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Review Article

Proton pump inhibitors and their relationship with the gastrointestinal microbiota: Do the benefits outweigh the risks?

Inibidores da bomba de prótons e sua relação com a microbiota gastrointestinal: O benefício compensa o risco?

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ABSTRACT: Background: This study aimed to investigate the impact of prolonged exposure to PPIs on the gastrointestinal microbiota, as well as to assess its potential implication on the development of gastrointestinal diseases. Methods: This literature review was based on the "National Library of Medicine" (PubMed) research platform, using the descriptors (intestinal microbiota OR gastrointestinal microbiomes OR gut microbiota OR gastrointestinal flora) AND (Proton pump inhibitors OR PPIs). The applied filters for work selection were: published within the last 5 years; written in Portuguese, English, or Spanish; excluding systematic reviews and meta-analyses. Results: Recent studies have revealed a series of alterations in the gastrointestinal microbiota, which have been associated with the exacerbation of pre-existing pathologies or the onset of new conditions. Prolonged use of PPIs has shown considerable impacts on the quantity of gastrointestinal microorganisms such as *Streptococcus, Lactobacillus, Bacteroidetes, Veillonellaceae*, among others. In addition, an increased incidence of diseases such as hepatic encephalopathy, gastroesophageal reflux disease (GERD), cirrhosis, spontaneous bacterial peritonitis, and intestinal infections have been found. Conclusion: The results showed that the dysbiosis triggered by chronic use of PPIs leads to an increased risk of gastrointestinal diseases. Therefore, it is crucial to adopt a rational prescription of these drugs, carefully considering the risks and benefits to ensure safe and effective use in clinical practice. Furthermore, there is a need for further research to define possible risk groups related to chronic use of PPIs, such as patients with hepatic cirrhosis or hepatitis B.

KEY WORDS: Proton pump inhibitor; PPI; Omeprazole; Microbiota; Microbiome; Gatrointestinal Microbiota; Dysbiosis.

RESUMO: Objetivo: Este estudo teve como propósito investigar o impacto da exposição prolongada de IBP sobre a microbiota gastrointestinal, bem como avaliar esta possível implicação sobre o desenvolvimento de doenças do TGI. Métodos: Esta revisão bibliográfica teve como base de dados a plataforma de pesquisa "National Library of Medicine (Pubmed)", na qual foram utilizados os descritores (intestinal microbiota OR gastrointestinal microbiomes OR gut microbiota OR gastrointestinal flora) AND (Inhibitors proton pump OR proton pump inhibitors). Os filtros aplicados para a seleção dos trabalhos foram: publicados nos últimos 5 anos; escritos em português, inglês ou espanhol; excluindo revisões sistemáticas e meta-análises. Resultados: Estudos recentes têm revelado uma série de alterações na microbiota gastrointestinal, as quais têm sido associadas ao agravamento de patologias pré-existentes ou ao desencadeamento de novas. O uso prolongado de IBPs demonstrou impactos consideráveis na quantidade de microorganismos do TGI como *Streptococcus*, *Lactobacillus*, *Bacteriodetes*, *Veillonellaceae,* entre outros. Bem como um aumento da incidência de doenças como encefalopatia hepática, doença do refluxo gastroesofágico (DRGE), cirrose hepática, peritonite bacteriana espontânea e infecções intestinais. Conclusão: Os resultados mostraram que a disbiose desencadeada pelo uso crônico de IBP acarreta no aumento do risco de doenças no TGI. Diante disso, é crucial adotar uma prescrição racional dessas drogas considerando cuidadosamente os riscos e benefícios para garantir um uso seguro e eficaz na prática clínica. Além da necessidade de continuação de mais pesquisas para definir possíveis grupos de risco relacionados ao uso crônico de IBPs, como pacientes com cirrose hepática ou hepatite B.

PALAVRAS CHAVES: Inibidor da bomba de prótons; IBP; Omeprazol; Microbiota; Microbioma; Microbiota gastrointestinal; Disbiose.

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INTRODUCTION

Over the last 30 years, proton pump inhibitors (PPIs) have established themselves as a highly effective treatment for reducing acidity in the gastrointestinal tract. However, studies indicate a gap in knowledge among health professionals regarding the drug's mechanism of action and its consequences, resulting in indiscriminate prescriptions. A study carried out in China in 2019 revealed that the PPI usage rate among doctors was 50.85%[1]. Therefore, research into the appropriate use of this therapeutic class is crucial for advancing and improving clinical practice.

The mechanism of action of PPIs consists in blocking H^+/K^+- ATP located in the parietal cell canaliculi of the stomach in a specific and non-competitive manner, potentially inhibiting basal acid secretion stimulated by a meal[2]. Therefore, PPI is mainly indicated in cases of maintenance therapy with aspirin (34.8% of indications), gastroesophageal reflux (25.3%), gastroduodenitis (13.2%) and peptic ulcers (10%). Importantly, published clinical guidelines rarely recommend PPI use for more than 8-12 weeks[3].

Chronic treatment with PPIs results in an increase in gastrin levels and subsequent hyperplasia of gastric ECL cells resulting in a transient hypersecretion of HCl, an effect called "rebound hypersecretion". One of the important roles of gastric acid is the inactivation of external pathogenic bacteria due to its acidity, so it is believed that the reduction of this acid alters the microbial community, causing dysbiosis[4].

Dysbiosis is defined as the change in the composition and function of the microbiota when it is unable to return to its normal state after being subjected to environmental or host changes. According to Koch's postulate, it consists of a state of microbial community composed of disease-causing agents in the absence of a healthy host[5].

The human microbiota colonizes a wide variety of habitats throughout the body, including the mouth, nasal cavity, throat, stomach, intestine, and urogenital tract. These microorganisms (MOs) establish a mutualistic relationship with the host, playing a crucial role in maintaining human health[6].

Thus, prolonged use of PPIs can lead to changes in the gastrointestinal microbiota, such as changes in its composition, unregulated growth of bacteria and translocation of oral bacteria to distal parts of the intestine. Therefore, there is an increased risk of enteric infections, bloating, flatulence, abdominal pain, changes in stool frequency and poor absorption of vitamin B12, in addition to interfering with the metabolization of other drugs by enzymatically transforming the drug structure, altering its bioavailability[7].

Therefore, this study aimed to investigate the impact of prolonged PPI exposure on the gastrointestinal microbiota, as well as evaluate this possible implication on the development of GIT diseases.

PROPOSED METHOD

This work was conducted on a bibliographical review which used the "National Library of Medicine (Pubmed)" research platform as a database. The search used the following descriptors: (intestinal microbiota OR gastrointestinal microbiomes OR gut microbiota OR gastrointestinal flora) AND (Proton pump inhibitors OR proton pump inhibitors). The filters applied to select the works were: published in the last 5 years, and written in Portuguese, English or Spanish.

The exclusion criteria applied to the results were: publications in the format of systematic reviews and meta-analyses, in addition to works which did not present the relationships between PPI x Microbiota or PPI x Diseases.

After performing the search and applying the filtering criteria, the resulting sample consisted of 185 articles. The articles were initially excluded based on the analysis of the titles, then through an evaluation of the abstracts, and finally through a complete reading of the articles. This screening process was conducted to ensure selecting the most relevant studies which suited the research objectives.

Studies which addressed the imbalance of microorganisms resulting from prolonged use of PPIs were reviewed, and these affected MOs were recorded in a table. Next, the works that discussed the relationship between diseases and each of these MOs were analyzed. A correlation was then made between the microorganisms unbalanced by the use of PPIs and the diseases associated with each of them.

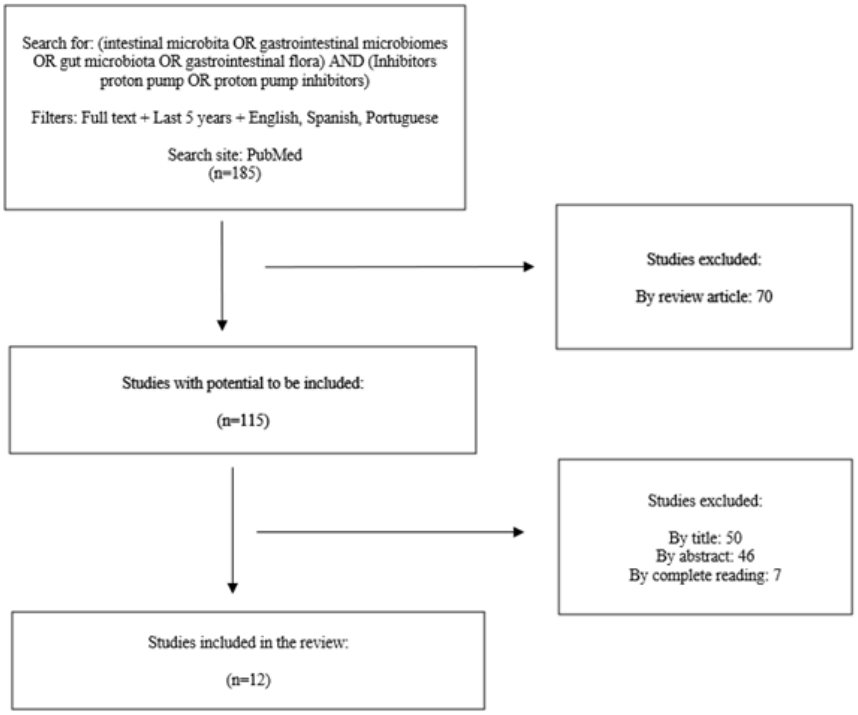

Figure 1- Presents the flowchart of the methodology used in this study

RESULTS

Table 1 summarizes the changes observed in the composition of the gastrointestinal microbiota of patients using PPIs, relating these changes to different pathological conditions. Thus, the information gathered in the studies examined can be seen below.

Table 1 - Changes found in the intestinal microbiota of patients using PPIs and relationship with pathologies based on selected studies

0	MICROORGANISMS	DISEASES	REFERENCES
INCREASE	*Streptococcus*	Reflux esophagitis	8
		Bacterial translocation	8
		Hepatical cirrhosis	9
		Hepatic encephalopathy	9
		Spontaneous bacterial peritonitis	9
		GERD	10
		Worsening of hepatitis C in liver cirrhosis	11
	Lactobacillus	Reflux esophagitis	8
		Hepatic cirrhosis	9
		Hepatic encephalopathy	9
		Spontaneous bacterial peritonitis	9
		GERD	10
	Bacteriodetes	Hepatic cirrhosis	9
		Hepatic encephalopathy	9
		Spontaneous bacterial peritonitis	9
		GERD	10
	Ruminococcus	Hepatic cirrhosis	9
		Hepatic encephalopathy	9
		Spontaneous bacterial peritonitis	9
		GERD	9
	Haemophilus spp	Hepatic cirrhosis	9
		Hepatic encephalopathy	9
		Spontaneous bacterial peritonitis	9
		Worsening of hepatitis C in liver cirrhosis	11
	Selenomonas	Hepatic cirrhosis	9
		Hepatic encephalopathy	9
		Spontaneous bacterial peritonitis	9
	Campylobacter	Hepatic cirrhosis	9
		Hepatic encephalopathy	9
	Enterococcaceae	GERD	10
		Fatty liver disease	12
	Micrococcaceae	GERD	10
	Flavobacteriaceae	GERD	10
	Sutterellaceae	Hepatic cirrhosis	10
	Enterobacter spp	Worsening of hepatitis C in liver cirrhosis	11
DECREASE	*Faecalibacterium*	Ulcerative colitis	13
		Crohn's disease	13
		Inflammatory bowel diseases	13
	Ruminococcus	Hepatic cirrhosis	9
		Hepatic encephalopathy	9
		Spontaneous bacterial peritonitis	9
	Firmicutes	Hepatic cirrhosis	14
		Hepatic encephalopathy	14
		Spontaneous bacterial peritonitis	9
	Bacteroides	GERD	10

DISCUSSION

Given the results presented, we can firstly observe changes in the gastrointestinal microbiota that have already been well described in the literature. For example, the evident increase in predominantly oral bacteria, including *Streptococcus*, *Lactobacillus*, *Rothia*, *Stomatobaculum*[15]. In addition, a significant decrease in beneficial genera such as *Faecalibacterium*, *Ruminococcus*, and *Firmicutes*,[9] and a reduction in Alpha diversity, bacterial overgrowth in the small intestine and manifestations of oral bacteria in more distal parts of the intestine were also observed[11].

An increased presence of *S. salivarius* and *S. oralis* bacteria in the intestine was reported in the work of Hojo et al., usually found as commensals in the oral cavity. These findings reiterate the hypothesis of bacterial translocation associated with prolonged PPI use, increasing the risk of bacterial peritonitis in cirrhotic patients with ascites or cryptogenic liver abscess, which may progress to sepsis[8].

Patients with liver cirrhosis who take PPIs are at increased risk of developing spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy (HE). It is believed that this occurs due to a possible alteration of the acid barrier in the stomach caused by an increase in pH, which can lead to changes in intestinal immunity and excessive growth of bacteria, making patients more vulnerable[9]. Additionally, studies conducted by Fasullo et al.[16] indicate that cirrhotic patients who use PPIs for long periods tend to have more severe HE, resulting in longer hospitalizations, often in intensive care units.

Furthermore, prolonged use of PPIs in cirrhosis patients with chronic hepatitis C caused by HCV may increase the risk of infections through alteration of the microbiota.[13] Therefore, due to so many outcomes suffered by cirrhotic patients, it is concluded that they can be considered a possible risk group for prolonged use of PPIs.

Another aspect of great relevance is that the chronic use of PPIs in patients with GERD may be associated with an increase in esophageal adenocarcinoma incidence. The main theory suggests that prolonged use of these medications leads to atrophy of acid-secreting cells, resulting in a more alkaline secretion. This can trigger lesions, epithelial changes, and consequently development of esophageal adenocarcinoma[17,18,19]. An increase in esophageal squamous cell carcinoma is also noted less prominently in most indications for PPIs, not only restricted to at-risk groups[17, 18].

Decreased gastric acid production can also cause enteric bacterial overgrowth, producing nitrites and N-nitroso compounds, potentially carcinogenic substances. Thus, Wey. et al. shows that long-term PPI use has been linked to microscopic colitis, being associated with a greater risk of colorectal cancer due to chronic inflammation[19].

Moreover, adverse effects related to prolonged PPI use have been documented, such as decreased bone metabolism, increased risk of bone fractures, pneumonia, iron deficiency anemia and deficiencies in molecules such as magnesium and vitamin B12[15].

Given the wide range of evidence pointing to changes in the composition and quantity of microorganisms in the gastrointestinal microbiota, along with signs of adverse outcomes associated with long-term use of PPIs, a number of studies have been undertaken to explore alternative therapies, including the use of probiotics. Hojo, M. et al. highlight synbiotic interventions with the potential to mitigate the adverse effects of long-term PPI therapy in cirrhotic and healthy liver patients[8].

Additionally, Horvath et al. conducted a therapeutic study in patients on long-term PPI therapy evaluating the effects of a 3-month intervention with a multispecies synbiotic. The study explored several parameters, including intestinal barrier function, intestinal microbiota composition, routine laboratory results, intestinal inflammation and quality of life. As a result, a reduction in the abundance of *Stomatobaculum* and an increase in *Bacillus* in the microbiota was observed during the intervention. Furthermore, there were significant increases in albumin, alkaline phosphatase, and thrombocyte count levels, along with a considerable reduction in aspartate transaminase levels. These changes resulted in significant improvements in gastrointestinal quality of life[15].

The evidence brought by these works suggests a promising future in the development of complementary therapies, focused on modulating the gastrointestinal microbiota for patients on long-term therapy with PPIs. However, more research is needed to optimize the dosage and duration of the intervention.

CONCLUSION

Given the above, it can be concluded that a series of changes in the gastrointestinal microbiota attributed to the prolonged use of PPIs were observed, including an increase in the incidence of some GIT diseases.

It was also observed that there are specific risk groups in which the prescription of PPIs is not advisable, such as patients with liver cirrhosis or hepatitis B. However, there are situations in which the benefits of omeprazole outweigh the risks. In some cases, such as GERD, it is important to highlight that excessive use of PPIs can result in a worsening of the initial condition due to changes in the gastrointestinal microbiota.

Therefore, it is crucial to adopt a rational prescription of these drugs which carefully consider the risks and benefits in each case to ensure safe and effective use in clinical practice. In addition, there is a need for further research to better define possible risk groups and pathologies related to the chronic use of PPIs.

Authors' participation: Aline Namie Tanimaru (main author): responsible for preparing the work, analyzing and selecting articles for the systematic review, data collection, writing the work, approving the final manuscript and publishing the article.
Anderson Benegas Mendes (co-author): responsible for collaborating on data collection, writing the work, critical review of the work, approval of the final manuscript and publication of the article. Danilo de Ferreira Mello Saragiotto (co-author): responsible for assistance in preparing the project, critical review of the work, approval of the final manuscript and publication of the article. Fabiana Gonzalez Mendes (supervisor):

responsible for suggesting the theme, creating the body of the project, corrections and continuous monitoring of the writing until its final version. Celine de Furtado Carvalho (co-supervisor): helped in idealizing the proposed theme, in the search within the Pubmed platform, in preparing the body of work and in the approval of the final version for publication. All authors declare that they have had sufficient participation in the work to assume responsibility for the entire content.

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