# Success Rate and Safety of Dental Implantology in Patients Treated With Antiresorptive Medication: A Systematic Review

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There is no agreement of data on the subject of implant failure and the development of osteonecrosis in patients receiving antiresorptive agents. The purpose of this systematic review is to evaluate whether dental implants placed in patients on antiresorptive medication have an increased failure rate and whether the implant placement or the implant existence are risk factors for developing medication-related osteonecrosis of the jaw (MRONJ). An electronic search was conducted in PubMed/Medline, and all publications fulfilling the inclusion criteria were included. The search was completed by a hand research of the references cited in all electronic identified publications, resulting in 411 articles. Based on the inclusion criteria, 32 studies were included, with a total of 5221 patients, 12 751 implants, 618 cases of implants loss, and 136 cases of MRONJ analyzed. Because of the small number of studies, most of which were characterized by a low level of quality, it cannot be established that the use of antiresorptive medication affects dental implant survival rates. The risk of MRONJ as an early or late complication is also not well established. Therefore, successful dental implant procedures in patients receiving antiresorptive medication might be possible, but more studies need to be carried out in the future to verify this topic. Apart from intravenous antiresorptive drugs, which remain an absolute contraindication, the use of antiresorptive medication is not a contraindication to dental implantology, but it must be accompanied by careful treatment planning, informing patients about possible complications, and essential long follow-up periods.

***Key Words: antiresorptive medication, dental implant success, medication-related osteonecrosis of the jaw, systematic review***



## INTRODUCTION

There is a wide range of diseases in which the balance of bone resorption and bone formation is disturbed, such as osteoporosis, Paget disease, metastatic bone disease, multiple myeloma, and rheumatoid arthritis. The quality of life of the population affected by these conditions can be low, and therefore antiresorptive drugs have been developed to reduce pain and bone loss associated with these diseases.[1] The most common antiresorptive drugs are bisphosphonates (BPs) and denosumab.

Bisphosphonates are pyrophosphate analogues.[2] They are very strong inhibitors of osteoclastic activity, suppress bone turnover, and have antiangiogenic properties.[3] Their pharmacologic effects on the bone assign them a significant role on skeletal disorders, characterized by bone-remodeling rates out of balance. The route of administration is either oral or intravenous (IV), which affects the skeletal uptake of the medication. Oral BPs are absorbed by the intestine, with less than 1% bioavailability because of their hydrophilicity, whereas IV BPs are entirely bioavailable.[4] The IV BPs are used to manage cancer-related conditions, such as hypercalcemia of malignancy; to treat skeletal-related events associated with bone metastases in the context of solid tumors such as breast, prostate, and lung cancer; and to manage lytic lesions in the setting of multiple myeloma.[5] Oral BPs are most commonly used for osteopenia and osteoporosis.[6] They are also used in rarer conditions such as Paget disease and osteogenesis imperfecta.[7,8] Because of their high affinity for $Ca^{2+}$ ions, BPs create a strong bond to the bone hydroxyapatite. They accumulate in areas with exposed hydroxyapatite, where bone is formed and resorbed, such as in the jawbones, which have a very high bone-remodeling rate. These are areas with high osteoclastic activity. Because of the bone resorption process promoted by osteoclasts in these areas, BPs dissociate from the bone surface and enter into osteoclasts by fluid phase endocytosis.[9–12] Two groups of BPs are available, with different mechanisms of action once inside osteoclasts. First-generation non–nitrogen-containing BPs such as clodronate, etidronate, and tiludronate bind to molecules of newly formed adenosine triphosphate (ATP). They inhibit multiple ATP-dependent cellular processes, leading to osteoclast apoptosis. Second- and third-generation BPs, such as alendronate, risedronate, pamidronate, ibandronate, and zoledronic acid, contain nitrogen in their side chains and adhere tighter to hydroxyapatite.

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They bind to farnesyl pyrophosphate synthase, a key regulatory enzyme in the mevalonic acid pathway important for the production of cholesterol; other sterols; and isoprenoid lipids, inhibiting their activity and eventually leading to osteoclast apoptosis.[13] The relatively long skeletal half-life of BPs is responsible for their prolonged presence in mineralized bone, in which they remain buried for years.[14,15] This is an important fact to consider, as there are studies associating prolonged BP exposure with an increased risk of atypical femur fractures, but so far, the reduction of typical osteoporotic fractures in patients with high fracture risk due to BP medication outweighs this risk.[16,17] Because of their hydrophilicity, oral BPs have been linked to esophageal irritation and esophageal ulceration, as they bind to the gastrointestinal mucosa and replace hydrophobic and acid-resistant phospholipids involved in the mucosal barrier mechanism,[18,19] especially if they are administrated concomitantly with antithrombotic agents and nonsteroidal anti-inflammatory drugs.[20]

Denosumab is a fully humanized antibody that inhibits osteoclast function, reduces bone resorption, and increases bone density. More precisely, its mechanism of action causes the inhibition of receptor activator of nuclear factor-kappa B ligand.[21–23] Denosumab is widely used for the prevention of fractures in postmenopausal women with osteoporosis and for the treatment of bone metastases[24,25] and is administrated subcutaneously. In contrast to BPs, denosumab does not bind to the bone and is thought to be cleared from the bloodstream through the reticuloendothelial system with a half-life time of approximately 26 days.[26] Osteoclastic activity is suppressed while denosumab is in the circulation, but the effect is reversed when the drug is cleared from it.[27] Denosumab has been shown to have equal or greater capacity to suppress bone turnover than BPs.[28,29] However, discontinuation of denosumab has been linked to an increased risk of multiple vertebral fractures.[30–32] Its discontinuation may result in a rebound response of bone turnover markers, and although strong evidence for such an effect is lacking, a treatment break of denosumab should not be advised without considering follow-up treatment with an alternative antiresorptive medication, in order to prevent this complication.[33,34]

A therapy option for perversion of osteoporosis is hormone therapy with estrogen, as estrogen deficiency is the major cause in the pathogenesis of osteoporosis.[35] Hormone therapy has shown to be effective in reducing fractures in postmenopausal women,[36] with efficacy similar to that of BPs.[37,38] However, the American College of Physicians (ACP) does not support this therapy, stating that it may be associated with an increased risk of venous thromboembolic cerebrovascular events and invasive breast cancer.[39] Selective estrogen receptor modulators, a class of nonsteroidal compounds that interact with estrogen receptors, are antiresorptive agents with a moderate effect on bone mineral density, but the risk of thromboembolic events remains a concern for most of them and they are therefore not widely used.[40,41] Strontium ranelate, a drug that both increases bone formation and reduces bone resorption,[42,43] has a very limited use because of an increased risk of cardiac events, including myocardial infarction.[44] Calcitonin, a calciotropic hormone that primarily inhibits bone resorption by decreasing the number and activity of osteoclasts, is no longer widely used for osteoporosis treatment either.[39,45]

A well-known and one of the most serious local side effects of BPs is BP-related osteonecrosis of the jaw (BRONJ), first mentioned in 2003.[46] However, the number of osteonecrosis cases in patients associated with other antiresorptive and antiangiogenic therapies, such as denosumab, bevacizumab, and sunitinib has grown quickly.[25,47–50] In 2014, the term *medication-related osteonecrosis of the jaw* (MRONJ) was introduced by the American Association of Oral and Maxillofacial Surgeons (AAOMS). The condition is characterized by exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks, current or previous treatment with antiresorptive or antiangiogenic agents, and no history of radiation therapy to the jaws or metastatic disease to the jaws.[5] The first cases of BRONJ were associated with tooth extraction and other conditions that increase the demand for bone turnover.[46] Dentoalveolar surgical procedures and especially tooth extraction are a major risk factor for developing MRONJ.[5] There are studies showing that tooth extraction was the predisposing event for 52%–61% of patients with developed osteonecrosis.[51–53] Mavrokokki et al[54] found that tooth extraction was the predisposing event in 73% of the cases included in their study, and Badros et al[55] found that 47% of the patients with established osteonecrosis had a dental extraction beforehand.

There is no agreement of data on the subject of implant failure and the development of osteonecrosis in patients receiving antiresorptive agents, and because of that, the American Association of Oral and Maxillofacial Surgeons (AAOMS) considers the risk of developing osteonecrosis after dental implant placement to be similar to that of the risk after tooth extraction. Implant therapy is considered a contraindication in patients with oncologic doses of IV antiresorptive drugs, because of the high rate of developing MRONJ, and oral BPs are considered safer.[5] However, there are documented cases of BRONJ in osteoporotic patients.[56,57] The success rates of implant placement, even in patients with oral BPs, report opposing results.[58–61] Furthermore, there are studies that associate the existence of already osseointegrated dental implants with MRONJ, suggesting that, not only is the implant placement a surgical act but also other peri-implant factors could be linked to osteonecrosis, such us micro-cracks or peri-implantitis and could lead to later implant failure.[62–66]

The aim of this study is to conduct a systematic review to evaluate the success rate of dental implants in patients on antiresorptive therapy, the risk of developing MRONJ, and the possibility that already osseointegrated implants could be affected by antiresorptive therapy.

## Materials and Methods

### *Search strategies*

The PubMed (Medline) database of the United States National Library of Medicine was used for a literature search of articles, and no limitation on the publication date was imposed. The term "dental implant" was used in combination with the

following search terms: "bisphosphonates," "denosumab," "antiresorptive agents," "antiresorptive therapy," "antiresorptive drugs," "antiresorptive medication," "osteonecrosis of the jaw," "bisphosphonate related osteonecrosis of the jaw," and "medication related osteonecrosis of the jaw." The search was completed with a review of the references of the selected articles to identify additional studies not found in the initial search.

### *Inclusion criteria*

The inclusion criteria were as follows:

- Studies including patients with a history of medication with antiresorptive agents and at least 1 dental implant before, during, or after their treatment
- Prospective studies (randomized controlled, nonrandomized controlled, cohort)
- Retrospective studies (controlled, case control, single cohort)
- Case series with more than 5 cases

### *Exclusion criteria*

The following were the exclusion criteria:

- Articles published in a language other than English
- In vitro or animal studies
- Systematic reviews and literature reviews
- Case series with fewer than 5 patients and case reports
- Studies with subjects who had osteonecrosis of the jaw secondary to radiation therapy
- Studies including patients receiving dental implants while under menopausal hormone therapy for the treatment of osteoporosis
- Studies referring to the topical administration of BPs
- Letters to the editor and commentaries

Studies that evaluated dental implant outcomes in patients under hormone therapy were excluded. The American Association of Clinical Endocrinologists and American College of Endocrinology,[67] North American Menopause Society,[68] Endocrine Society,[69] and American College of Rheumatology[70] provide popular clinical guidelines for the treatment of osteoporosis, and none of them considers hormone therapy as a front-line therapy for osteoporosis, whereas the ACP[39] specifically recommends against its use. Therefore, clinical interest in dental implantology outcomes in patients under antiresorptive medication with hormone therapy being the treatment of choice is rather low, and it may be even lower in the future.

Topical administration of BPs around the implant surface leads to a high concentration of the drug in the interested site, a state that is much harder to obtain with systemic administration. This fact appears to favor new bone formation in alveolar defects and to increase bone density around the implants. In topical administration, the BPs act on the early phases of bone healing, are mainly absorbed by the adjacent bone, and only a small part of the total amount is released into circulation.[71,72] However, this application is different from systemic administration, and it is not considered an antiresorptive medication for diseases in which bone resorption and bone formation are disturbed, such as osteoporosis or metastatic bone disease, but rather as a strategy to benefit early dental implant survival. Therefore, studies evaluating topical administration of BPs were excluded.

### *Study selection*

The search results were evaluated initially by reading each abstract. The criteria listed above dictated which articles were included in the review. Any study that did not meet the inclusion criteria was excluded. For studies appearing to meet the inclusion criteria, full texts were evaluated. Studies with a title and abstract that did not allow for making a clear decision were evaluated by reading the full report.

### *Quality assessment*

The quality of the studies was evaluated by applying Newcastle-Ottawa Scale (NOS), a representative tool developed to assess the quality of nonrandomized and observational studies to be used in a systematic review.[73] The NOS calculates the study quality by covering 3 dimensions—selection, comparability, and outcome/exposure—and by assigning points for each dimension. A maximum of 4, 2, and 3 points can be awarded for selection, comparability, and outcome, respectively. The full score is 9 points, and a score less than 6 indicates low quality, whereas a study that scores 6 or more points is considered a study of high quality. The NOS score was assessed independently by 2 reviewers, and disagreements about final scores were resolved through discussion.

## Results

### *Literature search*

The initial search resulted in a list of 411 articles. The titles were analyzed, and based on the aforementioned criteria, 248 abstracts were selected. After reading these abstracts, 210 articles were excluded. The full manuscripts of the remaining 38 articles were read. Of the remaining 38 articles, 6 studies were excluded, because their content was, eventually, irrelevant with the aim of this review. Therefore, 32 articles fulfilled the inclusion criteria (Figure). The 32 studies were divided into 2 groups. The first group of studies (n = 22) evaluated the success rate of dental implant placement in patients with a medical history of antiresorptive medication from the aspect of implant osseointegration and absence of MRONJ. The details of this group of studies are summarized in Table 1. The second group (n = 10) includes studies that describe MRONJ cases in patients with dental implants and history of antiresorptive medication. The details of this group of studies are summarized in Table 2. Both tables present the type of study, number and age of patients, type and duration of the antiresorptive medication used, number of implants placed, implant failures and loss of implants, follow-up period, number of MRONJ cases, and their location.

### *Description of the studies*

Four studies were prospective,[60,74–76] 7 were case series,[57,77–82] and 21 were retrospective.[58,59,61–63,65,66,83–96] This systematic

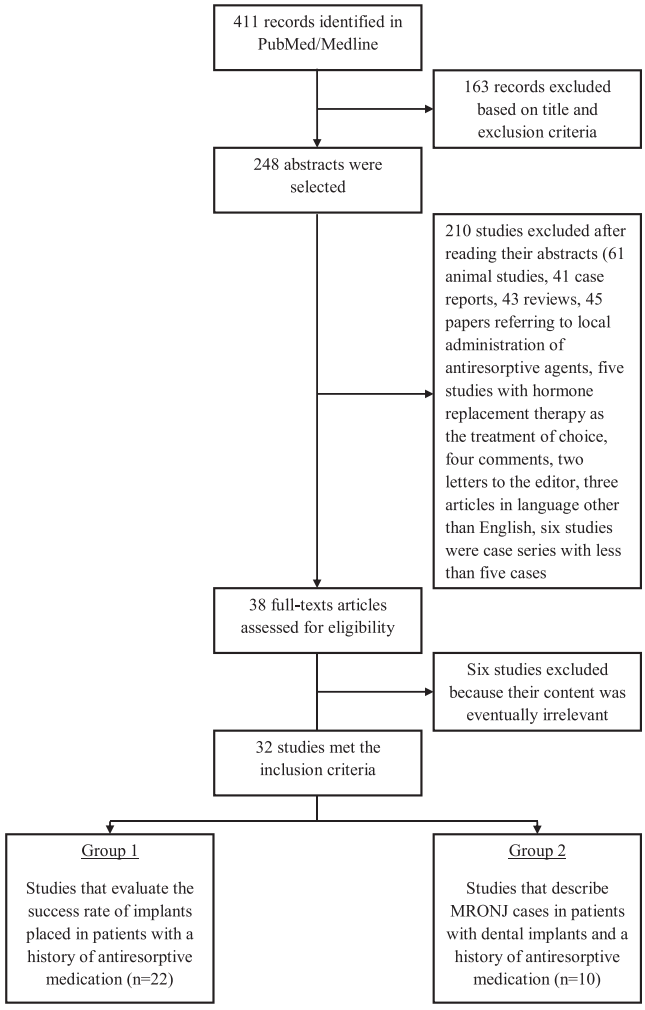


**Figure.** Flow diagram of literature search and selection.

review analyzed 5221 patients in total (1684 patients with a history of antiresorptive medication and 3537 patients without history of antiresorptive medication). The total number of implants placed was 12 751 (3583 in patients on antiresorptive agents and 9168 in control patients), and there were 618 cases of implant loss and 141 MRONJ cases (101 in the mandible and 40 in the maxilla). In some studies, the exact location of the MRONJ lesions was also reported.[57,63,66,77,79,82] In these studies, most MRONJ lesions were in the posterior areas (63 in posterior areas versus 15 in anterior areas). The most common antiresorptive agent was alendronate, which was included in all but 4 studies. One study included patients who had been treated with zoledronic acid,[76] and 3 other studies did not mention the type of the antiresorptive drug.[83,85,95] The other antiresorptive drugs were risedronate, pamidronate, zoledronic acid, ibandronate, and pamidronate. Two studies included clodronate,[65,78] one study included etidronate,[65] and 2 studies included denosumab.[65,81] The patients' ages ranged from 12–90 years, and most of them were females. The follow-up period ranged from 1 to 132 months. There were no studies that matched the inclusion criteria with patients in antiresorptive therapy with selective estrogen receptors modulators, strontium ranelate, or calcitonin.

### *Quality assessment*

Because of the nature of this systematic review and the existence of 2 groups of studies, each establishing a different question, the NOS scale was used individually for the 2 groups. Each dimension has individual components, and they are all presented in Tables 3 and 4. For the component of the outcome "follow-up long enough," 5 years of follow-up were considered to be enough for the outcome "implant failure" to occur. Six studies were of high quality, while 26 studies scored less than 6 points, which is considered an indication of low quality.

## Discussion

The purpose of this study was to evaluate the success rate of dental implants in patients on antiresorptive therapy, the risk of developing MRONJ, and the possibility that already osseointegrated implants could be affected by antiresorptive therapy. The use of antiresorptive drugs is widespread, and this fact combined with the increasing placement of dental implants nowadays and the growing number of MRONJ cases in patients receiving antiresorptive medication leads to a necessity to evaluate the success and the safety of dental procedures in these patients.

The success rate of dental implants in patients on antiresorptive therapy could not be adequately estimated with the available evidence, which is presented in Table 1. Most of the included studies showed very low implant failure rates. All but 4 studies supported that dental implant success rates are not affected by antiresorptive medication, and their success criteria comprise osseointegration and the absence of MRONJ. Zahid et al[94] examined whether patients who receive oral BPs are at greater risk of implant failure than patients not taking these drugs. Although a connection between BPs and implant failure was not found, their data suggested that dental implants placed in patients receiving BPs may be at greater risk of peri-implant bone loss, with 13 implants exhibiting thread exposure among the 51 implants placed. Kasai et al[58] retrospectively compared 35 dental implants placed in 11 patients receiving BPs for more than 3 years, with 161 dental implants in 40 patients with no history of BP administration, and the failure rates were 14.29% and 4.35%, respectively. Although their results showed no cases of MRONJ, these authors concluded that oral BPs may decrease the integration of dental implants and therefore increase their failure rate. The retrospective study by Yip et al[61] also indicates that women with implant failure had increased odds of reporting a history of oral BP use as compared with those without implant failure and highlights the increased risk of implant failure in these patients. The study by Martin et al,[80] although meeting the inclusion criteria, focused on patients who reported dental implant complications and not directly on the survival of dental implants. Their study suggests that implant failure patterns and late dental implant failures in BP users require further examination.

The remaining studies of group 1 reported no MRONJ cases and present very low dental implant failure rates, but there is an evident lack of quality for most of them. Some of the studies included control groups,[61,74,76,83–86,88,90,91,93–95] but the differ-

ence in dental implant failure rates between patient groups and control groups was not statistically significant in any of them, with the exception of the study by Yip et al.[61] Therefore, the dental implant success rate could not be fully evaluated. In addition, the quality of some studies was low. For instance, the retrospective analysis by Grant et al[88] did not report cases of MRONJ, but of the 115 patients in the case group, only 72 were seen for a follow-up clinical and radiographic examination. The remaining 43 patients answered a questionnaire to detect MRONJ. The question was, "Are you experiencing pain, swelling, or exposed bone around any of your implants?" Although MRONJ is known to present severe symptoms, it can also appear as exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of an infection.[5] Bone exposure when asymptomatic and, in areas of difficult access, could go undetected by the patients. A MRONJ diagnosis is not possible without clinical and radiographical examination; therefore, it cannot be concluded from this study that the placement of dental implants is safe, and possible late dental implant failures could not be evaluated.

Khoury and Hidajat[78] in their case series including 15 patients under BP therapy, performed 61 bone-grafting procedures and placed 71 dental implants, with only 1 failure. The authors concluded that bone augmentation and implantation in patients under low doses of BP treatment can be successfully performed. In the retrospective study by Mozzati et al[96] in 2015, the authors evaluated 235 patients under BP therapy with a total of 1267 dental implants placed, while 54 of the cases required sinus lift procedures. Only 16 dental implants failed, leading to the conclusion that neither oral BP therapy nor osteoporosis seem to affect dental implant survival. The authors claimed that procedures that could enhance and support healing, such as the application of plasma rich in growth factor, should be recommended in these cases. In the study by Suvarna et al,[92] bone grafting prior to implant placement was carried out in 82 occasions in 55 patients receiving antiresorptive agents, with no postoperative complication. These last 3 studies present optimistic results and show that surgical procedures are not unsafe in patients receiving antiresorptive drugs.

Although most of the studies in the first group present very low dental implant failure rates and nearly no cases of MRONJ, they have many limitations. First, most of the included studies were retrospective analyses, and the nature of a retrospective analysis often results in defects because of lack of information, incomplete results, and data, which may have not been included in the initial examination and which patients cannot provide, such as the duration of the antiresorptive medication. In some studies, patients received BPs for less than 3 years before implant placement, which is a short period of time,[59,75,76] while in other studies, this information is not provided at all or is partially absent.[61,85,90,92–95] This is a very important factor to examine, as BPs have a prolonged presence in the mineralized bone, in which they remain buried for years.[14,15] Without this information, the effect of the duration on BP treatment on the implant failure rate and on the risk of developing MRONJ cannot be analyzed. Other studies in group 1 had no control group.[59,60,75,78,80,87,92,96] Moreover, many of the studies had limited patient samples and short follow-up periods. Not only can longer follow-ups lead to an increased failure rate, but MRONJ, according to some studies, can also appear much later after the surgical procedure.[62,63,65,66,81] This is something that also affects the implant survival rates and the safety of dental implantology procedures on these patients. The main focus of some studies was not the dental implant success rate on patients under antiresorptive medication.[85,93,95] In addition, most of the studies included patients using oral BPs, and none of the studies in group 1 involved denosumab as the antiresorptive medication. The route of administration is very important, as IV BPs accumulate in bone at a rate 142 times higher than oral BPs.[97] To evaluate the effect of antiresorptive medication on the dental implant survival rate, more studies need to be carried out in the future, with larger numbers of patients and longer follow-up periods.

The second part of this review evaluates the risk of the development of MRONJ in patients under antiresorptive medication and the possibility that already osseointegrated implants could be affected by antiresorptive therapy.

Studies in group 2 examined MRONJ cases associated with dental implants to evaluate dental implantology procedures as a risk factor for MRONJ in patients under antiresorptive therapy. Many studies have examined the possibility that MRONJ is a late complication that occurred around already osseointegrated dental implants. Most of the studies in the second group are case series, with a few retrospective studies of low quality. It cannot be accurately concluded from the analysis of these studies whether dental implantology is safe or unsafe in patients taking antiresorptive drugs or whether dental implants can be affected, after their successful osseointegration, by antiresorptive medication. The patient samples in all studies were low, ranging from 6 patients, as in the study by Tam et al,[82] to 27 patients, as in the study by Lazarovici et al.[79]

Three of the studies could not come to a clear conclusion as to whether MRONJ is associated with dental implantology, and the need for more studies assessing this matter was highlighted by the authors.[57,82,89] Six studies concluded that MRONJ can occur as a late complication around dental implants and that the presence of an osseointegrated dental implant itself can be a risk factor for developing MRONJ.[62,63,65,66,79,81] Giovannacci et al[62] in 2016 concluded that not only is the surgical insertion of dental implants a potential risk factor for MRONJ development but the presence of an implant itself could also function as a risk factor, as 9 patients developed MRONJ years after the surgical procedure and the successful osseointegration of dental implants. In the study by Lazarovici et al,[79] BRONJ was usually not related to the surgical procedure of dental implant placement, as 77.8% of the BRONJ cases developed after an average of 11 months following the implant placement. There were also 4 cases of BRONJ associated with dental implants that were placed a few years before BP treatment was started. Pogrel and Ruggiero[81] also agreed with these conclusions, claiming that implant failure can occur when patients with osseointegrated implants start antiresorptive therapy. Kwon et al[63] also concluded that already osseointegrated dental implants can cause osteonecrosis around them after BP administration, as 9 of their patients developed BRONJ after their dental implants were successfully osseointegrated for an

TABLE 1

Studies evaluating the success rate of dental implants in patients with history of antiresorptive medication*

| Author | Year | Study Type | Patients Cases/Controls | Age Range, y | Number of Implants, Cases/Controls | Failed Implants, Cases/Controls |
|---|---|---|---|---|---|---|
| Jeffcoatl[74] | 2006 | PS | 25/25 | 30–79 | 102/108 | 0/0 |
| Wagenberg and Froum[93] | 2006 | RA | 24/867 | 14–94 (mean 58) | 75/1850 | 2/75 |
| Fugazzotto et al[87] | 2007 | RA | 61/0 | 51–83 | 169/— | 0/— |
| Bell and Bell[84] | 2008 | RA | 42/? | Mean 67 | 100/734 | 5/26 |
| Grant et al[88] | 2008 | RA | 115/343 | >40 (mean 67.4) | 468/1450 | 2/14 |
| Kasai et al[58] | 2009 | RA | 11/40 | 52–73 | 35/161 | 5/7 |
| Martin et al[80] | 2010 | Case series | 589 | Mean 70 | ? | 26/— |
| Koka et al[90] | 2010 | RA | 55/82 | 50–93/(mean 71) | 121/166 | 1/3 |
| Shabestari et al[59] | 2010 | RA | 21/0 | 42–79 (mean 53) | 46/— | 0/— |
| Bell et al[85] | 2011 | RA | 655 in total | ? | 24/898 | 0/15 |
| Famili et al[86] | 2011 | RA | 22/98 | >50 | 75/272 | 1/0 |
| Zahid et al[94] | 2011 | RA | 26/274 | 17–87 (mean 56) | 51/610 | 3/16 |
| Leonida et al[75] | 2012 | PS | 9/0 | 45–68 | 54/— | 0/— |
| Memon et al[91] | 2012 | RA | 100/100 | 47–90 (mean 63) | 153/132 | 10/6 |
| Yip et al[61] | 2012 | RA | 20/317 | >40 (mean 57) | 74/1107 | 20/143 |
| Wagenberg et al[95] | 2013 | RA | 541 in total | 12–88 (mean 58) | 35/1151 | ?/? |
| Al-Sabbagh et al[83] | 2015 | RA | 20/183 | 21–90 (55.5) | 46/469 | 0/0 |
| Mozzati et al[96] | 2015 | RA | 235/0 | 48–79 (60.7) | 1267/— | 16/— |
| Tallarico et al[60] | 2015 | PS | 32/0 | 46–80 (mean 64,6) | 98/— | 1/— |
| Siebert et al[76] | 2015 | PS | 12/12 | >54 | 60/60 | 0/0 |
| Khoury and Hidajat[78] | 2016 | Case series | 15 | 55–72 | 71/— | 1/— |
| Suvarna et al[92] | 2016 | RA | 112/0 | ? | 140/— | 10/— |

*— indicates non-existent; ?, not mentioned in the study; IV, intravenous; PS, prospective study; RA, retrospective analysis.

TABLE 2

Studies that describe cases of MRONJ in patients with dental implants and a history of antiresorptive medication*

| Author | Year | Study Type | Patients | Age | Number of Implants | Number of Implant Failures |
|---|---|---|---|---|---|---|
| Lazarovici et al[79] | 2010 | Case series | 27 | Mean 70 | ? | ? |
| Goss et al[77] | 2010 | Case series | 7 | 49–75 (mean 65.7) | 19 | 9 |
| Lopez-Cedrun et al[57] | 2013 | Case series | 9 | 66 | 57 | 12 |
| Jacobsen et al[66] | 2013 | RA | 12 | ? | 23 | 12 |
| Tam et al[82] | 2014 | Case Series | 6 | 72 | 15 | 10 |
| Holzinger et al[89] | 2014 | RA | 13 | 65.7 | 47 | 30 |
| Kwon et al[63] | 2014 | RA | 19 | 42–85 | 23 | 23 |
| Giovannacci et al[62] | 2016 | RA | 15 | 64 | 34 (22 in ONJ sites) | 52 |
| Troeltzsch et al[65] | 2016 | RA | 19 | 71 | 117 (62 in ONJ sites) | 62 |
| Pogrel and Ruggiero[81] | 2018 | Case series | 11 | ? | ? | ? |

*? indicates not mentioned in the study; IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw; ONJ, osteonecrosis of the jaw; p/a, posterior/anterior; RA, retrospective analysis.

Table 1

Extended

| MRONJ Cases | Drug/Route of Administration | Duration of Medication Before Implant placement, mo | Failure Rate of Implants, Cases/Controls | Follow-up, mo |
|---|---|---|---|---|
| 0 | Alendronate, risedronate/oral | 12–48 | 0%/0% | >36 |
| 0 | Alendronate/? | ? | 0.026%/0.040% | 12–193 (mean 71) |
| 0 | Alendronate, risedronate/oral | 40 | 0% | 12–24 |
| 0 | Alendronate, risedronate, ibandronate/oral | 6–132 | 5%/3.54% | 37 |
| 0 | Alendronate, risedronate, ibandronate/oral | 38 (26 patients received medication after implant placement) | 0.43%/0.97% | ? |
| 0 | Alendronate/oral | >36 | 14.29%/4.35% | 64–186 (mean 84) |
| 0 | Alendronate, risedronate ibandronate/oral | 3–108 | ? | 1–132 |
| 0 | Alendronate/oral | Some patients <36<br>Some patients >60<br>Some patients 36–60 | 0.83%/1.81% | ? |
| 0 | Alendronate/oral | 20.5 | 0%/— | 96 |
| 0 | ? | ? | 0%/1.67% | 3–93 (mean 20) |
| 0 | Alendronate, risedronate, ibandronate/oral | 6 patients 6–12<br>9 patients >12<br>5 patients >60<br>2 patients ? | 1.33%/0% | 30 |
| 0 | Alendronate, ibandronate/oral | 6–192 (information for 11 patients missing) | 5.88%/2.62% | 2–78 (mean 26) |
| 0 | Alendronate, risedronate/oral | <36 | 0%/— | 24 |
| 0 | Alendronate, risedronate, ibandronate/oral | 20 patients <12<br>19 patients 12–36<br>15 patients >36<br>42 patients: ? | 6.54%/4.54% | 4–6 |
| 0 | Alendronate, risedronate/oral | ? | 27.03%/12.92% | 3.96–142.8 (mean 72) |
| 0 | Alendronate/? | ? | ?/? | 12–264 (mean 120) |
| 0 | ?/Oral | >36 | 0 | 10–120 (mean 94) |
| 0 | Alendronate, risedronate, ibandronate/oral | 7–87 (mean 39) | 1.26%/— | 24–120 |
| 0 | Alendronate/oral | >36 | 1.02%/— | 47.6 |
| 0 | Zoledronic acid/IV | 12–36 | 0%/0% | 12 |
| 0 | Alendronate, ibandronate, risedronate, clodronate/oral Ibandronate/IV | 12–120 | 0.014%/— | >36 |
| 0 | Alendronate, risedronate, ibandronate/oral | ? | 7.14%/— | >36 |

Table 2

Extended

| Drug/Route of Administration | Duration of Medication Before Implant Placement, mo | MRONJ Cases/ Location | Time of MRONJ From Implant Placement, mo |
|---|---|---|---|
| Alendronate/oral, pamidronate, zoledronic acid/IV | 0–108 | 27/mandible (p/a, 15/5) maxilla (p/a, 4/3) | 0–53 |
| Alendronate, risedronate/oral | 3–120 | 5/mandible (p/a, 3/1) maxilla (p/a, 1/0) | ? |
| Alendronate, ibandronate, risedronate/oral | ? | 9/mandible (p/a, 7/1) Maxilla (p/a, 1/0) | 60 |
| Zoledronic acid, pamidronate, ibandronate/IV, alendronate/oral | 38 for IV users, 50 for oral users | 12/mandible (p/a, 5/3) Maxilla (p/a, 4/0) | 20.9 |
| Alendronate, zoledronate/oral and IV | ? | 6/mandible (p/a, 3/1) Maxilla (p/a, 2/0) | 1–17 (5 patients 1–4) |
| Zoledronate, ibandronate/IV, alendronate, pamidronate/oral | Group 1: 0<br>Group 2: 65–140<br>Group 3: 39–243 | 13/12 mandible, 1 maxilla | Group 1: 80–220<br>Group 2: 0–66<br>Group 3: 6–72 |
| Alendronate, risedronate, zoledronate/oral; ibandronate/oral and IV; pamidronate/IV | 6–108 | 19/mandible (p/a, 10/1) Maxilla (p/a, 8/0) | 6–35 (mean 24) |
| Alendronate, ibandronate/oral; zoledronic acid, pamidronate/IV | Group 1: 83.7<br>Group 2: 27.8 | 20/11 mandible, 9 maxilla | Group 1: 2–10<br>Group 2: 12–180 |
| Alendronate/oral, zoledronic acid, pamidronate, ibandronate, denosumab, clodronate, etidronate | Most of them 0 | 19/14 mandible, 5 maxilla | 23–45.4 (mean 38) |
| Alendronate, zoledronate, denosumab/? | 0 | 11/9 mandible, 2 maxilla | 24–156 (mean 57.6) |

TABLE 3

Assessment of quality (NOS) for studies of Table 1†

| | Selection of Patients | | | | Comparability | | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Representativeness of the Exposed Cohort | Selection of Nonexposed Cohort | Ascertainment of Exposure | Outcome of Interest not Present at the Start | Main Factor (Age) | Additional Factor (Smoking) | Assessment of Outcome | Follow-up Long Enough | Adequacy of Follow-up | Total |
| Jeffcoat et al[74] | — | * | * | * | * | * | * | — | — | 6/9 |
| Wagenberg and Froum[93] | — | * | * | — | * | * | * | * | — | 6/9 |
| Fugazzotto et al[87] | — | — | * | — | — | — | * | — | — | 2/9 |
| Bell and Bell[84] | * | * | * | — | * | * | * | — | — | 6/9 |
| Grant et al[88] | — | * | — | — | * | — | — | — | — | 2/9 |
| Kasai et al[58] | — | * | * | — | * | * | * | * | — | 6/9 |
| Martin et al[80] | — | — | * | — | — | — | * | — | — | 2/9 |
| Koka et al[90] | — | * | * | — | * | * | * | — | — | 5/9 |
| Shabestari et al[59] | — | — | * | — | — | — | * | * | — | 3/9 |
| Bell et al[85] | — | * | * | — | * | — | * | — | — | 4/9 |
| Famili et al[86] | * | * | * | — | * | — | * | — | — | 5/9 |
| Zahid et al[94] | * | * | * | — | * | * | * | — | — | 6/9 |
| Leonida et al[75] | — | — | * | * | — | — | * | — | — | 3/9 |
| Memon et al[91] | — | * | * | — | * | — | * | — | * | 5/9 |
| Yip et al[61] | — | * | * | — | * | * | * | * | — | 6/9 |
| Wagenberg et al[95] | — | * | * | — | * | — | * | * | — | 5/9 |
| Al-Sabbagh et al[83] | * | * | — | — | * | — | — | * | — | 4/9 |
| Mozzati et al[96] | — | — | * | — | — | — | * | — | — | 2/9 |
| Tallarico et al[60] | — | — | * | * | — | — | * | — | — | 3/9 |
| Siebert et al[76] | — | * | * | * | * | * | * | — | — | 4/9 |
| Khoury and Hidajat[78] | — | — | * | — | — | — | * | — | — | 2/9 |
| Suvarna et al[92] | — | — | * | — | — | — | * | — | — | 2/9 |

†NOS indicates Newcastle-Ottawa Scale; *, high quality item; —, low quality item.

average of 35 months. They highlighted that the role of micro cracks around the dental implant surface needs to be further investigated and that bone destruction around this area is different from peri-implantitis bone destruction. A later study by Troeltzsch et al[65] results in similar conclusions, claiming that there are indications that peri-implant pathology such as peri-implantitis may be associated with MRONJ occurrence. Authors believe that a higher risk of MRONJ developing around dental implants in patients under antiresorptive medication is a fact. MRONJ cases presented in studies of group 2 are mostly located in the posterior areas of the mandible, a fact that agrees with the AAOMS position paper.[5] Therefore, the need for careful calculation before implant placement in such areas and frequent follow-ups are recommended, as Jacobsen et al[66] suggested. Holzinger et al[89] could not come to any conclusions about the incidence of BRONJ in connection with dental

TABLE 4

Assessment of quality (NOS) for studies in Table 2†

| | Selection | | | | Comparability | | Exposure | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Case Definition Adequate | Representativeness of the Cases | Selection of Controls | Definition of Controls | Main Factor | Additional Factor | Ascertainment of Exposure | Same Method of Ascertainment for Cases and Controls | Nonresponse Rate | Total |
| Lazarovici et al[79] | * | * | — | — | — | — | * | — | — | 3/9 |
| Goss et al[77] | * | * | — | — | — | — | * | — | — | 3/9 |
| Lopez-Cedrun et al[57] | * | * | — | — | — | — | * | — | — | 3/9 |
| Jacobsen et al[66] | * | * | — | — | — | — | * | — | — | 3/9 |
| Tam et al[82] | * | * | — | — | — | — | * | — | — | 3/9 |
| Holzinger et al[89] | * | * | — | — | — | — | * | — | — | 3/9 |
| Kwon et al[63] | * | * | — | — | — | — | * | — | — | 3/9 |
| Giovannacci et al[62] | * | * | — | — | — | — | * | — | — | 3/9 |
| Troeltzsch et al[65] | * | * | — | — | — | — | * | — | — | 3/9 |
| Pogrel and Ruggiero[81] | * | * | — | — | — | — | * | — | — | 3/9 |

†NOS indicates Newcastle-Ottawa Scale; *, high quality item; —, low quality item.

implants, although they stated that the duration of BP therapy has an influence on the development of BRONJ. They also concluded that the occurrence of BRONJ is delayed when dental implants have been placed before the initiation of BP administration. Lopez-Cedrun et al[57] emphasized that more studies are needed to evaluate possible risk factors other than the duration of BP treatment. Although most of these studies came to similar conclusions, their limited evidence prevents us from reaching an indisputable conclusion about the safety of dental implantology in patients under antiresorptive medication. A quite interesting fact is that of 138 patients included in this group of studies, 91 developed MRONJ at least 6 months after dental implant placement, as shown in Table 2. The limitations of the studies, such as the absence of control groups and small patient samples, prevents us from claiming that MRONJ is more likely to occur as a late complication than as an early complication related to the surgical procedure of dental implant placement. However, it is an observation worth mentioning, and we highlight the need for future studies evaluating this aspect.

The safety of dental implantology in patients under antiresorptive medication is a matter of great significance, as dental implants can improve the quality of life in patients under antiresorptive therapy,[98] analogous to patients without antiresorptive therapy,[99] whereas MRONJ has an enormous negative impact on the quality of life of affected patients. An alternative treatment option to dental implants is the denture, but even this option can be a risk factor, as denture pressure sores can be a trigger factor for the development of MRONJ.[100–103] A need to weigh in the possible gain of quality of life by an implant-supported restoration and the possible risk of developing MRONJ is very important.

An interesting fact is that the AAOMS position paper of 2014 suggested that a drug holiday is a prudent approach for patients with extended exposure history (>4 years), although the group of experts acknowledged the fact that there are limited data to support or refute the benefits of this strategy.[5] Drug holiday is a discontinuation of the antiresorptive therapy to allow bone marrow recovery and the formation of new osteoclasts so they can reach previous numbers prior to their reduction.[97] According to the American Dental Association Council on Scientific Affairs,[104] there is not enough evidence to recommend a holiday from antiresorptive medication or waiting periods before performing dental treatment. In the studies included in this review, some authors support the recent recommendations of the AAOMS,[61] whereas others suggest that such a strategy is not needed.[90]

As for denosumab, a drug that does not bind to the bone,[26] there are no studies to make any clear conclusions. Unlike BPs, the antiresorptive effects of denosumab should be mostly dissipated within 6 months of ceasing drug intake. However, there are no studies to support or reject the strategy of quitting denosumab therapy in the prevention or treatment of MRONJ.[5] It is necessary to compare the benefits of a drug holiday before dental implant placement, with the risk of osteoporosis progression in the absence of an antiresorptive medication. There were no studies evaluating dental implant outcomes in patients under treatment with selective estrogen receptor modulators, strontium ranelate, or calcitonin that matched the inclusion criteria. Hormone therapy for the treatment of osteoporosis and its possible dental implant outcomes was not evaluated is this study, as it is prescribed in a rather limited extent.

Oral hygiene should be improved before antiresorptive medication begins, as it is an important factor to the prevention of MRONJ.[105] Dental implant placement, being a surgical procedure, is often followed by an inadequacy of mechanical plague control because of pain and discomfort, leading to poor oral hygiene.[106] Chlorhexidine mouthwashes appear effective in reducing inflammation and biofilm during these early healing periods.[107,108] Patients should also be informed about the possible association between peri-implantitis and the development of MRONJ.[65] Antibiotic prophylaxis also seems to be a tool for decreasing MRONJ frequency after a surgical procedure.[105,109] Ata-Ali et al[110] in their meta-analysis in 2014 demonstrated that antibiotic use lowered the dental implant failure rate by 66.9%. A similar strategy should be followed in patients under antiresorptive medication who are going to receive dental implants, both to reduce implant failure rates and to possibly minimize the risk of developing MRONJ. In some studies, grafting procedures and sinus lifts before dental implant placement were successfully performed, and the authors reported no cases of MRONJ. The use of plasma rich in growth factors to enhance the healing process was also mentioned.[78,92,96] However, there is not enough evidence about the safety and success of these procedures in patients under antiresorptive medication, and they should therefore be avoided, whereas minimally invasive operations are preferred. An exact planning phase, primary wound closure, a diet of liquid or soft food, and frequent follow-ups are recommended, similar to teeth extractions.[111] It is worth mentioning that patients with additional risk factors such as prior or current glucocorticoid exposure (in combination with BPs), rheumatoid arthritis, diabetes, and smoking are at higher risk for developing MRONJ. Therefore, the above-mentioned safety practices are even more important, and determining the individual risk of each patient is the strategy of choice.[5]

## Conclusion

The results of the included studies cannot claim that antiresorptive medication reduces the success rate of dental implants nor that antiresorptive medication does not affect implant survival rates. This is because of a high number of studies with a limited number of cases, no control groups, and short follow-up periods. Therefore, the accurate success rate of dental implants placed in patients receiving antiresorptive medication cannot be established. Based on the current literature, the accurate risk of MRONJ development in dental implant patients cannot be established either, as a result of the limited number of studies with a proper patient sample. Some studies present cases in which MRONJ occurred as a later complication of previously successful osseointegrated dental implants, but more studies are needed to verify this assertion. Successful dental implant placement is possible in patients who receive antiresorptive medication, but these patients must be informed about the importance of oral hygiene and the possible risk of developing MRONJ as an early or late

complication. Minimally invasive procedures are preferred, and evaluating the individual risk of each patient is very important. A perioperative antibiotic prophylaxis and careful treatment planning with many and frequent follow-ups are recommended. Dental implant placement in patients receiving IV antiresorptive drugs is an absolute contraindication. For patients with benign diseases, antibiotic prophylaxis, or even in some cases, a drug holiday could be the strategy of choice. Nonetheless, more scientific evidence is needed for definitive conclusions on the matter.

## Abbreviations

AAOMS: American Association of Oral and Maxillofacial Surgeons
ACP: American College of Physicians
ATP: adenosine triphosphate
BP: bisphosphonate
BRONJ: bisphosphonate-related osteonecrosis of the jaw
IV: intravenous
MRONJ: medication-related osteonecrosis of the jaw
NOS: Newcastle-Ottawa Scale

## Conflict of Interest

The authors report no conflict of interest.

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