Dental Implant Placement in Patients With a History of Medications Related to Osteonecrosis of the Jaws: A Systematic Review

Judd Sher[1]
Kate Kirkham-Ali[1]
Jie Denny Luo[1]
Catherine Miller, BSc(Hons), PhD[2]
Dileep Sharma, PhD[1,*]

The present systematic review evaluates the safety of placing dental implants in patients with a history of antiresorptive or antiangiogenic drug therapy. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed. PubMed, Cochrane Central Register of Controlled Trials, Scopus, Web of Science, and OpenGrey databases were used to search for clinical studies (English only) to July 16, 2019. Study quality was assessed regarding randomization, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases using a modified Newcastle-Ottawa scale and the Joanna Briggs Institute critical appraisal checklist for case series. A broad search strategy resulted in the identification of 7542 studies. There were 28 studies reporting on bisphosphonates (5 cohort, 6 case control, and 17 case series) and 1 study reporting on denosumab (case series) that met the inclusion criteria and were included in the qualitative synthesis. The quality assessment revealed an overall moderate quality of evidence among the studies. Results demonstrated that patients with a history of bisphosphonate treatment for osteoporosis are not at increased risk of implant failure in terms of osseointegration. However, all patients with a history of bisphosphonate treatment, whether taken orally for osteoporosis or intravenously for malignancy, appear to be at risk of "implant surgery-triggered" medication-related osteonecrosis of the jaw (MRONJ). In contrast, the risk of MRONJ in patients treated with denosumab for osteoporosis was found to be negligible. In conclusion, general and specialist dentists should exercise caution when planning dental implant therapy in patients with a history of bisphosphonate and denosumab drug therapy. Importantly, all patients with a history of bisphosphonates are at risk of MRONJ, necessitating this to be included in the informed consent obtained before implant placement.

Key Words: dental implants*, *antiresorptive drugs*, *antiangiogenic drugs*, *osseointegration*, *MRONJ

INTRODUCTION

Successful placement and longevity of dental implants largely depends on achieving osseointegration during wound healing. Osseointegration is a dynamic process that requires normal functioning of inherent biological activities that occur during bone remodeling, specifically, the resorption of old bone by osteoclasts and the formation of new bone by osteoblasts.[1] The formation of new immature blood capillaries (angiogenesis) is essential in fueling these activities because bone cells, like all cells in the human body, require an adequate blood supply.[2] Therefore, drugs that interfere with bone remodeling and angiogenesis may compromise osseointegration and result in premature implant loss.[1]

Antiresorptives are a class of drugs known to affect bone homeostasis by inhibiting osteoclast differentiation and function. This effect supports their use in treating bone disorders characterised by excessive bone resorption such as osteoporosis and certain skeletal malignancies.[3] A patient's quality of life is significantly improved with these drugs as they can prevent fractures and limit bone pain and metastatic spread.[4] Today, there are 4 principal classes of antiresorptive drugs in use: bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin, and monoclonal antibodies such as denosumab.[5]

Antiangiogenics are a class of drugs used in cancer to restrict tumor vascularization.[4] They are considered a novel and targeted approach in cancer treatment, relying on the concept that tumours cannot grow larger than 1–2 mm^3 without generating their own blood supply.[6] Most antiangiogenic drugs are monoclonal antibodies or small-molecule inhibitors that target the vascular endothelial growth factor (VEGF) pathway, as more than half of malignant tumours express high concentrations of VEGF. Examples of antiangiogenics in clinical practice include bevacizumab, pazopanib, and everolimus.[7]

A delayed wound healing condition associated with the use

[1] College of Medicine & Dentistry, James Cook University, Smithfield, Queensland, Australia.
[2] College of Public Health, Medical and Veterinary Sciences, James Cook University, Smithfield, Queensland, Australia.
* *Corresponding author,* e-mail: dileep.sharma@jcu.edu.au
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of antiresorptive and antiangiogenic drugs is known as medication-related osteonecrosis of the jaw (MRONJ). MRONJ is characterized by exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks in patients with a history of treatment with antiresorptive or antiangiogenic drugs, with no history of radiation therapy to the jaws or obvious metastatic disease of the jaws.[8] Although rare, the effects of MRONJ can be devastating, including secondary infection, swelling, painful lesions, various dysesthesias, and pathologic bone fracture.[9] Some cases do not respond to any form of treatment, and there is no evidence to suggest that stopping drug therapy will aid in resolution of the lesion. Hyperbaric oxygen reportedly has minimal to no effect. Antibiotics cannot enter necrotic tissue, so they are only used to manage infection in adjacent tissues. The current recommendations involve palliative care or conservative treatment in symptomatic lesions.[10] When surgery is indicated, large resections and complex reconstructions are often performed with limited success and often leave patients with rather notable facial deformities.[11] At present, the pathogenesis of MRONJ is poorly understood. Various etiopathogenic mechanisms under investigation include suppression of bone turnover, inhibition of angiogenesis, toxic effects on soft tissue cells, and infection. One of the strongest predisposing factors is dentoalveolar surgery; however, despite this, the risk of MRONJ after the placement of dental implants is currently unknown.[4]

With an increasing number of patients reporting a history of antiresorptive or antiangiogenic drug therapy, general and specialist dentists will be faced with the decision of whether it is safe to place dental implants in this patient group. Although not currently contraindicated for dental implant therapy, there are biologically plausible arguments that could be made to suggest a risk of implant failure and MRONJ development in these patients.[12] Previous systematic reviews on this topic mainly focussed on bisphosphonates and the reported effect that these drugs had in relation to implant failure and MRONJ varied.[13] Two systematic reviews were unsuccessful in their attempt to retrieve studies on denosumab.[3,14] Furthermore, to date, no systematic reviews have included studies of patients treated with antiangiogenic drugs. Therefore, the aim of the present systematic review was to systematically research the literature to address these deficits and answer the following focus question: "When compared to placing dental implants in healthy patients, are patients with a history of antiresorptive or antiangiogenic drug therapy at increased risk of implant failure and MRONJ?"

Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[15]

Eligibility criteria

Studies were required to meet strict inclusion criteria. These included the following: (1) English language; (2) randomized controlled trials, cohort studies, case-control studies, or case series; (3) retrospective, cross-sectional, or prospective design; (4) $\geq$5 patients with a history of antiresorptive or antiangiogenic drug therapy before implant placement; (5) clear reporting of sufficient relevant data worthy of discussion; and (6) full version available. Studies that did not meet the inclusion criteria were automatically excluded.

Information sources

An electronic search was performed in PubMed, Cochrane Central Register of Controlled Trials, Scopus, and Web of Science databases. Furthermore, a search of the OpenGrey database was used to identify any unpublished studies (gray literature); the last search was July 16, 2019.

Search

To increase the sensitivity of the search, the search strategy only included terms concerning the population and intervention. Furthermore, no date restriction was used. The full search string used in each of the databases can be found in the registered protocol on the PROSPERO database (see Note).

Study selection

Two reviewers (JS, KKA) independently began the identification phase using the abovementioned search strategy. Citations of identified articles were exported into reference managing software (EndNote X8), and duplicates were removed. The screening phase was performed by the same reviewers where the titles and abstracts of all remaining studies were independently screened for studies that potentially meet the inclusion criteria. In the eligibility phase, the full-text version of all remaining studies was independently assessed by the same reviewers for eligibility into the included phase. Any disagreements over the eligibility of studies were resolved through discussion with a third reviewer (JDL).

Data collection process

A standardized, prepiloted Microsoft Excel spreadsheet was used to extract data from the included studies for evidence synthesis and assessment of study quality. Two reviewers (JS, KKA) extracted the data independently, and any discrepancies were resolved through discussion with a third reviewer (JDL). Where possible, missing data were requested from study authors.

Data items

The data collected from the included studies were tabulated in the following fields: (1) study design; (2) number of cases (patients with a history of antiresorptive or antiangiogenic drug therapy) and, when available, number of controls (patients without a history of antiresorptive or antiangiogenic drug therapy); (3) number of implants in cases and controls; (4) patient characteristics (systemic diseases/age/sex/smoking status); (5) details regarding antiresorptive or antiangiogenic drug history (type of drug, indication for intake, administration route, and intake before implant placement); (6) whether patients were taking the drug at the time of implant placement and implant follow-up; (7) reported outcome parameters (implant

loss/failure/success/survival and incidence of MRONJ); and (8) reported outcome. Where data was missing, the term "not specified" was used.

Quality assessment

Assessment of methodologic and reporting quality was conducted to establish the internal validity and risk of bias of studies that met the inclusion criteria.

Newcastle-Ottawa Scale

The methodologic and reporting quality of the included cohort and case-control studies was assessed independently by 2 reviewers (JS, KKA) applying a modified Newcastle-Ottawa scale (NOS)[16] as described by Stavropoulos et al.[3] In the present systematic review, a percentage <50% was considered to indicate low quality, 50–70% was moderate quality, and >75% was high quality. Furthermore, for each specific item, the percentage of positive scored studies was calculated. Where there were disagreements between the 2 reviewers, a third reviewer (JDL) was involved.

Joanna Briggs Institute Critical Appraisal Checklist for Case Series

The methodologic and reporting quality of the included case series was assessed independently by 2 reviewers (JS, KKA) applying the Joanna Briggs Institute (JBI) critical appraisal checklist for case series.[17] In the present systematic review, a percentage <50% was considered to indicate low quality, 50–70% was moderate quality, and >75% was high quality. Furthermore, for each specific item, the percentage of positive scored studies was calculated. Where there were disagreements between the 2 reviewers, a third reviewer (JDL) was involved.

Results

Study selection

The combinations of search terms resulted in a total of 7542 titles. Of these, 1469 were found to be duplicates; as a result, 6073 references were reviewed. In turn, 6018 studies were excluded based on the evaluation of the title and abstract, leaving 55 studies to be assessed for eligibility. Of these, 26 studies were excluded for various reasons, and 29 studies met the inclusion criteria and were thus selected for inclusion in the present systematic review (Figure 1). There were no additional studies identified through cross-referencing or by contacting study authors of retrieved publications that met the inclusion criteria. Of the included studies, 28 reported on bisphosphonates,[18–45] and 1 reported on denosumab.[46] No studies reporting on SERMs, calcitonin, or antiangiogenics were identified.

Study characteristics

Table 1a through c presents characteristics of the included studies. Table 2 presents a summary of the outcome measures from all included studies on bisphosphonate and denosumab intake. Where there was missing information required for the interpretation, estimations were calculated on a pro rata basis or by assuming the minimum number of implants placed/failed in cases and controls.

Studies on Bisphosphonate

There were five cohort studies,[21,27,28,44,45] 6 case-control studies,[18,22,23,30,31,39] and 17 case series,[19,20,24–26,29,32–38,40–43] reporting on bisphosphonate intake included in the present systematic review. Twenty studies were retrospective,[19,22–24,27,28,30–38,40–42,44,45] 4 were cross-sectional,[20,21,25,26] and 4 were prospective.[18,29,39,43] Most of the studies were based only on information obtained from patient records. In 5 studies,[24–26,34,35] bisphosphonate intake before and after implant placement was reported; the cases in which implants were placed before initiating bisphosphonate treatment were excluded. Nisi et al[38] included 90 patients with MRONJ caused by various reasons; only the 9 cases of MRONJ caused by implant placement were included. French et al[45] evaluated several risk factors associated with marginal bone loss and prevalence of mucositis/peri-implantitis; only information pertaining to bisphosphonate therapy was used. Among studies, cases (patients with a history of bisphosphonate drug therapy) ranged from 6 to 235, whereas the number of implants placed in cases ranged from 14 to 1267 implants. Controls (patients without a history of bisphosphonate drug therapy) when present, ranged from 12 to 2026, whereas the number of implants placed in controls ranged from 28 to 4507 implants. Six studies did not specify the number of cases/controls on the patient or implant level.[21,24,26,31,35,38] The follow-up period after implant placement ranged from 0.3 to 12.2 years. Collectively, 20 studies provided information regarding implant loss/failure/success/survival,[18–23,25–31,37,39,41–45] and 22 studies provided information regarding the incidence of MRONJ.[18–25,27,28,32–42,44] More detailed single-patient data was able to be extracted from 6 studies.[20–23,28,44]

Studies on Denosumab

A single case series by Watts et al[46] reporting on denosumab intake was eligible to be included in the present systematic review. This study was retrospective and based on information obtained from a questionnaire. Information on invasive oral procedures and events (dental implants, tooth extraction, natural tooth loss, scaling/root planing, and jaw surgery) in long-term/crossover patients treated with denosumab was assessed, and details of positively adjudicated MRONJ cases were presented; only the patients who received dental implants were included. The number of cases (patients with a history of denosumab drug therapy) was 212, whereas the number of implants placed was not specified. The follow-up period after implant placement was also not specified. Some type of information was provided regarding the incidence of MRONJ. More detailed single-patient data were able to be extracted from this study.

Quality assessment

NOS

Tables 3 and 4 present the quality assessment of the included cohort and case-control studies. Cohort studies received from 1 to 5 stars (14%–71%; low-moderate quality), whereas case-control studies received from 5 to 7 stars (63%–88%; moderate-high quality). For each item, the percentage of positive scored studies ranged from 0% to 100% for cohort studies and from 50% to 100% for case-control studies.

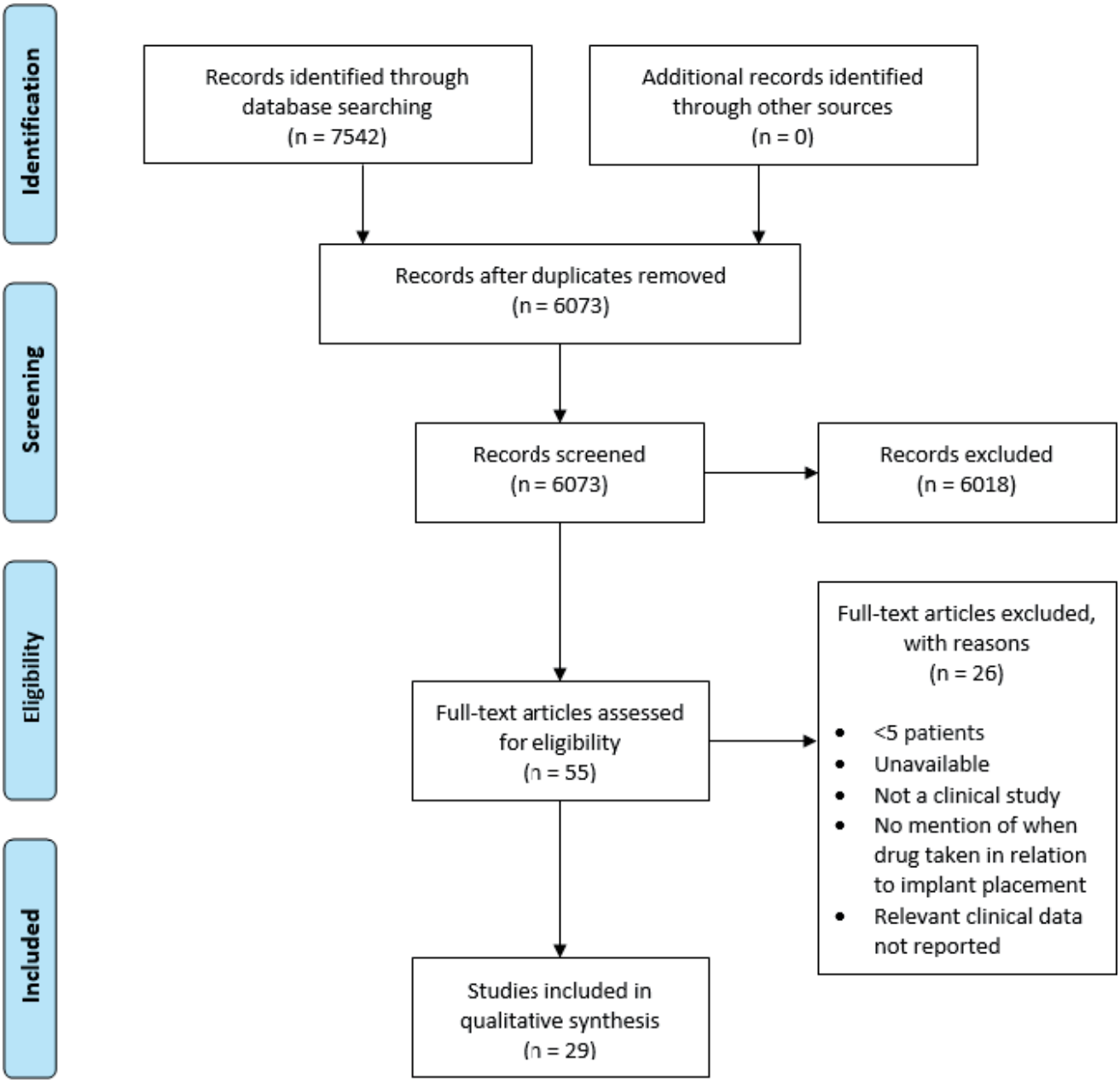

Figure 1. PRISMA flow diagram of the search processes and results.

JBI Critical Appraisal Checklist for Case Series

Table 5 presents the quality assessment, based on the JBI critical appraisal checklist for case series, of the included case series. Studies received from 5 to 10 yes answers (50%–100%; moderate-high quality). The percentage of yes answered case series per question ranged from 67% to 100%.

Results of individual studies

Studies on Bisphosphonate

Oral bisphosphonates were prescribed for osteoporosis treatment in most studies; only 9 studies reported intravenous administration of bisphosphonates,[24,32,34–36,38–41] and 6 of these studies reported bisphosphonate administration related to malignancies.[24,32,35,36,38,40] The most frequently prescribed bisphosphonate for osteoporosis was oral alendronate; at times oral clodronate, ibandronate, or risedronate were prescribed as an alternative or with alendronate. There were some instances where intravenous ibandronate, pamidronate, or zoledronic acid was prescribed for osteoporosis alone or with oral alendronate. For all cases of malignancy, intravenous zoledronic acid was prescribed alone or with other intravenous bisphosphonates such as ibandronate or pamidronate. The number of years of bisphosphonate intake before implant placement ranged from approximately 0.25 to 20.3 years.

Other than Kasai et al,[22] where implant success rate for cases was 85.7%, and Yajima et al,[44] where implant survival rate

TABLE 1A

Characteristics of the studies meeting the inclusion criteria. Additional study characteristics are available in Tables 1b and c*

Study	Study Design	No. of Cases/ Controls	No. of Implants in Cases/ Controls	Systemic Disease	Age Range/Mean	Sex M/F (%)	Smokers (%)
Jeffcoat[18]	Prospective Case-control Clinical data	25/25	102/108	Osteoporosis	NS/NS (postmenopausal)	0/100	4
Fugazzotto et al[19]	Retrospective Case series Medical records	61/0	169/0	NS (excluded: uncontrolled diabetes, immune diseases, or other contraindicating systemic conditions; radiation therapy in the head and neck region in the 12-month period prior to the proposed therapy; chemotherapy in the 12-month period prior to the proposed therapy; uncontrolled periodontal disease and/or unwillingness to undergo needed periodontal therapy around remaining teeth; severe psychologic problems; or unwillingness to commit to a long-term post therapy maintenance program)	51–83/NS	0/100	NS
Bell and Bell[20]	Cross-sectional Case series Medical records and clinical data	42/0	100/0	Osteoporosis (42 patients)	NS	5/95	NS
Grant et al[21]	Cross-sectional Cohort Questionnaire and partly clinical data	89/343	NS/1450	NS	>40/NS	0/100	NS
Kasai et al[22]	Retrospective Case-control Medical records	11/40	35/161	Osteoporosis (cases: 11; controls: 4; excluded: uncontrolled diabetes, rheumatic disease under corticoid medication)	>36/NS (cases: 52–73)	0/100	0
Koka et al[23]	Retrospective Case-control Medical records and interview	55/82	121/166	Diabetes (cases: 10; controls: 8), hormone replacement therapy, estrogen (cases: 31; controls: 48), steroids (cases: 5; controls: 5)	Cases: 50–93/71; controls: 50–89/66	0/100	Cases: 4, controls: 11
Lazarovici et al[24]	Retrospective Case series Medical records	23/0	NS/0	NS	NS/NS	NS/NS	NS
Martin et al[25]	Cross-sectional Case series Questionnaire and partly medical records	12/0	16/0	NS	NS/NS	0/100	NS
Shabestari et al[26]	Cross-sectional Case series Clinical data	7/0	NS/0	NS (excluded: immune deficiency, diabetic condition, head or neck radiation therapy, anticoagulation therapy)	NS/NS (postmenopausal)	0/100	NS
Famili et al[27]	Retrospective Cohort Medical records	22/98	75/272	Osteoporosis (cases: 22; controls: 5), osteoarthritis (cases: 1; 1 of the cases had both osteoporosis and osteoarthritis)	NS/NS (>50)	0/100	NS

TABLE 1A

Continued

Study	Study Design	No. of Cases/ Controls	No. of Implants in Cases/ Controls	Systemic Disease	Age Range/Mean	Sex M/F (%)	Smokers (%)
Zahid et al[28]	Retrospective Cohort Medical records	26/274	51/610	Osteoporosis (8% of the study population)	17–87/56	37/63	9
Leonida et al[29]	Prospective Case series Clinical data	9/0	54/0	Osteoporosis (excluded: history of chemotherapy/radiation, taking concomitant glucocorticosteroid therapy)	45–68/NS	10/90	0
Memon et al[30]	Retrospective Case-control Medical records	100/100	153/132	Diabetes (cases: 3; controls: 4)	Cases: 46–91/66; controls: 47–90/63	0/100	Cases: 3; controls: 5
Yip et al[31]	Retrospective Case-control Medical records	20/317	NS/NS (1181 in total)	Hormone replacement therapy (36), diabetes (20), thyroid disorders (36), hypothyroidism (29), cardiovascular diseases, high blood pressure (67), heart attack (6), stroke (5)	≥40/57	0/100	15
Jacobsen et al[32]	Retrospective Case series Medical records	14/0	23/0	Osteoporosis (5), breast cancer (5), multiple myeloma (2), prostate cancer (1), lung cancer (1)	NS/NS	21/79	NS
Lopez-Cedrun[33]	Retrospective Case series Medical records	9/0	57/0	Hypertension (3), corticosteroid (2) (1; had both hypertension and corticosteroid)	61–78/66	11/89	22.2
Holzinger et al[34]	Retrospective Case series Medical records	10/0	39/0	NS	NS/NS	NS/NS	NS
Kwon et al[35]	Retrospective Case series Medical records	16/0	NS/0	Diabetes, renal, hypertension, myocardial infarction, osteoarthritis, hypothyroidism, rheumatoid arthritis, steroid, cerebrovascular accident, asthma	42–85/66.7	12.5/87.5	NS
Tam et al[36]	Retrospective Case series Medical records	6/0	14/0	Osteoporosis (4), breast cancer (1), hypertension (1), multiple myeloma (1), chemotherapy (1)	65.3–78.3/71.8	0/100	NS
Mozzati et al[37]	Retrospective Case series Medical records	235/0	1267/0	Diabetes (21), corticosteroids (24)	48–79/61		22
Nisi et al[38]	Retrospective Case series Medical records	9/0	NS/0	NS	NS/NS	NS/NS	NS
Siebert et al[39]	Prospective Case-control Clinical data	12/12	60/60	None (excluded: steroids)	>54/NS	0/100	0
Giovannacci et al[40]	Retrospective Case series Medical records	15/0	52/0	NS	45–83/64.3	26.7/73.3	13.3
Khoury and Hidajat[41]	Retrospective Case series Medical records	15/0	71/0	Osteoporosis (15)	55–72/NS	0/100	0
Suvarna et al[42]	Retrospective Case series Medical records	112/0	140/0	NS	NS/NS	30/82	NS
Tallarico et al[43]	Prospective Case series Clinical data	32/0	98/0	NS	46–80/65	0/100	NS, no "heavy smokers" (>10 cigarettes/day)

Table 1A

Continued

Study	Study Design	No. of Cases/ Controls	No. of Implants in Cases/ Controls	Systemic Disease	Age Range/Mean	Sex M/F (%)	Smokers (%)
Yajima et al[44]	Retrospective Cohort Medical records	11/14	25/28	Osteoporosis (cases: 11; controls: 14; excluded: patients with a steroid prescription, metabolic bone disease other than osteoporosis, type 2 diabetes mellitus, smoking habit, poor dental hygiene, severe periodontal disease) Controls: 8, selective estrogen receptor modulator; 6, parathyroid hormone intake	Cases: >60/70; controls: >60/67	0/100	0
French et al[45]	Retrospective Cohort Medical records	34/2026	84/4507	NS	NS/NS	NS/NS	NS
Watts et al[46]	Retrospective Case series Questionnaire	212/0	NS/0	Osteoporosis	NS/NS (postmenopausal)	0/100	NS

*NS indicates not specified.

was 88%, there were no substantial differences observed between cases/controls, with implant success rate ranging from 92.9% to 100% for cases and 95.5% to 100% for the controls. Implant losses were more likely to occur in the posterior maxillary region and shortly after placement. When including estimations because of missing data, the overall implant failure rate when combining the included studies was 2.8% for cases and 2.1% for controls. When cohort/case-control studies and case series were separated, the percentage of failed implants in cases did not differ substantially (3.1% and 2.5%, respectively).

Several studies reported no MRONJ in relation with implant placement, whereas 8 case series reported otherwise.[24,32–36,38,40] From these case series, more than 33 patients developed MRONJ in the mandible and 12 in the maxilla. Most of the MRONJ lesions were diagnosed in the posterior regions. In 28 patients, implant surgery was described as the trigger of MRONJ (4 cases attributed implant removal as the triggering factor), whereas in 26 patients, the trigger was considered the presence of the implant. Furthermore, in 9 patients, the trigger could not be identified, and in 4 studies (totaling 39 patients), a triggering factor was not specified.[32–34,36] Bisphosphonate intake was indicated for osteoporosis (or related conditions) in 49 patients and malignancy in 43 patients. Although Holzinger et al[34] did not specify an indication for bisphosphonates, cases of MRONJ developing with both oral and intravenous bisphosphonate use were investigated. The time frame between the start of bisphosphonate drug therapy and MRONJ development ranged from 1 to 223 months, whereas the time frame between when the implant was first placed and MRONJ developing ranged from 0 to 180 months. When including estimations because of missing data, the overall incidence of MRONJ when combining the included studies was 12.3%. However, when cohort/case-control studies and case series were separated, the percentage of MRONJ cases differed substantially (0% and 17.6%, respectively).

Studies on Denosumab

In the case series by Watts et al,[46] denosumab was prescribed for osteoporosis; 60 mg administered every 6 months. Of 212 patients receiving dental implants, there was only 1 case of MRONJ identified (0.5% incidence). This patient had 2 implants placed in the posterior maxilla with simultaneous tooth extractions and a sinus lift and subsequently developed MRONJ related to delayed osseointegration. However, the patient continued to receive denosumab (8 doses) while being successfully treated for MRONJ and managed to also retain the implants.

Discussion

Osteoclast-mediated bone resorption plays an important role during osseointegration and peri-implant bone homeostasis.[3] Because bisphosphonates and denosumab interfere with osteoclast function, it is reasonable to consider that these drugs may have a negative effect on implant success in terms of osseointegration. However, most of the studies included in this systematic review indicated that patients with a history of bisphosphonates for osteoporosis treatment are not at increased risk of implant failure in terms of osseointegration compared with patients without a history of such medications. With estimations made in studies that failed to specify the exact number of implants placed/failed in each patient and irrespective of study design, only 85 of 3074 implants placed in 930 patients with a history of bisphosphonates failed. Compared with 182 implants failing of 8605 implants placed in

TABLE 1B

Characteristics of the studies meeting the inclusion criteria. Additional study characteristics are available in Tables 1a and c*

Study	Type of Drug (No. Patients)	Indication for Intake (No. Patients)	Administration Route	Intake Before Implant Placement Range/Mean in Years (No. Patients)
Jeffcoat[18]	Alendronate, risedronate	Osteoporosis	Oral	1–4/3
Fugazzotto et al[19]	Alendronate (51), risedronate (10) (35 or 70 mg/wk)	NS	Oral	1–5/3.3
Bell and Bell[20]	Alendronate (34), risedronate (6), ibandronate (2)	Osteoporosis	Oral	0.5–11/NS
Grant et al[21]	Alendronate (66), risedronate (21), ibandronate (2)	NS	Oral	>3 (33), <3 (56)/NS
Kasai et al[22]	Alendronate	Osteoporosis	Oral	≥3/NS
Koka et al[23]	NS	Osteoporosis (32), Osteopenia (18), unspecified (5)	NS	<3 (16), 3–5 (20), >5 (19)/NS
Lazarovici et al[24]	Alendronate: 70 mg/week or 10 mg/day (10), zoledronic acid: 4 mg every 3–4 wk (5), pamidronate: 90 mg every 3–4 wk (5), combination of pamidronate and zoledronic acid: 90/4 mg every 3–4 wk (3)	Osteoporosis (alendronate; 10), malignant disease (13)	Oral (alendronate) and intravenous (zoledronic acid, pamidronate)	0–9/3
Martin et al[25]	Alendronate	Osteoporosis	Oral	NS/NS
Shabestari et al[26]	Alendronate (35–70 mg/wk)	Osteoporosis	Oral	NS/NS
Famili et al[27]	Alendronate (15), risedronate (4), ibandronate (1), combination of alendronate and ibandronate (2)	Osteoporosis (22), osteoarthritis (1)	Oral	0.5–1 (6), 1–5 (9), >5 (5), unknown (2)/NS
Zahid et al[28]	Alendronate, ibandronate	Osteoporosis	Oral	0.5–16 (11 not available)/NS
Leonida et al[29]	Risedronate (5), alendronate (4)	Osteoporosis	Oral	<3/NS
Memon et al[30]	Alendronate (72), risedronate (23), ibandronate (5)	Osteoporosis	Oral	<1 (20), 1–3 (19), >3 (15), unspecified (46)/NS
Yip et al[31]	Alendronate, risedronate	Osteoporosis	Oral	NS/NS
Jacobsen et al[32]	Alendronate (2), pamidronate (1), ibandronate (1), combination of alendronate and pamidronate (1), zoledronic acid (8), combination of pamidronate and zoledronic acid (1)	Osteoporosis (alendronate, pamidronate, ibandronate, combination of alendronate and pamidronate [5]), malignancy (zoledronic acid, combination of pamidronate and zoledronic acid [9])	Oral (alendronate) and intravenous (pamidronate, ibandronate, zoledronic acid)	NS/NS
Lopez-Cedrun[33]	Alendronate (5), alendronate plus calcium (1), ibandronate (2), risedronate (1)	Osteoporosis (alendronate, alendronate plus calcium, ibandronate [7]), polymyalgia rheumatica (risedronate [1]), osteoarthritis (ibandronate [1])	Oral	NS/NS
Holzinger et al[34]	NS	NS	Oral and intravenous	3.3–20.3/7.5

3331 patients without a history of bisphosphonates (2.8% vs 2.1% implant failure rate, respectively), this corresponds to a 2.8% implant failure rate in 8.3% of cases vs a 2.1% implant failure rate in 4.1% of controls. When assessing the numbers from cohort/case-control studies and case series separately, the implant failure rate did not differ substantially (3.1% and 2.5%, respectively). A recent systematic review evaluating the survival of dental implants in healthy patients found a 5.4% failure rate over an average follow-up of 13.4 years.[47] This observed failure rate is similar to that observed in patients who had used bisphosphonates in the present systematic review; therefore, it seems that implants placed in patients with a history of bisphosphonate use are not at increased risk of failing. Although most patients in the implant failure studies were taking oral bisphosphonates, one study by Siebert et al[39] examined implant survival in patients with osteoporosis receiving yearly infusions of intravenous zoledronic acid (5 mg). In this study, the implant success rate was found to be

Table 1B

Continued

Study	Type of Drug (No. Patients)	Indication for Intake (No. Patients)	Administration Route	Intake Before Implant Placement Range/Mean in Years (No. Patients)
Kwon et al[35]	Zoledronic acid (1), alendronate (6), ibandronate (1), pamidronate (1), risedronate (3s), combination of alendronate and ibandronate (1), combination of alendronate and risedronate and ibandronate (1), combination of alendronate and risedronate (2)	Multiple myeloma (zoledronic acid [1]), osteoporosis (15)	Oral (alendronate, ibandronate, risedronate) and intravenous (zoledronic acid, ibandronate, pamidronate)	0.5–9/NS
Tam et al[36]	Alendronate (3), zoledronic acid (2), combination of alendronate and ibandronate (1)	Osteoporosis (4), malignancy (2)	Oral (alendronate) and intravenous (zoledronic acid, ibandronate)	0.25–6/3
Mozzati et al[37]	Alendronate (141), risedronate (45), ibandronate (68)	Osteoporosis	Oral	0.6–7.3/3.4
Nisi et al[38]	Zoledronic acid	Malignancy	Intravenous	NS/NS
Siebert et al[39]	Zoledronic acid (5 mg once/yr)	Osteoporosis	Intravenous	2–3/NS
Giovannacci et al[40]	Alendronate (4), ibandronate (1), combination of ibandronate and alendronate (1), zoledronic acid (6), combination of ibandronate and zoledronic acid (1), combination of zoledronic acid and pamidronate (1), pamidronate (1)	Osteoporosis (6), breast cancer (1), other malignant disease (8)	Oral (alendronate, ibandronate) and intravenous (zoledronic acid, ibandronate, pamidronate)	1.3–10.9/4.6
Khoury and Hidajat[41]	Alendronate, risedronate, ibandronate, clodronate	Osteoporosis	Oral (alendronate, risedronate, ibandronate, clodronate) and intravenous (ibandronate)	0.25–10/NS
Suvarna et al[42]	Alendronate, risedronate, ibandronate	NS	NS	NS/NS
Tallarico et al[43]	Alendronate (70 mg/wk)	Osteoporosis	Oral	>3/NS
Yajima et al[44]	Alendronate	Osteoporosis	Oral	1–3 (5), >3 (6)/NS
French et al[45]	NS (bisphosphonate)	NS	NS	NS/NS
Watts et al[46]	Denosumab (60 mg every 6 mo)	Osteoporosis	Subcutaneous	NS

*NS indicates not specified.

100% in both groups (intravenous zoledronic acid and controls). Another study by Khoury and Hidajat[41] investigated implant loss in patients with osteoporosis receiving both oral and intravenous (ibandronate) and found that, of 71 implants placed in 15 patients, only 1 immediately loaded implant failed after 5 months, and it was successfully replaced. In contrast, 2 studies by Kasai et al[22] and Yajima et al[44] cast doubt on this concept and reported that there were substantial differences in success and survival rates of dental implants between cases and controls (85.7% and 88%, respectively). In general, it seemed that there was a larger amount of early implant failures reported in bisphosphonate patients and more often in the posterior maxilla. However similar patterns to this have been observed in the general population.[48] Unfortunately, a risk assessment of implant failure in patients with a history of bisphosphonates for cancer or those with a history of denosumab could not be performed because there was insufficient data available from the studies included.

The concerns for an increased risk of implant failure in bisphosphonate users should also be seen in light of MRONJ. As mentioned previously, one of the strongest predisposing factors for MRONJ appears to be dentoalveolar surgery;

TABLE 1C

Characteristics of the studies meeting the inclusion criteria. Additional study characteristics are available in Tables 1a and b*

Study	Drug Therapy at Time of Implant Placement, Yes/No (No. Patients)	Implant Follow-Up Range/Mean (yr)	Outcome Parameters	Outcome	Additional Information
Jeffcoat[18]	NS	At least 3	Implant success	Cases: 100%; controls: 99.1%	—
			Incidence of MRONJ	0	
Fugazzotto et al[19]	NS	1–2	Implant success	100%	22 patients had 39 immediate implants placed, 39 patients had 130 implants placed into healed sites (nonsubmerged)
			Incidence of MRONJ	0	
Bell and Bell[20]	Yes (34)	0.3–7.4/3.1	Implant loss	5 implants in 5 patients/95% implant success rate (all 5 patients later had the implant successfully replaced)	Case 1: female, 6-mo history of bisphosphonates prior to implant placement, nonsmoker, no bone grafting, loss after 3 mo Case 2: female, 3-yr history of bisphosphonates prior to implant placement, smoker, socket bone grafting, loss after 2 mo Case 3: female, 2-yr history of bisphosphonates prior to implant placement, nonsmoker, sinus lift, loss after 5 mo Case 4: female, 5-yr history of bisphosphonates prior to implant placement, nonsmoker, limited implant stability at time of implant placement, loss after 3 wk Case 5: female, 3-yr history of bisphosphonates prior to implant placement, nonsmoker, sinus lift, loss after 2 mo Location of implant failures: 3 in the posterior maxilla (sinus lift), 1 in maxillary lateral incisor area (immediate implant installation), and 1 in mandibular cuspid area (overdenture during healing)
			Incidence of MRONJ	0	
Grant et al[21]	NS	NS	Implant success	Cases: 2 implants in 2 patients due to unsuccessful osseointegration (1 successfully replaced); controls: 14 losses due to unsuccessful osseointegration	Case 1: posterior maxilla (25), 3-yr history of bisphosphonates prior to implant placement but no longer taking at time of implant placement or thereafter, following year implant failed and subsequently removed, replaced successfully several months later Case 2: posterior mandible (37), >4-yr history of bisphosphonates prior to implant placement, failed to osseointegrate and was removed 1 mo later without replacement, healed uneventfully, patient remained on oral bisphosphonates
			Incidence of MRONJ	0	
Kasai et al[22]	Yes (all patients)	Cases: 5.3–12.2/7; controls: NS	Implant loss/success	Cases: 5 implants in 3 patients/85.7% implant success rate; controls: 7 implants/95.7% implant success rate	Case 1: 2 implants, anterior maxilla (lack of osseointegration) Case 2: 2 implants, posterior mandible (after 33 mo) Case 3: 1 loss in the anterior maxilla (after 11 mo)
			Incidence of MRONJ	0	

Table 1c

Continued

Study	Drug Therapy at Time of Implant Placement, Yes/No (No. Patients)	Implant Follow-Up Range/Mean (yr)	Outcome Parameters	Outcome	Additional Information
Koka et al[23]	Yes (all patients)	NS	Implant loss	Cases: 1 implant/99.2% implant success rate; controls: 3 implants in 2 patients/98.2% implant success rate	Case: 82 years, nonsmoker, additional hormone replacement therapy, osteoporosis, alendronate (70 mg/wk) for 6 yr prior to implant placement Controls: 65/76 yr, 1 was a smoker, both taking hormone replacement therapy
			Incidence of MRONJ	0	
Lazarovici et al[24]	NS	NS	Incidence of MRONJ	23 (only patients with MRONJ in association with bisphosphonate therapy and dental implants included in the study)	Bisphosphonate-MRONJ: 10–115 mo Bisphosphonate-implant: 0–108 mo Implant-MRONJ: 0–53 mo Triggering factor: implant surgery (6 patients), implant presence/spontaneous (17 patients) N.b. study included cases with bisphosphonate intake prior to and after implant placement; the 4 cases in which implants were placed before initiating bisphosphonate treatment were excluded
Martin et al[25]	Yes (all patients)	NS	Implant loss	Early losses: 8 implants in 8 patients Late losses: 8 implants in 6 patients (2 patients had both early and late losses)	N.b. study included cases with bisphosphonate intake prior to and after implant placement; the 4 cases in which 10 implants were placed before initiating bisphosphonate treatment were excluded
			Incidence of MRONJ	0	
Shabestari et al[26]	Yes (all patients)	NS	Implant loss	0	N.b. study included cases with bisphosphonate intake prior to and after implant placement; the 14 cases in which implants were placed before initiating bisphosphonate treatment were excluded
Famili et al[27]	NS	NS	Implant loss	Cases: 1 implant did not osseointegrate (successfully replaced within 1 yr)/98.7% implant success rate; controls: 0 implants/100% implant success rate	—
			Incidence of MRONJ	0	
Zahid et al[28]	Yes (all patients)	0.17–6.5/2.17	Implant loss	Cases: 3 implants/94.1% implant success rate; controls: 16 implants/97.4% implant success rate	Case 1: 72 yr, female, posterior mandible, alendronate (70 mg/wk for unknown period), loss after 7 wk, successfully replaced Case 2: 75 yr, female, anterior mandible, ibandronate (150 mg/mo for unknown period), loss after 8 wk, successfully replaced Case 3: 75 yr, female, immediate, posterior maxilla, alendronate for 4 yr, no initial stability, loss after 4 wk, not replaced
			Incidence of MRONJ	0	

TABLE 1C

Continued

Study	Drug Therapy at Time of Implant Placement, Yes/No (No. Patients)	Implant Follow-Up Range/Mean (yr)	Outcome Parameters	Outcome	Additional Information
Leonida et al[29]	No (bisphosphonate therapy suspended 1 mo prior to implant placement and resumed 1 mo after implant placement)	2	Implant survival	100%	32 implants were placed in the interforaminal area; 22 implants were placed into areas distal to the foramen (19 of those into fresh extractive sockets)
Memon et al[30]	Yes (all patients)	4–6 mo (until stage-2 surgery)	Early implant loss/ implant success	Cases: 10 implants in 10 patients/93.5% implant success rate; controls: 6 implants/95.5% implant success rate	Drugs involved in implant losses: alendronate (6), risedronate (1), and ibandronate (3)
Yip et al[31]	Yes (all patients)	0.3–11.9/6	Implant loss	Cases: 11/20 had $\geq$1 implant failure; controls: 103/317 had $\geq$1 implant failure	Implant failure more likely in oral bisphosphonate users than controls (OR = 2.7; 95% CI, 1.49–4.86); no significant interaction between bisphosphonate use and implant location; stratified analyses suggested that association between oral bisphosphonate use and dental implant failure was stronger in maxilla (OR = 2.60; 95% CI, 1.36–4.96) than in mandible (OR = 1.38; 95% CI, 0.51–3.73)
Jacobsen et al[32]	Yes (all patients)	NS	Incidence of MRONJ	14 (only patients with MRONJ in association with bisphosphonate therapy and dental implants were included in the study)	MRONJ localization: maxilla (3), mandible (11); bisphosphonate-MRONJ: 38 mo for patients with malignant disease, 50 mo for patients with osteoporosis; implant-MRONJ: 17 mo for patients with malignant disease, 25.6 mo for patients with osteoporosis
Lopez-Cedrun[33]	Yes (all patients)	NS	Incidence of MRONJ	9 (only patients with MRONJ in association with bisphosphonate therapy and dental implants were included in the study)	MRONJ localization: posterior maxilla (1), posterior mandible (7), anterior mandible (1); bisphosphonate-MRONJ: 6–120 mo; implant-MRONJ: 1–96 mo

Table 1c

Continued

Study	Drug Therapy at Time of Implant Placement, Yes/No (No. Patients)	Implant Follow-Up Range/Mean (yr)	Outcome Parameters	Outcome	Additional Information
Holzinger et al[34]	Yes (7) bisphosphonate therapy concluded		Incidence of MRONJ	10 (only patients with MRONJ in association with bisphosphonate therapy and dental implants were included in the study)	Group 2—Bisphosphonate started and stopped prior to implant placement: 3 patients (19 implants); bisphosphonate intake: 65–122/93 mo; bisphosphonate-MRONJ: 6–108/57 mo; bisphosphonate-implant: 48–119/83 mo; implant-MRONJ: 0–66/33 mo Group 3—Bisphosphonate prior and continued after implant placement: 7 patients (20 implants); bisphosphonate intake: 39–243/88 mo; bisphosphonate-MRONJ: 18–223/77 mo; bisphosphonate-implant: 0–187/50 mo; implant-MRONJ: 6–73/32 mo N.b. study included cases with bisphosphonate intake prior to and after implant placement; the 3 cases (Group 1) in which 8 implants were placed before initiating bisphosphonate treatment were excluded
Kwon et al[35]	Yes (all patients)	NS	Incidence of MRONJ	16 (only patients with MRONJ in association with bisphosphonate therapy and dental implants were included in the study)	MRONJ localization: posterior mandible (9), posterior maxilla (6), anterior mandible (1); bisphosphonate intake: 12–120/60.5 mo; bisphosphonate-implant: 6–108 mo; implant-MRONJ: 3–82 mo; triggering factor: implant surgery (3), implant removal (4), and unknown (9) N.b. study included cases with bisphosphonate intake prior to and after implant placement; the 3 cases in which implants were placed before initiating bisphosphonate treatment were excluded
Tam et al[36]	Yes (all patients)	NS	Incidence of MRONJ	6 (only patients with MRONJ in association with bisphosphonate therapy and dental implants were included in the study)	MRONJ localization: posterior maxilla (2), posterior mandible (3), anterior mandible (1); bisphosphonate-implant: 2–72 months; implant-MRONJ: 0–12 mo
Mozzati et al[37]	Yes (all patients)	Minimum 2, up to 10	Implant loss	16 implants in 15 patients/98.7% implant success rate (all failed 1–3 mo after surgery and all successfully replaced)	Implant losses: 51–77 yr, smokers (9), diabetes (3), corticosteroids (3), alendronate (6), risedronate (5), ibandronate (4), bisphosphonate intake 2–82 mo prior to implant placement, maxillary anterior (3 implants)/posterior (9 implants), mandibular anterior (2 implants)/posterior (2 implants), immediate loading (1 implant), sinus lift (7 implants), and immediate placement (9 implants); significant risk factors: risedronate, diabetes, corticosteroids, and smoking
			Incidence of MRONJ	0	

TABLE 1C
Continued

Study	Drug Therapy at Time of Implant Placement, Yes/No (No. Patients)	Implant Follow-Up Range/Mean (yr)	Outcome Parameters	Outcome	Additional Information
Nisi et al[38]	NS	NS	Incidence of MRONJ	9 (only patients with MRONJ in association with bisphosphonate therapy and dental implants were included in the study)	78% of patients had undergone radiotherapy so it is unclear whether the head and neck region was affected and whether the implant patients were affected; risk factors for MRONJ staging: cumulative bisphosphonate dose, smoking, steroid intake, and the maxillary location; triggering factor: implant surgery N.b. study included 90 patients with MRONJ due to various reasons; only the 9 cases of MRONJ due to implant placement were included
Siebert et al[39]	Yes (all patients)	1	Implant survival Incidence of MRONJ	100% 0	All implants immediately placed, anterior mandible
Giovannacci et al[40]	NS	NS	Incidence of MRONJ	15 (0nly patients with MRONJ in association with bisphosphonate therapy and dental implants were included in the study)	Group 1—Implant surgery as trigger: 6 patients (17 implants); bisphosphonate intake: 36–131/83.7 mo; implant-MRONJ: 2–10 mo Group 2—Implant presence as trigger: 9 patients (35 implants); bisphosphonate intake: 15–60/27.8 mo; implant-MRONJ: 1–15 yr
Khoury and Hidajat[41]	Yes (all patients)	3–6	Implant loss Incidence of MRONJ	1 implant (immediately loaded; failed after 5 mo; successfully replaced) 0	Implants placed simultaneously (28 implants) or 3 mo after bone augmentation (43 implants); in second-stage surgery cases implants were loaded after 4–8 wk
Suvarna et al[42]	Yes (58 patients)	Minimum of 3	Implant loss Incidence of MRONJ	10 implants in 10 patients/92.9% implant success rate; 3 losses within 3 wk, 3 losses within 1 mo, 2 losses within 2 mo, 2 losses within 6 mo 0	Implant losses: 8 females (3 patients: smokers, bone grafting; 2 patients: bisphosphonate since 1 yr, nonsmokers, sinus lift; 3 patients: bisphosphonate since 3 yr, smokers, sinus lift), 2 male (bisphosphonate since 5 mo, nonsmokers, no bone grafting), 70% in posterior maxilla
Tallarico et al[43]	No (implants placed 6 mo after alendronate administration stopping)	3–6/4	Implant survival	1 implant loss/99% implant survival rate	Implant failed to osseointegrate (before loading), maxilla
Yajima et al[44]	Yes (all patients)	Cases: 3.2; controls: 5.2	Implant loss Incidence of MRONJ	Cases: 3 implants in 3 patients all within 1 yr/88% implant survival rate; controls: 0 implants/100% implant survival rate 0	Case 1: 68 yr, posterior mandible bisphosphonate-implant: 12 mo Case 2: 67 yr, posterior mandible bisphosphonate-implant: 48 mo Case 3: 75 yr, posterior mandible bisphosphonate-implant: 60 mo
French et al[45]	Yes (all cases)	2.68	Implant failure	Cases: 0 implants, controls: 32 implants	N.b. study evaluated several risk factors associated with marginal bone loss and prevalence of mucositis/peri-implantitis; only information pertaining to bisphosphonate therapy was used

Table 1c

Continued

Study	Drug Therapy at Time of Implant Placement, Yes/No (No. Patients)	Implant Follow-Up Range/Mean (yr)	Outcome Parameters	Outcome	Additional Information
Watts et al[46]	Yes (all cases)	NS	Incidence of MRONJ	1	Case: 2 implants, posterior maxilla, simultaneous tooth extractions (25, 26) and a sinus lift, developed MRONJ related to delayed osseointegration, continued to receive denosumab (8 doses), successfully treated for MRONJ and retained the implants N.b. study assessed information on invasive oral procedures and events—dental implants, tooth extraction, natural tooth loss, scaling/root planing, and jaw surgery in long-term/crossover patients treated denosumab and presented details of positively adjudicated MRONJ cases; only the patients who received dental implants were included

*NS indicates not specified; MRONJ, medication-related osteonecrosis of the jaw.

therefore, it is likely that implant surgery may trigger the development of MRONJ. Furthermore, infection has long been considered an important component of MRONJ development as bone in these cases may be more vulnerable to infection because of decreased remodeling. Studies have identified a complex multiorganism biofilm consisting of bacteria (especially *Actinomyces* species), fungi, and viruses in biopsied specimens of necrotic bone removed in patients with MRONJ.[8] Therefore, the presence of an implant itself may place a patient at risk of developing MRONJ. Results from this systematic review suggest there is a risk of MRONJ developing after implant placement in patients with a history of bisphosphonates, regardless of whether taken for osteoporosis or malignancy. With some estimations made in studies that failed to specify the exact number of implants placed in each patient and irrespective of study design, of a total of 830 patients exposed to bisphosphonates who underwent placement of $\geq$1 dental implant (2841 implants in total), 102 cases of MRONJ were diagnosed, and the approximated incidence was 12.3%. When cohort/case-control studies and case series were separated, the percentage of MRONJ cases differed substantially (0% and 17.6%, respectively). This is simply explained by the fact that all of the MRONJ cases were identified in 8 case series.[24,32–36,38,40] Estimates for developing MRONJ after tooth extraction among osteoporosis and cancer patients exposed to bisphosphonates ranges from 0.5 to 14.8%.[8] Therefore, it is not surprising how a similar risk estimate for MRONJ after implant placement was found. In terms of localization, almost 3 times as many patients exposed to bisphosphonates developed MRONJ in the mandible than in the maxilla. Although these results are consistent with those reported in the literature,[49] the reason for MRONJ preferentially affecting the mandible in bisphosphonate users remains unknown. Furthermore, both implant surgery-triggered and implant presence-triggered cases of MRONJ were identified, suggesting that not only can the surgical trauma from implant placement or removal predispose to MRONJ but so can the mere presence of an implant in the oral cavity. Implant presence-triggered MRONJ could, therefore, develop in people who have dental implants placed before bisphosphonate drug treatment is initiated. This supports the potential role of infection in the development of MRONJ and the importance of long-term follow-up in patients with dental implants who later start taking bisphosphonates.

On the other hand, patients treated with denosumab for osteoporosis appear to be at a much lower risk of developing MRONJ after implant placement. In the case series by Watts et al,[46] there was only 1 case of MRONJ identified out of 212 patients receiving dental implants, suggesting a risk estimate of 0.5% patients treated with denosumab. Furthermore, the patient was fortunate enough to maintain the 2 implants while continuing denosumab treatment and being successfully treated for MRONJ. Because this study only included patients treated for osteoporosis, the risk of MRONJ in cancer patients treated with denosumab receiving dental implants could not be determined. To date, there has only been 1 other case report of MRONJ developing around a dental implant in a patient treated with denosumab for osteoporosis.[50] However, in this case, the patient had a 15-year history of bisphosphonates (alendronate) before swapping to denosumab treatment. Bisphosphonates can persist in skeletal tissue for significant periods of time, with alendronate having a half-life in bone of around 10 years. Therefore, MRONJ in this case may have been from a combination of bisphosphonate and denosumab treatment.

To assess the quality of the included cohort and case-control studies in the present systematic review, a modified NOS was used.[3,16] For the included case series, the JBI critical appraisal checklist for case series was used.[17] In general, most

TABLE 2

Summary of studies reporting figures on one or more of the evaluated outcome parameters (implant loss/failure/success/survival and incidence of MRONJ)*

Studies on Bisphosphonate Outcome	Administration Route (Not Specified/ Oral/ Intravenous/Both)	Number of Studies	Number of Cases (Implants)	Number of Controls (Implants)	Event	Interpretation
Implant failure (all studies)	3/15/1/1	20	930 (3074)	3331 (8605)	Cases: 85 implants failed in 77 patients Controls: 182 implants failed in 137 patients	Cases: ≈2.8% of implants failed in 8.3% of patients Controls: ≈2.1% of implants failed in 4.1% of patients
Implant failure (cohort and case–control studies)	2/8/1/0	11	405(1152)	3331 (8605)	Cases: 36 implants failed in 33 patients Controls: 182 implants failed in 137 patients	Cases: ≈3.1% of implants failed in 8.1% of patients Controls: ≈2.1% of implants failed in 4.1% of patients
Implant failure (case series)	1/7/0/1	9	525 (1922)	0 (0)	49 implants failed in 44 patients	≈2.5% of implants failed in 8.4% of patients
MRONJ (all studies)	2/11/2/7	22	830 (2841)	888 (2855)	102 cases of MRONJ	≈12.3% incidence of MRONJ
MRONJ (cohort and case–control studies)	1/6/1/0	8	251 (845)	888 (2855)	0 cases of MRONJ	0% incidence of MRONJ
MRONJ (case series)	1/5/1/7		579 (1996)	0 (0)	102 cases of MRONJ	≈17.6% incidence of MRONJ

Studies on Denosumab Outcome	Number of Studies	Number of Cases (Implants)	Number of Controls (Implants)	Event Cases/Controls	Interpretation
Implant failure	0	-	-	-	-
MRONJ (case series)	1	212 (not reported)	0 (0)	1 case of MRONJ	0.5% incidence of MRONJ

*Estimations for implant failure studies: Grant et al[21]: 376 implants placed in cases (pro rata), 3 controls lost the 14 implants (pro rata); Kasai et al[22]: 2 controls lost the 7 implants (pro rata); Shabestari et al[26] 7 implants placed in cases (minimum number); Zahid et al[28]: 2 cases lost the 3 implants (pro rata), 7 controls lost the 16 implants (pro rata); Memon et al[30]: 5 controls lost the 6 implants (pro rata); Yip et al[31]: each person received 3.5 implants (cases: 20, controls: 1111) (pro rata), 11 implant failures in cases (minimum number), 103 implant failures in controls (minimum number); French et al[45]: 14 controls experienced the 32 implant failures (pro rata). Estimations for MRONJ studies: Grant et al[21]: 376 implants placed in cases (pro rata); Lazarovici et al[24]: 23 implants placed in cases (min number); Kwon et al[35]: 16 implants placed in cases (minimum number); Nisi et al[38]: 9 implants placed in cases (minimum number). CI, confidence interval; OR, odds ratio.

of the included cohort studies were of moderate quality (the study of Grant et al[21] was of low quality), most of the included case-control studies were of moderate quality (the study of Yip et al[31] was of high quality), and most of the included case series were of high quality (studies of Giovannacci et al[40] and Khoury and Hidajat[41] were of moderate quality). Of note, there were no cohort studies that reported long enough follow-ups to receive a star according to the modified NOS. Otherwise, all quality

TABLE 3

NOS methodologic and reporting quality assessment of cohort studies

	Grant et al[21]	Famili et al[27]	Zahid et al[28]	Yajima et al[44]	French et al[45]	Overall %
Selection (3)						
Representativeness of the exposed cohort (1)		*	*	*	*	80
Selection of the nonexposed cohort (1)	*	*	*	*	*	100
Ascertainment of exposure (1)		*	*	*	*	80
Comparability (2)						
Comparability based on design of analysis (2)			*	*	*	60
Outcome (3)						
Assessment of outcome (1)		*	*		*	60
Follow-up long enough for outcomes to occur (1)						0
Adequacy of follow-up cohorts (1)	x†	x	x	x	x	
Overall %	14	57	71	50	71	

*A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

†x, data are based on retrospective or cross-sectional assessment, which does not allow to judge "adequacy of follow-up of cohorts."

TABLE 4

NOS methodologic and reporting quality assessment of case-control studies

	Jeffcoat[18]	Kasai et al[22]	Koka et al[23]	Memon et al[30]	Yip et al[31]	Siebert et al[39]	Overall %
Selection (4)							
Adequate case definition (1)	*				*	*	50
Representativeness of the cases (1)		*	*	*	*		67
Selection of controls (1)		*	*	*	*		67
Definition of controls (1)	*	*	*	*	*	*	100
Comparability (2)							
Comparability based on design of analysis (2)	*	*	*	**	*	*	58
Exposure (3)							
Ascertainment of exposure—cases (1)	*		*		*	*	67
Ascertainment of nonexposure—controls (1)	*	*	*	*	*	*	100
Nonresponse rate (1)	*	x†		x	x	*	67
Overall %	67	63	67	75	88	67	

*A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

†x, data are based on medical records, which do not allow to judge "nonresponse rate."

reporting items were met by more than half of the studies per item, suggesting an overall moderate quality of evidence across the studies.

Although no studies reporting antiangiogenics that met the inclusion criteria were identified, a recent case report found that MRONJ can develop around dental implants in these patients.[51] In this case, the patient was being treated for renal cell carcinoma with pazopanib. After 6 months of treatment, the patient changed medications to everolimus. Seven weeks later, bone exposure was observed in both mandibular posterior regions surrounding the 35, 37, 46, and 47 implants, which were placed 6 years prior. This case highlights the potential for implant-presence triggered MRONJ in these patients, which may contraindicate their placement in the first instance.

Limitations

There were several limitations in the present systematic review that should be discussed. First is the small number of studies and limited information available in the literature regarding bisphosphonates and denosumab and the lack of studies reporting on SERMs, calcitonin, and antiangiogenics. In fact, no single study available reported all the relevant data described previously, and therefore, inclusion criteria (5) was eased to allow for studies that reported enough relevant data worthy of discussion, as opposed to all relevant data. Including studies with missing data negatively affected the validity of our results as missing data meant that (1) some estimations were required for the summary calculations (Table 2) and (2) controlling for covariables such as systemic disease, age, sex, and smoking was not possible. A second limitation of this systematic review is that there were no randomized controlled trials (RCTs) available to be included. Unfortunately, only observational studies, which are considered a lower level of evidence than RCTs, were available. The absence of any RCTs means that the conclusions are based on rather limited evidence, and because most of the available studies were case series without control groups to compare the outcomes, the results lack statistical validity. Furthermore, there was only a single case series identified for denosumab, so generalizations about its lack of impact on MRONJ risk after implant placement cannot truly be drawn. In terms of study quality, most of the cohort and case-control studies were of moderate quality and despite most of the case series being of high quality, these are considered as having one of the lowest levels of evidence of all the clinical study designs. An overall moderate quality found across the studies indicates a decreased internal validity and increased risk of bias, so the conclusions herein should be interpreted with caution. The last limitation of this systematic review is that the criteria for implant success or failure varied slightly between the studies. For example, Jeffcoat[18] defined implant success as "<2mm of alveolar bone loss over the three-year study period, lack of mobility, lack of infection and absence of pain, and osteonecrosis of the jaws," whereas in Zahid et al,[28] the criteria for implant success was "clinical and radiographic evidence of osseointegration and bone loss <0.2 mm annually after the first year of service." Ideally, all the studies would have followed the same criteria, allowing for greater uniformity in interpretation and discussion.

CONCLUSION

The results of the present systematic review suggest the following:

- There is a lack of data available in the literature regarding the risk of implant failure or MRONJ in patients with a history of SERMs, calcitonin, or antiangiogenics.
- Patients with a history of bisphosphonate treatment for osteoporosis are not at increased risk of implant failure compared with that of healthy patients.
- There is a lack of data available in the literature regarding the risk of implant failure in patients with a history of bisphosphonate treatment for cancer or patients with a history of denosumab.
- Patients with a history of bisphosphonate treatment are at risk of developing MRONJ after implant placement.
- Patients treated with denosumab for osteoporosis have a negligible risk of developing MRONJ after implant placement.

TABLE 5

JBI appraisal checklist tool methodologic and reporting quality assessment of case series

	Fugazzotto et al[19]	Bell and Bell[20]	Lazarovici et al[24]	Martin et al[25]	Shabestari et al[26]	Leonida et al[29]	Jacobsen et al[32]	Lopez-Cedrun[33]	Holzinger et al[34]	Kwon et al[35]
Were there clear criteria for inclusion in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the case series have consecutive inclusion of participants?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Did the case series have complete inclusion of participants?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Was statistical analysis appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall %	100	90	90	100	90	90	100	100	90	100

TABLE 5

Extended

	Tam et al[36]	Mozzati et al[37]	Nisi et al[38]	Giovannacci et al[40]	Khoury and Hidajat[41]	Suvarna et al[42]	Tallarico et al[43]	Watts et al[46]	Overall %
Were there clear criteria for inclusion in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Was the condition measured in a standard, reliable way for all participants included in the case series?	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	89
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	94
Did the case series have consecutive inclusion of participants?	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	83
Did the case series have complete inclusion of participants?	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	83
Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	83
Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Were the outcomes or follow up results of cases clearly reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes	Unclear	Yes	No	Unclear	No	Yes	Yes	67
Was statistical analysis appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Overall %	90	90	90	50	70	90	100	100	

- There is a lack of data available in the literature regarding the risk of developing MRONJ after implant placement in cancer patients treated with denosumab.

In conclusion, the current literature still leaves gray areas in terms of the safety of placing dental implants in patients with a history of antiresorptive or antiangiogenic drug therapy. Until new studies of a higher quality become available, general and specialist dentists should carefully select patients with due consideration for medications. Importantly, all patients with a history of bisphosphonates are at risk of MRONJ, necessitating this to be included in the informed consent obtained before

implant placement. Further researchers in this area should consider conducting RCTs involving patients with a history of bisphosphonate and denosumab drug therapy, as well as similar observational studies looking at patients with a history of other antiresorptives and antiangiogenics. A further systematic review on this topic is required once additional studies become available.

Abbreviations

JBI: Joanna Briggs Institute
MRONJ: medication-related osteonecrosis of the jaw
NOS: Newcastle-Ottawa scale
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT: randomized controlled trial
SERM: selective estrogen receptor modulators
VEGF: vascular endothelial growth factor

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