

Analysis of impact of consumption of proton pump inhibitor on osseous integration of dental implants to the alveolar bone: A systematic critical appraisal

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Abstract

Proton pump inhibitors are one of the most frequently prescribed medicines primarily for reducing the production of gastric acid. Every medicine has some adverse effects associated with it, including effects on the bone tissues. Dental implant is one of the most preferred options for teeth replacement. The current literature review was planned to evaluate the association between intake of proton pump inhibitors and its impact on the bone around the dental implant. Literature review entailed search on Google Scholar, Web of Science and PubMed databases using a range of search terms. Chronic intake of proton pump inhibitors has been associated with decrease in the density of bone, which eventually leads to increased risk of dental implant failure. However, since limited studies have been carried out, further research is required, especially clinical trials, to evaluate the relationship between the intake of proton pump inhibitors and the failure of dental implants.

Keywords: Proton pump inhibitors, Dental implants, Alveolar bone, Bone density, Periodontium.

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Introduction

Proton pump inhibitors (PPIs) are a group of drugs that are primarily used to suppress gastric acid secretion by their inhibitory action on the gastric hydrogen potassium adenosine triphosphate synthase (H⁺/K⁺ ATPase) proton pump located in the parietal cells in the gastric mucosa. The commonly used PPIs include medicines like omeprazole, pantoprazole, esomeprazole and lansoprazole. PPIs are prescribed to patients for the treatment and prevention of diseases associated with increased acid production and its consequences on the stomach, oesophagus and duodenum. Moreover, PPIs are also used in ulcers, ulcers associated with the use of non-

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steroidal anti-inflammatory drugs (NSAIDs) and Zollinger-Ellison Syndrome.¹ PPIs are also used in combination with antibiotics for the eradication of *Helicobacter (H.) pylori* which causes peptic and duodenal ulcers. One study reported that PPIs were one of the 10 medicines frequently prescribed to patients, and that the rate at which PPIs are being prescribed is on the rise continuously.²

When PPIs are consumed by patients, physiologically there is a decrease in acid production, which then leads to a reduction in the absorption of nutrients.³ One of the nutrients essential for the bones is calcium which is affected by the reduction in gastric acid levels. In diet, calcium is consumed in the form of insoluble calcium salts, which are then converted to soluble salts in the presence of gastric acid. The intake of PPIs leads to a decrease in calcium absorption in the proximal intestines since an acid environment is required for its absorption.⁴ Since the absorption of calcium is impaired, the function of osteoclasts is affected. Therefore, this leads to a reduction in bone density.

Although it has been shown that PPIs may lead to a reduction in bone density, there is some evidence about its protective effects. Evidence suggests that PPIs have a direct effect on the osteoclasts as these cells have proton pumps that can be inhibited by PPIs, therefore, having the potential to alter the osteoclasts.⁵ In one study, it was found that pantoprazole led to an indirect reduction in the resorption of the bone by inhibition of osteoclastogenesis.⁶ Inhibition of bone resorption by PPIs is further supported by the evidence that omeprazole led to reduced calcium release from the calvaria of a mouse, as well as a reduction in the secretion of calcium in the urine of humans.⁷

Parathyroid glands are one of the key glands that are responsible for the maintenance of serum calcium levels by secretion of parathyroid hormone (PTH). The intake of PPIs leads to an increase in gastrin levels called hypergastrinaemia. The state of hypergastrinaemia leads to an increase in the secretion of PTH from the parathyroid glands.⁸ PTH is responsible for maintaining serum calcium levels by increasing the resorption of bone by stimulating osteoclasts.⁹ Moreover, PTH increases the secretion of

reabsorption of calcium from the renal system and increased the production of calcitriol. All of these cascades of functions lead to an eventual increase in the reabsorption of calcium from the proximal small intestine. When the patients consume PPIs for a long period of time, this leads to continuously elevated levels of PTH which has a negative impact on bone density due to persistent resorption of bone.¹⁰ The state of bone density is further worsened if the patient is suffering from calcium deficiency due to dietary insufficiency.

PPIs are responsible for the reduction in the secretion of gastric acid. When taken for longer periods of time, negative consequences are inevitable. Gastric acid is one of the most essential barriers due to various different microorganisms that reach the stomach via the oral cavity.¹¹ The acidic potential of hydrogen (pH) of the stomach eliminates most of the microorganisms before they pass on forward in the gastrointestinal system. Since this gastric barrier is disturbed by the PPIs, this creates an opportunity for different microorganisms which was not possible in the state of the normal secretion of gastric acid. The chronic consumption of PPIs poses an increased risk for clostridium difficile-related infections along with the increased activity of firmicutes in the gastrointestinal system.¹²

Loss of teeth for many reasons, such as periodontitis, trauma and extractions, leads to functional and aesthetic effects on the patient's wellbeing. Although there are many modalities available to replace missing teeth, a dental implant offers the best choice due to its great functional and aesthetic properties for both partially and completely edentulous patients. The dental implant is inserted directly into the alveolar bone. For complete integration of the dental implant in the alveolar bone, osseointegration is of vital importance for the implant to survive. There are factors that might affect the process of osseointegration, such as ageing, use of tobacco (smoking), diabetes mellitus (DM), periodontitis, radiotherapy in the regions of head and neck, and hormone replacement therapy (HRT) in post-menopausal women.¹³ Intake of certain medicines have also shown to be responsible for impacting osseointegration, such as selective serotonin reuptake inhibitors (SSRIs), anti-hypertensives and PPIs.¹⁴ Since PPIs are known to impact bone density, and the level of bone density directly affects osseointegration, studies were carried out to determine this association. Different studies were carried out to determine the association between chronic intake of PPIs and osseointegration of dental implants. Some studies reported that patients on chronic PPIs possessed a greater risk of dental implant failure compared to patients not taking such medicines.¹⁵⁻¹⁷ Since

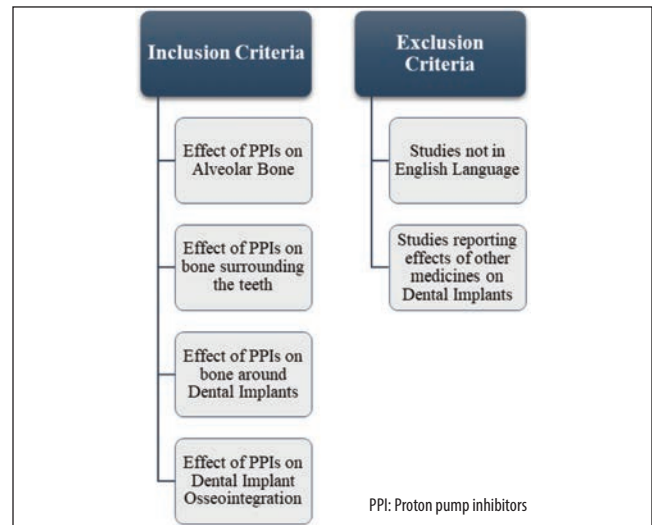


Figure-1: Eligibility criteria for the studies analysed.

PPIs are routinely prescribed to patients and dental implants are one of the best teeth replacement options, the current systematic review was planned to conduct literature review to determine the association between PPIs and osseointegration of dental implants.

Materials and Methods

The systematic review entailed electronic search on PubMed, Google Scholar and Web of Sciences databases using key words, including "Proton Pump Inhibitors", "PPI", "Omeprazole", "Lansoprazole", "Pantoprazole", "Esomeprazole", "Rabeprazole", "Dental Implants", "Osseointegration", "Alveolar Bone Loss", "Bone Density", "Teeth Loss", "Teeth", and "Resorption of Bone". The titles, abstracts and full texts of the studies were part of the search strategy using specific eligibility criteria (Figure 1).

All search results were scrutinised by two reviewers for removing the duplicates and irrelevant studies. For resolution of any conflict, a third reviewer was consulted. Data was extracted on a predesigned proforma and subjected to analysis.

Results

Of the 756 studies, 41(5.42%) passed the initial scrutiny. Of them, 20(48.78%) studies were excluded due to the unavailability of full text, 10(24.39%) for being duplicates, and 3(7.31%) for being in languages other than English. The final analysis, as such, comprised 8(19.51%) studies^{15,18-24} and 7(87.5%) of them had a retrospective design (Table).

A study by Masri et al.¹⁵ investigated the association between the intake of PPIs and the failure risk of osseointegrated dental implants. The study included 687 patients having 2,971 implants. Early implant failure in PPIs

Table: Characteristics of the studies analysed in detail.

S.No.	Authors and Year of Publication	Type of Study	Sample Size	Main Outcomes of the study
1.	Masri et al. 2023 ¹⁵	Retrospective study	2,971 Implants n=87	The use of PPI significantly increases the chances of Early Implant Failure
2.	Chrcanovic et al. 2017 ¹⁹	Cohort Retrospective	3,559 implants n=999	Intake of PPIs may lead to increased risk of failure of dental implant
3.	Altay et al. 2019 ¹⁸	Cohort Retrospective	1,918 implants n=592	Intake of PPIs may lead to early failure of dental implants
4.	Ursomanno et al. 2020 ²⁴	Retrospective clinical	1,480 implants n=635	PPIs medicines lead to increased bone loss at crestal region where implants are located
5.	Romandini et al. 2021 ²²	Cross-sectional	458 implants n=99	Implants placed for more than one year, PPIs led to decreased chances of dental implant failure
6.	Ursomanno et al. 2019 ²³	Retrospective	1480 implants n=635	Use of PPIs led to increased bone loss around implants
7.	Rogoszinski et al. 2020 ²⁰	Cohort Retrospective	881 implants n=284	Decreased risk of peri-implantitis in patient taking PPIs
8.	Rogoszinski et al. 2021 ²¹	Cohort Retrospective	933 implants n=284	There was no independent association between PPI intake and failure of implant or peri-implantitis

PPI: Proton pump inhibitors; n: Number of Patients

vs. non-PPIs users was 19.3% vs. 14.3%, suggesting that chronic use of PPIs was associated with an increased risk of early implant failure.

Altay et al.¹⁸ evaluated the association between systemic consumption of PPIs and failure of dental implants. There were 592 patients with 1,918 implants. The failure rate of dental implants was 8.3%. However, of the 11 participants who did not take PPIs, the dental implant failure rate was 1.9% ($p=0.002$). The failure rate was 4.30 times more in participants taking PPIs before the placement of dental implants.

Chrcanovic et al.¹⁹ evaluated the intake of PPIs with the risk of failure of dental implants. The retrospective study recruited 999 patients having 3,559 implants. The intake of PPIs was associated with a greater risk of failure of dental implants. Factors such as clenching teeth, location of implant, prophylactic antibiotics and smoking had a significant impact on the failure of the dental implant.

Rogoszinski et al.²⁰ evaluated the bone loss associated with the placement of dental implants. Only patients with dental implants placed for at least 5 years were recruited. There were 284 patients with 881 implants. Patients who had been taking PPIs were associated with a decreased risk of peri-implantitis (29.7%). This was the only study found in literature to suggest the protective role of PPIs. However, one major drawback of the study was that the implants that failed before the 5-year period were excluded.

In a fresh study, Rogoszinski et al.²¹ evaluated the bone loss around dental implants and its association with the intake

of PPIs. There was no independent association between PPI intake and failure of implant or peri-implantitis.

Romandini et al.²² evaluated the risk factors associated with the development of peri-implantitis. There were 99 patients with 458 implants. An inverse relationship was found between PPI intake and peri-implantitis.

Ursomanno et al.²³ assessed the incidence of bone loss around implants with the intake of PPIs in patients suffering from inflammatory bowel disease. There was greater bone loss associated with the use of PPIs.

Ursomanno et al.²⁴ used radiographs by directly measuring the crestal bone, and concluded that the intake of PPIs was associated with greater loss of crestal bone as determined by radiographs at the location of dental implants. The study suggested that better periodontal therapy might be required for such patients.

Discussion

Frequently, patients are prescribed PPIs for various gastrointestinal conditions and, similarly, more patients are opting for dental implants as the more favourable modality for the replacement of missing teeth. Therefore, the possible interaction between PPIs and the dental implant has been a focus of study in the literature, with most studies reporting PPIs' negative impact leading to the failure of the dental implant due to the failure of osseointegration.

In terms of animal studies, research has been carried out in rats to assess the impact of PPIs on dental implants. Both positive and negative outcomes have been reported. Tekin et al. concluded that no change in biomarkers and

biomechanical properties of dental implants was found.²⁵ Al Subaie et al. concluded that when omeprazole was systemically administered in rats, this led to decreased bone healing around the dental implant.¹ Gul et al.²⁶ aimed at evaluating the biomechanical and biochemical effects of PPIs on peri-implant bone regeneration in rats, and found that the biomechanical and biochemical parameters of PPIs did not affect the peri-implant bone-guided bone regeneration.

Sometimes when patients are taking PPIs for any gastrointestinal disturbances, there are other co-morbid conditions that they are suffering from. Systemic conditions, like DM, are associated with greater bone loss compared to non-diabetic individuals.²⁷ With the known effect of PPIs on bone density around the dental implants, patients concomitantly suffering from diabetes can be at an increased risk of bone loss around the dental implants. Moreover, ageing also has an effect on the bone density of patients. Ageing along with PPI intake can increase bone resorption of the patients, and, therefore, may negatively affect the bone density around the dental implant. Smoking is known to decrease the blood supply to different tissues of the body, including bones.²⁸ Smoking also decreases the absorption of calcium by the body.²⁹ These factors in conjunction with the use of PPIs can further deteriorate the density of the bones, especially around the dental implants.

The use of PPIs has been known to increase in proliferation of gut microbiota, such as an increase in the colonies of streptococcus in the upper region of the gastrointestinal tract. Since the gastric pH is no longer maintained at its usual limits due to a decrease in the secretion of gastric acid, an increase in oral bacteria is noted. Kiecka et al. found that a significant difference was present in terms of salivary bacteria between consumers and non-consumers of PPIs.³⁰ As a consequence, a modification in bacterial population associated with PPI usage may impact the quantity and organisation of periodontopathic microorganisms, which may also influence the amount or degree of periodontal pathology, and, hence, affect attachment levels around teeth.

There are various modalities by which PPIs can affect the bone surrounding the dental implant (Figure 2).

Makrygiannakis et al. reported that the intake of PPIs was associated with greater orthodontic movement of the teeth.³¹ These findings were taken to be a result of increase in resorption of the bone compared to the formation of the bone.³¹ In an animal study, rats were administered pantoprazole to evaluate orthodontic tooth movement. The study concluded that there was a decrease in the

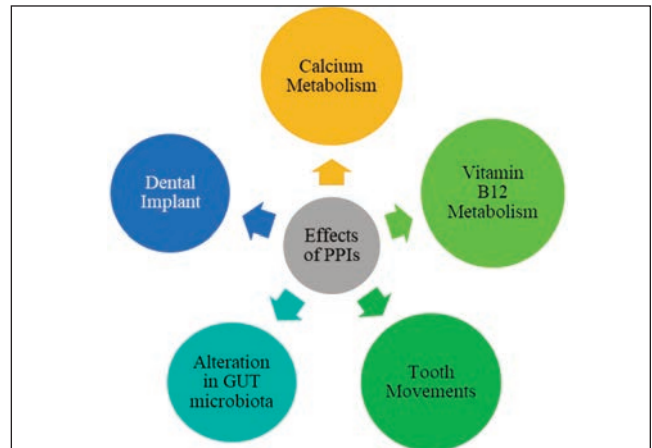


Figure-2: Different ways by which proton pump inhibitors (PPIs) affect the bone surrounding dental implants.

density of the bone with a decrease in calcium absorption as one of the mechanisms.³²

Chawla et al. reported that the intake of PPIs led to a decrease in the absorption of calcium from the proximal part of the small intestine.³³ Schinke et al. concluded that a decrease in the gastric pH negatively affected calcium metabolism with either dysfunction of the osteoclasts or via hyperparathyroidism.³⁴ Amity et al. concluded that omeprazole caused inhibition of H⁺/K⁺ ATPase and further inhibits the Vacuolar-type ATPase (V-ATPase) proton pump, decreasing the capacity of bone resorption.³⁵ Since calcium is of vital importance for bone formation, a decrease in calcium can also have an impact on the alveolar bone surrounding the dental implant.

For Vitamin B12 to be absorbed in the small intestine, the presence of gastric acid is important. With the continuous long-term intake of PPIs, the pH of the stomach is increased and the absorption of vitamin B12 is decreased. A few studies have reported that when there is a decrease in vitamin B12 in the blood, the levels of biomarkers of the formation of bone are also decreased.³⁶ Therefore, such a negative consequence of the intake of PPIs on vitamin B12 levels can affect the bone density around the dental implant.

Since the current literature suggests that PPIs do in fact have an impact on the osseointegration of dental implants to the alveolar bone, alternatives to PPIs should be looked for. Moreover, chronic intake of PPIs does lead to a deficiency of essential substances, such as vitamin B12, calcium and iron, that affect bones, so supplements should be prescribed to the patients alongside PPIs. Such a treatment approach will counter the adverse effects associated with PPIs, limiting the impact of PPIs on bone density. Some studies recommend that PPIs should not be taken for an indefinite period, and should be tapered off

gradually as the patients gain control of their symptom.³⁷

Dentists should consider the risk factor before the placement of dental implants. For such patients, dentists can plan frequent visits to improve and keep the periodontal health in check.

The current systematic review has a limitation which it encountered owing to the fact that there are currently only a few studies that evaluated the long-term impact of chronic use of PPIs on osseointegration of dental implants.

Clinical trials should be carried out to further understand the association of PPIs with dental implants and bone density around dental implants. Furthermore, studies should also focus on the specific mechanisms by which PPIs affect the bone and tissue attachment around the dental implant.

Conclusions

There is a negative association between PPIs and dental implant as PPIs may lead to dental implant failure.

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AL: Drafting, study design, data interpretation.

FU: Critical revision.

OP: Conceptualization, data analysis, data interpretation, final review.