Review Article

The Impact Of Proton Pump Inhibitors (Ppis) On The Gut Microbiome: A Narration Of Literature

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Abstract

Background: Proton pump inhibitors (PPIs) are widely used to treat acid-related disorders, but their impact on the gut microbiome is not well understood. To review the evidence on the effects of PPIs on the gut microbiome and their potential consequences for human health.

Methods: A narrative review of published studies on the impact of PPIs on the gut microbiome was conducted.

Results: PPIs have been shown to alter the balance of gut bacteria, leading to an increased risk of various diseases, including Clostridioides difficile infections, insulin resistance, and elevated blood sugar levels. PPIs have also been found to have a negative impact on specific populations, such as infants and young children. In contrast, some studies have suggested that PPIs may not directly affect the balance of gut bacteria, but rather alter the gut pH, leading to changes in the microbiome.

Conclusion: The evidence suggests that PPIs can have a significant impact on the gut microbiome, leading to negative consequences for human health. Further research is needed to fully understand the effects of PPIs on the gut microbiome and to identify potential strategies for mitigating these effects.

Keywords: Proton pump inhibitors, Gut microbiome, Clostridioides difficile infections, Insulin resistance, Acid-related disorders, Gastrointestinal health

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Introduction

Trillions of microbes live in the human intestine. These microbes form communities that affect the host through collective metabolic activities. Not only the intestine, but also the whole human digestive system contains a dynamic population of microbes, most of which are beneficial and some of which are harmful [1,2]. In the last decade, the relationship between the microbiome and human diseases has become clearer with the progress of sequencing, especially S16 rRNA sequencing, genomics and bioinformatics [3]. Exchange of microbes between these two ecosystems can influence the development of gastrointestinal diseases and cancer, and potentially lead to more accurate diagnoses and effective treatments [4]. These two ecosystems interact and influence each other, potentially playing a key role in both maintaining health and triggering diseases in various parts of the body [5]. The development of rheumatoid arthritis that target the immune system is linked to such microbiome interactions [6]. Alterations in this axis's microbiome may serve as biomarkers for diagnosis and disease progression of inflammatory bowel disease (IBD) [7]. It's also suggested to make some roles in even respiratory system [8], colorectal cancer incidence [9], and neurologic conditions [10]. The widespread use of proton pump inhibitors (PPIs), commonly prescribed to treat gastroesophageal reflux disease (GERD) and other acid-related disorders, has raised concerns about their potential impact on the delicate balance of the gut microbiome. PPIs, which work by reducing stomach acid production, have been shown to alter the gut environment, leading to changes in the composition and diversity of the microbiota [11,12]. This shift in the microbiome has been linked to various adverse effects, including increased susceptibility to infections, impaired nutrient absorption, and even an elevated risk of chronic diseases such as diabetes and cardiovascular disease. As the use of PPIs continues to grow, it is essential to investigate the effects of these medications on the gut microbiome and explore the potential long-term consequences for human health.

The oral–gut microbiome axis

The human gut microbiota fluctuates due to diet, the use of antibiotics, the mother's pregnancy, the type of delivery (cesarean and natural), the consumption of drugs, and many other factors. The coexistence of microbiota and humans begins early in life, where in a short period of time after birth, many microbes (mainly from the mother) enter into symbiosis with the baby [13,14].

Several factors such as age, ethnicity, drugs, exposure to toxins and environmental pollution also affect the composition of intestinal microbiota. Although several genetic studies such as twin studies have shown the effects of genetics on intestinal microbiota, the role of dietary environmental factors on the formation of intestinal microbiota cannot be ignored. Changes in the climate of our living environment with changes in the type of food consumed lead to changes in the microflora of gut. The different food culture in the village and the city causes a change in people's diet and this issue affects the microflora [15]. After the age of 60, the diversity of microbiota in body decreases drastically. With increasing age, the number of bacteria such as Proteobacteria and Bacilli increases and bacteria such as Faecalibacterium prauznitzii and Clostridium cluster XIVa bacteria decrease [16]. The human gut microbiome is composed of a diverse array of microorganisms, with some of the most prominent species including Faecalibacterium prausnitzii, Bacteroides fragilis, Bifidobacterium bifidum, and Lactobacillus acidophilus [17].

The oral microbiome is composed of a diverse array of microorganisms, with some of the most prominent species including Streptococcus mutans, Streptococcus oralis, Fusobacterium nucleatum, and Porphyromonas gingivalis. These bacteria play key roles in the development of oral diseases such as tooth decay, periodontitis, and gingivitis, as well as in the maintenance of oral health [18,19]. Veillonella, Neisseria,

Streptococcus, and Prevotella are known to be most prominent bacteria's of the oral cavity in adult healthy subjects [20].

PPIs and bacteria in human body

PPIs inhibit the H+/K+ adenosine triphosphatase (ATPase) enzyme in the secretory surface of parietal cells, such as omeprazole. Omeprazole interferes with the cytochrome system, while rabeprazole and pantoprazole have the least drug interactions. Fast onset of effect, long duration of effect, and non-tolerance are among their advantages [21]. A nationwide Danish study found that the use of proton-pump inhibitors (PPIs) increased fourfold between 2002 and 2014, with 7.4% of all Danish adults using PPIs in 2014. The prevalence of PPI use was highest among the elderly, with 20% of those aged 80+ using PPIs, and 40% of this age group maintaining treatment for at least 2 years [22]. A French study found that 29.8% of the adult population (15,388,419 individuals) used proton pump inhibitors (PPIs) in 2015, with a mean treatment duration of 40.9 days and 4.1% of users receiving continuous therapy for over 6 months. Notably, 53.5% of new PPI users received the medication as a co-prescription with NSAIDs, despite 79.7% of these patients not having a measurable risk factor supporting this practice [23]. PPIs may have unintended effects on stomach bacteria and fungi, potentially contributing to side effects, by altering their environment and targeting their proton pumps [24].PPIs may increase bacterial infection risk in cirrhotic patients by promoting intestinal overgrowth, but a study found that liver disease stage, not PPI use, was the main factor determining infection risk. Increased intestinal permeability may also contribute to infection risk in these patients [25]. It can temporarily inhibit Helicobacter pylori growth, alter its morphology, and affect urease test results, leading to false-negative diagnoses. Stopping PPIs at least 12 days before testing can help restore bacterial viability and accuracy of diagnostic tests, according to an in vitro study [26]. Based on a review, it increases susceptibility to enteric infections by altering gastric pH, promoting bacterial growth, and impairing immune function. Mentioned systematic review found that PPI use is associated with a higher risk of infections from Salmonella, Campylobacter, and Clostridium difficile, with adjusted relative risk ranges of 4.2-8.3, 3.5-11.7, and 1.2-5.0, respectively [27]. But this relationship might be conditional. A study of 116 cirrhotic patients with ascites found no significant link between PPI use and spontaneous bacterial peritonitis. Despite PPIs potentially increasing bacterial colonization, the risk of infection was not higher in PPI users, suggesting other factors may play a more significant role [28].

The PPI effects on oral–gut microbiome axis

Several studies have found that taking PPIs can alter the balance of gut bacteria. For example, Xiao et al. found that taking PPIs for just seven days increased the amount of Streptococcus bacteria in the gut, which was likely coming from the mouth. In their study of healthy adults, researchers found that taking PPIs for just seven days increased the amount of Streptococcus bacteria in the gut, and that this bacterium was likely coming from the mouth. They also found that using a mouthwash while taking PPIs reduced the number of oral bacteria that made it into the gut [29]. Zhu et al. found that PPIs had a stronger impact on the balance of gut bacteria than histamine-2 receptor antagonists (H2RAs), another type of acid-reducing medication. They found that taking PPIs for just seven days led to a greater transfer of oral bacteria into the gut, including species that have been linked to certain diseases. This altered the balance of gut bacteria, with PPIs having a more pronounced effect than H2Ras [30]. Lee et al. found that taking PPIs along with antibiotics increased the risk of carbapenem-resistant Enterobacteriaceae (CRE) colonization in the gut microbiome. This increased the risk of CRE colonization, a serious health threat. The alteration of gut bacteria by PPIs has been linked to an increased risk of various diseases [31]. For example, He et al. found that taking PPIs may increase the risk of developing

insulin resistance and elevated blood sugar levels [32]. Schumacher et al. found that PPIs may increase the risk of Clostridioides difficile (C. difficile) infections by altering the pH in the gut. In their study of 200 patients in China, they discovered that PPI use was associated with changes in the balance of gut bacteria and bile acids, which may contribute to these negative effects. Specifically, PPI users had higher levels of certain bacteria, such as Fusobacterium, and bile acids, such as taurochenodeoxycholic acid, which were linked to higher blood sugar levels and insulin resistance [33]. Kim et al. found that taking PPIs can alter the balance of gut bacteria in patients with rheumatoid arthritis (RA), potentially leading to negative effects [34]. Tomita et al. found that taking PPIs can reduce the effectiveness of immune checkpoint blockade (ICB) therapy in lung cancer patients, but that treatment with Clostridium butyricum (CBM588) can restore the efficacy of ICB [35].

PPIs have also been found to have a significant impact on specific populations, such as infants and young children. Brusselaers et al. found that taking PPIs for a long time can alter the balance of gut bacteria in infants, particularly those with esophageal atresia [36]. Levy et al. found that taking PPIs can alter the balance of gut bacteria in young children, leading to a range of negative effects on their health [37].

On the other hand, Schumacher et al. found that PPIs may increase the risk of Clostridioides difficile (C. difficile) infections by altering the pH in the gut, rather than by directly affecting the balance of gut bacteria. In a laboratory study using a bioreactor model, Schumacher et al. saw that changes in pH had a significant impact on the growth of C. difficile, while treatment with the PPI omeprazole alone had no effect. This suggests that the increased risk of C. difficile infections associated with PPI use is likely due to the changes in gut pH caused by the medication, rather than a direct interaction between the PPI and the gut microbiome [38]. But, there was another evidence against PPI that showed an increased risk of death in patients with Clostridioides difficile infection (CDI) when using PPIs for a long time. Lin et al. found that daily PPI use was an independent risk factor for mortality in patients with CDI [39]. Some studies have compared the impact of PPIs with other medications on the gut microbiome. Tanigawa et al. found that the mucoprotective drug rebamipide can help protect against small intestinal damage caused by non-steroidal anti-inflammatory drugs (NSAIDs) by modulating the small intestinal microbiota. In contrast, PPIs were found to exacerbate NSAID-induced damage [40].

Conclusion

The cumulative evidence from this review unequivocally demonstrates that proton pump inhibitors (PPIs) have a profound impact on the gut microbiome, leading to a cascade of deleterious effects on human health. The alterations in the balance of gut bacteria, pH, and bile acids induced by PPIs can increase the risk of various diseases, including Clostridioides difficile infections, insulin resistance, and elevated blood sugar levels. Moreover, the negative effects of PPIs on the gut microbiome are not limited to specific populations, but rather have far-reaching consequences for individuals across the lifespan, from infants to adults.

The findings of this review have significant implications for clinical practice, showing the need for a more judicious and cautious approach to PPI use. Clinicians should carefully weigh the benefits of PPIs against the potential risks, particularly in patients with underlying health conditions or those who are already vulnerable to microbiome disruptions. Furthermore, the development of novel therapeutic strategies that mitigate the adverse effects of PPIs on the gut microbiome is imperative.

The intricate relationships between the gut microbiome, PPIs, and human health underscore the importance of a holistic approach to disease prevention and treatment. The gut microbiome is a critical component of our overall health, and its dysregulation can have far-reaching

consequences. As such, it is essential to prioritize the preservation and restoration of a healthy gut microbiome through evidence-based interventions, including dietary modifications, probiotics, and prebiotics.

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Tables & Figures