

# Risks of proton pump inhibitors for gastroesophageal reflux disease and a diet alternative

## Abstract

Gastroesophageal reflux disease (GERD) is one of the most common digestive conditions treated by gastroenterologists. The most commonly prescribed drugs for GERD are proton pump inhibitors (PPIs) that reduce stomach acid. While these medications are effective for relieving GERD symptoms, their long-term use is associated with several side effects and chronic diseases. Several publications have questioned the long-term safety of PPIs. Moreover, recent studies have demonstrated that the Mediterranean Diet may be more effective than PPIs for people suffering from GERD.

**Keywords:** GERD, mediterranean diet, proton pump inhibitors, PPI, acid reflux, LES, lower esophageal sphincter, omeprazole, prilosec

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## Introduction

Gastroesophageal reflux disease (GERD) is one of the most common digestive conditions treated by gastroenterologists and primary care doctors. Typical symptoms include heartburn, regurgitation, and throat pain, while less common symptoms may include coughing, chest pain, and wheezing.<sup>1</sup> The prevalence of GERD varies strongly between continents; in North America, the prevalence is highest and is estimated to be between 18.1% to 27.8%.<sup>2</sup>

## Pathophysiology of GERD

With GERD, there is a backwash of stomach acid into the esophagus, and in more severe cases, into the mouth. This abnormality occurs due to the lower esophageal sphincter (LES) not working correctly. Normally when one swallows, the LES relaxes and allows food and liquid to flow into the stomach. The LES subsequently tightens again to keep the stomach content in the stomach. When the LES relaxes too much or weakens, it does not stop stomach acid from flowing up into the esophagus. Over time acid reflux can cause scar tissue in the esophagus, which creates a narrowing and problems swallowing, esophageal ulcer, and precancerous changes to the esophagus known as Barrett's esophagus.<sup>3</sup>

## GERD risk factors

Risk factors for GERD include obesity, bulging of the top of the stomach up into the diaphragm (hiatal hernia), pregnancy, connective tissue disorders such as scleroderma, genetic predisposition, and delayed stomach emptying.<sup>3</sup>

## GERD aggravating factors

Aggravating factors for GERD are factors that stimulate acid reflux in general: smoking, eating large meals or eating late at night, eating certain foods (triggers) such as fatty or fried foods, drinking certain beverages such as alcohol and coffee, and taking certain medications such as aspirin.<sup>3</sup>

## Proton pump inhibitors to treat GERD

The most commonly prescribed drugs for GERD are proton pump inhibitors (PPIs).<sup>2</sup> PPIs currently available on prescription in the USA are: dexlansoprazole (Dexilant), esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprazole (Aciphex).<sup>4</sup> Of these, the PPI omeprazole is the most commonly prescribed PPI with about 58 million total prescriptions per year, and pantoprazole is the next most common with a yearly total of 27 million prescriptions.<sup>5</sup> In total, PPIs were prescribed more than 100 million times in 2017.<sup>5</sup> The cost of these prescriptions was almost 12 billion US\$ in the U.S in 2015.<sup>6</sup> In addition to the prescription PPIs also many over the counter PPIs<sup>4</sup> that do not require a prescription were used, such as Prevacid 24h, Nexium 24 h, Prilosec OTC, and Zegerid. The last one is a combination of a PPI with an antacid.

PPI medications suppress stomach acid secretion by the parietal cells of the stomach. The mechanism involves blocking an enzyme (hydrogen-potassium-ATPase) that prevents hydrogen (proton) from being pumped into the stomach lumen to produce hydrochloric acid.<sup>7</sup> The PPIs bind to the hydrogen-potassium-ATPases, thus inhibiting them.

## Side effects of PPIs

There are several potential side effects of PPIs known, with the most common side effects being headache, diarrhea, nausea, and vomiting.<sup>4</sup> Most concerning is however a study by the U.S. Department of Veterans Affairs, which found PPI use was associated with deaths, in particular from cardiovascular disease, chronic kidney disease, and upper gastrointestinal cancer. That study was performed in a large cohort that included over 157,000 PPI users and nearly 57,000 users of H2 blockers – which is another type of stomach acid suppressor.<sup>8</sup> One of the lead researchers of that study was Ziyad Al-Aly, MD, assistant professor of medicine at the Washington University School of Medicine in St. Louis. He stated his concerns that “Given

the millions of people who take PPIs regularly, this translates into thousands of excess deaths every year.<sup>9</sup> Furthermore, since many people take PPI medications long-term, he warned: “Taking PPIs over many months or years is not safe, and now we have a clearer picture of the health conditions associated with long-term PPI use.”<sup>9</sup>

Another side effect suggested to be associated with PPIs includes nutrient deficiencies. In particular the micronutrients magnesium, vitamin B12, calcium, iron, and vitamin C appear to be affected, although, except for magnesium, the proof for these nutrient deficiencies is not conclusive yet. The cause of the potential deficiencies appears to be malabsorption of the micronutrients in the stomach and duodenum, and perhaps even more distal.<sup>10, 11</sup>

Various cancers associated with the use of PPIs include gastric, esophageal, and liver cancer.<sup>10</sup> It appears that the use of PPIs stimulates infections of the gastrointestinal tract, such as bacterial overgrowth in the intestine (SIBO),<sup>10</sup> *Clostridium difficile* infection,<sup>4</sup> and spontaneous bacterial peritonitis in patients with liver cirrhosis.<sup>4</sup> These infections and changes in the microbiome are thought to contribute to the development of gastrointestinal cancers.

In regards to the renal system, PPIs can cause acute interstitial nephritis and chronic kidney disease.<sup>10</sup> While acute interstitial nephritis itself is rare, PPIs have been found to be its most common cause, as was shown in an excellent review by Moledina and Perazella.<sup>12</sup> The mechanism behind these kidney problems is, however, still unknown.

Also, there is a concern with long-term PPI use and fracture risk. The risk is likely due to reduced nutrient absorption, in particular reduced absorption of calcium. For example, the US Pharmacist reports a 41% reduction in calcium absorption after 14 days of omeprazole therapy.<sup>4</sup> PPI use has shown in some studies to be associated with an increased risk of fracture. However, not all studies show this.<sup>10</sup> Ambizas and Etzel concluded in an overview: “Although findings from various studies have been inconsistent, there is enough evidence to prompt revision of PPI labeling to include information about possible increased risk of fractures of the hip, wrist, and spine.”<sup>4</sup> For instance, a large study including over 13,000 elderly people with hip fractures as well as over 135,000 elderly controls showed that especially long-term PPI use was associated with hip fractures.<sup>13</sup> In an even larger study, comparing over 124,000 people with any type of fracture with over three times as many controls, it was found that PPI use in the past year significantly increased the risk of fractures, especially of the hip and the spine.<sup>14</sup> Another large study also found that PPI was associated with hip fractures, but only if also another risk factor was present.<sup>15</sup> A recent review therefore concluded that there is a strong positive association between PPI use and the risk of fractures.<sup>16</sup>

In terms of cognitive health, there are conflicting epidemiological studies on the correlation between the use of PPIs and an increased incidence of dementia and Alzheimer’s disease.<sup>10</sup> However, a recent review concludes: “The findings of most research studies described above indicate that there is a direct association between the onset of dementia and depression on one side and the long-term use of PPIs on the other.”<sup>16</sup>

Several studies have shown an association between PPI use and developing community-acquired pneumonia. A meta-analysis showed, however, that while short term use of PPIs was indeed associated with community-acquired pneumonia, long-term use of PPIs was not.<sup>17</sup> The proposed mechanism is that lowering the gastric pH with PPIs

may allow the overgrowth of bacteria in gastric juices that potentially lead to microaspiration and lung colonization. All-in-all, the research was not conclusive, and other risk factors for community-acquired pneumonia may play a more important role.<sup>4</sup>

The autoimmune condition Subacute Cutaneous Lupus Erythematosus (SCLE) has also been found to be associated with PPI use.<sup>4</sup> SCLE manifests as skin lesions, typically occurring on sun-exposed areas of the body, including the neck, back, shoulders, and upper extremities. Fortunately, the condition usually resolves spontaneously after stopping the PPI medication in on average three months.<sup>18</sup>

There is also the risk of some medications not being absorbed well due to the hydrochloric acid-suppressive effects of PPIs.<sup>4</sup> An extensive review of the various PPIs and the specific medications they affect was written by Wedemeyer and Blume in 2014.<sup>19</sup> The interactions that have thus far been found to be most clinically relevant are with clopidogrel, methotrexate, and possibly acetylsalicylic acid (aspirin).<sup>19</sup>

In addition to awareness of adverse reactions associated with the use of PPIs, clinicians should also be aware that the discontinuation of PPIs without tapering can cause hypergastrinemia,<sup>4</sup> which is a rebound hyperacidity that causes the worsening of GERD symptoms. And the final concern about the long-term use of PPIs is that researchers found in one study that almost half of the PPI users took these acid-suppressive drugs without a medical need.<sup>4, 20</sup>

## Diet and lifestyle recommendations

Lifestyle modifications should be the cornerstone of treatment for GERD. However, this approach is often overlooked by doctors and not adhered to by many patients.<sup>2</sup> Obesity is, for instance, a significant component of GERD, and research shows that a reduced body mass index can significantly reduce the frequency of GERD symptoms.<sup>2</sup> General diet and lifestyle guidelines include: avoiding large, spicy and fatty meals, losing weight, elevating the head of the bed and avoid sleeping on right side of the body, avoid eating at least three hours prior to bedtime, turning off lights at bedtime to optimize sleep.<sup>2</sup>

## Mediterranean diet effective for GERD

Doctors do not often focus on diet changes with GERD, and instead, most resort to prescribing PPIs right away. Part of the reason for this reluctance may be that the results of research on dietary changes for GERD have been mixed.<sup>21</sup> However, for some people with GERD, diet changes can be quick and dramatic. For instance, one study evaluated patients with laryngopharyngeal reflux, which is similar to GERD, except stomach acid is ascending into the larynx.<sup>22</sup> Eighty-five of the patients were treated with PPIs, while 88 other patients followed a Mediterranean-style diet (restricting animal products more than typical) and drank alkaline water. Also, both groups avoided foods known to commonly trigger acid reflux such as coffee, tea, soda, greasy and fatty foods, chocolate, spicy foods, and alcohol. Interestingly, the researchers found that of those who made the diet changes, 62.6 percent showed a clinically meaningful improvement, while of those taking PPIs, 54.1 percent showed a clinically meaningful improvement. The reduction in reflux symptom index also was significantly better in the diet group (39.8%) than in the PPI group (27.2%).<sup>22</sup>

Another study found that a Mediterranean dietary pattern in Albanian adult men and women “was related to a decreased risk

of GERD irrespective of socioeconomic characteristics and other lifestyle factors.<sup>22,23</sup> The study compared the effect of a Mediterranean Diet to a non-Mediterranean Diet in 817 participants. The researchers also found that there was no single component of the Mediterranean Diet that significantly influenced GERD risk. Instead, the protective effect seemed to be due to the Mediterranean Diet as a whole.<sup>23</sup>

### Possible mechanisms of the mediterranean diet for GERD

The benefit of the Mediterranean Diet with GERD may be related to its effect on the LES since dietary intake affects LES pressure.<sup>21</sup> Imbalances with the intrinsic tone of the LES and incomplete closure may include external pressure of the diaphragm, as well as neural, hormonal, and paracrine factors.<sup>21</sup> In addition, gas production in the stomach from the consumption of food, medications, and air causes a vasovagal reflex and LES relaxation, which increases susceptibility to GERD.<sup>21</sup> Large boluses of foods or those with high viscosity may slow down peristalsis and increase intra-abdominal pressure and inhibit LES closure.<sup>21</sup>

### Conclusion

In conclusion, GERD is a widespread digestive condition that is most commonly treated with PPI medications. However, the long-term treatment of GERD with PPIs can result in various side effects as well as increase the risk of serious diseases. PPI medications are not supposed to be used long-term unless no other options are available for severe GERD. Fortunately, there is emerging research demonstrating that a modified Mediterranean Diet can be safe and more effective for the treatment of GERD.

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### Conflicts of interest

None.

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