Review

Effect of proton pump inhibitors on dental implants: A systematic review and meta-analysis

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Abstract

Aim: The present systematic review aims to determine the evidence on the impact of proton pump inhibitors (PPIs) on dental implants.

Settings and Design: This secondary qualitative and quantitative research was done using a pre-specified question and inclusion criteria.

Materials and Methods: A systematic search was conducted in electronic databases such as PubMed, Ovid, and Cochrane. All the studies that assessed the effect of PPIs on dental implants were included, irrespective of the design. Literature review, letter to editors, short commentaries, and opinion articles were excluded.

Results and Statistical Analysis Used: A total of three publications fulfilled the inclusion criteria. All these included articles were retrospective cohort studies; the methodological quality was assessed using Newcastle–Ottawa scale. A total of 452 implants were placed in 149 PPI users, whereas 6798 were positioned in 2241 nonusers. Of these, 43 and 212 implants failed in users and nonusers, respectively (odds ratio: 2.91, 95% confidence interval: 2.06–4.11). The meta-analysis was performed using the statistical software Review Manager, and a fixed-effect model was used to obtain the odds ratio. The success rate of implants based on age, gender, smoking, and bone augmentation could be combined only from two studies, which revealed a considerable effect of these factors.

Conclusion: As far as the available evidence is considered, it seems as if the usage of PPI has a detrimental effect on the success of dental implants. This influence needs justification as none of the included studies segregated the data based on confounding factors. Hence, there is a need to conduct well-designed, prospective, randomized clinical trials with balanced confounding factors to derive a proper conclusion.

Keywords: Dental implant, meta-analysis, proton pump inhibitors

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INTRODUCTION

The current and predictable treatment modalities for replacing missing teeth, in either fully or partially edentulous patients, are dental implants.[1,2] However, the success and prognosis of the implants depend on many factors, of which healthy bone metabolism plays a vital role.[3-5] The medications taken for systemic conditions, either directly or indirectly, influence bone metabolism.[6] Proton pump inhibitors (PPIs) are one such group of

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drugs that are commonly prescribed. These days, there is a marked increase in the usage of PPIs; many individuals are using PPIs as continuous or long-term therapy.[7,8] A significant association between PPI usage and the high risk of fractures is reported in the literature and is ascribed to osteoporotic changes.[9-15] Many studies proposed the reduction in the absorption of calcium from the intestine due to PPI-induced hypochlorhydria and disturbance in bone metabolism as the reason for decreased bone mineral density,[16-23] whereas few studies reported contradictory findings.[24-33] Although the literature is highlighting many adverse effects, many patients undergoing implants unknowingly take these medications. Hence, there is a need to systematically analyze the available evidence on the association between the intake of PPIs and the risk of dental implant failure. The proposed null hypothesis is that there exists no association between the intake of PPIs and dental implant failure.

MATERIALS AND METHODS

Focused research question

According to the PICO framework, "Does usage of PPIs (Intervention) in individuals undergoing dental implantation (Population) influence the success of an implant (Outcome) compared to controls (Control)?"

Data sources and search strategy

Comprehensive search, up to July 2019, was conducted in three major electronic databases, namely Medline via PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Ovid (http://ovidsp.ovid.com/), and Cochrane (http://www.cochranelibrary.com/). The following specific MeSH terms were used following PICO format: "Inhibitors," "Proton pump," "Dental implant," "Dental implantation," "Osseointegrated," "Failure," "Safety," "Treatment outcome." Table 1 represents the relevant MeSH terms, as well as the alternative entry terms. The PICO themes were created separately using the operator "OR" to search for terms appearing as either explored subject headings or in title or abstract. The Boolean operator "AND" was then employed to combine the descriptors of all the themes. The reference list of the final text articles was screened thoroughly for additional studies.

Study selection

Two reviewers (DNV and RK) independently selected the studies for inclusion into the review. Initially, all the identified papers were screened according to the title and abstract. Then, according to the eligibility criteria, full-text articles were retrieved. The studies that did not provide enough information to decide on inclusion or exclusion were retained for full text. Thus, the procedure involved reading and excluding the irrelevant articles in three phases: titles, abstracts, and complete articles.

Data collection and data items

All the studies that have compared the success rate of dental implants in PPI users and nonusers were included for the review. The study designs included were randomized clinical trials, nonrandomized trials, and prospective and retrospective cohort studies. Studies published in any language, until July 2019, were included. The single-arm trials, systematic and narrative reviews, opinion articles, editorials, commentaries, gray literature, and letters to the editor were excluded. In case of any disagreement between the reviewers, a consensus was attempted through discussions.

The collected information from the studies included author and year of publication, study design, sample size, participant's demographic characteristics, and the criteria considered for the success or failure of an implant.

Risk of bias in individual studies

The Newcastle–Ottawa scale for cohort studies was employed for assessing the methodological quality of selected studies by two reviewers using a system of points.[34] The assessment score consisted of three categories; group selection, comparability, and outcome assessment. The study was considered to be of good quality, if "3 or 4 stars in selection domain," "1 or 2 stars in comparability domain," and "2 or 3 stars in outcome/exposure domain" are recorded. It was considered to be of fair quality if the study gets "2 stars in selection domain," "1 or 2 stars in comparability domain," and "2 or 3 stars in outcome/exposure domain." In contrast, the study is considered to be poor if it gets "0 or 1 star in selection domain," "0 stars in comparability domain," or "0 or 1 stars in outcome/exposure domain."

Table 1: Search terms used for the systematic review

PICO	Population	Intervention	Comparison	Outcome
Characteristics considered	Adults undergoing dental implantation	PPI users	Control	Success rate
MeSH terms	Dental implant, dental implantation, osseointegrated	Inhibitors, proton pump	Control	Failure, osteoclastic bone loss
Alternative terms	Osseointegration	PPIs		Negative impact, osteoclastic activity, loss of osseointegration

PPIs: Proton pump inhibitors

Data synthesis

A meta-analysis was performed using the statistical software Review Manager (Version 5.3 Clicktime.com, Inc., San Francisco, CA, USA). A fixed-effect model was used to obtain the odd's ratio with a confidence interval (CI) of 95% to evaluate the effect of PPI usage on implant success rate. I^2 was used to quantify the impact of statistical heterogeneity. If $I^2 > 50\%$, it was considered as high heterogeneity.

RESULTS

Study selection

The response to the search strategy yielded 5428 results after duplicates removal. A total of 5404 were excluded as they did not meet the inclusion criteria. Of the 24 articles included, five full-text articles were assessed for eligibility. Of these, three publications, all retrospective cohort studies, fulfilled the inclusion criteria and were included for qualitative synthesis.[35-37] These articles were also involved in the quantitative analysis. The flow diagram showing the details of the study selection is displayed in Figure 1.

Study characteristics

The details of the study characteristics of all the included studies are represented in Table 2. The common baseline characteristics in all the studies were age, gender, and implant position. The variables such as smoking, bone augmentation, implant length, and implant diameter were considered in two articles.[35,36] On the other hand, Wu *et al.*[35] additionally mentioned the characteristics such as implant number, nonsteroidal anti-inflammatory drug (NSAIDs), and type of prosthesis. On the other hand, Chrcanovic *et al.*[36] considered implant surface, implant type, prophylactic antibiotics, bruxism, antihypertensive drugs, antidepressants, bisphosphonates, antithrombotic drugs, and immunosuppressives as baseline characteristics. The implant success and failure rates in the considered common characteristics are mentioned in Table 3.

Assessment of risk bias

The risk of bias according to the Newcastle–Ottawa scale for cohort studies of the included studies is represented in Table 4. All the studies were considered to be of good

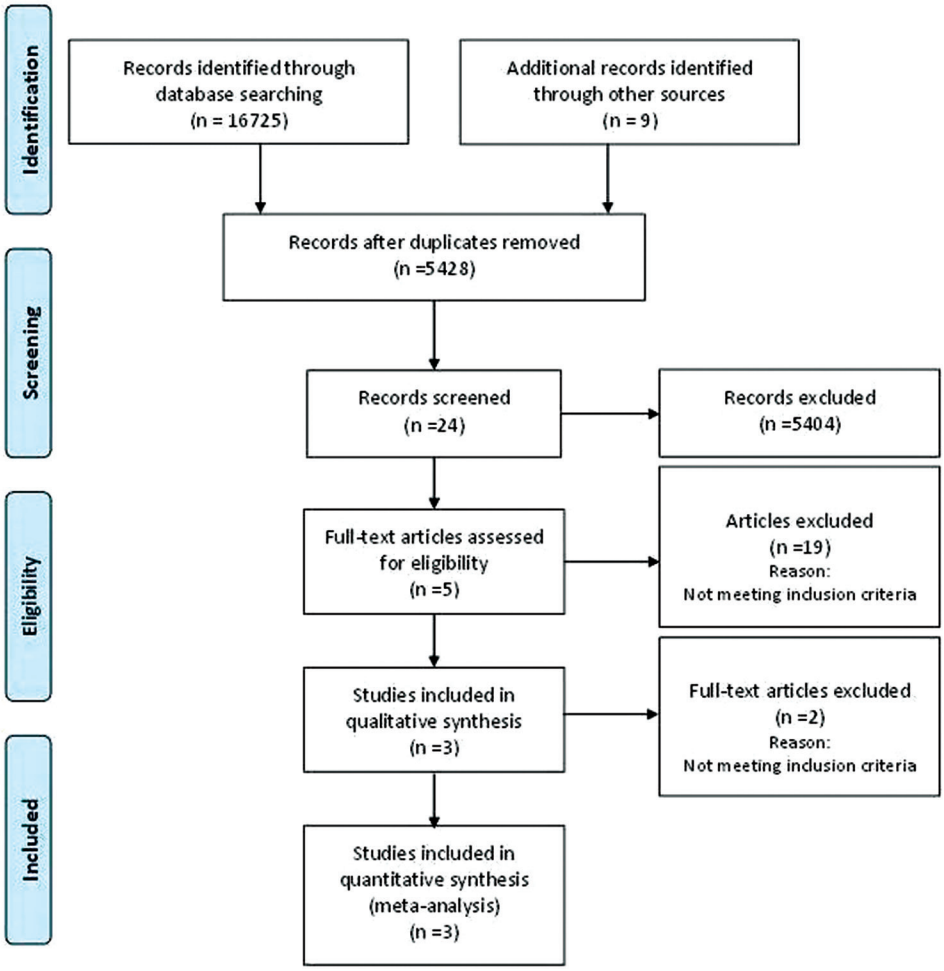

Figure 1: PRISMA diagram to show the process of study selection

Table 2: Assessment of quality of the included studies using "Newcastle-Ottawa scale for cohort studies"

Item	Chrcanovic *et al*. (2017)	Wu *et al*. (2017)	Altay *et al*. (2019)
Selection			
Representativeness of the exposed cohort	*	*	*
Selection of the nonexposed cohort	*	*	*
Ascertainment of exposure	*	*	*
Demonstration that outcome of interest was not present at start of study			
Comparability			
Comparability of cohorts controlled for confounders	**	**	**
Outcome			
Assessment of outcome	*	*	*
Was follow-up long enough for outcomes to occur	*		
Adequacy of follow-up of cohorts	*	*	*
Quality of the study	Good	Good	Good

Table 3: Common characteristics mentioned in the included studies

Variables	Chrcanovic *et al*. (2017) (*n**=999/3559)			Wu *et al*. (2017) (*n**=799/1773)			Altay *et al*. (2019) (*n**=592/1918)
	Subgroups	PPI users (*n*=67*/250)	PPI nonusers (*n*=932*/3309)	Subgroups	PPI users (*n**=58/133)	PPI nonusers (*n**=741/1640)	PPI users (*n**=24/69) and PPI nonusers (*n**=568/1849) subgroups not segregated
Age	≤30	1#	159#	≤60	75$	940$	1023$ in 316# females
	31-≤60	24#	361#	>60	57$	670$	Mean age: 48.96±13.15 years; range: 18-84
	>60	42#	412#	Missing	1$	30$	895$ in 276# males
Gender	Male	28#	451#	Male	69$	805$	Mean age 50.65±14.21 years; range: 17-87
	Female	39#	481#	Female	64$	835$	Of all, 18# females and 6# males were PPI users
Smoking	Yes	16#	247#	Yes	14$	173$	Not mentioned
	No	47#	666#	No	119$	1467$	
	Former smoker	4#	19#	Not mentioned	Not mentioned	Not mentioned	
Bone augmentation	Yes	7#	62#	Yes	56$	696$	Not mentioned
	No	64#	900#	No	77$	944$	
Implant length	6.0-10.0	29#	306#	≤10	26$	272$	Not mentioned
	10.5-14.0	52#	677#	>10	104$	1320$	
	15.0-20.0	19#	430#	Missing	3$	48$	
Implant diameter	3.0-3.5	6#	129#	Mean value of placed ones	4.2±0.5	4.1±0.4	Not mentioned
	3.7-4.1	61#	806#				
	4.2-5.0	5#	54#				
Implant location, *n* (%)	Anterior maxilla	31#	458#	Anterior	110$	1273$	506$ (26.4)
	Posterior maxilla	32#	360#	Posterior	23$	367$	603$ (31.4) in premolar region and 809$ (42.2) in molar region
	Anterior mandible	20#	235#	Maxillary	77$	1081$	961$ (50.1)
	Posterior mandible	24#	302#	Mandibular	56$	559$	957$ (49.9)

*n: Number of patients/number of implants, #Represented as number of patients, $Represented as number of implants. PPI: Proton pump inhibitors

quality. One study[36] received three stars in the selection domain, two stars in the comparability domain, and three stars in the outcome domain. Similarly, the remaining two studies[35,37] also received three stars in the selection domain, two in the comparability domain, but only two in the outcome domain. Three stars in the selection domain were given as the intervention cohort was somewhat representative of accountable care organizations, selection of nonintervention cohort was from the same community, and ascertainment of the intervention was from a secure record. Two stars in the comparability domain were given as study cohort was comparable to controls such as age, gender, and additional factors such as implant length, diameter, surface, type, location, bone augmentation, smoking, usage of other medications, and having habits such as bruxism. Three stars for one study[36] in the outcome domain were for the assessment using record linkage; enough follow-up time for the outcome to occur and for complete follow-up; and no loss to follow-up, whereas the remaining two studies[35,37] could gain only two as the follow-up time was not enough for the outcome to occur. The minimum follow-up time required for the implant success is considered to be 5 years, but the mean follow-up time of the included

studies by Wu *et al.*[35] and Altay *et al.*[37] was 16.5 months and 28.97–29.02 months, respectively. Only the study that was done by Chrcanovic *et al.*[36] had a follow-up of 94.8 months.

Data synthesis

Meta-analysis using the fixed-effect model was conducted to combine the three included studies. A total of 452 implants were placed in 149 PPI users, whereas 6798 were placed in 2241 nonusers. Of these, 43 and 212 implants failed in users and nonusers, respectively (odds ratio of 2.91; CI: 2.06–4.11), indicating significant success in nonusers [Figure 2]. The success and failure rates of the implants based on the confounding factors were mentioned only in two studies.[35,36] When the success rate in males and females was considered, 106 implants failed in a total of 2647 males whereas 134 failures occurred in a total of 2685 females (odds ratio of 0.79; CI: 0.61–1.03), projecting significant success in males [Figure 3]. When the success rate of the implants based on age was considered and combined, in subjects ≤60 years, 153 implants failed in a total of 2527 participants, whereas 86 failed in a total of 2774 participants whose age was >60 years (odd's ratio of 2.13; CI: 1.62–2.80), thus pointing significant success in participants whose age is >60 years [Figure 4]. When the success rate of the implants based on the smoking status was combined, 96 implants out of 1268 failed in smokers whereas 133 failed in 3969 nonsmokers (odds ratio of 2.28; CI: 1.72–3.02), indicating significant success in nonsmokers [Figure 5]. When the success rate of the implants based on bone augmentation was

Table 4: Dental implant success and failure rates in the included studies based on the considered variables

Factor	Sub-groups	Chrcanovic *et al.* (2017) (*n*=3559)		Subgroups	Wu *et al.* (2017) (*n*=1773)		Subgroups	Altay *et al.* (2019) (*n*=1918)	
		Survived implants, *n* (%)	Failed implants, *n* (%)		Survived implants, *n* (%)	Failed implants, *n* (%)		Survived implants, *n* (%)	Failed implants, *n* (%)
PPI usage	Users	220 (88)	30 (12)	Users	124 (93.2)	9 (6.8)	Users	65 (94.2)	4 (5.8)
	Nonusers	3161 (95.5)	148 (4.5)	Nonusers	1587 (96.8)	53 (3.2)	Nonusers	1838 (99.4)	11 (0.6)
Age	≤30	244 (96.1)	10 (3.9)	≤60	973 (95.9)	42 (4.1)	*	*	*
	31-≤60	1157 (92)	101 (8)	>60	708 (97.4)	19 (2.6)	*	*	*
	>60	1980 (96.7)	67 (3.3)	Missing	30 (96.8)	1 (3.2)	*	*	*
Gender	Male	1695 (95.6)	78 (4.4)	Male	846 (96.8)	28 (3.2)	*	*	*
	Female	1686 (94.4)	100 (5.6)	Female	865 (96.2)	34 (3.8)	*	*	*
Smoking	Yes	999 (92.4)	82 (7.6)	Yes	173 (92.5)	14 (7.5)	*	*	*
	No	2298 (96.4)	85 (3.6)	No	1538 (97)	48 (3)	*	*	*
	Former smoker	84 (88.4)	11 (11.6)	*	*	*	*	*	*
Bone Augmentation	Yes	122 (89.1)	15 (10.9)	Yes	719 (95.6)	33 (4.4)	*	*	*
	No	3259 (95.2)	163 (4.8)	No	992 (97.2)	29 (2.8)	*	*	*
Implant length	6.0-10.0	642 (89.5)	75 (10.5)	≤10	288 (96.6)	10 (3.4)	*	*	*
	10.5-14.0	1682 (96.2)	67 (3.8)	>10	1373 (96.4)	51 (3.6)	*	*	*
	15.0-20.0	1057 (96.2)	36 (3.3)	Missing	50 (98)	1 (2)	*	*	*
Implant diameter	3.0-3.5	287 (93.8)	19 (6.2)	*	*	*	*	*	*
	3.7-4.1	3022 (95.1)	157 (4.9)	*	*	*	*	*	*
	4.2-5.0	72 (97.3)	2 (2.7)	*	*	*	*	*	*
Implant location	Anterior maxilla	1141 (94)	73 (6)	Anterior	*	*	*	*	*
	Posterior maxilla	663 (94.2)	41 (5.8)	Posterior	*	*	*	*	*
	Anterior mandible	925 (97.4)	25 (2.6)	Maxillary	*	*	*	*	*
	Posterior mandible	652 (94.4)	39 (5.6)	Mandibular	*	*	*	*	*

*Not reported in the article. *n*: Number of implants

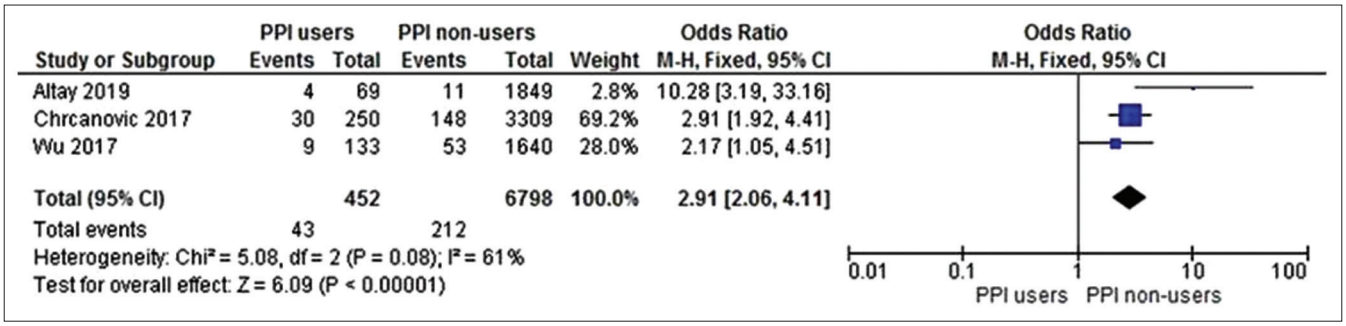

Figure 2: Forest plot from the fixed-effect meta-analysis evaluating the difference in implant failure between proton pump inhibitor users and nonusers

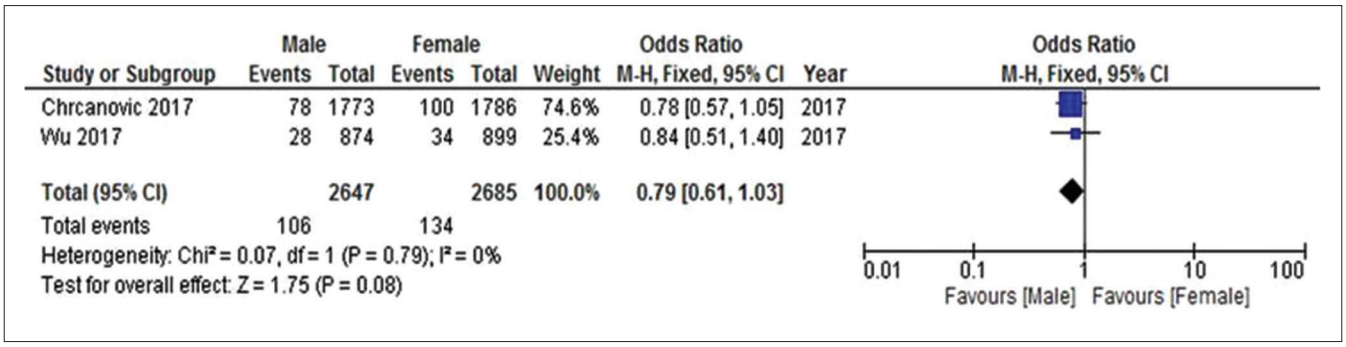

Figure 3: Forest plot from the fixed-effect meta-analysis evaluating the difference in implant failure between males and females

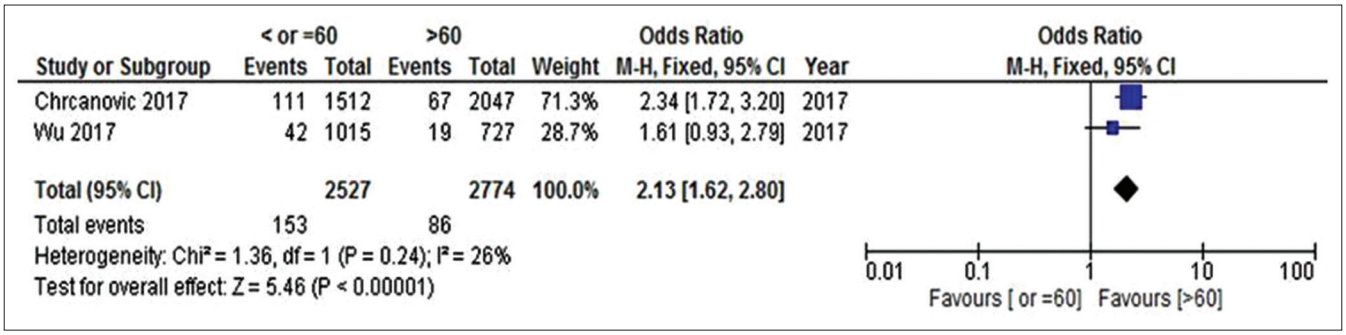

Figure 4: Forest plot from the fixed-effect meta-analysis evaluating the difference in implant failure between ≤60 and >60 years of age groups

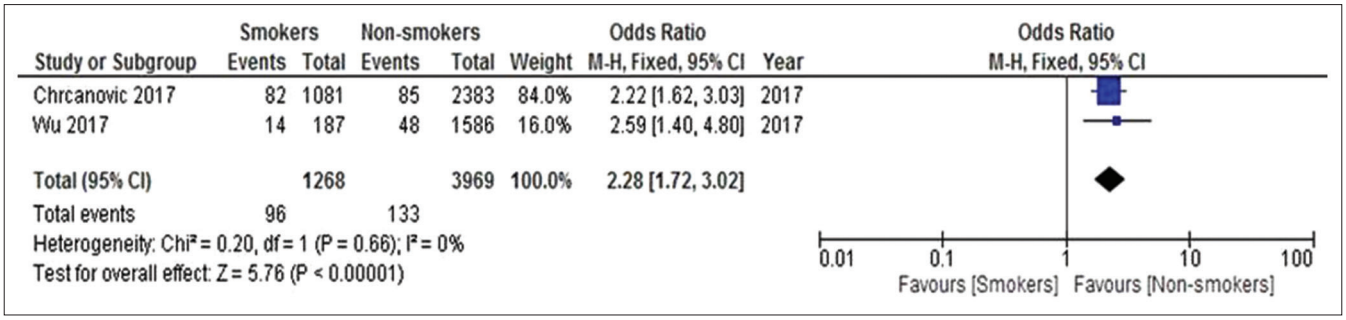

Figure 5: Forest plot from the fixed-effect meta-analysis evaluating the difference in implant failure between smokers and nonsmokers

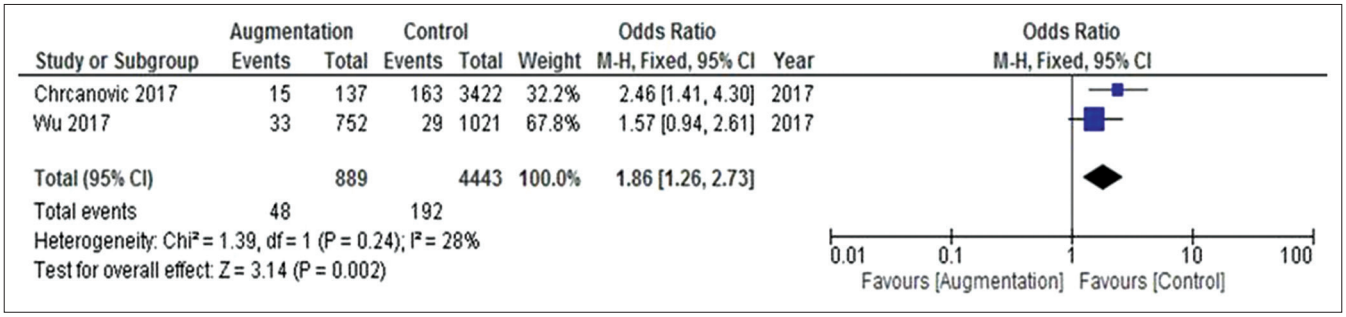

Figure 6: Forest plot from the fixed-effect meta-analysis evaluating the difference in implant failure between bone augmentation and control

considered, 48 implants out of 889 failed in patients who have undergone bone augmentation, whereas 192 failed in 4443 patients who did not undergo augmentation (odd's ratio of 1.86; CI: 1.26–2.73), projecting significant success in nonaugmentation cases [Figure 6].

DISCUSSION

The association between PPI usage and bone metabolism has been studied extensively with contradictory findings.[22-33] The mechanism has been attributed to the influence of the medication on calcium metabolism by

reducing its absorption.[17-20] It has been reported in the literature that postprandial calcium concentration did not increase in subjects on PPI, whereas control subjects demonstrated an apparent increase in serum calcium. In addition, reduced urine excretion of calcium in PPI users compared to control was also observed.[18] It has been attributed to the reduction in gastric acid production, thereby decreasing the calcium solubility, which is a prerequisite for the intestinal absorption of calcium to occur from ingested food or calcium salts. However, certain studies have negated this association and reported that PPI could not influence calcium absorption. These studies have attributed this observation to the fact that calcium absorption occurs in the small intestine where the pH of the contents is typically between 6 and 7, even without PPI therapy.[38,39] Thus, regardless of the secretion of gastric acids, as the pH of the chyme in the duodenum remains relatively constant, PPI does not affect the absorption. In a study done on postmenopausal women,[24] 30 days of continuous PPI therapy could not decrease intestinal calcium absorption. Even no change in parathyroid hormone (PTH), serum calcium, and urine calcium levels was observed, providing further evidence that PPIs do not alter calcium absorption or calcium balance in the short term. Thus, there is still uncertainty in the association between PPI-related hypochlorhydria and a decrease in calcium absorption.

Another mechanism that has been proposed was that PPI suppresses gastric acid production by inhibiting the hydrogen/potassium adenosine triphosphatase (H+/K+ ATPase) located on the parietal gastric cells.[23,40] These proton pumps are also found in the plasma membrane of osteoclasts, which decrease the osteoclast activity. Thus, another possibility is the interference of PPIs on bone cells by reducing bone turnover. The inhibition of phosphoetanol amine/phosphocholine phosphatase and tissue nonspecific alkaline phosphatase in the bone matrix vesicles has been anticipated as the reason for decreasing osteoblastic matrix mineralization.[41] Further, it has been proposed that PPI also reduces the expression of bone formation markers such as bone morphogenetic protein 2, bone morphogenetic protein 4, and cysteine-rich protein.[42] However, a short-term study found no significant effect on bone turnover in children although osteoblast and osteoclast activities are more intensive during childhood and adolescence than in adulthood.[32] The indirect effect of PPI on the induction of hyperplasia and hypertrophy of parathyroid glands resulting in elevated PTH, leading to disturbance in bone strength and quality, is a possible alternative explanation suggested.[43]

Additional mechanisms are also proposed that might have an adverse effect on bone metabolism only on the prolonged use of PPI. The first one, being the effect of hypochlorhydria on Vitamin B12 leading to deficiency, leading to peripheral neuropathy, which increases the risk of fractures due to falls.[13] Another possibility is the influence on the cross-linking of bone collagen due to high homocysteine levels due to Vitamin B_{12} deficiency.[44] Hypomagnesemia, due to reduced absorption of magnesium, might also exert both direct and indirect unfavorable effect on bone metabolism.[45] The underlying condition for which the medication is prescribed might also be the reason for osteoporosis.

Although adverse effects of PPI on bone have been extensively studied,[9-33,40-43] the adverse effect on bone-related clinical conditions such as osseointegration of dental implants has been barely studied. The osseointegration of the dental implant, which is the structural and functional connection between living bone and the dental implant surface, depends on bone metabolism. Furthermore, the bone formation and remodeling play a crucial role in the survival of the implant. Thus, any medication that affects bone homeostasis can influence the osseointegration of the dental implant. PPIs are one such systemic medication, most widely prescribed worldwide, that is proposed to influence bone metabolism. The results of the present review also suggest that the intake of PPIs is associated with an increased risk of dental implant failure. However, the results need to be understood with caution. Many factors affect the success and prognosis of the dental implant. The influence of these confounding factors is one aspect that has been neglected in the included retrospective studies. The studies have mentioned the distribution of participants based on the demographic characteristics such as age, gender, use of other medications such as NSAIDs, antibiotic prophylaxis, parafunctional habits such as bruxism, implant length, implant diameter, implant position, quality of bone, bone augmentation, and lifestyle changes such as smoking and type of prosthesis.[35-37] However, none of these have assessed the success rate of implants based on these factors. The present meta-analysis has projected that age, gender, smoking, and bone augmentation have a clear influence on the success of implants. The success was favoring males, age group >60 years, nonsmokers, and those who did not undergo bone augmentation. Another important aspect that is not given proper importance is the difference between short-term and chronic users, as duration and even dose components are both important factors that need to be considered. Even the type of PPI used is important as different PPIs have different

effects on bone quality. Further, the effect of prosthetic loading on the success of an implant is also an essential factor, which was considered only in one study.[37] The retrospective studies have additional limitations such as incomplete records leading to gaps in the information. All these aspects necessitate the requirement to conduct well-balanced studies with prospective cohort design and long-term randomized clinical trials with a large sample size to derive proper conclusions.

CONCLUSION

Based on the included retrospective studies, there seems to be an association between PPI and implant failure and theoretically may influence the success of a dental implant. However, in the included studies, there is no segregation of success rate, based on the confounding factors. Because of this methodological limitation, the results of these studies are difficult to interpret and apply clinically. Hence, there is a definite need to conduct well-balanced, randomized clinical trials to know the exact association.

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Conflicts of interest
There are no conflicts of interest.

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