DENTAL IMPLANT OUTCOMES IN OSTEOPOROSIS

OSTEONECROSIS OF THE JAW AND DENTAL IMPLANT FAILURE RELATED TO ANTIRESORPTIVE THERAPY FOR OSTEOPOROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2023) Hamilton, Ontario (HEI)

TITLE: Osteonecrosis Of The Jaw And Dental Implant Failure Related To Antiresorptive Therapy For Osteoporosis: A Systematic Review And Meta-Analysis

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NUMBER OF PAGES: x, 45 pages

Lay Abstract

We sought to generate an up-to-date and comprehensive analysis of whether standard treatment for osteoporosis with anti-resorptives increases the risk of adverse outcomes when undergoing dental implantion.

We conducted a search of all studies published on this between 1946 and 2022, and found 793 studies. Nine studies provided numbers related to dental implant outcomes. We are very uncertain whether anti-resorptive increase or reduce the absolute risk of dental implant failure. The estimated worst case scenario is that anti-resorptives cause 3 more implant failures per 100 patients.

We also looked at the rare outcome of death of the jaw bone (osteonecrosis). We found this occurs 0.4% of time in patients undergoing implant when exposed to anti-resorptive drugs. We estimate that exposure to anti-resorptives increases the risk of osteonecrosis of the jaw by 3 per 1000 patients. The evidence supporting this is from one moderate quality study.

Abstract

Purpose: We conducted a systematic review and meta-analysis evaluating dental implant failure and osteonecrosis related to antiresorptive therapy for osteoporosis.

Methods: We searched 5 databases between 1946 and January 2022. We included interventional and non-interventional studies reporting rates of dental implant failure or osteonecrosis in those with osteoporosis or osteopenia. Two reviewers independently screened all titles and abstracts, and full-texts. Risk of bias was assessed using the modified Ottawa-Newcastle scale, and the evidence was assessed using the GRADE framework. We adhered to PRISMA 2020 and MOOSE reporting standards.

Results: Our search revealed 793 unique citations that underwent title and abstract screening. We included 112 studies for full text screening, 33 underwent data abstraction, and ultimately nine (n=655) were included for the implant failure analysis. Random effects meta-analysis revealed a point estimate suggesting a decrease in relative risk of implant failure in those exposed to antiresorptives (RR 0.82, 95% CI 0.52 – 1.28, p = 0.38, very low certainty). We identified 128 cases of MRONJ in implant recipients. The rate of MRONJ following implantation in those exposed to antiresorptive therapy is 0.40% pooled from 20 cohorts. A single comparative study assessed risk adjusted MRONJ in osteoporotic patients undergoing dental implant placement and found use of bisphosphonates increased osteonecrosis of the jaw by 3 cases per 1000 patients (adjusted HR 4.09, 95% CI 2.75 – 6.09, p<0.001, moderate certainty).

Conclusions: The limited evidence does not suggest an association between antiresorptive therapy for osteoporosis and dental implant failure. The certainty of evidence is very low due to serious methodologic concerns. Antiresorptive therapy likely causes MRONJ in osteoporotic patients receiving dental implants with moderate certainty evidence.

Acknowledgements

I am ever grateful I met Professor Gordon Guyatt and embarked on this path with him a decade ago. Gordon, your flexibility in allowing me to pursue my own path is a breath of fresh air compared to the academy otherwise. You see the world clearly, and speak truly, neither of which is common in any setting. You go out of your way for me and I think you like me. And the best part: There's always a touch of jest.

Mom and dad, thanks for always being there.

Enzo and Cyrus, I love you dearly.

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Lists of Figures and Tables

List of Abbreviations and Symbols

AAOMS: American Association of Oral and Maxillofacial Surgeons
AR: Anti-resorptive agents
ASBMR: American Society for Bone and Mineral Research
BMD: Bone mineral density
BP: Bisphosphonates
DXA: Dual-energy X-ray absorptiometry
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
HR: Hazard ratio
IV: Intravenous
PO: Per os (by mouth)
ONJ: Osteonecrosis of the jaw
OP: Osteoporosis
MA: Meta-analysis
MRONJ: Medication related osteonecrosis of the jaw
NR: Not reported
RR: Relative Risk
SC: Subcutaneous
SR: Systematic Review

Declaration of Academic Achievement

Dr. Reza Mirza led the study design, data abstraction, analysis, methodology, management, and writing. Dr. Gordon Guyatt supervised the paper, provided methodology expertise, and played a major editorial role. Drs. Mohamed El Rabbany and Dalal Ali participated in data abstraction and assisting in writing and revising. Drs. Aliya A. Khan, Sotirios Tetradis, Archibald Morrison, Salvatore Ruggiero lead the ONJ taskforce that posed this question to inform their guidelines for practitioners, in addition they provided content expertise and provided key editorial input.

Chapter 1. Background

1.1 Anti-resorptive Therapy

Antiresorptive therapies, including bisphosphonates (BPs) and denosumab, are widely used for the management of osteoporosis; management of bone pain, skeletal events, and hypercalcemia in patients with malignancy; and Paget's disease.[1–5] Two specific anti-resorptive medications, zoledronic acid (intravenous) and denosumab (subcutaneous) are given for both oncology and osteoporosis indications. For patients with cancer, the recommended cumulative annual dose of both zoledronic acid and denosumab is "high," at 10-12x greater than the recommended cumulative annual dose for patients with osteoporosis, which is considered "low." The recommended cumulative annual absorbed dose of orally-administered bisphosphonates, such as alendronate, risedronate, and ibandronate, is "low," effectively approximating that of the osteoporosis dose of zoledronic acid.

Although the mechanism of action of BPs and denosumab differ, they both result in the suppression of osteoclasts activity and function. BPs can further lead to apoptosis of osteoclasts.[6] This leads to suppression of bone resorption and increase in bone mass over time.

When considering antiresorptive therapies, the risk of adverse dental outcomes must be considered: namely, dental implant failure and the risk of medication-related osteonecrosis of the jaw (MRONJ). Dental implant survival is determined by patient factors (comorbidities, oral hygiene, regular semi-annual dental maintenance visits, quality of bone and tissue quality) and

implant factors (surgical technique).[7] There are no randomized clinical trials to establish an association between the use of antiresorptive therapy and dental implant failure. Two reviews report a majority of studies investigating the effect of anti-resorptive therapy for osteoporosis on dental implant survival report a survival rate similar to that in non-anti-resorptive patients. These reviews also suggest that though dental implants in patients with cancer who take anti-resorptives are contraindicated, dental implants are acceptable in patients with osteoporosis who take antiresorptives, so long as all other negative risk factors are minimized.[8,9] Most showed safety of bisphosphonates used at low doses for osteoporosis prior to and post dental implant surgery with a success rate ranging between 95% and 100%,[10–24] while others describe an increased risk of implant failure.[12,25–32] With limited evidence available on the effect of antiresorptive therapy on dental implants, the American Association of Oral and Maxillofacial Surgeons (AAOMS) considers the risk of developing MRONJ after dental implant to be similar to that after tooth extraction.[33] The 2022 European Calcified Tissue Society (ECTS) position paper deems implant to be low risk for triggering MRONJ.[34]

1.2 Osteonecrosis of the Jaw (ONJ)

MRONJ is a rare occurrence in the setting of antiresorptive therapy use in patients with osteoporosis[35] and is defined by the American Society for Bone and Mineral Research (ASBMR)[36] and the American Association of Oral and Maxillofacial Surgeons (AAOMS)[33,37] as an exposed bone area in the maxillofacial region which does not heal for up to 8 weeks in patients who are currently (or previously) treated with antiresorptive therapy, in the absence of prior radiation exposure to the jaw or maxillofacial region. MRONJ is the preferred term when

osteonecrosis of the jaw occurs during antiresorptive or antiangiogenic therapy,[33,38] it was initially referred to as bisphosphonate-related osteonecrosis of the jaw (BRONJ).[39]

Staging of MRONJ was originally described in the AOOMS 2007 position paper, modified in 2009 to include Stage 0, and has since remained consistent including their 2022 update: Stage 0 (no exposed bone but non-specific symptoms and clinical or radiographic findings); Stage 1 (exposed bone without pain or infection); Stage 2 (exposed bone with pain and infection); and Stage 3 (exposed bone or fistula with infection and significant complications).[33,39,40]

MRONJ is more common in patients with cancer (1.8–5% incidence) than with osteoporosis (0.01-0.03% incidence).[24,33,35,41,42] Both clinical and preclinical data strongly suggest that most MRONJ requires the coexistence of systemic risk factors (anti-resorptives or angiogenesis inhibitors) and local oral risk factors that include tooth extraction, local inflammation (e.g., periodontal or periapical infection), trauma from removable dental prostheses, and potentially, dental implants.[43–48] 60% of MRONJ cases follow dental procedures, particularly tooth extraction. Other less-frequently-cited systemic risk factors include diabetes, chemotherapy, anti-angiogenics, corticosteroid therapy, and smoking.[49–56] Despite these advances in the basic tissue level understanding of MRONJ and the high likelihood that ongoing research will be gradually reveal more details, the molecular events underlying these tissue level observations remain to be elucidated.

Although authors have offered estimates of absolute MRONJ risk from 1 to 10 per 100 000 person-years in patients treated with BPs,[35,36] uncertainty regarding incidence remains. In patients treated with denosumab, the initial exposure-adjusted MRONJ rate from the FREEDOM Extension trial was 5 in 10,000.[57] The incidence of MRONJ, thought to be dose related, is higher in patients on antiresorptive therapy for cancer management, between 1% and 2% with denosumab[58,59] and up to 10% with intravenous BPs.[60] Other risk factors for MRONJ include diabetes, chemotherapy, corticosteroid therapy, smoking, age greater than 65, periodontal disease, periodontitis, denture use, poor oral hygiene, invasive dentoalveolar surgery including tooth extraction, as well as dose and duration of antiresorptive therapy.[37,50–56]

National and international consensus statements have addressed the incidence, classification, diagnosis, and management of MRONJ in both the osteoporosis and oncology populations.[35,61] In patients with osteoporosis on antiresorptive therapy who develop clinical MRONJ (Stage 1 or higher), the AAOMS (and ECTS) suggest considering withholding antiresorptive treatment until complete soft tissue healing of the surgical site, which usually occurs in 6 to 8 weeks[35,61], however this remains controversial.[33,34] For instance, in the case of denosumab there is risk of rebound multiple vertebral compression fractures if treatment is withheld.

1.3 Purpose of This Study

The International ONJ Taskforce is a cross-disciplinary group of investigators including dentistry, oral surgery, rheumatology, endocrinology, and metabolic bone disease specialists who published a consensus statement in 2015 regarding management of osteonecrosis of the jaw.[35]

The taskforce has re-convened to update their recommendations (in review). To inform the taskforce's recommendations, we were tasked with generating the most up-to-date estimates of the excess risk of implant failure and MRONJ associated with use of antiresorptives in patients with osteoporosis undergoing dental implantation.

Chapter 2. Methodology

We assembled an international collaboration of experts (the International Consensus on MRONJ Task Force) who conceived this question. We conducted this systematic review and meta-analysis. The protocol was registered at the time of update (CRD42022307412), but was not pre-registered.

Chapter 2.1 Search Strategy

A health sciences information specialist experienced in systematic review developed the search strategy that included five databases (MEDLINE, EMBASE, Cochrane Central, CINAHL, Web of Science) between 1946 and November 2020, and updated using the same search terms in January 2022. Appendix B presents the detailed search strategy. We also conducted a manual review of citations from existing systematic reviews and contacted content experts for further references.

Chapter 2.2 Eligibility criteria

We included published and unpublished observational and interventional studies that reported rates of dental implant failure or osteonecrosis of the jaw in patients who underwent dental implant placement with a history of osteopenia or osteoporosis. Antiresorptive therapy included bisphosphonates and denosumab for treatment of osteopenia or osteoporosis. We had no geographic restriction. Both prospective and retrospective studies were included. Case series were included if they included at least 5 patients with MRONJ. Abstracts were considered admissible if they reported the requisite information. Non-English articles were screened using machine translation. We excluded studies pooling outcomes in patients with malignancy, and studies whose population represented a smaller subgroup of an already included study.

Screening Citations and Extracting Data

Two reviewers conducted eligibility screening independently and in duplicate of all citations. Screening was done on the Covidence.org platform. All reviewers had domain expertise, and one reviewer (RM) with domain expertise and methods experience reviewed every citation. All articles in the title and abstract screening included relevant data and underwent full-text screening. We included articles for data abstraction when the full-text screen confirmed eligibility criteria and measurement of at least one relevant outcome. The two reviewers extracted the following data: study methodology; interventions and comparator; population; start and end of data collection; duration of follow-up; number of patients and implants; dental implant failure events, rate, and definition; osteonecrosis of the jaw events and rate, prognostic factors; and drug indication, exposure, dose, and average duration. In cases where the authors

did not report occurrence of MRONJ, we assumed no MRONJ had occurred. Disagreements at any stage between the two reviewers that persisted after discussion were resolved by a senior methodologist (GG) if methodologic in nature, the guideline panel if related to content expertise, or both.

Unpublished Data

In cases where more information was required for inclusion. 23 authors were contacted, nine authors responded, six providing new information allowing inclusion of six studies, one providing information allowing for exclusion, and two indicating the data requested was unavailable.

Dr. Watts provided follow-up data from Amgen. Dr. Tallarico confirmed the indication for bisphosphonates was osteoporosis, allowing for inclusion. Dr. Famili confirmed her two studies described non-overlapping populations, allowing for inclusion of both. Dr. Pogrel confirmed all patients were on bisphosphonates for osteoporosis, and four patients with osteoporosis did not take bisphosphonate therapy, allowing for the inclusion of his study. Dr. Clauser informed us his study included a single patient with osteoporosis, allowing its exclusion[62]. Mr. Cheng shared the number of patients with dental implant failure in the unexposed osteoporosis group, allowing for inclusion. Dr. Koka confirmed all his patients had osteoporosis or osteopenia, allowing for inclusion.

Risk of Bias and Quality of Evidence

Two reviewers independently assessed risk of bias of studies included in the analysis using the modified Ottawa-Newcastle scale[63,64] across eight domains: selection bias, exposure to intervention, outcome measurements both at the start and end of trial, assessment of prognostic features, appropriate adjustment of prognostic imbalances, adequacy of follow-up, and similarity of intervention between groups. A third reviewer (DA) addressed whether one study bias in all included studies, and was blinded with regards to the purpose of the third review.

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to assess the certainty of evidence,[65] rating our certainty in a non-zero effect.[66] If 10 or more studies were included, we addressed publication bias using funnel plots. We used Magicapp to create our GRADE tables.

Dental Implant Outcome Analysis

Our pre-specified primary analysis was evaluating dental implant failure at the level of the patient. During the peer-review process, limitations of evaluating dental implant failure were raised: it is a rare event leading to imprecise estimates, and studies with no events would not provide any information to the meta-analysis. A reviewer suggested this would be mitigated by looking at dental implant success instead. We therefore repeated our analyses based on the reviewer's suggestion. We performed and present both approaches.

Pooled estimates for the excess relative and absolute risk of dental implant failure were generated using random-effects meta-analysis in Review Manager 5.4. A random-effects model was chosen given the significant heterogeneity among study populations (e.g. post-menopausal women versus all comers), drug intervention (e.g. denosumab, intravenous zoledronic acid, and oral bisphosphonates), and implant procedure (e.g. number and location of implants, associated sinus lift, or dental extraction). The primary outcome was analyzed at the patient level (i.e. if a patient had more than one implant, events counted for the patient, not the implants).

Two post-hoc sensitivity analyses were conducted for relative risk of dental implant failure: analysis at the level of dental implant, and analysis when excluding two studies deemed to have unusually high estimates of risk of dental implant failure.

Osteonecrosis of the Jaw Analysis

We intended to evaluate the excess risk of osteonecrosis using a similar analysis as specified for in dental implant failure. An additional analysis of interest was the incidence of osteonecrosis in patients using antiresorptive agents.

Chapter 3. Results

The systematic search identified 1503 citations, of which 793 remained for screening by titles and abstracts following automated de-duplication. Title and abstract screening revealed 112 potentially eligible studies. Full text screening identified 31 relevant studies, and experts identified two additional studies, leading to 33 included studies. The additional two articles found by experts were published after the final search in one case, and between the searches in the other. See Appendix A for PRISMA diagram.

3.1 Dental Implant Outcomes

Nine studies reported comparative risk estimates of dental implant outcomes in patients with osteoporosis or osteopenia between those taking and not taking antiresorptive agents. We evaluated both dental implant failure and success.

Table 1 presents study characteristics of eligible studies reporting on dental implant success. The nine studies included 655 patients and at least 1715 implants (some studies did not report number of implants, in which case we presumed one implant per patient). Seven studies were conducted in the United States, one study in Japan, and one in India. Table 2 presents studies that were considered for inclusion, but ultimately excluded, alongside reason for exclusion.

Table 1. Included Studies Reporting Dental Implant Success

Citation	Study Design	Antiresorptive Implant Success Rate (% of patients)	Control Implant Success Rate (% of patients)	Number of Implants (antiresorptive / control)	Population Definition	Exposure (dose duration)	MRONJ	Follow-up
Al-Sabbagh 2015[13]	Chart review	20/20 (100%)	9/9 (100%)	46 / NR	Self reported OP	Oral BPs (NR)	0	NR
Famili 2011[14]	Chart Review	21/22 (95%)	5/5 (100%)	75 / 7	Self reported OP	Oral BPs (NR)	0	NR
Famili 2015[67]	Prospective non-interventional	2/2 (100%)	18/18 (100%)	2 / 19	BMD defined OP	Oral BPs (NR)	0	2 years minimum
Jeffcoat 2006[15]	Prospective Non-interventional	25/25 (100%)	24/25 (96%)	102 / 108	BMD defined OP	Alendronate or risedronate (average 3 years duration)	0	3 years minimum
Kasai 2009[29]	Chart Review	8/11 (72%)	4/4 (100%)	35 / 7	Self reported OP	Alendronate (NR)	0	Mean 6.95 years
Pandey 2019[16]	Prospective non-interventional	14/15 (93%)	14/15 (93%)	26 / 32	BMD defined OP	Alendronate (10mg daily for 1.5 years)	0	NR
Yajima 2017[30]	Prospective non-interventional	8/11 (72%)	14/14 (100%)	25 / 28	Previous diagnosis of OP	Alendronate (greater than one year)	0	3.2 years (BP), 5.2 years (control)
Koka 2010[19]	Retrospective cohort with prospective follow-up	54/55 (98%)	80/82 (98%)	121 / 166	Chart diagnosis of Osteoporosis / osteopenia	~4 years of bisphosphonate use on average.	0	1mo - 3years
Cheng 2022[68]	Retrospective cohort	105/124 (85%)	158/199 (79%)	417 / 640	Presumed self reported	Oral and IV BP, and denosumab.	1	Mean 8.8 years

NR = Not reported. OP = osteoporosis. BMD = bone mineral density. BP = bisphosphonate. IV = intravenous.

Table 2. Studies Excluded from Meta-Analysis, and Reason for Exclusion.

Study	Findings	Reason for Exclusion
Fugazzotto 2007[17]	61 patients (169 implants) exposed to oral BPs (mean 3.3 years) had no failed implants at 12-24 months.	Indication for bisphosphonates not stated. No comparator group.
Bell 2008[11]	42 patients (100 implants) taking oral BPs. 5 patients lost one implant each. Follow-up 0.3-7 years.	Single arm study in which all patients took bisphosphonates. No comparative risk estimate can be generated.
Shabestari 2009[18]	21 patients (46 implants) exposed to oral BPs with no failed implants. Follow-up range 0.6-8.1 years.	Single arm study, wherein all patients received bisphosphonate therapy.
Martin 2010[28]	16 of 589 patients exposed to oral BPs had dental implant failure.	Single arm series of patients with dental failure and bisphosphonate use.
Zahid 2011[12]	Of 26 patients (51 implants) exposed to oral BPs, 3 lost one implant each. Follow-up 2-78 months.	Outcomes not separately reported for osteoporotic patients not taking bisphosphonates.
Leonida 2012[20]	9 patients (54 implants) with OP exposed to oral BPs had zero failures at 2 years.	Single arm study wherein all patients were taking bisphosphonates.
Memon 2012[31]	100 patients (153 implants) exposed to oral BPs had 10 implant failures.	Osteoporosis status not reported for control arm.
Al-Sabbagh 2015[21]	In 59 patients with OP, 39 were exposed to oral BPs. Implant loss not reported by group.	Sample appears to overlap with an included study by the same author. Implant failure definition includes patient satisfaction.
Siebert 2015[22]	12 patients with OP taking zoledronic acid yearly had no implant failures at 1 year.	Control group did not have osteoporosis.
Tallarico 2016[23]	In 32 patients (98 implants) exposed to oral BPs, only one implant failed at 3 years (minimum).	Single arm study, wherein all patients received bisphosphonates.
Kim 2020[69]	In 80 patients (344 implants) exposed to anti-resorptives 309 implants failed at 85 months follow-up (mean).	Control group does not have osteoporosis.
Albander 2008[70]	In 115 patients (467 implants) exposed to anti-resorptives, 1 implant failed.	Single arm study.
Skrepnek 2010[71]	In 637,209 patients with osteoporosis, only IV bisphosphonates were associated with ONJ.	No evaluation of dental implantation.
Akintoye 2012[72]	Case control study of 337 women showing 2.5 odds of BP use in those with dental implant failure.	Control arm did not have osteoporosis.

Escobedo 2020[73]	Case series of 7 cases of osteonecrosis related to implantation.	Single arm study with inclusion of patients with malignancy.
Tam 2014[74]	Case series of six patients with ONJ after implantation.	Single arm study including patients with malignancy.

N.B. Many of these studies are included in the ONJ incidence analysis.

Risk of bias was deemed high in seven of the nine studies (Appendix C). All seven studies with high risk of bias failed to statistically adjust for confounders. Other common issues included failure to mention how participants were recruited, duration of follow-up, and whether any participants were lost to follow-up. Publication bias could not be assessed given the limited number of papers.

Random effects meta-analysis revealed a relative risk of 0.82 (95% confidence interval 0.52 – 1.28, p = 0.38) for dental implant failure in osteoporotic patients using antiresorptive therapy, and RR 1.01 (95% confidence interval 0.97 – 1.05, p = 0.51) for dental implant success. See Figures 1 and 2 for Forest Plot.

Figure 1. Forest Plot of Dental Implant Failure (patient level)

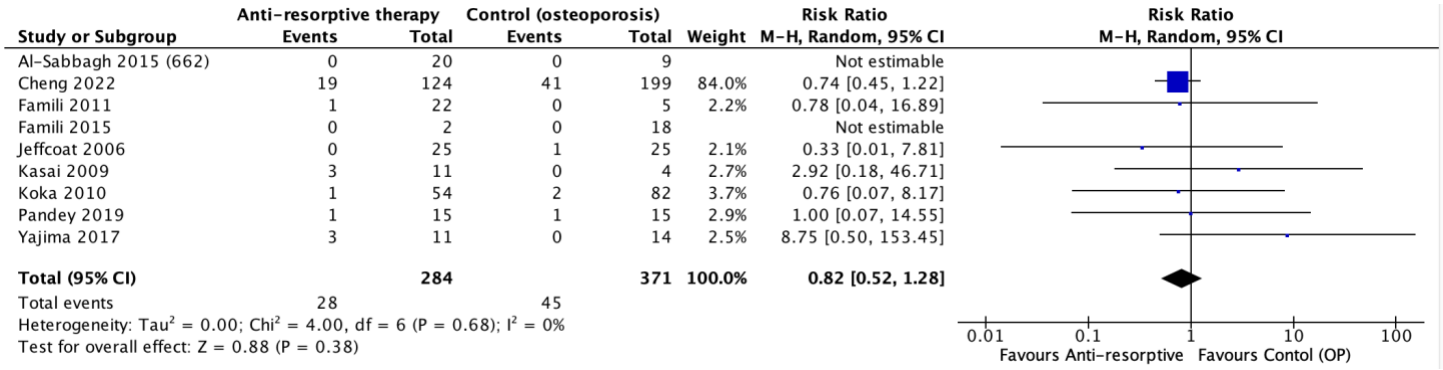
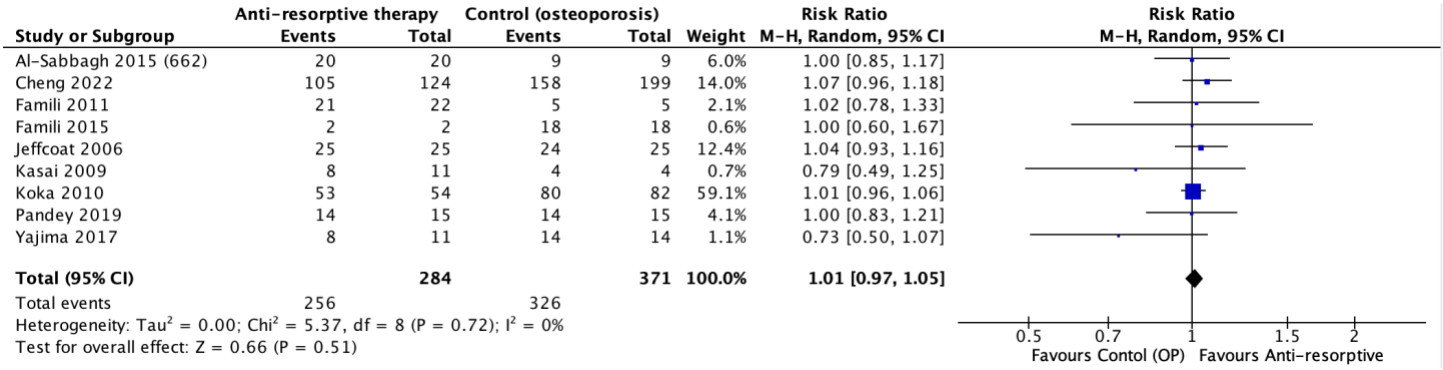
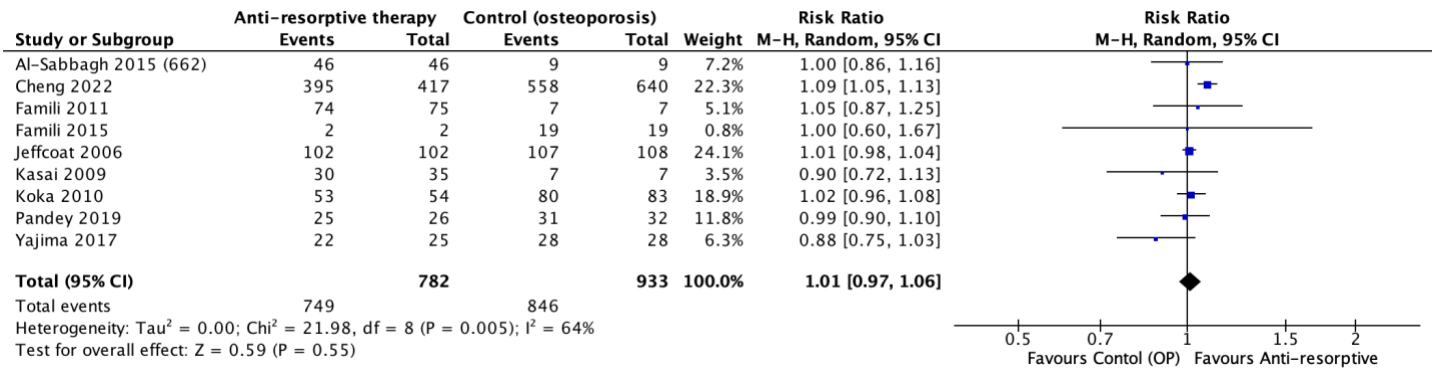


Figure 2. Forest Plot of Dental Implant Success (patient level)



We conducted two post-hoc sensitivity meta-analyses of the data. First, we conducted the original analysis at the level of the implant (as opposed to the level of the patient) which did not change the results substantially (Figure 3, dental implant success RR 1.01, 95% confidence interval 0.97 – 1.06, p = 0.55). Second, we excluded Yajima and Kasai given the rate of implant failure in the antiresorptive arm was an order of magnitude above the other studies (27% vs 2%). This did not change the point estimate or confidence interval given their little weight contributing towards the meta-analysis.

Figure 3. Forest Plot of Dental Implant Success (implant level)



The certainty of evidence with respect of dental implant failure (and success) by GRADE standards was very low. The certainty was low to begin, given the observational nature of the evidence. This was further rated down given serious risk of bias as described above and serious imprecision because the confidence interval includes the possibility of harm and benefit. See Figure 5 for GRADE assessment.

Figure 5. GRADE Assessment of Dental Implant Success Evidence

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No exposure to anti-resorptives	**Absolute effect estimates** Exposure to anti-resorptives	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Dental Implant Success Follow up Variable	Relative risk: 1.01 (CI 95% 0.97 - 1.05) Based on data from 685 participants in 9 studies	**871** per 1000	**880** per 1000 Difference: **9 more per 1000** (CI 95% 26 fewer – 44 more)	**Very low** Due to serious risk of bias[1] and serious imprecision	We are uncertain whether anti-resorptives increase or reduce dental implant success.

1. **Risk of Bias: serious.** Risk of bias was deemed high in seven of the nine observational studies.

3.2 Osteonecrosis of the Jaw Outcomes

The 32 eligible studies reported 128 cases of MRONJ in patients who received dental implants (Table 3). We included the nine dental implant failure studies in addition to eleven retrospective cohorts,[11,12,18–20,22,32,68,75–78] eleven case series,[10,26–28,79–85] one prospective cohorts,[57] and one case-control study.[86]

Table 3. Table of Included Studies Reporting MRONJ in Patients receiving Implants

Author Year	Study Design	Country	Total sample	Total Implants	Exposure	Average years duration (range)	MRONJ Cases
Mozzati 2015	Retrospective Cohort	Italy	235	1267	Oral BPs	3.3 (0.5-7.3)	0
Lopez-Cedrun 2013	Case series	Spain	7	47	Oral BPs	5 (0.5-10)	7
Pichardo 2020	Retrospective Cohort	Netherlands	11	33	Oral and IV BPs	5 (1.5-14)	11
Koka 2010	Retrospective Cohort	USA	50	121	BPs	NR: ~3-5	0
Shabestari 2010	Retrospective Cohort	Iran	7	NR	Oral BPs	1.7	0
Brugger 2015	Retrospective Cohort	Switzerland	23	NR	Oral and IV BPs	4	0
Leonida 2012	Retrospective Cohort	Italy	9	54	Oral BPs	All less <3	0
Bell 2008	Retrospective Cohort	USA	42	100	Oral BPs	NR	0
Jeffcoat 2006	Prospective Cohort	USA	25	102	Oral BPs	3	0
Siebert 2015	Retrospective Cohort	Slovakia	12	60	Zoledronic acid 5mg IV yearly	NR	0
Famili 2011	Retrospective Cohort	USA	22	75	Oral BPs	<1 year n=6 1-5 years n=9 >5 years n=5	0
Goss 2010	Case series	Australia	≥7	19	Oral BPs	~4 (0.2 to 10)	5
Zahid 2011	Retrospective Cohort	USA	26	51	Oral BPs	~3.4 (0.5-16)	0
Giovannacci 2016	Case series	Italy	6	NR	Oral BPs	6 (3-9)	6
Kwon 2014	Prospective Cohort	Korea	18	NR	BPs (79% oral)	5 (1-10)	18
Famili 2015	Case-Control	USA	2	NR	Oral BPs	NR	0
Watts 2019	Prospective Cohort	Multicentre	212	NR	Denosumab	5 years	1
Troeltzsch 2016	Retrospective Cohort	Germany	5	31	Oral BPs	NR	5
Martin 2010	Case series	USA	16	44	Alendronate	3.1 (0.25-5.75)	0
Jacobsen 2013	Case series	Switzerland	5	NR	Oral BPs	4.1	5
Yajima 2017	Retrospective Cohort	Japan	11	25	Alendronate	NR	0
Kasai 2009	Retrospective Cohort	USA	11	35	Alendronate	NR	0
Lazarovici 2010	Case series	Israel	11	NR	BPs (?oral)	Unclear	11
Khoury 2016	Retrospective Cohort	Germany	15	71	BPs (10/15 oral)	Oral: 3.8 (0.25-10) IV: 1.4 (1-2.5)	0
Favia 2015	Case series	Italy	12	NR	BPs	NR	12
French 2019	Retrospective Cohort	Canada	34	84	BPs	NR	0
Pandey 2019	Retrospective Cohort	India	15	26	Alendronate 10mg daily	~1.5	0
Al-Sabbagh 2015	Retrospective Cohort	USA	20	46	Oral BPs	NR	0
Otto 2022	Retrospective Cohort	Germany	11	NR	NR	NR	0
Ryu 2021	**Case-Control**	**Korea**	**22,450**	**NR**	**NR**	**NR**	**41**
Holzinger 2014	Case series	Austria	5	NR	NR	NR	5
Cheng 2022	Retrospective Cohort	Unstated	199	640	Oral/IV BPs, denosumab.	NR	1

We only report cases associated with dental implant in patients with osteoporosis or osteopenia. Tilde (~) suggests approximation based on data available.

Given there was only a single comparative study that compared a risk-adjusted difference in both exposed and unexposed patients, we did not conduct a meta-analysis. Of the 20 papers reporting an incidence rate, only Ryu[86] reported the adjusted risk of MRONJ in osteoporotic patients taking bisphosphonates following dental implant placement. Ryu reported 41 events among 9738 (0.4%) osteoporotic dental implant patients taking bisphosphonates, and 11/12712 (0.09%) in a propensity matched osteoporotic cohort undergoing implant placement not taking bisphosphonates (adjusted HR 4.09, 95% CI 2.75 – 6.09, p<0.001, moderate certainty as per GRADE assessment in Figure 6). This translates to 3 more MRONJ cases per 1000 patients with use of bisphosphonates.

We are moderately certain in the causal association between bisphosphonates and osteonecrosis in the context of dental implantation. There were no serious risk of bias, imprecision, indirectness, heterogeneity, or publication bias detected. Given the large sample size, we deemed there was no concern regarding optimal information size. Our certainty increased from low to moderate given the strong association.

Of the 20 papers providing an incidence rate (i.e. providing a denominator of patients at risk), three reported a non-zero incidence rate of MRONJ in dental implant patients exposed to anti-resorptives. Ryu reported a 0.42% rate using nation-wide claims registry data (41/9738) without stating how many underwent extraction. Watts[57] reported an incidence of 0.47% using the denosumab trial long-term extension data: 1 case of adjudicated MRONJ in 212 osteoporotic women who underwent dental implant placement while receiving denosumab, however this

one patient also underwent dental extraction, a known risk factor for MRONJ. Cheng reported an incidence of 0.8%. We conducted a pooled incidence rate of MRONJ demonstrating an incidence rate of 0.4% following implant placement. Of note, some cases included extraction, a known risk factor for ONJ.

Figure 6. GRADE Evidence Table for MRONJ Excess Risk

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No exposure to anti-resorptives	**Absolute effect estimates** Exposure to anti-resorptives	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Medication Related Osteonecrosis of the Jaw Follow up unclear	Adjusted Hazard Ratio: 4.09 (CI 95% 2.75 – 6.09) Based on data from 22,450 participants in 1 study	**11/12712 (0.1%)** Difference: **3 more per 1,000** (CI 95% 2 more - 4 more)	**41/9738 (0.4%)**	**Moderate** Observational study with large effect.	Anti-resorptives probably increase the risk of osteonecrosis in dental implant patients with osteoporosis

Chapter 4. Discussion

4.1 Summary of Findings

We conducted a systematic review to inform recommendations for an International Task Force on dental implant outcomes in patients osteoporosis on anti-resorptive therapy. Taken together, the nine comparative studies are very uncertain whether antiresorptive therapy increases or decreases the risk of dental implant failure in patients with osteoporosis or osteopenia. Reasons for the very low certainty of the evidence included the observational nature of the studies and the high risk of bias associated with the individual study methodologies. Sensitivity analyses by considering dental implant success (as opposed failure), and analysis at the level of the implant, did not change the certainty.

A single study calculated risk adjusted rates of MRONJ providing moderate certainty that bisphosphonates cause 3 more events of MRONJ per 1000 patients. Our best estimate of MRONJ incidence after implant placement while undergoing antiresorptive therapy is 0.4% (1 case among 250 osteoporotic patients receiving dental implants) in the pooled analysis including some concomitant dental extraction.

4.2 Relationship to Other Reviews

Several systematic reviews of dental implant survival in persons taking anti-resorptives,[8,9,56,87–99] four of which include a meta-analysis,[87,88,99,100] have been published and similarly provided very low certainty evidence. While the earlier studies tended to mix high and low dose

antiresorptive patients, sometimes without acknowledging their presence, more recent studies have generally avoided this mistake. Some studies include control groups. The follow-up times vary from a few months to seven years, with a mean of approximately three years. It is notable that universal agreement already exists that dental implants placed face worse outcomes in patients taking high doses of antiresorptives, when compared to implants placed in patients taking low doses of antiresorptives, particularly with respect with MRONJ and associated implant failure. More recent review articles have begun to coalesce around the general idea that dental implant survival in patients taking low doses of antiresorptives does not differ from dental implant survival in either untreated patients with osteoporosis or healthy patients of a similar age.

4.3 Strengths

The strengths of our review include addressing all the aforementioned issues and in particular we were careful to ensure our control populations were matched for osteoporosis to avoid confounding by indication. We followed the GRADE approach to assess the certainty of evidence[65], as well as best-practice reporting standards. Finally, we sought out data from many authors, and were successful in 9 requests, allowing for the additional inclusion of 6 studies.

4.4 Limitations

Our study faces limitations both from our approach, as well as the evidence itself. We engaged in several additional sensitivity analyses. Notably, our primary analysis changed during the review process at the suggestion of a reviewer. Although the reasons for switching are

reasonable, this was post-hoc in context of all the data being available, potentially introducing bias. This is somewhat mitigated by the fact that the absolute risk difference is identical with both approaches, indicating no important difference.

With respect to the evidence, there were few comparative studies on dental implant outcomes and only one risk-adjusted study for MRONJ. The implant studies were generally small, at high risk of bias with poor reporting, and were highly heterogenous with regards to populations studied, dose and duration of treatment, comparator, and follow-up. We have significant concerns about unresolved confounding by indication: Patients with osteoporosis who receive treatment are likely to have a higher fracture risk and worse bone quality compared to those who do not receive treatment.

Given the limited data we cannot answer key clinical questions including whether cessation of antiresorptives reduces the risk of implant failure or MRONJ, or when to time surgery relative to antiresorptive dosing. Similarly, our data does not bear upon the extent to which antiresorptive treatment duration predicts MRONJ. The ECTS suggests continuing antiresorptives in those at low MRONJ risk undergoing dental work, whereas in high-risk patients they recommend considering holding bisphosphonates and waiting until the end of the dosing cycle for those receiving denosumab.

There is important heterogeneity in the osteoporosis literature, treatment indications vary enormously by year and location, which allows prognostically different populations to be

pooled in the meta-analyses, and worse, in an uncontrolled fashion. The historic paradigm based treatment decisions on bone mineral density, and even therein there was heterogeneity in the T-score cut-off. Since the early 2000s, the current paradigm shifted towards treatment by fracture risk.[101] Within the current paradigm, primary prevention is indicated in patients with a high 10 year risk of major osteoporotic fracture. Even this cut-off varies dramatically (two-fold) by locale: the cut-off ranges between 10% when low bone mass is present in the recent NHS Scotland guidelines[102], to 15% in Japan[103], and 20% in Canada[104] and the United States[105].

4.5 Analytic Considerations

We planned and initially analyzed our data with respect to dental implant failures given this was the event of interest. One reviewer felt we should change this for two broad classes of reasons. First, relating to methodology, the reviewer suggested studies with no dental implant failures could contribute to the analysis if we looked implant success instead (allowing the inclusion of two more studies), and moreover we would generate a more precise estimate given the event rate was no longer rare. The second broad reason relates to the dental implant literature: the reviewer suggested the literature ought to shift towards the outcome of 'implant success' given high rates of success, typically close to 96% at a decade.[106]

Consider the primary patient-level analyses with respect to 'implant failure' and 'implant success'. The direction of the point estimate in both favour exposure to anti-resorptive therapy (a trivial RR of 1.01 in the success analysis, while moderately in favour in the failure analysis with RR 0.82). In both cases, the confidence intervals cross the null line. There is no serious

inconsistency in the estimates between the two analyses. The certainty of evidence in both are similarly very low.

One of the reasons the estimates appear so different when using a relative risk is that the baseline rate of the event in question (success versus failure) is very different between these two analyses. That is to say, the baseline rate of dental implant failure is between 2% versus the rate of dental implant success in 98% at short-term follow-up. The absolute difference exposes that this apparent difference is a small one (given the rarity of dental implant failure). The risk difference in the failure analysis (RR 0.82) amounts to -1% in those exposed to anti-resorptives, and our RR 1.01 of success amounts to +1%. The effect of anti-resorptives is small regardless of the direction given the rarity of the implant failure, especially in context of a small relative risk. Therefore our conclusion of the absolute effect, which we believe is the most transparent way to discuss dental implant failure rates, is identical regardless of outcome definition.

4.6 Implications

Our systematic review provides the most up-to-date, comprehensive, and methodologically rigorous assessment. Because the evidence is very limited, and it is difficult or impossible to prove a negative, we contend the evidence does not suggest an association between antiresorptive therapy and implant failure. Whereas use of antiresorptive therapy appears to increase the risk of MRONJ by about 3 cases per 1000 patients with osteoporosis undergoing dental implantation. Decisions regarding antiresorptive therapy should be made with respect to factors beyond implant failure, such as skeletal health, adverse effects such as MRONJ, and

costs of therapy. High-quality randomized-controlled trials to increase the certainty of evidence are encouraged, such as whether discontinuation of anti-resorptives pre-procedurally is associated with less dental or greater skeletal events. Similarly, controlled studies of higher quality that include adjusted analyses, include patients with long-term exposure to low doses antiresorptives, and evaluate dental implant survival at 10 years are recommended.

Chapter 5. References

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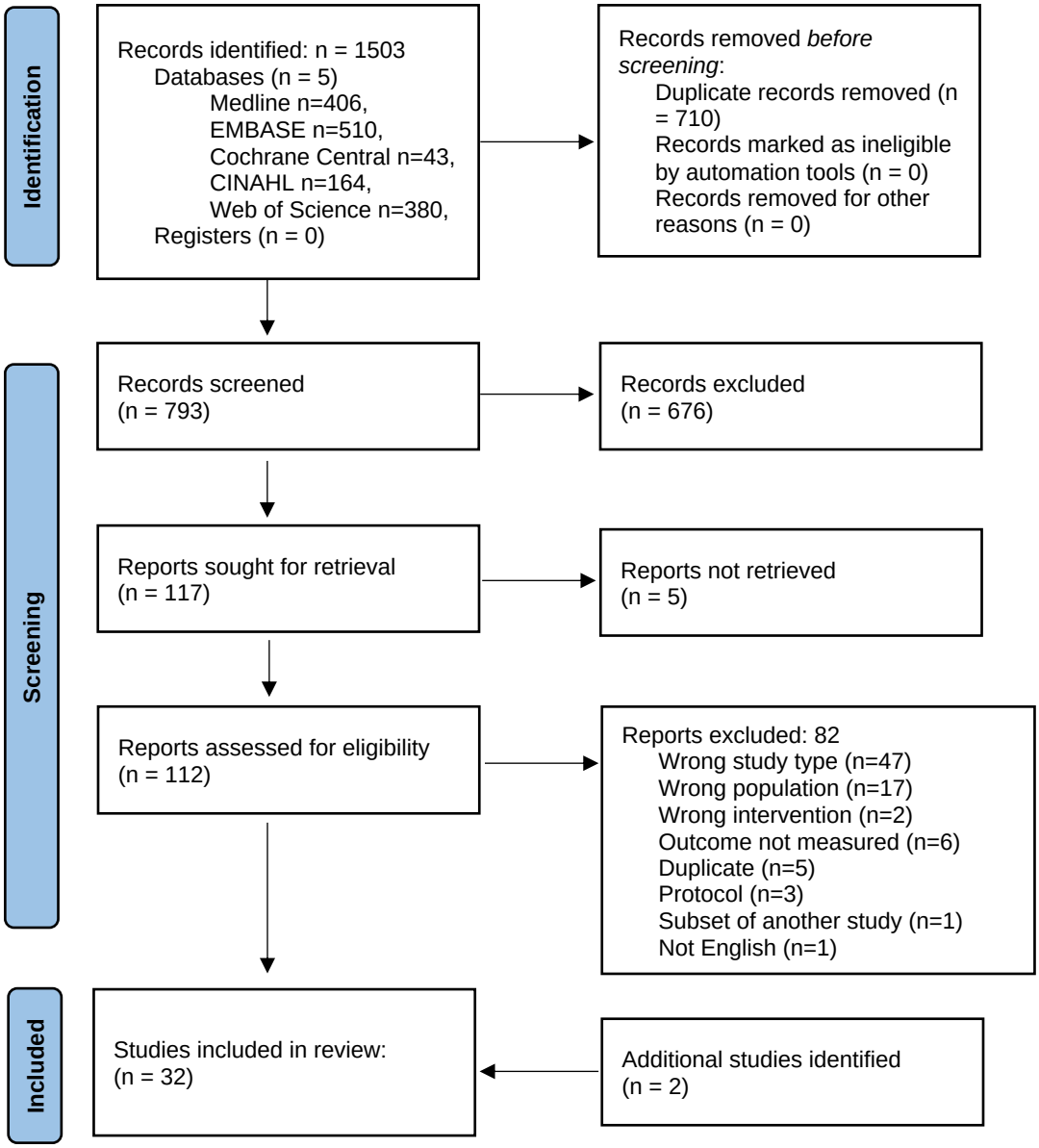
Chapter 6. Appendix

Appendix A. PRISMA Diagram (2020 version)



Appendix B: Search Strategy

2022 Summary of search and strategy Dental Implant

Database	total	since Nov 2020
MEDLINE	406	26
EMBASE	510	72
Cochrane Central	43	5
CINAHL	164	17
Web of Science	380	26
Subtotal	1503	146
-dupes		
Total		

Total screened = 692 from Nov 2020 plus

Jan 19, 2022

MEDLINE

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

---

1 Dental Implants/ (24357)

2 exp Dental Implantation/ (22957)

3 Dental Restoration Failure/ (8842)

4 ((dental or tooth or teeth) adj3 implant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word,

organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (46971)

5 ((dental or tooth or teeth) and (implant adj3 (failure or loss))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3204)

6 or/1-5 (51244)

7 exp Bone Density Conservation Agents/ (138834)

8 exp Diphosphonates/ (27165)

9 (Bisphosphonate* or alendron* or risedron* or zoledron* or etidron* or clodron* or ibandron* or pamidron*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (29832)

10 or/7-9 (151183)

11 6 and 10 (445)

12 limit 11 to yr="2003 -Current" (406)

13 limit 12 to ed=20201110-20220122 (26)

EMBASE (OVID)

Database: Embase <1974 to 2022 January 18>

Search Strategy:

---

1 exp tooth implant/ (16538)

2 tooth implantation/ (27539)

3 dental restoration/ (5775)

4 ((dental or tooth or teeth) adj3 implant*).mp. (44332)

5 ((dental or tooth or teeth) and (implant adj3 (failure or loss))).mp. (3119)

6 or/1-5 (48885)

7 bone density conservation agent/ (3863)

8 exp bisphosphonic acid derivative/ (71706)

9 (Bisphosphonate* or alendron* or risedron* or zoledron* or etidron* or clodron* or ibandron* or pamidron*).mp. (63151)

10 or/7-9 (78117)

11 6 and 10 (525)

12 limit 11 to yr="2003 -Current" (510)

13 limit 12 to dc=20201110-20220119 (72)

Cochrane Library (Wiley)

Search Name: 2020-11-10 dental implant

Date Run: 19/01/2022 17:27:43

Comment:

ID	Search Hits
#1	MeSH descriptor: [Dental Implants] explode all trees 1577
#2	MeSH descriptor: [Dental Implantation] explode all trees 1342
#3	MeSH descriptor: [Dental Restoration Failure] explode all trees 1091
#4	((dental or tooth or teeth) near/3 implant*) 3750
#5	((dental or tooth or teeth) and (implant near/3 (failure or loss))) 499
#6	#1 or #2 or #3 or #4 or #5 4410
#7	MeSH descriptor: [Bone Density Conservation Agents] explode all trees 1671
#8	MeSH descriptor: [Diphosphonates] explode all trees 2651
#9	Bisphosphonate* or alendron* or risedron* or zoledron* or etidron* or clodron* or ibandron* or pamidron* 6156
#10	#7 or #8 or #9 6940
#11	#6 and #10 with Cochrane Library publication date Between Jan 2003 and Jan 2022 43
#12	#11 In Trials with Cochrane Library publication date Between Nov 2020 and Jan 2022 5

CINAHL

#	Query	Results
S12	S11 Limiters - Published Date: 20200101-20221231	17
S11	S7 AND S10	164
S10	S8 OR S9	11,688
S9	TX Bisphosphonate* or alendron* or risedron* or zoledron* or etidron* or clodron* or ibandron* or pamidron*	8,275
S8	(MH "Diphosphonates+")	9,624
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	19,557
S6	TX ((dental or tooth or teeth) and (implant N3 (failure or loss)))	1,577
S5	TX ((dental or tooth or teeth) N3 implant*)	14,936
S4	(MH "Dental Restoration, Permanent")	5,202
S3	(MH "Dental Prosthesis, Implant-Supported")	2,840
S2	(MH "Dental Implantation")	4,408
S1	(MH "Dental Implants")	9,817

Web of Science (Clarivate)

6

#5 Publication date 2020-2022

26

Add to query

5

#3 AND #4

380

Add to query

4

TS=(diphosphonate* or Bisphosphonate* or alendron* or risedron* or zoledron* or etidron* or clodron* or ibandron* or pamidron*)

44,114

Add to query

3

#1 OR #2

28,684

Add to query

2

TS=((((dental or tooth or teeth) and (implant near/3 (failure or loss)))))

3,964

Add to query

1

TS=((((dental or tooth or teeth) near/3 implant*)))

28,406

Appendix C. Modified Ottawa-Newcastle Risk of Bias for Dental Implant Outcomes

Study	Same population?	Confident in exposure assessment?	Outcome Not Present at Onset?	Control Confounders?	Assessment of Confounders?	Confident in Outcome Assessment?	Follow-up Adequate?	Similar co-interventions?	Overall risk of bias
Al-Sabbagh 2015	Probably yes	Probably no	Definitely yes	Definitely no	Definitely yes	Definitely yes	Definitely no	Definitely no	High
Famili 2011	Definitely yes	Definitely yes	Definitely yes	Probably yes	Probably no	Probably yes	Definitely no	Definitely no	Low
Famili 2015	Probably yes	Definitely yes	Definitely yes	Definitely no	Definitely no	Definitely no	Probably yes	Definitely no	High
Jeffcoat 2006	Definitely yes	Definitely no	Definitely yes	Probably no	Definitely no	Probably no	Probably no	Definitely no	High
Pandey 2019	Probably yes	Definitely no	Definitely yes	Probably no	Definitely no	Definitely no	Definitely no	Definitely no	High
Yajima 2017	Definitely yes	Definitely no	Definitely yes	Probably no	Definitely no	Definitely no	Probably no	Definitely no	High
Kasai 2009	Probably yes	Definitely no	Definitely yes	Probably no	Definitely no	Definitely yes	Definitely no	Definitely no	High
Koka 2010	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably no	Probably yes	Probably no	Definitely no	High
Cheng 2022	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably yes	Definitely yes	Probably no	Probably yes	Low

Study	**Risk of Bias Comments**
Al-Sabbagh 2015	The number of patients who did not wish to participate is not provided.
Famili 2011	OP self-reported. Adjusted analysis.
Famili 2015	DXA performed by investigators. Included osteopenic patients. One non-BP patient on calcitonin. Two year follow-up. Unadjusted analysis.
Jeffcoat 2006	Three years follow-up. Unadjusted analysis.
Pandey 2019	Patient selection methodology unstated. Comparator arm exposed to PTH analogue. Unadjusted analysis, but patients with confounding risk factors excluded.
Yajima 2017	Patient selection methodology unstated. Unadjusted analysis. Loss to follow-up unstated.
Kasai 2009	Patients self-reported OP and BP exposure. Unadjusted analysis.
Koka 2010	Patients who did not respond to telephone call were excluded. Only age controlled for.
Cheng 2022	Prophylactic antibiotic use appears variable, and was not controlled.

Appendix D. Risk of Bias for MRONJ

Study	Same population?	Confident in exposure assessment?	Outcome Not Present at Onset?	Control Confounders?	Assessment of Confounders?	Confident in Outcome Assessment?	Follow-up Adequate?	Similar co-interventions?	Overall risk of bias
Ryu 2021	Definitely yes	Probably yes	Definitely yes	Probably yes	Definitely yes	Probably no	Probably yes	Probably no	Low

Appendix E. PRISMA 2020 Abstract Checklist

PRISMA 2020 for Abstracts Checklist

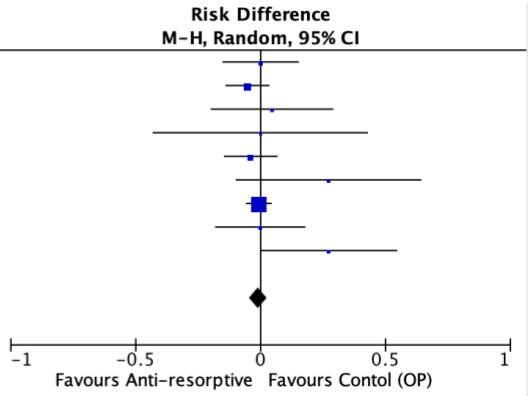
Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

Appendix F. Risk Difference Analyses

Absolute Risk Difference of Dental Implant Failure (patient level)

Study or Subgroup	Anti-resorptive therapy Events	Total	Control (osteoporosis) Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Al-Sabbagh 2015 (662)	0	20	0	9	5.8%	0.00 [-0.15, 0.15]
Cheng 2022	19	124	41	199	18.3%	-0.05 [-0.14, 0.03]
Famili 2011	1	22	0	5	2.2%	0.05 [-0.20, 0.29]
Famili 2015	0	2	0	18	0.7%	0.00 [-0.43, 0.43]
Jeffcoat 2006	0	25	1	25	12.1%	-0.04 [-0.14, 0.06]
Kasai 2009	3	11	0	4	1.0%	0.27 [-0.10, 0.64]
Koka 2010	1	54	2	82	54.0%	-0.01 [-0.05, 0.04]
Pandey 2019	1	15	1	15	4.1%	0.00 [-0.18, 0.18]
Yajima 2017	3	11	0	14	1.8%	0.27 [-0.00, 0.55]
Total (95% CI)		**284**		**371**	**100.0%**	**-0.01 [-0.05, 0.03]**
Total events	28		45			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.01$, df = 8 (P = 0.43); $I^2 = 0\%$
Test for overall effect: Z = 0.50 (P = 0.62)



Absolute Risk Difference of Dental Implant Success (patient level)

Study or Subgroup	Anti-resorptive therapy Events	Total	Control (osteoporosis) Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Al-Sabbagh 2015 (662)	20	20	9	9	5.8%	0.00 [-0.15, 0.15]
Cheng 2022	105	124	158	199	18.3%	0.05 [-0.03, 0.14]
Famili 2011	21	22	5	5	2.2%	-0.05 [-0.29, 0.20]
Famili 2015	2	2	18	18	0.7%	0.00 [-0.43, 0.43]
Jeffcoat 2006	25	25	24	25	12.1%	0.04 [-0.06, 0.14]
Kasai 2009	8	11	4	4	1.0%	-0.27 [-0.64, 0.10]
Koka 2010	53	54	80	82	54.0%	0.01 [-0.04, 0.05]
Pandey 2019	14	15	14	15	4.1%	0.00 [-0.18, 0.18]
Yajima 2017	8	11	14	14	1.8%	-0.27 [-0.55, 0.00]
Total (95% CI)		**284**		**371**	**100.0%**	**0.01 [-0.03, 0.05]**
Total events	256		326			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.01$, df = 8 (P = 0.43); $I^2 = 0\%$
Test for overall effect: Z = 0.50 (P = 0.62)