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A Systematic Review on Proton Pump Inhibitor

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ABSTRACT

PPIs, or proton pump inhibitors, are among the most frequently prescribed drugs in the world. The management of gastroesophageal reflux disease and peptic ulcer disease has significantly improved as a result of their use. Although PPIs have an acceptable safety profile, growing evidence raises questions regarding their prolonged usage. A literature search was done to find relevant original and review studies in order to offer a thorough evaluation of the issues with long-term PPI use. Despite the limitations of some studies, the overall body of knowledge strongly points to an elevated risk of nutritional deficits and infectious consequences. Less compelling data exist about any increased risk of colon or stomach cancer. With a large margin of safety, PPIs have revolutionised the treatment of acid-related illnesses and their complications. However, given the data now available, attempts to reduce the dosage or stop using PPIs must be routinely re-evaluated.

Keywords- PPI, Large margin of safety, Acid peptic disorders, H^+ K^+ ATPase, etc.

INTRODUCTION

PPIs are the most effective drugs now on the market for reducing stomach acid output.These effective acid suppressants have rapidly taken on a prominent role in the treatment of acid-peptic disorders since their debut in the late 1980s.Because of their exceptional efficacy and safety, they are now among the most frequently prescribed medications in the world. Global spending on these medications was expected to be around $24 billion in 2006. Even though these medications are deemed safe and their long-term usage has been authorised, some long-term safety concerns have been highlighted. Long-term PPI use has been linked in recent years to potential negative effects, including an increased risk of respiratory infections, infection with Clostridium difficile, and most recently, bone fractures. [1,2]

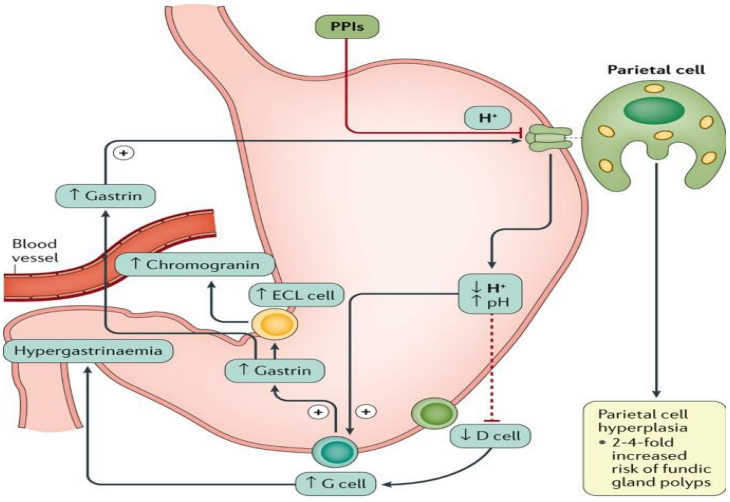
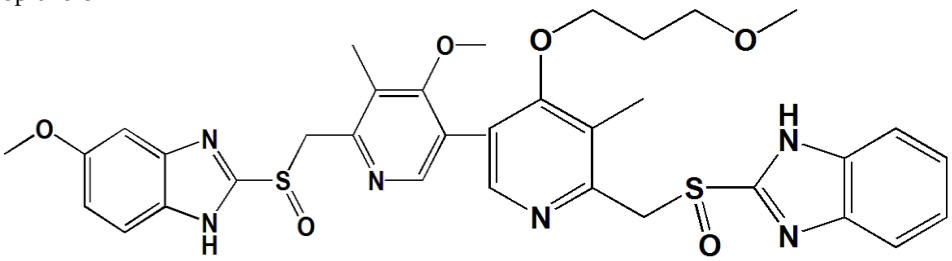


Figure- Mechanism of action of PPI [3]

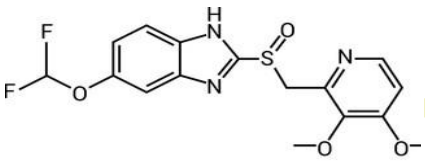
Over the past ten years, proton pump inhibitors have significantly changed how acid-peptic disorders are treated. Three of these medications—omeprazole (on the market since 1989), lansoprazole (1995), and pantoprazole—are currently widely accessible (1997). In several nations, rabeprazole is now also available. The gastric hydrogen/potassium adenosine triphosphatase (H+/K+-exchanging ATPase), a component of the proton pump that completes the last stage of the acid secretory process, is selectively and permanently inhibited by these substances. Thus, regardless of the type of activation of parietal cells, they prevent both basal and stimulated stomach acid release. Peptic ulcer illness, gastro-oesophageal reflux disease, Barrett's oesophagus, Zollinger-Ellison syndrome, and the eradication of Helicobacter pylori as part of combination regimens are among the clinical uses. [4,5]
Examples of PPI-

1. Omeprazole
2. Rabeprazole
3. Pantoprazole
4. Lansoprazole

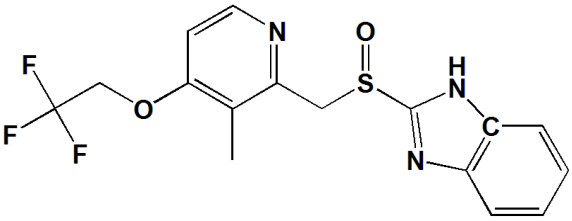


Omeprazole

Rabeprazole



Pantoprazole



Lansoprazole

Pharmacology Of Proton Pump Inhibitors-
PPIs are substituted benzimidazole derivatives that prevent the stomach's parietal cells from producing the proton pump (H/K adenosine triphosphatase). PPIs function by building up in the acid-secreting parietal cell's secretory canaliculus, where they are protonated to their active form, a cationic sulfonamide. The proton pump's sulfhydryl group is then bound by this active form, which then blocks acid secretion into the gastric lumen through irreversible inhibition. Acid secretion is suppressed for a long period of time (24–48 hours), only resuming following the synthesis of new pump molecules. PPIs have a negligible renal clearance and a rapid first-pass and systemic hepatic metabolism by hepatic cytochrome P, notably cytochrome P2C19 and cytochrome P3A4. PPIs are prescribed for a variety of medical issues. [6]

Table 1 Common Clinical Uses of Proton Pump Inhibitors

Clinical Uses of Proton Pump Inhibitors
Gastroesophageal reflux disease
Peptic ulcer disease
Helicobacter pylori eradication
Risk reduction of NSAID-associated gastric ulcer
Non-ulcer dyspepsia
Zollinger-Ellison syndrome

NSAID = nonsteroidal anti-inflammatory drug.

Table- common clinical uses of PPI [7]

Overuse Of Proton Pump Inhibitors-
PPIs' potential for abuse and overuse is a big concern. The overuse of these medications in both inpatient and outpatient settings has been supported by numerous research. It is discovered that 50 to 60 percent of acid-suppressive drug prescriptions given to hospitalised patients lack the necessary justifications. [8-10]

Figure- Overuse of PPI

Clinical Significance-

- PPIs are the most effective drugs now on the market for reducing stomach acid output. Given the extensive usage of PPIs, the long-term safety concerns must be considered.
- The body of knowledge strongly implies an increased risk of dietary deficits and infectious problems.
- Despite having a physiologic theoretical foundation, data on the risk of increased stomach and colon cancer are less convincing.
- PPIs' long-term requirement must constantly be re-evaluated.

Side Effects Of Proton Pump Inhibitors-

PPIs often have few negative effects. Headaches, nausea, pain in the abdomen, constipation, flatulence, and diarrhoea are the most frequent adverse effects. Most of the time, these adverse effects are minor, self-limiting, and unrelated to dosage or age. However, PPI side effects over the long term have recently received more attention. Several studies have examined different side effects that could be related to PPI use over the long run. There is a thorough discussion of these negative effects.

Iron Deficiency-

Dietary iron can be found in food as heme iron or non-heme iron. Gastric acid significantly increases the absorption of dietary non-heme iron. Numerous clinical studies indicate that stomach acid hyposecretion, particularly for an extended length of time, may cause clinically significant iron malabsorption. Patients with achlorhydria15 and different stomach acid-hyposecretory disorders (gastric resection, vagotomy, atrophic gastritis) have been shown to have decreased non-heme iron absorption. Stewart et al16 examined 109 patients with Zollinger-Ellison syndrome who were receiving long-term treatment with stomach antisecretory medications to evaluate iron storage and the development of iron-deficiency anaemia.

Continual use of omeprazole for six years or of any stomach antisecretory medication for ten years did not result in diminished body iron reserves or iron deficiency. The monitoring for iron deficit is not required considering these findings, which indicate that iron insufficiency secondary to decreased stomach acid output is theoretically feasible but has not been clinically established. Zollinger-Ellison syndrome is a rare illness;thus, the findings cannot be generalised to PPI users. There is a need for long-term safety data trials in the average patient population utilising PPIs for more general purposes, such as reflux disease, since the outcomes of such studies cannot be generalised in the absence of such data. [11-14]

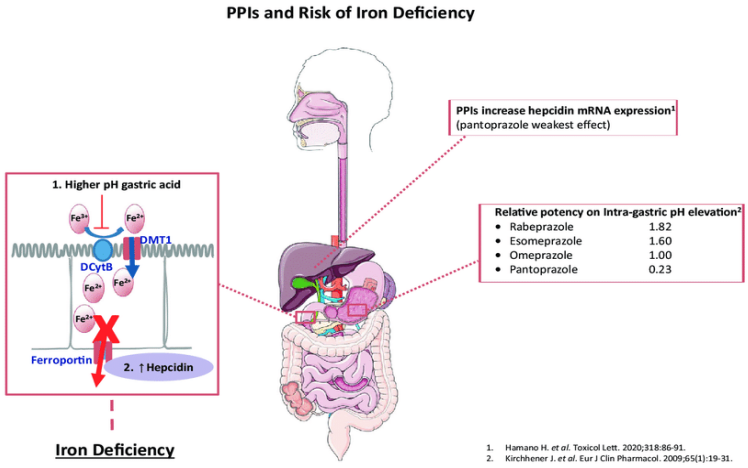


Figure- Risk of iron deficiency

Vitamin B12 Deficiency-

Protein-bound vitamin B12 is often eaten. It must be released from this bound condition by gastric acid in order to attach to the R protein. Through the activity of pancreatic enzymes in the duodenum, the vitamin is separated from the R protein, bound to intrinsic factor, and then absorbed in the small intestine. It has long been understood that taking an H2 blocker reduces the absorption of protein-bound vitamin B12. Initial omeprazole data did not demonstrate this impact; however, subsequent research revealed reduced vitamin B12 absorption with PPI treatment. In one study, subjects taking 20 mg of omeprazole daily experienced a drop in cyanocobalamin absorption from 3.2% to 0.9% (P.031); the effect was significantly more pronounced at larger doses. Serum folate and vitamin B12 levels were assessed in a trial of 131 patients receiving either omeprazole (n111) or histamine H2-receptor antagonists (n20). Omeprazole treatment lasted an average of 4.5 years. Patients receiving omeprazole had significantly (P.03) reduced levels of vitamin B12 but not serum folate. The relationship between B12 deficiency and PPI usage in elderly individuals is also corroborated by numerous case reports that have been published in the past ten years. Recent case-control research, however, looked at 125 long-term (3 years) PPI users who were 65 years of age or older. There were no changes between long-term PPI users and their partners in mean vitamin B12 levels (P.73). Therefore, the authors did not advise routine testing of vitamin B12 levels in elderly patients undergoing PPI medication for an extended period. In more recent times, measurements of homocysteine and methylmalonic acid levels have been utilised to evaluate subclinical cyanocobalamin (vitamin B12) changes that occur before a fall in serum B12 levels. One-third of individuals on long-term PPI therapy were found to have subclinical B12 insufficiency symptoms. Acid suppression along with vitamin B12 insufficiency is noteworthy. Mixed findings have come from studies. Most case series and case-control studies have found evidence to support the link between vitamin B12 insufficiency and PPI use, while some have not. The studies that demonstrate how inhibiting acids affect absorbing vitamin B12 are presented in Table for review. Most of the current data between long-term PPI usage and B12 insufficiency is derived from small, nonrandomized retrospective investigations. The link between PPI usage and B12 insufficiency cannot be conclusively proven until sizable prospective randomised studies are carried out, and routine B12 level monitoring is not advised. [11, 15-20]

Table 2 Studies Performed to Evaluate the B_{12} Deficiency with Acid Inhibition

Author	Study Design	Drug Used	No. of Patients	Duration of Study	Results
Steinberg et al[8]	Case control	Cimetidine	12	Unknown	Reversible malabsorption of protein-bound cobalamin
Koop and Bachem[9]	Case series	Omeprazole	34	2 y	No change in B_{12} levels
Marcuard et al[10]	Case series	Omeprazole	10	2 wk	Decrease cyanocobalamin absorption in dose-dependent manner
Termanini et al[11]	Case series	Omeprazole/ranitidine	131	4.5 y PPI 10 y H2 blockers	Duration of omeprazole treatment inversely correlated with B_{12} levels
den Elzen et al[12]	Case control	PPIs	125	>3 y	No association found
Hirschowitz et al[13]	Case series	Lansoprazole	61	Up to 18 y	10% loss in B_{12} level, 31% subclinical decrease by MMA and HC

MMA = methylmalonic acid; HC = homocysteine; PPI = proton pump inhibitor.

Table- Studies performed to evaluate the B12 deficiency with acid inhibitor [7]

Calcium Deficiency and Risk of Osteoporosis-

It is believed that calcium's solubility is crucial to its absorption. The gastrointestinal tract's acidic environment aids in the release of ionised calcium from insoluble calcium salts. Calcium carbonate dissolves and disintegrates in vitro depending on the pH. Disintegration and dissolution slow as pH rises, dropping from 96% at pH 1 to 23% at pH 6.1. Theoretically, severe hypochlorhydria, especially in the older population, could impair calcium absorption. Studies on both animals and people have suggested that PPI medication may reduce bone density or insoluble calcium absorption. PPIs may also lessen bone resorption by blocking osteoclastic vacuolar H-K-adenosine triphosphatase, according to limited in vitro and clinical studies. The results of these contradicting effects have been the subject of several clinical studies. a crossover, randomised, double-blind, placebo-controlled study. Another substantial case-control study of the Danish population revealed that PPI usage is linked to a higher risk of fracture (odds ratio [OR] 1.45 for hip fracture) compared to H2 blocker use (OR 0.69). Another well-conducted case-control research found that patients who used PPI for more than a year had a higher risk of hip fracture, particularly if they received doses greater than once daily. For hip fracture linked to more than a year of PPI medication, the adjusted OR was 1.44 Patients who received long-term, high-dose PPI prescriptions had a significantly higher risk of hip fracture (adjusted OR, 2.65; P < 001).It is not recommended that all individuals taking long-term PPI therapy undergo an osteoporosis screening. The studies that link PPI to calcium shortage are constrained by their retrospective designs, and the one prospective trial is constrained by its brief (1-week) duration. As a result, the long-term effects of PPI cannot be understood. It is not recommended that all individuals taking long-term PPI therapy undergo an osteoporosis screening. The studies that link PPI to calcium shortage are constrained by their retrospective designs, and the one prospective trial is constrained by its brief (1-week) duration. As a result, the long-term effects of PPI cannot be understood. The current body of evidence does not permit the long-term use of PPIs by patients without osteoporosis screening. However, a better understanding of the effects of PPIs on calcium metabolism is urgently needed due to the rise in the prevalence of both acid-related gastrointestinal diseases and osteoporosis. [21-27]

Risk of Infections-

Loss of the normal stomach acidity has been linked to colonisation of the normally sterile upper gastrointestinal tract. Gastric acidity is a key defensive mechanism against ingested microorganisms. Acid-inhibiting the gastric pH is raised by substances like PPIs and H2-receptor antagonists, and leukocyte function has been linked to PPIs. These elements contribute to the links between an increased risk of respiratory tract infections and enteric infections, including diarrhoea caused by Clostridium difficile that develops in hospitals and nursing homes. Loss of the normal stomach acidity has been linked to colonisation of the normally sterile upper gastrointestinal tract. Gastric acidity is a key defensive mechanism against ingested microorganisms. Gastric pH is raised by acid-suppressing medications like PPIs and H2-receptor antagonists, and leukocyte function has been linked to PPI use. [28-32]

Pneumonia-

In critical care units, H2 blockers and PPIs are frequently utilised as a stress ulcer prevention strategy. Cook et al.45's meta-analysis from 1996 demonstrated that H2 receptor antagonists, such cimetidine and ranitidine combined, are superior than placebo for this therapeutic reason. However, there has always been concern about the rise in pneumonia and other respiratory tract infections, particularly in patients who depend on ventilators. The cytoprotective drug was found to be related with less respiratory tract infections in earlier trials that contrasted sucralfate with H2 blockers. The link between acid suppression and pneumonia, particularly in critically ill patients, was verified by another research. Recently, the use of stress ulcer prophylaxis was questioned. In a Faisy et al. observational research, stress-ulcer prevention had no effect on the rate of clinically significant gastrointestinal bleeding in patients in intensive care units or the cost of its therapy.Significant stress-related upper gastrointestinal bleeding was observed in 1%, 3%, 4%, and 1% of patients assigned to receive omeprazole, famotidine, sucralfate, and placebo, respectively, in a recent randomised, placebo-controlled study of 287 patients with high risk for stress-related upper gastrointestinal haemorrhage (>48 h mechanical ventilation, coagulopathy). Patients allocated to receive omeprazole, famotidine, sucralfate, or placebo each experienced stress-related upper gastrointestinal bleeding in 1%, 3%, 4%, and 1% of cases, respectively (P >28). Patients with coagulopathy experienced bleeding substantially more frequently than the other patients (10% vs 2%; P = 006). The study did not demonstrate that the already low frequency of clinically significant stress-related bleeding in high-risk patients in surgical intensive care units can be affected by omeprazole, famotidine, or sucralfate prevention. Additionally, the information implied that drugs that raise gastric pH may raise the chance of nosocomial pneumonia. These findings suggest that even in high-risk patients, routine prophylaxis against stress-related bleeding is not warranted. Ranitidine was found to be ineffective in preventing gastrointestinal bleeding in patients receiving intensive care and may raise the risk of pneumonia, according to a meta-analysis conducted by Messori et al. A sizable nested case-control analysis including more than 300,000 people was carried out in 2004. Incidence rates for pneumonia were 0.6 and 2.45 per 100 person-years, respectively, among non-acid-suppressive drug users and acid-suppressive drug users. When comparing people who are still on PPIs to people who have stopped taking them, the adjusted relative risk for pneumonia was 1.89. Numerous studies have shown that long-term PPI use carries the risk of a few illnesses. However, given the studies' retrospective nature and modest size, the findings must be regarded with caution. It

must be remembered that none of the PPIs raise intragastric pH > 4 for a period of 24 hours, even though gastric acid suppression has been hypothesised to be the cause of increased infections related to a lack of defensive mechanism and growth of dangerous microorganisms. Only between 9 and 15 hours per day can intragastric pH > 4 be maintained by any of the current PPIs when taken as a once-daily dose. The hazards of many diseases, including C. difficile and other intestinal illnesses, existed prior to the availability of sizable prospective research. [30, 33-38]

Clostridium difficile Infection-

According to recent statistics, nosocomial C. difficile-associated diarrhoea is becoming more common and more severe. It is theoretically conceivable that a decrease in gastric acid may be related to the acquisition of C. difficile. because vegetative cells are extremely vulnerable to acid, despite the spores' greater resistance to it. The biological plausibility of an increased risk of C. difficile-associated diarrhoea with gastric acid-suppressive medications has been questioned because it is thought that the main method of transmission of C. difficile is through spores, which are acid resistant. In a hamster model, it was shown that 75% of ingested spores went into the vegetative stage an hour after ingestion, when they were already in the small intestine. Elevated gastric pH levels may help C. difficile spore survival in humans if the organism is converting to the vegetative phase while the spores are still in the stomach. Other pathways are also conceivable, such as impacts on immunological response and gastrin-mediated direct effects on colonic mucosa. Previous research showed a weak correlation between C. difficile infection and acid suppression. Shah et al. discovered a higher correlation with antibiotics (P.0004), tube feeding (P.0005), and hypoalbuminemia (P.01) in their retrospective data of 126 patients. 34 Similar results were obtained in another study, which indicated a 0.92 OR between PPI use and the probability of C. difficile infection. Recent investigations have revealed a connection between PPI medication and C. difficile. The higher prevalence of hypochlorhydria in the elderly may be a factor in this patient population's increased C. difficile incidence. It would also be consistent with the findings that post-pyloric tube feeding was linked to diarrhoea caused by C. difficile with an OR of 11.4 if the stomach acid barrier was bypassed. whereas pre-pyloric tube feeding had an OR of 3.5 (95% CI, 0.19-66.5), pre-pyloric tube feeding had a 95% CI of 1.3-103.7. The adjusted OR of C. difficile-associated diarrhoea with current PPI use was reported to be 2.9 in a sizable population-based case-control research. According to a recent comprehensive study, people who have C. difficile infection run a higher chance of needing antisecretory medication (pooled OR 1.94; 95% CI, 1.37- 2.75). In comparison to H2-receptor antagonist use (OR 1.40; 95% CI, 0.85-2.29), the relationship was stronger for PPI use (OR 1.96; 95% CI, 1.28-3.00).[29, 39-47]

Table 3 Studies Performed to Evaluate the Risk of Enteric Infections with Acid Suppression

Author	Study Design	Patient No.	Infection Type	Results
Neal et al[42]	Case-control	188	Salmonella	RR of 2.4 with H_2 blockers
Neal et al[43]	Case-control	211	Campylobacter	RR of 10.5 with use of PPI
Neal[68]	Case-control	531	Campylobacter	RR of 3.4 with use of PPI
Doorduyn[69]	Case-control	573	Salmonella	RR of 4.2 with use of PPI *Salmonella enteritidis* RR of 11.2 with *S. typhimurium* DT104
Leonard et al[39]	Meta-analysis	11,280	Enteric infections	RR of 3.3 with use of PPI

RR = relative risk; PPI = proton pump inhibitor.

Table- Studies performed to evaluate the risk of enteric infections with acid suppression [7]

Other Enteric Infections-

Because other components of gastric juice appear to have minimal impact on the barrier function, it is believed that the "gastric bactericidal barrier" primarily reflects the low pH. The term "gastric bactericidal barrier" was really coined many years ago. Based on observations showing dysentery and kindred diseases were over-represented in people with deficient gastric acid secretion, Hurst claimed in 1934 that "the Services would have avoided much invaliding if personnel with achlorhydria were not sent to the tropics." Severe gastrointestinal infections have been linked to hypochlorhydria brought on by gastric acid inhibitors. Recent juvenile population data indicated that individuals taking acid-suppressive medications had an increased risk of developing acute gastroenteritis (OR 3.58; 95% CI, 1.87-6.86) and pneumonia (OR 6.39; 95% CI, 1.38-29.70). According to Leonard et Al systematics review, those with enteric illnesses have a higher likelihood of taking acid suppressors (OR 2.55; 95% CI, 1.53-4.26). Compared to H2-receptor antagonist use (OR 2.03; 95% CI, 1.05-3.92), the association was stronger for PPI use (OR 3.33; 1.84-6.02). Table 3 summarises significant research that were conducted to determine whether long-term usage of acid-suppressive medicine increased the incidence of enteric infections. [47,48-52]

Fundic Gland Polyps and Gastric Cancers-

The most prevalent stomach polyps are fundic gland polyps. Up to 1.9% of the general population and up to 84% of people with familial adenomatous polyposis are found to have them. Fundic gland polyps have traditionally been thought of as benign lesions with low-grade dysplasia at most (intraepithelial neoplasia). However, there have been case reports of fundic gland polyps that, when connected to familial adenomatous polyposis, harbour severe dysplasia or even stomach cancer. PPI use and the probable link to fundic gland polyps has long been a source of discussion.After taking omeprazole for a year, 3 incidences of fundic gland polyps were documented in 1992. The

use of PPIs was then linked to an increased risk of fundic gland polyp dysplasia, and routine endoscopies were advised for patients on long-term PPI therapy to keep an eye on the growth of fundic gland polyps. Another case-control research of 599 patients revealed a higher risk of fundic gland polyps with long-term (>1 year) PPI usage (OR 2.2; 95% CI, 1.3-3.8) compared to short-term (OR 1.0; 95% CI, 0.5-1.8). -Catenin gene alterations have been linked to sporadic fundic gland polyps, albeit the specific aetiology is yet unknown. Despite the frequent occurrence of these polyps with PPI therapy, dysplastic alterations in fundic gland polyps are uncommon and have only been documented in a few cases.Nearly all patients who receive severe acid-suppressive medication develop hypergastrinemia. As a result of severe acid suppression, persistent hypergastrinemia in rats leads to the hyperplasia of enterochromaffin-like cells. In the end, this may result in the development of stomach carcinoid. However, no other animals have ever had this phenomenon recorded.10% to 30% of chronic PPI users in humans show diffuse, linear, or micronodular hyperplasia of enterochromaffin-like cells. Most patients with Helicobacter pylori who also have significantly higher gastrin levels exhibit this observation. Dysplasia or invasive carcinoid development have not been reported in long-term PPI users, hence monitoring PPI maintenance users is not necessary. Instead of hypergastrinemia, PPIs and related gastritis alterations have garnered more attention recently. H. pylori primarily colonises the gastric antrum in people whose acid production is unaffected. Antral-predominant gastritis is linked to this colonisation pattern. Antral mucosal inflammation induces gastrin secretion, which keeps acid production at a normal to high level and preserves the pattern. Contrarily, H. pylori also colonises the stomach's body in people whose acid production is reduced through any technique, including the use of PPIs, resulting in a corpus dominated gastritis. Despite the rise in gastrin brought on by the concurrent inflammation of the antrum and the cycle of decreased acid secretion, inflammation of the gastric corpus mucosa further hinders acid secretion. The development of body gastritis along with a decline in parietal cell function increases PPIs' ability to inhibit acid production. Numerous research has also investigated the possibility that severe acid-suppressive therapy may contribute to bacterial overgrowth of non-Helicobacter species in the stomach. Increased serum cytokine levels and more severe gastritis have both been linked to this bacterial overgrowth. These observations' clinical relevance must be assessed. It is unclear whether bacterial overgrowth contributes to or is a cause of atrophic gastritis among PPI users. The pattern and severity of H. pylori gastritis are impacted by PPI medication, which also hastens the loss of corpus glands. There is now no evidence to support a higher risk of stomach cancer as a result. Limited circumstantial evidence, however, suggests that persistent corpus predominant gastritis and atrophy are important risk factors for the emergence of gastric cancer in both Japan and Europe. Eliminating H. pylori can mitigate these side effects without affecting PPI treatment for gastroesophageal reflux illness. Due to these factors, the Maastricht consensus panel recommended H. pylori eradication in 2005 for patients who needed long-term PPI medication. [53-62]

Colon Cancer-

The peptide hormone gastrin is secreted from the stomach antrum more often as a result of hypochlorhydria. The entire gastrointestinal system is affected by the trophic properties of gastrin. Colon cancer cells in vitro have been shown to thrive and proliferate in response to high gastrin levels. It has been demonstrated that patients with hypergastrinemia brought on by Zollinger-Ellison syndrome exhibit enhanced rectal mucosa proliferation. According to case-control research using frozen sera, baseline gastrin levels above normal are linked to a 4-fold increased risk of colon cancer. Robertson et al65 recently completed a population-based case-control analysis and did not discover a higher risk of colon cancer in PPI users. Singh et al. investigated the clinical importance of the trophic effects of long-term PPI-related hypergastrinemia on colon polyps, however they found no correlation between these factors and adenomatous polyp frequency, growth, or histology. More recently, a sizable case-control study that included more than 457,000 patients and evaluated the risk of colorectal cancer in that group did not find an elevated risk in the PPI group.As a result, despite strong theoretical and in vitro findings suggesting an increased risk for colorectal cancer with elevated gastrin levels, no clinically meaningful increase in the risk of malignancy or the number or size of adenomatous polyps has been demonstrated. [63-69]

CONCLUSIONS

Over the past 20 years, the use of PPIs has completely changed how acid-related illnesses are treated. Even though there is a significant margin of safety for PPI use over the long term, concerns have been raised about possible dangers. Although numerous research has investigated the potential impact of PPI therapy on vitamin B12 absorption, no conclusive link has been found. The studies' modest size and retrospective methodology place restrictions on them. At this time, it is not advised to monitor B12 levels in patients taking long-term PPI therapy until more prospective randomised trials have verified the association. Despite the theoretical arguments, there is not much evidence that PPI medication leads to iron insufficiency. There is no evidence that using PPIs under typical clinical conditions causes an iron deficit. Iron level monitoring on a regular basis is not advised. PPIs should be prescribed with caution to patients who are already iron deficient, and proper iron supplements should be considered.

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