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Review Article

Antiresorptive Therapy to Reduce Fracture Risk and Effects on Dental Implant Outcomes in Patients With Osteoporosis: A Systematic Review and Osteonecrosis of the Jaw Taskforce Consensus Statement

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Abbreviations: BMD, bone mineral density; BP, bisphosphonates; Dmab, denosumab; HR, hazard ratio; MRONJ, medication-related osteonecrosis of the jaw; PDL, periodontal ligament; RR, risk ratio.

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ABSTRACT

Objective: Placement of a dental implant in a patient on antiresorptive therapy has been hypothesized to increase the risk of medication-related osteonecrosis of the jaw (MRONJ) and/or impact implant survival. In patients with osteoporosis, the risk of MRONJ with antiresorptive therapy is only marginally higher than observed in the general population.
Methods: The International ONJ Taskforce conducted a systematic review of the literature and evaluated the outcomes of implant placement in individuals with osteoporosis receiving antiresorptive therapy.
Results: The data were reviewed by the International Taskforce, and consensus was achieved on the following GRADEd recommendation. In patients with osteoporosis on antiresorptive therapy, the Taskforce suggests that antiresorptive therapy does not need to be stopped prior to proceeding with dental implant (weak recommendation, very low-quality evidence). Long-term bisphosphonate use maybe associated with a small increase in the risk of MRONJ (3 cases per 1000 patients; adjusted hazard ratio: 4.09, 95% CI: 2.75-6.09, $P < .001$, moderate certainty).
Conclusion: Current evidence does not suggest an association between antiresorptive therapy in patients with osteoporosis and dental implant failure. Implants may be safely placed in the presence of concomitant use of bisphosphonates or denosumab in patients with osteoporosis with no evidence of an increased risk of implant failure/compromise.

The Osteonecrosis of the Jaw Taskforce GRADEd Recommendation

In patients with osteoporosis receiving antiresorptive therapy, the Taskforce suggests that antiresorptive therapy does not need to be stopped prior to proceeding with dental implants (weak recommendation, very low-quality evidence).
Comment: The effect of antiresorptive therapy on implant failure is very uncertain at this time.

Introduction

Dental implants improve quality of life for individuals with tooth loss from a variety of causes. In the patient population with osteoporosis, the incidence of medication-related osteonecrosis of the jaw (MRONJ) is very low.[1-3] However, concern has been raised regarding a possible relationship between antiresorptive therapy and dental implant survival. Antiresorptive medications have 2 approved uses: first, to reduce the risk of osteoporotic fractures in individuals with low bone density or prior fragility fractures; second, to lower the risk of complications of bone metastases in

patients with cancer. The osteoporosis treatment requires a low medication dose, whereas the cancer-related use necessitates a high dose, with a more than 10-fold difference. The prevalence of MRONJ in patients with osteoporosis who take antiresorptive medications is approximately 0.01% to 0.03%.[4] The prevalence of MRONJ in patients with cancer who take antiresorptive medications is approximately 2% to 5%.[1] Dental implant failure occurs infrequently in healthy individuals and is defined as loss of boney integration resulting in implant mobility. This can be confirmed clinically and/or radiographically beyond the expected norm.[5] Implant failure can occur early (within 6 months) or later. Multiple factors contribute to implant failure and include thermal trauma, infection (peri-implantitis), poor bone quantity and/or quality, lack of primary stability, and early mechanical overloading (occlusal trauma and overloading).[6-8]

Extensive progress has been made in the use of dental implants as both single tooth replacements and abutments for fixed and removable dental prostheses.[9-11] In the United States, the prevalence of dental implants in adults missing at least 1 tooth was 0.7% in 1999-2000 and 5.7% in 2015-2016, an eightfold increase in a mere 15 years. With current trends, that percentage is projected to rise to 17% by 2026.[12] In 2016, of the 100 million US individuals aged >55 years, approximately two thirds have 27 or fewer teeth,[10] making them candidates for dental implants. Of those 100 million, approximately 23% have no remaining teeth.[13] Thus, it is not surprising that >60% of patients with dental implants are aged >55 years,[12] the population segment most at risk of osteoporosis, and hence, treatment with antiresorptive medications.

The longevity of today's dental implants is impressive.[9-11] Data from tens of thousands of implants have been reported with follow-up times reaching 2 decades. The 10-year mean survival of dental implants used to replace single or multiple teeth (through fixed or removable dental prostheses), without regard to positive or negative risk factors, is approximately 95%.[14-17] Risk factors affecting dental implant survival include operator skill,[18] smoking (negative),[19] poor bone quality (negative),[20] history of severe periodontitis (negative),[21] bruxism (negative),[20] lack of primary stability, early mechanical overloading (occlusal trauma and overloading), semiannual dental checkups (positive),[22] as well as certain systemic diseases (eg, diabetes, cardiovascular disease, and osteoporosis).[7,8,23,24]

About two thirds of implants that fail do so during the osseointegration phase that lasts 9 to 12 months past insertion. It is not uncommon for dental implant trials using patients who are nonsmokers with no history of severe periodontitis who attend semiannual dental appointments to report 99% survival at 10 years.

During the past decade, dental implants have become a routine part of restorative dentistry. Because of the sheer number of dental implants now being placed in individuals aged >55 years with or without antiresorptive medications, thorough and accurately reported data concerning the survival of dental implants in persons taking antiresorptive medications are not only needed, but possible over the next decade.

Dentists and oral surgeons have been concerned regarding concomitant use of antiresorptive therapy in individuals scheduled to receive dental implants. The potential for antiresorptive therapy adversely affecting alveolar bone healing has been raised. This is of particular concern in a large group of patients with osteoporosis or osteopenia who are receiving antiresorptive therapy for the prevention of fragility fractures. Due to concerns that placement of dental implants in patients on antiresorptive therapy may increase the risk of MRONJ and/or impact implant survival, we conducted a systematic review of the literature evaluating the relationship between antiresorptive therapy and impact on dental implant outcomes in individuals with osteoporosis. The aim of this systematic review and consensus statement was to explore the outcomes of implant placement in patients with osteoporosis who are receiving antiresorptive therapy and to provide clinical recommendations to guide management during implant placement.

Highlights

- Antiresorptive therapy has not been shown to increase the risk of implant failure
- There is no evidence that cessation of bisphosphonate or denosumab therapy improves implant survival or reduces the development of medication-related osteonecrosis of the jaw
- Cessation of denosumab is not advised as it has been associated with rebound bone loss and an increased risk of multiple vertebral fractures
- Patients on antiresorptive therapy should receive routine comprehensive oral examination and maintain good dental hygiene
- Individualized management is advised balancing the risks and benefits of continuing pharmacotherapy in patients with osteoporosis undergoing dental implant placement

Clinical Relevance

Dental implants are common in older individuals, a population also at risk of osteoporosis and the need for drug therapy. A systematic review and meta-analysis by the International Osteonecrosis of the Jaw Taskforce found no association between antiresorptive therapy and dental implant failure. This finding supports the safe placement of implants without discontinuation of antiresorptive therapy used for osteoporosis management.

Methods

We conducted a systematic review to inform our GRADEd recommendation (details below) and a narrative review to address questions where data were insufficient to conduct a systematic review. Due to the limited published literature on implant survival with concomitant antiresorptive therapy in individuals with osteoporosis, we included case reports and case series in addition to clinical trials and systematic reviews. Inferences from translational studies were performed and informed some of the recommendations. We searched PubMed, EMBASE, and Cochrane databases for relevant papers. The key questions addressed were as follows:

1. Are there differences in bone healing post implant vs post dental extraction?
2. Do antiresorptive agents affect dental implant survival (short- and long-term effects)?
3. Does the duration of antiresorptive therapy affect dental implant survival following placement of dental implants?
4. Which additional risk factors impact implant failure due to MRONJ?
5. What local factors affect the risk of MRONJ following dental implant placement?
6. Are there differences between antiresorptive agents and the risk of MRONJ post dental implant?
7. What are the risks and benefits of interrupting antiresorptive therapy prior to implant placement?
8. Is there any value in using an anabolic agent, in patients with a history of long-term antiresorptive treatment, prior to or following implant placement?

9. Is there an optimal time for implant placement following or prior to administration of an antiresorptive agent?
10. Do patients with dental implants on antiresorptive therapy for osteoporosis require additional monitoring?

Systematic Review Methodology

The Methodology of the Accompanying Systematic Review

A systematic review and meta-analysis was undertaken to address this specific question: "Do antiresorptive therapies, bisphosphonates (BP) and/or denosumab (Dmab) increase the risk of dental implant failure or MRONJ in patients with osteoporosis receiving dental implants?" MEDLINE, EMBASE, Cochrane Central, CINAHL, and Web of Science were searched from origin of database (1946) to May 2024. We also conducted a manual review of citations from existing systematic reviews and contacted topic experts for further references.[25] We included case reports and case series with 5 or more patients, interventional and noninterventional cohorts, and systematic reviews addressing the question. The review used methods designed to produce reliable results including a structured clinical question, a comprehensive search of relevant literature, duplicate assessment of eligibility, risk of bias, and data abstraction. We applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence. The GRADEd recommendation followed a structured process that included framing questions in the patient/intervention/ comparator/outcome format,[26] conduct of a systematic evidence search, specification of values and preferences,[27] and classifying and presenting the recommendations as strong or weak with the corresponding quality of evidence.[28] See the accompanying systematic review by Mirza et al[25] for further details.

Are There Differences in Bone Healing Post Implant vs Post Dental Extraction?

Both in dental extraction and in implant osseointegration, osteoclasts and osteoblasts play a critical role in repair of the surrounding bone through the process of bone remodeling, in which osteoclastic bone resorption is followed by and coupled to formation and subsequent bone mineralization. Following dental extraction or implant placement, osteoclasts are recruited to the relevant sites by vascular, inflammatory, and mechanical stress mediators resulting in targeted osteoclastic resorption of bone and the subsequent action of osteoblasts to produce osteoid, which then undergoes mineralization. There are suggestions that the dental implant surface may have a greater dynamic interaction with adjacent osteoclasts than those simply involved in physiologic bone remodeling with complement activation by the implant surface which triggers osteoclast formation.[29]

Wound repair including bone repair following extraction has been extensively studied.[30,31] Upon tooth extraction, acute bleeding from the dental and periodontal ligament (PDL) vessels results in blood clot immediately filling the socket and is followed by an intense acute inflammatory response. Subsequently, the blood clot is replaced by richly vascular granulation tissue that contains the necessary cells to perform bone reconstruction of the space, akin to callus formation in bone fracture repair. Growth factors including epidermal growth factor, bone morphogenetic factors, fibroblast growth factor, platelet-derived growth factor, transforming growth factor beta, and insulin-like growth factor play important roles in this process.[30,32]

The unique situation with implants is that bone must heal against a titanium surface resulting in intimate bone-to-implant surface contact. This process results when a strict set of procedural rules is followed during implant placement and with the assumption that host factors promote a normal healing phase. After 5 years, the survival of dental implants in patients with osteoporosis does not differ significantly from that in age-matched persons without osteoporosis.[33-40]

Animal studies have highlighted the potential contribution of cell populations (including stem cells)[41] of the residual PDL to healing of an extraction wound.[42,43] Interestingly, the healing process may be altered in an estrogen-deficient mouse model.[44] Similar cell populations may contribute to osseointegration of implants placed immediately after extraction, but not of implants placed in healed edentulous sites.

Several events can modify this process, such as high-speed bone drilling to facilitate tooth removal and gross removal of bone during the extraction process. When high-speed drills are used on bone, heat is produced, and bone cells can be irreversibly damaged. A temperature threshold of 47 ^{o}C for <1 minute has been established as the protocol to prevent bone necrosis within the wounded bone.[45] Although bone temperature is not measured during implant site preparation, this original protocol is followed to minimize risk of bone injury and subsequent nonintegration or lost integration of the implant. Specifically, the bone drill rotates at relatively low speed (<1200 rpm) and site preparation is done with copious irrigation to maintain temperature less than 47 °C. There may be more or less ridge resorption via osteoclastic activity which can vary dramatically from site to site and host to host. Remodeling at the site continues indefinitely as in the rest of the skeleton.

A similar process of bone healing occurs with implant placement, ultimately leading to the phenomenon of osseointegration.[45] Consistent with the proper site preparation for placement, there is necessarily the intent to perform this surgical procedure with the least amount of trauma to the bone.[45] This may be more difficult to achieve in the dense bone of the atrophic anterior mandible.[46] The size of the final osteotomy is slightly smaller than the diameter of the threaded implant, thus enabling the implant to be seated in a self-threading fashion. The purpose of this is to achieve as intimate a bone-to-implant surface contact as possible and to allow for primary stability of the implant within the bone. This will lead to a minimization of granulation tissue formation in the intervening space between implant surface and bone socket and ultimate intimate contact between bone cells and the titanium oxide layer of the implant surface.[46] With good primary stability there is less likelihood of movement of the implant with function, thus leading to successful osseointegration of the implant.[45]

An additional difference between extraction socket and peri-implant bone healing is the soft tissue response. In both cases, a

Key Points

- Extraction healing and implant osteotomy healing appear to share similar mechanisms, although no direct clinical data comparing the 2 mechanisms exist.
- There is potentially decreased osteoclastic activity in implant osteotomy site healing compared with extraction healing due to strict drilling protocols. By strictly controlling the drilling, the attempt is to minimize the inflammatory healing response and thus the number of osteoclasts recruited to the surgical site. Therefore, there would be less osteoclasts to be susceptible to antiresorptive action.
- Potentially more cells are available for differentiation into bone repair cells in the extraction site due to the presence of PDL.
- Soft tissue healing at an extraction site vs around a dental implant is potentially different.

healthy underlying bone response enables the formation of a soft tissue barrier separating the intra bone (corporeal) area from the intra oral (extra corporeal) environment. It is well established how the healing process leads to formation of the soft tissue barrier for both the extraction site and that of the implant, although each is unique in its characteristics.[31,47] The former results in normal oral tissue over the now edentulous ridge, whereas during implant placement a specialized attachment of the gingival tissues to the implant surface forms.[47]

Do Antiresorptive Agents Interfere With the Integration of a Dental Implant (Short- and Long-Term Effects)?

Several risk factors have been associated with early and late implant failure in the absence of antiresorptive therapy as mentioned earlier in this paper.

The potential for antiresorptive medications to affect implant integration has been studied in animals. Early studies have focused on the effect of BP that were delivered locally or systemically. These studies have demonstrated higher rates of early osseointegration and a reduction in peri-implant bone resorption. Osteonecrosis was not reported. However, most of these studies involved extraoral sites (axial skeleton) and had no long-term data.[48,49] In a controlled study, Abtahi et al[48] analyzed the effect of local zoledronate-coated screw vs systemic delivery of alendronate (200 μg/kg; subcutaneously once daily for 14 days), on maxillary implant integration in a rat model. Necrosis was observed in all animals that received systemic BP but not with local administration.[48,50] Kim et al[49] explored the effect of systemically administered BP on implant integration in a controlled study where implants were placed into extraction sites in a rabbit model. Although there was good early integration (4 weeks), there was significant impairment of late integration with histologic evidence of necrosis in all animals that received BP.[51]

Although preclinical data suggest that antiresorptive therapy may influence implant integration, the clinical data are not as convincing. Several systematic reviews have highlighted the lack of randomized clinical trial data needed to establish a relationship between antiresorptive therapy and implant failure or implant-related osteonecrosis. Systematic reviews that explored the relationship between antiresorptive therapy and implant placement are conflicting. Granate-Marques et al[50] reported an elevated risk of implant-related MRONJ associated with long-term BP therapy (>3 years) and concomitant use of glucocorticoid therapy. On the other hand, other systematic reviews reported no such risk.[51,52]

Case reports and case series have reported implant failures in patients receiving antiresorptive medication prior to and after implant placement.[52-58] Goss et al[54] performed a dental specialist survey of MRONJ associated with implant placement in the state of South Australia, approximately 28 000 implants had been placed in 16 000 patients. Seven cases of implant-related necrosis were reported (0.89%), where in 4 of the 7 cases of necrosis occurred at sites where implants were placed prior to antiresorptive therapy. In a retrospective series, Lazarovici et al[56] identified 145 cases of MRONJ in which 27 (18.6%) were associated with implant placement. Eleven of the 27 cases (41%) were exposed to oral BP. Most of the implant-related MRONJ cases developed within 6 months of placement, but 4 cases were reported in which BP therapy was initiated well after implant placement. In a single institutional review of implant-related MRONJ, groups were segregated based on the timing of implant placement relative to the initiation of BP therapy. Necrosis occurred more rapidly when BP therapy was concurrent with or preceded implant placement.[59] In a multi-institutional case review, Pogrel and Ruggiero[58] analyzed the failure of 11 implants that were placed prior to antiresorptive therapy. All patients had been exposed to antiresorptive therapy (alendronate, zoledronate, or Dmab) for at least 2 years. However, the pattern of implant failure in all these cases was distinctly different from each other. The implants remained integrated into the necrotic bone as they were removed with the sequestrum with no involvement of the surrounding natural dentition. They hypothesized that the lack of a PDL at the bone implant interface may have created an area of increased strain, microfracture, and increased bone turnover that might be more susceptible to the actions of antiresorptive therapy. A similar pattern of implant-related necrosis was also reported in a clinical study by Giovannacci et al.[60]

A systematic review and meta-analysis commissioned as part of this consensus statement assessed this question: do antiresorptive therapies (BP and/or Dmab) increase the risk of dental implant failure in patients with osteoporosis?

Nine comparative observational studies were identified (Fig. 1) that could inform the risk of dental implant failure in patients taking antiresorptive therapy (BP and Dmab) for osteopenia or osteoporosis.[25] A random effects meta-analysis revealed a relative risk of 0.82 (95% CI: 0.52-1.28, $P = .38$, very low certainty) for dental implant failure at the patient level in patients with osteoporosis on antiresorptive therapy (Fig. 1). A post hoc sensitivity analysis at the level of the implant narrowed the CI, suggesting that BPs approximately halve the risk of implant failure (risk ratio [RR]: 0.53, 95% CI: 0.34-0.81, $P = .003$, very low certainty). A further post hoc sensitivity analysis, excluding 2 studies with a risk of failure an order of magnitude above the other studies (27% vs 2%), moved the risk estimate in favor of BP agents, but the estimate remained imprecise and nonsignificant.

In summary, antiresorptive therapy does not appear to be associated with increased rates of dental implant failure among patients with osteoporosis. However, the level of evidence is weak due to small studies with few events, large variation in risk estimates, high risk of bias, and the absence of controlled trials. Additionally, we are uncertain whether antiresorptives increase or reduce dental implant failure (Fig. 2).

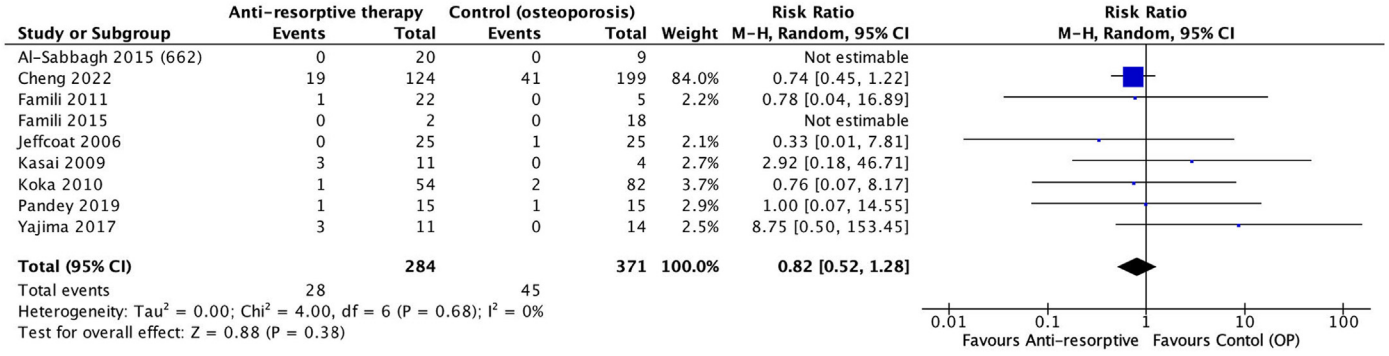

Fig. 1. Forest plot of dental implant failure (patient level). Random effects meta-analysis revealed a relative risk of 0.82 (95% CI: 0.52-1.28; $P = .38$, very low certainty) for dental implant failure in patients with osteoporosis on antiresorptive therapy.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		No exposure to antiresorptives	Exposure to antiresorptives		
Dental Implant Failure in patients with osteoporosis receiving dental implants	Relative risk: 0.82 (CI 95% 0.52 – 1.28) Based on data from 655 participants in 9 studies Follow up Variable	**121** per 1000	**99** per 1000 Difference: **22 fewer per 1000** (CI 95% 58 fewer – 34 more)	**Very low** Due to serious risk of bias[1] and serious imprecision[2]	We are uncertain whether antiresorptives increases or reduce dental implant failure.

Fig. 2. GRADE assessment of dental implant failure in patients on antiresorptive therapy for osteoporosis. [1]Risk of bias: serious. Risk of bias was deemed high in 7 of the 9 observational studies. [2]Imprecision: serious. CIs are very wide and include both markedly higher risk of dental implant failure and half the risk of implant failure. *GRADE* = Grading of Recommendations Assessment, Development and Evaluation; *RR* = risk ratio.

Key Points

- Animal studies suggest there is potential benefit for implant integration enhancement in the presence of antiresorptive therapies.
- Individual case reports and case series that report MRONJ in patients with dental implants receiving osteoporosis doses of antiresorptives have been published. High-quality data in the form of randomized clinical trials are lacking.
- Evidence in the form of systematic reviews to establish a relationship between implant survival and antiresorptive therapies is limited and inconsistent.

Does the Duration of Antiresorptive Therapy Affect the Risk of MRONJ Following Placement of Dental Implants?

The aforementioned systematic review associated with this consensus identified 11 case series[25,54,56,57,60-68] (Table 1). The average duration of antiresorptive therapy for patients with osteoporosis prior to MRONJ development around dental implants is similar among all 11 studies and is reported to be from 3.9 to 5.7 years with an average of 4.8 years. The range of antiresorptive therapy was quite extensive spanning from 3 months to 10 years. The long-term extension of the Dmab FREEDOM trial, a 3-year randomized controlled trial with a 7-year extension, identified one case of MRONJ associated with dental implantation.[69] A claims database study from South Korea in patients aged >70 years by Ryu et al[57] in 2021 identified 41 cases of MRONJ but did not provide or analyze duration of therapy with BP. Given that the prospective trials either had single event or did not report duration of therapy, and otherwise only case series were available in the literature, no risk ratios can be calculated for the disease in relation to the duration of antiresorptive therapy.

Key Points

- The average duration of antiresorptive therapy prior to the development of MRONJ around implants is approximately 5 years. However, the duration of therapy is highly variable (3-120 months).

Which Additional Risk Factors Impact Implant Failure due to MRONJ?

There are numerous risk factors, lifestyle factors, and medications described, which may on their own or in conjunction with antiresorptive therapy contribute to the risk of MRONJ. These include diabetes mellitus, osteoporosis, rheumatoid arthritis, malignancy, peptic ulcer disease, smoking, poor oral hygiene, infection, inflammatory dental disease, use of corticosteroids, proton pump inhibitor, and conditions associated with immune suppression. There is scant literature regarding the effect of conditions and medications on the risk of MRONJ in patients with dental implants.

In a recent single-center observational study addressing the risk of MRONJ in patients with osteoporosis in a real-world setting, smoking, glucocorticoid therapy, type 2 diabetes, and rheumatoid arthritis were identified risk factors.[70]

A recent meta-analysis of 10 eligible studies involving 1071 subjects investigated dental implant survival in patients with normal or low bone mineral density (BMD). Overall, this showed no difference on implant survival for up to 5 years ($P > .05$) in patients with low and normal BMD.[37] The quality of evidence is very poor based on the designs of the studies included, marked heterogeneity in results between studies as well as wide confidence interval. In some studies, modified implant surgical procedures such as stepped osteotomy, lateral bone condensation, and modified implant design were used to avoid the risk of MRONJ. No data were presented on the influence of comorbidities, concomitant medications, or antiresorptive therapies on implant failure or MRONJ. Some but not all studies excluded patients on BP or with concerning comorbidities. The rate of implant failure in most studies was low and precluded analysis by comorbid disease subgroups.

Another meta-analysis involving 8859 patients with 29,798 implants[35] showed no difference on implant survival rate in patients with or without osteoporosis, both at the patient level (RR: 0.98; 95% CI: 0.50-1.89; $P = .94$) and at the implant level (RR: 1.39; 95% CI: 0.93-2.08; $P = .11$). Overall, implant failure rate at the implant level in patients with osteoporosis was 4.7% vs 3.5% in the control group, and implant failure at the patient level in patients with osteoporosis was 5.8% vs 4.9% in the control group. In this analysis, greater peri-implant bone loss was associated with low bone density (0.18 mm, 95% CI: 0.05-0.30; $P = .005$). In one of the studies included in this analysis, individuals with osteoporosis who smoke or have Crohn's disease experienced a higher implant failure rate, reaching 13%.[71] Implant length and diameter were also associated with implant failure.[71]

Our accompanying systematic review identified a national cohort study from South Korea involving 44 900 patients with

Table 1
Antiresorptive Therapy in Patients with Osteoporosis Receiving Implants

Citation	Patient (n)	AR (y)	Range (mo)	Patients on ARs prior implant placement (n)	Patients on ARs after implant placement (n)	Surgical placement related (n)	MRONJ after implant loading (n)	Maxilla	Mandible
Goss et al[54]	7	4.9	3-120	3	4	3	4	2	5
Lazarovici et al[56]	11	5.7	18-111	9	1	7	4	NR	NR
Jacobsen et al[62]	5	4.2	NR	NR	NR	0	5	1	4
López-Cedrún et al[64]	9	5	6-120	NR	NR	3	6	1	8
Holzinger et al[61]	3	4.6	12-32	2	1	1	2	NR	NR
Kwon et al[63]	18	4.3	12-120	15	3	3	15	8	10
Tam et al[66]	4	3.9	18-72	3	1	3	1	2	2
Giovannacci et al[60]	6	6	36-108	5	1	5	1	2	4
Pichardo et al[65]	11	5	18-168	NR	NR	4	7	3	8
Troeltzsch et al[67]	5	3	NR	NR	NR	NR	NR	NR	NR
Tempesta et al[68]	19	2	27	NR	NR	NR	NR	13	24
Total	98	4.4	3-120	37	11	29	45	32	65

Abbreviations: AR = antiresorptive; MRONJ = medication-related osteonecrosis of the jaw; NR = not reported.
The table presents the citations of 11 case series describing the duration of antiresorptive therapy use and the incidence of MRONJ in association with dental implants.

osteoporosis aged >70 years between 2014 and 2016.[57] This propensity score-matched analysis suggests that antiresorptive therapy, specifically BP, may increase the risk of MRONJ in older patients (adjusted hazard ratio [HR]: 4.09; 95% CI: 2.75-6.09). The study also included patients who underwent dental implantation and developed MRONJ (n = 41/9738, 0.42%, $P < .01$).[57]

Oral surgical procedures, when performed transorally, are considered clean-contaminated surgery. This includes the placement of dental implants. There is extensive literature on whether antibiotic prophylaxis is required or not to minimize infection and/or complication rates of implant placement.[72-74] There is an ongoing debate on this issue, with concerns regarding the emergence of antibiotic resistance weighed against the potentially limited benefits of antibiotic prophylaxis.[70] If one chooses to use antibiotics prophylactically, then a preoperative dose is likely better than a 7-day postoperative course of treatment.[74] For clinicians opting to use antibiotics a typical regimen would be amoxicillin 2 g or clindamycin 300 to 600 mg orally at 30 to 60 minutes preoperatively.

Key Points

- Risk factors including diabetes mellitus, rheumatoid arthritis, malignancy, peptic ulcer disease, glucocorticoid use, smoking history, proton pump inhibitor use, poor oral hygiene, infection, and inflammatory dental disease have been associated with an increased risk of implant failure due to MRONJ.
- There is no difference in implant survival in patients with or without osteoporosis.

What Local Factors Affect the risk of MRONJ Following Dental Implant Placement?

The 11 case series of Table 1 were reviewed.[54,56,60-66] In addition, 3 case series by Pogrel and Ruggiero,[58] by Escobedo et al,[75] and by Park et al[76] focusing on MRONJ around loaded and functioning dental implants were considered. Pogrel and Ruggiero[58] reported on 8 patients on osteoporotic and 3 patients on oncologic antiresorptive doses without separating between them. The agents used were alendronate in 8 cases, zoledronate in 1 case, and Dmab in 2 cases.[58] Four patients on osteoporosis antiresorptive doses were included in the Escobedo et al[75] and Park et al[76] studies.

MRONJ around dental implants can occur at the initial surgical phase of implant placement or develop long after dental implants have been loaded and functional. Indeed, MRONJ occasionally occurred during the surgical placement of the implants (0-6 months after implant placement in all papers except in Giovannacci et al[60] where this period was defined as (0-10 months) in 28 of 73 patients (38%) or after the implant was loaded in 45 of 73 patients (62%).

In most cases of patients treated with osteoporosis doses, dental implants were placed after initiation of the antiresorptive therapy. However, development of MRONJ around well-osseointegrated and functioning dental implants has been reported in patients who initiated antiresorptive therapy after implant placement. Of 48 patients, 37 (77%) were on antiresorptive treatment at the time of the implant placement, whereas in 11 of 48 patients (23%) antiresorptive treatment commenced after implant placement.

Finally, MRONJ incidence is associated with dental implant location. A total of 65 of 97 implants (67%) were placed in the mandible, whereas 32 of 97 implants (33%) were placed in the maxilla (Table 1). When focusing on MRONJ developed around functioning implants, 16 of 19 implants (84%) were placed in the mandible and 3 of 19 implants (16%) were placed in the maxilla.[58,75,76] For both jaws, implants were more often located in the posterior sextants. MRONJ is more commonly located in the mandible also in individuals who have not been subjected to dental implant placement, as reported in guideline papers.[1]

No data on oral hygiene or presence of dental disease are described. For the patients who developed MRONJ during the healing period after surgical placement, most probably MRONJ was related to the surgical trauma. For the patients who developed MRONJ after implant loading, the instigating local factors are not clear. Implant loading refers to that point in time when the final prosthesis is attached and under masticatory and occlusal function. Pogrel and Ruggiero[58] described the sequestration of the peri-implant bone and exteriorization of the dental implant with the associated necrotic bone firmly adherent to the implant. This finding does not follow the typical appearance of peri-implantitis, which typically presents with circumferential peri-implant inflammation and bone loss, usually at the crestal aspect of the implant. The authors concluded that MRONJ developing around functional implants does not appear to represent a localized form of

peri-implantitis. Here, we should note that dental inflammation has been associated with MRONJ presence,[1] and as such appropriate measures to decrease peri-implant disease should be taken in all patients, including patients with osteoporosis on antiresorptive therapy. Placement of implants and prosthetic rehabilitation should be designed to allow proper oral hygiene for plaque removal by the patient and effective implant care and surveillance by the dental professional.[77]

Key Points

- MRONJ, which can occur at the initial surgical phase of implant placement or around osseointegrated functional dental implants, has been reported most often in patients already on antiresorptive therapy; however, it has also been reported around dental implants placed before the commencement of antiresorptive therapy.
- The mandible is the most common site for MRONJ development around dental implants in patients on osteoporotic antiresorptive doses.

Are There Differences Between Antiresorptive Agents and the Risk of MRONJ Post Dental Implant?

Implant failure and the risk of MRONJ have been evaluated with the use of BP and Dmab.[75] There are case reports describing the development of MRONJ with BP as well as raloxifene use.[78-81] Current literature consists mostly of case series and is of limited quality.[54,56,58,60-64,66,75,82]

In a recent retrospective cohort study involving 944 801 patients with osteoporosis of whom 38 230 had dental implants, the risk of MRONJ following dental implant was relatively lower than that following tooth extraction with HR of 0.51 (0.36-0.71) and 5.63 (3.55-8.92), respectively.[57] After propensity score matching, of 22 450 patients with dental implants, 52 (0.23%) developed MRONJ, whereas 100 of 22 450 (0.45%) had MRONJ without dental implants.[57] In another retrospective chart review and phone interview study, BP users and non-BP users had relatively similar cumulative implant survival rate 99.17% and 98.19%, respectively.[83]

Key Point

- There are no head-to-head data comparing the effect of BP to Dmab on implant failure or the development of MRONJ.

What Are the Risks and Benefits of Stopping Antiresorptive Therapy Prior to Implant Placement?

A systematic review by Mendes et al[84] suggests that patients who underwent surgical trauma during the installation of dental implants may be more susceptible to MRONJ. A preexisting implant prior the initiation of antiresorptive therapy appeared to be of greater risk for the development of MRONJ than having a new implant surgically placed as the loading period with prolonged exposure to antiresorptive therapy appears to be greater in the former group.[75] A case series and literature review conducted by Escobedo et al[75] examined patients undergoing antiresorptive therapy who developed MRONJ. They categorized them into 2 groups: the "implant presence-triggered MRONJ group," which included 74 cases of individuals developing MRONJ between 1 and 15 years after implant placement, and the "implant surgery-triggered MRONJ group," which consists of 27 cases where MRONJ occurred immediately after implant placement (within 2-10 months). The study reported a significantly higher number of MRONJ cases in the implant presence-triggered MRONJ group compared with the implant surgery-triggered MRONJ group.[75] It was hypothesized that the use of antiresorptive medications causes MRONJ in patients with implants that are subjected to functional loading, and this occurs at a higher frequency than what is observed after implant placement surgery.[75] Watts et al[69] reported that the Dmab exposure-adjusted MRONJ rate in FREEDOM Extension was 5.2 per 10 000 person-years in postmenopausal women with osteoporosis. Out of 212 cases who underwent dental implants in the trial, 1 case developed MRONJ related to delayed osseointegration.[69] We lack adequate clinical trials to demonstrate that stopping antiresorptive therapy prior to implant placement decreases the risk of MRONJ in patients who underwent this therapy. BPs remain in the skeleton and continue to act for months or even years after their discontinuation; therefore, there seems to be no advantage on discontinuing them for a short period before implant installation. Flichy-Fernández et al[85] reported MRONJ occurrence in a patient after 6 months of BP discontinuation prior to dental implant placement.

In a multicenter retrospective study, Hasegawa et al[86,87] demonstrated no advantage of BP discontinuation on the prevention of MRONJ in either osteoporosis or oncology patients whose teeth were extracted. Concerns regarding MRONJ are frequently raised in clinical practice and contribute to the magnitude of the "treatment gap" after a fragility fracture. In a recent questionnaire-based survey from Japan, about 16% of patients treated for osteoporosis completely stop their BP as advised by their treating dentists.[88,89] Additionally, an increased risk of osteoporotic fractures was observed, in a study from Japan, during drug discontinuation.[88,89] Cessation of Dmab has been associated with a rebound osteoclastogenesis, decreases in BMD, and an increased risk of fracture, most notably multiple vertebral fractures[90-93] and mainly in patients with prevalent vertebral fracture.[94] Dental professionals should avoid recommending interruption of Dmab therapy. According to a recent review by the European Calcified Tissue Society, dental procedures should be performed 5 to 6 months following the last Dmab injection, when the effects of Dmab on bone turnover are depleted.[95]

In summary, at this time, there does not appear to be any benefit from stopping antiresorptive therapy in patients with osteoporosis prior to implant placement. Implants may be safely placed in the presence of concomitant use of BP or Dmab in patients with osteoporosis with no evidence of an increased risk of implant failure/compromise.

Key Points

- There is no evidence to support interruption of antiresorptive therapy in patients with osteoporosis prior to or after implant surgery.
- Cessation of Dmab is not advised as it has been associated with rebound bone loss and increased risk of multiple vertebral fractures.

Is There Any Value in Using an Anabolic Agent, in Patients With a History of Long-Term Antiresorptive Treatment, Prior to or Following Implant Placement?

There are no published data on the use of anabolic therapy prior to implant placement in patients who have been on long-term antiresorptive therapy. Therefore, the use of this group of agents in preventing MRONJ in these patients remains to be explored. Two publications reported a case where teriparatide was used for treating MRONJ that developed after a dental implant[96,97] and in both, the authors suggest a positive effect of the treatment. Another case report describes a patient who was switched from alendronate to teriparatide during the treatment of an implant associated MRONJ. The patient had received prior treatment with alendronate for more than 10 years, but no clear benefit from this treatment switch is reported.[98]

One open-label feasibility study analyzed the osseointegration of titanium implants in a series of 24 patients treated with either teriparatide or placebo for 28 days and performed histomorphometry afterward. Osseointegration was reported to be improved in the active-treatment arm.[99]

Key Point

- There are no published data on the use of anabolic therapy prior to or following implant placement in patients on prior long-term use of antiresorptive therapy.

Is There an Optimal Time for Implant Placement Following or Prior to Administration of an Antiresorptive Agent?

At present, there is no research addressing the optimal time for implant placement in relation to antiresorptive administration in patients with osteoporosis. The most common treatment for osteoporosis management is oral BP therapy.[100] The risk of developing MRONJ from oral BP therapy is presumed to be very low.[2,3] The risk of MRONJ from dental implant therapy for patients on oral BP therapy is low, and the osseointegration failure rate has been found to be essentially the same as that for nonusers of oral BP.[52,55] A thorough systematic review was conducted by Stavropoulos et al[52] looking at the effect of antiresorptive drugs on implant therapy. The majority of studies involved oral BP, and there was no demonstrated difference in implant success rate from that seen in the general population. In 71% of patients who developed MRONJ related to dental implants, MRONJ occurred at 3 years or longer after dental implant placement.[52] Walter et al[101] performed a systematic review looking at MRONJ in patients with osteoporosis who had received implant therapy, no cases were found. Although Guazzo et al[102] noted a lack of high-quality studies on this subject, they suggest that it is important to be aware of the possible risks related to the development of MRONJ and implant failure in this patient group.

Interestingly, observations in humans and animals suggest that BPs accumulate in areas of alveolar bone with high turnover including sites of tooth extraction or periodontal or periapical disease.[103-105] It is reasonable to hypothesize that increased levels of BP would also accumulate around sites of active healing during implant osseointegration. Bagan et al[106] have presented 10 cases of MRONJ that developed in patients relatively soon after they were switched from BP to Dmab. Only one case underwent implant placement as an inciting event.

With respect to the use of IV zoledronate, a study in rats demonstrated a beneficial effect on early bone-to-implant surface area contact and therefore enhanced osseointegration with the use of zoledronate.[107] In humans there is no good evidence for or against implant placement in patients on once yearly zoledronate for osteoporosis. One case series demonstrated MRONJ development after zoledronate once yearly for osteoporosis.[108] Interestingly, all 8 of these patients had undergone long-term oral BP therapy prior to institution of IV zoledronate. However, in none of them was implant placement the triggering event. As with the earlier discussion on relatively rapid development of MRONJ in patients switched from BP to Dmab, there was a similar finding here. Otherwise, the literature on this specific question seems to be restricted to case reports.[109]

Key Points

- Although risk of MRONJ may increase with implant placement in individuals on long-term antiresorptive therapy for osteoporosis, there is no significant difference from controls in dental implant survival rate in patients with osteoporosis receiving antiresorptive therapy.
- There is no evidence to support interruption of antiresorptive therapy or suggest optimal timing recommendations with regard to medication administration and implant placement.

Do Patients With Dental Implants on Antiresorptive Therapy for Osteoporosis Require Additional Monitoring?

Data in the form of randomized clinical trials are not available to adequately address this question. Dental implant failure and development of MRONJ has been observed in patients who take either low doses or high doses of antiresorptive therapy.[110] However, in a retrospective case series, implant failure and MRONJ at the implant site have been observed.[60] In Lazarovici et al[56]'s series of 27 implant patients who developed MRONJ, 11 of them were taking oral BP. Among this group, 77.8% experienced spontaneous necrosis as a late complication, with an average onset occurring at 16.2 months.[56] Four of those cases had implants placed 2 to 10 years prior to the initiation of BP therapy. Similarly, Pogrel and Ruggiero[58] reported late implant failures in 11 patients who were associated with local bone necrosis and sequestrum formation. In majority of the cases, including 8 on oral BP and 1 on IV zoledronate, the implant restorations had been successful and functional for years prior to initiating antiresorptive therapy.[58] Systematic reviews aimed at this topic are limited due to inherent bias and the lack of randomized controlled trials and overall, the literature focused on this topic is not robust. Many existing publications that discuss dental implant outcomes in patients taking antiresorptives differentiate poorly between patients taking osteoporosis doses and patients taking high doses as part of cancer treatment. Among those that differentiate well, it is most often stated that adverse findings are less frequent in patients taking osteoporosis doses than in patients taking “high” doses for cancer. It would be highly beneficial for both the osteoporosis and oncology fields if future papers on this topic clearly distinguish dental implant outcomes in patients taking osteoporosis doses of antiresorptives from those receiving higher doses used in cancer therapy.

Key Points

- Long-term implant surveillance that provides robust 10+ year dental implant survival rate data in patients with osteoporosis who are treated with antiresorptives is needed.
- Evidence in the form of case series documents the occurrence of dental implant failure in patients receiving long-term antiresorptive therapy for osteoporosis. A systematic review found that dental implant survival in patients receiving long-term antiresorptive therapy for osteoporosis for approximately 5 years did not differ from that in controls.
- Additional data on 10+ year dental implant survival rate in patients receiving antiresorptive therapy for osteoporosis are needed to adequately resolve this question.
- Short- and long-term implant maintenance strategies should be performed according to published guidelines (Table 2).

This Paper Has Been Endorsed by the Following Societies:

- American Society of Bone and Mineral Research
- American Association of Oral and Maxillofacial Surgeons
- Canadian Association of Oral and Maxillofacial Surgeons
- Canadian Academy of Oral and Maxillofacial Pathology and Oral Medicine
- European Calcified Tissue Society
- International Osteoporosis Foundation

Future Areas for Research

1. Are there any differences in implant survival between existing or “prevalent” implants and implants in patients receiving antiresorptive treatment (“incident” implants) in developing MRONJ or implant failure?
2. Does anabolic therapy improve implant survival in patients on antiresorptive therapy?

Table 2
Summary of Key Points

Questions	Key Points
1. Are there differences in bone healing postimplant vs postdental extraction**?**	• Potentially more cells are available for differentiation into bone repair cells in the extraction site due to the presence of periodontal ligament. • Soft tissue healing at an extraction site vs around a dental implant is potentially different.
2. Do antiresorptive agents interfere with the integration of a dental implant (short- and long-term effects)?	• Animal studies suggest there is potential benefit for implant integration enhancement in the presence of antiresorptive therapies. • Individual case reports and case series that report MRONJ in patients with dental implants receiving osteoporosis doses of antiresorptives have been published. • High-quality data in the form of randomized clinical trials are lacking. • Evidence in the form of systematic reviews to establish a relationship between implant survival and antiresorptive therapies is limited and inconsistent.
3. Does the duration of antiresorptive therapy affect the risk of MRONJ following placement of dental implants?	• The average duration of antiresorptive therapy prior to the development of MRONJ around implants is approximately 5 y. However, the duration of therapy is highly variable (3-120 mo). • Currently, there are no data to address this question.
4. Which additional risk factors impact implant failure due to MRONJ?	• Risk factors including diabetes mellitus, rheumatic disease, malignancy, peptic ulcer disease, glucocorticoid use, smoking history, proton pump inhibitor (PPI) use, poor oral hygiene, infection, and inflammatory dental disease have been associated with an increased risk of implant failure due to MRONJ. • There is no difference in implant survival in patients with or without osteoporosis.
5. What local factors affect the risk of MRONJ following dental implant placement?	• MRONJ, which can occur at the initial surgical phase of implant placement or around osseointegrated functional dental implants, has been reported most often in patients already on antiresorptive therapy; however, it has also been reported around dental implants placed before the commencement of antiresorptive therapy. • The mandible is the most common site for MRONJ development around dental implants in patients on osteoporotic antiresorptive doses.
6. Are there differences between antiresorptive agents and the risk of MRONJ postdental implant?	There are no head-to-head data comparing the effect of bisphosphonates with denosumab on implant failure or the development of MRONJ.
7. What are the risks and benefits of stopping antiresorptive therapy prior to implant placement?	• There is no evidence to support interruption of antiresorptive therapy in patients with osteoporosis prior to or after implant surgery. • Cessation of denosumab is not advised as it has been associated with rebound bone loss and increased risk of multiple vertebral fractures.
8. Is there any value in using an anabolic agent, in patients with a history of long- term antiresorptive treatment, prior to or following implant placement?	There are no published data on the use of anabolic therapy prior to or following implant placement in patients on prior long-term use of antiresorptive therapy.
9. Is there an optimal time for implant placement following or prior to administration of an antiresorptive agent?	• Although risk of MRONJ may increase with implant placement in individuals on long-term antiresorptive therapy for osteoporosis, there is no significant difference from controls in dental implant survival rate in patients with osteoporosis receiving antiresorptive therapy. • There is no evidence to support interruption of antiresorptive therapy or suggest optimal timing recommendations with regard to medication administration and implant placement.
10. Do patients with dental implants on antiresorptive therapy for osteoporosis require additional monitoring?	• Long-term implant surveillance studies (10+ y) are needed to assess dental implant survival in patients with osteoporosis on antiresorptive therapy. • A systematic review found no difference in 5-y implant survival rates between patients on long-term antiresorptives and controls. • Data from case series documents the occurrence of dental implant failure in patients receiving long-term antiresorptive therapy for osteoporosis. • Implant maintenance should follow established guidelines for both short- and long-term care.

Abbreviation: MRONJ = medication-related osteonecrosis of the jaw.
The table summarizes the key answers to the 10 questions outlined by the MRONJ Task Force.

3. Need to develop an animal model focusing on implant osseointegration in the context of antiresorptive therapy use with consideration of using human doses of antiresorptives.
4. Are there any benefits from delaying the implant placement or loading?

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Author Contributions

D.S.A., A.A.K., A.M., and S.T. are shared first authors and have contributed equally to the development and finalization of the manuscript. A.A.K., A.M., S.T., and S.L.R.: design/conceptualization of the project. D.S.A., R.D.M., M.E.R., A.A.K., A.M., S.T., G.G., and S.L.R.: data acquisition, review, analysis, methodology. A.A.K., A.M., S.T., and S.L.R.: project Administration, including acquisition of funding. D.S.A., A.A.K., A.M., S.T., and S.L.R.: original drafting and preparation of the manuscript. D.S.A., A.A.K., A.M., S.T., R.D.M., M.E.R., B.A., T.L.A., H.A.A., R.A., A.D.A., M.B., J.J.B., M.L.B., R.B.P., J.P.B., A.M.C., J.C., C.C., A.D.P., S.L.F., G.G., D.H., N.C.H., R.G.J., D.L.K., S.K.H., S.K., B.L.L., C.M., B.K.M., S.L.M., S.N.M., N.N., B.O.P., A.P., J.P., E.P., D.D.P., R.R., D.P.S., C.M.S., R.S., A.T., S.T., N.B.W., J.Z., M.C.Z., and S.L.R.: review/editing of the manuscript.

Data Availability Statement

The data that support the findings in this study are openly available in PubMed, EMBASE, and the Cochrane databases.

Ethical Statement

These papers are retrospective reviews and did not require ethics committee approval.

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