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REVIEW ARTICLE

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# Effect of agents affecting bone homeostasis on short- and long-term implant failure

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## Abstract

**Objectives:** To review the current evidence on the relationship between agents that affect bone homeostasis and dental implant failures.

**Materials and Methods:** Electronic searches for bisphosphonates, denosumab, methotrexate, corticosteroids, romosozumab, sunitinib, and bevacizumab were performed using PubMed, MEDLINE (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials (Cochrane Library), Cochrane Oral Health Group Trials Register (Cochrane Library) and Web of Science (Thomson Reuters). Manual searches were also conducted to complement the digital searches for recent issues.

**Results:** Previous publications suggested that bisphosphonates do not compromise the survival of dental implants. However, one study documented an increased risk of implant failure in patients who had received high-dose of intravenous bisphosphonate therapy after implant rehabilitation. There has been an issue of MRONJ around implants in patients who have successfully received implant therapy before and after antiresorptive therapy, leading to late implant failure. Despite evidence on the detrimental effects of denosumab, methotrexate and corticosteroids on bone metabolism, their role in implant survival is not conclusive.

**Conclusions:** At present, there is insufficient evidence to establish a potential connection between agents that affects bone homeostasis and implant failure. However, some studies have reported negative results for implant therapy. In addition, implant-related sequestration in patients who received anti-resorptive therapy, despite of successful osseointegration, is also noticeable. Although limited studies are available at present, clinicians should still carefully consider the potential hazards and take appropriate precautions to minimize the risks associated with the medications and implant therapy.

KEYWORDS
bisphosphonate, corticosteroids, denosumab, dental implant, endosseous implant, implant failure, methotrexate, MRONJ

The present review was prepared as part of the 7th International Team of Implantology (ITI) Consensus Meeting.

## 1 | INTRODUCTION

With the increase in the aging population across several countries, the demand for implant-supported rehabilitation is on the rise. Moreover, aging populations suffering bone metabolic diseases are becoming increasingly common, and the use of medications altering bone metabolism is accordingly on the increase for the management of various bone diseases, including osteoporosis, rheumatic disease, and bone malignancies. Therefore, the longevity and survival of dental implants in patients taking such medications must be of interest to dental clinicians. Although dental implantation is certainly a highly successful prosthetic option for replacing missing teeth, any medication that modifies bone metabolism may jeopardize the homeostasis of the bone tissue (Abtahi et al., 2013; Baron et al., 2011; He et al., 2020; Kanagawa et al., 2016; Kondo & Yoda, 2011; Teitelbaum, 2015).

Remodeling of the bone tissue around the implant fixture continues to occur during and after osseointegration of dental implants (Guglielmotti et al., 2019). After insertion of the implant fixture, the dynamic action of osteoclasts and osteoblasts allows a direct structural and functional connection between the bone and implant surface, and the peri-implant bone is subsequently adapted and remodeled as a response to mechanical load (Isidor, 2006). Therefore, it is important to understand how medications that regulate osteoclast or osteoblast activity affect the prognosis of dental implants.

Bisphosphonates (BPs) and denosumab are currently the most widely prescribed anti-resorptive medications for metabolic bone diseases, bone malignancies, and bone metastases to reduce skeletal-related events (Body, 2012; Drake et al., 2008; Gul et al., 2016; Hernlund et al., 2013). Methotrexate (MTX) and corticosteroids (CS) are also known to alter bone metabolism and reported to contribute to the development of medication-related osteonecrosis of the jaw (MRONJ) (Henien et al., 2017; Milosavljevic et al., 2022; Weinstein, 2012). This review aimed to explore the relationship between dental implant failure and the intake of medications that affect bone metabolism. Furthermore, previous reports on MRONJ developed around dental implant and late implant failure, referred to as implant presence-related osteonecrosis or peri-implantitis like MRONJ, is reviewed and discussed.

## 2 | SEARCH STRATEGY

The focus questions were as follows: In patients who had taken medications known to alter bone metabolism (BPs, denosumab, MTX, and CS) before or after implant installation, if implant failure occurred more frequently than in those who had not taken the medications, and if biological complications (peri-implant marginal bone level, soft tissue reaction) and comorbidities (type of medication, therapy length, and other medications) (secondary outcomes) were associated with implant failure in such patients.

Electronic databases including PubMed, MEDLINE (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials (Cochrane Library), Cochrane Oral Health Group Trials Register (Cochrane Library) and Web of Science (Thomson Reuters) were electronically searched for articles published up to July 31, 2022. The searches were limited to the English language. The search strategy in the electronic databases were as follows: (bisphosphonate* OR "diphosphonates" [Mesh term] OR "denosumab" [Mesh term] OR Xgeva OR AMG 162 OR Prolia OR "Methotrexate" [Mesh term] OR Amethopterin OR Methotrexate OR Mexate OR Methotrexate Sodium OR "Arthritis, Rheumatoid" [Mesh term] OR Rheumatoid Arthritis OR "Bone Density Conservation Agents" [Mesh term] OR Anti-resorptive Agent* OR Bone Resorption Inhibitor* OR Antiresorptive Drug* OR "Steroids" [Mesh term] OR Steroid* OR Corticosteroid*) AND ("Dental Implants" [Mesh term] OR Dental Implant* OR dental implant failure* OR dental implant survival* OR (Dental AND Implant*)).

Manual searches were also conducted to complement the digital searches on recent issues in the following scientific journals: Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, European Journal of Implantology, Implant Dentistry, International Journal of Oral Maxillofacial Implants, International Journal of Oral Maxillofacial Surgery, International Journal of Periodontics and Restorative Dentistry, International Journal of Prosthodontics, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Oral Implantology, Journal of Oral and Maxillofacial Surgery, Journal of Oral Rehabilitation, and Journal of Periodontology.

In addition, grey literature was perused for potential candidates to be included in the New York Academy of Medicine grey literature report (http://greylit.org) and the registry of clinical studies hosted by the US National Institutes of Health (www.clinicaltrials.gov). The reference lists of relevant full-text articles were cross-checked and screened for assessment.

## 3 | LITERATURE SELECTION AND DATA EXTRACTION

Clinical studies, including prospective or retrospective cohort, case–control, cross-sectional, or randomized controlled trials investigating the influence of relevant medications on implant survival or failure, were considered for inclusion by two independent examiners (JJ and GJS). The selected data were subsequently extracted and presented in Table 1. Publications that did not meet the inclusion criteria but contained significant clinical and pre-clinical data at all levels of evidence were presented in Tables 2–5. Studies on the local application of the medications were excluded. The overall findings for each medication are summarized and discussed in a narrative manner.

## 4 | ANTI-RESORPTIVE DRUGS AND THEIR POTENTIAL EFFECT ON HEALING AROUND DENTAL IMPLANTS

### 4.1 | Bisphosphonates

Bisphosphonates, especially nitrogen-containing BPs, are effective anti-resorptive medications for the management of metabolic bone diseases and cancer-related conditions (Drake et al., 2008; Hernlund

et al., 2013). Owing to their high affinity for hydroxyapatite, BPs deposit and accumulate in bone tissues and serve their purpose to interfere with osteoclast functions and differentiation by suppressing the mevalonate pathway (Amin et al., 1992; Singh et al., 2015). Since osteonecrosis of the jaw was first described as an adverse effect of BPs in 2003, MRONJ has become a well-recognized complication of BP therapy (Alhussain et al., 2015; Campisi et al., 2020; Patil et al., 2020; Ruggiero et al., 2022).

The inhibitory effects of BPs on the mevalonate pathway, leading to cell apoptosis, extend beyond osteoclasts. Several in vitro studies have demonstrated that osteoblasts, vascular cells, and fibroblasts are also susceptible to apoptosis induced by BPs (Jung et al., 2018; Misso et al., 2012; Walter et al., 2011). This nonspecific action of BPs not only inhibits bone turnover but also suppresses angiogenesis and cause soft tissue toxicity (Ruggiero et al., 2022). Consequently, in the presence of inflammation and infection accompanied by tissue injury, such as those resulting from dentoalveolar surgery and tooth extraction, surgical wound healing is impaired, and it provides a conducive setting for the development of MRONJ along with suppressed bone remodeling. Accordingly, this raised the question of whether there is an association between BPs and dental implant failure. The invasive surgical procedure involved in dental implant insertion, coupled with the multiple detrimental effects of BPs, may act as a trigger for the onset of MRONJ and impede osseointegration, thereby increasing the risk of early implant failure (Ruggiero et al., 2022). In addition, the acidic environment resulting from bone and soft tissue injury, along with local inflammation, may lead to an increased release of BPs (Otto, Hafner, et al., 2010; Otto, Pautke, et al., 2010), further contributing to the pathophysiological progression of MRONJ or implant failure.

Another notable characteristic of BPs is their long elimination terminal half-life, exceeding 10 years due to their skeletal retention (Khan et al., 1997). Consequently, the long-term administration of BPs becomes a risk factor for developing MRONJ, especially when a high dose is administered (Ruggiero et al., 2022). In a systematic review, the risk of MRONJ in cancer patients exposed to zoledronate was reported to be 1.6%–4% after 2 years and 3.8%–18% after more than 2 years (Ng et al., 2021). However, in patients receiving low-dose BPs for osteoporosis management, the prevalence of MRONJ was found to be 0.05% at 2–4 years and 0.21% after 4 or more years (Lo et al., 2010). Although the risk of MRONJ associated with low-dose anti-resorptive drugs is still a topic of debate, it remains relatively low, and the risk of implant failure and related complications in patients receiving low-dose BPs might also be low, accordingly.

Meanwhile, the development of osteonecrosis related to previously osseointegrated implants has also been reported (Goss et al., 2010; Jacobsen et al., 2013; Pichardo et al., 2020). Local inflammation, such as peri-implantitis, and mechanical stress caused by occlusal force being transferred directly to the bony structure, have been suggested as potential factors associated with MRONJ and late implant failure (Allen & Burr, 2011; Hoefert et al., 2010; Pichardo et al., 2020). Moreover, since the accumulation of BPs occurs in the bone, driven by both chemical and biological factors, patients with prolonged treatment with BPs would be at an increased risk of MRONJ and dental implant failure (Allen, 2008; Granate-Marques et al., 2019).

## 4.2 | Denosumab

Denosumab, a human monoclonal IgG2 antibody, is also used to manage osteoporosis, metabolic bone diseases, and bone metastasis (Body, 2012; Gul et al., 2016; Polyzos et al., 2019; Reid & Billington, 2022). A market analysis for osteoporosis treatment in 2018 estimated that denosumab accounted for approximately 15.5% of the osteoporosis market, and it is expected that there will be an increase in its use as an effective anti-resorptive drug as well as for oncological patients (McClung et al., 2006). In addition to the specific inhibition of osteoclast formation and function, its convenience in medication adherence, which requires a subcutaneous injection every 6 months, is another advantage over oral osteoporotic drugs.

In contrast to BPs, the action of denosumab is highly specific to osteoclasts (Baron et al., 2011). Its target is to block the receptor activator of the nuclear factor kappa-B ligand (RANKL), and it subsequently prevents the binding of RANKL to its receptor, the receptor activator of nuclear factor kappa-B (RANK). Eventually, the development of multinucleated osteoclasts through the fusion of monocytes and macrophages is inhibited, thereby achieving the goal of denosumab treatment, which is to decrease bone resorption (Baron et al., 2011).

Although its potential to suppress bone turnover is not inferior to that of BPs (Miller et al., 2016; Reid & Billington, 2022), the specific inhibition of RANKL by denosumab raised the hope of decreasing the well-known adverse effects of BPs, MRONJ. Whereas BPs are known to induce apoptosis in various cell types (Jung et al., 2018; Misso et al., 2012; Walter et al., 2011) and have a long retention half-life in bone tissue, denosumab only targets the inhibition of osteoclasts and has a relatively short half-life (15–30 days), which is distinct from that of BPs (Chen et al., 2018; Laskowski et al., 2016). However, denosumab is used as a substitute for BPs, MRONJ in patients treated with denosumab has also begun to emerge (Aghaloo et al., 2010; Taylor et al., 2010), and it serves as a momentum to change the term BRONJ to MRONJ. Several clinical trials have reported MRONJ occurrence as an adverse effect. The incidence of MRONJ in cancer patients receiving high-dose denosumab ranged from 0.76% to 6.88%. When compared with zoledronate, the use of denosumab was associated with a statistically significant increase in the risk of MRONJ (Boquete-Castro et al., 2016). A systematic review also reported that the prevalence of MRONJ in cancer patients varies from 0.5% to 3.2% depending on the exposure time, which is significantly higher in patients receiving denosumab than in those receiving BPs (Limones et al., 2020). However, osteoporosis patients receive a relatively low dose of denosumab (60 mg/6 months), and accordingly, the incidence ranges from 0 to 30.2 per 100,000 patient-years, although data on this subject are currently very limited (Khan et al., 2015).

**TABLE 1** Implant failures in patients on ARD.

| Authors (year) | Study design and mean follow-up (months) | Systemic condition | Other controlled factors | Confounding factors reported (subjects; *n*) a: success b: failed | MRONJ incidence (*n*) | Medication (subjects; *n*) | Dosage (mg/mL) | Therapy length (months) (*n*) | Administration route |
|---|---|---|---|---|---|---|---|---|---|
| Prior to implant placement | | | | | | | | | |
| Pandey et al. (2019) | RC<br>84 | Osteoporosis | Age, gender, steroids intake, type II DM, periodontal disease, other bone resorptive disorder | NR | NR | BPs<br>Parathyroid hormone derivative | 10 mg once daily<br>Teriparatide 20 mcg once daily | 12–36 months<br>N | Oral<br>Subcutaneous |
| French et al. (2019) | RC<br>32.2 ± 26.8 | NR | N | Autoimmune disease, smoking | NR | BPs<br>NSM | NR | NR | NR |
| Yajima et al. (2017) | RC<br>39.12 ± 15.6 | Osteoporosis | Age, gender, steroids intake, smoking, type II DM, severe periodontal diseases, other metabolic bone disease | NR | N | BPs<br>Selective estrogen receptor modulator (8)/ parathyroid hormone (6) | NR | 12–36 months (5), >36 months (6)<br>NR | NR |
| Al-Sabbagh et al. (2015) | RC<br>NR | NR | N | Smoking (a: 39, b: 7), DM (a: 37, b: 6), osteoporosis (a: 51, b: 8) | N | BPs<br>NSM | NR | NR | NR |
| Siebert et al. (2015) | PC<br>12 | Osteoporosis<br>ASA I-II | Age, gender, smoking, chemotherapy, radiation, steroids intake | NR | N | Zoledronate<br>NSM | 5 mg/year<br>N | 12–36 months | IV<br>N |
| Memon et al. (2012) | RC<br>NR | Osteoporosis | Age, gender, IV BPs | Smoking (3), type II DM (3), bone graft (44) | NR | Alendronate (72), risedronate (23), ibandronate (5) | NR | ≤12 months (20), 13–35 months (19), ≥36 months (15), unspecified (46) | Oral |
| | | ASA I-II | | Smoking (5), type II DM (4), bone graft (44) | | NSM | N | N | N |

| Subjects (*n*) | Age (years) | Gender (M/F) | Implants (*n*) | Failure (months) | Marginal bone loss (mm) | Implant survived (rate: %) | Implant failure (rate: %) | Biological complications | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 30 | 62.4 | NR | 26 | NR | NR | 25 (96.16%) | 1 (3.84%) | NR | Retrospective radiographic study. Non-BP group had also osteoporosis with teriparatide hormone therapy. Statistical analysis methods were not clarified. Poor demographic data. |
| | 63.1 | | 32 | | | 31 (96.88%) | 1 (3.12%) | | |
| 2060 | 50.58 ± 12.96 | 992/1138 | 84 | N | NS | 84 (100%) | 0 (0%) | NR | All implant surgery was performed by one clinician as well as radiographic assessment. Poor demographic data. The regime and duration for BPs treatment were not specified. The length of marginal bone loss was not specified; however, marginal bone loss was greater in BPs. |
| | | | 4507 | NR | | 4475 (99.3%) | 32 (0.7%) | 22 failed before loading, 4 failed related to peri-implantitis, 6 failed due to biomechanical reason | |
| 11 | 69.6 ± 5.2 | NR | 25 | <12 | NR | 22 (88.9%) | 3 (11.1%) | NR | Retrospective radiographic study on university setting. Poor demographic data. Patients taking BP with early implant failure had significantly higher cortical BMD. All three implants failed within 1 year. The type of BPs was not reported. |
| 14 | 67.3 ± 4.2 | | 28 | NR | | 28 (100%) | 0 (0%) | | |
| 415 | 59.4 ± 13.3 | 174/237 | 39 | NR | NR | 35 (89.7%) | 4 (10.3%) | NR | Increasing age and no use of BP were associated with implant failure. Multiple surgeons involved in implant installment. MRONJ was not reported as consequence of implant therapy. The regime and duration for BPs treatment were not specified. |
| | | | 376 | | | 318 (84.6%) | 58 (15.4%) | | |
| 24 | ≥54 | F | 60 | N | NR | 60 (100%) | 0 (0%) | NR | Prospective cohort study with university setting- Subjects in BP group received IV zoledronate for 2–3 years. Single implant system (3.7-mm wide and 16-mm long) was used and all implants were immediately inserted after extraction in the anterior mandibles. 1 year of follow up. |
| | ≥54 | | 60 | | | 60 (100%) | 0 (0%) | | |
| 100 | 66 ± 9 | F | 153 | Before loading | 0.81 ± 1.02 mm | 143 (93.5%) | 10 (6.5%) | NR | Retrospective database on university and local clinic setting. Patients were excluded from the test group if a history of intravenous bisphosphonate use. No data of long-term dental implant failure, overall follow up was not specified. |
| 100 | 63 ± 9 | | 132 | Before loading | 0.78 ± 0.71 mm | 126 (95.5%) | 6 (4.5%) | | |

(Continues)

**TABLE 1** (Continued)

| Authors (year) | Study design and mean follow-up (months) | Systemic condition | Other controlled factors | Confounding factors reported (subjects; *n*) a: success b: failed | MRONJ incidence (*n*) | Medication (subjects; *n*) | Dosage (mg/mL) | Therapy length (months) (*n*) | Administration route |
|---|---|---|---|---|---|---|---|---|---|
| Zahid et al. (2011) | RC<br>26 (2–78)<br>NR | Osteoporosis | Adequate oral hygiene, absence of local inflammation or diseases, pocket depths ≤3 mm | Smoking (56), osteoporosis (51), bone graft (173) | N | BPs | 35 mg/week (5), 70 mg/week (12), unspecified (7), Boniva (2) | ≤12 months (1), 13–35 months (7), ≥36 months (8), unspecified (10) | NR |
| | | ASA I-II | | | | NSM | N | N | N |
| Bell et al. (2011) | RC<br>NR | NR | N | Smoking, DM, periapical lesion | NR | BPs | NR | NR | NR |
| | | | | | | NSM | N | | |
| Famili et al. (2011) | RC<br>12<br>NR | Osteoporosis, osteoarthritis | Age, gender, IV BPs | Smoking, DM | N | BPs | NR | <12 months (6), ≥12 months (9), ≥60 months (5), unspecified (2) | Oral |
| | | | | | | NSM | N | N | N |
| Koka et al. (2010) | RC<br>NR | Osteoporosis/osteopenia | Age, gender | Smoking (a: 2, b: 0), DM (a: 10, b: 0), osteoporotic (a: 49, b: 0), steroids (a: 5, b: 0), HRT (a: 30, b: 1) | NR | BPs | NR | <36 months (16), 36–59 months (20), ≥60 months (19) | NR |
| | | NR | | Smoking (a: 7, b: 1), DM (a: 8, b: 0), steroids (a: 5, b: 0), HRT (a: 46, b: 2) | | N | N | N | N |
| Kasai et al. (2009) | RC<br>84.3 (64–146) | Osteoporosis | Age, gender, date and number of implants | NR | N | Alendronate | NR | >36 months | Oral |
| | | NR | | | | N | N | N | N |
| Grant et al. (2008) | RC<br>NR | NR | Age, gender and number of implants | Steroids (3), DM (2), bone graft (6) | N | N | N | N | N |
| | | | | Bone graft (26) | | | | | |
| Jeffcoat (2006) | PC<br>36 | Osteoporosis | Age, gender, two-stage installment | Smoking (1) | N | BPs (alendronate & risedronate) | NR | 3 ± 0.1 years | Oral |
| | | | | Smoking (1) | | N | N | N | N |

| Subjects (*n*) | Age (years) | Gender (M/F) | Implants (*n*) | Failure (months) | Marginal bone loss (mm) | Implant survived (rate: %) | Implant failure (rate: %) | Biological complications | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 26 | 56 (17–87) | 1/25 | 51 | <2 | NR | 48 (94.1%) | 3 (5.9%) | NR | Retrospective database on university setting. A statistically significant association was found between implant thread exposure and use of BP ($p = .001$; odds ratio = 3.25). Cases without follow up radiographs were excluded. |
| 274 | | NR | 610 | NR | | 594 (97.4%) | 16 (2.6%) | | |
| 655 | NR | NR | 24 | N | NR | 24 (100%) | 0 (0%) | NR | Retrospective database on private clinic setting. All implants were immediately inserted after extraction. Poor demographic data. Type of BPs, therapy length, and systemic conditions were not specified. |
| | | | 898 | NR | | 883 (98.3%) | 15 (1.7%) | | |
| 22 | ≥50 | F | 75 | Early | NR | 74 (98.7%) | 1 (1.3%) | NR | Retrospective cohort study based on university setting. Lack of long-term outcome of dental implant. 7 implants were placed in osteoporotic patients, but data on patient-level were not reported. The number of each type of BPs was not specified. Poor demographic data. |
| 5 | ≥50 | | 7 | N | | 7 (100%) | 0 (0%) | | |
| 55 | 71 (50–93) | F | 121 | NR | NR | 120 (99.2%) | 1 (0.8%) | NR | Retrospective review on medical chart and phone survey. As data collection relied on self-reporting, reliability and accuracy of data may be insufficient. |
| 82 | 66 (50–89) | | 166 | NR | | 163 (98.2%) | 3 (1.8%) | | |
| 11 | 52–73 | F | 35 | Early (2), 33 months (2), 11 months (1) | NR | 30 (85.7%) | 5 (14.3%) | NR | Retrospective database on university setting. Poor demographic data. Confounding factors are not specified. |
| 40 | >36 | | 161 | NR | | 154 (95.7%) | 7 (4.3%) | | |
| 40 | >36 | F | 161 | NR | NR | 154 (95.7%) | 7 (4.3%) | NR | Retrospective review on medical chart and online survey regarding BPs. Systemic conditions were not specified. Patients who received BPs prior to implant placement were only included. Poor demographic data. |
| 343 | | | 1450 | | | 1436 (99%) | 14 (1%) | | |
| 25 | NR | F | 102 | N | NR | 102 (100%) | 0 (0%) | NR | Prospective single-blind controlled study. Confounding factors are not specified. Two-stage installment and fixed screw-retained protheses were used. |
| 25 | | | 108 | NR | | 107 (99.2%) | 1 (0.8%) | | |

(Continues)

**TABLE 1** (Continued)

| Authors (year) | Study design and mean follow-up (months) | Systemic condition | Other controlled factors | Confounding factors reported (subjects; *n*) a: success b: failed | MRONJ incidence (*n*) | Medication (subjects; *n*) | Dosage (mg/mL) | Therapy length (months) (*n*) | Administration route |
|---|---|---|---|---|---|---|---|---|---|
| After implant placement | | | | | | | | | |
| Kim et al. (2020) | RC 85.26 ± 36.72 83.49 ± 41.51 | NS | Age, gender, extensive MRONJ, surgical resection in the jaw | Smoking (30), DM (95), alcohol (31), bone graft (80), HTN (124) | 11 | Denosumab (55), ibandronate risedronate alendronate and zoledronate | NR | ≤12 months (87), 13–35 months (130), ≥36 months (127) | IV (71), oral (218), Subcutaneous (55) |
| | | ASA I-II | | Smoking (21), DM (82), alcohol (27), bone graft (97), HTN (111) | N | NSM | N | N | N |

*Note*: Studies reporting on implant failure in patients exposed to ARD were only listed, and single-arm case studies were excluded.

Abbreviations: ARD, anti-resorptive drugs; ASA, American Society of Anesthesiologists; BP, bisphosphonate; DM, diabetes mellitus; F, female; HRT, hormone replacement therapy; M, male; MRONJ, medication-related osteonecrosis of the jaws; N, none; NR, not reported; NSM, no specific medications; PC, prospective cohort; RC, retrospective cohort.

Inhibited differentiation and activation of osteoclasts by denosumab, which in turn decreases bone turnover, suggests that dental implant installation may trigger the development of MRONJ. Trauma caused by drilling in bone tissue requires active bone remodeling, and peri-implant inflammation during the healing period or induced by the deposition of dental plaque may interfere with normal physiological bone metabolism at these sites. Additionally, decreased bone turnover may impair the repair of microcracks or cause microdamage to the alveolar bone around the implant fixture under load, leading to sequestration around the implant. Therefore, it may be hypothesized that denosumab contributes to the occurrence of MRONJ around the early or late stages of implant function and incidence of implant failure.

## 5 | IMPLANT THERAPY IN PATIENTS RECEIVING BISPHOSPHONATES

### 5.1 | Implant failure

Although several attempts have been made to reveal the possible association between BPs and dental implant failure, this review still noted the absence of well-designed prospective studies. Most of the studies included in this review were retrospectively designed cohort studies and only two were controlled prospective studies.

Thirteen studies on implant failure in patients exposed to BPs at the time of implant placement were found according to the inclusion criteria and listed in Table 1 (Al-Sabbagh et al., 2015; Bell et al., 2011; Famili et al., 2011; French et al., 2019; Grant et al., 2008; Jeffcoat, 2006; Kasai et al., 2009; Koka et al., 2010; Memon et al., 2012; Pandey et al., 2019; Yajima et al., 2017; Zahid et al., 2011). Altogether, 1263 dental implants were placed in individuals who had been exposed to BPs. Of them, 30 implants failed with an overall survival rate of 97.6%. Individuals not exposed to BPs received 8535 implants, of which 153 implants failed. Thus, the overall survival rate was 98.2%. Results from the literature suggest that individuals exposed to BPs may not be at a higher risk of dental implant failure than that of individuals not exposed to BPs. Nine out of 13 studies specified the timing of implant failure. Again, seven studies that had at least one implant failure reported that 20 out of 22 failed implants were early failures. These occurred less than 1 year after implant placement. In addition, none of the studies reported the incidence of MRONJ after implant placement, regardless of implant failure.

A previous consensus review study (Chappuis et al., 2018) was in accordance of this finding, which demonstrated that the effect of BPs could not be concluded (OR: 1.11). Another systematic review also reported that low-dose BP administration did not negatively affect the outcomes of dental implant therapy (Stavropoulos et al., 2018). According to a retrospective propensity-matched national cohort study, dental implant placement was not a risk factor, and patients with dental implants presented with a rather low hazard ratio, while dental extraction was confirmed as a risk factor (Ryu et al., 2021). Nonetheless, since BPs have a relatively longer retention half-life, confounding factors, including given dosages and therapy duration, must be considered as well as additional surgical procedures. Owing to the limitations of retrospective studies, these factors were reported heterogeneously among the studies, making it impossible to analyze them. These provided us with headroom for the interpretation of the presented data. It is noteworthy that the odds of oral BPs use was 2.5 times greater in patients with implant failure than those without implant failure in a case–control study, which was not listed due to the patient-level data (Yip et al., 2012).

### 5.2 | Late failures after loading

According to the literature reporting late failure, the timing of anti-resorptive drug (ARD) therapy in patients who have received implant therapy is not well reported (Table 2). The continuous effects

| Subjects (*n*) | Age (years) | Gender (M/F) | Implants (*n*) | Failure (months) | Marginal bone loss (mm) | Implant survived (rate: %) | Implant failure (rate: %) | Biological complications | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 344 | 67.7 ± 7.2 | 38/340 | 344 | NR | NR | Overall 310 (90.12%), denosumab 50 (90.91%), Oral 204 (93.58%), IV 56 (78.9%) | Overall 34 (9.88%), denosumab 5 (9.09%), Oral 14 (6.42%), IV 15 (21.1%) | NR | Retrospective cohort study with university setting. A reason for anti-resorptive treatment was not report. The length of marginal bone loss was not specified. IV administration of anti-resorptive had the highest implant failure rate. |
| 378 | 67.0 ± 7.3 | 30/314 | 378 | | | 363 (96.03%) | 15 (3.97%) | | |

of previous or current antiresorptive therapy after osseointegration of implants are unclear. Since most dentists are now aware of the possible risk of failure related to long-term ARD therapy and avoid dental surgeries as much as possible, number of late failures in patients receiving ARD therapy started before implant placement is rarely reported from the literature.

In the first report on osteonecrosis related to dental implants, the authors suggested two clinically possible subtypes based on the time elapsed from implant placement to the development of osteonecrosis (Lazarovici et al., 2010). Among the 27 patients, 77.8% had 'spontaneous' osteonecrosis and this might suggest that the successfully integrated implants might be a risk for MRONJ. However, there have been no prospective cohort studies or systematic reviews on late implant failure related to sequestration, and only a few retrospective single-arm cohort studies and case series are available (Table 2).

Regarding the nomenclature, there is no widely accepted terminology describing osteonecrosis around successfully integrated implants.

- BRONJ associated with dental implant (Lazarovici et al., 2010).
- Implant-related BRONJ (Kwon et al., 2014).
- Peri-implant MRONJ (Troeltzsch et al., 2016).
- Implant presence-triggered osteonecrosis (Escobedo et al., 2020; Giovannacci et al., 2016).
- Peri-implantitis like MRONJ (Tempesta et al., 2022).

Among the terms proposed in the above studies, "implant presence-triggered osteonecrosis" may be the most frequently used to refer to this type of failure of long-term functioning implants. This is because this term may be differentiated from implant failure due to the surgical trauma of implant surgery, referred to as "implant surgery-triggered osteonecrosis" (Escobedo et al., 2020). Nevertheless, the presence of an implant cannot establish a cause- and -effect relationship because of the lack of scientific evidence. Therefore, the term "implant presence-triggered osteonecrosis" is currently considered premature.

The common clinical feature is "en block" style failure wherein the implant is still osseointegrated in the dead bone (Kwon et al., 2014; López-Cedrún et al., 2013; Pogrel & Ruggiero, 2018). This phenomenon is distinct from traditional type of implant failure, which may result from osseointegration failure or progression of peri-implantitis. We propose the term implant-related sequestration (IRS) to refer to this type of late implant failure combined with sequestration.

Recently, Escobedo et al. (2020) claimed that a functional load of 6 months or more would be a critical point in determining whether necrosis is implant-triggered. In most studies reporting IRS, the onset time of MRONJ lesions ranged from 6 to 126 months, although some missing records were observed (Table 2). According to a review (Escobedo et al., 2020), the loading time before the onset of MRONJ was 44.4 months based on their literature review and 89.6 months in their cases.

### 5.2.1 | Peri-implantitis as a risk of late failure or implant- related sequestration

As mentioned above, peri-implantitis may play a role in the development of IRS (Pichardo et al., 2020; Tempesta et al., 2022; Troeltzsch et al., 2016). Troeltzsch et al. (2016) reported that 39% (46 out of 117) of implants involved in MRONJ lesions showed signs of peri-implantitis. In a small retrospective cohort study, the majority of cases (14 out of 18 cases) showed signs of peri-implantitis (Pichardo et al., 2020). Another study reported that 19 osteoporosis patients had MRONJ associated with peri-implantitis (Tempesta et al., 2022).

Although peri-implantitis is considered a possible risk factor of IRS, the pathological mechanism has not yet been fully elucidated. Large areas of bone resorption were observed at the implant-bone interface, which might suggest that peri-implantitis may contribute

to IRS (Tempesta et al., 2022). This peri-implantitis origin theory of IRS is a part of the "outside-in" process (Hansen et al., 2006) suggested for the development of MRONJ, which may start from the soft tissue breakdown due to peri-implant mucositis, and infection may spread down to the bone. The pivotal role of infections in the pathogenesis of MRONJ is generally accepted (Boff et al., 2014; Sedghizadeh et al., 2008; Wei et al., 2012; Zirk et al., 2019) and the microbial profile may be similar to that of pre-existing dental infection, such as periodontitis or any odontogenic infection (Kumar et al., 2010). Inflammatory reactions, whether it is derived from infection or not, are considered a potential risk factor for the development of MRONJ (Lesclous et al., 2009; Otto, Hafner, et al., 2010; Otto, Pautke, et al., 2010).

Local inflammation may result in acidic conditions, which may aggravate the cytotoxicity of N-BPs (Otto, Hafner, et al., 2010; Otto, Pautke, et al., 2010). It may also be assumed that increased acidity during

**TABLE 2** Studies reporting on medication-related osteonecrosis of the jaw involved in dental implant.

| Authors (year) | Study design | Implant surgery or implant presence | Subjects (sample size) | Timing of ARD therapy (IMP-ARD/ ARD-IMP) | Systemic condition (*n*) | Medication (*n*)/duration (months) |
|---|---|---|---|---|---|---|
| Tempesta et al. (2022) | Case series | Presence | 19 | 19/0 | Osteoporosis (19) | Alendronate (6)/NR<br>Denosumab (5)/NR<br>Risedronate (4)/NR<br>Clodronate (2)/NR<br>Ibandronate (2)/NR |
| Seki et al. (2021) | Case report | Presence | 1 | 1/0 | Hypercalcemia and Osteoporosis due to Hyperparathyroidism (Thyroid cancer) | Alendronate/NR |
| Escobedo et al. (2020) | Case series | Presence | 7 | NR | Multiple myeloma (3)<br>Osteoporosis (2)<br>Rheumatoid arthritis (1)<br>Spondylitis (1) | Zoledronate IV (3)/NR<br>Risedronate + Denosumab (1)/NR<br>Alendronate + Denosumab (1)/NR<br>Alendronate (2)/NR |
| Pichardo et al. (2020) | RC | Presence | 18 | 14/4 | Osteoporosis (11)<br>Cancer (7) | Zoledronate IV (2)/NR<br>Pamidronate IV (3)/NR<br>Alendronate (8)/NR<br>Risedronate (2)/NR<br>Denosumab (3)/NR |
| Nisi et al. (2020) | Case series | Presence | 15 | NR | Osteoporosis (7)<br>Metastatic breast cancer (4)<br>Multiple myeloma (3)<br>Metastatic prostate cancer (1) | Alendronate (6)/64.5 months<br>Ibandronate (2)/48 months<br>Neridronate (2)/40 months<br>Zoledronate IV (6)/18.3 months<br>Denosumab (1)/10 months |
| Pogrel and Ruggiero (2018) | Case series | Presence | 11 | 11/0 | Osteoporosis (8)<br>Metastatic bone disease (2) | Alendronate (8)<br>Zoledronate (1)<br>Denosumab (2)<br>All longer than 24 months |
| Zushi et al. (2017) | Case report | Presence | 1 | 0/1 | Osteoporosis | Alendronate/48 months |
| Giovannacci et al. (2016) | RC | Surgery | 6 | NR | Osteoporosis (5) | Ibandronate/60 months<br>Ibandronate + Alendronate/108 months<br>Alendronate/67.7 months<br>Ibandronate + Zoledronate IV/131 months |
| | | Presence | 9 | | Breast cancer (5)<br>Lung cancer (1)<br>Multiple myeloma (3)<br>Osteoporosis (1) | Zoledronate IV/73 months<br>Zoledronate and/or Pamidronate IV 35. 6 months<br>Alendronate |
| Troeltzsch et al. (2016) | RC | Surgery<br>Presence | 1<br>15 | 34/0 | Cancer (1)<br>Cancer (12)<br>Osteoporosis (3) | Zoledronate IV/32.3 months<br>Zoledronate IV/32.3 months Pamidronate IV/32.3 months Ibandronate/32.3 months Denosumab/32.3 months |
| Favia et al. (2015) | Case report | Presence | 1 | 1/0 | Breast cancer | Zoledronate IV/33 months |

inflammatory conditions caused by periodontal pathogens may increase BP release from the alveolar bone, where BP accumulated due to long-term anti-resorptive therapy. The released BP may exert detrimental effects on various cells near dental implants, resulting in worsened local conditions via increased cytotoxicity to osteoclasts, endothelial cells, and gingival soft tissue cells (Figure 1). However, it is important to note that the possible role of acidic conditions in the development of osteonecrotic lesions remains yet an experimental theory.

### 5.2.2 | Mechanical stress as a risk of late failures

Long-term BP therapy may decrease the toughness of the bone and long-term mechanical stress may damage the bony structure by developing microcracks (Allen & Burr, 2011). Microdamage and microcracks are repaired by osteoblasts because of the release of local mediators from the bone by osteoclastic bone resorption (Canalis et al., 2007). The possible role of mechanical trauma begins with understanding

| Location of MRONJ (*n*) | MRONJ stage | No. implant with MRONJ/No. implant placement | Time from implant to MRONJ (months) | Treatment | Outcome (*n*) | Peri-implantitis |
|---|---|---|---|---|---|---|
| Mn (14) Mx (6) | NR | Mn (24)<br>Mx (13) | 45 | Explantation | NR | Yes |
| Mx. | II | 2/2 | 126 | Explantation<br>Sequestrectomy | Resolution | Yes |
| Mx (1)<br>Mn (2) | II (1)<br>III (6) | 13 (total) | NR | Sequestrectomy (6)<br>Sequestrectomy and Osteosyntesis (1) | Favorable (5)<br>No resolution (2) | NR |
| Mx (6)<br>Mn (12) | II (9)<br>III (9) | 30/47 | NR | Sequestrectomy | Resolution | NR |
| Mn (10) | II (3)<br>III (12) | 11/29 | NR | Sequestrectomy | Resolution (86.7%) | NR |
| Mx (2)<br>Mn (9) | NR | NR | NR | Explantation<br>Sequestrectomy | Resolution | NR |
| Mn (1) | III | 2/13 | 24 | Sequestrectomy | Resolution | Yes |
| Mx (2)<br>Mn (2)<br>Both (2) | I–III | 3/12 | 2–10 | Sequestrectomy | Resolution | NR |
| Mx (1)<br>Mn (5)<br>Both (3) | II (5)<br>III (2)<br>NR (2) | 5/22 | 18–96 | NR | | |
| NR<br>Mx (13)<br>Mn (2) | NR | 2/117<br>15/117 | NR<br>37.6 | Sequestrectomy | NR | Yes |
| Mn (1) | NR | 4/7 | 60 | Mandibular partial resection with involved 4 implants + antibiotics | Resolution | NR |

(Continues)

TABLE 2 (Continued)

| Authors (year) | Study design | Implant surgery or implant presence | Subjects (sample size) | Timing of ARD therapy (IMP-ARD/ ARD-IMP) | Systemic condition (*n*) | Medication (*n*)/duration (months) |
|---|---|---|---|---|---|---|
| Marín-Fernández et al. (2015) | Case report | Presence | 1 | 1/0 | Breast cancer | Zoledronate IV/14 months |
| Junquera et al. (2014) | RC | Surgery | 1 | NR | Osteoporosis | Alendronate/48 months |
| | | Presence | 1 | | Multiple myeloma | Zoledronate IV/17 months |
| Holzinger et al. (2014) | RC | Surgery | 13 | 3/10 | Multiple myeloma (3)<br>Osteoporosis (5)<br>Breast cancer (3)<br>Lung cancer (1)<br>HLC (1) | Zoledronate IV (7)/NR<br>Alendronate (3)/NR<br>Pamidronate (2)/NR<br>Ibandronate (1)/NR |
| | | Presence | 15 | | Cancer (12)<br>Osteoporosis (3) | Zoledronate IV/32.3 months<br>Pamidronate IV/32.3 months<br>Ibandronate/32.3 months<br>Denosumab/32.3 months |
| Kwon et al. (2014) | Case series | Surgery | 3 | | Osteoporosis (2)<br>Multiple myeloma (1) | Alendronate/22 months<br>Ibandronate IV/9 months<br>Zoledronate IV/55 months |
| | | Presence | 16 | 16/3 | Osteoporosis (16) | Pamidronate IV/18 months<br>Risedronate/57 months<br>Alendronate/24 months |
| López-Cedrún et al. (2013) | Case series | Presence | 9 | NR | Osteoporosis | Alendronate/71 months<br>Ibandronate/62 months<br>Risedronate/48 months |
| Jacobsen et al. (2013) | RC | Presence | 14 | NR | Multiple myeloma (2)<br>Breast cancer (5)<br>Prostate cancer (1)<br>Lung cancer (1)<br>Osteoporosis (5) | Zoledronate IV (8)<br>Pamidronage IV (2)<br>Pamidronate + Zoledronate IV (1)<br>Alendronate (2)<br>Ibandronate (1) |
| Yuan et al. (2012) | Case report | Presence | 1 | 1/0 | Osteoporosis | Risedronate/24 months<br>Alendronate/1 months |
| Lazarovici et al. (2010) | Case series | Surgery | 6 | NR | Osteoporosis (11)<br>Multiple myeloma (7)<br>Breast cancer (7)<br>Prostatic cancer (2) | Alendronate (6)/63.5 months<br>Zoledronate IV (1)/13 months |
| | | Presence | 21 | 4/17 | | Alendronate (5)/72.4 months<br>Zoledronate IV (6)/57 months<br>Pamidronate IV (5)/50.2 months<br>Pamidronate + Zoledronate IV (4)/53 months |
| Goss et al. (2010) | Case series | Surgery | 3 | | Osteoporosis | Alendronate (1)/60 months<br>Risedronate (2)/68 months |
| | | Presence | 4 | 4/0 | | Alendronate (4)/58.5 months<br>Risedronate (1)/10.5 months |
| Shirota et al. (2009) | Case report | Presence | 1 | 1/0 | Breast cancer (1) | Pamidronate + Zoledronate IV/17 months |

Abbreviations: ARD, antiresorptive drug; ARD-IMP, ARD therapy before implant therapy; IMP-ARD, the implants before ARD therapy; Mn, mandible; MRONJ, medication-related osteonecrosis of the jaws; Mx, Maxilla; NR, not reported; RS, retrospective single-arm study.

the action of osteocytes in monitoring trauma and transmitting injury signals. Since an empty lacuna is a typical histological hallmark of MRONJ, mechanotransduction factors may be considered as a possible etiological factor of MRONJ (George et al., 2018, 2019). According to traditional biomechanical theory, excessive strain (>3000 με) would cause pathologic mechanical bone failure (Stanford & Brand, 1999), and such a strain may be observed in the peri-implant bone under an oblique load of 100 N (Chou et al., 2010).

Some studies have investigated the possible relationship between microcracks and MRONJ. In a scanning electro-microscopic study of human histopathological specimen, microcracks were significantly more frequent in MRONJ samples (82%) than in ordinary osteomyelitis of the jaw or osteoradionecrosis which is another type of avascular necrosis (Hoefert et al., 2010). In this study, no microcracks were observed in OM or RA. This finding was confirmed by an animal study that showed that unrepaired microcracks may be associated with the development of MRONJ (Kim et al., 2016).

Long-term occlusal stress demands increased bone remodeling, and as the BP-accumulated bone cannot meet the upregulated

| Location of MRONJ (*n*) | MRONJ stage | No. implant with MRONJ/No. implant placement | Time from implant to MRONJ (months) | Treatment | Outcome (*n*) | Peri-implantitis |
|---|---|---|---|---|---|---|
| Mx (1) | III | 1/3 | 60 | Subtotal maxillectomy | Resolution | Yes |
| Mn (1)<br>Mx (1) | III<br>II | 1/2<br>2/2 | 5<br>18 | Sequestrectomy | Resolution | NR |
| Mx (1)<br>Mn (12) | NR | 10/47 | 4 | NR | Resolution | NR |
| Mx (13)<br>Mn (2) | | 20/47 | 50.8 | Sequestrectomy | | |
| Mx (3) | II, III | 2 (total) | 4 | Sequestrectomy (1) | NR | NR |
| Mx (7)<br>Mn (8)<br>Both (1) | III (14)<br>II (2) | 19 (total) | 30.18 | Sequestrectomy (14) | | |
| Mx (3)<br>Mn (11) | NR | 12/57 | 34 | Sequestrectomy | Resolution (7)<br>No resolution (2) | NR |
| Mx (4)<br>Mn (8) | NR | 12/23 | 20.9 months (Malignant disease: 17 months Osteoporosis: 25.6 months) | Sequestrectomy (10) | Resolution (9) - one patient died due to underlying disease | Yes |
| Mn. | NR | 2/2 | 120 | Sequestrectomy<br>Explantation | Resolution | Yes |
| Mx (7)<br>Mn (20) | NR | NR | 1.8<br>23.8 | Antibiotics<br>Explantation | Resolution (12)<br>No resolution (15) | NR |
| NR | NR | 3/7<br>6/12 | 3<br>NR | NR | Resolution | NR |
| Mx (1) | NR | 2/2 | NR | Sequestrectomy | Resolution | NR |

remodeling, this may lead to sequestration of the microdamaged area due to failure of the bone repair mechanism (Mine et al., 2022). Because MRONJ may be primarily an aseptic process (Lesclous et al., 2009), long-term occlusal trauma would cause inflammation in the bone, and this may initiate osteonecrosis underneath the soft tissue. However, there are no clinical data on IRS due to mechanical stress, and only experimental data are available. The pathophysiology of MRONJ and IRS is multifactorial. Therefore, it does not sufficiently account for the relationship between mechanical overload and IRS.

### 5.3 | Implant failures related to other factors

Among the 13 studies that reported implant failure in patients previously exposed to BPs before implant placement, 9 studies specified the therapeutic indication for BPs treatment. All these studies demonstrated that BPs were administered to osteoporosis patients, and this implied that low-dose regimens were used. A total of 648 implants in the studies were placed and 24 implants failed, with a survival rate of 96.3%, which was comparable to the overall survival rate of 97.6%. There was only one prospective study that investigated

**TABLE 3** Adverse events of denosumab related to dental implant and/or osteonecrosis of the jaw.

| Authors (year) | Study design | Subjects (sample size) | Follow up (months) | Systemic condition | Dosage (mg/mL) | Therapy duration (months) | Outcome parameter | Implant related events | ONJ incidence | Drug therapy at time of implant |
|---|---|---|---|---|---|---|---|---|---|---|
| Andersen et al. (2022) | PS | 7 (15 implants) | 5 | Malignancy | Various | 25 | Implant failure | 0 | 0 | Drug holiday at least 2 months |
| Kim et al. (2020) | RC | 55 | 85.26±36.72 | NS | NS | NS | Implant failure | 5 out of 55 implants failed | 0 | Implants inserted before medication |
| Watts et al. (2019) | RCT | 4550 | ≤120 | Osteoporosis (female) | 60 mg/6 months | 120 | Adverse effect | 1 out of 212 patients developed ONJ around implant | 13 | Yes |
| Raje et al. (2018) | RCT | 850 | 24 | Malignancy | 120 mg/4 weeks | 15.8 | Adverse effect | NR | 35 | NR |
| Stopeck et al. (2016) | RCT | 465 | 34–41 | Malignancy | 120 mg/4 weeks | 10.2–18.4 | Adverse effect | NR | 32 | NR |
| Henry et al. (2014) | RCT | 792 | 24–30 | Malignancy | 120 mg/4 weeks | 6.7 | Adverse effect | NR | 6 | NR |
| Chawla et al. (2013) | RCT | 281 | 24 | Malignancy | 120 mg/6 months | 7–20 | Adverse effect | NR | 3 | NR |
| Scagliotti et al. (2012) | RCT | 395 | NR | Malignancy | 120 mg/4 weeks | NR | Adverse effect | NR | 3 | NR |
| Lipton et al. (2012) | RCT | 2841 | 8.2 | Malignancy | 120 mg/4 weeks | NR | Adverse effect | NR | 52 | NR |
| Smith et al. (2012) | RCT | 676 | 36 | Malignancy | 120 mg/6 months | 20.2 | Adverse effect | NR | 33 | NR |
| Henry et al. (2011) | RCT | 878 | 27 | Malignancy | 120 mg/4 weeks | 7 | Adverse effect | NR | 10 | NR |
| Fizazi et al. (2011) | RCT | 943 | 41 | Malignancy | 120 mg/4 weeks | 12.2 | Adverse effect | NR | 22 | NR |
| Stopeck et al. (2010) | RCT | 1020 | 34 | Malignancy | 120 mg/4 weeks | 8 | Adverse effect | NR | 20 | NR |

*Note*: The studies from Kim et al. (2020) and Andersen et al. (2022) consisted of patients taken various anti-resorptive drugs such as bisphosphonate and denosumab, and the data related to denosumab were only extracted, accordingly.

Abbreviations: N, none; NR, not reported; NS, not specified; ONJ, osteonecrosis of the jaws; PS, prospective case series; RC, retrospective cohort; RCT, randomized controlled trial.

**TABLE 4** Methotrexate and dental implant.

| Authors (year) | Study design | Subjects (sample size) | Follow up (months) | Systemic condition | Medication & dosage (mg/mL) | Therapy duration (months) | Outcome parameter | Implant related outcome | ONJ incidence | Drug therapy at time of implant |
|---|---|---|---|---|---|---|---|---|---|---|
| Weinlander et al. (2010) | Case series | 22 (89 implants) | 36 | RA, CTD | CS, MTX | 14–91 | Implant failure | 3 of 89 implants failed | NR | Yes |
| Eder and Watzek (1999) | Case report | 1 (6 implants) | 60 | Osteoporosis, Polyarthritis | 7.5 mg/week MTX | 72 | Implant failure | None failed | 0 | Yes |
| Tavakoli et al. (2018) | Animal study | 8 (48 implants) | 1 | N | 2.5 mg/week MTX | 1 | Osseointegration | Lesser BIC in MTX group | 0 | Yes |
| Carvas et al. (2011) | Animal study | 24–32 (24–34 implants) | 4 | N | 3 mg/kg/week MTX | 1.5 | Osseointegration | Not significant reductions of cortical thickness, total bone area and BIC | 0 | Yes |

Abbreviations: BIC, bone to implant contact; MTX, methotrexate; N, none; NR, not reported.

implant failure in patients who were exposed intravenous (IV) BPs for 2–3 years before implant therapy (Siebert et al., 2015). This demonstrated that the failure did not occur in all groups. In this study, although BPs were administered intravenously, a low-dose regimen was used for osteoporosis patients, and these results may be different from that in patients with malignancy receiving high-dose BPs. A limitation of this study was the follow-up period. Although the study was prospectively designed, data were only collected 1 year after functional loading. Since the prolonged effect of BPs is not negligible, studies on the long-term survival of these implants are crucial.

It is generally accepted that the dose regimen of ARD is much more influential than its route of administration is. However, there is a possibility that IV BPs may be riskier than oral BPs because of the low availability of oral BPs, which is reported to be approximately 0.6% (Gertz et al., 1995). When BPs were orally administered, the proportion of BPs bound to bone tissue is relatively low compared to the total dose administered. A daily or weekly low-dose regime of oral BPs also requires a relatively long time to significantly impact the implant and bone metabolism compared to the effect of a high-dose regime of IV BPs with a low frequency. However, it is inappropriate to focus only on the administration route, and the medication regimen and potency should be considered first.

Current data are insufficient to analyze the long-term survival of implants in patients exposed to BPs. Four studies had a mean follow-up duration of >3 years. The survival rate was 95.2% (179/188) in osteoporosis patients on BPs, while it was 97.3% (320/329) in those not on BPs. However, owing to insufficient sample size and heterogeneous study designs, the longevity of implants in patients receiving BPs remains unclear. The duration and dosage of ARD therapy are also crucial factors for the survival of implants, although the risk could not be estimated, because each study included varying durations of ARD therapy. Considering that BPs have a relatively longer retention half-life, periodic check-ups and maintenance periodontal therapy are recommended to ensure optimal and safe outcomes.

Despite the heterogeneity of the study design and confounding factors, these results suggest that dental implants are viable option for patients receiving BP therapy. However, it would be wise to exercise caution when treating patients with dental implants who are receiving or have received high-dose BPs, particularly in cases where there has been prolonged exposure to them. The major limitation of this review is the absence of well-designed prospective controlled clinical trials. Owing to the potential hazards and medical importance of medications that affect bones, it may be challenging to randomly assign participants. However, a prospective study that controls for other confounding factors, such as the type of medication, therapy duration, follow-up time, and local and systemic conditions must be possible, which is necessary to gain a better understanding of the impact of these medications on implant failure. Additionally, information on peri-implant health was not included in the available studies. Standardized measurement and reporting of these factors would help reveal how peri-implant tissues respond to these medications and potentially lead to implant failure.

TABLE 5 Corticosteroids and dental implant.

| Authors (year) | Study design | Subjects (sample size) | Follow up (months) | Systemic condition | Medication & dosage (mg/mL) | Therapy duration (months) | Outcome parameter | Implant related outcome | ONJ incidence | Drug therapy at time of implant |
|---|---|---|---|---|---|---|---|---|---|---|
| Carr et al. (2019) | RC | 6358 | 70 | Various | Various | NR | Implant failure (patient level data) | HR 0.72 (0.60–0.86) | NR | Yes |
| Krennmair et al. (2010) | Case series | 34 (126 implants) | 47.6 | RA, CTD | CS, NSAID | NR | Implant failure | 7 of 126 implants failed | NR | Yes |
| Weinlander et al. (2010) | Case series | 22 (89 implants) | 36 | RA, CTD | CS, MTX | 14–91 | Implant failure | 3 of 89 implants failed | NR | Yes |
| Carvas et al. (2010) | Animal study | 18 (18 implants) | 4.5 | N | 0.35 mg/kg CS | 4.5 | Osseointegration | Statistically significant decreases of osseointegration and BMD | 0 | Yes |
| Keller et al. (2004) | Animal study | 40 (40 implants) | 2 | N | 7.5 mg/kg CS | 1 | Osseointegration | Statistically significant decrease of BIC | 0 | Yes |
| Fujimoto et al. (1998) | Animal study | 12 (48 implants) | 3 | N | 10 mg/kg CS | 2 | Osseointegration | No significant difference in removal torque | 0 | No |

Abbreviations: BIC, bone to implant contact; BMD, bone mineral density; CS, corticosteroid; CTD, connective tissue diseases; HR, hazard ratio; MTX, methotrexate; N, none; NR, not reported; RA, rheumatoid arthritis; RC, retrospective cohort study.

## 6 | EFFECT OF BISPHOSPHONATE ADMINISTERED AFTER SUCCESSFUL OSSEO INTEGRATION OF IMPLANTS

### 6.1 | Late failures in functioning implants

The available studies do not provide sufficient information regarding the timing of ARD therapy initiation with the presence of functioning implants. However, some studies have distinguished the timing of ARD therapy based on the presence of functional implants (Table 2). In most cases, implant therapy preceded ARD therapy, which addresses the timing issue. This finding implies that long-term ARD therapy may pose a risk for late failure or IRS. Some studies have included only late failures in patients who received ARD therapy after implant placement (Kim et al., 2020; Pogrel & Ruggiero, 2018; Tempesta et al., 2022; Troeltzsch et al., 2016).

Among them, only one cohort study has investigated the effect of BP treatment in patients with previously osseointegrated implants (Kim et al., 2020). The reported survival rate of implants was 90.0% (260/289). These rates were lower than the overall survival rates reported for patients receiving BP therapy before implant placement mentioned earlier, although statistical comparisons with control groups were not conducted. The mean follow-up period beyond 7 years was longer than that in most other studies, which might explain the difference in results other than dose regime. Besides, delayed exposure to BPs after implant surgery could be a contributing factor, or it is possible that both a longer follow-up period and delayed BP exposure were responsible for the lower implant survival rates observed in this study. However, the specific pathophysiological mechanisms that determine whether delayed BP exposure is more detrimental or not have not been be currently elucidated, and further studies are required to verify them.

Interestingly, 11 of the 34 failed implants were associated with the presence of sequestration, which may be classified as an IRS. The action of BPs may also contribute to detrimental environments even around successfully integrated dental implants. Peri-implantitis, characterized by local inflammation and infection, can exacerbate the cytotoxic effects of N-BPs (Otto, Hafner, et al., 2010; Otto, Pautke, et al., 2010). Additionally, a decreased bone toughness and a long-term occlusal stress causing microcracks around implants may require upregulated bone remodeling, leading to late implant failure and IRS. It is reasonable to think that the same pathophysiology as in the development of IRS and late failure in patients receiving ARD therapy before implant placement could be applied, although it has yet been a hypothetical theory based on retrospective single-arm case studies and experimental models (George et al., 2018, 2019; Mine et al., 2022; Pichardo et al., 2020; Tempesta et al., 2022; Troeltzsch et al., 2016).

### 6.2 | Implant failures related to other factors

In a cohort study that investigated the effect of BPs treatment in patients who had previously osseointegrated implants (Kim et al., 2020), the survival rates were 93.58% (204/218) for patients treated with

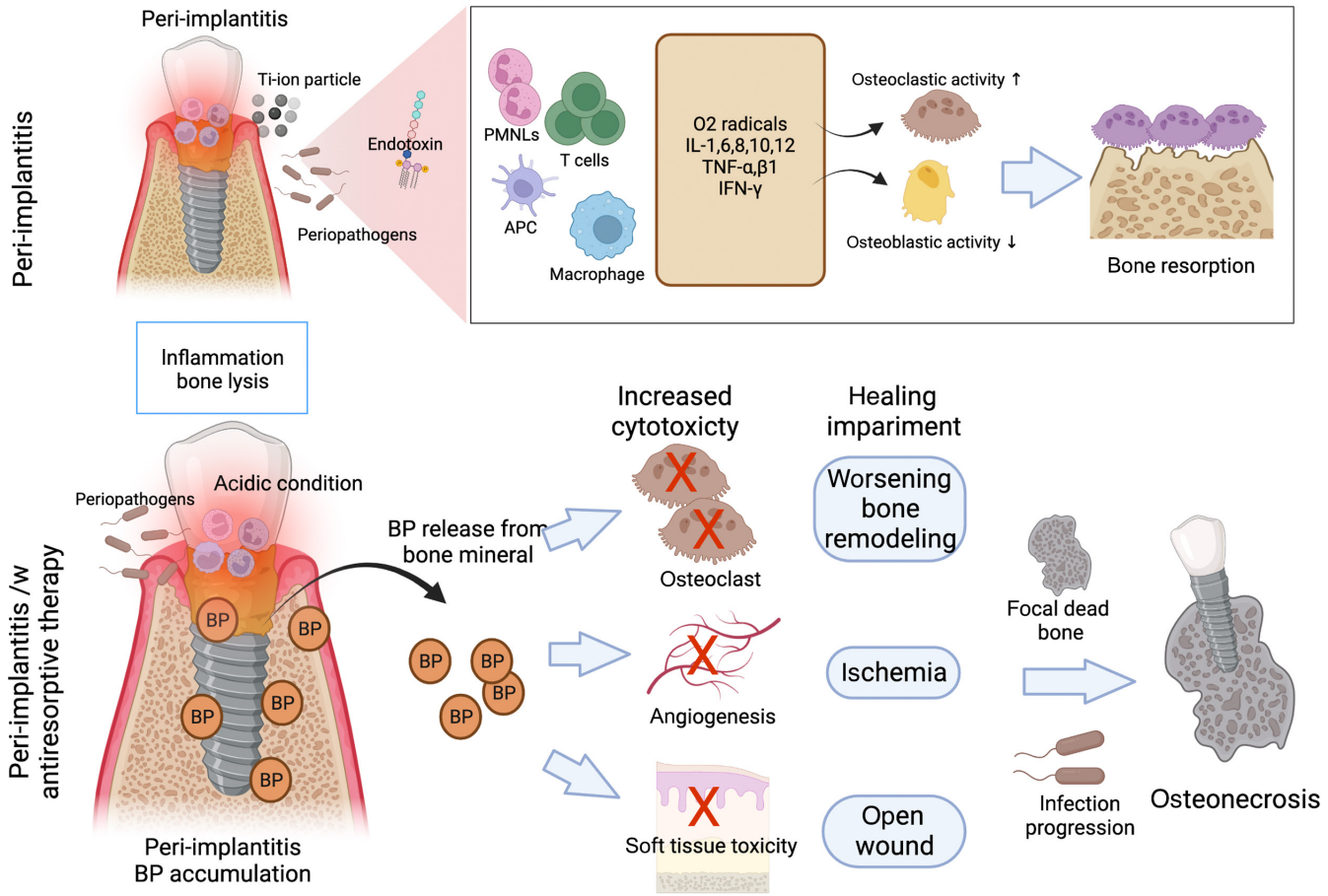


FIGURE 1 Pathophysiology of implant-related sequestration.

oral BPs and 78.9% (56/71) for those treated with IV BPs. The therapeutic indication for IV BPs was not specified in the study; however, considering that IV BPs have usually been prescribed for oncology patients who require high doses at frequent intervals, whereas oral BPs have been administered in low doses for osteoporosis patients (Ensrud, 2021; Khan et al., 2015; Lipton, 2003), it is assumed that a high dose regimen might have been used in majority of patients. Additionally, as mentioned above, the route of administration might also have had an influence on implants failure.

When the cumulative dose reaches a level that may disrupt bone metabolism around functioning implants, the increased metabolic demand caused by peri-implantitis may initiate IRS, as elaborated above (Pichardo et al., 2020). In cases where ARD therapy begins after the successful osseointegration of implants, it may take a considerable amount of time to reach the cumulative dose. Consequently, the development of IRS may be slower compared to patients receiving ARD therapy before implant placement (Pichardo et al., 2020). According to a nationwide study in Japan, the cumulative incidence of MRONJ has increased in a time-dependent manner (Ishimaru et al., 2022). Therefore, the cumulative dose or sustained effect of ARD therapy could be a crucial factor in the late failure or IRS, regardless of the timing difference between ARD and implant therapies.

Regarding the severity of the lesions, staging information was available for 67 patients of the 168 patients who were diagnosed with IRS. Altogether, 46 out of 67 patients (69%) presented with stage 3 lesions. This suggests that when an IRS is detected, it may already be at an advanced stage. No cases of stage 1 disease have been reported in the literature, indicating that early detection of IRS may be challenging. Fortunately, many studies have reported favorable treatment outcomes consistent with the surgical outcomes of MRONJ, as described in Table 2.

Researches investigating the influence of BP duration and dosage on osseointegrated implants are extremely limited. Furthermore, relying solely on one cohort study and case series is insufficient to draw any definitive conclusions on this topic. Given the characteristics of BPs, which accumulate in bone tissue and exert a prolonged suppressive effect on bone remodeling, we can only speculate based on the pathophysiology of MRONJ, and IRS and late failures might also be influenced by the duration and dosage of BP treatment. It is imperative to conduct further research in order to determine the effects of BPs on successfully osseointegrated implants, as the existing literature on this topic is currently very limited.

## 7 | DENOSUMAB AS A RISK FACTOR FOR DENTAL IMPLANTS

Despite a thorough search, only one retrospective cohort study was found, which investigated the implant failure rate in patients

receiving denosumab or BPs along with non-ARD users (Kim et al., 2020) (Table 3). It demonstrated that the implant survival rates were 96.03% in non-ARD (363/378) and 90.91% (50/55) in denosumab users. However, this study investigated the effect of denosumab in patients who treated with dental implants before ARD therapy, and statistical analysis between the two groups was not performed. Instead, the overall implant survival rate in ARD users was reported to be 90.12%, with a statistically significant difference ($p < .003$) compared to that in non-users. The major limitations of this study include the absence of a comparison of the survival rate of denosumab users with that of controls. In addition, the duration of treatment and dose regimen of denosumab was not demonstrated. Therefore, the results should be interpreted with caution.

Two other studies have mentioned the influence of denosumab on dental implants (Andersen et al., 2022; Watts et al., 2019) (Table 3). However, these were single-arm observational studies in terms of denosumab usage. The overall design of the Phase III clinical trial was a randomized controlled study (Watts et al., 2019); however, of the 212 patients treated with dental implants over the 7 years of data collection, both control and experimental groups received denosumab injections when dental implants were installed (Watts et al., 2019). In this study, only one case of implant-related MRONJ was reported in 212 patients treated with dental implants and it was successfully treated without fixture removal. Another prospective single-arm study demonstrated that there were no early implant failures after 15 implant insertions in seven patients, despite a relatively higher dose regimen for malignancy (Andersen et al., 2022). In addition to the study design and small sample size, the major weakness of this study was that follow-up was not conducted after the implant prosthesis.

Unlike BPs, denosumab does not have an affinity for bone minerals. Based on its pharmacokinetic properties, the effect of denosumab is expected to be eliminated approximately 6 months after injection. Despite the completely different modes of action of BPs and denosumab, some cases of IRS associated with denosumab have also been reported (Pichardo et al., 2020; Pogrel & Ruggiero, 2018; Tempesta et al., 2022; Troeltzsch et al., 2016). In contrast to the release of accumulated drugs such as BPs near dental implants, this does not occur in cases of local infections such as peri-implantitis. However, it is plausible that suppressed bone remodeling and subsequent impaired response to mechanical stress and inflammation could similarly contribute to IRS for both BPs and denosumab.

Due to insufficient data and uncontrolled study design, the impact of denosumab on implant survival is inconclusive, despite the well-documented detrimental effect of denosumab on bone metabolism. Furthermore, drug holidays or therapeutic window periods before implant placement were not included in these studies. Accordingly, whether a drug holiday plays a critical role in implant therapy and how long the drug-free status should be maintained, remain questionable. Owing to the rarity and inconsistency of these outcomes, further studies should be encouraged to thoroughly analyze the topic. Nevertheless, considering the higher prevalence of MRONJ in patients with malignancies, implant rehabilitation should be approached cautiously when high-dose denosumab is administered or is expected.

## 8 | METHOTREXATE AND CORTICOSTEROIDS AS RISK FACTORS FOR DENTAL IMPLANTS

### 8.1 | Methotrexate

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disorder characterized by progressive joint destruction and various systemic manifestations such as skin, ocular, oral, gastrointestinal, pulmonary, neurological, cardiovascular, and hematological events (Cojocaru et al., 2010; Friberg, 1994; Radu & Bungau, 2021). High levels of proinflammatory cytokines and inflammatory cells have been found in RA patients. The key drugs employed in RA treatment include CS and disease-modifying anti-rheumatic drugs (DMARDs). MTX has long been considered the most effective DMARD and a safe treatment for RA. Initially, high doses of MTX were prescribed as anti-neoplastic agents, but low-dose MTX is now widely administered to patients with RA. However, hindered osseointegration has been suggested because of suppressed osteoclast activation by decreasing RANKL-induced calcium influx into osteoclast progenitors (Cranney et al., 2001; El Miedany et al., 1998; Kanagawa et al., 2016; May et al., 1994; Suematsu et al., 2007).

Administration of MTX may impair osteoblast proliferation. An in vitro study assessed the effects of short-term administration of low-dose MTX in bovine osteoblasts by incubating them for 14 days. Osteoblast proliferation and mitochondrial metabolism were significantly reduced, suggesting that MTX may inhibit bone healing and osseointegration of implants (Annussek et al., 2012). Following these results, animal studies have reported a negative effect on dental implants. In a study using a canine model, a low-dose MTX reduced bone-to-implant contact (BIC), although osseointegration of inserted implant was acceptable (Tavakoli et al., 2018). On the other hand, another study demonstrated that cortical thickness, total bone area and BIC were not significantly different between the control and MTX groups in a rabbit model (Carvas et al., 2011). In a retrospective case series analyzing implant treatment in patients with RA and connective tissue disease (CTD), 13 implants were inserted in patients receiving MTX, and they all survived (Weinlander et al., 2010) (Table 4). A case report also showed that implant failure and peri-implantitis did not occur, despite old age, severe osteoporosis, chronic polyarthritis, and long-term MTX administration during a 4-year observation period (Eder & Watzek, 1999). Although MRONJ has been reported in association with MTX (Furukawa et al., 2018; Henien et al., 2017), only case reports have been found, and additional research is required to determine the relationship between MTX and MRONJ.

Studies on MTX and dental implants are scarce, and contradictory results highlight the need for further studies to determine the effect of MTX on the osseointegration of dental implants and their long-term prognosis.

### 8.2 | Corticosteroids

Anti-inflammatory, immunomodulatory, and antineoplastic properties of CS are known to be useful in numerous conditions, such as allergic reactions, asthma exacerbations, chronic obstructive pulmonary disease, and autoimmune conditions (Morand, 2007; Wan et al., 2012). However, several studies have indicated that long-term use of CS may lead to osteoporosis in humans as it initially enhances bone resorption and subsequently reduces bone formation and bone turnover (Woolf, 2007). The use of CS induces osteoblast apoptosis, reduces the number of pre-osteoblasts and promotes the differentiation of bone marrow stromal cells into adipocyte-lineage cells (Pereira et al., 2002; Smith et al., 2002; Weinstein, 2001). This results in an imbalance between the osteoclasts and osteoblasts in the bone microenvironment. The effects of CS on bone metabolism, apoptosis, lipid metabolism, and inflammatory pathways have been found to play a role in steroid-induced osteonecrosis (Chang et al., 2020). Likewise, it may be applied to the jaws, which, in turn, increases the risk of MRONJ (Saad et al., 2012). Several studies have discussed CS as a risk factor for the development of MRONJ (Aghaloo & Tetradis, 2017; McGowan et al., 2018; Tsao et al., 2013).

Several have investigated whether CS negatively affects bone healing, bone remodeling, and implant osseointegration (Table 5). In an in vitro study, the cellular attachment to the implant surface was significantly lower in dexamethasone-treated osteoblasts than in the controls (Cho et al., 2006). The CS group also showed a significant reduction in lumbar spine and tibia bone mineral density, BIC, and peri-implant bone area, which were considered osseointegration measurements in a preclinical study (Carvas et al., 2010). Another study reported cortical thinning, irregular trabecular patterns, and impaired extracellular matrix formation, and mineralization were observed as well as decreased BIC after CS administration (Keller et al., 2004). However, the removal torque of implants in the mandible was not significantly different between the CS and non-CS groups in an animal study (Fujimoto et al., 1998).

Only a few clinical studies have reported an association between CS administration and the prognosis of dental implants (Table 5). A retrospective cohort study evaluated the clinical outcomes of dental implants and biological complications in patients with RA with or without CTD. In both groups, marginal bone resorption and bleeding index were slightly higher in patients receiving CS, although the implant survival rate was 100% (Krennmair et al., 2010). Another study also reported a 100% implant survival rate for 46 implants placed in patients receiving CS (Weinlander et al., 2010). Interestingly, a reduced risk of implant failure was reported in a retrospective cohort study wherein CS was used at the time of placement (Carr et al., 2019).

In contrast to preclinical studies reporting decreased BIC, the survival of dental implant may not be influenced by CS treatment, although the evidence is very weak. Well-designed clinical studies regarding the use of CS and dental implants are necessary to determine whether the medication is influential in practice.

## 9 | OTHER MEDICATIONS AFFECTING BONE METABOLISM

### 9.1 | Romosozumab

Romosozumab, a monoclonal antibody against sclerotin, has recently been introduced in osteoporosis patients in several countries (AMGEN, 2019; European Medicines Agency, 2019). Unlike anti-resorptive agents that targets the attenuation of osteoclastic function and differentiation, romosozumab targets sclerotin (Baron et al., 2011), an osteocyte-secreted glycoprotein that inhibits osteoblastic activity and differentiation through Wnt/β-catenin signaling, leading to an anabolic effect (Lewiecki, 2014). However, as bone formation increases, a reduction in bone resorption markers has been observed in clinical trials which may lead to the development of MRONJ (McClung & Grauer, 2014; Padhi et al., 2011; Saag et al., 2017). Two events consistent with the definition of MRONJ occurred in a study of 3576 patients during a 24-month trial (Cosman et al., 2016); however, they were not associated with dental implants but with ill-fitting dentures and tooth extraction. Another study reported one case of MRONJ in 230 patients treated with romosozumab for 12 months. In contrast, an animal study using a rat model of MRONJ did not show any suspected osteonecrotic lesions, such as epithelial discontinuity or bone exposure (Hadaya et al., 2019). The number of empty osteocyte lacunae and osteoclasts in the study did not differ from those in the control group. Increased bone mass following romosozumab treatment may help consolidate implant therapy, whereas it may be related to the development of MRONJ and late implant failure. Studies exploring the association among romosozumab and MRONJ are scarce, not to mention dental implant. Further investigations are required to understand how romosozumab affects oral health and rehabilitation.

### 9.2 | Sunitinib

Sunitinib is an anti-angiogenic agent that inhibits different groups of tyrosine kinase receptors, including receptors for platelet-derived growth factor, vascular endothelial growth factor (VEGF), and stem cell factor (Hoefert & Eufinger, 2010; Mendel et al., 2003; Ramírez et al., 2015). Since angiogenesis plays a significant role in bone healing and remodeling, it has been suggested that sunitinib may alter bone metabolism in alveolar bone, and eventually affect the osseointegration of dental implants (Baldazzi et al., 2012; Paragliola et al., 2023). In addition, the suppression of growth factors may negatively affect biological complications in peri-implant

tissues and osseointegration. In an animal study, the ratio of bone volume to total volume and BIC were significantly lower in the sunitinib-treated group than in the control group (Al-Jandan et al., 2018). Although a clinical study regarding dental implants is yet to be conducted, several case reports and reviews of sunitinib-related osteonecrosis of the jaw have demonstrated abnormal bone healing and remodeling after sunitinib treatment (Abel Mahedi Mohamed et al., 2018; Vallina et al., 2019). Therefore, caution should be exercised when planning dental implants in patients receiving sunitinib until further research identifies the influence of this medication.

### 9.3 | Bevacizumab

Bevacizumab is a monoclonal antibody used for the treatment of solid, advanced cancers (Ferrara et al., 2004). Bevacizumab induces regression of the immature tumor vasculature and inhibits angiogenesis by preventing the interaction of vascular endothelial growth factor-A with its receptors and subsequent activation (Eguchi et al., 2022). Since angiogenesis is a biologically crucial step in new bone formation and osseointegration of dental implants, anti-angiogenic activity, such as inhibition of the VEGF signaling pathway, may negatively affect the integration of dental implants in the jaw (Raines et al., 2010). In an animal study, osseointegration measured using BIC was significantly lower in the bevacizumab group than in the control group (Al-Jandan, 2019). These findings suggest that impairment of angiogenesis by bevacizumab may have a negative impact on the osseointegration of titanium implants. Although there are no human studies on the relationship between bevacizumab and dental implant failure, some case reports have shown bevacizumab-related osteonecrosis of the jaw around the dental implant (Abel Mahedi Mohamed et al., 2018; Maluf et al., 2019; Ueda et al., 2022).

## 10 | CONCLUSION

In conclusion, this review highlights the complex relationship between dental implant rehabilitation and medications that alter bone metabolism. While previous publications have generally suggested that BPs do not compromise the survival of dental implants, there has been a report of increased failure of functioning implants after intravenous administration, which is speculated to be a high dose in oncological patients. Furthermore, there is an issue of implant-related sequestration, contributing to late implant failure in patients who had successfully undergone implant therapy before and after antiresorptive therapy. Although evidence is still lacking, peri-implantitis causing local inflammation and accumulation of micro-damage on peri-implant alveolar bone due to impaired bone repair might be associated; however, clinical data are too scarce to conclude the specific mechanisms behind the events. While the impact of denosumab, MTX, and CS on implant survival remains unclear due to insufficient data, their well-documented detrimental effects on bone metabolism underscores the importance of exercising caution when performing implant therapy.

To minimize the risks associated with medications that affect bone homeostasis and implant therapy, clinicians should carefully consider the potential hazards and take appropriate precautions. Additionally, well-designed prospective studies are needed to better understand the mechanisms underlying implant failure and inform clinical practice.

## AUTHOR CONTRIBUTIONS

**Junho Jung:** Methodology; data curation; formal analysis; validation; visualization; writing – original draft; writing – review and editing; investigation. **Jae-In Ryu:** Validation; formal analysis; writing – original draft. **Gyu-Jo Shim:** Data curation; investigation; writing – original draft. **Yong-Dae Kwon:** Conceptualization; methodology; validation; project administration; writing – original draft; writing – review and editing; supervision.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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