

Medication-related dental implant failure: Systematic review and meta-analysis

Vivianne Chappuis¹  | Gustavo Avila-Ortiz²  | Mauricio G. Araújo³ | Alberto Monje¹ 

¹Department of Oral Surgery and Stomatology, School of Dental Medicine, University of Bern, Bern, Switzerland

²Department of Periodontics, College of Dentistry, University of Iowa, Iowa City, IA, USA

³Department of Dentistry, State University of Maringa, Maringa, Brazil

Correspondence

Vivianne Chappuis, Department of Oral Surgery and Stomatology, School of Dental Medicine, University of Bern, Bern, Switzerland.

Email: vivianne.chappuis@zmk.unibe.ch



Abstract

Objectives: The aim of this systematic review was to investigate the association between the intake of systemic medications that may affect bone metabolism and their subsequent impact on implant failures.

Material and methods: Electronic and manual literature searches were conducted. Implant failure (IF) was the primary outcome, while biological/mechanical and the causes/timing associated with IF were set as secondary outcomes. Meta-analyses for the binary outcome IF and odds ratio were performed to investigate the association with medications.

Results: A final selection of 17 articles was screened for qualitative assessment. As such, five studies focused on evaluating the association of implant failure and non-steroidal anti-inflammatory drugs (NSAIDs), two on selective serotonin reuptake inhibitors (SSRIs), two on proton pump inhibitors (PPIs), seven on bisphosphonates (BPs), and one on anti-hypertensives (AHTNs). For PPIs, the fixed effect model estimated a difference of IF rates of 4.3%, indicating significantly higher IF rates in the test compared to the control group ($p < 0.5$). Likewise, for SSRIs, the IF was shown to be significantly higher in the individuals taking SSRIs ($p < 0.5$) as estimated a difference of 7.5%. No subset meta-analysis could be conducted for AHTNs medications as only one study fulfilled the inclusion criteria, which revealed an increased survival rate of AHTN medication. None of the other medications yielded significance.

Conclusions: The present systematic review showed an association of PPIs and SSRIs with an increased implant failure rate. Hence, clinicians considering implant therapy should be aware of possible medication-related implant failures.

KEYWORDS

biological complications, dental implant, drug, endosseous implant, epidemiology, failure, medication

1 | INTRODUCTION

Increasing life expectancy of global demographical trends revealed not only an estimated increase in a world population of 50 million

The present systematic review was prepared as part of the 6th International Team of Implantology (ITI) Consensus Meeting hold in Amsterdam in April, 2018.

annually (Srinivasan et al., 2017), but as populations are aging, the prevalence of disabling disease and the related intake of medications increases steeply with age (Collaborators, 2017). Even though implant-supported rehabilitations are a highly successful treatment option with predictable long-term success rates after 10 and 20 years (Chappuis et al., 2013; Chappuis et al., 2018), the possible

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impact of disabling systemic diseases on implant rehabilitation has been described in systematic reviews (Beikler and Flemmig, 2003; Bornstein et al., 2009; Diz et al., 2013; Donos and Calciolari, 2014; Mombelli and Cionca, 2006; Scully et al., 2007). These uncontrolled medical conditions may have an effect at the local or systemic level and have been associated with an increased risk of breakdown of the peri-implant tissues (Heitz-Mayfield & Huynh-Ba, 2009; Heitz-Mayfield, Needleman, Salvi & Pjetursson, 2014; Lang et al., 2011; Lang et al., 2004; Monje, Catena & Borgnakke, 2017). Systemic diseases as obesity, arthritis, and other chronic diseases induce a low-grade systemic inflammatory condition associated with high levels of circulating pro-inflammatory cytokines that favor the chemotaxis and activations of monocytes, neutrophils, and adipose tissue macrophages, which may ultimately contribute to the establishment of bone loss and peri-implant disease (Hill, Reid Bolus & Hasty, 2014; Straub et al., 2015; Wei, Tarling, McMillen, Tang & LeBoeuf, 2015).

In addition to uncontrolled systemic diseases itself, the systemic intake of medication such as thiazide diuretics, β -blockers, anti-inflammatory drugs, proton pump inhibitors, or serotonin reuptake inhibitors have shown to further modulate bone metabolism (Abrahamsen and Vestergaard, 2013; Brater, 1998, 2011; de Vernejoul et al., 2012; Geusens et al., 2013; Haney & Warden, 2008; Vestergaard, 2008; Wiens et al., 2006). These medication-related side effects are less understood and may exert an important influence on implant-related outcomes. Therefore, in recent demographical trends with an aging population, a comprehensive assessment and understanding of the patient's medical background is important, as related medication-specific side effects are able to influence bone metabolism (Insua, Monje, Wang & Miron, 2017; Kremers et al., 2016).

Osteocytes play a crucial role in bone turnover processes, such as osseointegration, and are a major source of receptor activator of nuclear factor-kappaB ligand (RANKL) in bone (O'Brien, Nakashima & Takayanagi, 2013), which is required for osteoclast differentiation and activation (Kong et al., 1999). Hence, in case of medication-induced disruption of osteocyte metabolic activities, adequate peri-implant bone remodeling in early stages of healing may be jeopardized. Likewise, anti-hypertensive medications, such as β -blockers or angiotensin-converting enzyme inhibitors, have been shown to inhibit the normal physiologic function of osteoclasts on bone by blocking surface β -2 adrenergic receptors, which may result in shifting the balance toward bone formation by blocking the renin-angiotensin system (Brater, 1998, 2011). Furthermore, the action of serum serotonin reuptake inhibitors (SSRIs) on certain receptors and serotonin transporters, such as 5-HT1B, 5-HT2B or 5-HT2C, may result in a direct detrimental effect on bone metabolism by increasing osteoclast differentiation (Haney & Warden, 2008; Vestergaard, 2008), which may negatively impact the process of osseointegration.

A comprehensive assessment and understanding of the patient's medical background and current medications is important for life-long implant-supported rehabilitations. Therefore, the aim of this systematic review was to investigate the association between the intake of medications that may affect bone metabolism and implant outcomes.

2 | MATERIAL AND METHODS

This systematic review was conducted according to the guidelines of the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). The review protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) hosted by the UK's National Institute for Health Research (NHS), University of York, Centre for Reviews and Dissemination, under the code CRD42017067170 (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017067170)

2.1 | Focused questions

1. Is there an association between medication intake and implant outcomes (i.e., implant failure)? (Primary question)—If answer is “yes,” then:
2. What are these medications and the respective dosage associated with implant failure? (Secondary question)
3. Does implant failure occur in the early stages of healing or after osseointegration is attained (i.e., biological complications) (Secondary question)
4. Are these patients associated with more mechanical complications?
5. Are there any other confounders associated with implant failure in medicated patients? (Secondary question)
6. What is the strength of the evidence for associations between medication intake and implant failure? (Secondary question)

2.2 | PECO question (population, exposure, comparison, and outcome measures) (Stone 2002).

P: Completely or partially edentulous human adults wearing implant-supported prostheses.

E: Regular intake of oral, intramuscular, or intravenous medications/drugs that may affect bone metabolism.

C: Individuals not taking any known relevant medication (Non-specific medication dependent for the treatment of a medical condition.)

O: Dental implant failure (primary outcome), peri-implant marginal bone loss (secondary outcome), and biological (i.e., peri-implant mucositis or peri-implantitis) or mechanical complications reported at the implant or patient level (secondary outcomes).

2.3 | Eligibility criteria

Prospective or retrospective cohort, case-control, cross-sectional, or randomized controlled trials exploring the association of medication intake and implant failure in humans were considered for inclusion.

2.3.1 | Literature search protocol

Electronic and manual literature searches were conducted independently by two authors (AM, VC) in several databases, including

PubMed, MEDLINE (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials (Cochrane Library), Cochrane Oral Health Group Trials Register (Cochrane Library), Web of Science (Thomson Reuters), and SciVerse (Elsevier). Studies published up to May 2017 were considered, without any language restrictions. For the PubMed library, combinations of controlled terms (MeSH and Emtree) and keywords were used whenever possible, and other terms not indexed as MeSH and filters were also applied. The search strategy used was (((("dental implants" OR ("dental implantation, endosseous") OR "dental implantation, endosseous"[MeSH Terms]) AND "abnormalities, drug-induced"[MeSH Terms]) OR "serotonin uptake inhibitors"[MeSH Terms]) OR "anti-inflammatory agents, non-steroidal"[MeSH Terms]) OR "adrenergic beta-antagonists"[MeSH Terms]) OR "angiotensin-converting enzyme inhibitors"[MeSH Terms]) OR "proton pump inhibitors"[MeSH Terms]) OR "bisphosphonates"[MeSH Terms]) OR "bisphosphonate-associated osteonecrosis of the jaw"[MeSH Terms]) AND "survival analysis"[MeSH Terms] AND ((Classical Article[ptyp] OR Clinical Study[ptyp] OR Clinical Trial[ptyp]) AND "humans"[MeSH Terms]). Moreover, a less specific screening using non-MeSH index terms was conducted to ascertain the articles to be evaluated. The screening strategy was as follows: (((medication-related[Title/Abstract] OR drug-related[Title/Abstract] OR bisphosphonate-related[Title/Abstract]) AND dental implant failure[Title/Abstract]) OR dental implant survival[Title/Abstract]) OR (("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("dental"[All Fields] AND "implant"[All Fields]) OR "dental implant"[All Fields]) AND biological complication[Title/Abstract]) OR (("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("dental"[All Fields] AND "implant"[All Fields]) OR "dental implant"[All Fields]) AND technical complication[Title/Abstract]). On the other side, for the EMBASE Library, the key terms used were as follows: ('dental implant'/exp OR 'dental implants') OR ('endosseous implant' OR 'endosseous implants') AND ('medication-related'/exp OR 'medications-related') OR 'drug-related'/exp OR 'drugs-related' AND 'implant failure'/de AND 'human'/de AND 'article'/it. For searching the remaining electronic databases, combinations of 'medication-related' OR 'drug-related' AND 'dental implant' AND 'failure' OR 'survival', limited to titles and abstracts.

Additionally, the "grey literature" available at the New York Academy of Medicine Grey Literature Report (<http://greylit.org>) and the register of clinical studies hosted by the US National Institutes of Health (www.clinicaltrials.gov) was searched to further identify potential candidates for inclusion. Moreover, the authors conducted manual searches in selected journal issues published between January 2017 and August 2017 (i.e., *Journal of Dental Research*, *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Oral and Maxillofacial Implants*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *The International Journal of Periodontics & Restorative Dentistry*, and *the International Journal of Oral and Maxillofacial Surgery*). Bibliographies of identified relevant publications were also cross-searched.

2.4 | Literature selection and data extraction protocol

Corresponding authors were contacted for clarifying information about studies lacking clear information. Two independent examiners (AM and VC) extracted the data. Data of interest were extracted based on the general study characteristics (authors and year of publication, type of study), population characteristics (number of participants), implant and prosthetic characteristics (number of implants, implant location, type of prosthetic loading, follow-up period after implant placement), and primary and secondary outcomes.

2.5 | Risk of bias

The methodological and reporting quality of all selected full-text reports was assessed according to the STROBE statement for observational studies (Shea et al. 2009; von Elm et al. 2007). Moreover, the Assessment of Multiple Systematic Reviews guidelines (AMSTAR) was followed (Shea et al. 2009).

2.6 | The Newcastle–Ottawa Scale for assessing the quality of non-randomized studies (NOS)

Assessment of the quality of non-randomized, non-interventional studies is essential for proper evaluation of the evidence provided by each study. We followed the Newcastle–Ottawa System (NOS) protocol (Wells et al. 2011). The items evaluated were selection of study groups, comparability of participants, and outcome. Each included study received a maximum score of 13 points for cohort studies and 10 points for case–control studies (Table S1). The Cohen's kappa coefficient was calculated to assess inter-rater agreement (AM and GAO).

2.7 | Statistical analysis

The statistical analysis was performed with the statistical software package R 3.1.1 (The R Project for Statistical Computing, www.r-project.org). The feasibility of conducting specific quantitative analyses (meta-analyses) was explored. If feasible, the additional package "meta" was used. Meta-analyses for the binary outcome implant failure (IF) were performed. The numbers of implants in both experimental and control groups were extracted directly from the data; the numbers of failures had to be calculated from the reported failure rates. As aforementioned, studies with missing information were excluded from the quantitative analysis.

The odds ratio of failure in the test group (individuals in-taking medications) vs. failure in the control group (individuals not taking any known relevant medication) was analyzed. Estimated odds ratios together with 95% confidence intervals were calculated for every included study as well as for the pooled set of studies. The studies were pooled using the inverse variance method. Both fixed and random weights were applied, yielding two different estimates

of the population odds ratio. The heterogeneity among the included studies was measured computing I^2 and a p value for the null of homogeneous studies. This p value was compared to the level of significance of 5%.

3 | RESULTS

3.1 | Study selection (Figure 1)

A total of 430 entries were identified through the electronic search, and after removal of duplicates. The initial pool was not supplemented with any further article identified through manual search or cross-reference assessments. Of these 430, forty articles were assessed for full-text evaluation, resulting in a final selection of 17 articles for qualitative assessment (Table 1) (Alissa et al., 2009; Al-Sabbagh, Robinson, Romanos & Thomas, 2015; Chrcanovic, Kisch, Albrektsson & Wennerberg, 2017a,b; Famili, Quigley & Mosher, 2011; Grant, Amenedo, Freeman & Kraut, 2008; Jeffcoat et al., 1995; Koka, Babu & Norell, 2010; Memon, Weltman & Katancik, 2012; Reddy, Jeffcoat & Richardson, 1990; Siebert, Jurkovic, Statelova & Strecha, 2015; Urdaneta, Daher, Lery, Emanuel & Chuang, 2011; Winnett, Tenenbaum, Ganss & Jokstad, 2016; Wu et al., 2014, 2016, 2017; Zahid, Wang & Cohen, 2011). A total of 23 articles did not meet the eligibility criteria and were subsequently excluded (Table 2).

The studies included for qualitative assessment were pooled according to the medication category. As such, five studies were focused on evaluating the association of implant failure and non-steroidal anti-inflammatory drugs (NSAIDs) (Alissa et al., 2009; Jeffcoat et al., 1995; Reddy et al., 1990; Urdaneta et al., 2011; Winnett et al., 2016), two on selective serotonin reuptake inhibitors (SSRIs) (Chrcanovic et al., 2017b; Wu et al., 2014), two on proton pump inhibitors (PPIs) (Chrcanovic et al., 2017a; Wu et al., 2017), seven on oral bisphosphonates (BPs) (Al-Sabbagh et al., 2015; Famili et al., 2011; Grant et al., 2008; Koka et al., 2010; Memon et al., 2012; Siebert et al., 2015; Zahid et al., 2011), and one on anti-hypertensives (AHTNs) (Wu et al., 2016).

3.2 | Studies methods

With regard to research methodology, the vast majority of the included articles (12) were based on retrospective cohort studies (RC) (Chrcanovic et al., 2017a,b; Famili et al., 2011; Grant et al., 2008; Koka et al., 2010; Memon et al., 2012; Urdaneta et al., 2011; Winnett et al., 2016; Wu et al., 2014, 2016, 2017; Zahid et al., 2011), three were randomized controlled trials (RCT) (Alissa et al., 2009; Jeffcoat et al., 1995; Reddy et al., 1990), one prospective cohort (PC) (Siebert et al., 2015), and one case-control (CC) (Al-Sabbagh et al., 2015).

3.3 | Association of medication-related implant failure

Overall, five groups could be pooled according to the medication type. For hypertension-related medication-associated implant

failure (i.e., beta-blockers or ACE inhibitors), only one study could be identified and accordingly, no subset meta-analysis could be carried out. For NSAIDs, the analysis could not be performed, as the vast majority of studies reported no failures in any of the control or experimental groups. For PPIs, the homogeneity of the two included studies was rejected at the 5% level ($I^2 = 0.93$, $p < .01$). Hence, the results should be interpreted carefully. Both the fixed effects and the random effects model estimated a difference of implant failure (IF) rates of 4.29% and 4.53%, meaning significantly higher IF rates in the test compared to the control group ($p < .01$) (Figure 2). Likewise, for SSRIs, the homogeneity of the two studies was rejected at the level 5% ($p < .01$). Both the fixed effects and the random effects model estimated a large positive difference of 7.48% and 7.50%, rendering significantly higher IF rates in the test compared to the control group ($p < .01$) (Figure 3). With regard to IF associated with the intake of BPs, one study (Al-Sabbagh et al., 2015) was excluded from the analysis due to missing IF in the control group. Using the IF rate as the primary outcome in the analysis, studies with a 0 IF rate in either the experimental or the control group were assigned a weight of 0, because the estimated standard deviation is 0. The remaining six studies were weighted and the estimated differences were -0.13 in the fixed effects model and 0.86 in the random effects model (Figure 4). These results must be interpreted cautiously due to a high heterogeneity of $I^2 = 98\%$ ($p < .01$ for the test of homogeneity among the included studies).

No analysis was conducted for secondary outcomes. Implant survival (IS) was redundant to the primary outcome IF, whereas marginal bone loss (MBL) and timing of failure (TF) were reported in too few studies.

3.4 | Odds ratio for implant failure according to the medication intake

No subset meta-analysis could be conducted for AHTNs medications as only one study fulfilled the inclusion criteria, which revealed an increased survival rate of AHTN medication. For PPIs, the homogeneity of the two studies could not be rejected at the 5% level ($I^2 = 0$, $p = 0.78$). Both the fixed effects and the random effects model estimate an odds ratio of a failure in the experimental group against a failure in the control group of 2.02. The corresponding 95% confidence interval does not contain 1.00, so there is a significant effect of the medication ($p < .05$) (Figure 2). Likewise, for SSRIs, the homogeneity of the two studies could be rejected at the 5% level ($I^2 = 0$, $p = .36$). The fixed effects model estimated an odds ratio of IF in the experimental group against failure in the control group of 2.92; the random effects model resulted in 3.00 (Figure 3). Thus, a significant effect of the experimental medication was found ($p < .05$). When analyzing oral BPs, one study (Al-Sabbagh et al., 2015) was excluded from the analysis due to missing IF in the control group, as previously mentioned. For the remaining six studies, the homogeneity could not be rejected at the 5% level ($I^2 = 27$, $p = .24$). The fixed effects model estimated an odds ratio of failure in the experimental group against failure in the control group of 1.11, while the random effects model indicated an

TABLE 1 On the medication-related implant failure: systematic review [In PDF format, this table is best viewed in two-page mode]

Authors (year)	Study design	Mean follow-up	Systemic condition	Medication	Dosage (mg/ml)	Therapy length (months)	Administration method	Subjects (n)	Age (years)
Wu et al. (2016)	RC	17.1 ± 16.6	Hypertension	AM (beta-blockers - 18.9%, thiazide diuretics - 5.4%, ACE inhibitors - 29.7%, ARBs - 24.3%, others - 21.6%)	NR	NR	Oral	142	57.7 ± 12.1
			ASA I-II	NSM	N	N	N	586	
Alissa et al. (2009)	RCT	6	ASA I-II	NSAIDs (Ibuprophen)	600 mg	4×/day 7 d	Oral	29	NR
				NSM	N	N	N	29	
Jeffcoat et al. (1995)	RCT	12	ASA I-II	NSAIDs (Flurbiprofen)	50 mg	2× day 3 mo	Oral	29	47.2
				Flurbiprofen	100 mg	2× day 3 mo	Oral		
				NSM	N	N	N		
Winnett et al. (2014)	RC	NR	NC	NSAIDs (Ibuprophen)	600 mg	4× day 2w	Oral	60	NR
				NSM	N	N	N	44	
Urdaneta et al. (2011)	RC	70.7	Arthristis, CDV prevention	NSAIDs (Ibuprophen, celecoxib, acetylsalicydic, rofecoxib, nabumetone, naproxen, etodolac)	ibuprophen (600–1600 mg), celecoxib (200 mg), acetylsalicydic (325 mg), rofecoxib (25 mg), nabumetone (500 mg), naproxen (375 mg), etodolac (400 mg)	Daily	Oral	13	NR
			ASA I-II	NSM	N	N	n	68	
Wu et al. (2016)	RC	16.6 ± 16.3	Gastric function abnormalitis	PPI	NR	NR	Oral	58	56.6 ± 13.7
			ASA I-II	NSM	N	N	n	741	
Wu et al. (2014)	RC	36	Depressive condition	SSRIs (citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, indalpine, paroxetine, sertraline, venlafaxine, zimeline)	NR	NR	Oral	50	56.4 ± 13.7
			ASA I-II	NSM	N	N	N	440	
Reddy et al. (1990)	RCT	4	ASA I-II	NSAIDs (Flurbiprofen)	100 mg	2× day 4 mo	Oral	NR	NR
				NSM	N	N	N		
Chrcanovic et al. (2017)	RC	94.8 ± 78.7	Gastric function abnormalitis	PPI	NR	NR	NR	67	60.4 ± 15.9
			ASA I-II	NSM	N	NR	NR	932	
Chrcanovic et al. (2017)	RC	90.11 ± 74.23	Depressive condition	SSRIs	NR	NR	NR	18	55.9 ± 18.5
			ASA I-II	NSM	N	N	NR	282	
Al-Sabbagh et al. (2014)	CC	84.6	Osteoporosis	BP	NR	>3	Oral	20	515
			ASA I-II	NSM			N	183	
Siebert et al. (2013)	PC	12	Osteoporosis	Zoledronic	5 mg/year	NR	IV	12	54 ± 12
			ASA I-II	NSM	N	N	N	12	

(Continues)

TABLE 1 (additional columns)

Gender (M/F)	Implants (n)	Failure (month)	Marginal bone loss (mm)	Implant survival rate(%)	Implant failure rate (%)	HR (95% CI)	Biological complications	Comments
375/353	327	NR	NR	99.4	0.6	0.12 (0.03–0.49)	NR	1. BA was performed more often in AH drug users (OR = 0.71) 2. Age, gender, implant length, implant torque, implant loading and BA did not affect SR 3. HT patients not taking AH drugs had a failure of 4.7% 4. Smoking was associated with increased implant failure (HR: 3.59)
	1172	NR	NR	95.9	4.1	1	NR	
NR	41	N	1.09 ± 0.99	100	0	NR	0	1. The multiple linear regression test showed that MBL was not SS associated with: age, gender, anatomic location, treatment group and examiner
	48	N	1.19 ± 0.96	100	0	NR	0	
NR		N	0.65	100	0	NR	NR	1. Quantitative digital subtraction radiography was used to assess bone mass loss 2. Placebo and low-dose flurbiprophen lost a mean of 11.2 ± 3.89 and 14.6 ± 3.69 mg, respectively.
		N	1.6	100	0	NR		3. High-dose flurbiprophen lost a mean of 2.60 ± 4.13 mg
		N	1.1	100	0	NR		4. Smooth surface dental implants
NR	273	Early:72%; late:28%	NR	56	44	NR	NR	1. Retrospective data based on university setting. 2. The NSAIDs experienced 3.2× more case of radiographic bone loss 1/2 and 1.9× greater than 1/2 of the implant height
	203	Early:65%; late:35%		62	38	NR		
NR	61	NR	0.06	100	0	NR	NR	1. Study on extra-short locking-taper implants 2. Main goal was to analyze crestal bone gain 3. Crestal bone gain was significantly correlated with type of opposing structure, tooth, type of restoration, crown cemented on prefabricated titanium abutment, hydroxiapatite coating, implant site and daily intake of NSADS (p = 0.04) 4. Similar bone gain was observed in men/woman, maxilla/mandible
	265		0.42	97.74	2.26	NR	NR	
369/430	133	NR	NR	93.2	6.8	2.73 (1.10–6.78)	NR	1. Large RC study with different implan ttypes, protocols and grafting procedures 2. NSAIDs were taken more by PPI users (OR = 1.73) 3. Smoking was associated with IF (p = 0.001) 4. Patients gender, age implant length, and bone augmentation had no significant association with IF
	1,640			96.8	3.2	1		
198/292	94	4–14 mo	NR	89.4	10.6	6.28 (1.25–31.61)	NR	1. Large RC study with different implan ttypes, protocols and grafting procedures 2. Smoking habit (p = 0.01) and small implant diameters (p = 0.02) were associated with higher IF 3. Bone augmentation was associated with higher implant failure
	882			95.4	4.6	1		
NR	NR	NR	NR	100	0	NR	NR	1. Main goal was to assess the peri-implant bone remodeling testing the feasibility of digital subtraction radiography 2. No data on patients demographics nor implant characteristics 3. Individuals intaking the NSAIDs experienced greater peri-implant bone density during healing
				100	0	NR		
479/520	250	Early:late = 1.34:1	NR	88	12	2.81 (1.13–6.93)	NR	1. Retrospective database on university setting. 2. Multilevel mixed effects parametric survival analysis conducted for the association between PPI and IF 3. Multifactorial analysis detected bruxism (HR = 2.86), smoking (HR = 2.36, short implant length (HR = 1 to >10 mm HR = 0.39), prophylactic antibiotic regimen (HR = 0.49) and location (anterior maxilla as the highest HR = 1; anterior mandible the lowest HR = 0.53) 3.
	3309	NR		93.5	4.5	1		
145/155	48	Early = 31.4%; late = 51.4%	NR	87.5	12.5	4.10 (0.67–24.96)	NR	1. Retrospective data based on university setting. 2. Kaplan Meier showed SS in the cumulative survival rate (p < 0.001) 3. Multilevel mixed effects equations did not detect SS association with IF. 4. Multivariate generalized estimating equations logistic regression model showed SS association with IF and smooth implants (HR = 1; rough surface = HR = 0.08) and location (anterior maxilla presented the highest HR = 1; anterior mandible the lowest HR = 0.12) 5. Time in function demonstrated to SS influence IF (p < 0.001)
	883			96.5	3.3	1		
40.9%/59.1%	472	N	NR	100	0	0	NR	CC study conducted at the university setting - Lack of control for confoundings - No report on data regarding the control group - Poorly defined eligibility criteria
	46	NR	NR	NR	NR	NR	NR	
0%/100%	60	NR	NR	100	0	0	NR	Prospective case-control study on immediate placement therapy - Common implant characteristics: 3.7 × 16 mm - Patients received pre-implant therapy ATB - No mention on MBL, although authors state no SS difference between groups
	60	NR	NR	100	0	0	NR	

(Continues)

TABLE 1 (Continued) [In PDF format, this table is best viewed in two-page mode]

Authors (year)	Study design	Mean follow-up	Systemic condition	Medication	Dosage (mg/ml)	Therapy length (months)	Administration method	Subjects (n)	Age (years)
Grant et al. (2008)	RC	48	Osteoporosis	Prior to implant placement: Fosamax (66), Actonel (21), Boniva (2) After implant placement: Fosamax (27), Actonel (5) Boniva (1)	NR	38	Oral	115	40
			ASA I-II	N	N	N	N	343	
Koka et al. (2010)	RC	>36	Osteoporosis (32)/ osteopenia (18)	BP	NR	NR	Oral	55	71
			NR	NSM	N	N	N	82	66
Zahid et al. (2011)	RC	66	Osteoporosis	BP		26	Oral	26	56
			ASA I-II	N	N	N	N	274	
Memon et al. (2012)	RC	54	Osteoporosis	Risedronate (23), Ibandronate (5), Alendronate (72)	NR	<1 y (20), 1–3 y (19), >3 y (15), unspecified (46)	Oral	100	66 ± 9
			ASA I-II	N	N	N	N	100	63 ± 9
Famili et al. (2014)	RC	12	Osteoporosis (21)/ osteoarthritis (1)	Fosamax/Boniva/Actonel	NR	NR	Oral	22	≥50 (120)/ <50 (91)
			ASA I-II	NSM	N	N	N	98	

ASA, American Society of Anesthesiologists; BP, bisphosphonate; HRT, hormone replacement therapy; MBL, marginal bone level; N, none; NR, not reported; NSM: no specific medications; RC, randomized, controlled.

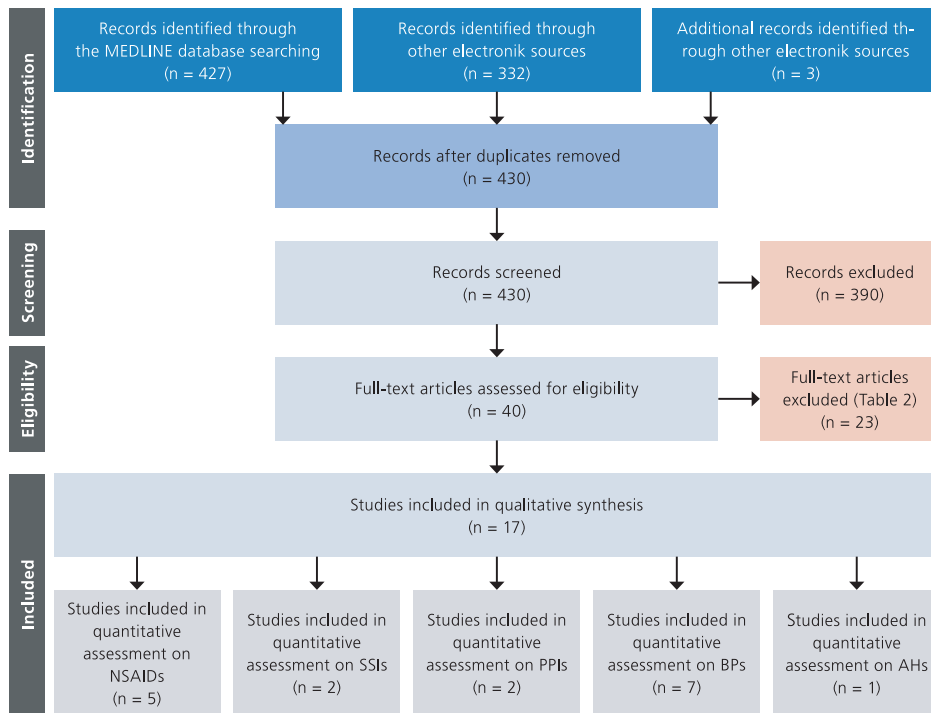


FIGURE 1 PRISMA flowchart of the screening process

TABLE 1 (additional columns - continued)

Gender (M/F)	Implants (n)	Failure (month)	Marginal bone loss (mm)	Implant survival rate(%)	Implant failure rate (%)	HR (95% CI)	Biological complications	Comments
0%/100%	468	<6	NR	99.5	0.5	NR	NR	Retrospective cohort study with poor data regarding implant outcomes - Patients were reached through mail to answer a survey to be examined - Implants in the case group had early failure - None of the 115 included in the case group had osteonecrosis as consequence of implant therapy - Diabetes and steroids could be other confounding factors
	1450	NR	NR	99	1	NR	NR	
0%/100%	121	NR	NR	99.17	0.83	NR	NR	Retrospective cohort study with vague data acquisition - Failures in the non-BP group occurred concomitant to the intake of steroids, calcium and vitamin D and in smokers and diabetics - Failures in the BP group occurred in patients intaking HRT-estrogen, calcium and vitamin D
	166	NR	NR	98.19	1.81	NR	NR	
38.1%/62.9	51	<2	NR	94.11	5.88	NR	NR	Retrospective radiographic study - Poor descriptive and statistic analysis - Possible confounders: smoking (8.5% - OR = 1.28), bone graft (26.2 OR = 1.31) and thread exposure (10.9% - OR = 3.25) - Statistically significant associations were found between the use of BP and thread exposure ($p = 0.001$) - No cases of osteonecrosis as consequence of implant therapy were registered
	610	NR	NR	97.1	2.6	NR	NR	
0%/100%	153	Early (10)	0.66 ± 0.70	93.5	6.5	NR	NR	Retrospective-chart based study - MBL evaluated at stage 2 - MBL was only available from 73 patients in both groups - Multiple implant systems were evaluated - Failures by BP: Alendronate (6) ibandronate (3) and risedronate (10) - By proportion, ibandronate had the highest percentage of failures (25%)
	132	Early (6)	0.80 ± 0.65	95.5	4.5	NR	NR	
0%/100%	75	Early	NR	98.7	1.3	NR	NR	Retrospective University-based study on females with/-out osteoporosis - Vague definition on success rate - Authors did not identify confounders - No data regarding the number of patients according to the BP - Lack on data in regards to the time period taking BP - Poor demographics
	272	N	NR	100	0	NR	NR	

TABLE 2 Excluded papers based on full text evaluation

Author (year)	Medication	Reason for exclusion
Nisi et al. (2015)	Bisphosphonate	No data on implant failure
Holzinger et al. (2014)	Bisphosphonate	Data on BRONJ after implant therapy
Lopez-Cedrun et al. (2013)	Bisphosphonate	Data on BRONJ after implant therapy
Kim and Kwon et al. (2010)	Bisphosphonate	Case report
Lazarovici et al. (2010)	Bisphosphonate	Data on BRONJ after implant therapy
Kwon et al. (2014)	Bisphosphonate	Data on BRONJ after implant therapy
Grant et al. (2008)	Bisphosphonate	No data on implant failure
Favia et al. (2015)	Bisphosphonate	No data on implant failure
Mattheos et al. (2013)	Bisphosphonate	Case report
Kwon et al. (2016)	Bisphosphonate	No data on implant failure
Kwon et al. (2016)	Bisphosphonate	Single-arm case study
Jacobsen et al. (2013)	Bisphosphonate	No data on implant failure

(Continues)

TABLE 2 (Continued)

Author (year)	Medication	Reason for exclusion
Tam et al. (2014)	Bisphosphonate	Single-arm case study
Lazarovici et al. (2010)	Bisphosphonate	Data on BRONJ after implant therapy
Shabestari et al. (2010)	Bisphosphonate	Single-arm case study
Goss et al. (2010)	Bisphosphonate	Data on BRONJ after implant therapy
Bell and Bell (2010)	Bisphosphonate	Single-arm case study
Gomez-Moreno et al. (2016b)	Anticoagulant	Report on bleeding complications
Gomez-Moreno et al. (2016a)	Anticoagulant	Report on bleeding complications
Karbuda et al. (2007)	COX-2 inhibitor	Report on analgesic and inflammatory response
Chrcanovic et al. (2016c)	Anticoagulant	Multivariate analysis
Chrcanovic et al. (2016a)	NSM	Multivariate analysis
Chrcanovic et al. (2016b)	Anticoagulant	Multivariate analysis

BRONJ, Bisphosphonate-related osteonecrosis of the jaw; COX, Cyclooxygenase; NSM, No-specific medication.

odds ratio of 1.21. Hence, an effect of the experimental medication could not be concluded ($p > .05$ for the null of no effect) (Figure 4).

3.5 | Quality assessment

After the screening process, we found 13 studies included in the qualitative assessment that could be analyzed with NOS (Table S1). A Cohen's kappa inter-rater agreement rate of .92 was reached. After discussing the disagreements between the examiners (AM and GAO), a mean NOS score of 6.38 ± 2.43 was obtained.

4 | DISCUSSION

4.1 | Principal findings

Although survival in implant dentistry does not represent a challenge anymore, failures and complications still occur (Brugger et al., 2015). The present systematic review revealed an insight into the possible effect of some medications on implant failure. Interestingly, PPIs used to reduce the production of acid by blocking the enzyme in the wall of the stomach that produces acid (Colmenares & Pappas, 2016) and SSRIs used for depression and anxiety conditions (Galli, Macaluso & Passeri, 2013) exhibited an increased risk of implant failures. On the other side, unexpectedly, the use of oral BPs for the treatment of osteoporosis did not yield significance when analyzing their impact on implant failure. This finding is of special interest as oral BPs intake was reported to be associated with a significantly higher risk to develop osteonecrosis of the jaw due to the blocking of osteoclastic activity (Edwards et al., 2007). To the best of authors' knowledge, this systematic review was the first one in highlighting

the potential implications of medications upon implant longevity. Nevertheless, findings from this study cannot be conclusive due to the studies' design and consequently, the number of inherent uncontrolled confounders. Accordingly, it is encouraged to prospectively study the effect of these medications upon early and late implant failure controlling other known risk factors for the stability of the peri-implant tissues.

4.2 | Are our findings biologically plausible?

The effect and interaction of some medications with bone homeostasis has been extensively documented in preclinical studies (David, Nguyen, Barbier & Baron, 1996; Galli et al., 2013; Haney & Warden, 2008; Insua et al., 2017; Nyman, Schroeder & Lindhe, 1979; Robinson, Tashjian & Levine, 1975; Rzeszutek, Sarraf & Davies, 2003; Vestergaard, 2008). Recently, in vivo clinical reports have been of great interest in the field of implant dentistry due to the likely role of these medications upon osseointegration (Winnett et al., 2016; Wu et al., 2014, 2016, 2017). The present meta-analysis yielded statistical significance to feature the possible relevance of PPIs and SSRIs on IF.

Proton pump inhibitors aim at inhibiting the acid output to the stomach for the treatment of gastroesophageal reflux or gastric ulcers. The underlying mechanism that could negatively impact osseointegration leans on the impaired effective calcium uptake through the intestines (Kopic & Geibel, 2010, 2013). Calcium is an essential mineral for the proper formation and maintenance of the skeleton as it may impact upon the bone mineral density (Tai, Leung, Grey, Reid & Bolland, 2015). In point of fact, a calcium intake of at least 1,000–1,200 mg/day has been recommended to minimize the risk of

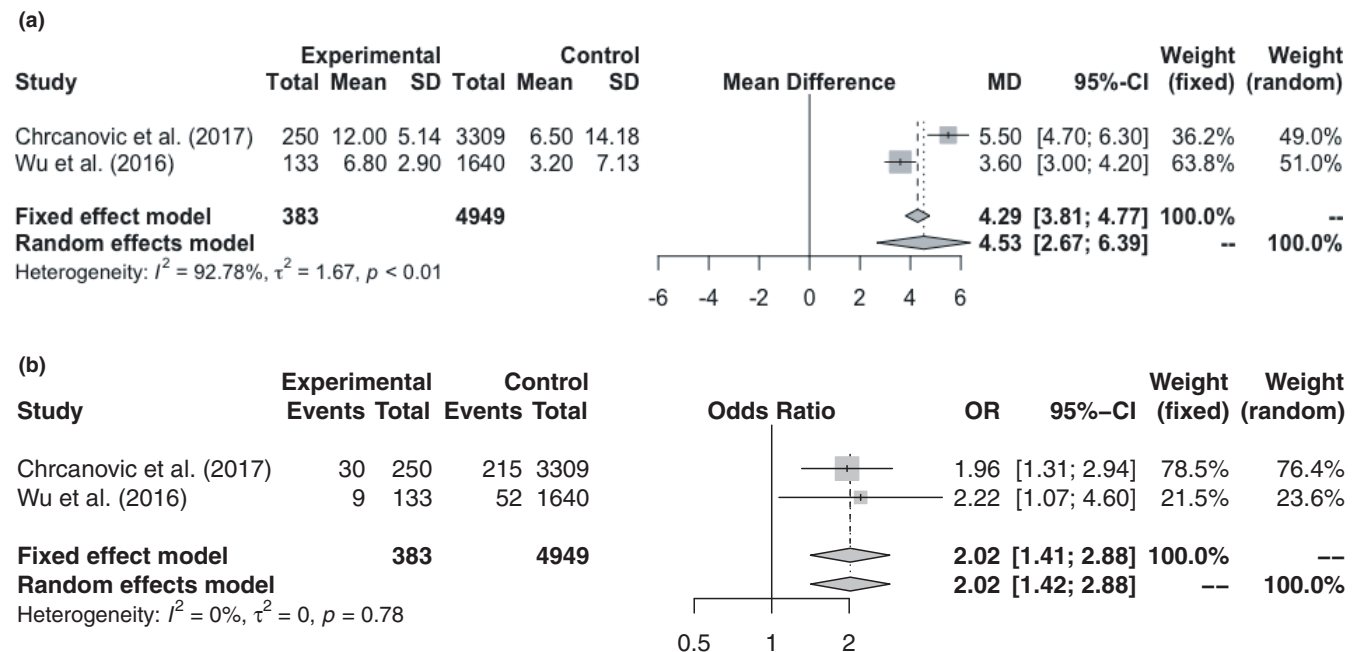


FIGURE 2 (a) Meta-analysis of mean and 95% confidence interval of implant failure for patients taking proton pump inhibitors (PPIs). (b) Meta-analysis of mean and 95% confidence interval of odds ratios for patients taking proton pump inhibitors (PPIs)

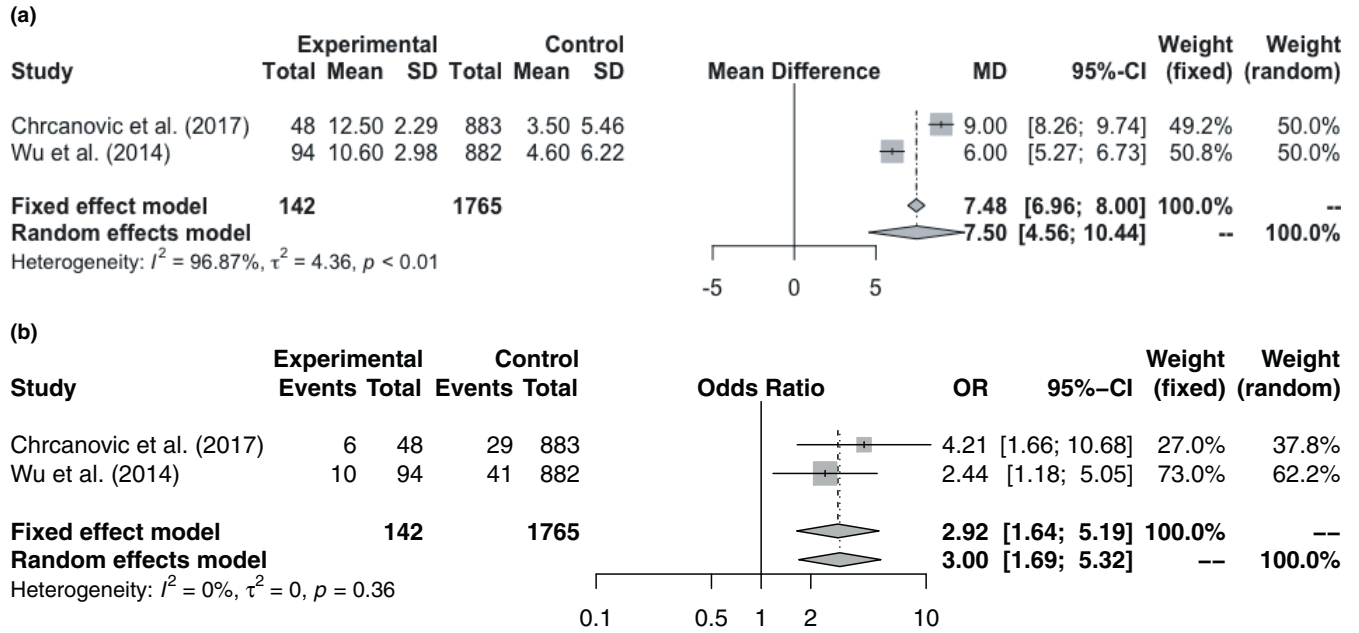


FIGURE 3 (a) Meta-analysis of mean and 95% confidence interval of implant failure for patients taking serum serotonin reuptake inhibitors (SSRIs). (b) Meta-analysis of mean and 95% confidence interval of odds ratios for patients taking serum serotonin reuptake inhibitors (SSRIs)

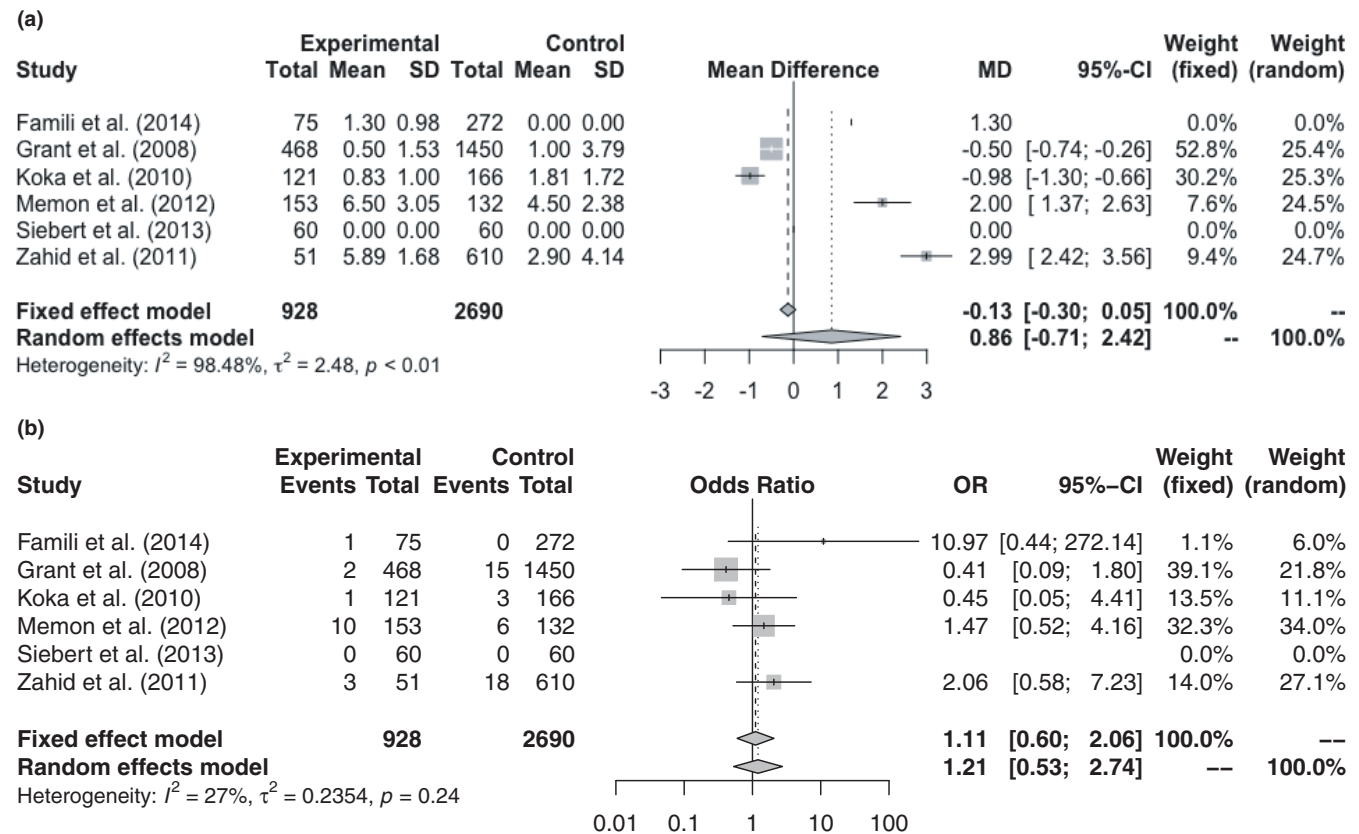


FIGURE 4 (a) Meta-analysis of mean and 95% confidence interval of implant failure for patients taking bisphosphonates (BPs). (b) Meta-analysis of mean and 95% confidence interval of odds ratios for patients taking bisphosphonates (BPs)

osteoporosis (Tang, Brooks, Wetmore & Shireman, 2015). O'Connell, Madden, Murray, Heaney and Kerzner (2005) examined for 7 days the intake of omeprazole 20 mg QD and found out a reduced calcium absorption when compared to a placebo medication in postmenopausal women. A further study confirmed that urine calcium excretion was reduced when in-taking omeprazole 20 mg TD (Graziani et al., 1995). Hence, understanding the effect of PPIs on calcium reduction and the detrimental result upon bone homeostasis highlight the clinical implications of the intake of PPIs on IF.

Along the same lines, SSRIs used for depressive or anxiety conditions have been further identified to play a pivotal role on the osteoblast/osteoclast balance. As such, serotonin can regulate osteoclast activation and differentiation as osteoclasts derive from hematopoietic cell precursors (Battaglino et al., 2004). As a matter of fact, the activity of the serotonin transporter and receptor is present in bone. Consequently, SSRIs have demonstrated to have detrimental effect on bone mineral density and trabecular microarchitecture through their anti-anabolic skeletal effects (Kahl et al., 2006). For this reason, it might be hypothesized to negatively influence the process of osseointegration. Recently, a preclinical *in vivo* study has elucidated the effect of SSRIs on osteoblast differentiation and bone regeneration in rats. Interestingly, SSRI medication significantly reduced osteogenic differentiation and mineralization with concomitant reduction of osteoblast marker genes including alkaline phosphatase, Osterix, and osteocalcin, indicating its putative impact on the regulation of bone metabolism (Nam et al., 2016). Hence, such cellular findings would be in concordance with the results obtained by Wu et al. (2014), who demonstrated that patients in-taking SSRIs experienced an increased risk of IF (hazard ratio: 6.28; 95% confidence interval: 1.25–31.61; $p = .03$). In addition, it should also be considered that the higher risk of implant failures may be influenced as well by the psychological condition of the patient rather than by the intake of SSRI.

On the other side, medications reported in the literature to possibly interfere with osseointegration or bone homeostasis such as NSAIDs or oral BPs have failed to show statistical significance. As aforementioned, these findings must be cautiously interpreted, as there are other confounding factors such as the absence of an effect on implant survival due to the given dosages. The largest and longer term study analyzing failing osseointegration of 197 implants revealed that patients using NSAIDs peri-operatively experienced 44% IF, while 38% IF rate was occurred in patients, who did not take NSAID peri-operatively. Moreover, the NSAIDs cohort experienced 3.2 times more cases of radiographic bone loss >30% of the overall height and 1.9 times more cases of cluster failures (Winnett et al., 2016). Accordingly, it might be speculated that the intake of peri-operative NSAIDs may inhibit the inflammatory bone metabolism, especially in vulnerable populations while having minimal clinical effect in healthy patient populations (Winnett et al., 2016). In contrast, the use of AHTNs has been suggested to have a beneficial impact on implant longevity. The biological plausibility of this finding rests on the fact that AHTNs drugs can affect bone metabolism by inhibiting osteoclasts catabolic effects on

bone by blocking their β_2 adrenergic receptors (beta-blockers), to enhance bone formation by increasing calcium absorption at the distal convoluted tubule (thiazides) or by shifting the balance toward bone formation by blocking the renin-angiotensin system (ACE inhibitors) (Wu et al., 2016). In addition, oral BPs did not show to substantially contribute to IF. This is an interesting finding, as this medication mainly used for osteoporosis or cancer therapy is likely the most widely documented medication affecting the skeletal bone characteristics (Brufsky & Mathew, 2015; Rachner, Khosla & Hofbauer, 2011; Sambrook & Cooper, 2006). Briefly, BPs inhibit the digestion of bone by promoting the apoptosis or cell death of osteoclast, thereupon decreasing the rate of bone resorption along the therapy (Migliorati, Siegel & Elting, 2006). One of the most common complications in our field has been the increased risk of osteonecrosis of the jaw as a consequence of dental extraction or otherwise oral surgery (Ruggiero et al., 2009). Authors want to reiterate that when interpreting these results must be exercised cautiousness due to the lack of homogeneity with regard to the dosage and timing in-taking oral BPs reported in the studies, but apparently seems not to represent a contraindication for implant therapy in osteoporotic patients. Contrarily, bone malignancies/metastases involving the intake of intra-venous BPs represent an absolute contraindication for implant therapy.

4.3 | Limitations and future directions

The findings of the present study should be interpreted with great caution. First of all, due to the nature of the included study designs in the present systematic review, no "cause-effect" relationship can be established, but "association" and thus, findings from the present review encourage to investigate in a prospective manner the impact of medications on implant outcomes controlling other known confounders (i.e., smoking, plaque control, or other local and systemic contributing factors) that could potentially interfere in the implant stability. Moreover, the timing of implant failure must be adequately reported. In this sense, this would help to gain perspective on possible underlying mechanisms that elicit implant failure. Along these lines, it is encouraged to investigate the effect of poly-medication on osseointegration and implant failure. Furthermore, a major limitation that was found when investigating the biological complications was the lack of standardization with regard to the definition of peri-implant disease. Hence, it is strongly advised to follow the guidelines recommended by the European Federation of Periodontology and the American Academy of Periodontology to report on biological complications using clinical and radiographic assessments.

5 | CONCLUSIONS

Findings from the present systematic review showed an association of proton pump inhibitors and selective serotonin reuptake inhibitors with implant failure. Hence, the effect of these medications should

be further investigated in future studies as potential confounders for implant outcomes.

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CONFLICT OF INTEREST

The authors do not have any direct financial interests with the products and instruments listed in this manuscript.

ORCID

Vivianne Chappuis  <http://orcid.org/0000-0003-1227-7587>

Alberto Monje  <http://orcid.org/0000-0001-8292-1927>

Gustavo Avila-Ortiz  <http://orcid.org/0000-0002-5763-0201>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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