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REVIEW ARTICLE

Antiresorptive therapy influence on peri-implant diseases: Clinical implications and osteoimmunological perspectives

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Abstract

Background/Aim: Antiresorptive therapy represents a cornerstone in the management of osteoporosis and cancer-related bone disease through suppression of osteoclast-mediated bone resorption. As implant therapy becomes more common in aging populations, clinicians increasingly encounter patients receiving these medications, thus making their impact on peri-implant tissues clinically relevant.

Materials and Methods: This narrative review critically examines clinical evidence on implant survival, peri-implant bone stability, peri-implantitis progression, and treatment considerations in patients receiving antiresorptive therapy, while integrating mechanistic insights.

Results: Evidence suggests that implant survival and marginal bone loss in osteoporotic patients are generally comparable to untreated individuals, indicating that suppression of bone resorption does not inherently compromise osseointegration. However, these outcomes may not fully reflect peri-implant tissue dynamics. Antiresorptives alter osteoclast functions and bone remodeling, potentially affecting the osteoimmune balance required to adapt to mechanical and oral microbial challenges. While these effects may remain subclinical under healthy conditions, they may become relevant during chronic peri-implant inflammation or repeated surgical interventions, where remodeling demands are increased. Altered remodeling may result in lesion persistence, impaired structural recovery, and late complications. Although medication-related osteonecrosis of the jaw remains rare, antiresorptives may modify osteoimmune interactions within inflamed tissues. Therefore, peri-implantitis may act as a contextual modifier influencing healing outcomes.

Conclusions: Antiresorptive therapy should not be regarded as an absolute contraindication to implant therapy in appropriately selected patients, particularly those receiving osteoporosis-dose regimens. However, chronic peri-implant inflammation, repeated surgical intervention, and high-dose oncologic antiresorptive exposure may impair osteoimmune adaptation and increase susceptibility to delayed healing and MRONJ-related complications.

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Clinical Relevance: Early control of peri-implant inflammation, individualized risk stratification, and strict supportive maintenance should be considered central components of clinical management in antiresorptive-exposed patients.

KEYWORDS
antiresorptive therapy, bone remodeling, denosumab, MRONJ, osteoimmunology, peri-implantitis

1 | INTRODUCTION

Antiresorptive therapy has become a cornerstone in the management of skeletal disorders characterized by excessive or deregulated bone resorption, including osteoporosis, bone metastases, multiple myeloma, and Paget's disease.[1] Initially regarded as an unavoidable consequence of aging or disease, systemic bone loss can now be effectively controlled through pharmacological interventions that primarily target osteoclast differentiation and activity.[2] Among these strategies, bisphosphonates remain the most widely prescribed antiresorptive agents in routine clinical practice, while monoclonal antibodies such as denosumab provide an alternative approach for patients with bisphosphonate intolerance or impaired renal function, while maintaining comparable efficacy in reducing fracture risk and improving patients' quality of life.[1,3,4] In addition, endocrine-based therapies and supportive nutritional strategies—particularly adequate calcium and vitamin D intake—are commonly integrated into osteoporosis management to support bone homeostasis and prevent hypocalcemia.[4,5] More recently, dual-action agents such as romosozumab, a monoclonal antibody targeting sclerostin, have been introduced. By simultaneously inhibiting bone resorption and stimulating bone formation, these therapies reflect a progressive shift toward more targeted modulation of bone remodeling dynamics in selected clinical contexts.[5,6] Consequently, antiresorptive medications now form part of the systemic therapeutic background of many individuals seeking dental treatment.

As implant dentistry has been positioned as a central component of contemporary oral rehabilitation, implant-supported restorations are increasingly being delivered to aging populations, including patients affected by osteoporosis and other chronic systemic conditions requiring long-term pharmacologic management. This reality creates a clinically relevant interface between systemic antiresorptive therapy and local peri-implant tissue biology, with potential implications for peri-implant tissue maintenance and the development of biological complications affecting peri-implant bone stability. In this context, peri-implantitis is a chronic inflammatory disease characterized by the presence of dysbiotic biofilms, persistent immune deregulation, and osteoclast-mediated bone destruction.[7] Similarly to periodontitis, when uncontrolled, this condition leads to progressive loss of peri-implant supporting bone, ultimately leading to implant loss.[8] As excessive bone resorption represents a central pathological feature of these diseases, increasing attention has been directed toward systemic conditions and pharmacologic therapies capable of modulating osteoclast activity and bone remodeling within the oral cavity. These interactions are increasingly interpreted within an osteoimmunological framework, where immune-mediated inflammation and bone remodeling processes are tightly interconnected and jointly determine the progression or resolution of peri-implant tissue breakdown.

However, clinical discussion has largely been centered on concerns related to medication-related osteonecrosis of the jaw (MRONJ) and, to a lesser extent, to implant survival outcomes. Although MRONJ represents a severe complication—particularly in oncology patients receiving high-dose intravenous antiresorptive therapy—most implant patients receiving commonly prescribed low-dose oral antiresorptive therapy for osteoporosis will never develop osteonecrosis. Nevertheless, systemic suppression of bone turnover may still influence key pathways regulating peri-implant bone remodeling over time,[9] particularly under conditions of continuous mechanical load, defect regeneration, microbial challenge, or inflammatory disease.

As peri-implantitis and periodontitis are driven by inflammatory osteolysis associated with deregulated host immune responses,[9,10] suppression of osteoclast function could theoretically attenuate local bone loss and limit disease progression. However, prolonged inhibition of bone remodeling may also interfere with physiological bone turnover and inflammation-resolution–associated healing processes within peri-implant tissues. Consequently, the biological implications of antiresorptive therapy extend beyond the question of whether these medications lead to catastrophic complications. Long-term implant success depends on the stability of peri-implant tissues, the capacity of peri-implant bone to adapt to functional loading, and the ability of the peri-implant system to respond effectively to inflammatory challenge; therefore, implant survival alone cannot fully capture these dynamics.

In this context, understanding how antiresorptive therapies influence peri-implant tissues is necessary for optimizing treatment strategies and patient outcomes in oral care settings. Particular emphasis is therefore placed on the interaction between systemic suppression of bone turnover and peri-implant inflammation, as this interaction may represent the biological context in which the clinical consequences of antiresorptive therapy become most evident. Accordingly, this narrative review critically examines current clinical and experimental evidence regarding these interactions, highlighting both potential benefits

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and limitations of antiresorptive agents in relation to peri-implant tissue health, peri-implant diseases, bone remodeling, and possible associated complications. Early implant failure and impaired osseointegration during the initial healing phase are beyond the scope of this review.

2 | EVOLUTION OF ANTIRESORPTIVE THERAPY AND THEIR CLINICAL EFFECT ON PERI-IMPLANT HEALTH OUTCOMES: FROM BISPHOSPHONATES TO TARGETED MONOCLONAL ANTIBODIES

2.1 | Prevalence of antiresorptive therapy in implant patients

The increasing prevalence of osteoporosis, together with the widespread use of implant-supported restorations, means that clinicians now frequently encounter patients receiving antiresorptive therapy in routine implant practice. Aging populations in many countries have led to a substantial rise in the number of individuals undergoing both skeletal therapy and oral rehabilitation. Although robust population-level estimates of patients receiving implants under antiresorptive therapy are lacking, the expanding body of clinical evidence on their coexistence suggests that such cases are no longer exceptional but represent an increasingly common clinical reality.

A large retrospective study analyzing 944 401 patients with osteoporosis reported that approximately ≈4% (38 230 patients) underwent dental implant placement.[11] A more recent analysis from the same cohort suggested that the incidence of dental implant placement in a year may reach up to 25% among osteoporotic patients older than 65 years.[12] Together, these observations highlight the growing clinical relevance of implant therapy in patients exposed to antiresorptive medication.

Against this background, understanding clinical characteristics of peri-implant tissue in these patients becomes essential. In terms of peri-implant health, overall clinical parameters such as probing depth (PD), bleeding on probing (BOP), and marginal/crestal bone loss (CBL) appear largely comparable to those observed in unexposed patients, particularly under supportive periodontal care.[13,14] However, recent longitudinal evidence suggests a more nuanced pattern. An observational study with a mean follow-up of 13.2 ± 6.4 years reported significantly greater increases in maximum PD (Δ1.1 ± 2.0 mm; $p = 0.0006$) and BOP changes (Δ0.2 ± 0.4; $p < 0.01$) in patients receiving antiresorptives—including bisphosphonates and denosumab—after implant placement compared with controls.[15,16] Although the adjusted odds ratio for PD change was elevated (OR: 1.86; 95% CI: 0.75–4.58), the wide confidence interval reflects considerable uncertainty.[15] Moreover, inconsistent reporting and lack of direct comparisons between exposed and unexposed cohorts have precluded pooled analysis across studies.[17] Collectively, these findings suggest that antiresorptive therapy may subtly modulate the trajectory of peri-implant tissue changes, with worsening of PD and BOP potentially indicating a risk of progression to peri-implantitis. Accordingly, regular monitoring of peri-implant PD and BOP sites is recommended.

With respect to CBL—the hallmark of peri-implantitis pathogenesis—available evidence from multiple meta-analyses and observational studies generally do not demonstrate a consistent or clinically significant increase in CBL among patients receiving low-dose antiresorptive therapy for osteoporosis compared with controls.[18,19] Nevertheless, greater longitudinal change in CBL has been reported when antiresorptive therapy is initiated after implant placement (Δ2.0 ± 6.4 mm; $p < 0.05$), whereas controls tend to exhibit more limited progression.[16] Notably, most implants remain stable over time, and established risk factors—such as a history of periodontitis and a severe mandibular cortical index indicative of advanced osteoporosis—appear to exert a stronger influence on outcomes than antiresorptive therapy alone.

Despite these insights, epidemiological data on the prevalence of peri-implant diseases in patients receiving antiresorptive therapy remain heterogeneous and insufficiently characterized. A systematic review of 10 observational studies reported prevalence estimates of approximately ≈20% for peri-implant mucositis and ≈22% for peri-implantitis in patients with osteoporosis, not being significantly higher than in systemically healthy controls.[17] In contrast, more recent observational studies have reported higher implant-level peri-implantitis prevalence (26.9–28.1%) in antiresorptive users compared with 9.7% in matched controls, identifying antiresorptive therapy as an independent risk factor (adjusted OR ≈3.91), specifically when antiresorptive treatment is initiated after implant placement.[15,16] Such discrepancies may reflect differences in study design, exposure timing, and potential interactions between altered bone remodeling and local inflammatory burden.

This convergence of systemic therapy and implant dentistry raises several clinically relevant questions. Can implants be placed safely in patients receiving antiresorptive therapy? Does systemic suppression of bone turnover influence osseointegration or long-term peri-implant bone stability? And how does antiresorptive therapy interact with peri-implant inflammatory diseases such as peri-implantitis? Importantly, these effects are unlikely to be uniform across agents and must be interpreted within the context of the evolving therapeutic landscape of antiresorptive medications. Over time, treatment strategies have shifted from hormone-based approaches to more targeted antiresorptive agents with distinct mechanisms of action, potency, and pharmacokinetic profiles, which may differentially influence peri-implant tissue dynamics. Addressing these questions therefore requires integrating mechanistic insights with longitudinal clinical evidence, while accounting for these temporal and pharmacological differences. In this context, the following sections examine the evidence according to the chronological development and biological characteristics of major antiresorptive therapies, beginning with hormone replacement therapy, followed by bisphosphonates, and more recently, denosumab. However, given the heterogeneity between mechanisms

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of action, indications, and historical development of antiresorptive agents, the following subsections are structured according to major therapeutic classes, while integrating available clinical evidence on peri-implant outcomes.

2.2 | Hormone replacement therapy (HRT)

The therapeutic landscape of antiresorptive therapy began to evolve in the 1940s, when estrogen was first shown to counteract postmenopausal calcium loss. HRT—typically administered as conjugated estrogens in combination with progestins (e.g., Bijuva or Prempro)—became the mainstay of osteoporosis management from the 1960s onward. Its efficacy was attributed to its ability to inhibit bone resorption while maintaining bone formation. Although early studies lacked robust fracture outcomes data, later evidence demonstrated improvements in bone mineral density, with variable and population-dependent effects on fracture risk.[20,21] However, the risk associated with long-term use—including increased incidence of breast cancer, coronary heart disease, stroke, and venous thromboembolism—were shown to outweigh the fracture-prevention benefits initially offered, for the general population.[22] Moreover, upon discontinuation of estrogen therapy, bone mineral density rapidly declines toward baseline levels, limiting sustained benefit unless therapy is continued, which in turn further increases cumulative risks.[23] Consequently, HRT is currently considered primarily for younger postmenopausal women (< 60 years) without significant vasomotor symptoms and elevated fracture risk, after careful risk–benefit assessment.[24]

Despite its historical relevance in skeletal management, its translational impact on peri-implant health appears limited. Overall, available evidence does not support a consistent or clinically meaningful effect of HRT on implant related outcomes. While a meta-analysis of six studies reported that HRT was associated with reduced odds of CBL (OR = 0.59; 95% CI: 0.50–0.70) in HRT users compared to non-users[25]; data on other peri-implant clinical parameters remain ill reported. In contrast, another systematic review reported that HRT does not consistently improve implant osseointegration or reduce implant loss rates.[26] Furthermore, some observational cohorts have reported higher implant loss rates among women receiving HRT; however, these findings are inconsistent and may be influenced by underlying systemic or behavioral factors.[26,27]

Even though HRT has been recently associated with modest improvements in certain periodontal parameters in postmenopausal women—lower clinical attachment level (CAL) and alveolar bone height—,[28] these effects appear variable across studies and have not been consistently translated to peri-implant outcomes yet. Moreover, given the potential systemic adverse events associated with long-term hormone therapy, HRT cannot be recommended as a primary intervention for the management of osteolytic oral diseases.[26] Overall, these effects remain inconsistent and have not translated into peri-implant outcomes, and its use should be interpreted strictly within its systemic indications rather than implant-related considerations.

2.3 | Selective estrogen receptor modulators (SERMs)

Empirically derived agents such as calcitonin, an endogenous peptide hormone secreted by thyroid parafollicular C cells, acts by directly binding to calcitonin receptors on mature osteoclasts. This interaction suppresses osteoclasts resorptive activity, promotes apoptosis, and disrupts cytoskeletal organization and adhesive structures, resulting in reduced calcium release and bone turnover.[29] Although calcitonin demonstrated antiresorptive effects and limited preclinical evidence suggests attenuation of alveolar bone loss,[30,31] its lack of evident immune-modulatory activity, modest fracture-prevention efficacy and restricted indications have led to its decline in routine clinical use. Accordingly, given its limited relevance in current skeletal management (e.g., salmon or eel calcitonin [elcatonina], nasal spray or injection) and the absence of robust clinical data in periodontal or peri-implant settings, calcitonin will not be further addressed in this review.[32]

Similarly, raloxifene (e.g., Evista), another selective estrogen receptor modulator, has shown only modest efficacy for fracture prevention and similarly restrictive indications, resulting in a gradual decline in its routine prescription since 2012.[33] To date, no large-scale human clinical studies have specifically evaluated the association between raloxifene use and peri-implant health parameters, peri-implant disease, or implant loss. Evidence regarding its effects on peri-implant tissues remains limited and largely derived from preclinical models assessing osseointegration and peri-implant bone formation.[34,35] Accordingly, the absence of clinical data precludes definitive conclusions and limits raloxifene's current clinical relevance in peri-implant diseases management.

2.4 | Bisphosphonates

Subsequently, the use of more potent, repurposed compounds such as bisphosphonates rose, establishing these agents as the current mainstay of modern antiresorptive therapy.[36] From these, oral bisphosphonates, including alendronate or risedronate, are considered the first-line therapy due to their favorable cost-effectiveness and tolerability. Intravenous formulations, such as zoledronic acid, are reserved for patients with gastrointestinal intolerance or poor adherence to oral therapy, while also providing substantial fracture risk reduction.[37]

2.4.1 | Oral bisphosphonates

Evidence on the impact of oral bisphosphonates on peri-implant health is mixed. Several studies have shown that patients receiving oral bisphosphonates for osteoporosis exhibit similar peri-implant PD and BOP comparable to controls, with no significant differences in clinical or radiographic outcomes.[38] Meta-analyses and retrospective studies have further confirmed that marginal bone

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loss is not increased in these patients.[18,39,40] However, more recent observational studies where oral bisphosphonate therapy was initiated after successful implant osseointegration (19/24 patients on oral alendronate/risedronate) reported significantly greater PD and mean BOP changes after a mean follow-up of 3.6 years compared to controls.[15,16] As oral bisphosphonate therapy timing appears critical, authors suggest it may promote a persistent inflammatory state that could compromise peri-implant health and increase the risk of peri-implantitis. Given this uncertain role, oral bisphosphonates are not recommended as adjunctive therapy for peri-implant diseases. Current clinical recommendations emphasize the application of standard non-surgical therapy and regular peri-implant maintenance monitoring for patients receiving these medications.[41]

Taken together, clinical evidence specifically addressing the effects of oral bisphosphonates on peri-implantitis course and peri-implant treatment outcomes remains limited. Recent systematic reviews report no significant differences in marginal bone loss or implant loss rates—key indicators of peri-implantitis progression—between exposed and unexposed patients. However, implant level analyses have suggested a potential increase in implant loss and MRONJ risk among exposed individuals. In a case series, patients who initiated oral bisphosphonate therapy 3–14 years after successful implant osseointegration developed advanced peri-implantitis requiring implant removal, after which MRONJ was observed.[42] While these findings are based on a small number of studies with substantial heterogeneity and very low certainty of evidence, the possible association between peri-implant disease, surgical intervention, and MRONJ should be interpreted with caution.[18,43]

In contrast, multiple meta-analyses suggest evaluating that adjunctive oral or locally delivered bisphosphonate therapy, particularly alendronate, may provide modest improvements in PD reduction, CAL gain, and bone defect fill for periodontitis for up to 12 months, especially among postmenopausal women.[44,45] However, these findings cannot be directly extrapolated to peri-implantitis management.

2.4.2 | Systemically administered bisphosphonates

In contrast to oral bisphosphonates used for osteoporosis, patients receiving intravenous or high-dose oncologic bisphosphonate regimens represent a distinct clinical scenario, primarily due to the relatively increased risk of MRONJ. Even in the context of limited evidence, this risk constitutes a major constraint when considering implant therapy in this population.

Emerging clinical data remain scarce but suggest that implant therapy may be feasible under carefully controlled conditions. A recent prospective feasibility study in cancer patients receiving oncologic-dose bisphosphonates or denosumab reported 100% implant survival and 97.4% implant success at 2 years—defined as absence of mobility, PD > 5 mm, BOP, or suppuration—with no MRONJ events directly attributable to implant placement.[46] Peri-implant mucosal inflammation was observed in 17% of sites, largely associated with plaque accumulation, with modified plaque index scores ranging from 20% to 40%.[46] Notably, implant placement timing appears to be a critical determinant of outcomes. Implant placement performed prior to the initiation of oncologic-dose bisphosphonate therapy was independently associated with substantially lower odds of implant disease progression compared with placement after treatment initiation (adjusted OR: 0.16; 95% CI: 0.08–0.33; $p < 0.0001$).[47]

Even though most evidence comes from case series and preclinical studies, these data may collectively suggest a potential clinical interplay between peri-implant inflammation and MRONJ in patients receiving high-dose bisphosphonates; however, this association remains incompletely understood and should be interpreted cautiously. Case series and clinical reports describe patients receiving oncologic-dose bisphosphonates therapy commonly reporting pain and suppuration associated with functioning implants, with variable findings including BOP, peri-implant PD ≥ 5 mm, and mucosal recession, ultimately leading to MRONJ diagnosis and requiring surgical intervention, including implant removal and debridement.[48–50] Notably, MRONJ cases have been reported even years after successful osseointegration, suggesting that the timing of high-dose bisphosphonate exposure relative to implant placement may represent an important modifying factor. Consistent with these findings, preclinical evidence supports these clinical observations. Rat peri-implantitis models exposed to oncologic-dose zoledronic acid have demonstrated histological evidence of increased detection of non-vital bone areas, along with variable increases in pro-inflammatory mediator expression and inflammatory cell infiltration as assessed by immunohistochemistry.[51,52]

Importantly, peri-implant inflammatory conditions and MRONJ represent biologically and clinically distinct entities. While peri-implantitis is primarily driven by dysbiosis-associated deregulated inflammation, MRONJ is characterized by impaired bone remodeling and necrosis in the context of antiresorptive exposure. Although peri-implant inflammation and surgical interventions may act as local modifying factors in MRONJ development, the available evidence does not support a direct causal relationship between peri-implantitis and MRONJ.

Indirect clinical evidence also indicates increased susceptibility to inflammatory breakdown in this population. In cancer patients with bone metastases receiving intravenous bisphosphonates, significant deterioration in periodontal parameters—including increased PD, CAL, and bleeding indices—has been reported, alongside worsening oral hygiene status.[53] While not implant-specific, these findings reinforce the concept of an impaired host response to oral inflammation.

Overall, although implant survival may be achievable in carefully selected cases, the elevated risk of MRONJ and the potential for rapid progression in the presence of peri-implant inflammation warrant a highly cautious, individualized approach in patients receiving high-dose systemic bisphosphonates. In contrast, the risk of MRONJ in patients receiving oral bisphosphonates for osteoporosis appears to remain extremely low during the first

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years of therapy and does not significantly exceed that observed in placebo-treated populations for up to 2 years. With longer exposure, however, the risk gradually increases, reflecting the cumulative skeletal retention and prolonged suppression of bone remodeling associated with bisphosphonate therapy. Reported MRONJ incidence rates range from approximately 0.2 to 10 cases per 10 000 patient-years, with the highest risks observed in patients receiving long-term therapy and in the presence of additional local or systemic risk factors.[54,55] Therefore, treatment duration should be considered as one component of an individualized clinical risk assessment rather than an isolated determinant of treatment decisions.

2.5 | Antiresorptive monoclonal antibodies: Denosumab and dual-action osteoanabolic/antiresorptive Romosozumab

A pivotal shift occurred around the year 2000, when drug development became increasingly guided by molecular insights into bone biology, rare skeletal diseases and the limitations of earlier therapies—including gastrointestinal intolerance, renal contraindications, and rare but serious adverse events like MRONJ.[21,56] These advances led to the introduction of targeted biologics, notably denosumab (e.g., Prolia), a monoclonal antibody against RANKL, and more recently romosozumab (e.g., Evenity), an anti-sclerostin antibody. Both were developed following the recognition of the pivotal role of RANKL in osteoclast-mediated bone resorption, whereas romosozumab targets sclerostin, thereby enhancing Wnt/β-catenin signaling to stimulate bone formation while concomitantly suppressing bone resorption.[54,57] Their administration has demonstrated significant reductions in overall fracture incidence, with efficacy comparable or exceeding conventional bisphosphonate therapy in specific populations. However, to mitigate the risk of rebound-associated vertebral fractures after denosumab discontinuation and the potential cardiovascular adverse events observed with romosozumab, therapy must be transitioned to another antiresorptive agent to maintain bone mass and continued fracture protection.[54,57]

2.5.1 | Denosumab

In the context of peri-implant health, a substantial gap in the literature remains, as no studies to date have systematically evaluated peri-implant clinical parameters such as PD, BOP, or plaque accumulation as primary outcomes in patients receiving denosumab. Available retrospective studies report implant survival rates ranging from 90.9% to 98.1% in denosumab-treated patients (5/55 and 2/104 implants lost), with no significant differences compared to non-exposed individuals or those receiving bisphosphonates.[58,59] Similarly, peri-implant CBL appears comparable across groups, with slightly lower mean CBL reported in denosumab-treated patients at 36 months (−0.90 ± 0.57 mm), although these differences were not statistically significant.[58]

At present, there is no evidence supporting the adjunctive use of denosumab in the treatment of peri-implantitis. A preclinical study found no significant differences in peri-implant defect fill or implant loss in animals receiving denosumab in the context of experimental peri-implantitis treatment compared to other antiresorptive therapies or non-exposed controls.[9] However, additional experimental data suggest that RANKL inhibition may modulate peri-implant bone loss under inflammatory conditions. In a murine peri-implantitis model, local administration of an anti-RANKL antibody to the palatal gingiva (three applications at two-day intervals) significantly reduced bone loss compared to ligature-only controls.[60]

Additional preclinical studies, although not specific to peri-implantitis, provide mechanistic insights into the effects of RANKL inhibition on peri-implant bone. In rat models, subcutaneous weekly anti-RANKL therapy has been shown to improve screw fixation in cancellous bone, with increased bone volume fraction (BV/TV) comparable to that achieved with high-dose bisphosphonates.[61] Similarly, biweekly subcutaneous anti-RANKL (OPG), alone or in combination with intermittent parathyroid hormone (iPTH), has been associated with increased periprosthetic bone volume and bone area under loading conditions.[62] While these findings suggest that RANKL inhibition may enhance peri-implant bone density and mechanical stability when administered locally or systemically, their direct relevance to peri-implantitis treatment remains uncertain, where inflammatory-driven bone loss and biofilm-related factors play a central role.

Available clinical studies have primarily focused on safety outcomes rather than potential therapeutic efficacy, particularly the risk of MRONJ, with heterogeneous and sometimes conflicting results. Earlier analyses suggested that denosumab might be associated with a higher risk of MRONJ compared with conventional bisphosphonates (RR 1.61; 95% CI: 1.05–2.48).[63] However, more recent evidence indicates lower exposure-adjusted MRONJ incidence rates in patients receiving denosumab for osteoporosis—approximately 5.2 per 10 000 person-years—and an updated meta-analysis found no statistically significant association between denosumab use and MRONJ. Notably, the extremely wide confidence intervals reported (RR 25.98; 95% CI: 0.31–2165.63) highlight substantial imprecision and limited certainty of the available evidence.[18,64]

2.5.2 | Romosozumab

Unlike purely antiresorptive agents, romosozumab exerts a dual effect by simultaneously stimulating osteoblastic bone formation and inhibiting osteoclast-mediated resorption through sclerostin inhibition. Accordingly, romosozumab occupies an intermediate position between antiresorptive and anabolic therapies, functionally resembling agents such as teriparatide, although via distinct molecular

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pathways. However, available evidence regarding its effects on oral inflammatory bone diseases remains extremely limited. Current data are derived primarily from preclinical models of osseointegration, bone regeneration and periodontitis, and no studies have specifically evaluated its impact on peri-implant health parameters or peri-implantitis.

From a safety perspective, large clinical trials evaluating romosozumab for osteoporosis treatment have reported MRONJ only rarely, and most commonly in association with invasive oral procedures.[54,65] Preclinical data suggest a potential benefit of romosozumab on implant osseointegration under osteoporotic conditions. In a rat implant fixation model of osteoporosis, romosozumab significantly increased bone-to-implant contact, bone area fraction, and implant stability, outperforming both parathyroid hormone (PTH) alone and combined PTH plus denosumab regimens.[66] Otherwise, in another rat study, implant surface functionalization with an anti-sclerostin coating did not result in significant improvements in implant stability or micro-CT-derived bone parameters under osteoporotic conditions.[67] However, whether these anabolic effects translate into clinically meaningful benefits in inflammation-driven peri-implant bone loss remains to be determined.

Overall, while romosozumab demonstrates administration-dependent anabolic effects on peri-implant bone under both healthy and osteoporotic conditions in preclinical models, its role in inflammation-driven conditions such as peri-implantitis remains undefined.

2.6 | Summary and clinical implications

Collectively, the available evidence suggests that antiresorptive therapies exert heterogeneous and agent-specific effects on peri-implant tissues, largely influenced by their mechanism of action, dosage, and timing of administration (Table 1). While conventional agents such as bisphosphonates and denosumab do not appear to substantially compromise implant survival or marginal bone stability under controlled conditions, subtle changes in peri-implant inflammatory parameters may occur, particularly when therapy is initiated after implant placement.

Importantly, high-dose antiresorptive regimens used in oncologic settings remain associated with a clinically relevant risk of MRONJ, warranting careful patient selection and risk stratification. In contrast, earlier therapies such as hormone replacement therapy and selective estrogen receptor modulators show limited and inconsistent evidence regarding peri-implant outcomes, reducing their clinical relevance in this context. Emerging biologics such as romosozumab offer mechanistically distinct approaches to bone modulation; however, their role in peri-implant health and disease remains largely unexplored. Overall, current data support the safe use of implant therapy in most patients receiving antiresorptive medications, provided that individualized risk assessment, strict infection control, and long-term peri-implant maintenance are ensured.

3 | OSTEOIMMUNOLOGY OF ANTIRESORPTIVE THERAPY ON PERI-IMPLANT BIOLOGY

Although antiresorptive therapies are primarily prescribed to modulate skeletal bone turnover, growing evidence suggests that these agents may also influence immune pathways involved in peri-implant tissue homeostasis and inflammatory osteolysis. In the context of peri-implant diseases, where osteoclast activation is tightly coupled to immune dysregulation, these osteoimmune interactions may contribute to differences in tissue response, inflammatory resolution, and susceptibility to bone resorption.[68] However, the clinical relevance of these mechanisms remains incompletely established, and much of the current evidence derives from experimental or preclinical models rather than direct peri-implant clinical studies. Accordingly, the following sections focus on osteoimmune pathways with potential translational relevance to peri-implant tissue homeostasis, inflammatory breakdown, and wound healing (Figure 1).

3.1 | Monocyte lineage cells and T lymphocytes as potential drivers of peri-implant osteolysis

A substantial body of evidence has established that the immune system exerts a profound influence on bone turnover under both physiological and pathological conditions. Pathological bone resorption during peri-implantitis is driven by immune dysregulation, whereby aberrant activation of immune cell subsets leads to excessive production of osteoclastogenic mediators and sustained osteoclast activity.[68,69] At the core of this process lies the osteoclast, the final common effector of inflammatory bone resorption and the principal cellular target of antiresorptive therapy.[70,71] In peri-implant tissues, hematopoietic precursors are continuously recruited from the circulation and locally differentiate into osteoclasts under the influence of a pro-inflammatory microenvironment enriched in macrophage colony-stimulating factor (M-CSF) and RANKL during peri-implantitis.[72] Accordingly, antiresorptive therapies may influence peri-implant tissue outcomes not only through direct suppression of osteoclast activity but also by modifying the inflammatory cellular networks that regulate osteoclastogenesis and tissue healing.

Beyond serving as osteoclast precursors, cells of the monocyte lineage—including macrophages and dendritic cells—actively shape the osteoclastogenic niche.[73] Macrophages in peri-implant lesions exhibit a predominantly M1 pro-inflammatory phenotype,[74] characterized by the production of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, all of which promote osteoclast differentiation either directly or through upregulation of RANKL expression in stromal and osteoblastic cells.[75,76] Moreover, these cells contribute to sustained inflammation and tissue breakdown, reinforcing a feed-forward loop that perpetuates osteolysis. Importantly, the plasticity of monocyte-derived cells suggests that shifts in their activation state may critically determine the balance between tissue destruction and resolution.[76,77] Because peri-implantitis is characterized by

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TABLE 1 Human clinical studies evaluating antiresorptive therapy on implant-related outcomes.

Antiresorptive	Reference	Study design	Sample	Drug indication	Route/dose//duration	Follow-up	Peri-implant Results	MRONJ incidence
HRT	August M. et al. (2001)	Retrospective cohort	Postmenopausal women; 75 HRT users, 168 non-users	Estrogen – Osteoporosis (menopause)	Oral or transdermal/ NR/NR	Mean 3.6 years	Implant survival: ns Failure: HRT 6.3% vs. 13.6% non-users ($p=0.039$)	NR
SERMs	*No human studies evaluating implant-related outcomes*							
Oral bisphosphonates	Bell BM. et al. (2008)	Retrospective cohort	42 patients/101 implants	Alendronate, risedronate, ibandronate – NR	Oral/ NR/6 months-11 years prior to implants	Mean 3.08 years (range 0.25–7.42 years)	Implant failure: 5% (early) (ns) MBL: 2 mm in 1 implant BOP, PD change: none	No MRONJ
	Memon et al. (2012)	Retrospective cohort	71 BP users/71 controls; 114 BP/144 control implants	Alendronate, risedronate – Osteoporosis	Oral/NR/NR	Mean 68.2 months (BP); 71.9 months (control)	Survival: 99.1% BP vs. 99.3% controls (ns); MBL: ns	NR
	Tallarico et al. (2016)	Prospective multicenter observational	18 patients; implants NR	Alendronate – Osteoporosis (menopause)	Oral/NR/Mean 8.3 years (range 3–17 years)	12 months	Implant survival: 100% MBL: ns	NR
	Vivek et al. (2024)	RCT	60 patients (30 BP, 30 control); implants NR	Alendronate – Osteoporosis	Oral/70 mg/wk/NR	12 months	Implant survival: 100% (ns) PD, BOP, plaque, peri-implant diseases: ns	NR
	Ciardo et al. (2023)	Retrospective observational cohort	NR patients (antiresorptive subset); exact implant count NR	Alendronate, risedronate, and denosumab – Osteoporosis	Oral and SC/NR	NR	Implant survival: ns PD, BOP, plaque, peri-implant diseases: ns	NR
	Seki K. et al. (2024)	Prospective cohort	30 ART users/49 controls; implant count NR	Alendronate, risedronate, and denosumab – Osteoporosis	Oral and SC/NR therapy initiated after implant placement	Mean 13.2 ± 6.4 years	Implant survival: ns PD change: ART 1.1 +/− 2.0 mm; $p=0.0006$ BOP change: ART 0.2 +/− 0.4; $p<0.01$	NR
	Seki K. et al. (2025)	Nested case–control study	61 patients; 192 implants (ART $n=24$, control $n=37$)	Alendronate, risedronate, and denosumab – Osteoporosis	Oral and SC/NR/therapy initiated after implant placement	Mean 13.2 ± 6.4 years	Implant survival: ns Peri-implantitis: ART adjusted OR: 3.91 [95% CI: 1.29–11.9] Disease progression: ART adjusted OR: 1.86 ([95% CI: 0.75–4.58]) for PD/BOP changes	NR
	Hjortholt CO et al. (2024)	Prospective cohort	27 patients/39 implants (22 completed prosthetic tx; 13 patients/23 implants at 2-year follow-up)	High-dose ART – Cancer (bone metastases, multiple myeloma, hematological malignancy)	IV BPs and/or denosumab/Mean 25 months (range 3–68 months) at inclusion	2 years after prosthetic loading	Implant survival: 100% Plaque: 47% implants Mucositis: 17%–39% implants Peri-implantitis: 0	2 MRONJ cases NOT related to implant placement

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TABLE 1 (Continued)

Antiresorptive	Reference	Study design	Sample	Drug indication	Route/dose//duration	Follow-up	Peri-implant Results	MRONJ incidence
IV bisphosphonates	Ahmed A. et al. (2026)	Retrospective cohort	366 patients/915 implants	High-dose ART – Cancer (breast cancer 68%, multiple myeloma 25%, lung/prostate cancer)	IV Zoledronic acid (4 mg); SC denosumab (120 mg); oral alendronate (70 mg/week)/NR	≥ 18 months after last invasive dental procedure; ≥ 12 months after implant loading	Implant failure: Pre-ART: 5.9%; Intra-ART: 28.2%; Post-ART: 36.0% pre-ART implant placement lower failure odds (OR: 0.16; [95% CI: 0.08–0.33]; $p < 0.0001$)	1 MRONJ case after implant placement intra-ART
	Son J. et al. (2024)	Retrospective cohort	38 patients with MRONJ adjacent to implants	High-dose ART – Cancer (bone metastases)	IV BPs and denosumab	NR	Peri-implantitis present prior to MRONJ in 68.4% of cases	MRONJ in all cases
	Kim JY. et al. (2020)	Retrospective cohort	80 ART users (344 implants)/80 matched controls (378 implants)	Ibandronate (oral 150 mg/month; IV 3 mg/3-month), risedronate (oral 35 mg/week), alendronate (oral 70 mg/week), zoledronate (IV 4 mg/5 mL yearly) denosumab (SC 60 mg/6-month) – Osteoporosis and multiple myeloma, therapy initiated after implant placement	Mean 85.3 months (SD 36.7)		Implant survival: 89.83% ART vs. 96.03% controls ($p < 0.05$) Implant Failure: Higher in ART ($p = 0.0026$), 14/15 had peri-implantitis, Ibandronate IV = 21.1%, Zoledronate = 21.2%, Higher in Pre-existing MBL ($p < 0.0001$) Pre-existing MBL aggravated after ARD in 71.1% of cases; Pre-existing peri-implantitis: HR 7.32 for implant failure	11/35 failed implants were associated to MRONJ
Denosumab	Watts NB. et al. (2019)	RCT (secondary analysis)	3591 postmenopausal women; 1621 reporting ≥ 1 invasive oral procedure including implants	Denosumab -Osteoporosis (menopause)	SC 60 mg every 6 months/up to 10 years	Up to 10 yrs	No implant failures	MRONJ: 0.68% in OPE group vs. 0.05% without OPE 13 MRONJ cases over 10 yr.; exposure-adjusted rate: 5.2/10000 person-years
	Hwang J. et al. (2026)	Retrospective cohort	806 postmenopausal women; 1694 implants/ART vs. controls	ART including Denosumab – Osteoporosis (menopause)	SC 60 mg every 6 months/min 12 months	Mean 35.59 ± 20.25 months	Implant survival: DMAB 98.08% vs. 98.24% controls (ns) Peri-implantitis: 2 BPs, 10 control, and 0 DMAB PI-failed implants MBL: DMAB mean −0.90 ± 0.57 vs. −0.90 ± 0.57 mm control (ns) at 36 months	0 MRONJ cases in DMAB group
Romosozumab	Cosman F. et al. (2016)	Multicenter RCT	7180 postmenopausal women	Romosozumab – Osteoporosis (menopause)	SC 210 mg monthly × 12 months, then denosumab 60 mg SC every 6 months × 12 months	24 months	NR	2 MRONJ cases not associated to implant placement (ill-fitting denture and tooth extraction) Incidence: 0.056% over 24 months

Note: Included: Human primary studies (RCT, prospective cohort, retrospective cohort, case–control, cross-sectional with ≥ 5 patients) evaluating the effect of antiresorptive therapy on peri-implant outcomes (implant survival/failure, marginal bone loss, peri-implantitis, peri-implant mucositis, peri-implant clinical parameters, or MRONJ around or related to dental implants). Excluded: Animal studies, in vitro studies, case reports, case series with < 5 patients, reviews/systematic reviews/meta-analyses (consulted only to identify primary studies).

Abbreviations: ART, antiresorptive therapy; BOP, bleeding on probing; BP, bisphosphonate; DMAB, denosumab; HRT, hormone replacement therapy; MBL, marginal bone loss; MRONJ, medication-related osteonecrosis of the jaw; NR, not reported; ns, no significant difference between groups; OPE, oral procedure/event; PD, probing depth; RCT, randomized controlled trial; SC, subcutaneous.

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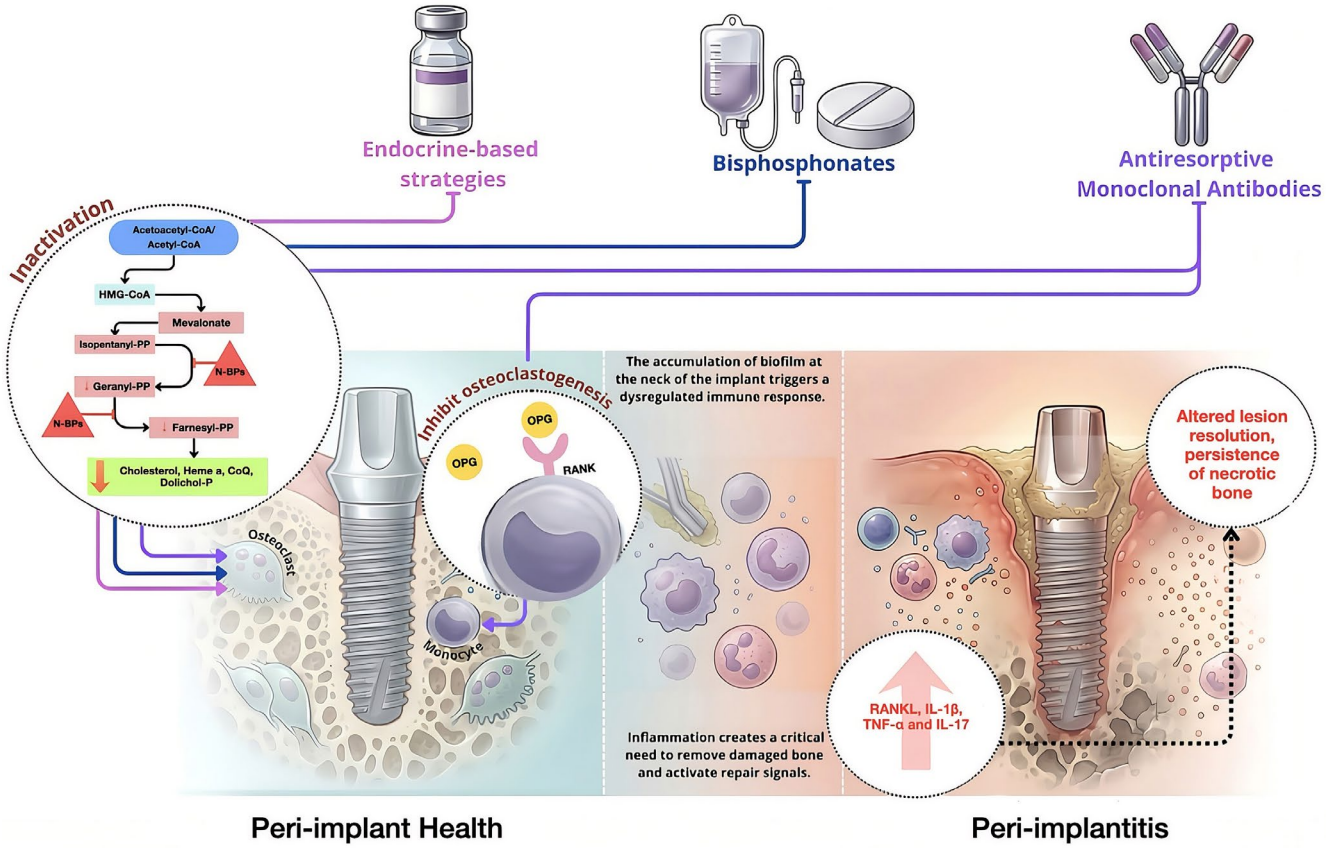

FIGURE 1 Antiresorptive therapy influences peri-implant tissue homeostasis and inflammatory responses. Endocrine-based therapies and bisphosphonates suppress osteoclast activity through modulation of the mevalonate pathway, whereas the anti-RANKL monoclonal antibody denosumab inhibits osteoclast differentiation by preventing RANKL–RANK interaction on osteoclast precursors. Both mechanisms ultimately reduce osteoclast formation and bone resorptive activity. Under peri-implant health, osseointegration and immune homeostasis are maintained. Following bacterial challenge, antiresorptive therapy may further modify an already dysregulated host immune response, impairing osteoimmune adaptation and inflammatory resolution. In susceptible individuals, these changes may contribute to the persistence of peri-implant inflammation, defective clearance of inflammatory debris and necrotic or avascular bone, and sustained expression of pro-inflammatory mediators, including receptor activator of nuclear factor κB ligand (RANKL), interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), and IL-17, ultimately promoting peri-implant tissue destruction.

persistent inflammatory osteolysis, alterations in macrophage activation states may influence not only bone resorption but also inflammation resolution and healing around implants.

Within this osteoclast-centric framework, activated T lymphocytes play a pivotal role in osteoclastogenesis through the expression of osteoclastogenic mediators, most notably RANKL in both its membrane-bound and soluble forms.[78,79] In addition to RANKL-dependent mechanisms, T cells further amplify osteoclastogenesis through production of TNF-α, IL-17, among other pro-inflammatory mediators, thereby reinforcing inflammatory bone resorption.[80] Furthermore, T cell–derived TNF-α can synergize with RANKL to amplify osteoclast formation and activation, while also inducing RANKL expression in mesenchymal cells, thus expanding the osteoclastogenic pool.[81,82]

Among T lymphocyte populations, the balance between T helper type 17 (Th17) and T regulatory (Treg) cells has emerged as a central determinant of pathologic bone remodeling dynamics in peri-implantitis.[68,83] Th17 cells, mainly through secretion of interleukin (IL)-17 and RANKL—supported by the characteristic enrichment of inflamed tissue IL-6 and IL-23 that promotes their phenotype expression maintenance—directly and indirectly promote osteoclast differentiation and activation, thereby enhancing bone resorption.[84,85] In contrast, Tregs exert an opposing, bone-protective role by suppressing the Th17-mediated osteoclastogenesis via the expression of transforming growth factor (TGF)-β1, interleukin-10, and IL-35, as well as by direct cell–cell contact–dependent inhibition of osteoclast precursors.[83,86] An imbalance favoring Th17 polarization—frequently observed in chronic inflammatory diseases—disrupts this osteoimmune balance, resulting in heightened osteoclastic activity and bone loss.[84,87] As inflammatory osteolysis is central to peri-implantitis pathogenesis, disruption of the Th17/Treg balance may represent a clinically relevant mechanism contributing to impaired inflammatory resolution and sustained peri-implant bone loss.

Taken together, pathological peri-implant osteolysis results from the interaction between osteoclast precursor expansion and persistent immune-mediated osteoclastogenic signaling, largely driven by monocyte lineage cells and activated T lymphocytes.[60,88] Within this framework, antiresorptive therapies may influence peri-implant

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tissue dynamics not only through suppression of osteoclast activity, but also through indirect modulation of immune pathways involved in inflammatory bone remodeling. However, the extent to which these osteoimmune effects translate into clinically meaningful peri-implant outcomes remains unclear, particularly given the limited availability of human peri-implant studies.[89]

3.2 | Bisphosphonates

Beyond their antiresorptive properties, bisphosphonates have been shown to exert immunomodulatory effects that may influence inflammatory bone remodeling, as well as adverse events in bone and peri-implant tissues. These agents—classified as nitrogen-containing (e.g., alendronate, zoledronate, ibandronate) and non–nitrogen-containing (e.g., etidronate, clodronate)—primarily target osteoclasts by interfering with the mevalonate pathway. Specifically, nitrogen-containing bisphosphonates (N-BP) inhibit farnesyl pyrophosphate synthase, thereby preventing the prenylation of small GTP-binding proteins essential for cytoskeletal organization, vesicular trafficking, and cell survival.[90] Nevertheless, as bisphosphonates rapidly bind to mineralized bone surfaces and exhibit limited systemic immune-cell exposure under routine clinical conditions, the direct clinical relevance of these immunomodulatory effects in peri-implant tissues remains uncertain.

Importantly, this biochemical disruption is not restricted to mature osteoclasts but extends to osteoclast precursors within the monocyte–macrophage lineage, including circulating monocytes, tissue macrophages, and dendritic cells.[91] In postmenopausal women with osteoporosis, N-BP therapy has been associated with a significant reduction in circulating monocyte populations and decreased expression of key surface markers such as M-CSFR and CD11b, by 53% and 49%, respectively ($p < 0.01$), resulting in a marked decrease in their numbers after 48 weeks of treatment.[92] In vitro, N-BPs—particularly zoledronate—reduce monocyte viability and impair their differentiation into osteoclasts,[93,94] reinforcing their primary antiresorptive mechanism.[94,95] These findings suggest that bisphosphonates may influence inflammatory cell function beyond osteoclast suppression, although the translational significance of these observations in peri-implant tissues remains unclear.

3.2.1 | Macrophage polarization and inflammatory reprogramming

Apart from their effects on monocyte viability and differentiation, bisphosphonates have been reported to influence macrophage functional polarization.[96] Exposure to N-BPs promotes a shift toward a pro-inflammatory M1 phenotype, characterized by enhanced production of IL-1β, IL-6, and TNF-α, alongside suppression of M2-mediated tissue repair and angiogenic responses.[97,98]

The M1 polarization profile is also considered a hallmark of peri-implantitis immunopathogenesis,[74,75] where M1 macrophages are enriched within peri-implant inflamed tissues and amplify pro-inflammatory cytokine production, perpetuate chronic inflammation, and promote the recruitment of Th1 and Th17 lymphocytes, reinforcing osteoclastogenic peri-implant bone breakdown.[99,100] Accordingly, the overexpression of M1 phenotype markers correlates with disease severity, whereas macrophage depletion or M2 induction attenuates inflammation and bone loss.[77,101] Collectively, these observations suggest that bisphosphonates' influence on the macrophages' functional profile may have an impact on the development of peri-implant diseases.

Clinical evidence of the direct immune-modulatory effect of bisphosphonates on patients affected by peri-implantitis remains limited. Otherwise, preclinical studies further support a bisphosphonate-driven shift toward pro-inflammatory macrophage responses. Animal models have shown that systemic N-BPs administration—particularly zoledronic acid—increases the number of $CD68^+$ and $iNOS^+$ macrophage populations, reflecting an enhanced M1 polarization.[96] In experimental peri-implantitis, bisphosphonates exposure is associated with elevated $CD68^+$ and $CD11b^+$ M1 macrophage infiltration, as well as increased detection of TNF-α and IL-1β in peri-implant tissues.[51,52,102] Additionally, bisphosphonates have been shown to facilitate bacterial invasion by periodontal pathogens, in particular *Porphyromonas gingivalis*, demonstrating intracellular infection of epithelial cells and upregulation of IL-1β and IL-6 expression both in vivo and in vitro,[103] potentially amplifying local M1-driven inflammatory cascades and suggesting a possible contribution to dysbiosis-associated inflammation.

Collectively, these findings indicate that while bisphosphonates suppress osteoclastogenesis, they may simultaneously favor pro-inflammatory M1 macrophage polarization under chronic inflammatory conditions, raising the possibility that similar osteoimmune alterations could influence the peri-implant disease microenvironment.

3.2.2 | Antiresorptive modulation of the Treg/Th17 axis

N-BPs, particularly zoledronic acid (ZA), can exert significant immunomodulatory effects over the Treg/Th17 axis, a central regulator of osteoimmune homeostasis. Experimental and clinical evidence indicates that ZA can impair Treg expansion, migration, and suppressive function in a dose-dependent manner. In postmenopausal patients receiving zoledronate, reductions in soluble CTLA-4 levels—a checkpoint receptor expressed in Tregs—correlate with acute-phase reactions.[104] Consistently, Tregs from ZA-treated *patients* exhibit an altered phenotype characterized by decreased capacity to suppress inflammation and T cell proliferation.[105] Given the established role of the Treg/Th17 balance in peri-implant inflammatory osteolysis,[68] these findings raise the possibility that high-dose bisphosphonate therapy could influence inflammatory resolution and tissue homeostasis in susceptible peri-implant environments.

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In parallel, ZA has been shown to influence Th17 responses, although findings remain context-dependent. In experimental models of MRONJ, ZA administration promotes a shift toward a pro-inflammatory phenotype, characterized by reduced Treg activity and increased Th17-like responses.[106] In contrast, clinical studies in osteoporotic patients treated with N-BPs have reported reductions in circulating Th17-associated cytokines alongside increased levels of Treg-associated mediators after a year of therapy.[107] Similarly, intragastric administration of alendronate attenuates Th17-associated cytokine production in an airway inflammation model.[108] These divergent findings likely reflect differences in dosage, treatment duration, and inflammatory context, highlighting the complexity of extrapolating systemic immune profiles to local peri-implant tissue responses.

Importantly, studies in oncologic settings—where higher doses of ZA are administered—provide more consistent evidence of Treg impairment. In patients with skeletal metastases, ZA treatment significantly reduces circulating Treg frequencies without substantially affecting their viability, suggesting functional dysregulation rather than simple depletion.[105] The relevance of this imbalance is particularly evident in MRONJ models, where adoptive transfer of Tregs prevents the development of MRONJ-like lesions and improves socket healing following tooth extraction in ZA-treated animals. Conversely, additional immunosuppression affecting Tregs—such as anti-CD25 treatment—further exacerbates MRONJ-like disease.[109] Together, these findings support the concept that impaired Treg function, coupled with unchecked inflammatory responses, may contribute to defective mucosal healing and persistent osteoimmune dysregulation under high-dose bisphosphonate exposure.

Taken together, N-BP–induced alterations in the Treg/Th17 axis may represent one potential osteoimmune mechanism contributing to impaired healing and susceptibility to MRONJ under conditions of surgical injury or persistent inflammation. By disrupting the balance between immune regulation and inflammation, bisphosphonates may not only affect osteoclast activity directly but also impair the immune control of tissue homeostasis, particularly in the context of peri-implant environments exposed to microbial challenge and surgical instrumentation.

3.2.3 | γδ T cells dysregulation and osteoimmune consequences

Apart from their well-characterized effects on the monocyte–macrophage lineage, N-BPs have also been reported to influence distinct immunomodulatory actions on T lymphocytes, particularly γδ T cells. The inhibition of the farnesyl pyrophosphate synthase within the mevalonate pathway by N-BPs,[110] leads to the intracellular accumulation of isopentenyl pyrophosphate (IPP)—a potent phosphoantigen selectively recognized by Vγ9Vδ2 T cells (γδ T cells).[111,112] The consequent activation of γδ T cells induces the rapid release of pro-inflammatory cytokines, including interferon (IFN)-γ and TNF-α, which underlies the acute-phase reactions commonly observed following systemic N-BP administration (occurring after 7-8 days).

Over time, however, repeated or chronic exposure to N-BPs appears to desensitize the γδ T-cell axis. This initial activation phase is followed by progressive exhaustion and depletion of γδ T cells, resulting in a marked decline in circulating Vγ9Vδ2 cell populations.[113,114] This reduction is particularly evident in patients receiving long-term intravenous bisphosphonate therapy, in whom γδ T-cell deficiency becomes apparent after approximately 1 year of treatment, whereas those on oral regimens, such as ibandronate, exhibit a more gradual decline.[115]

Given that monocytes are the primary cells internalizing bisphosphonates and presenting IPP-derived antigens,[115,116] this interaction establishes a direct functional link with γδ T-cell responses. Moreover, the observed inverse relationship between circulating monocytes and γδ T cells further suggests a role for γδ T cells in regulating monocyte homeostasis, potentially limiting the persistence of dysfunctional or pro-inflammatory monocyte-derived cells.[115,116] Accordingly, their depletion may allow the accumulation of long-lived, multinucleated monocyte-derived cells—resembling giant osteoclasts observed in patients undergoing N-BP therapy, which exhibit impaired resorptive activity and delayed apoptosis.[117]

Within oral tissues γδ T cells represent a major physiological source of IL-17, underscoring their central role in balancing protective immunity and inflammatory homeostasis.[118,119] Disruption of this axis may contribute to IL-17-driven osteoclastogenesis under chronic inflammatory conditions, including peri-implantitis. Experimental models highlight the context-dependent role of γδ T cells in these settings. While their absence appears to have limited impact during early dysbiosis-driven inflammation,[120] γδ T cells may promote sustained inflammatory bone loss under conditions of systemic bacterial exposure—particularly following *P. gingivalis* oral gavage—through enhanced recruitment of neutrophils and monocytes.[121] Although direct evidence in peri-implantitis remains scarce, shared osteoimmune pathways suggest that γδ T cell–mediated IL-17 responses may similarly contribute to peri-implant bone resorption, representing a relevant gap in current knowledge.

Beyond their pro-inflammatory role, γδ T cells contribute to tissue repair and homeostasis through the production of mediators such as amphiregulin (AREG) and IL-17A, which support epithelial regeneration, immune regulation, and bone formation under physiological conditions.[122,123] Accordingly, depletion of γδ T cell-derived AREG exacerbates experimental periodontitis severity, whereas the administration of exogenous AREG rescued pathologic osteolysis.[124] Mechanistically, AREG promotes the expansion of Tregs and M2 macrophages, thereby facilitating mucosal healing and supporting inflammation resolution.[125] In parallel, γδ T-derived IL-17A is central for the differentiation of mesenchymal cells to osteoblasts during intramembranous osseous healing,[123] thus potentially contributing to guided bone regeneration and implant osseointegration.

Collectively, γδ T cells appear to exert context-dependent roles in oral inflammatory homeostasis, contributing both to inflammatory

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osteolysis and tissue repair. Chronic depletion or functional dysregulation of these cells during long-term bisphosphonate therapy could theoretically impair mucosal healing and regenerative responses within peri-implant tissues. However, direct peri-implant clinical evidence supporting these mechanisms remains limited.

Taken together, these findings suggest that the immunomodulatory effects of N-BPs involve coordinated alterations in innate and adaptive immune responses, simultaneously modulating osteoclast function, macrophage polarization, T-cell responses, and inflammatory resolution which may influence peri-implant inflammatory homeostasis. The proposed osteoimmune mechanisms are summarized in Figure 2.

3.3 | Denosumab

Denosumab represented a major advancement in antiresorptive therapy by preventing the interaction between RANKL and its receptor RANK on osteoclast precursors. Through this mechanism, denosumab effectively suppresses osteoclast differentiation, activity, and survival, thereby reducing bone resorption.[126] However, RANKL signaling extends beyond osteoclastogenesis and plays a broader role in immune regulation, including dendritic cell maturation and thymic T-cell selection, underscoring the central role of the RANK/RANKL axis in coordinating skeletal and immune homeostasis. Nevertheless, most available evidence derives from osteoporosis or oncologic settings, and direct peri-implant clinical studies remain scarce.

3.3.1 | RANKL-dependent modulation of monocyte lineage cells and macrophage polarization

At the level of the monocyte–macrophage lineage, denosumab indirectly modulates osteoclast precursor dynamics by blocking RANKL-dependent differentiation signals. In patients with osteoporosis, denosumab administration has been associated with a rapid increase in circulating $CD14^+$ monocytes, likely reflecting reduced differentiation into osteoclasts and consequent accumulation in peripheral tissues.[127] In contrast to bisphosphonates, denosumab does not appear to impair macrophage viability or differentiation in vitro, supporting a more selective effect on osteoclastogenesis rather than broad suppression of the monocyte lineage.[93]

Beyond precursor dynamics, emerging evidence suggests that RANKL inhibition may also influence macrophage functional

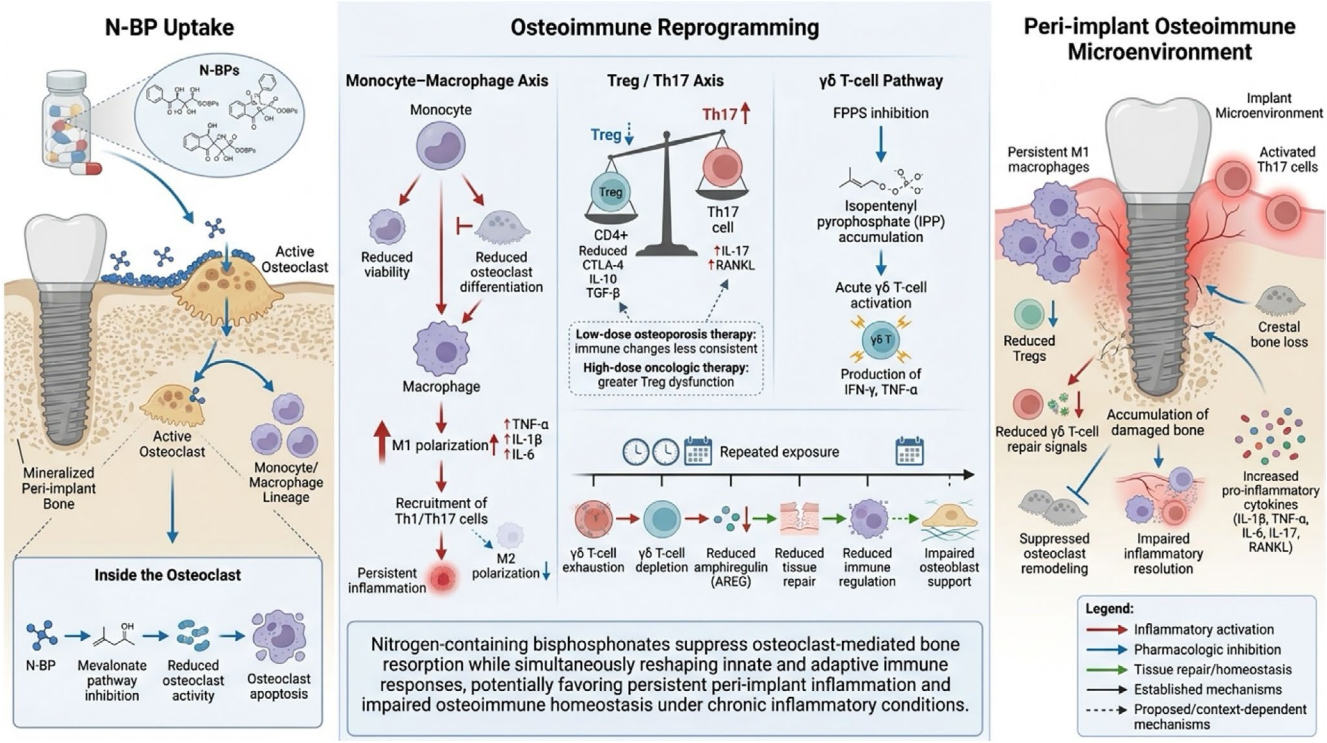

FIGURE 2 Osteoimmune mechanisms by which nitrogen-containing bisphosphonates modulate peri-implant tissue homeostasis and inflammatory bone remodeling. Nitrogen-containing bisphosphonates (N-BPs) inhibit the mevalonate pathway, suppressing osteoclast differentiation, function, and survival. Beyond their antiresorptive effects, N-BPs may also modulate innate and adaptive immunity by promoting pro-inflammatory M1 macrophage polarization, altering the Treg/Th17 balance, and inducing context-dependent γδ T-cell dysregulation. Collectively, these effects may impair inflammatory resolution and bone remodeling, thereby promoting persistent peri-implant inflammation in susceptible individuals. Solid arrows indicate established mechanisms, whereas dashed arrows represent proposed pathways with limited peri-implant evidence.

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polarization. In preclinical models, denosumab-functionalized nanoparticles reduce pro-inflammatory M1 macrophages while promoting M2 polarization, in association with enhanced mesenchymal stem cell proliferation and osteogenic differentiation.[128] These findings support a role for RANKL signaling in shaping the inflammatory microenvironment and suggest that its inhibition may favor tissue repair under certain conditions.

However, this regulatory effect appears to be highly context-dependent. In experimental models of medication-related osteonecrosis of the jaw (MRONJ), particularly under high-dose anti-RANKL regimens and in combination with chemotherapy, alterations in macrophage dynamics have been linked to impaired wound healing. Notably, cessation of anti-RANKL therapy results in increased infiltration of both M1 and M2 macrophages, with a relative shift toward M2 polarization within extraction socket tissues. This dynamic reprogramming is accompanied by persistent inflammation and delayed tissue repair, indicating that disruption of macrophage homeostasis—rather than a fixed polarization state—may underlie defective healing responses.[129,130]

Collectively, these findings suggest that denosumab exerts a modulatory, rather than cytotoxic, effect on the monocyte–macrophage compartment, influencing both osteoclast precursor availability and macrophage functional states. Such alterations may be particularly relevant in peri-implant tissues, where coordinated macrophage transitions are required for resolution of inflammation and maintenance of tissue homeostasis. While this may support regenerative processes under controlled conditions, dysregulation of macrophage polarization dynamics in complex clinical contexts may contribute to impaired wound healing and susceptibility to MRONJ.

3.3.2 | RANKL-dependent modulation of lymphocytes responses

In parallel to its effects on the monocyte lineage, RANKL inhibition by denosumab induces modest but measurable alterations in adaptive immune cell populations. In patients with osteoporosis, treatment has been associated with increased B-cell counts persisting for up to 1 year, as well as transient elevations in circulating T-cell numbers during the first 6 months of therapy.[131] These changes coincide with a transient increase in infection risk during early treatment phases, suggesting a temporary perturbation of immune homeostasis rather than sustained immunosuppression.[132]

While current evidence does not support a direct role of anti-RANKL therapy in modulating Th17 differentiation in osteoporosis settings, its effects on Tregs appear to be more relevant. RANKL signaling contributes to Treg development, recruitment, and functional stability, particularly within specialized microenvironments such as tumors.[133] Accordingly, its inhibition may disrupt Treg-mediated immune regulation, reducing their suppressive capacity and altering immune equilibrium in a context-dependent manner.[134,135] In a model of inflammatory osteolysis, RANKL blockade effectively limited bone resorption but was simultaneously associated with Tregs' impaired function, resulting in a sustained, non-resolving inflammatory response.[135] Such mechanisms may be relevant to peri-implantitis, where Tregs deregulation is associated with inflammatory bone loss and defect severity.[68]

The immunomodulatory effects of denosumab appear more pronounced under high-dose oncologic regimens. In these settings, RANKL blockade has been associated with downregulation of osteopontin (SPP1), a molecule predominantly expressed by myeloid lineage cells and implicated in immunosuppressive tumor microenvironments. This is accompanied by enhanced $CD8^+$ cytotoxic T-cell activity and an increased CD8A:SPP1 ratio, which correlates with improved clinical outcomes in giant cell tumor of bone.[136] In contrast to bisphosphonates, denosumab does not appear to induce γδ T-cell depletion and may preserve or even enhance T-cell activation profiles, indicating a distinct immunological footprint.[137,138] However, when combined with chemotherapy or corticosteroids, denosumab can be associated with more complex immune alterations, including upregulation of inhibitory immune checkpoints such as CTLA-4 and TIM-3, as well as changes in natural killer cell and monocyte populations.[138]

3.3.3 | Integrated osteoimmune effects and peri-implant implications

From a peri-implant perspective, preclinical studies using murine anti-RANKL antibodies demonstrate attenuation of alveolar bone resorption in ligature-induced peri-implantitis models, supporting the concept that direct inhibition of RANKL-mediated osteoclastogenesis can modulate peri-implant tissue breakdown.[60] Nevertheless, the absence of robust clinical evidence precludes the use of denosumab as a therapeutic adjunct in peri-implant diseases at present.

Collectively, denosumab inhibits the RANKL-dependent osteoclastogenic axis while exerting selective, context-dependent immunomodulatory effects, particularly on Treg-mediated immune homeostasis. Compared with bisphosphonates, it appears less disruptive to immune cell viability, especially within the monocyte lineage and γδ T-cell compartment. In peri-implant tissues, these effects may theoretically influence the balance between inflammatory resolution and persistent osteoimmune activation, with potential consequences for bone loss and tissue healing. These proposed mechanisms are summarized in Figure 3.

4 | CLINICAL TRANSLATION OF OSTEOIMMUNE DYSREGULATION: ORAL LESIONS FOLLOWING ANTIRESORPTIVE THERAPY

Antiresorptive therapies influence not only osteoclast activity but also multiple components of the osteoimmune network involved in inflammatory regulation, wound healing, and tissue homeostasis. Although the extent to which these immunomodulatory effects

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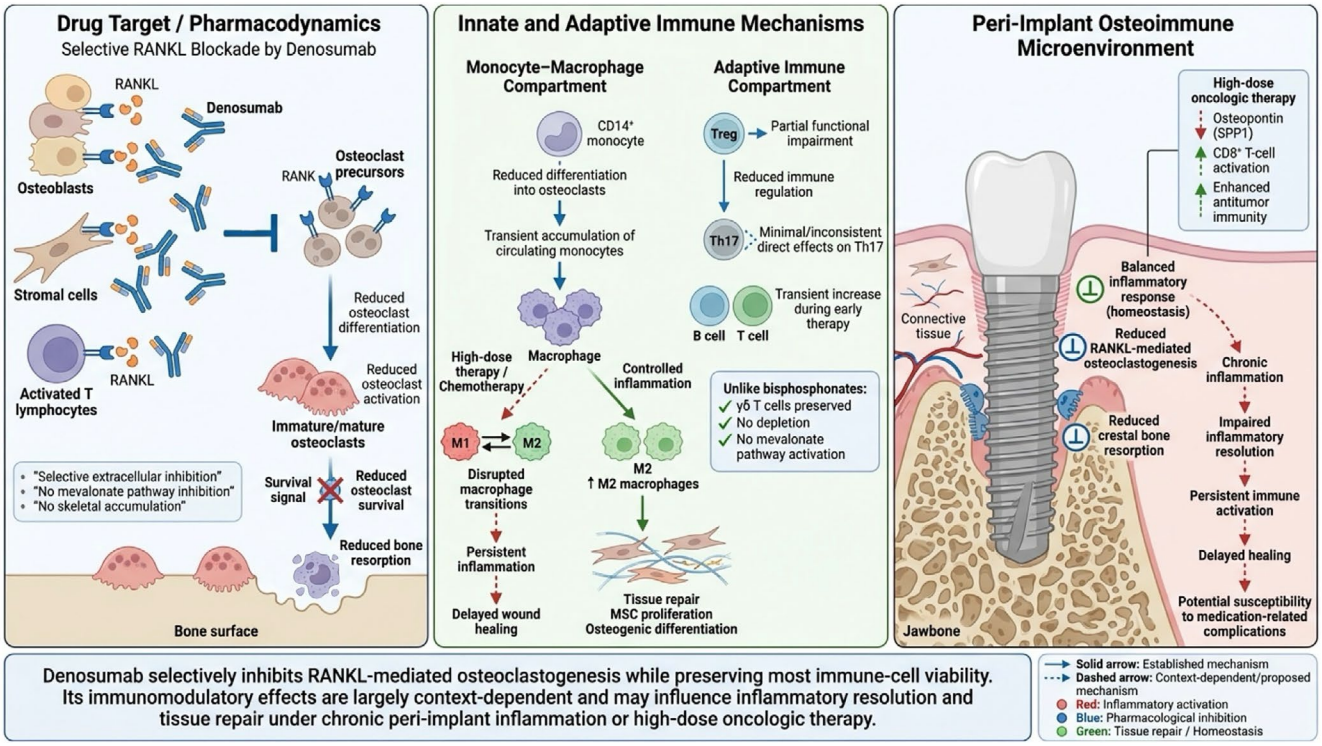

FIGURE 3 Osteoimmune mechanisms by which denosumab modulates peri-implant tissue homeostasis and inflammatory bone remodeling. Denosumab inhibits RANKL-dependent osteoclast differentiation, activity, and survival through selective extracellular blockade of the RANKL–RANK interaction. Beyond its antiresorptive effects, denosumab exerts context-dependent immunomodulatory actions by altering osteoclast precursor dynamics, macrophage polarization, and Treg-mediated immune regulation while largely preserving γδ T-cell viability. These effects may influence inflammatory resolution and tissue repair within peri-implant tissues, particularly under chronic inflammation or high-dose oncologic therapy. Solid arrows indicate established mechanisms, whereas dashed arrows represent proposed pathways with limited peri-implant evidence.

directly contribute to peri-implant disease progression remains incompletely defined, their clinical relevance becomes particularly evident within the oral cavity—a uniquely challenging barrier tissue constantly exposed to microbial biofilms, mechanical stress, and microinjury.[139–141]

While these osteoimmune alterations may remain clinically silent under stable conditions, they can become particularly relevant in situations requiring active tissue remodeling and inflammatory resolution, such as tooth extraction, peri-implant inflammation, or mucosal injury.[142] In this context, antiresorptive-associated alterations of immune regulation[91,96] and tissue surveillance,[65] may clinically manifest as delayed mucosal healing, atypical inflammatory responses, and, in more severe cases, MRONJ.[142,143]

Accordingly, the following subsections examine how antiresorptive-associated osteoimmune dysregulation may contribute to the development of oral lesions, with particular emphasis on peri-implant inflammation and MRONJ.

4.1 | Medication-related osteonecrosis of the jaw

MRONJ represents the most severe oral complication associated with antiresorptive therapy, clinically manifesting as exposed necrotic bone often accompanied by pain, swelling, and secondary infection, thus having a substantial impact in patients' quality of life. Although suppression of osteoclast activity and impaired bone remodeling remain central to its pathogenesis, accumulating evidence highlights the critical role of the host immune response in shaping individuals' susceptibility and MRONJ severity.[143]

In parallel with treatment intensity, individual variations between hosts' immune competence—including monocyte function, macrophage polarization, and γδ T-cell activity—may critically determine MRONJ risk. These defective osteoimmune adaptations can render the oral mucosa and underlying bone particularly vulnerable to microbial challenge and trauma, lowering the threshold for inflammation-driven tissue breakdown. Accordingly, MRONJ is increasingly understood as a multifactorial condition arising from the convergence of antiresorptive exposure, local inflammation, microbial dysbiosis, and impaired tissue repair mechanisms.

4.1.1 | Macrophages and Tregs and role in MRONJ

Macrophage polarization and T-cell–mediated immune regulation appear to play interconnected roles in MRONJ pathogenesis and tissue healing outcomes. At early stages of MRONJ, a predominance of M2 macrophages has been observed, characterized by increased M2 density, reduced M1/M2 ratios, and elevated IL-10 expression—suggesting

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an initial, albeit insufficient, reparative response.[144] As the disease progresses, this balance shifts toward a pro-inflammatory M1 phenotype, with increased M1 macrophage infiltration, higher M1/M2 ratios, and overexpression of IL-6, correlating with tissue breakdown and lesion progression.[144] Experimental models further support this transition, showing that zoledronate promotes M1 polarization via toll-like receptor (TLR)4 signaling while suppressing M2-associated responses; notably, pharmacological inhibition of TLR4 improves socket healing and attenuates M1-driven inflammation.[145]

These macrophage alterations appear closely linked to Th17-driven inflammatory responses. In MRONJ lesions, increased IL-17 levels associate with M1 polarization, inhibition of M2 differentiation, and elevated M1/M2 ratios, suggesting that Th17-associated immune responses may reinforce pro-inflammatory macrophage polarization and local tissue injury.[98] In parallel, Tregs exert a protective role by maintaining immune homeostasis and limiting excessive inflammation. In murine models, combined administration of zoledronate and dexamethasone induces MRONJ-like lesions through suppression of Treg activity and expansion of pro-inflammatory Th17 responses, resulting in a reduced Treg/Th17 ratio.[109] Restoration of this balance through adoptive Treg transfer significantly improves tissue healing, providing direct evidence that Treg dysfunction is a key driver of MRONJ pathogenesis.[109]

Altogether, these findings suggest that altered coordination between macrophage polarization and Treg/Th17-mediated immune regulation may contribute to defective inflammatory resolution and persistent tissue breakdown during MRONJ. Given that similar osteoimmune pathways are implicated in peri-implantitis, these mechanisms may partially explain the overlap between peri-implant inflammation and MRONJ susceptibility in antiresorptive-exposed patients.

4.1.2 | MRONJ and peri-implantitis

The relationship between peri-implant inflammation and MRONJ remains incompletely understood and is likely multifactorial. Although implant placement is often regarded as a relatively aseptic surgical procedure associated with a relatively low MRONJ incidence,[146] clinical data suggest that the risk of MRONJ in patients receiving antiresorptive therapy can be strongly influenced by peri-implant inflammation and dysbiosis. In a retrospective study of 355 implants—112 of which developed MRONJ—, the presence of peri-implantitis was associated with a more than seven-fold increase in the odds of MRONJ (OR = 7.43; 95% CI, 2.74–20.14).[147] Similarly, another retrospective cohort of 34 MRONJ patients with 117 implants found that 39% of affected implants showed clinical and radiographic signs of peri-implantitis prior to necrosis in patients treated with oncological doses of antiresorptives.[148] In a systematic review encompassing data from 111 patients with peri-implant–associated MRONJ, most lesions developed several years after implant placement—on average 46.5 ± 33.2 months—and predominantly in cases showing severe signs of peri-implant inflammation, characterized by suppuration, probing depth ≥ 6 mm, bone sequestra, and implant mobility, thereby making implant explantation frequently required for MRONJ therapy success.[149] In addition, a case–control study involving patients who began antiresorptive therapy after implant placement showed that antiresorptive therapy was an independent risk factor for peri-implantitis (adjusted OR: 3.91, 95% CI: 1.29–11.9) and for disease progression by means of changes in probing depth and bleeding on probing (adjusted OR: 1.86; 95% CI: 0.754–4.58).[15] Collectively, these observations support the hypothesis that MRONJ susceptibility may not be only influenced by drug exposure and osseous surgical intervention, but also by local inflammatory burden and altered host–microbial interactions.

Experimental data are not entirely consistent to support a mechanistic association between peri-implantitis and MRONJ risk. In murine models, ligature-induced peri-implantitis under ZA exposure is associated with significantly less peri-implant bone loss compared with ligature alone. However, when peri-implantitis is combined with oncologic-dose zoledronate, lesions exhibit exaggerated inflammatory infiltration, increased proportions of non-vital bone, and heightened expression of TNF-α and IL-1β compared with either zoledronate exposure or peri-implantitis alone.[51,52] Moreover, increased neutrophil and monocyte infiltration, disorganized collagen architecture, and bone sequestration with empty lacunae have also been described in peri-implantitis–associated MRONJ-like lesions.[51] This synergistic effect may contribute to deregulation of the inflammatory response and exacerbate local tissue damage, increasing the risk for MRONJ. However, not all experimental studies corroborate this interaction. Some models report that antiresorptive therapy does not significantly modify the course of experimental peri-implantitis, nor does it increase immune cell infiltration or bone loss compared with peri-implantitis alone.[9,102] Likewise, treatment outcomes of experimental peri-implantitis under different antiresorptive regimens—whether via open flap debridement or reconstructive approaches—did not consistently demonstrate impaired healing. Taken together, experimental evidence suggests that peri-implant inflammation may amplify osteoimmune dysregulation under high-dose antiresorptive exposure in susceptible individuals, although inconsistencies among models and dosing regimens currently preclude definitive conclusions.

Clinically, MRONJ most frequently develops following invasive dental procedures or in the presence of chronic oral inflammation. Accordingly, optimization of plaque control, early management of peri-implant inflammation, and minimization of surgical trauma remain central preventive strategies in antiresorptive-exposed patients, particularly under high-dose oncologic regimens and affected by multiple morbidities.[150]

5 | ANTIRESORPTIVE DRUG HOLIDAYS: RECOMMENDATIONS AND IMPLICATIONS FOR ORAL CARE

The concept of an antiresorptive "drug holiday" refers to the temporary discontinuation of therapy—most commonly bisphosphonates

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or denosumab—prior to invasive dental procedures in an attempt to reduce the risk of MRONJ. For bisphosphonates, this strategy is biologically plausible given their rapid binding to mineralized bone surfaces and accumulation within the skeleton for prolonged periods, particularly at sites of active remodeling. Although circulating bisphosphonate levels decline rapidly after administration, the clinically relevant issue is their persistence within newly forming bone during post-surgical healing, where suppression of osteoclast-mediated remodeling may interfere with coordinated bone turnover and tissue repair. However, despite this rationale, the clinical effectiveness of drug holidays remains controversial. A recent position paper from the American Association of Oral and Maxillofacial Surgeons reported no consensus referring to insufficient evidence to support routine drug interruption before invasive oral procedures,[151] despite earlier recommendations suggesting a 2–3 month discontinuation period.[152]

Recent evidence from a nationwide retrospective cohort including 152 299 older adults diagnosed with osteoporosis reported a significantly lower MRONJ risk when intravenous bisphosphonate therapy was paused for more than 90 days (HR 0.57; 95% CI: 0.47–0.70; $p < 0.001$) with the lowest risk observed when interruption exceeded 1 year. The reduction appeared more consistent with ibandronate, whereas for zoledronate, only interruptions longer than 1 year were associated with a meaningful decrease in risk (HR 0.51; 95% CI: 0.33–0.79).[153] Similarly, smaller observational studies have reported reduced MRONJ incidence following an intravenous bisphosphonate holiday of ~5 months, including up to a 3.75-fold decrease in incidence; these studies also noted significantly fewer complications among patients receiving oral compared with intravenous bisphosphonates ($p = 0.0364$).[154] In contrast, other observational analyses have reported that oral surgery may heal uneventfully without treatment interruption, especially among patients receiving oral bisphosphonates for osteoporosis. However, these studies frequently included heterogeneous populations (osteoporosis and oncology patients), pooled different antiresorptive agents, or predominantly evaluated oral bisphosphonates alone, thereby limiting comparability and inference.[153,155,156] Importantly, prolonged interruption of intravenous bisphosphonate therapy has been associated with an increased risk of fragility fractures without a significant impact on the immune response, underscoring the need for careful, individualized risk–benefit assessment when determining the optimal timing of oral surgery in patients receiving IV bisphosphonates.

Unlike bisphosphonates, denosumab does not accumulate in bone, thus its antiresorptive effects are rapidly lost after treatment cessation.[140] Discontinuation is associated with rebound bone turnover, accelerated bone loss, and, in some cases, an increased risk of vertebral fractures. Mechanistically, preclinical studies suggest that cessation of RANKL inhibition may lead to rebound osteoclastogenesis via rapid differentiation of osteoclast precursors and osteoclast hyperactivation, suggesting a link between denosumab withdrawal, immune-mediated osteolysis, and accelerated bone turnover.[157] Accordingly, current evidence does not support routine drug holidays for denosumab. If temporary interruption is deemed necessary for high-risk oral surgery, careful scheduling within the dosing interval—preferably toward the end of the 6-month cycle—and transition to an alternative antiresorptive agent are essential to mitigate rebound-associated fracture risk.[36,140]

For romosozumab, which is administered for a limited 12-month course and exerts a predominantly anabolic effect during the first 6 months followed by a moderate suppression of bone resorption,[158] there are currently no specific recommendations supporting drug holidays in the oral surgical context. Available reports on MRONJ incidence remain comparatively reassuring, being a rare finding in osteoporosis clinical trials occurring during ongoing therapy or subsequent antiresorptive maintenance phases rather than immediately following dental interventions. Nevertheless, current long-term evidence remains insufficient to justify routine therapy interruption before dental procedures.

Importantly, current consensus does not support drug holidays as a preventive strategy for MRONJ in patients undergoing non-surgical peri-implant or periodontal maintenance therapy. Greater emphasis should instead be placed on comprehensive risk assessment, meticulous control of peri-implant and periodontal inflammation, atraumatic surgical technique when possible, and optimization of oral hygiene prior to invasive procedures. In all cases, management should be interdisciplinary and individualized, integrating the patient's fracture risk profile, cumulative antiresorptive exposure, systemic comorbidities, and invasiveness of the planned oral intervention.

6 | FUTURE DIRECTIONS: CLINICAL CONSIDERATIONS IN PERI-IMPLANT CARE AND RESEARCH

The expanding body of evidence linking antiresorptive therapy, peri-implant inflammation, and MRONJ underscores a central paradigm: Necrotic complications appear to arise not solely from suppressed osteoclast activity but from a context-dependent deregulation of the osteoimmune response. Increasing evidence suggests that peri-implantitis and periodontitis may act as local inflammatory modifiers capable of influencing impaired bone healing in susceptible individuals. However, the precise causal and mechanistic relationships between antiresorptive exposure, dysbiosis-associated inflammation, and MRONJ development remain incompletely understood.

6.1 | Peri-implant inflammation as modifiable risk amplifiers

Emerging data indicate that MRONJ risk may be influenced by the inflammatory microenvironment in which surgical or dysbiotic insults occur. Both clinical and experimental studies suggest that chronic peri-implant and periodontal inflammation may contribute to reducing the threshold for necrotic complications during antiresorptive therapy. Future studies should prospectively stratify patients

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by peri-implant and periodontal health and status at baseline, rather than treating inflammation as a secondary finding.

6.2 | Rethinking bone healing: Regeneration is not remodeling

Maxillofacial bone heals predominantly through intramembranous ossification, a process that, in its early phase, does not strictly depend on osteoclast-mediated resorption. Initial wound healing following extraction or implant placement is driven by clot stabilization, angiogenesis, mesenchymal cell recruitment, and osteoblast-mediated bone deposition. Osteoclastic remodeling becomes more relevant in later maturation phases that may be particularly relevant in inflamed peri-implant tissues.

However, the assumption that early regenerative events are independent of osteoclast function has not been rigorously verified in the context of antiresorptive therapy. Osteoclasts contribute not only to matrix resorption but also to coupling signals, immune modulation, and vascular interactions. Suppressing their activity may alter early inflammatory resolution, macrophage polarization, and angiogenic signaling—processes critical for successful regeneration. Accordingly, several mechanistic and translational questions, between regeneration (new bone formation) and remodeling (coupled resorption–formation) in drug-exposed environments, remain insufficiently addressed, including:

- The temporal contribution of osteoclast activity during early healing following extraction, peri-implantitis debridement, and guided bone regeneration under antiresorptive exposure.
- The role of macrophage–osteoclast interactions and Treg/Th17 dynamics during post-surgical bone healing.
- Biological differences between oncologic high-dose antiresorptive regimens and osteoporosis-related dosing protocols in translational peri-implant models.

6.3 | Timing of antiresorptive therapy in relation to implant therapy

A clinically relevant but insufficiently explored question is whether completing peri-implant maintenance/periodontal stabilization or implant therapy before initiation of antiresorptive treatment modifies long-term risk. In oncology settings, pre-therapy dental clearance is standard; however, in osteoporosis care, systematic periodontal and peri-implant assessment prior to therapy initiation has not been uniformly implemented into routine care. Well-designed longitudinal cohorts are needed to evaluate:

- Outcomes of peri-implant/periodontal and implant therapy performed before versus after antiresorptive initiation.
- Whether cumulative drug exposure interacts with baseline peri-implant inflammatory burden.
- The impact of maintenance adherence on MRONJ incidence in implant patients.

6.4 | Clinical considerations based on current evidence: A risk-stratified assessment

Based on currently available evidence and existing position papers, antiresorptive therapy alone should not necessarily be regarded as a contraindication to periodontal, peri-implant, or implant therapy in patients treated for osteoporosis. Nevertheless, individualized risk assessment remains important, particularly in patients presenting with additional systemic or local modifying factors (Figure 4).

Current evidence supports the importance of maintaining periodontal and peri-implant health before and during antiresorptive therapy, especially in oncology patients receiving high-dose regimens. Accordingly, several clinical risk considerations may be relevant within interdisciplinary patient management:

- Pre-therapy optimization

When feasible, comprehensive peri-implant and periodontal health assessment preceding initiation of antiresorptive therapy may help identify active inflammatory conditions requiring treatment, particularly in oncologic settings where MRONJ risk is increased.

- Inflammatory burden control

Peri-implant and periodontal inflammation appear to act as contextual amplifiers of MRONJ susceptibility. Thus, supportive maintenance protocols and early management of mucositis/peri-implantitis or gingivitis/periodontitis could be clinically impactful, particularly for oncologic patients.

- Drug holiday considerations

Decisions regarding temporary interruption of antiresorptive therapy should remain individualized and aligned with existing medical and surgical guidelines. For bisphosphonates, interruption potential benefit remains uncertain and must be weighed against fracture risk and systemic disease control. In this context, the presence of active peri-implantitis or periodontal disease should also be taken into consideration. For denosumab, routine drug holidays are not supported due to rebound fracture risk. Thus, coordination with the prescribing physician is essential.

- Patient-specific risk modifiers

Factors such as antiresorptive indication and dose (osteoporosis vs. oncologic), cumulative duration of therapy, route of administration, concomitant corticosteroid, chemotherapy or other immunomodulatory medication use, smoking status, and existing

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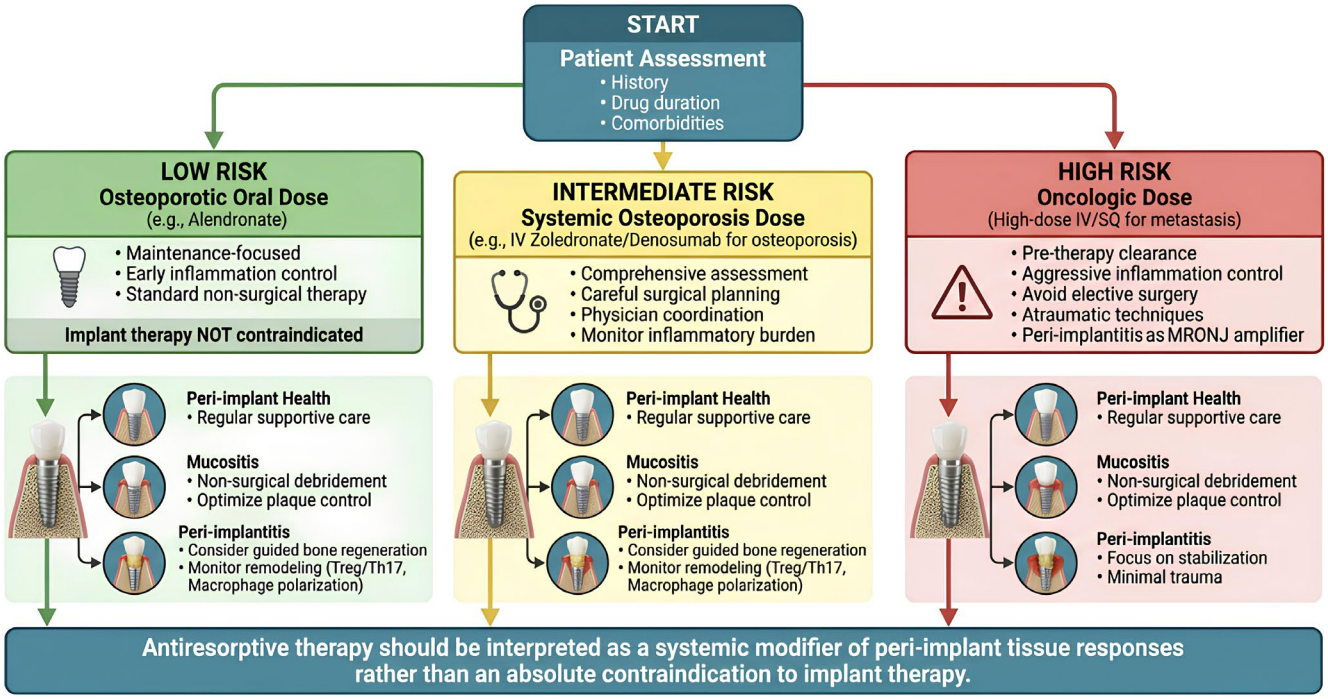

FIGURE 4 Risk-stratified clinical management algorithm for peri-implant inflammation in patients receiving antiresorptive therapy. Clinical decision-making is initiated by a comprehensive patient assessment, including medical history, antiresorptive indication, drug type and duration, route of administration, and relevant comorbidities, followed by stratification into low-, intermediate-, and high-risk categories according to the pharmacological regimen. Low-risk patients (oral osteoporosis-dose antiresorptive therapy) are primarily managed through supportive peri-implant maintenance, early control of peri-implant inflammation, and conventional non-surgical therapy, with reconstructive surgical treatment considered when indicated for peri-implantitis. Intermediate-risk patients (systemic osteoporosis-dose regimens) require comprehensive risk assessment, multidisciplinary coordination, careful surgical planning, and close monitoring of peri-implant inflammatory burden before adopting similar disease-specific management strategies. High-risk patients (oncologic-dose antiresorptive therapy) require pre-treatment oral stabilization, meticulous control of peri-implant inflammation, avoidance of elective implant surgery whenever possible, and minimally traumatic surgical approaches. In this setting, peri-implantitis may act as a contextual modifier that increases susceptibility to medication-related osteonecrosis of the jaw (MRONJ), favoring conservative management focused on disease stabilization.

peri-implant or periodontal disease may influence overall patients' risk assessment and should be integrated into multidisciplinary individualized treatment decision-making.

6.5 | Limitations

This review has multiple limitations that should be acknowledged. As a narrative review, it was not based on a predefined systematic search strategy or formal study selection process. Consequently, although the literature was critically evaluated to provide a comprehensive overview of the topic, some relevant studies may not have been identified or included. In addition, the available evidence regarding peri-operative management strategies in patients receiving antiresorptive therapy remains highly heterogeneous. Recommendations for measures such as antibiotic prophylaxis,[159] antiseptic protocols, and peri-operative medication management vary considerably across studies and are largely derived from observational analyses and limited translational applicability.[160]

Therefore, the proposed clinical considerations should be interpreted within the context of the current evidence base and refined as higher-quality prospective and mechanistic studies become available.

7 | CONCLUSION

Antiresorptive therapy should be considered a systemic modifier of peri-implant tissue responses rather than an absolute contraindication to implant therapy or an independent risk factor for peri-implant diseases. Current evidence indicates that implant survival and peri-implant bone stability are generally maintained in patients receiving osteoporosis-dose antiresorptive therapy, particularly under adequate supportive care. However, suppression of bone remodeling may become clinically relevant under conditions of chronic peri-implant inflammation, repeated surgical manipulation, or high-dose oncologic antiresorptive exposure, where impaired osteoimmune adaptation and delayed inflammatory resolution may increase susceptibility to biological complications, including MRONJ.

Therefore, peri-implant inflammation may act as a contextual risk amplifier in susceptible antiresorptive-exposed patients rather than as an isolated bacterial plaque-associated condition.

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Therefore, individualized patient selection, comprehensive risk stratification, early diagnosis and control of peri-implant mucositis and peri-implantitis, minimization of surgical trauma, and long-term supportive maintenance should represent central components of peri-implant care in patients receiving antiresorptive therapy. Future translational and longitudinal studies are needed to clarify how antiresorptive pharmacodynamics, inflammatory burden, and osteoimmune dysregulation interact to influence peri-implant tissue stability and healing outcomes over time.

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DATA AVAILABILITY STATEMENT

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