this community's health is its microbial diversity and the enormous variety and proportional uniformity of the species present. High diversity is the critical factor that confers functional redundancy, providing a metabolic safety net that allows the system to continue functioning reliably even under environmental stressors.

This functional capacity is evident in the fermentation of complex dietary fibers into short-chain fatty acids (SCFAs). Butyrate, for instance, plays an essential multifaceted role, serving as a primary energy source for intestinal cells, actively mediating anti-inflammatory pathways, and reinforcing the integrity of the epithelial barrier [17].

This microbial community establishes the necessary baseline for health. In stark contrast, dysbiosis, a structural and functional disorder widespread in gastrointestinal disease, is characterized by a significant decrease in overall diversity, a concurrent decline in beneficial SCFA-producing organisms, and a proliferation of potentially pathogenic taxa. A particular example of perturbation is observed with the widespread clinical use of PPIs. Studies reveal that chronic PPI use exacerbates this imbalance, diminishing key beneficial genera such as *Lactobacillus* and SCFA producers while increasing the relative abundance of Proteobacteria, a shift that fundamentally alters the healthy profile toward a state commonly asso-

ciated with disease [17]. Consequently, it is mandatory to differentiate between the robust, diverse microbial baseline and a pharmacologically or pathologically induced state of structural compromise in order to evaluate GI health and develop effective clinical strategies.

3.3. Impact of PPIs on Microbiota Composition

In most studies, PPI treatment did not affect the microbiological spectrum and variety but was associated with distinct taxonomic alterations. In the upper gastrointestinal tract, PPI users showed overgrowth of orally derived bacteria, mostly Streptococcaceae (across six independent cohorts comprising 126 PPI users).

In some studies, patients under PPI treatment were included in *Helicobacter pylori* eradication protocols in which antibiotics may directly influence the composition of the gut microbiota. Antibiotic exposure was adjusted for or excluded in some studies and showed that PPI-associated changes persisted, such as increases in oral-origin taxa and decreases in SCFA-producing bacteria, although the magnitude of dysbiosis was usually smaller than that seen with combined PPI-antibiotic exposure.

Findings from mixed PPI-user cohorts (non-PUD-dominant populations) in faecal samples showed increased multiple taxa from the orders *Bacillales* (e.g., *Staphylococcaceae*), *Lactobacillales* (e.g., *Enterococcaceae*, *Lactobacillaceae*, *Streptococcaceae*), and *Actinomycetales* (e.g., *Actinomycetaceae*, *Micrococcaceae*), the families Pasteurellaceae and Enterobacteriaceae, and the genus *Veillonella*. Taxa decreased by PPIs include Bifidobacteriaceae, Ruminococcaceae, Lachnospiraceae, and Mollicutes (findings in faecal samples across 19 independent cohorts with 790 PPI users) [18].

In addition, PPI use at low and high doses, administered for 28 days, resulted in decreases in observed operational taxonomic unit (OTU) counts at both 1 week and 1 month. This decrease resulted in OTU levels similar to those observed in treatment-naïve *Clostridium difficile* infection (CDI) patients, which were partially reversible after a 1-month recovery period. The specific adverse effects associated with prolonged PPIs were necrotizing enterocolitis, late-onset sepsis in premature infants, *Clostridium difficile* infection, asthma, obesity, and small intestine bacterial overgrowth in young children. Studies on the use of probiotics to counteract the adverse effects of PPIs were limited [18] [19].

As PPIs can alter the gastrointestinal microbiome, these changes may disrupt the gastrointestinal barrier, potentially allowing the entry of pathogens. This can increase the risk of infections, ranging from mild to severe. *Clostridium difficile* (*C. difficile*) is a primary bacterial infection that can often lead to hospitalization and is increasing in incidence. Other enteric infections that can occur due to gut dysbiosis include *Salmonella*, *Shigella*, and *Campylobacter*. Subsequently, it is thought that the alkalinity in the gastrointestinal tract caused by PPIs allows pathogenic microbes that would otherwise be unable to survive normal gastric acid to survive, leading to their colonization of the gut microbiota.

3.4. Mechanisms of Microbiota Alteration by PPIs

Numerous studies have shown that proton pump inhibitors (PPIs) can cause significant changes in the composition and diversity of gut microbiota [10] [11] [18]. These changes are mostly due to a decrease in gastric acid secretion, which raises the pH of the stomach. In addition, Several of the observed microbiome changes were stimulated by the concomitant antibiotic exposure in *H. pylori* eradication therapy.

Research indicates that diminished gastric acidity facilitates the survival and colonization of oral and upper gastrointestinal bacteria within the intestinal tract, with a heightened prevalence of genera such as *Streptococcus*, *Rothia*, and *Veillonella* noted among long-term PPI users [10] [11].

These changes in microbes have also been linked to a higher risk of getting *Clostridium difficile* infection and small intestinal bacterial overgrowth (SIBO) [16] [18].

Changes in intestinal pH have been linked to shifts in microbial composition, notably the proliferation of facultative anaerobes and opportunistic organisms [10] [16]. Studies have also shown that levels of *Lactobacillus* and *Streptococcus* species go up after PPI therapy [19]. There have also been reports of indirect effects on the gut microbiota, such as changes in the availability of nutrients and the production of short-chain fatty acids (SCFAs), as well as changes in the production of mucin and the activity of antimicrobial peptides [16] [18] [20].

4. Discussion

4.1. Adverse Effects of Proton Pump Inhibitors on Gut Microbiota

Long-term PPI use has been linked to notable changes in gut microbiota, including decreased microbial diversity and increased colonization by taxa including *Veillonella* and *Streptococcus* [11] [19] [20]. These alterations have been connected to small intestine bacterial overgrowth (SIBO) and an increased vulnerability to infections, such as *Clostridium difficile* [10] [21].

Intestinal inflammation, compromised epithelial barrier function, and modified immunological responses have been linked to PPI-associated dysbiosis. These effects may be caused by changes in the microbial makeup, such as higher *Enterococcus* abundance and lower levels of advantageous taxa like *Faecalibacterium* [21] [22].

Furthermore, changes in immunological response, food absorption, and metabolic control have been associated with decreased production of short-chain fatty acids (SCFAs) [20]. Long-term PPI usage may be linked to a higher risk of metabolic syndrome, micronutrient deficiencies, and altered immune responses, according to emerging data.

These results emphasize how crucial it is to prescribe PPIs carefully and according to evidence. It is advised to utilize the lowest effective dose for the shortest amount of time and to regularly reevaluate therapy. Probiotics and other microbiota-targeted therapies are examples of adjunctive strategies that may be taken

into consideration [21] [23].

4.2. Gaps and Limitations in Existing Research

Despite increasing evidence, several limitations remain in the current literature. A major proportion of included studies were conducted in non-PUD populations, and findings may not fully generalize to patients with peptic ulcer disease. Also, Many studies are constrained by small sample sizes, reducing statistical power and limiting generalizability to broader populations of patients with peptic ulcer disease. This also restricts the ability to assess interindividual variability influenced by factors such as age, disease severity, and treatment duration.

In addition, most studies have relatively short follow-up periods, despite PPIs often being prescribed for long-term use. Consequently, long-term microbiota changes and delayed adverse outcomes may not be fully captured.

Furthermore, Additional limitations include important confounding factors that may influence gut microbiota composition independent of PPI use. These consist of dietary patterns, concomitant medications such as antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs), comorbidities, hospitalization status, and indication bias, where patients on PPIs may already differ systemically from non-users. These factors could partly explain the observed associations between PPI use and microbiome changes.

5. Conclusions

In individuals with peptic ulcer disease, long-term use of proton pump inhibitors (PPIs) is consistently linked to notable changes in the makeup of the gut microbiota. Prolonged PPI medication is associated with different taxonomic alterations and decreased microbial diversity in population-based, clinical, and experimental research, indicating a possible disruption of gut microbial homeostasis.

Despite the strong evidence for the link, cross-sectional designs, short follow-up periods, and differences in microbiome assessment techniques limit causal inference and cross-study comparability.

Overall, these results imply that long-term acid suppression may affect gut microbial balance in ways that are clinically meaningful. To better understand the permanence and therapeutic importance of these microbiome alterations in individuals undergoing long-term PPI medication, well-designed, longitudinal investigations are needed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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