

Impact of Long-Term PPI Therapy on Vitamin C Levels: Emerging Concerns

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ABSTRACT

PPIs are the most popular medications used in treatment of gastric diseases based on acids, and they turn out to be the strongest agents to suppress the acids. But extended use has been associated with hypochlorhydria and micronutrient deficiency Vitamin C being one. The efficacy of altered gastric acidity on the absorption of ascorbic acid and increasing its oxidation and subsequent reduced stomach and plasma levels of Vitamin C is studied in this narrative review, which is based on available clinical trials, case reports and mechanistic studies in the past 2 decades. Clinically, it cause dysfunctioning of collagen synthesis, immune deficiency, oxidative stress and in severe condition, scurvy. The vulnerable groups affected are the elderly, the malnourished, the post bariatric surgical and the *Helicobacter pylori* infected. Diet can help returning levels of the Vitamin C to normal, but close monitoring and actual nutritional planning are inevitable. This review gives relevance to increased clinical awareness, the individualization of supplementation strategy, and further research to reach some established regulations as to the prevention of nutrient deficiencies in long-term PPI users.

Keywords: Proton pump inhibitors, Vitamin C deficiency, Hypochlorhydria, ascorbic acid, acid suppressive therapy.

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INTRODUCTION

Scurvy is a systemic illness caused by chronic ascorbic acid deficiency, which impairs collagen synthesis, immune function and iron metabolism - eventually leading to gum bleeding, brittle capillaries and impaired wound healing (Khalife *et al.*, 2019). This occurs when the body content of Vitamin C decreases below about 300mg usually after a period of 60 to 90 days of poor intake (Gandhi *et al.*, 2023a). Clinically scurvy presents with symptoms like weakness, bleeding gums, Petechiae, corkscrew hair, joint pains and failure of wound healing (Geber and Murphy, 2012). Scurvy is classically observed among seafarers, but it still occurs in some populations today such as in elderly the restrictive dietary post-bariatric surgery patients, alcoholics or those with psychiatric illness and those living in food deprivation situations (Fenech *et al.*, 2019). Recent Australian and European case reports suggest a resurgence of scurvy even in the economically advanced countries where people face deprivation or poor diet (Agarwal *et al.*, 2015). Humans are especially prone to this deficiency because lack of enzyme responsible for synthesizing

Vitamin C in the body (Carr and Maggini, 2017). Vitamin C is essential for the hydroxylation of collagen precursors as well as its antioxidant role and immune function (Ashor *et al.*, 2019). Long term use of PPIs will likely lead to scurvy due to inadequate oral intake of Vitamin C as well as reduced absorption and stability of the vitamin in the gastrointestinal tract.

METHODOLOGY

The evidence base of this systematic review on vitamin C deficiency, and its association with the use of PPI, is the English-language publications of 2004-2024 that were retrieved using PubMed, Scopus, Science Direct, and Google Scholar.

Physiological Roles of Vitamin C: Immunity, Collagen Synthesis, and Antioxidant Function

Vitamin C also known as ascorbic acid and it is important for humans because it helps in making collagen, protects against free radicals and works in the immune system, however it must be acquired through food (Li and Schell horn, 2007). Up to 20% of adults have a light deficiency that can cause fatigue, slow wound healing, bleeding gums and a likelihood to bruise easily. People are still getting true scurvy which causes bleeding. This is especially true for elderly, low-income, restricted diet or post bariatric surgery patients (Velandia *et al.*, 2008).



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GI Handling of Vitamin C

The human stomach has a very acidic lining (1-3) which is important for both digesting protein and making micronutrients available to the body (Fujimori, 2020). In particular stomach acid keeps ascorbate in its reduced, bioactive state and makes it possible for oxidized dehydroascorbic acid (DHAA) to be reduced to ascorbate and keeps the mucosa healthy (Carabotti *et al.*, 2021). Active secretion of vitamin C into gastric juice which is usually several times higher than plasma levels is significant for its role as an antioxidant and in controlling the conversion of nitrite to nitrosamine which may lessen the risk of cancer (Schorah *et al.*, 1991).

Gastrointestinal physiology is important for getting Vitamin C into the body (Carabotti *et al.*, 2021). The connection between Vitamin C and the stomach helps explain how long-term PPI medication can lead to scurvy which is the main topic of this narrative review. Omeprazole, *Helicobacter pylori* status, and alterations in the intragastric milieu facilitating bacterial N-nitrosation (Mowat *et al.*, 2000).

Patterns and Risks of Long-Term Proton Pump Inhibitor Use

PPIs including omeprazole, pantoprazole and esomeprazole rank among the most prescribed medications globally (Shanika *et al.*, 2023). They are routinely used to treat gastro esophageal reflux disease, peptic ulcer disease, *H. Pylori* eradication and NSAID induced (Schnoll-Sussman *et al.*, 2020). Indeed, PPIs account for approximately 6% of all prescriptions and up to 15% of adults in some regions take them chronically (Jaynes and Kumar, 2019).

Despite strong safety profile short-term accumulating evidence links prolonged PPI use systemic effects including nutrient malabsorption, hypomagnesaemia altered gut microbiome and increased infection risk (Heidelbaugh, 2013a).

Masked Malabsorption by PPIs

Long-term PPI treatment not only suppresses gastric acid secretion but also hampers absorption of numerous essential nutrients leading to a cascade of nutritional consequences (Khalili *et al.*, 2012). Hypochlorhydria prevents release of calcium from insoluble salts, increasing fracture risk by about 1.3 times, particularly in elderly individuals taking high dose PPIs. Magnesium absorption is also affected by observational reports and case reports demonstrate a 1.6 - 2 times risk increase in hypomagnesaemia leading to symptoms including muscle cramps, arrhythmias and therefore the FDA called a safety alert in 2011 (William and Danziger, 2016). In addition, reduced gastric acidity inhibits pepsin activation blocking the extraction of Vitamin B₁₂ from dietary proteins and elevating the risk of deficiency after two years of continuous PPI use, especially in the elderly or in *H. Pylori* infected persons (Lam *et al.*, 2013). Iron uptake is blocked by impaired conversion from ferric to ferrous

forms and reduced facilitation by ascorbate. Some reports reduced haemoglobin concentrations and increased anemia among PPI users (Koyyada, 2021). Early evidence also suggests that Vitamin D and zinc stores could be affected though the evidence is still inconsistent (Schorah *et al.*, 1991b).

Vitamin C under Siege

This imbalance in diet has an important impact on the metabolism of Vitamin C which is normally secreted in gastric juice in its active form and protected from irreversible inactivation at low pH is rendered labile by the hypochlorhydric conditions created with PPIs (Padayatty and Levine, 2016). Dehydroascorbic acid does not get regenerated and undergoes hydrolysis irreversibly reducing the overall available Vitamin C reduced availability of ascorbate worsens impaired calcium absorption since collagen-based bone matrix synthesis is dependent upon Vitamin C and impairs iron absorption by preventing iron-ascorbate complexes thus aggravating anemia (Carr and Maggini, 2017). This group of deficiencies largely caused by decreased Vitamin C may lead to significant systemic effects including anemia, demineralization, neuromuscular disease and mucosal fragility thus emphasizing the need for overall nutrient surveillance and targeted supplementation in individuals undergoing extended PPI therapy (Jacob and Sotoudeh, 2002).

Mechanistic Link: PPIs and Vitamin C Loss

PPIs irreversibly inhibit the gastric H⁺/K⁺ ATPase pump in parietal cells so hypochlorhydria persists and the stomach pH increases <2 to >6 (Mowat *et al.*, 1999).

Vitamin C in the stomach which was initially secreted as biologically active ascorbate becomes chemically unstable at higher pH levels DHAA is unable to revert to active ascorbate and instead degrades to 2, 3-diketogulonic acid, particularly in the presence of trace metals and under normal body temperatures (Mohn *et al.*, 2018). This degradation reduces the bioavailability of Vitamin C in both the stomach and the body reducing its potential as an antioxidant and leading nutrients to be lost before they can be absorbed in the small intestine. Gastric mucosal secretion aggravates the issues: under normal acidity of the stomach it concentrates ascorbate in gastric juice above plasma levels and actively converts DHAA to ascorbate via glutathione-dependent pathways. Hypochlorhydria disrupts the latter which depletes the protective levels of ascorbate very rapidly and compromises the mucosal defences. This involves altering nitrite chemistry and reducing the antioxidant reservoir (O'Connor *et al.*, 1989a).

Dual Threat to Vitamin C: *H. pylori* and Low Acid

When the pH level of the stomach increases and *helicobacter pylori* infection occurs a molecular cascade begins to occur (Freedberg *et al.*, 2014a). *H. Pylori* caused gastritis causes parietal cells to function less effectively, increases pH and accelerates the oxidation of ascorbate both in and out of cells. This occurs

because bacteria absorb ascorbate and produce oxidative stress (Årskov and Andersen, 1995). Research indicates that individuals with *H. pylori* have significantly lower stomach levels of ascorbate, significantly higher levels of DHAA and don't completely recover after a dose of Vitamin C (Årskov and Andersen, 1995). This is consistent with the notion the hypochlorhydria and microbial stress interact to exacerbate. Fewer Vitamin C prevents the synthesis of collagen. This makes blood vessel weak which manifests as gingival bleeding, petechiae and delayed wound healing- scurvy signs. Furthermore, vitamin C's capacity to reduce Fe^{3+} to Fe^{2+} is compromised which may result in iron deficiency anemia in individuals who have been on PPI for years (Figure 1) (O'Connor *et al.*, 1989b).

Clinical Clues: PPIs and C Deficiency

Clinical trials have shown that PPIs cause an immediate decline in Vitamin C levels in the blood gastric environment of healthy subjects (HENRY *et al.*, 2005).

In a controlled trial by Henry *et al.*, in 29 healthy volunteers it was found that four weeks of daily dosing with 40 mg omeprazole caused a significant 12.3% drop in plasma Vitamin C level, irrespective of dietary factors. This effect was seen in both *H. Pylori* positive and negative subjects (HENRY *et al.*, 2005).

In parallel in another study by Mowat and McColl in fasting samples revealed a significant reduction in intra-gastric Vitamin C level; initial gastric ascorbate level ($\sim 3.8 \mu\text{g/mL}$) fell to $\sim 0.7 \mu\text{g/mL}$ under omeprazole therapy (with pH rising from ~ 1.4 to ~ 7.2) (Mowat and McColl, 2001). These observations unmistakably show that even a short course of PPI therapy destabilizes Vitamin C reducing its efficacy as an antioxidant in the gastric environment (Henry *et al.*, 2005).

In vitro Proof of PPI Toxicity

Research into the role of Vitamin C also provides this connection. McColl and others found that omeprazole increased the pH of the stomach reduced the levels of antioxidant active ascorbic acid and increased the levels of nitrite in the stomach particularly in individuals infected with *H. Pylori* (Woodward *et al.*, 2001). Further in *in vitro* research demonstrates that omeprazole induces thiol-oxidative stress on gastric epithelial cells that can be prevented by concurrent consumption of Vitamin C (Kohler *et al.*, 2010). This demonstrates that vitamin C provides protection against mucosal effects from PPI. Though there are fewer of these observational studies support the hypothesis that PPI users are low in Vitamin C particularly among those who lack adequate amounts of it in the first place or who have a high rate of infections (HENRY *et al.*, 2005).

Scurvy in the PPI Era

Key case studies of scurvy there is sparse clinical evidence that long term use of PPIs can lead to scurvy but what there is a very

strong. A middle aged western Australian man presented with bleeding gums, petechial rash, anemia and plasma Vitamin C undetectable. He was of low socioeconomic status and had a poor diet and had been on omeprazole for several years following bariatric surgery. Supplementation with 1g Vitamin C daily multivitamin corrected the symptoms (Weinstein *et al.*, 2001).

Fragile Populations: A Rising Concern

A study talked about a teenager with eosinophilic esophagitis who was on long term PPI therapy (omeprazole) and had joint bleeding a rash blood problems and undetectably low serum Vitamin C by mouth. These cases show how hypochlorhydria along with other conditions like inadequate nutrition, mal-absorption and co-morbidities can collectively worsen conditions. Though rare, the clinical expression is similar to that in patients with a history of scurvy (Gallizzi *et al.*, 2020). This demonstrates the dangers that are not being mitigated in patients with chronic PPI exposure. *Helicobacter pylori* infection decreases the acidity of the stomach and enhances oxidative stress, which increases the breakdown of Vitamin C. PPI treated infected patients have reduced gastric ascorbate levels and are more delayed in complete recovery when PPI is given. Long-term inhibition of acid prevents active ascorbate synthesis in the stomach from taking place, making it harder for the body to reduce dehydroascorbic acid and weaken antioxidant protection. PPI long term use greatly impacts the stomach's function leading to long term hypochlorhydria (gastric $\text{pH} > 6$) and this increases the challenge of the stability and variability of Vitamin C. This elevates the body chemistry to induce Vitamin C loss and potential scurvy in susceptible individuals (Heidelbaugh, 2013b). These include individuals of age on dialysis, smokers, alcohol consumers or those with eating disorders. Older age is a risk of factor for achlorhydria and disease states and malnutrition increase the risk of Vitamin C deficiency even among hospitalized and mental patients (up to 30% deficient) (Schleicher *et al.*, 2009).

Clinical Focus: Ascorbate Deficiency from PPIs

The vitamin C may be impaired by chronic PPI therapy. There should always be vigilance in patients on prolonged PPI therapy for Vitamin C deficiency even scurvy (Schleicher *et al.*, 2009). This should particularly be done for those with additional risk factors including restrictive diets, low socioeconomic status, *H. Pylori* infection, bariatric surgery or being elderly (Heidelbaugh, 2013d). As a part of standard nutritional screening and history-taking individuals should be questioned regarding their consumption of foods rich in Vitamin C, gastrointestinal symptom presence and presence of any other diseases that can worsen their insufficiency, when risk is present, serum or leukocyte ascorbate measurement is an inexpensive and insensitive method to diagnose it (Fadda *et al.*, 2025).

Supplement, Simplify, Stabilize

Regular oral supplementation, typically between 300 to 1000mg daily may cause symptoms to resolve within a few days. Maintenance dose typically a minimum of 100 mg daily may prevent the recurrence of symptoms. A person with mal absorption or acute scurvy such as following bariatric surgery, might require receiving the medication intravenously. It is also important to consider whether continuous PPI therapy is still required. Physicians should consider switching H₂- receptor antagonists, switching to on demand or intermittent dosing or discontinuing PPIs when appropriate (Forgacs and Loganayagam, 2008). This approach to de prescribing is consistent with updated stewardship guidance and reduces the overall physiological burden of acid suppression. Monitoring procedures must entail frequent reassessment like nutrient profiles every 6 to 12 months in at risk populations to detect subclinical deficits prior to causing apparent illness.

Healthcare Systems and Society

In addition to Vitamin C monitoring must also examine the related micronutrients like B12, iron, magnesium, zinc and calcium that are usually impaired by inhibiting stomach acid. For healthcare systems the integration of nutrient monitoring into

electronic prescribing systems could automatically trigger alerts for long term PPI prescriptions informing doctors to reassess the patient's risk and consider prescribing Vitamin C as a preventive measure (Heidelbaugh, 2013b). Lastly, public health initiatives can possibly consider socioeconomic issues such as food insecurity and the inaccessibility of fresh fruits and vegetables. The reason is that cost and access issues are a leading reason for cases of PPI related scurvy in populations with economic issues. By incorporating nutrient-centered monitoring and counselling into PPI prescription pathways, physicians can prevent deficient pathways early and maintain their patient's nutritional status while continuing to control their acid levels effectively (Van BOXEL *et al.*, 2009).

Exploring the Unknown: PPIs and Vitamin C

The impact of long term PPI therapy on Vitamin C status is poorly defined because there are many study flaws. Most of the clinical studies are brief, typically consisting of healthy subjects receiving 40mg of omeprazole for four weeks which had a roughly 12% decrease in plasma Vitamin C (Woodward *et al.*, 2001). These controlled trials are not relevant to clinical patients who often present with comorbidities variable dietary intake and concomitant factors like H. Pylori infection that influence Vitamin C metabolism (McColl, 2009).

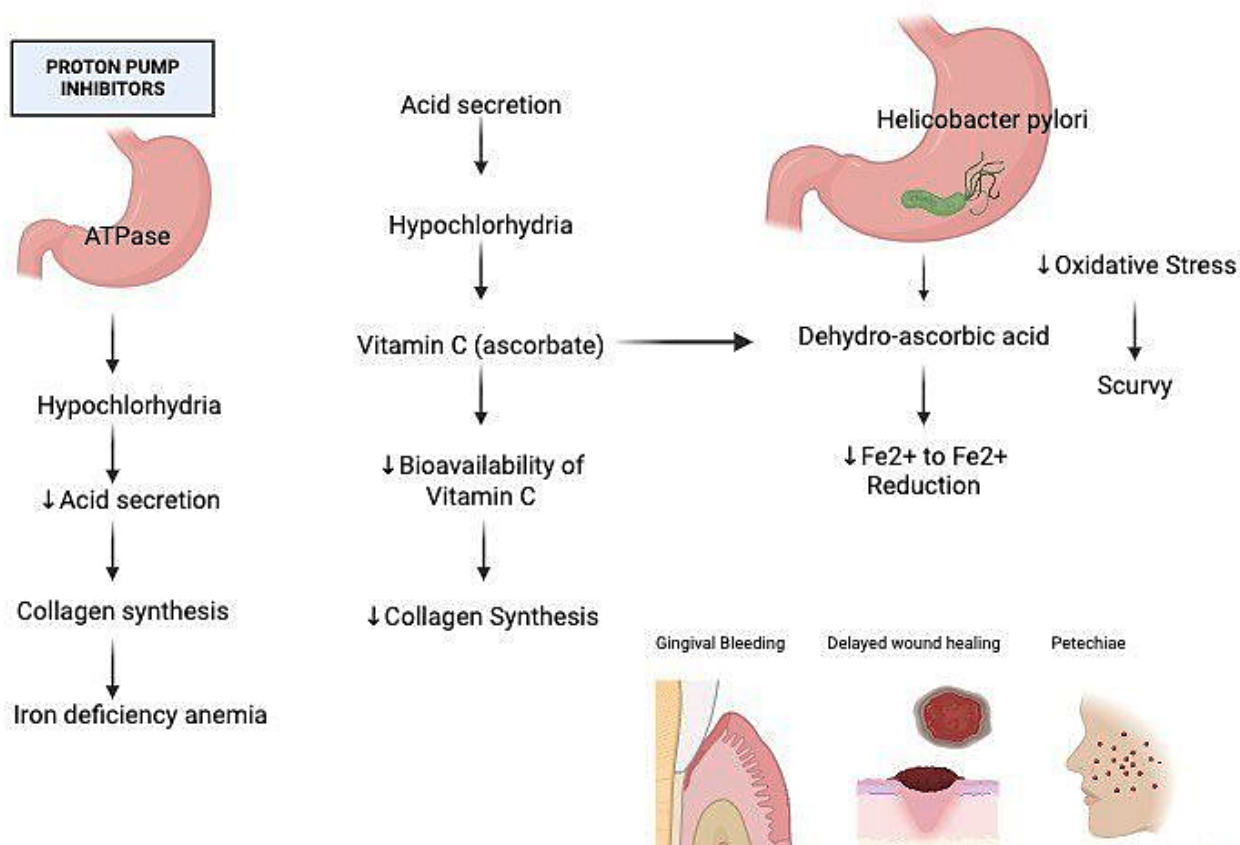


Figure 1: Biochemical pathway of PPI induced hypochlorhydria leading to ascorbate deficiency.

Evidence Gaps and Biological Clues

Observational reports on dietary deficiencies associated with PPI use highlight reductions in Vitamin B₁₂, D, magnesium and iron but rarely measure Vitamin C levels leaving extensive gaps in analysis of ascorbate (Heidelbaugh, 2013d). Mechanistic research has clarified that hypochlorhydria tips gastric ascorbate towards instability resulting in lower intragastric and systemic amounts yet the interconnection between gastric depletion and effects of clinical relevance like scurvy remains uninvestigated (McColl, 2009).

Research data suggest an unequivocal need for future longitudinal research observing plasma and gastric Vitamin C levels in patients receiving long-term PPI therapy. Short-term studies showed a decrease of approximately 12% in plasma Vitamin C after 28 days of omeprazole treatment. Adult PPI users with ongoing biochemical monitored augmented by food diaries and symptom surveys should be included in future studies to ascertain the ascorbate levels at which subclinical insufficiency evolves into overt scurvy (White *et al.*, 2002).

Alternative Care, Measured Impact

Comparative studies that compare PPIs to other acid suppressants like H₂ receptor antagonists or potassium-competitive blockers will ascertain whether less intense acid suppression strategies better preserve Vitamin C bioavailability (Heidelbaugh, 2013d).

CONCLUSION

The long-term use of Proton Pump Inhibitor (PPI) is effective in the management of acid-spectrum ailments; nevertheless, vitamin C deficiency that can be explained by the case of hypochlorhydria is a major issue. The empirical data shows that the plasma and gastric ascorbate levels decrease significantly during a few weeks, and long-term consequences of the given phenomenon are not thoroughly studied. Ascorbate degradation is encouraged in environments of ongoing hypergastrinemia and high gastric pH, setting up patient's scurvy, especially with preexisting nutrition predispositions. Even though vitamin C supplementation is easily accessible, there is no active systematic surveillance. It should thus be encouraged that practitioners consider adjunctive employment of vitamin C and the assessment of dietary sufficiency. Prospective, long-term and randomized trials are essential to elucidate the secondary incidence, pathway and implications of this Halloween effect and to guide more prudent nutrient-savvy PPI prescriptions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PPI: Proton Pump Inhibitors; **DHAA:** Dehydroascorbic Acid; **H. pylori:** *Helicobacter pylori*; **NSAID:** Non-Steroidal Anti-Inflammatory Drug; **FDA:** Food and Drug Administration; **B₁₂:** Vitamin B12; **GI:** Gastrointestinal; **ATPase:** Adenosine Triphosphatase.

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