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Review Article

Impact of proton pump inhibitors on periodontal health – A systematic review

Hajer A. Aldulaijan

Department of Periodontics, College of Dentistry, King Saud University, Riyadh 11451, Saudi Arabia

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ABSTRACT

Introduction: In recent times, proton pump inhibitors (PPI) are frequently prescribed to manage acid reflux and to aid in completion of course of medication, which cause gastric irritation. Although this practice may minimize compliance to drug therapies and probably prevent development of drug resistance, the adverse effects of chronic PPI use have to be assessed. Inadvertent chronic use of PPIs has been found to inhibit normal gastrointestinal microbiome and even bone metabolism. The current study aimed to review available evidence based literature to understand the beneficial effects of PPIs weighed against their adversities with respect to periodontal and peri-implant health.

Materials and Methods: The search strategy was followed according to the PRISMA guidelines for systematic reviews. Proton pump inhibitors, periodontal disease, dental implant (DI) and bone osseointegration were used as key MESH terms to search and select the required articles for review. While primary inclusion criteria were original researches, published in English, between 2014 to till-date, case reports, reviews and editorial communications were excluded.

Results: The overall search strategy resulted in 445 articles. Applying the inclusion and exclusion criteria 37 articles were selected. Scrutinizing the abstracts for relevance, 17 publications were finally selected for review. This included three in vivo animal studies evaluating DI osseointegration and 14 retrospective clinical studies (nine in patients with dental implants, four in patients with periodontitis and one evaluating bone quality using panoramic radiographs).

Conclusion: Findings from this systematic review revealed a plausible relationship between chronic PPI use and poor peri-implant bone health leading to early DI failure, and mandibular osteoporotic changes. On the contrary, use of PPI among patients with periodontitis, resulted in an improvement in periodontal health and reduction in periodontal disease severity.

1. Introduction

Proton pump inhibitors (PPI) are the most prescribed and widely used line of drugs to treat acid-related gastrointestinal (GI) diseases, like peptic ulcers, gastro-esophageal reflux disease (GERD), and Zollinger-Ellison syndrome, which are a major health concern in recent times. (Benmassaoud et al., 2016, Bruno et al., 2019) PPIs are efficacious prodrugs, which upon activation by acidic environment form covalent disulfide bonds with the parietal proton pump sulfhydryl groups and inhibit hydrogen/potassium adenosine triphosphatase (H+/K+-ATPase), thereby preventing gastric acid secretion.(Freedberg et al., 2015) In addition to the GI tract, PPI therapy has been shown to have off target pharmacological effects on several body environments (Jackson et al., 2016). PPIs with their target specific effect of inactivating the cellular proton pumps could exert their action in acidic micro-environments such as sites of inflammation and bone resorption. (Yoshioka et al., 2022) As a result of their ability to inhibit vacuolar ATPase, which has a similar mechanism of action like gastric H+/K+-ATPase, PPIs are capable of acting as anticancer drugs by altering extracellular pH of tumor cells.(Matsumura et al., 2022) However, with an increasing spectrum of usage the beneficial effects of PPIs need to be weighed against their side effects.

Inadvertent or excessive use of PPIs has been proven to alter the microbiome of the GI tract by increasing the pH and in few instances by directly inhibiting the commensal organisms' proton pump.(Jackson et al., 2016) Concomitant to chronic PPI use, an increase in the risk of GI

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E-mail address: haldulaijan@ksu.edu.sa.

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infections has been reported due to a shift in the bacterial spectrum to potentially pathogenic *Clostridium, Campylobacter, Salmonella* and *Shigella* species.(Imhann et al., 2016) In addition, patients taking PPIs for GERD management have been reported to experience increased salivary pH, which could trigger a shift even in the oral microbiome. (Mishiro et al., 2018) PPI induced hypochlorhydria and reduced gastric acid secretion leads to inadequate release of soluble calcium ions from foods and impaired calcium absorption in the proximal small intestine, ultimately resulting in minimal calcium bioavailability for deposition in bone tissue.(Sipponen and Härkönen 2010, Johnson 2016) Similarly, long term PPI use could also potentiate a reduction in the absorption of vitamin B12.(Yang 2012) All of this adversely affects bone mineral density and triggers compensatory hyperparathyroidism, which in due course could become chronic.(Hansen et al., 2010) Persistently elevated PTH levels could further augment bone turnover, induce osteoclast mediated demineralization and set in a vicious cycle of bone loss and fragility.(Khalili et al., 2012, Haffner-Luntzer et al., 2016) All the aforementioned findings thus provide a collective insight into the myriad mechanisms through which PPIs could influence the oral microbial flora and affect bone metabolism around dental implants and teeth.

Diseases affecting the periodontal complex primarily present as inflammatory conditions associated with plaque-biofilm formation, leading to destruction of the tooth-supporting complex. (Papapanou et al., 2018) Host response to microbial action in plaque biofilm, forms the basis for periodontal pathogenesis, namely gingivitis and periodontitis, characterized by soft-tissue inflammation, pocketing, loss of tissue attachment and alveolar bone destruction.(Targownik et al., 2008, Jo et al., 2015, Papapanou et al., 2018) Similar mechanisms are also responsible for development of inflammatory conditions surrounding dental implants (DI), including peri-implant mucositis and peri-implantitis.(Papapanou et al., 2018) Therefore, the mainstay of treatment for periodontal and peri-implant diseases involves modification of the oral microbial environment by removal of accumulated plaque and calculus.(Sundar et al., 2018) In addition, topical antimicrobial therapy through mouth rinses, gels and local drug delivery systems are also useful in their treatment.(Papapanou et al., 2018, Tonetti et al., 2018) The microbiological mediation of periodontal and peri-implant diseases, has led to the establishment of a plausible relationship between disease severity and any systemic factor affecting the oral microenvironment. (Tonetti et al., 2018) This could include systemic illnesses such as diabetes mellitus and immunocompromised states, oral habits like smoking and chewing tobacco, and also possibly long term PPI use.(Mishiro et al., 2018, Sundar et al., 2018) Evidence based studies, have demonstrated an association between PPI usage and reduced severity of periodontitis as evidenced by reduced probing pocket depths, even after adjustment for confounders such as smoking and systemic illness.(Yerke and Cohen 2019, Herrmann et al., 2022) On the other hand, PPIs have been shown to hasten osteoclastic activity, through the H+/K+-ATPase pathway, thereby altering bone turnover and metabolism.(Jo et al., 2015, Li et al., 2020) This could translate as a potential risk for periodontal and peri-implant bone loss, leading to loss of teeth and implants.(Masri et al., 2023) In addition, chronic PPI use and its associated gastric hypochlorhydria reportedly lead to osteoporosis as a result of calcium malabsorption, which could even translate to a risk of frequent bone fractures. (Targownik et al., 2008, Sipponen and Härkönen 2010).

In light of evidences from the literature supporting both beneficial and detrimental effects of chronic PPI use on periodontal and peri-implant health, it is alluring to understand and establish clinically valid decision making. Therefore the aim of the present systematic review was to analyze available evidence based literature, including clinical and in vivo studies, to understand the potential beneficial effects of long term PPI use weighed against their adversities, with respect to periodontal and peri-implant health.

2. Materials and methods

2.1. Research question and study criteria

The present study was registered in international prospective register of systematic reviews, PROSPERO (CRD42024519541). The research question was framed using the PICO standards of population, intervention, comparison and outcome. Wherein, population included both patients and animal model, intervention pertained to the use of PPI, comparison was made with a respective study population that did not receive PPI, and outcomes were evaluated with respect to periodontal and peri-implant health. Accordingly, the hypothesis under investigation was ascertained as, "Does chronic and excessive usage of proton-pump inhibitors adversely affect the periodontal and peri-implant health?" Original researches falling within the inclusion criteria of the research question were taken for the review (Table 1).

2.2. Literature review process

The current review was designed aligning to the guidelines of Preferred Reporting Items for Systematic reviews (PRISMA). An electronic literature search scrutinizing for relevant articles spanning a 10 year time-period from January 2014 until March 2024, was done using PubMed (Medline), Embase, Cochrane Central Register of Controlled Trials, Web of Science and Scopus databases. The searches were restricted to only English language publications and were done using Medical subject headings (MeSH), as search terms. Keywords representing proton pump inhibitors, dental implants, periodontium, gingivitis, periodontitis, peri-implant mucositis, peri-implantitis and dentoalveolar bone comprised the search terms, and were used to search databases in different combinations along with Boolean operators (AND, OR and NOT).

Identified article titles were scrutinized to eliminate duplicates and non-relevant studies. This was followed by an abstract review to identify full-text articles fulfilling the study selection criteria. Full texts were screened by two independent reviewers and articles for the systematic review were obtained based on agreement by both reviewers. Any disagreement during full-text review was resolved by rereading and discussion (Cohen's kappa score – 0.81). The entire study selection process for the systematic review is outlined in Fig. 1. While emphasis was made between the reviewers to select only studies with good quality of research and reporting, quality and risk of bias assessments were not done owing to the fact that the review included both clinical and in vivo studies.

Selected studies were tabulated for systematic data extraction, which was carried out for assessing data pertaining to the common variables

Table 1
Inclusion and exclusion criteria for selected studies in the review.

Inclusion criteria	Exclusion criteria
• Original researches including: • Retrospective/prospective clinical studies (cohort and case-control) • Case series (with at least 10 or more patients) • In vivo animal studies. • Use of proton pump inhibitors (generic or brand name) and evaluation of the effect on any of the following: • Soft tissue attachment loss/gain around teeth and/or dental implants (clinical) • Bone loss/gain around teeth and/or dental implants (radiographic or otherwise) • Bone density around teeth and/or dental implants • Overall periodontal/peri-implant health • Osseointegration of implants • Osteoporotic changes in the maxilla or mandible	• Literature reviews and case reports • Non-research communications including: • Letters to editors • Technical notes • Short communications. • Studies not published in English • Studies excluding usage of proton pump inhibitors

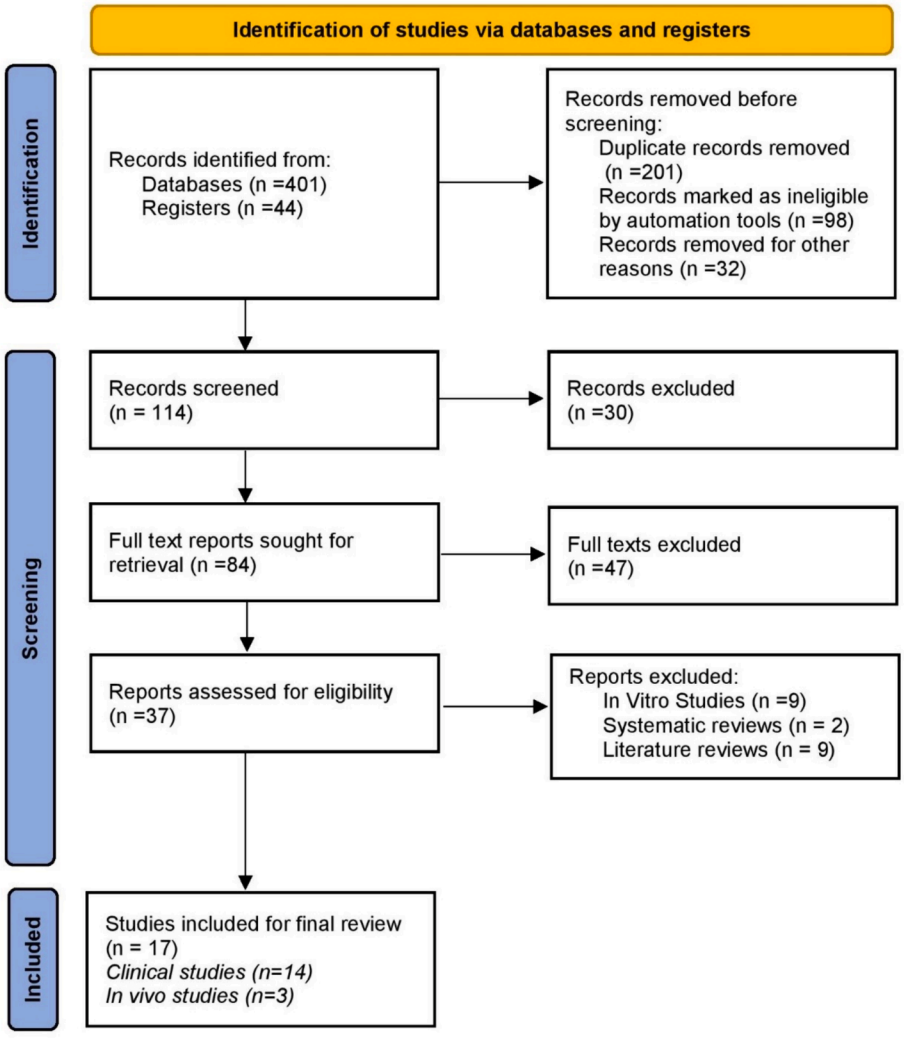

Fig. 1. Flowchart showing the process of article identification and selection of studies for the systematic review.

among the reviewed studies. The study data was presented as author name(s), year of publication, study design, sample characteristics – users of PPI compared to non PPI users, study objectives, nature/type of PPI evaluated and the study outcomes. Within the collected data, variables including (but not limited to) prevalence and severity of periodontal and peri-implant diseases, dental implant osseointegration, periodontal and peri-implant bone loss/gain, osteoporotic bone change and in-vivo peri-implant bone changes were analyzed.

3. Result

The preliminary search based on previously mentioned MeSH search terms yielded 445 publications (401 from electronic databases and 44 from registries). Further narrowing down the search strategy based on selection criteria and after removing duplicate study titles, 114 publications were identified for abstract review. Emphasizing on the use of PPI as study selection criteria and applying the inclusion criteria (Table 1), 84 abstracts were selected for full text review, out of which 37 were selected. Among the finally selected 37 studies, only 17 were eligible for systematic review, and these included 14 retrospective clinical studies and three in vivo studies based on animal models.

3.1. Clinical studies

Among the 14 evidence based clinical studies reviewed, nine studies evaluated effect of chronic PPI use on survival or failure of dental implants.(Chrcanovic et al., 2017, Wu et al., 2017, Altay et al., 2019, Ursomanno et al., 2019, Rogoszinski et al., 2020, Ursomanno et al., 2020, Romandini et al., 2021, Corbella et al., 2022, Rogoszinski et al., 2022, Masri et al., 2023) Within the above retrospective studies evaluating clinical DI survival, two studies by the same team of authors had reported similar data and outcomes. Therefore, these two studies were regarded as one for the purpose of review.(Ursomanno et al., 2019, Ursomanno et al., 2020) Four out of the 14 reviewed clinical studies reported about the effect of long term PPI use on periodontal disease severity,(Lisa et al., 2019, Yerke and Cohen 2019, Yerke et al., 2021, Chawla et al., 2022, Herrmann et al., 2022, Maresco 2023) and one study reported about osteoporotic bone changes in the mandible after PPI use.(Coşgunarslan et al., 2021) Amongst studies reporting about the effect of PPI use on periodontal health, three studies by a similar team of authors had repetitive data,(Lisa et al., 2019, Yerke and Cohen 2019, Herrmann et al., 2022) and were therefore considered as one study for the review. Table 2 describes in detail the systematic data extraction from the included studies.

In the nine retrospective clinical studies evaluating the effect of PPI use on peri-implant health, researchers analyzed the parameters for successful healing around 14,431 Dental Implants (Table 2). In general, there was a detrimental effect on dental implant survival among PPI users, when compared to non PPI users. While the rate of DI failure in PPI users ranged in the reported studies from 5.5 % to 19.3 %, it was

Table 2
Detailed description of the studies included for systematic review.

Author (year)	Study design	Sample characteristics	Study objective	PPI evaluated	Study outcomes
Alsubaie et al. (2016)	In vivo study (rat tibial implant and bone defect model)	24 rats (1.5 mm implant in left tibia and 2.5 mm defect in right tibia), (n = 12 per group) one group with PPI and another without PPI)	Effect of post-operative PPI on peri-implant Osseointegration and bone defect healing.	Omeprazole	• After 2 weeks, omeprazole adversely affects peri-implant bone healing • Poor BIC due to reduced volume of peri-implant bone tissue. • Bone defects in rats showed impaired healing with reduced new bone formation.
Wu et al. (2017)	Retrospective clinical study in patients with DI	1773 DI placed in 799 patients (PPI group – 58 patients with 133 DI/Non PPI group – 741 patients with 1640 DI)	Investigate the association between PPI use and failure of Osseointegration of DI	Not specified	• Failure of DI Osseointegration was significantly higher among PPI users (9/133 DI; 6.8 %) when compared to non-users (53/1640 DI; 3.2 %). • Statistically, PPI users are at a greater risk of DI failure than those who don't use PPI (HR 2.73; 95 % CI 1.10–6.78; $p < 0.05$) • Similar to the effect of smoking on DI failure when compared to non-smokers (HR 3.38; 95 % CI 1.60–7.17; $p < 0.01$).
Chrcanovic et al. (2017)	Retrospective clinical study in patients with DI	3559 DI placed in 999 patients (PPI group – 67 patients with 250 DI / Non PPI group – 932 patients with 3309 DI)	Investigate the association between PPI use and risk of DI failure	Not specified	• Risk of DI failure was significantly higher in PPI users (20/250 DI; 12 %) when compared to non-users (148/3309 DI; 4.5 %). • Statistically, use of PPIs had a significant effect on DI survival (HR 2.81; 95 % CI 1.14–6.94; $p < 0.05$), • Confounding variables included habits such as bruxism (HR 2.89; 95 % CI 1.09–7.62; $p < 0.05$) and smoking (HR 2.36; 95 % CI 1.34–4.18; $p < 0.01$), and short implant length (HR 0.39; 95 % CI 0.25–0.61; $p < 0.01$).
Altay et al. (2019)	Retrospective clinical study in patients with DI	1918 DI placed in 592 patients (PPI group – 24 patients with 69 DI / Non PPI group – 568 patients with 1849 DI)	Investigate the association between PPI use and risk of early DI failure	Not specified	• Risk of DI failure was higher among PPI users than non-users, • At the patient level (8.3 % or 2/24 patients among PPI users; 1.9 % or 11/568 patients among non-users) • At Implant level (5.8 % or 4/69 DI among PPI users; 0.6 % or 11/1849 DI among non-users). • The difference was statistically significant at the implant level. • Patients who were PPI users were 4.6 times more likely to have implant failures, • The odds of DI failure prior to loading was 4.3 time higher in PPI users.
Ursomanno et al. (2019) & Ursomanno et al. (2020)	Retrospective clinical study in patients with DI	1430 DI placed in 635 patients (PPI group – 201 DI / Non PPI group – 1229 DI)	Investigate the effect of systemic PPI use on peri-implant crestal bone loss (overall and after exclusion of confounders such as smoking, steroid therapy and systemic illnesses)	Not specified	• Overall DI failure rate was higher among PPI users (11/201 DI; 5.5 %) when compared to non-users (24/1229 DI; 1.95 %). • Peri-implant crestal bone loss was significantly higher ($p < 0.05$) in PPI users than non-users (overall mean difference – 0.59 mm; mean difference after excluding confounders – 0.83 mm). • Similarly, number of exposed DI threads was significantly ($p < 0.05$) higher in PPI users than non-users (overall mean difference – 0.25; mean difference after excluding confounders – 0.43).

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Table 2 (*continued*)

Author (year)	Study design	Sample characteristics	Study objective	PPI evaluated	Study outcomes
Yerke and Cohen (2019); Yerke et al (2019) & Herrmann et al. (2022)	Retrospective clinical study in patients diagnosed with periodontitis	518 patient with periodontitis (stages III and IV; grades B and C; chronic, moderate-severe and generalized periodontitis), were assessed for individual prevalence of pockets with PPD≥6mm.	Evaluate the effect of PPI on periodontal disease severity and decreasing bone loss in patients with periodontitis	Not specified	• Prevalence of teeth with PPD≥6 mm was significantly ($p < 0.01$) lesser among PPI users (15.7 %) when compared to non-users. • Use of PPI was associated with a significantly lower periodontal disease severity, as evidenced by prevalence of teeth with PPD≥6 mm, even after excluding patients with systemic conditions • PPI (PPI users – 13.1 %; non-users – 19.9 %; $p < 0.01$) and adjusting for confounders such as smoking and DM (PPI users – 12.7 %; non-users – 19.7 %; $p < 0.001$). • The study outcomes imply decreased severity of periodontal disease pathogenesis with PPI use.
Rogoszinski et al. (2020)	Retrospective clinical study in patients with DI	881 DI placed in 284 patients (PPI group – 323 DI / Non PPI group – 558 DI)	Evaluate the effect of PPI on prevalence of peri-implantitis around DI placed and followed up for at least 5 years	Not specified	• Prevalence of peri-implantitis was significantly lesser in PPI users (difference – 29.7 %; OR 0.703; 95 % CI 0.499–0.992; $p < 0.05$), • Reports beneficial effect of PPI on reducing risk of peri-implant inflammation.
Romandini et al. (2021)	Retrospective clinical study in patients with DI	458 DI placed in 98 patients (PPI group – 4 patients / Non PPI group – 95 patients)	Evaluate the prevalence of peri-implantitis and its association with several risk factors, including use of PPI	Not specified	• Patient level prevalence of peri-implantitis was higher among non PPI users (58.5 %; 55/94 patients) than in PPI users (25 %; 1/4 patients). • Statistically, the odds of PPI users developing peri-implantitis was signficantly lower than non-users (OR 0.08; 95 % CI 0.01–0.90; $p < 0.05$ • Study reports a protective role for PPI in peri-implant health.
Coşgunarslan et al. (2021)	Retrospective study using panoramic radiographs	402 patients (panoramic radiographs – PPI group – 201 / Non PPI group – 201)	Investigate mandibular bone changes possibly induced by long term PPI use	Esomeprazole (40.8 %) / Lansoprazole (28.9 %) / Pantoprazole (21.4 %) / Rabeprazole (8 %) / Omeprazole (1 %)	• Bone trabeculation in the area anterior to mental foramen, as measured by radiographic fractal analysis, was significantly lower (PPI group – 1.37; non PPI group – 1.40; $p < 0.01$) among PPI user than in non-users. • Similar significant difference (PPI group – 4.25; non PPI group – 4.51; $p < 0.01$) was observed in the mandibular cortical bone width in the mental foramen region, • Cortical and trabecular osteoporotic changes in the mandible among PPI users.
Tekin et al. (2021)	In vivo study (rat tibial implant model)	24 rats (titanium implants 1.5 mm dia and 4 mm length inserted in bilateral tibia), divided into 3 groups of 8 animals each (Control / PPI 1 / PPI 2)	Evaluate the effect of PPI on implant osseointegration and biochemical parameters, relevant to bone healing (ALP, Ca, P, AST, ALT, urea and creatinine)	PPI 1 – Omeprazole (5 mg/Kg once in 3 days) / PPI 2 – Omeprazole (10 mg/Kg once in 3 days)	• After 4 weeks, there was no statistically significant difference in the biomechanical reverse-torque measurement for implant osseointegration and biochemical parameters between the control and PPI groups. • Different doses of systemic omeprazole did not affect either implant osseointegration or biochemical parameters relevant to bone healing.
Yerke et al. (2021)	Retrospective clinical study in patients diagnosed with periodontitis	433 patient with periodontitis (stages III and IV; grades B and C; chronic, moderate-severe and generalized periodontitis), were assessed for periodontal disease severity by determining pockets with	Evaluate the effect of PPI use on influencing periodontal disease pathogenesis	Not specified	• After adjusting for risk factors affecting periodontal health, the prevalence of pockets with PPD either ≥ 5 mm (PPI users – 28.1 % / non PPI users – 55.8 %) or ≥ 6 mm (PPI users – 14.8 % / non PPI users – 31.1 %) was

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Table 2 (*continued*)

Author (year)	Study design	Sample characteristics	Study objective	PPI evaluated	Study outcomes
		either PPD≥5mm or PPD≥6mm.			significantly lower ($p < 0.01$) among PPI users than in non-users. • Systemic PPI use influences periodontal disease pathogenesis by reducing proportion of increased PPD.
Chawla et al. (2022)	Retrospective clinical study in patients diagnosed with periodontitis	744 patients with periodontitis (stages III and IV; grades B and C; chronic, moderate-severe and generalized periodontitis), were assessed for periodontal disease severity by determining pockets with either PPD≥5mm or PPD≥6mm.	Evaluate the relationship between PPI use and periodontal disease	Not specified	• After adjusting for predictive risk factors, smoking and DM, non PPI users had significantly higher prevalence of periodontal disease as evidenced by pockets with PPD either ≥ 5 mm (PPI users – 27.8 % / non PPI users – 40.5 % / $p < 0.05$) or ≥ 6 mm (PPI users – 13.9 % / non PPI users – 24.2 % / $p < 0.05$). • Similarly, excluding patients with systemic illnesses, PPI users had significantly lower prevalence periodontitis than non-users (PPD≥5mm in PPI users – 27.2 % / in non PPI users – 40 % / $p < 0.05$; PPD≥6mm in PPI users – 14 % / in non PPI users – 23.7 % / $p < 0.05$). • There was no statistical difference in the plaque index scores between PPI and non PPI users. • Use of PPI is associated with reduced prevalence of periodontal disease with PPD≥5mm or ≥ 6 mm.
Corbella et al. (2022)	Retrospective clinical study in patients with DI	1118 dental implants with moderately rough surface were analyzed among a total of 270 PPI and non PPI users.	Evaluate the effect of PPI (along with other medication) on long term clinical performance of DI	Not specified	• Among PPI, SSRI, antihypertensive and anti-inflammatory medication only anti-inflammatory drug significantly affected clinical DI performance resulting in greater risk of peri-implantitis. • Although PPI use was associated with greater odds of peri-implantitis and increased risk of implant failure, it was not statistically significant.
Gul et al. (2022)	In vivo study (rat tibial implant and bone defect model)	24 rats (2.5 mm diameter and 4 mm length implants in right tibia and bone defect around the implant to a depth of 2 mm), divided into 3 groups (control, PPI group 1 and PPI group 2; n = 8 per group)	Evaluate the effect of different doses of PPI on implant osseointegration and bone regeneration around implants	Omeprazole administered orally for 3 days per week, upto 8 weeks (group 1–5 mg/kg; group 2–10 mg/kg)	• After 8 weeks, based on biomechanical reverse torque assessment, there was no significant effect of PPI on implant osseointegration. • Nevertheless, the quantitative mean values were lower for PPI group 2 indicating impaired osseointegration with higher • PPI dosage. Biochemical analysis showed no significant difference between the groups for ALP, ALP, urea, Ca and P. • AST and creatinine were significantly higher in the PPI groups.
Rogoszinski et al. (2022)	Retrospective clinical study in patients with DI	323 DI placed in patients taking PPI (out of a total of 933 DI placed in 284 patients)	Evaluate how PPI intake may influence long term DI survival and risk of peri-implantitis	Not specified	• Based on logistic regression and after adjusting for confounders such as DM, smoking, bone grafting, illicit drug use, there was no statistically significant association between PPI use and long term DI failure (OR 0.73; 95 % CI 0.51–1.06; $p = 0.10$) or risk of peri-implantitis (OR 0.801; 95 % CI 0.56–1.15; $p = 0.24$).
Maresco (2023) Thesis	Retrospective clinical study in patients diagnosed with periodontitis	333 patients who were PPI users, presenting with moderate / severe periodontitis based on CDC/	Evaluate the relationship between PPI use and periodontal disease severity	Not specified	• Comparing 333 PPI users against 2914 non PPI users, prevalence of periodontal pockets with PPD≥5mm was 35.33 % lesser

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Table 2 (*continued*)

Author (year)	Study design	Sample characteristics	Study objective	PPI evaluated	Study outcomes
		AAP classification and having pockets with PPD≥5mm and ≥ 6 mm			among PPI users (95 % CI 1.55–4.48 %; p < 0.001), which further decreased upto 42.88 % (95 % CI 1.45–5.03 %; p < 0.001) after adjusting for smoking and DM. • SImilarly, pockets with PPD≥6mm, was 35.03 % (95 % CI 0.22–1.98 %; p < 0.05) lesser among PPI users and the same decreased upto 41.22 % (95 % CI 0.17–2.28 %; p < 0.05) after adjusting for smoking and DM.
Masri (2023)	Retrospective clinical study in patients with DI	2971 DI placed in 687 patients including PPI users (119 patients with 555 DI) and non PPI users (568 patients with 2416 DI)	Evaluate the effect of PPI on early DI failure	Not specified	• Early DI failure was higher among PPI users (19.3 %) than in non-users (14.3 %), at the patient level. • Considering at implant level, early DI failure was significantly higher (p < 0.05) in PPI users (5.4 %) than in non-users (3.5 %). • After adjusting for confounders such as smoking, DM, hypertension, hyperlipidemia, osteoporosis, ASA 2/3 and CVA, PPI use implied greater odds of early DI failure (OR 1.91, 95 % CI 1.19–3.08; p < 0.05).

PPI – Proton pump inhibitor; BIC – Bone implant contact; DI – Dental implant; HR – Hazard ratio; CI – Confidence interval;PPD – Probing pocket depth; DM – Diabetes mellitus; OR – Odds ratio; ALP – Alkaline phosphatase; Ca – Calcium; P – Phosphorus; AST – Aspartate aminotransferase; ALT – Alanine aminotransferase; SSRS – Selective serotonin reuptake inhibitor; CDC – Centers for disease control and prevention; AAP – American academy of periodontology; ASA – American society of anesthesiologists physical status classification; CVA – Cerebro-vascular accident.

lower in non-users and ranged between 3.2 % and 14.3 %. Most of the studies evaluating, DI survival in similar cohorts of PPI and non PPI users, reported significant risk of early implant failure in association with PPI use, even after adjustment for confounders such as smoking, systemic illness and parafunctional habits.(Chrcanovic et al., 2017, Wu et al., 2017, Altay et al., 2019, Ursomanno et al., 2019, Ursomanno et al., 2020, Masri et al., 2023) On the contrary, studies reported favorable outcomes in terms of severity of peri-implantitis among PPI users. (Rogoszinski et al., 2020, Romandini et al., 2021) Even after adjustment for confounders relating to systemic illness, smoking, drug use and ancillary dental procedures like bone grafting, Corbella et al., (2022) and Rogoszinski et al., (2022), based on two separate studies, reported no significant difference in severity of peri-implantitis between PPI users and non-users. In fact, Romandini et al., (2021) surmised a protective role for PPI use on peri-implant tissues based on their study findings. Few of the aforementioned studies further enumerated enhanced bone loss around dental implants in PPI users with an estimated 5.5 % failure rate or 4.60 times greater prevalence of implant loss. (Chrcanovic et al., 2017, Altay et al., 2019, Ursomanno et al., 2019, Ursomanno et al., 2020, Rogoszinski et al., 2022) In addition, early implant failure among PPI users was predominantly observed in anterior mandible (p < 0.001). (Masri et al., 2023) (Table 2).

Among the clinical studies assessing periodontal disease severity following long term PPI use, 2028 PPI users with periodontitis were assessed for presence of periodontal pockets in four retrospective studies. In general, these studies reported a reduction in periodontal disease severity among patients on long term PPI therapy, as evidenced by reduced prevalence of pockets with probing pocket depths greater than 5 mm (PPD>5 mm), which ranged from 14.8 % to 35.3 %. This was significantly lesser compared to non-PPI users, who had a prevalence of PPD>5 mm ranging from 40.5 % to 55.8 %. Even after adjustment for confounders that compromise periodontal health, such as diabetes mellitus, smoking and systemic illnesses, the reduction in periodontal disease severity was marked among PPI user than in non-users.(Lisa et al., 2019, Yerke and Cohen 2019, Chawla et al., 2022, Herrmann et al., 2022, Maresco 2023) Interestingly, the above findings were despite no significant differences in the plaque index scores, which is a major determinant of periodontitis, between equally matched cohorts of PPI users and non-users. (Table 2).

In the only reviewed study that reported an association between osteoporotic bone changes and chronic PPI use, Coşgunarslan et al., (2021) observed significant reduction in mandibular cortical width (MCW) and increased trabecular spaces in the bone anterior to the mental foramen. These findings were based on retrospective fractal analysis of 402 dental orthopantomograms (OPG/panoramic radiographs) and were indicative of cortical and trabecular osteoporosis in the mandible. They further noted that the osteoporosis inducing effect of PPI use was more prominent among males, as evidenced by a fairly greater effect on increased trabecular spaces. (Table 2).

3.1.1. *In vivo studies on animal models*

The results of the three reviewed in vivo studies were all based on assessment of osseointegration and healing of titanium micro-implants (diameter 1.5 mm – 2.5 mm, and length 2.5 mm – 4 mm) placed in the tibia of rat animal models. A total of 72 implants were evaluated during follow up period ranging from 2 to 8 weeks. In addition to evaluating the effect of PPI on osseointegration and bone-implant contact (BIC), two studies evaluated the effect of PPI dose on implant osseointegration and biochemical bone healing parameters (Tekin et al., 2021, Gul et al., 2022). While all the studies reported adverse effects of systemic PPI administration on peri-implant bone healing and BIC, there was neither a significant difference observed for osseointegration failure, measured biomechanically by reverse torque, nor for biomechanical bone healing parameters (Table 3). Although there was no significant differences observed in terms of implant failure based on PPI dosage, higher PPI dosage implied greater prevalence of impaired osseointegration, poor peri-implant bone healing and inadequate BIC. The outcomes of the reviewed in vivo animal studies are described in detail in

Table 3
Effect of proton pump inhibitors on peri-implant bone healing and osseointegration of implants placed in animal models.

Study by	PPI used	Follow-up	Effect on peri-implant bone healing and osseointegration
Al Subaie et al.	Omeprazole- Systemic administration of 5 mg/kg, daily.	2 weeks	Low peri-implant bone volume and bone-implant contact, large cortical defects and lower percentage of new bone formation was observed in the PPI group.
Tekin et al.	Omeprazole- 5 and 10 mg/kg, respectively, was administered by oral gavage three times a week.	4 weeks	Osseointegration of the dental implants was not affected
Gul et al.	Omeprazole-5 mg/kg through oral gavage three days a week.	8 weeks	Dental implants showed no significant changes in the biomechanical reverse torques values.

PPI – Proton pump inhibitor(s).

Tables 2 and 3.

4. Discussion

Proton pump inhibitors are popularly used as the most effective line of medication for many of the GI related symptoms for a long time. (Fuentes et al., 2018) However, their effectiveness has to be weighed against their adverse effects when being prescribed as preventive medication.(Johnson 2016) PPI users and the health care providers have to understand and assess the potential risks especially in patients undergoing interventions or replacement therapies.(Masri et al., 2023) The mechanism by which PPI induced gastric hypochlorhydria leads to calcium malabsorption and disturbs bone metabolism is well documented.(Sipponen and Härkönen 2010, Yang 2012, Johnson 2016) While the effects of chronic PPI use on osteoporotic changes and resultant orthopedic fractures has been reported extensively (Targownik et al., 2008, Khalili et al., 2012, Yang 2012, Li et al., 2020), there is limited evidence regarding PPI effects on periodontal or peri-implant health. Based on a literature review, Vinnakota and Kamatham (2020) reported that chronic PPI use leads to detrimental effects on dental implant osseointegration and risk of early failure. On the other hand, evidences reviewed from the literature indicate a positive relationship between periodontal health and chronic PPI usage.(Chawla et al., 2022) In light of these significant and clinically relevant relationships between PPI use and periodontal/peri-implant tissues, it is imperative to establish definitive and comprehensive evidence based on systematic reviews of literature. Therefore, the present review article focused on identifying clinical as well as in vivo findings reported in the literature with respect to the effect of PPI on periodontal and peri-implant health. Accordingly, based on the quality and relevance to research question hypothesized, a total of fourteen retrospective clinical studies and three animal studies were included for systematic review and data interpretation.

4.1. Effect of PPI on bone metabolism

Some of the earliest reported observations in the literature indicated an increase in the rate of orthodontic tooth movement in animal models treated with PPI due to osteoporotic bone changes.(Chawla et al., 2022) This was primarily attributed to the reduced calcium absorption arising as a result of long term PPI induced gastric hypochlorhydria.(Sipponen and Härkönen 2010) It has further been reported that chronic PPI administration also has an effect on osteoclast mediated bone turnover. (Jo et al., 2015) In the present review, the only clinical study implicating PPI use on bone metabolism and turnover in the dentofacial region, was the retrospective radiographic study reporting about mandibular osteoporotic changes in PPI users, by Coşgunarslan et al., (2021). They further observed an increased incidence of bone loss subsequent to PPI use among males and reported no confounding effects based on smoking or systemic illnesses. This was contrary to an earlier reported study, wherein women who were either present or past smokers and also received long term systemic PPI therapy, had a 50 % increased risk for osteoporotic hip fractures, than males or non-smokers.(Khalili et al., 2012) Although, no further clinical studies evaluating bone quality and PPI use could be identified within the purview of the present review, all the three in vivo studies reviewed herein reported impaired bone metabolism leading to poor peri-implant bone healing, based on histological observations.(Al Subaie et al., 2016, Tekin et al., 2021, Gul et al., 2022) These studies further noticed a down regulation of biochemical bone markers such as alkaline phosphatase, calcium and phosphorus, albeit not significantly. The aforementioned findings indicate a strong case in point for carefully evaluating the benefits of long term PPI use in light of their detrimental effects on bone. Furthermore, the adverse effects of PPIs associated with osteoporosis-related fracture were found to be more pronounced when there is increased duration and more dosage of the drug consumption, or in patients who were more than 60 years of age.(Targownik et al., 2008, Jo et al., 2015) This would especially be critical among elderly patient populations as they are frequently prescribed long term, high dose PPI therapies and may eventually be at risk of encountering fragile bone fractures due to falls.(Jo et al., 2015).

4.2. Effect of PPI on peri-implant bone healing

All the reviewed clinical studies indicated an adverse effect of chronic PPI use over dental implant success and osseointegration. However, this was predominantly observed in the early implant healing period than at later stages. In fact, there was no difference in implant survival rates between PPI users and non-users, when compared 10 years post-implant placement.(Corbella et al., 2022) The findings of the present review reporting a strong association between chronic PPI use and early implant failure, when compared to dental implant survival rates among non-PPI users, is in line with existing evidence available in the literature.(Vinnakota and Kamatham 2020) This conclusion is further strengthened by the finding that considerable crestal bone loss was observed at peri-implant sites among people with history of PPI usage. (Ursomanno et al., 2020) This was in spite of adjustment for confounders capable of affecting dental implant osseointegration, such as smoking, diabetes mellitus, systemic illnesses and parafunctional habits (Table 2). Nevertheless, when evaluating early implant failure among PPI users, old age and other comorbidities like hypertension, hyperlipidemia, diabetes mellitus, osteoporosis, cardiovascular accident (CVA), location (anterior mandible), shorter and narrower implants, and higher number of implants need to be considered as confounders, as these aforementioned variables are all capable of affecting implant survival by themselves.(Ramalingam et al., 2015, Masri et al., 2023) Similarly, impaired peri-implant bone healing could have also occurred as a result of concurrent use of NSAIDs and PPI, which together affects calcium absorption, circulating calcium levels and bone metabolism.(Wu et al., 2017).

Based on an in vivo rat animal model, Al Subaie et al., demonstrated impairment of bone healing and osseointegration around the dental implants after daily omeprazole administration (5 mg/Kg) and after 2 weeks of follow-up.(Al Subaie et al., 2016) However, upon observation for longer durations (4–8 weeks), the results elucidated from animal studies conveyed no significant effect on implant healing, peri-implantitis or bone regeneration (Table 3).(Tekin et al., 2021, Gul et al., 2022) Interestingly, the reviewed in vivo, rat model based studies evaluating the effects exerted by PPI administration on osseointegration of dental implants have observed varying results, reporting either a negative side effect of PPI use or no effect at all. In the study reported by

Tekin et al (2021), the authors could neither find significant differences in the levels of biochemical markers (serum calcium, alkaline phosphatase, creatinine, urea, phosphorus, alanine aminotransferase, aspartate aminotransferase) nor with respect to the biomechanical properties of implants (values measured as torque), between the groups of animals treated with or without omeprazole, after a follow up duration of 4 weeks.(Tekin et al., 2021) Although this study had a similar design to that of the one reported by Al Subaie et al. (2016), the findings were contrasting, wherein a reduction in the area of bone to implant contact was observed after omeprazole usage, for 2 weeks.(Al Subaie et al., 2016) This could probably be attributed to the variations in the properties between human mandibular/maxillary bones and the tibial bone in a rat model and in addition to the differences in bone tissue response after long-term/chronic PPI usage.(Tekin et al., 2021) Moreover, the period of study of 2 and 4 weeks is a very short period of time to evidence any significant observable effect. These limitations as explained above might have led to the contradictory observations of the authors reporting effects of PPI on peri-implant bone healing and osseointegration, based on in vivo studies than from those reporting through clinical observation. Nonetheless, based on the strength of clinical evidences obtained from the present review, chronic PPI usage needs to be regarded as having a detrimental effect on peri-implant bone tissue and as being capable of causing early dental implant failure due to impaired osseointegration.

4.3. Effect of PPI on periodontal health

In contrast to the unfavorable effects on dental implant osseointegration, PPI use is reportedly having a paradoxical beneficial impact over periodontal tissues and their health, as evidenced by their ability to reduce periodontal disease severity and prevalence of periodontal pockets (Table 2). In comparison to the dynamics of poor bone turnover associated with PPI use, there is an enhancement of periodontal and peri-implant soft tissue attachment resulting in favorable clinical outcomes.(Chawla et al., 2022) Findings from the present review reinforced the above fact, as an inverse relationship between severity of periodontal disease and PPI usage was reported.(Yerke and Cohen 2019) Similarly, studies reported observations supporting the protective effects of PPI on periodontal and peri-implant soft tissue attachment levels, both in the short term and long term.(Rogoszinski et al., 2020, Romandini et al., 2021, Rogoszinski et al., 2022) Interestingly, the aforementioned beneficial effects on periodontal tissues were observed in spite of no significant differences in oral hygiene status of patients, as evidenced by their plaque index scores (Table 2). Therefore, it would be alluring to hypothesize that the effect of PPI usage on altering the oral microbiome could potentially help alleviate periodontal disease severity.(Mishiro et al., 2018, Yerke et al., 2021, Maresco 2023).

The results of the present review can have an impact on the prescription of PPI in clinical practice. It must be borne in mind that for patients with significant risk of dental implant failure, effective alternatives to PPIs should be considered and due consideration must be given for over the counter antacids (or) H2 blockers as an alternative to PPIs.(Wu et al., 2017, Chawla et al., 2022) For the effective reduction of PPI associated risks, decrease in PPI usage (or) making risk specific supplements available to the patients is necessary. One possible adjuvant could be the use of probiotics, the effectiveness of which though reasonably proven in the prophylaxis of antibiotic associated diarrhea, has not been extensively tested for treatment in patients with chronic PPI usage.(Freedberg et al., 2015) It has further been recommended that once the symptoms are controlled, the indefinite usage of PPIs should be avoided.(Benmassaoud et al., 2016) Since an association between implant failure and PPI usage has been pointed out by various study findings, PPI usage can be included under the dentist's list of risk factors to be considered before commencement of implant surgeries. Also, more home care reinforcements and frequent maintenance visits can be considered by clinicians as a post procedural follow up option for dental implant patients with unavoidable indications for PPI usage.

4.4. Limitations

The language restriction for English in the current review caused inhibition in obtaining publications relevant to the topic from non-English database searches. The direct effect of PPIs on the tissue attachment, bone regeneration and implant healing were only enumerated. Confounding factors like chronic systemic disorders, concurrent usage of other medications and co-existing habit of smoking or other forms of tobacco habits in PPIs users were not assessed in the selected studies. Lastly, the heterogeneity of the included studies for review in terms of study population, variables evaluated and outcomes recorded was a major impediment to collate data in the form of a *meta*-analysis.

5. Conclusion

Findings from the present review are suggestive of the beneficial impact of PPIs for periodontal soft tissue attachment, potentially supporting a short term prescription to minimize the severity of periodontitis. But this recommendation of PPI as an adjunct for periodontal therapy can only be made after robust evidence is received from well controlled prospective clinical studies. Although the beneficial effect of PPI use was also observed with peri-implant soft tissue attachment, the same was not the case with peri-implant bone healing and osseointegration. While clinical studies clearly indicated a significant risk of early dental implant failure and osteoporotic jaw bone changes in patients under chronic PPI therapy, in vivo studies provided supportive evidence relating to impaired bone healing around implants and poor osseointegration based on BIC. In spite of preliminary reports suggesting the role of PPI on altering oral microbiome leading to periodontal benefits and PPI induced calcium malabsorption and osteoclastic bone lose causing poor implant osseointegration, definitive evidence needs to be established. The current review deems the necessity for additional translational and clinical studies to strengthen the aforementioned facts of association. Until such evidence is reported, health care practitioners and dentists should analyze the associated risks of PPI usage while considering the periodontal health and planned dental implant based interventions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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