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Systematic Review

Analysis of the Side Effects of Long-Term Proton Pump Inhibitor (PPI) Use in Patients with Gastroesophageal Reflux Disease (GERD)

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ABSTRACT

Background: Proton Pump Inhibitors (PPIs) are widely prescribed to manage gastrointestinal disorders, especially gastroesophageal reflux disease (GERD). However, long-term PPI use has been linked to serious side effects and potential complications. **Objective:** This study aims to analyze the side effects associated with prolonged PPI use in patients with GERD. **Methods:** A systematic review was conducted using Google Scholar and PubMed databases with relevant keywords. Article selection was carried out carefully based on inclusion and exclusion criteria to ensure the quality and relevance of the data. Additionally, a bibliometric analysis was performed to explore research trends related to the long-term use of PPIs. **Results:** The review found that prolonged PPI use is associated with various adverse effects, including an increased risk of dementia, progression of chronic kidney disease (CKD), gastric cancer, bone fractures, Frailty Syndrome, hypomagnesemia, iron deficiency, vitamin B12 deficiency, myocardial infarction, and esophageal cancer. The bibliometric analysis also indicated a growing trend of research focusing on the safety and complications of long-term PPI use. **Conclusion:** Long-term PPI therapy carries significant risks. Therefore, regular monitoring and appropriate discontinuation strategies are essential when using PPIs over extended periods to minimize potential harm.
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Introduction

Gastrointestinal disorders caused by the reflux of hydrochloric acid (HCl) into the esophagus are known as Gastroesophageal Reflux Disease (GERD)[1]. This condition can lead to clinical symptoms and complications, potentially decreasing an individual's quality of life[2]. In North America, the prevalence of GERD ranges from 18.1% to 27.8%, while in Europe it ranges from 8.8% to 25.9%, in East Asia from 2.5% to 7.8%, in the Middle East from 8.7% to 33.1%, in Australia it reaches 11.6%, and in the United States, it is about 23%[3]. Based on a study conducted in 2017, the prevalence of GERD in Indonesia was reported to be 57.6%, with risk factors including age over 50 years, male gender, and obesity[4].

GERD is known to be caused by poor lifestyle habits[5]. Proper management of GERD is essential, as it can disrupt the function of the digestive system and even increase the risk of esophageal cancer[2]. Several pharmacological therapies are available to manage GERD, including antacids, cisapride, H2 receptor antagonists, proton pump inhibitors (PPI), and combination therapies[6].

PPIs are recognized as the most effective medical therapy for treating GERD due to their ability to deeply and consistently suppress gastric acid production[3]. PPIs work by reducing the amount of acid secreted from parietal cells into the gastric lumen[1], making them the most effective medical therapy compared to other pharmacological treatments in controlling the symptoms of various phenotypic presentations of GERD[3].

In the context of long-term therapy, special attention should be given to the side effects of PPIs consumed by GERD patients. Many reports have documented the long-term side effects of PPI use, one of which is gastric cancer[7]. Given the increasing number of reports on the serious side effects associated with long-term PPI use, it is necessary to conduct studies that compile all reports related to these adverse effects, so that the risks and use of PPIs can be more carefully considered in order to maintain the quality of life of the population.

This article aims to examine the long-term side effects of PPI use in the pharmacological management of GERD. By understanding the side effect profile of PPIs, it is hoped that healthcare providers and the public can make better-informed treatment decisions, improve patient adherence to therapy, and minimize the negative impact of side effects on patients' quality of life.

Materials and Methods

Research Design

This study was designed as a systematic review aimed at reviewing and analyzing the side effects of long-term pharmacological Proton Pump Inhibitor (PPI) therapy in patients with Gastroesophageal Reflux Disease (GERD) as reported in the literature. The study focused on the population of patients diagnosed with GERD who underwent long-term PPI pharmacological therapy, with the objective of identifying the side effects associated with prolonged PPI use in these patients.

Sample

The sample in this study consisted of relevant research articles and scientific publications obtained from databases such as PubMed and Google Scholar using the Publish or Perish software. Keywords used in the search included "Side Effect," "Long Term Care," "Gastroesophageal Reflux Disease (GERD)," "Drug Therapy," "Proton Pump Inhibitor," as well as other related terms in both English and Indonesian that focused on the side effects of long-term PPI therapy.

Table 1. PICO *Framework*

PICO Framework	Description
Population	Patients with GERD
Intervention	Long-term pharmacological PPI therapy
Comparison	-
Outcome	Side effects of long-term PPI therapy in GERD patients

Data Collection Techniques

Data were collected based on inclusion and exclusion criteria. The inclusion criteria were research articles published within the last 10 years (2014–2024), including research articles, clinical trials, cohort studies, and Randomized Controlled Trials (RCTs), written in English or Indonesian, and involving adult patients (>18 years old) who were on long-term PPI pharmacological therapy. The exclusion criteria included articles that were not relevant to the topic of the study. The search process initially identified 341 articles. After a thorough screening based on the predetermined inclusion criteria, 10 relevant articles were selected and analyzed in this review. All selected articles focused on patients diagnosed with GERD.

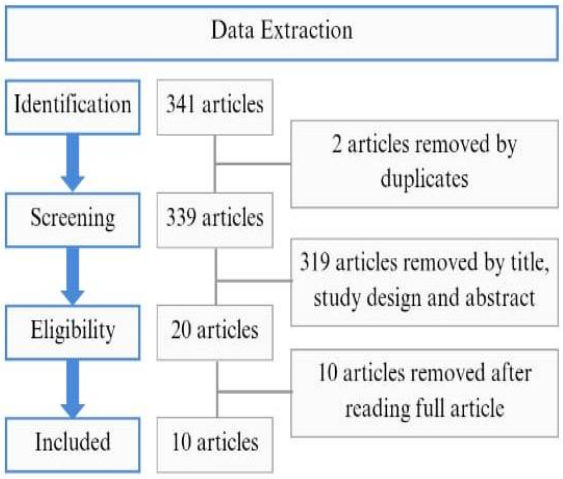

Figure 1. Data Extraction

Data Analysis Techniques

Data analysis was performed using bibliometric analysis to describe the research trends and topic development. The bibliographic data were collected using the Publish or Perish software, applying the keyword "Proton Pump Inhibitor" within the time range of 2014–2024. Data visualization was conducted using VOSviewer software to generate network visualization, density visualization, and overlay visualization, each offering a different perspective in data interpretation.

Ethical Consideration

This study used secondary data in the form of published research articles and did not involve human subjects directly. Therefore, ethical approval was not required. However, the study adhered to ethical standards by ensuring all sources were properly cited and that the literature review was conducted objectively and responsibly.

Results

The results of the studies that have been reported indicate that the use of Proton Pump Inhibitors (PPIs) is associated with various diseases caused by the long-term side effects of PPI use. Several studies have identified underlying mechanisms linking PPI use to these adverse effects. However, the currently reported mechanisms remain limited, highlighting the need for further research to better understand the pathways and processes behind the long-term side effects in PPI users.

Table 2. Systematic Review Results

Author	Title	Method	Result
Tai et al., 2017[8]	Risk of dementia from proton pump inhibitor use in Asian population: A nationwide cohort study in Taiwan	Cohort study involving 15,728 patients aged 40 years or older without dementia based on the National Health Insurance Research Database (NHIRD) in Taiwan. The study compared PPI users and non-users over a 3-year period.	PPI use in the Asian population is associated with a high risk of dementia, and cumulative PPI use is significantly linked to dementia.
Xie et al., 2016[9]	Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD	Cohort study involving 20,270 H2 blocker users and 173,321 PPI users based on the U.S. Department of Veterans Affairs national database, studied over 5 years.	PPI use is associated with an increased risk of incident CKD, CKD progression, and ESRD.
Peng et al., 2019[10]	Association between proton pump inhibitors use and risk of gastric cancer in patients with GERD	Case-control study using a sub-dataset from the National Health Insurance Research Database (NHIRD) in Taiwan involving 2,122 samples from 1996 to 2011.	PPI use is associated with an increased risk of gastric cancer in GERD patients.
Jo et al., 2015[11]	A Proton Pump Inhibitor's Effect on Bone Metabolism Mediated by Osteoclast Action in Old Age: A Prospective Randomized Study	Randomized Controlled Trial (RCT) in two groups receiving pantoprazole and revaprazan, each consisting of 13 patients, with various bone parameters measured	In the elderly, 8 weeks of PPI administration altered bone parameters, indicating that PPI can directly affect bone metabolism through vacuolar H^+ -ATPase in osteoclasts.

Author	Title	Method	Result
		before and after 8 weeks of treatment.	
Dewi et al., 2016[12]	The Effect of Long-Term Proton Pump Inhibitor Use on Frailty Syndrome in Elderly Patients	Consecutive subject selection from medical records, with the case group consisting of frail patients aged ≥60 years and the control group of non-frail patients.	Long-term PPI use increases the risk of frailty syndrome by 1.83 times compared to patients who do not use PPIs.
Shah & Sachdeva, 2014[13]	Association of Proton Pump Inhibitor with Hypomagnesaemia: A Cross-Sectional Study at a Tertiary Care Hospital of Anand District.	Cross-sectional study at a Tertiary Care Hospital involving 60 patients divided into PPI users and non-users.	Serum magnesium levels were significantly lower in patients receiving PPI therapy compared to those not using PPIs.
Lam et al., 2017[14]	Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use and Iron Deficiency	Case-control study at Kaiser Permanente, Northern California (KPNC) health care system involving 77,046 patients over a 14-year period.	PPI use for 2 years is associated with an increased risk of subsequent iron deficiency. The risk increases with the degree of acid suppression and decreases after discontinuation of therapy.
Mumtaz et al., 2022[15]	Association of Vitamin B12 deficiency with long-term PPIs use: A cohort study	Cohort study at the Department of Internal Medicine, KRL Hospital in Islamabad, Pakistan, involving 1,225 participants from May 2021 to May 2022.	Long-term PPI use is associated with an increased risk of vitamin B12 deficiency.
Shah et al., 2015[16]	Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population	Cohort study using data from Stanford University involving 1.8 million patients and Practice Fusion, Inc involving 1.1 million patients.	PPI use is associated with an increased risk of myocardial infarction (MI) in GERD patients.
Brusselaers et al., 2018[17]	Maintenance proton pump inhibition therapy and risk of oesophageal cancer	Population-based cohort study involving 796,492 adults exposed to maintenance PPI therapy in Sweden from 2005 to 2012.	Long-term PPI use is associated with an increased risk of esophageal adenocarcinoma, even in the absence of other risk factors.

Discussion

Analisis Bibliometrik "Proton Pump Inhibitor"

Bibliometric analysis is a method aimed at measuring scientific publications as well as studying patterns and trends in scientific literature[18]. By using mapping analysis with VOSviewer, researchers can identify the development of research on "Proton Pump Inhibitor" in relation to other topics. VOSviewer presents three types of visualizations: network visualization, overlay visualization, and density visualization[19].

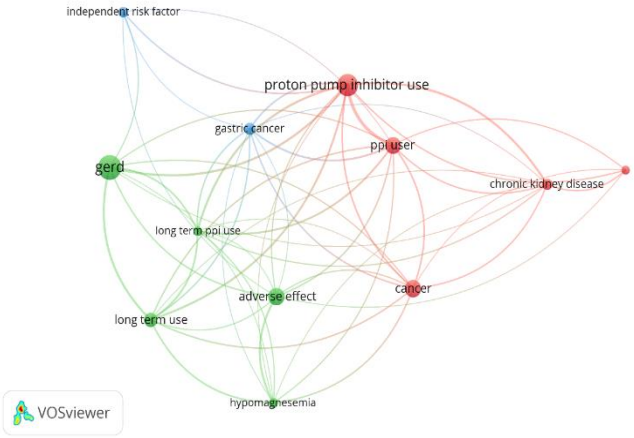

Figure 2. Network Visualization

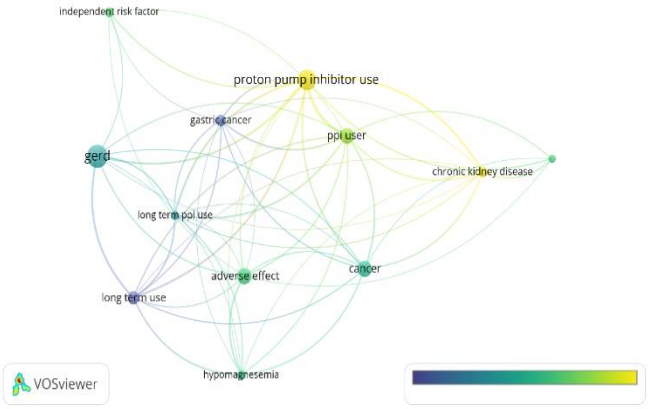

Figure 3. Overlay Visualization

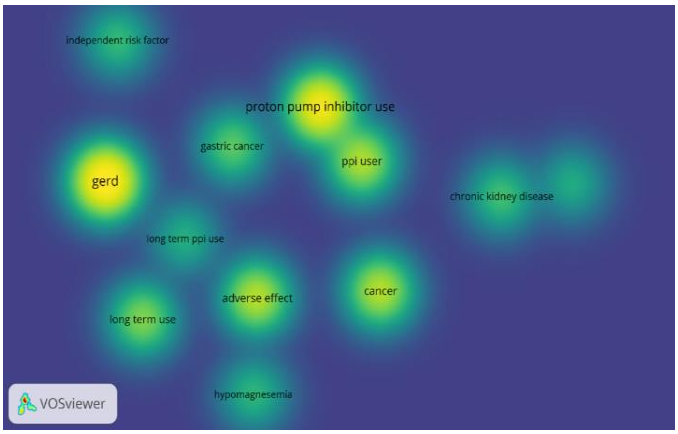

Figure 4. Density Visualization

Based on the results of the network visualization mapping, several clusters were identified, each marked with different colors and interconnected through their respective keywords. Cluster one is marked in red, cluster two in green, and cluster three in blue. The determination of clusters and the size of the circles are based on the frequency of keyword occurrences. The more frequently a keyword appears, the larger the size of the circle[18]. Based on the mapping results, topics such as independent risk factor, gastric cancer, long-term PPI use, long-term use, hypomagnesemia, chronic kidney disease, and acute kidney injury are areas that have not been extensively researched, while topics related to GERD, proton pump inhibitor use, adverse effect, cancer, and PPI user have been widely studied.

Based on the results of the overlay visualization, the findings indicate variations in the years of article publication within the time span of 2014 to 2024, with the highest number of studies conducted in 2023, as indicated by the yellow color. The more yellow a keyword appears, the more recent the research is[18]. The overlay visualization shows that the most recent studies are focused on the topics of proton pump inhibitor use and chronic kidney disease.

The density visualization results illustrate the research topics that have been extensively studied. The brighter the color pigment on a keyword, the more research has been conducted on that topic[18]. The density visualization shows that the topics which have been widely studied include GERD, proton pump inhibitor use, adverse effect, cancer, and PPI user, while topics such as independent risk factor, gastric cancer, long-term PPI use, long-term use, hypomagnesemia, chronic kidney disease, and

acute kidney injury have not been extensively researched.

Pathophysiology of GERD

Gastroesophageal Reflux Disease (GERD) is a pathological condition caused by the reflux of gastric acid into the esophagus, accompanied by various symptoms involving the esophagus, pharynx, larynx, and respiratory tract[20]. GERD can occur due to an imbalance between the aggressive factors and the defensive factors of the esophageal defense system[21]. Aggressive factors include gastric acid, pepsin, bile reflux, and trypsin, while the defensive factors mainly involve the pressure of the Lower Esophageal Sphincter (LES)[20].

Based on the aggressive factors, GERD is caused by an increase in gastric acid, gastric dilation, gastric distension, delayed gastric emptying, as well as elevated intragastric and intra-abdominal pressure[21]. From the perspective of defensive factors, GERD is caused by impaired Lower Esophageal Sphincter (LES) function and disruption of the esophageal clearance mechanism. Under normal physiological conditions, LES pressure decreases during swallowing. This reduction in LES pressure allows for antegrade flow from the esophagus into the stomach. In GERD patients, LES function is impaired, resulting in retrograde flow[6]. Normally, the esophagus has the ability to self-clear gastric refluxate. However, in GERD patients, the esophageal clearance mechanism is compromised, causing prolonged contact of the gastric refluxate with the esophageal lining, thereby increasing the risk of developing esophagitis[21].

Mechanism of Action of Proton Pump Inhibitors (PPIs)

Proton Pump Inhibitors (PPIs) are considered the most effective medical therapy for managing GERD because they can suppress acid secretion efficiently and consistently. The first compound in the PPI class, omeprazole, was introduced in the late 1980s[3], and by 2015, the FDA had approved several PPI drugs, including omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole[22].

The mechanism of action of PPIs involves inhibiting acid production at the final stage of the acid secretion process. This inhibition specifically targets the (H^+ , K^+)-ATPase enzyme of the parietal cells. This enzyme plays a crucial role in the ion exchange within the parietal cells that produces gastric acid (HCl)[23]. PPI drugs are recommended to be taken one hour after meals[24]. This timing is related to their mechanism of action, which inhibits the proton pumps responsible for producing activated HCl[25]. However, with long-term use, PPIs have been associated with an increased risk of side effects such as gastric neoplasia, kidney disease, fracture risk, dementia, liver disease, and nutritional deficiencies[25].

Long-Term Side Effects of Proton Pump Inhibitor (PPI) Use

It is essential to pay attention to the side effects that may arise from the use of PPI drugs, especially during long-term use. PPIs are among the most frequently prescribed classes of medications[26]. They are commonly administered in relation to conditions such as dyspepsia, gastritis, Gastroesophageal Reflux Disease (GERD), esophagitis, as well as for patients receiving acetylsalicylic acid (ASA) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)[12].

Dementia

Long-term use of PPIs has been identified as being associated with an increased risk of dementia among PPI users in Asia. This study indicated that cumulative PPI use is significantly linked to dementia; however, the biological mechanisms underlying the relationship between dementia and PPI use require further investigation[8]. These findings

are consistent with a cohort study conducted in Germany, which also associated PPI use with an increased incidence of dementia. Therefore, avoiding PPI use may contribute to the prevention of dementia[26].

Although the exact mechanism by which PPIs influence dementia is not yet fully understood, several contributing factors have been suggested. These include increased production of amyloid-beta (Aβ) and reduced degradation due to PPI interaction with certain brain enzymes involved in dementia development. Additionally, vitamin B12 deficiency associated with long-term PPI use has been linked to cognitive decline. Chronic exposure of human endothelial cells to PPIs may also accelerate endothelial aging, which can contribute to the development of dementia[8].

However, other studies have shown that PPI use is not associated with an increased risk of dementia. This research suggests that the incidence of dementia is more strongly influenced by factors such as age, depression, diabetes, and stroke. PPI use presents a higher risk of dementia particularly among patients with hypertension, diabetes, and depression[27]. Recent studies have also indicated that in the geriatric population, PPI use is not associated with the incidence of dementia, CIND (Cognitive Impairment, No Dementia), or cognitive decline over time[28]. Research regarding the association between PPI use and dementia remains limited, and further studies are necessary to confirm these findings in order to draw definitive conclusions about the relationship between PPIs and dementia.

Chronic Kidney Disease (CKD)

A study conducted in 2016 demonstrated a link between PPI use and an increased risk of CKD, the progression of CKD, and ESRD[9]. Other researchers also found an association between PPI use and chronic kidney disease. Independent PPI use has been associated with a 20-50% increased risk of developing CKD and Acute Kidney Injury (AKI) in the Atherosclerosis Risk in Communities (ARIC) study[29].

A 2017 study further confirmed the relationship between PPI use and CKD, even in the absence of AKI[30]. CKD is known to result from complex interactions between genetic and environmental factors, where environmental factors can be modified to help reduce the incidence of the disease[31].

The exact mechanism of this association is not yet fully understood, but research indicates a connection between PPI use and acute interstitial nephritis, which is an inflammatory condition of the kidneys. This inflammation increases the risk of kidney damage, characterized by elevated serum creatinine levels and a reduction in estimated glomerular filtration rate (eGFR) by more than 30%, potentially accelerating the decline in kidney function[9].

Gastric Cancer

PPI use has been associated with an increased risk of gastric cancer. A study conducted in 2019 showed a link between gastric cancer and PPI use in patients with GERD[10]. Findings from a large population-based cohort study also indicated that PPI use is associated with a higher risk of gastric cancer compared to the use of H2 receptor antagonists (H2RAs), although the absolute risk remains low[7]. A cohort study conducted in the Swedish population similarly demonstrated that PPI use is linked to an increased risk of gastric and esophageal cancer, with the risk remaining elevated throughout the follow-up period[32].

The risk of gastric cancer associated with PPI use may occur through several mechanisms. The first mechanism is that PPI use can cause hypergastrinemia, which may lead to gastric hyperplasia. The second mechanism is that long-term PPI use can alter the gut microbiome, which has been shown to contribute to the increased risk of gastric

cancer. The third mechanism is that acid suppression by PPI use is associated with atrophic gastritis, which is a major precursor to gastric cancer, although studies reporting this relationship remain limited[7].

Bone Metabolism

Long-term PPI use has also been associated with significant increases in serum calcium and urinary deoxypyridinoline levels, indicating changes in bone metabolism and potentially increasing the risk of fractures, particularly in older adults[11].

In geriatric patients, PPI use is known to impair calcium absorption, which can lead to osteoporosis and fractures[33]. The mechanism by which PPIs affect bone metabolism involves irreversible binding to the (H^+ , K^+)-ATPase in osteoclasts, which can alter osteoclast activity and subsequently impact bone metabolism[11].

Frailty Syndrome

Long-term PPI use has also been reported to significantly increase the risk of Frailty Syndrome by 1.83 times compared to patients who do not use PPIs. Previous studies have shown that prolonged PPI use is associated with hypomagnesemia, vitamin B12 and iron deficiencies, as well as an increased risk of malnutrition, all of which may contribute to the development of frailty syndrome[12].

Hypomagnesemia

Based on a 2014 study, long-term use of PPIs may be associated with subclinical magnesium deficiency, as significantly lower serum magnesium levels were observed in patients receiving PPI therapy compared to those not using PPIs[13]. However, several other studies have indicated that PPI use is not associated with the incidence of hypomagnesemia [34,35]. PPIs may influence hypomagnesemia by reducing serum magnesium levels; some studies suggest that PPIs can affect active magnesium transport channels, such as transient receptor potential melastatin subtype 6 (TRPM6), which is responsible for magnesium absorption in the kidneys and gastrointestinal tract[13].

Iron Deficiency

PPI use for a duration of two years has been associated with an increased risk of iron deficiency. The risk rises with higher acid suppression potency and decreases after discontinuation of the medication. PPIs can cause iron deficiency by suppressing gastric acid production, which is essential for the absorption of non-heme iron. Gastric acid plays a critical role in releasing iron from food particles and converting it from the ferric form to the ferrous form, which is more readily absorbed. By reducing acid production, PPIs can impair iron absorption, potentially leading to iron deficiency[14].

Vitamin B12 Deficiency

According to a 2022 study, long-term PPI use is associated with an increased risk of vitamin B12 deficiency[15]. However, other studies have shown that PPI use for 12 months does not result in clinically significant deficiencies of iron and/or vitamin B12[36]. Additionally, some research has reported no association between PPI use and vitamin B12 deficiency or hyperhomocysteinemia[37].

PPIs may contribute to vitamin B12 deficiency through mechanisms involving malabsorption and bacterial overgrowth in the intestines. Prolonged PPI use can reduce gastric acid secretion, which is essential for proper vitamin B12 absorption[36].

Vitamin B12 acts as a cofactor for two enzymes in humans: methionine synthase (MS) and methylmalonyl-CoA mutase. A deficiency in vitamin B12 can impair the activity of these enzymes, leading to the accumulation of homocysteine (Hcy) and methylmalonic acid (MMA) in higher concentrations in the plasma[38].

Myocardial Infarction (MI)

Based on existing studies, PPI use has been associated with an increased risk of Myocardial Infarction (MI) in patients with GERD. The elevated risk of MI linked to PPI use is thought to be mediated by increased levels of asymmetric dimethylarginine (ADMA) in the body. Research has shown that PPIs can increase ADMA levels in human endothelial cells by approximately 30% and raise serum ADMA levels in mice by about 20%. This increase in ADMA can impair endothelium-dependent vasodilation and reduce nitric oxide production, both of which are associated with an increased risk of MI in the general population[16].

Oseophageal Cancer

A 2018 study also showed that long-term PPI use is associated with an increased risk of esophageal adenocarcinoma, even in the absence of other risk factors[17]. A cohort study conducted in the Swedish population also demonstrated that PPI use is linked to an increased risk of gastric and esophageal cancer, with the risk remaining elevated throughout the follow-up period[32].

The mechanism by which PPIs influence esophageal cancer is related to PPI-induced hypergastrinemia. Hypergastrinemia can stimulate downstream signaling and promote cell proliferation, potentially increasing the risk of esophageal cancer. Additionally, PPI use can cause irreversible binding to the proton pumps of gastric parietal cells, which may lead to long-term changes in gastric pH levels and contribute to the development of esophageal cancer[39].

Given the numerous reported cases of adverse effects associated with long-term PPI use, it is essential to conduct regular monitoring of patients undergoing long-term PPI therapy. This monitoring is crucial for the early detection of potential side effects, which can help prevent the development of complications. According to Randomized Controlled Trial (RCT) studies, it is also necessary to implement strategies for discontinuing PPI use in patients on long-term therapy. These studies suggest that the proportion of patients who successfully discontinue PPIs is likely to be higher when the medication is tapered gradually rather than stopped abruptly[40].

Conclusion

Based on the literature review, Proton Pump Inhibitors (PPIs) are a class of drugs frequently used by patients to address digestive issues, particularly Gastroesophageal Reflux Disease (GERD). However, long-term PPI use has been associated with serious side effects. Several adverse effects have been reported with prolonged PPI use, including an increased risk of dementia, progression of Chronic Kidney Disease (CKD), higher risk of gastric cancer, increased fracture risk, higher risk of Frailty Syndrome, hypomagnesemia, iron deficiency, vitamin B12 deficiency, myocardial infarction, and esophageal cancer.

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