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Review

An evidence-guided review of preclinical strategies to counteract medication-related osteonecrosis of the jaw. What do rodent studies tell us?

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Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon but potentially serious complication associated with antiresorptive and antiangiogenic therapies, such as bisphosphonates and denosumab. Despite increasing clinical awareness, the pathophysiology of MRONJ remains poorly understood, and no universally accepted preventive strategies are currently available. Preclinical animal studies have served as a cornerstone for investigating potential preventive and therapeutic approaches, offering valuable insights into disease onset, progression, and intervention timing. This narrative, scoping-style review critically examines and maps the available preclinical evidence on preventive and therapeutic strategies aimed at mitigating MRONJ risk, with an emphasis on animal models that simulate clinical conditions. We methodologically explore and compare a wide range of proposed interventions, including laser and photobiomodulation therapies, ozone application, antibiotics, anti-inflammatory agents, natural compounds, and biologics such as BMPs, mesenchymal stem cells (MSCs), and platelet-rich plasma. The efficacy of these interventions is discussed in relation to their impact on inflammation, angiogenesis, bone remodeling, microbial control, and soft tissue healing. Among the most promising strategies, low-level laser therapy and the use of MSCs consistently demonstrated improved healing outcomes and reduced necrotic bone exposure in rodent models. Anti-inflammatory medications and natural compounds, such as resveratrol, showed favorable modulation of the inflammatory microenvironment, while some antibiotics were effective in reducing bacterial burden when administered at appropriate doses and timings. However, discrepancies in study design, animal species, drug administration protocols, and outcome measures often limit direct comparisons and translational conclusions. Taken together, the animal literature supports the potential of multimodal preventive strategies, particularly when interventions are applied before or immediately after dentoalveolar trauma. Nonetheless, further standardization of experimental models and validation in clinical settings are urgently needed. This review highlights the strengths and limitations of current preclinical evidence and proposes directions for future research to bridge the gap between bench and bedside in the management of MRONJ.

Keywords: MRONJ, medication-related osteonecrosis of the jaw, animal models, prevention, laser therapy, natural compounds, biologics, antibiotics, inflammation

Lay Summary

Medication-related osteonecrosis of the jaw (MRONJ) is a condition in which the jawbone fails to heal properly, leading to exposed bone, pain, necrosis, and risk of infection. This review summarizes animal studies testing strategies to prevent or treat MRONJ, including lasers, stem cells, bone-building hormones, natural compounds, antibiotics, and biomaterials. Some approaches, such as low-level laser therapy and stem cells, consistently improved healing, while others showed promise in specific settings. However, differences in experimental design and lack of standardization limit translation to patients. Future research should focus on standardized models, combination therapies, and clinical trials to bring these strategies from the laboratory to real-world care.

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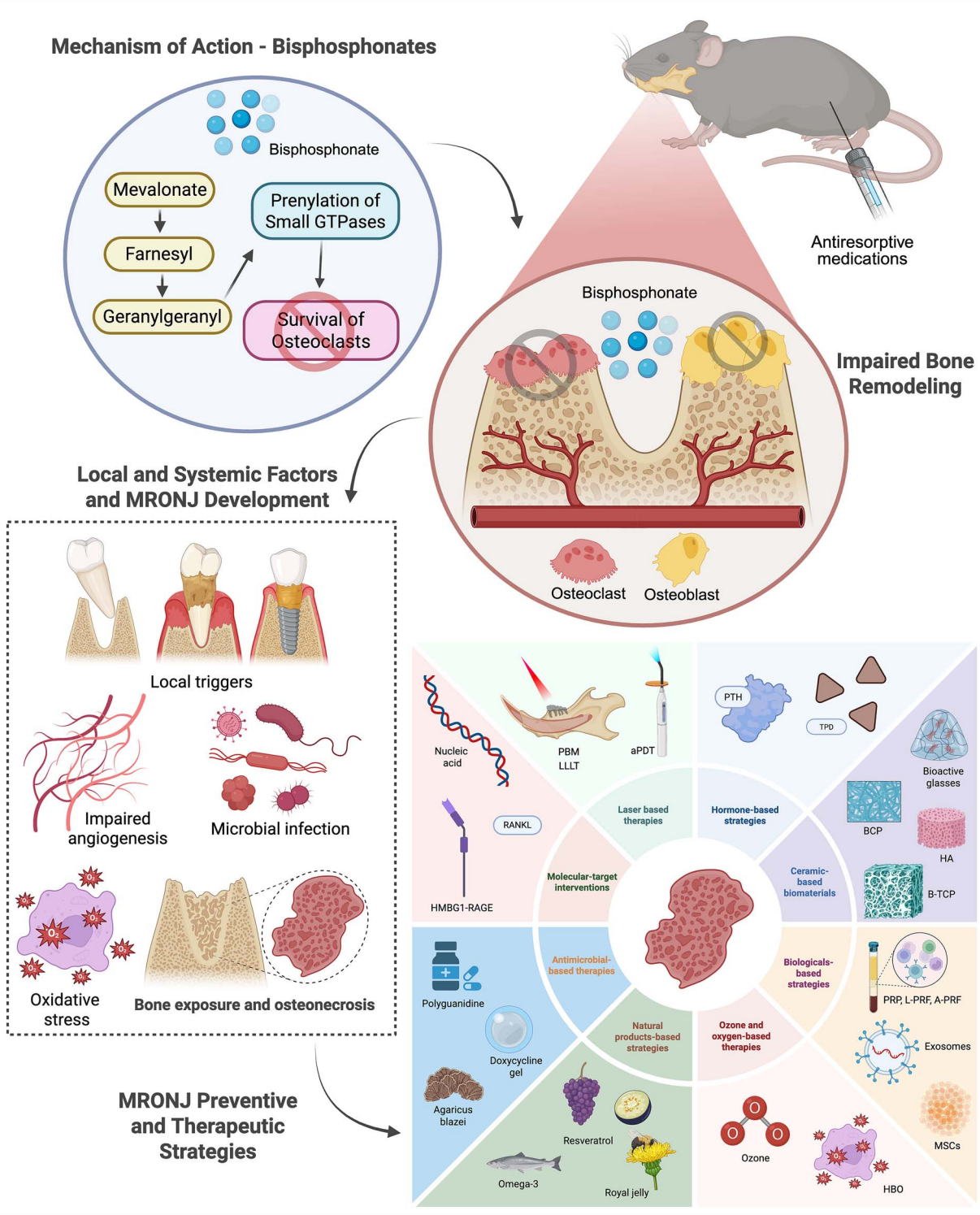
Graphical Abstract



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Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon yet potentially serious condition primarily associated with antiresorptive therapies such as bisphosphonates and denosumab, as well as with certain antiangiogenic medications.[1–3] First reported by Marx in 2003 and later by Ruggiero in 2004,[4] this condition manifests clinically as exposed necrotic bone in the maxillofacial region that persists for more than 8 wk,[5,6] in patients under antiresorptive therapies. The incidence of MRONJ varies according to the patient population, medication type, and treatment duration. According to the 2022 update of the American Association of Oral and Maxillofacial Surgeons (AAOMS) Position Paper, the estimated prevalence ranges from 0.2% to 6.7% among cancer patients receiving high-dose i.v. bisphosphonates or denosumab, and from 0.001% to 0.01% among patients treated for osteoporosis with low-dose oral formulations.[7] In contrast, the incidence among patients receiving antiangiogenic agents, such as bevacizumab or sunitinib, is generally lower, reported between 0.2% and 0.9%, though it may increase when combined with antiresorptives.[7] The significance of anti-angiogenic agents as an independent risk factor for MRONJ was highlighted in the 2014 AAOMS guidelines[1]; however, they were de-emphasized in the 2022 update due to insufficient support from current clinical evidence.[7] These variations highlight the influence of underlying disease, treatment regimen, and local risk factors on MRONJ development.[8,9] This wide variation underscores both the complexity of the condition and the importance of patient-specific risk factors in its development. Local factors that increase the risk of MRONJ include dental extractions, traumatic surgical procedures such as implant placement or removal, peri-implantitis, bone augmentation, orthodontic treatment, periodontitis, and poorly fitting dentures, although a significant proportion of cases may occur spontaneously without an evident local trigger. Systemic risk factors include chemotherapy, corticosteroid use, diabetes, smoking, and older age, all of which may impair bone remodeling and wound healing or alter immune responses. These cumulative factors contribute to interindividual variability in MRONJ susceptibility.[7]

The pathophysiology of MRONJ remains incompletely understood[10,11] despite extensive research efforts, with current hypotheses proposing a multifactorial etiology that includes suppressed bone remodeling, impaired angiogenesis, chronic inflammation, microbial infection, and immune dysregulation.[7,12–14] Bisphosphonates, the most commonly implicated drugs, exert their effects by inhibiting osteoclast-mediated bone resorption, which disrupts normal bone turnover and repair mechanisms.[15] This pharmacological action, while beneficial for conditions like osteoporosis and metastatic bone disease, creates a vulnerable environment in the jaw where the high remodeling rate and unique microbial flora predispose to necrotic changes following trauma or infection.[12] The jaw's specific susceptibility compared to other skeletal sites may also relate to its embryological origin, vascular supply, and the thin mucosa overlying cortical bone.

The clinical management of MRONJ presents significant challenges due to the lack of universally effective preventive or therapeutic strategies.[7,9,16,17] Current treatment approaches are primarily palliative and stage-dependent, ranging from conservative measures such as antimicrobial rinses for early stages to surgical debridement or resection for advanced cases. However, recurrence rates following surgical intervention differ substantially across patient populations. In individuals treated for osteoporosis, recurrence is generally low, ranging from 2% to 8%, whereas in cancer patients receiving high-dose antiresorptive or antiangiogenic therapy, recurrence may reach 15%-25%, particularly in advanced stages or in those with systemic comorbidities. These differences underscore the influence of underlying disease context and medication regimen on healing outcomes.[7,18,19] This therapeutic gap highlights the critical need for evidence-based prognostic and preventive strategies, particularly for high-risk patients undergoing oncologic or osteoporotic treatments who require invasive dental procedures.[7,9,16,17]

Preclinical animal models have served as indispensable tools for investigating MRONJ pathogenesis and evaluating potential preventive and therapeutic interventions.[20–28] The most commonly employed models utilize rodents treated with zoledronic acid (ZOL), alendronate (ALD), or RANKL inhibitors, often in combination with dexamethasone (DEX) or other immunosuppressive agents to enhance lesion development. A broad range of experimental models have been proposed by different groups to reproduce MRONJ-like features, including spontaneous models, disease-associated models, and surgical induction protocols. For instance, several studies comprehensively characterized rodent models with variations in drug dosing, disease triggers, and healing timelines, model reproducibility and lesion outcomes.[24,28–34] These collective efforts from independent laboratories underscore the translational utility and methodological diversity of MRONJ preclinical research.[21,25,27,35,36] Besides systemic administration of these antiresorptives, local factors play an important role for MRONJ development, for instance dental trauma, periodontal or periapical disease, and peri-implantitis (Figure 1). These models successfully replicate key clinical features of MRONJ, including osteonecrosis, non-healing extraction sockets, and chronic inflammation.[24,28,37–44] Larger animal models, such as dogs and pigs, while better approximating human jawbone physiology and oral microbiota, are used less frequently due to higher costs and ethical considerations.[45,46] Despite their utility, translational challenges persist due to heterogeneity in study designs, species-specific responses to medications, and inconsistent outcome measures across studies.[45,47]

Medication-related osteonecrosis of the jaw remains a challenging condition to manage due to its complex and multifactorial etiology and unknown pathogenesis.[11] The disease arises from a confluence of systemic and local factors that create a pathological environment prone to bone necrosis and unfavorable for tissue healing.[11] Anti-resorptive therapies suppress osteoclast activity leading to impaired bone remodeling and accumulation of microdamage. When compounded by local insults, such as dental extractions, periodontal or periapical infections, or peri-implantitis, the jawbone becomes particularly vulnerable.[11] The resulting necrotic tissue further amplifies inflammation through a cascade of immune dysregulation. This involves excessive production of reactive oxygen species (ROS), upregulation of pro-inflammatory cytokines like IL-1, IL-6, and IL-17, and a shift toward M1 macrophage polarization and Th17 dominance, alongside a reduction in regulatory T cells and M2 macrophages (Figure 2).[48–50] These immune alterations compromise wound healing and perpetuate a chronic

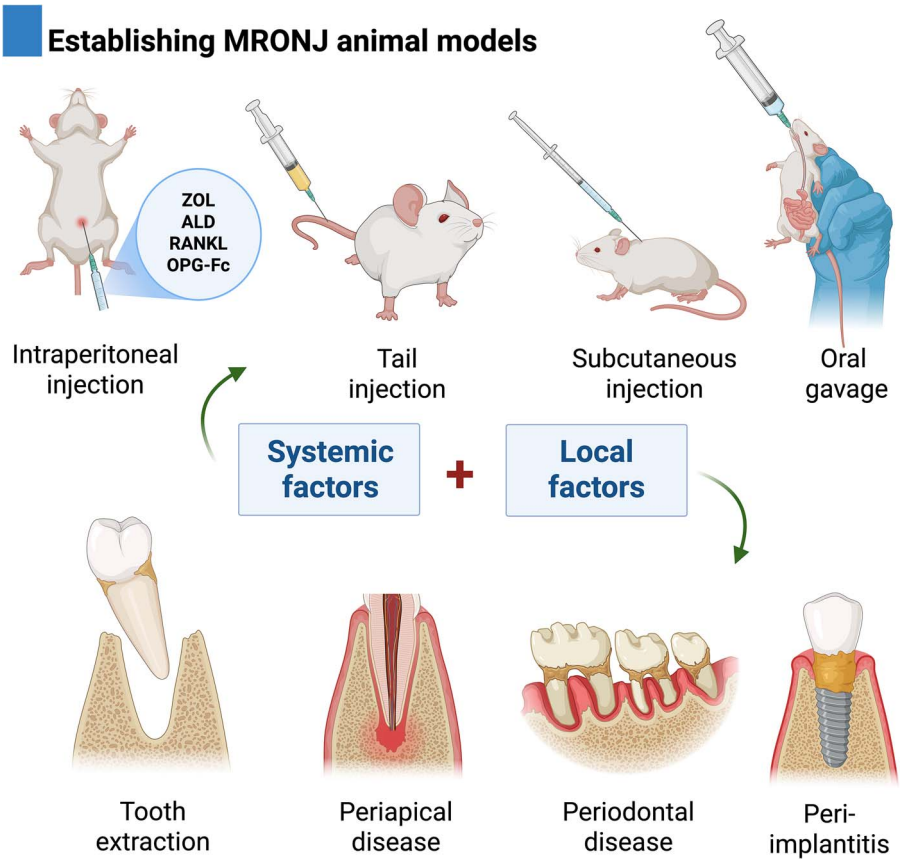

Figure 1. General approaches for establishing medication-related osteonecrosis of the jaw models in rodents involves a 2-step protocol. Initially, animals receive systemic administration of bisphosphonates or other antiresorptive/antiangiogenic agents through routes such as s.c., i.p., oral gavage, or i.m. injection. Subsequently, a local risk factor is introduced to trigger osteonecrosis, typically involving tooth extraction, periapical or periodontal disease, or peri-implantitis. Abbreviations: ZOL: zoledronate; ALD: alendronate; OPG-Fc: osteoprotegerin. Created with BioRender.com (License Number: TZ292C7PNM).

inflammatory cycle. Additionally, defective epithelial migration over exposed bone sustains the lesion and facilitates microbial colonization, exacerbating local tissue damage. This intricate interplay of suppressed bone turnover, immune dysregulation, and persistent infection underscores why MRONJ remains a therapeutic challenge and highlights the need for multifaceted preventive and therapeutic approaches.[11]

Recent preclinical investigations have explored a diverse array of strategies to prevent or mitigate MRONJ Figure 3 and Tables 1-6):

1. Biophysical modalities: including low-level laser therapy (LLLT), photobiomodulation (PBM), and antimicrobial photodynamic therapy (aPDT) demonstrate efficacy in enhancing tissue repair through anti-inflammatory and pro-osteogenic effects.[51–53] These non-invasive treatments appear to modulate cellular metabolism, reduce oxidative stress, and promote angiogenesis, addressing multiple aspects of MRONJ pathophysiology.[54,55]

2. Pharmacologic interventions: encompass a wide range of agents targeting different pathogenic mechanisms. Teriparatide (PTH), an anabolic bone agent, has shown promise in restoring bone turnover when administered perioperatively.[41,56–68] Other pharmacological approaches include statins for their pleiotropic anti-inflammatory effects,[69] antimicrobials to reduce bacterial burden,[70] and novel molecular targeted therapies addressing specific pathways like RANKL or HMGB1 signaling.[71,72]

3. Biologic therapies represent a rapidly advancing frontier, with cell-based therapies, including mesenchymal stem cells (MSCs), stromal vascular fraction cells, PBMCs, and other cell types, as well as platelet-rich plasma (PRP) demonstrating significant potential to promote angiogenesis and osteogenesis.[33,73] These approaches leverage the body's natural regenerative capacity, with cell-based therapies showing particular promise due to their immunomodulatory properties and ability to support tissue regeneration.[74,75]

4. Biomaterial-based strategies include ceramic scaffolds, hydrogels, and bioactive glasses designed to provide structural support while delivering therapeutic agents.[76–78] These materials can be functionalized with growth factors like BMP-2 or antibiotics to address both the structural and infectious components of MRONJ.[79,80]

Despite these advances, several critical knowledge gaps remain. The optimal timing and duration of preventive interventions, whether administered before, during, or after dental extractions, significantly influence outcomes but lack standardization across studies.[63,81] Additionally, the complex interplay between systemic drug effects and local tissue responses creates challenges in developing universally applicable therapies.[16] Most preclinical studies have focused on monotherapies, while MRONJ's multifactorial nature may require combinatorial approaches targeting multiple pathogenic pathways simultaneously.[82,83]

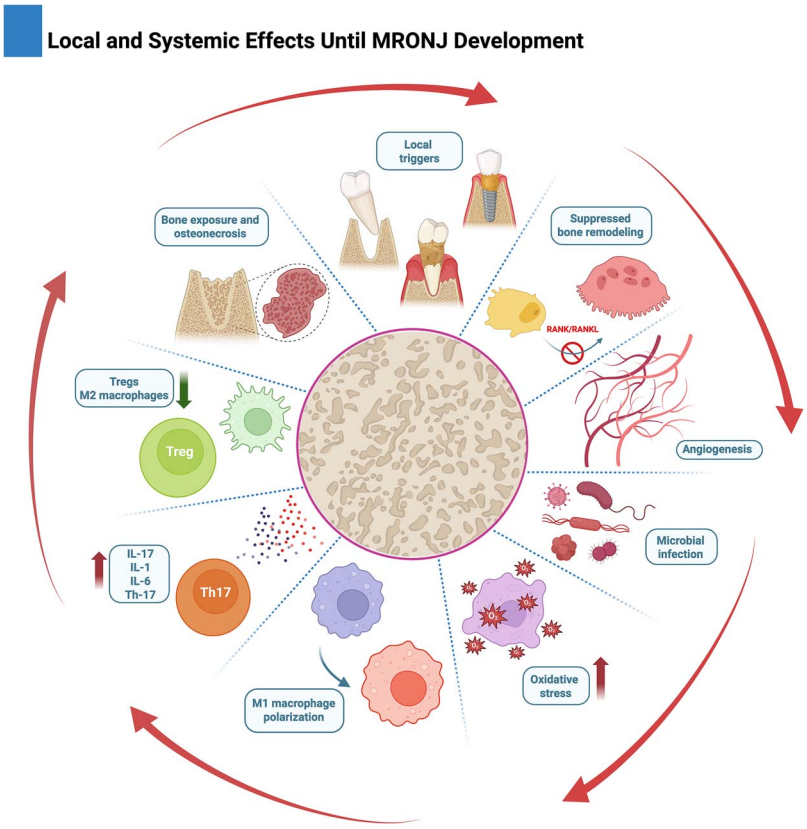

Figure 2. Schematic representation of medication-related osteonecrosis of the jaw (MRONJ) development. The development of MRONJ involves a complex interplay between systemic factors and local triggers. In individuals receiving antiresorptive agents, events such as tooth extraction, peri-implantitis, periodontitis or local inflammation can extend the inflammatory response into the alveolar bone. The combination of impaired angiogenesis, microbial colonization, and osteoclast inhibition disrupts normal bone resorption and remodeling. As a result, bone remains exposed to a hostile environment rich in inflammatory and infectious stimuli, ultimately leading to necrosis. The necrotic bone tissue further amplifies inflammation by promoting oxidative stress and elevating levels of pro-inflammatory cytokines, including IL-17, IL-1, and IL-6. This pro-inflammatory milieu skews immune responses toward M1 macrophage polarization and an increased Th17 cell profile, while simultaneously reducing the presence of regulatory T cells (Tregs) and M2 macrophages. Epithelial migration over necrotic bone and persistent bone exposure perpetuates this cycle, exacerbating inflammation and driving the progression of tissue destruction. Created with BioRender.com (License Number: GU292C7TUK).

This comprehensive review critically examines the current state of preclinical evidence regarding MRONJ prevention and treatment, evaluating the efficacy, mechanisms, and limitations of emerging interventions. By synthesizing findings from diverse therapeutic approaches and highlighting both consistent results and unresolved controversies, we aim to provide a roadmap for future research directions that will facilitate the translation of promising preclinical findings into clinically effective strategies. Importantly, when interpreting the current literature, one must also consider the potential impact of publication bias, as studies reporting positive outcomes are more likely to be published than those with negative or inconclusive results. This bias may artificially inflate the perceived effectiveness of certain interventions and underscores the need for more rigorous, transparent, and standardized reporting in preclinical MRONJ research.

Given the substantial heterogeneity among preclinical MRONJ studies, regarding animal models, antiresorptive regimens, experimental triggers, and outcome assessments, conducting a fully systematic review or meta-analysis was deemed infeasible. Instead, we adopted a narrative review framework with elements of a scoping review, aiming to comprehensively map and synthesize available evidence while identifying consistent trends, knowledge gaps, and translational challenges. In this context, we identified and included peer-reviewed preclinical studies that (1) employed recognized rodent MRONJ models, (2) reported defined preventive or therapeutic interventions, and (3) provided quantitative or histological outcomes relevant to bone or soft tissue healing. Studies were retrieved through PubMed and Scopus searches using combinations of the terms "MRONJ," "bisphosphonate-related osteonecrosis of the jaws (BRONJ)," "rodent model," "prevention," and "therapy". Where multiple studies addressed similar interventions, representative examples were selected to reflect methodological diversity, including timing, dosage, and delivery protocols. This approach follows a scoping rationale to map the breadth of experimental strategies rather than an exhaustive systematic review.

Laser-based preventive strategies

A total of 7 preclinical studies have evaluated the efficacy of various laser-based modalities, including LLLT, PBM, and aPDT, for the prevention or attenuation of MRONJ in rodent models (Table 1). Despite variations in animal species, laser parameters (wavelength, power, energy density), photosensitizers, and timing of intervention, the collective evidence indicates that laser-based approaches consistently improve both hard and soft tissue healing, reduce inflammation, and enhance bone regeneration.

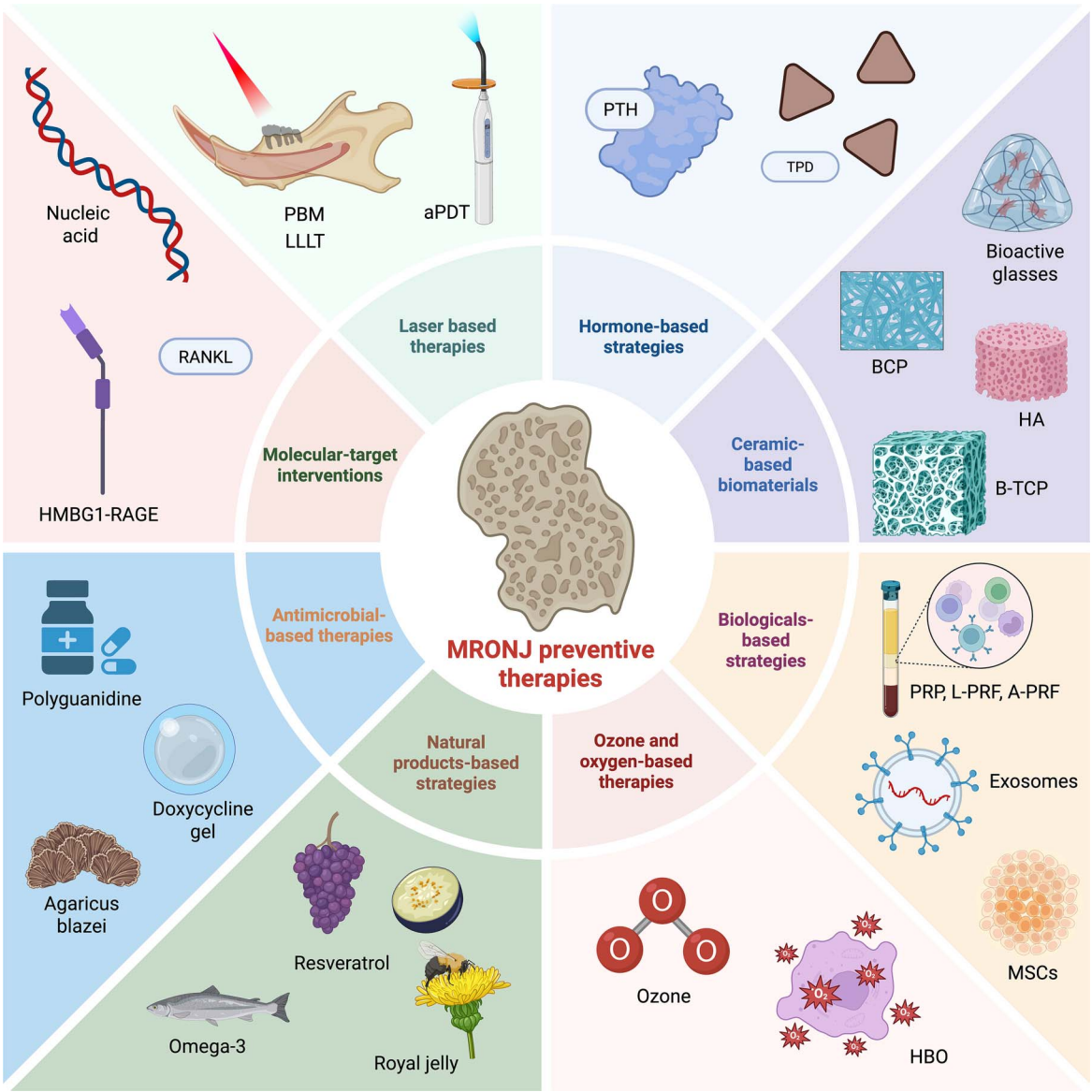

Figure 3. Preventive strategies to manage medication-related osteonecrosis of the jaw varying from laser-based therapies, hormone-based strategies, ceramic-based biomaterials, biologicals-based strategies, ozone and oxygen therapies, natural products-based strategies, antimicrobial compounds, and molecular-target interventions. Abbreviations: LLLT: low laser level therapy; PBM: photobiomodulation; aPDT: antimicrobial photodynamic therapy; TPD: Teriparatide; HA: hydroxyapatite; BTCP: beta phosphate tricalcium; BCP: calcium phosphate; PRP: platelet rich plasma; L-PRF: leukocyte- and platelet-rich fibrin; A-PRF: advanced platelet-rich fibrin; MSCs: mesenchymal stem cells; HBO: hyperbaric oxygen. Created with BioRender.com (License Number: SJ292C81JZ).

Basically, laser light in the red to near-infrared range, specifically 600-1200 nm, is absorbed by photoreceptors like cytochrome *c* oxidase within the mitochondria.[84–86] This absorption triggers a cascade of cellular events, including increased ATP production, modulation of ROS, changes in intracellular calcium levels, and activation of signaling pathways, ultimately promoting cellular healing, repair, and anti-inflammatory effects. The fundamental cellular changes stimulate the increased cell proliferation and migration, enhanced tissue oxygenation, reduced inflammation and accelerated wound healing.[54]

Low-level laser therapy and photobiomodulation

Several studies investigated the role of LLLT and PBM in promoting tissue repair and preventing MRONJ development. Özalp et al.[52] compared LLLT and ozone therapy, demonstrating that both modalities significantly improved bone healing in rats treated with ZOL, although the sham (saline) group exhibited the best outcomes. Similarly, Zheng et al.[53] revealed that 980 nm LLLT promoted gingival healing, suppressed proinflammatory cytokines (IL-1β, Tumor necrosis factor-α), and upregulated IL-1RA. Rescue experiments using IL-1RA-neutralizing antibodies nullified the benefits of LLLT, indicating a mechanistic link between laser therapy and modulation of inflammatory signaling.

Ayhan et al.[54] compared 4 laser wavelengths and found that 660 and 808 nm lasers significantly enhanced vitamin D levels, bone density, and epithelial regeneration while reducing necrosis and inflammation. Conversely, the 445 nm laser exacerbated tissue damage. These findings support a wavelength-specific therapeutic window for MRONJ prevention, with

Table 1. Characteristics of the included studies using laser-based therapies to prevent MRONJ.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Özalp et al. (2024)[52]	Compare LLLT and ozone therapy for preventing MRONJ post-tooth extraction	40 male Wistar rats	Rats divided into LLLT, OZ, and control. Received weekly IP injection of ZOL (0.06 mg/kg), and sham (saline) groups	The first application of laser diode or OZ was performed immediately after the surgery and repeated on third, fifth, seventh, and 10th postoperative days Rats in control and sham groups did not receive any adjunctive therapy following the extraction Using the following irradiation parameters: (AsGaAL; 808 nm; 0.5 W; 5 J/cm^2; 30 s)	Both LLLT and ozone improved bone healing vs control No difference between LLLT and ozone sham group showed the best healing	LLLT and ozone are effective adjunct therapies for preventing MRONJ and enhancing bone healing
Ayhan et al. (2024)[54]	**Compare laser various wavelengths for MRONJ treatment**	48 male Sprague-Dawley rats (12 wk old)	Rats received ZOL (0.06 mg/kg) for 4 wk, followed by molar extraction. Divided into sham, control, and 4 laser groups: laser diode (InGaN; 405 nm, InGaN; 445 nm, AlGaInP; 660 nm, AsGaAL; 808 nm)	PBM at different wavelengths was performed twice a week for 16 s for 4 wk Using the following irradiation parameters: 480 mW/cm^2 optical power intensity, 6 J/cm^2 irradiation dose, and 120 mW power in continuous operation mode. Consequently, 48 J/cm^2 energy was applied per rat by performing 1.5 J/point	660 nm and 808 nm lasers increased vitamin D, bone density, and epithelial regeneration, reduced inflammation and dead bone. 445 nm worsened outcomes	Combined 660 nm (bone) and 808 nm (soft tissue) lasers are promising for MRONJ treatment
Pontes et al. (2024)[55]	**Assess aPDT for repairing MRONJ by reducing NF-kB**	30 male Wistar rats (30 d old)	Rats received ZOL (250 μg/kg), except in the NC group for 7 wk, followed by tooth extraction Divided into groups: NC, ONE, ONE + PS, ONE + PBM, ONE + aPDT. Evaluated at 12 wk	aPDT (methylene blue 0.3% + laser LED), PBM (laser only), or PS (methylene blue only) was performed once a week for 4 wk. Using the following irradiation parameters: (660 nm, 50 mW power, energy of 2 J, energy dose of 66.67 J/cm^2 for 40 s)	aPDT and PBM groups showed mucosal repair, reduced necrosis, and decreased NF-kB. aPDT had the highest ECM deposition	aPDT and PBM are effective for MRONJ repair, reducing inflammation via NF-kB
Zheng et al. (2023)[53]	**Evaluate the effects of LLLT on promoting gingival wound healing and preventing MRONJ in mice and explore underlying mechanisms involving IL-1RA**	C57BL/6 N mice (6/8 wk old)	Mice treated with ZOL and tooth extraction, divided into Ctrl, ZOL, ZOL + LLLT, and ZOL + LLLT + IL-1RA NAb topically injected to extraction sockets. The local treatment was repeated 2 and 4 d after the tooth extraction Rescue experiments with IL-1RA neutralizing antibodies. In vitro migration assays with HaCaT cells	LLLT (980 nm laser) applied to extraction site at 0, 2, and 4 postoperative days. IL-1RA neutralizing antibodies are used to validate mechanism Using the following irradiation parameters: (980 nm; 0.5 W power, 63.87 W/cm^2, 45 s)	LLLT promoted gingival wound healing, reduced inflammation (IL-1β, TNF-α), increased IL-1RA, and improved bone regeneration. IL-1RA neutralization abolished LLLT effects. LLLT enhanced epithelial cell migration in vitro	LLLT prevents MRONJ by enhancing gingival wound healing via IL-1RA-mediated suppression of pro-inflammatory signaling

(continued)

Table 1. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Hadad et al. (2022)[83]	Evaluate preventive therapies for MRONJ after tooth extraction in rats treated with ZOL	72 male Wistar rats (3 mo old)	Rats received 4 IV ZOL doses, followed by molar extraction and randomized into 9 treatment groups: NC (saline), positive control (blood clot), β-TCP BG, DG, aPDT group (aG), and combinations (DBG, aBG, aDG, aDBG) Evaluated bone healing after 28 d	aPDT (methylene blue PS for 1 min), followed by a diode laser Using the following irradiation parameters: (AlGaInP; 660 ± 10 nm; 35 mW; 2.1 J/point; 74.2 J/cm^2; 60 s)	Highest bone volume (BV/TV) in aDBG (69.85%), lowest in positive control (42.17%). aDBG showed the highest neoformed bone area (82.44%) and mineral apposition rate (2.64). Necrotic bone only in positive control (37.94%)	Combination therapy (aDBG) was most effective in preventing MRONJ. β-TCP played a key role in promoting bone healing
Ervolino et al. (2022)[51]	To evaluate the effectiveness of aPDT mediated by BuTB in preventing MRONJ in rats after tooth extraction	28 senescent female Wistar rats (20 mo old)	MRONJ is induced via ZOL (100 μg/kg, IP every 3 d for 7 wk) + ligature-induced periodontitis + tooth extraction removed 3 wk post-treatment initiation, divided into: VEH, VEH-aPDT, ZOL and ZOL-aPDT Euthanasia at 28 d	aPDT: BuTB (0.5 mg/mL, 500 μL), followed by a diode laser applied at 0, 2, and 4 d post-extraction Using the following irradiation parameters: (InGaAlP; 660 nm; 35 mW; 74.2 J/cm^2; 60 s)	Clinical: ZOL group showed bone exposure and impaired healing; ZOL-aPDT had complete soft tissue repair Histology: ZOL-aPDT reduced non-vital bone vs ZOL and increased new bone formation; ZOL and ZOL-aPDT had fewer TRAP + osteoclasts vs controls; ZOL-aPDT showed reduced inflammatory infiltrate vs ZOL	aPDT mediated by BuTB prevented MRONJ-like lesions by promoting soft tissue healing, reducing non-vital bone, and modulating inflammation. The study supports BuTB-aPDT as a promising preventive strategy for MRONJ
Silva et al. (2022)[89]	To evaluate the efficacy of PDT and PBM therapy in treating ZOL induced MRONJ in rats	60 male Wistar rats (*Rattus novergicus*)	MRONJ induced via ZOL (0.20 mg/kg, i.v.), (days 0, 7, 14), and tooth extraction (day 42). Treatments applied post-extraction (days 42, 45, 49, 54), divided into: Saline solution (control), Saline-aPDT, ZOL, ZOL-MBO, ZOL-PBM therapy, and ZOL-aPDT Euthanasia at 70 d	aPDT: MOB (100 μg/mL), followed by a diode laser. PBM therapy or aPDT (same parameters) was performed on days 42, 45, 49, and 54 Using the following irradiation parameters: (AsGaAl; 660 nm; 100 mW; 214.28 J/cm^2; 60 s)	Increased radiolucency in ZOL groups ($p = .007$), indicating osteonecrosis ZOL + aPDT reduced apoptotic osteocytes vs ZOL ($p < .001$); ZOL + aPDT/PBM therapy reduced inflammatory cells (CD68+, CD3+) and cytokines (INF-γ, IL-8, MCP-1) ($p < .001$) MRONJ scores: ZOL + aPDT/PBM therapy groups showed lower severity (40%-60% score 1B/2A) vs ZOL (60% score 2A, 40% 2B)	aPDT and PBM therapy attenuated MRONJ severity by reducing inflammation (macrophages, T-cells, cytokines) and osteocyte apoptosis. aPDT showed superior antimicrobial and anti-inflammatory effects
Gol et al. (2020)[147]	To investigate the effects of LLLT and ESWT therapies on the healing of sockets after tooth extraction in rats treated for a long period with bisphosphonates	40 male Wistar-Albino rats	Rats in the control, LLLT, ESWT, and ESWT + LLLT groups received approximately 0.1 mg/kg of zoledronic acid i.p. (3 d a week for 8 wk). No treatment was given to the control group after molar tooth extraction. 810 nm wavelength GaAlAs laser was used in the LLLT group. In the ESWT group, 1000 pulses of 0.21 mJ/mm ESWT were applied, and both methods were applied simultaneously to the last group (ESWT + LLLT). Euthanasia: 4 and 8 wk after dental extractions	The GaAlAs laser with a wavelength of 810 nm was used in the LLLT group. In the ESWT group, 1000 ESWT pulses of 0.21 mJ/mm were applied, and the 2 treatment methods were applied simultaneously in the last ESWT + LLLT group	LLLT + ESWT: increased early bone volume. LLLT: increased new vessel volume and CD31 expression. LLLT and ESWT: increased MMP-2 expression	LLLT and ESWT promote similar effects on initial socket healing, but their combined application results in more effective recovery. LLLT stimulates CD31 expression, promoting blood vessel formation and soft tissue regeneration

(continued)

Table 1. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Sarkarat et al. (2019)[90]	To evaluate the effectiveness of aPDT in reducing or preventing MRONJ	20 male Wistar rats (2 mo old)	All rats received ZOL (0.04 mg, IV) for 5 wk → 2 wk later, molar extraction performed → randomly assigned to: control group (no further treatment) and aPDT group (immediately after extraction and weekly for 7 wk) Euthanized at wk 8 for clinical and histopathological evaluation	aPDT using indocyanine green (1 mg/mL), followed by a diode laser Using the following irradiation parameters: (808 nm, 250 mW, 39.04 J/cm^2)	aPDT reduced bone exposure (from 7/8 in control to 1/8 in aPDT group), inflammation, necrotic bone, and empty lacunae; increased live bone and osteoclast count, indicating active remodeling	aPDT significantly reduced clinical and histological signs of MRONJ in rats. It may be a promising non-invasive therapy to prevent or mitigate MRONJ development after dental extractions
Ervolino et al. (2019)[91]	Evaluate aPDT as a preventive therapy for MRONJ	28 senile female *Rattus norvegicus* Wistar rats (20 mo old)	Rats are induced ligature-induced periodontitis. MRONJ is induced via ZOL (100 mg/kg, IP every 3 d), tooth extraction removed 3 wk post-treatment, initiation divided into: VEH, VEH-aPDT, ZOL and ZOL-aPDT. Euthanasia at 28 d	MBO photosensitizer (100 μg/mL), followed by a diode laser applied at 0-, 2-, and 4-d post-extraction. Using the following irradiation parameters: (InGaAlP; 660 nm; 35 nW; 2.1 J/point; 74.2 J/cm^2; 60 s)	ZOL/aPDT showed clinical and histological characteristics of the extraction site, percentage of NFBT and percentage of mature collagen fiber similar to VEH. Percentage of NVBT and immunolabeling for inflammatory cytokines in ZOL/aPDT was lower than in ZOL. Immunolabeling for TRAP was lower in ZOL and ZOL/aPDT	Multiple aPDT sessions in the tooth extraction site improves alveolar repair process and prevents the occurrence of MRONJ-like lesions
Statkievicz et al. (2018)[87]	To evaluate PBM with multiple sessions (low-level laser) as preventive therapy for MRONJ	28 senile female *R norvegicus* Wistar rats (20 mo old)	Rats are induced ligature-induced periodontitis. MRONJ is induced via ZOL (100 mg/kg, IP every 7 wk), tooth extraction after 3 wk, initiation divided into: VEH, VEH-PBM, ZOL, and ZOL-PBM. Euthanasia at 28 d	PBM: 3 sessions (0, 2, 4 d post-extraction Using the following irradiation parameters: (InGaAlP; 660 nm; 35 mW; 2.1 J/point; 74.2 J/cm^2; 60 s)	ZOL: Impaired healing, osteonecrosis, ↓new bone formation (NFBT), ↓mature collagen, ↑TNFα/IL-1β ($p < .05$) - ZOL-PBM: Improved NFBT (+37%), collagen maturation, ↓TNFα/IL-1β vs ZOL ($p < .05$). No clinical bone exposure (vs 100% in ZOL)	PBM mitigated ZOL-induced tissue damage, enhancing bone/soft tissue repair. Multiple PBM sessions may prevent MRONJ onset post-extraction in high-risk patients
Weber et al. (2017)[88]	Evaluate the effects of LLLT on bone and soft-tissue repair in rats under ZOL and DEX therapy	28 male Wistar rats *R norvegicus* albinus (8 wk mean old)	Extractions were performed 36 d after the beginning of the medication regimen, which consisted of 35 d of DEX (AS at 1 mg/kg once daily) and 5 doses of ZOL (AS at 7.5 mg/kg every 7 d for 5 wk), divided into 4 groups: VEH, ZOL control (ZOL + DEX), and 2 experimental, which administered ZOL + DEX and treated with LLLT (685 and 830 nm wavelengths) Euthanasia 14 d after dental extractions	LLLT was applied intraorally during surgery and daily for 15 d post-extraction Using the following irradiation parameters: red range (AlGaAs; 685 nm; 5 W/cm^2; 4 J/energy; 67 J/cm^2; 134 s) Infrared range (AlGaAs; 830 nm; 15 W/cm^2; 67.5 J/cm^2; 45 s)	- LLLT groups showed improved wound healing and reduced bone exposure compared to the medication control group. Histologically, LLLT enhanced bone, and soft-tissue maturation. Weight loss was significant in ZOL + DEX groups	LLLT at 685 and 830 nm wavelengths positively influenced bone and soft-tissue repair in rats under ZOL and DEX therapy, suggesting its potential as an adjunct treatment for MRONJ

(continued)

Table 1. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Mergoni et al. (2016)[92]	Laser therapy's effect on extraction socket healing in rats in conditions at risk for MRONJ, on bone protein expression	30 male Sprague-Dawley rats (5 wk old)	Rats of group TG and TG + laser received ZOL (0.1 mg/kg) and DEX (1 mg/kg) every 2 d for 10 wk. After 9 wk, the tooth extraction, the rats were divided into groups: NC, TG, TG + laser and laser Euthanasia 8 d after dental extractions	Post-extraction laser therapy in the socket area at days 0, 2, 4, and 6 after surgery Using the following irradiation parameters: (Nd:YAG, 1064 nm, 1.25 W, 15 Hz, 5 min, 14.37 J/cm^2)	Rats of groups laser and TG + laser showed a significant higher expression of OCN compared to rats of groups NC and TG (+348% and +400%, respectively; $p = .013$ and $p = .002$, respectively)	Laser irradiation after tooth extraction can promote osteoblast differentiation, as demonstrated by the higher expression of OCN. Thus, laser irradiation could be considered a way to improve socket healing in conditions at risk for MRONJ development

Abbreviations: AlGaInP: aluminum gallium indium phosphide diode laser; aPDT: antimicrobial photodynamic therapy; AS: administered s.c.; AsGaAL: aluminum gallium arsenide diode laser; BG: biomaterial group; BTCP: β-tricalcium phosphate; β-TCP: β-tricalcium phosphate; BuTB: butyl toluidine blue; BV/TV: percentage of bone volume; DBG: doxycycline gel; DG: doxycycline group; DEX: dexamethasone; ECM: extracellular matrix; IL-1RA: IL-1 receptor antagonist; InGaN: indium gallium nitride diode laser; IV: injected i.v.; LLLT: low-level laser therapy; MBO: methylene blue; MRONJ: medication-related osteonecrosis of the jaws; Nab: neutralizing antibody; NC: negative control; NFBT: newly formed bone tissue; NVBT: non-vital bone tissue; OCN: osteocalcin; ONE: sexperimental osteonecrosis; OZ: ozone; PBM: photobiomodulation; PS: photosensitizer; TG: treatment group; TRAP: tatrate-resistant acid phosphatase; ZOL: zoledronate; ESWT: Extracorporeal Shock-Wave Therapy; AS: subcutaneously; AlGaAs: aluminum–gallium–arsenide.

the 660 nm and 808 nm wavelengths offering the most favorable effects on bone and soft tissue. Statkiewicz et al.[87] also reported that PBM significantly improved new bone formation and reduced inflammatory cytokine expression (TNF-α, IL-1β) in senile rats receiving ZOL and undergoing tooth extraction. Photobiomodulation-treated animals exhibited no clinical bone exposure, compared to 100% exposure in the untreated ZOL group. Weber et al.[88] extended these findings by demonstrating that LLLT at 685 and 830 nm accelerated bone and soft-tissue repair in rats treated with ZOL and DEX, suggesting a robust regenerative effect even in highly compromised metabolic environments.

Antimicrobial photodynamic therapy

Multiple studies underscored the efficacy of aPDT in modulating inflammation, promoting osteogenesis, and preventing MRONJ-like lesions. Pontes et al.[55] found that aPDT reduced NF-κB activation and enhanced extracellular matrix (ECM) deposition compared to control and PBM-only groups. Ervolino et al.[51] employed a novel photosensitizer, butyl toluidine blue (BuTB), combined with 660 nm laser irradiation and demonstrated significant improvements in both soft and hard tissue healing. Animals treated with ZOL and aPDT exhibited complete mucosal repair, reduced non-vital bone, and increased new bone formation, accompanied by decreased inflammatory infiltrate and fewer TRAP-positive osteoclasts.

Silva et al.[89] compared PDT and PBM with methylene blue as a photosensitizer and reported that both approaches attenuated bone necrosis and reduced markers of inflammation (CD68+, CD3+, INF-γ, IL-8, MCP-1). Photodynamic therapy was especially effective in decreasing apoptotic osteocytes and improving MRONJ scores. Consistently, Sarkarat et al.[90] observed reduced bone exposure (from 87.5% in controls to 12.5% in treated animals), diminished necrotic bone and empty lacunae, and increased osteoclast activity following PDT using indocyanine green and an 808 nm laser. Earlier work by Ervolino et al.[91] also confirmed the benefits of methylene blue-mediated aPDT, demonstrating improved tissue repair, reduced inflammatory burden, and prevention of osteonecrosis in rats co-treated with ZOL and DEX.

Combination therapies

Hadad et al.[83] evaluated various preventive strategies in a large cohort of rats ($n = 72$), including monotherapies and combination regimens. Notably, the combination of aPDT with β-tricalcium phosphate (β-TCP) and doxycycline gel (DBG) yielded the most favorable results, including the highest bone volume fraction (BV/TV = 69.85%), maximal neoformed bone area (82.44%), and mineral apposition rate (2.64 μm/d). Necrotic bone was present only in the positive control group, underscoring the synergistic effects of combining laser-based therapy with bone graft substitutes and local antimicrobials.

Biomolecular and histopathological correlates

Across studies, laser-based therapies consistently attenuated histological hallmarks of MRONJ, including necrotic bone, empty lacunae, and inflammatory infiltrates. Reductions in cytokines such as TNF-α, IL-1β, INF-γ, IL-8, and MCP-1 were frequently reported. Several studies also demonstrated increased osteoclast activity and improved bone remodeling, indicating active recovery of bone turnover. Importantly, laser

Table 2. Characteristics of the included studies using hormone-based therapies to prevent MRONJ.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Etemadi et al. (2024)[62]	Assess single dose teriparatide for MRONJ prevention in rats	30 male Wistar rats (12 wk old)	ZOL injections; tooth extraction followed by teriparatide (gelatamp or injection), divided into groups: TG, GC, TI, and IC	4 μg/kg teriparatide applied via gelatamp or local injection and sutured	Improved bone remodeling and reduced necrosis, especially with injection	Local teriparatide enhances bone healing and may prevent MRONJ
Park et al. (2023)[67]	Investigating preventive effects of TPD on MRONJ in ovariectomized rats treated with ZOL	30 female Sprague-Dawley rats (OVX-induced osteoporosis)	Periodontitis induced, molars extracted, and treatments administered for 8 wk, rats are divided into 3 groups: control, ZOL, and ZOL + TPD	ZOL (40 μg/kg weekly) + TPD (20 μg/kg daily) for 4 wk before extraction	ZOL + TPD group showed improved bone healing, reduced necrotic bone, and fewer MRONJ lesions compared to ZOL alone. TPD increased trabecular bone thickness and reduced inflammation	TPD administration before extraction reduced MRONJ incidence by promoting bone formation and healing
Castillo et al. (2023)[58]	Evaluate the efficacy of iPTH in healing MRONJ lesions in rice rats.	84 Rice rats *Oryzomys palustris* (4 wk old)	With induced localized periodontitis and MRONJ-like lesions 84 rice rats randomized into saline or ZOL groups, followed by iPTH or saline treatment for 6 wk, divided into groups: VEH/VEH, VEH/PHT, ZOL/VEH and ZOL/PHT	Intermittent PTH (40 μg/kg, 3x/wk) vs saline for 6 wk in established MRONJ lesions	iPTH reduced MRONJ prevalence (27% vs 93% in ZOL/VEH), enhanced bone turnover, and improved soft tissue healing	iPTH is an effective non-operative therapy for MRONJ, promoting bone and soft tissue healing
Jung et al. (2021)[63]	To investigate the timing (pre- vs post-op) of PTH administration for MRONJ prevention	48 female Sprague-Dawley rats (10-12 wk old)	MRONJ induced by ZOL+ dexamethasone, divided into groups: (1) Control (no PTH), (2) Additional ZOL (3 wk pre-op), (3) Pre-op PTH (20 μg/kg/d for 3 wk pre-extraction), and (4) Post-op PTH (20 μg/kg/d for 3 wk post-extraction). Sacrifice at 3 wk post-extraction	Subcutaneous PTH (20 μg/kg/d) pre- or post-extraction	Clinical: No improvement in pre-/post-op PTH vs control ($p > .05$). Histology: Pre-op PTH: ↓empty lacunae ($p = .004$), ↑blood vessels ($p = .002$); Post-op PTH: No significant differences vs control	Pre-op PTH improved bone viability (↓necrosis, ↑angiogenesis) but lacked clinical correlation. Timing matters, pre-op PTH may better prevent MRONJ. Further studies needed to validate dosing and clinical relevance
Liu et al. (2021)[56]	Compare icariin and teriparatide effects on MRONJ	50 female Sprague Dawley strain rats (ovariectomized, 8 wk)	33 rats diagnosed with MRONJ. ZOL + DEX for 8 wk, then tooth extraction. Rats divided into icariin (150 mg/kg), teriparatide (20 μg/kg), or untreated groups for 8 wk	Daily icariin was intragastrically or teriparatide was s.c. injected every day in T group post-MRONJ induction and no intervention to untreated group	Icariin reduced soft tissue wound area; teriparatide increased RANKL expression and reduced necrotic bone. Both showed higher BMP-2 expression	Icariin and teriparatide improve MRONJ symptoms but do not fully reverse it
Kim et al. (2021)	To investigate the effect of intermittent PTH administration before tooth extraction compared with tooth extraction on the risk of developing MRONJ in an experimental animal model	Twenty-five ovariectomized rats	Twenty-five ovariectomized rats received bisphosphonate therapy for 6 wk and were divided into 3 groups based on the timing of medication administration. Control group: Normal saline was administered before and after tooth extraction. Pre-PTH group: PTH was administered for 4 wk before tooth extraction. Post-PTH group: PTH was administered 4 wk after tooth extraction	Ovariectomized rats received bisphosphonate therapy for 6 wk and were divided into 3 groups based on the timing of medication administration. Control group: normal saline was administered before and after tooth extraction. Pre-PTH group: PTH was administered for 4 wk before tooth extraction. Post-PTH group: PTH was administered 4 wk after tooth extraction	The incidence of impaired healing was lower in the pre-PTH and post-PTH groups (11.11%) compared to the Control group (42.86%). Bone healing was more effective in the post-PTH group, moderate in the pre-PTH group, and inferior in the control group, as assessed by microCT and histomorphometry	The pre-PTH group was found to have a positive effect on extraction socket healing. PTH administration after tooth extraction was superior to its administration before tooth extraction

(continued)

Table 2. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Park et al. (2020)[66]	To investigate the effect of intermittent PTH administration on peri-implant bone in the jaws of ovariectomized rats that received BPs systemically	Thirty female Sprague-Dawley rats (8 wk old)	OVX-ZP group: 60 μg/kg zoledronate once weekly for 6 wk and 30 μg/kg PTH after implant placement. OVX-Z group: 60 μg/kg zoledronate once weekly for 6 wk and saline after implant placement. Control group: rats undergoing sham surgery and receiving saline. Euthanasia: 4 wk after implant placement	OVZ-ZP: 60 μg/kg zoledronate once weekly for 6 wk and 30 μg/kg PTH after implant placement. OVX-Z: 60 μg/kg zoledronate once weekly for 6 wk and saline after implant placement. Control: Rats undergoing sham surgery and receiving saline	The OVX-ZP group presented superior results to the OVX-Z group, with a higher percentage of bone area (53.4% $\pm$ 4.0% vs 28.9% $\pm$ 9.5%), greater bone-implant contact (50.8% $\pm$ 1.4% vs 16.9% $\pm$ 2.4%) and greater bone volume according to the microtomography (31.3% $\pm$ 19.8% vs 19.4% $\pm$ 9.3%), all with statistically significant differences. Trabecular thickness and separation were similar between the groups, but the number of trabeculae was significantly higher in the OVX-ZP group ($4.3/mm^3 \pm 1.33/mm^3$ vs $2.2 \pm 0.19/mm^3$)	The results indicate that intermittently administered PTH can promote peri-implant bone formation and may aid in the effective treatment of drug-related osteonecrosis of the jaw after dental implantation
Erten Taysi et al. (2019)[61]	Evaluate local hPTH delivery via chitosan microspheres/poloxamer gel for MRONJ treatment	48 female Sprague-Dawley rats (6 wk old)	Rats treated with ZOL for 3 wk, followed by molar extraction. Divided into 4 experimental groups: group 1. No treatment, group 2. Negative control, group 3. Treatment local injection of poloxamer hydrogel-containing hPTH 0.05 μg/μL and group 4. treatment local injection of poloxamer hydrogel containing hPTH-loaded microspheres 0.233 μg/L	Single or repeated local injections of hPTH-loaded microspheres in poloxamer gel	hPTH microspheres enhanced new bone formation and reduced necrosis, with efficacy similar to repeated injections	Local hPTH delivery is effective for MRONJ, with single-dose microspheres offering patient compliance advantages
Zandi et al. (2018)[68]	To evaluate the effects of different doses/durations of teriparatide on MRONJ resolution in rats	120 male Wistar rats	Phase 1: MRONJ induction (6 weekly ZOL injections + molar extraction). Phase 2: Randomized into 8 subgroups: 3 teriparatide doses (2, 10, 20 μg/kg/d) for 4 or 8 wk vs saline controls	Subcutaneous injections teriparatide (2, 10, 20 μg/kg/d) or saline for 4/8 wk. Clinical/histological assessment post-treatment	Clinical improvement: 72.2% (stage I), 61.5% (stage II), 40% (stage III) with teriparatide vs 20.8% (stage I) in controls. Histology: higher osteocytes (new bone) and fewer empty lacunae (necrosis) in 10/20 μg/kg groups ($p < .05$). No benefit of 8 vs 4 wk	Teriparatide improved MRONJ resolution dose-dependently (10-20 μg/kg optimal). Clinically relevant doses (2 μg/kg) were ineffective. Duration (4 vs 8 wk) did not affect outcomes
Zandi et al. (2017)[57]	To evaluate the effectiveness of short-term perioperative TPD therapy in preventing MRONJ in rats treated with ZOL	100 Male Wistar rats (10 wk old)	Divided into 2 protocols (A and B) for prevention of MRONJ, each with TPD-treated and control subgroups ($n = 25$ each): Protocol A: rats received 5 weekly ZOL injections (0.06 mg/kg). At wk 5, bilateral mandibular first molars were extracted, followed by 4 wk of TPD (20 μg/kg/d) or saline (control). Protocol B: same ZA regimen as Protocol A. TPD or saline started 1-wk post-BP (wk 5), with tooth extraction at wk 7	Subgroups received s.c. injection of 20 μg/kg day TPD for 28 d. Outcome Measures: Clinical: Presence of bone exposure/fistula. Histological: Osteocyte density in new bone and empty lacunae in alveolar bone	Clinical findings: Bone exposure/fistula incidence: Protocol A: 20% TPD vs 78% control; Protocol B: 14% TPD vs 78% control. Significant reduction in ONJ lesions with TPD ($p < .001$). Histological Findings: TPD groups showed higher osteocyte density and fewer empty lacunae, indicating improved bone healing and reduced necrosis ($p < .001$). There is no significant difference between protocols A and B TPD groups	Four weeks of perioperative TPD therapy, whether initiated at extraction or 2 wk prior, significantly reduced MRONJ incidence and improved bone healing in zoledronate-treated rats. The study supports TPD as a potential preventive strategy for MRONJ, though further clinical trials are needed to confirm efficacy in humans

(continued)

Table 2. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Kenkinruzgar et al. (2016)[64]	To investigate the histopathological effects of teriparatide in rats that developed osteonecrosis with the use of BP	Eighty Wistar albino male rats	All rats received weekly i.p. injections of ZA (0.4 mg/kg) for 7 wk. At wk 5, 6, and 7, DEX (1 mg/kg) injections were also administered. At the end of the seventh wk, under general anesthesia, the left maxillary first molars were extracted and 4-mm bone defects were created in the same region. Teriparatide was administered according to the protocols from previous studies. The animals were divided into a control group and 3 experimental groups according to the periods of teriparatide administration: preoperative (wk 5-7), postoperative (wk 8-10), and after the onset of osteonecrosis (wk 15-17)	Rats received weekly i.p. injections of ZA (0.4 mg/kg) for 7 wk. At wk 5, 6, and 7, injections of DEX (1 mg/kg) were also administered. After tooth extraction and bone defect formation, teriparatide was administered to the preoperative, postoperative, and after the onset of osteonecrosis groups	The osteoclast numbers were larger in the experimental groups (teriparatide administered before and immediately after tooth extraction) than in the control group (administered zoledronic acid). The inflammatory phase of bone healing was more pronounced in the experimental group (teriparatide administered before tooth extraction) than in the control group. There were significant differences in osteoclast numbers and in the inflammatory phase of bone healing between the experimental and control groups ($p < .05$). The osteoblast numbers and osteonecrotic areas were similar in size between the experimental and control groups. There were no significant differences ($p > .05$)	The experimental groups that received teriparatide before or immediately after tooth extraction had a higher number of osteoclasts compared to the control group treated with ZA. The inflammatory phase of bone healing was more pronounced in the group that received teriparatide before extraction. The differences in osteoclast number and inflammatory response between the groups were $p < .05$. The number of osteoblasts and the size of osteonecrotic areas were similar between the groups ($p > .05$)
Ersan et al. (2014)[60]	Establish a BRONJ rat model and analyze TPD effects	30 female Sprague-Dawley rats (10-12 wk old)	Rats treated with ZOL for 6 wk, followed by molar extraction. The rats were randomly divided into 3 groups: ZOL, ZOL + TPD, and control	Daily s.c. TPD injections (30 μg/kg) for 28 d pos-extraction	TPD increased BMD, reduced osteonecrosis area, and normalized osteoclast activity compared to ZOL-only group	TPD may effectively treat MRONJ by promoting bone formation and reducing necrosis
Kuroshima et al. (2014)[65]	To determine the effect of combined bisphosphonate and steroid therapy prior to bone injury on bone healing, to compare healing between tooth extraction sockets and tibial bone defects in bisphosphonate/steroid-treated rats, and to investigate the effects of PTH therapy on early wound healing in bisphosphonate/steroid-injured bones	Female Sprague Dawley rats (9 wk old)	All rats underwent OVX at 10 wk. One group received ALN from OVX, administered twice weekly (0.8 mg/kg) for 12 wk, and DEX daily (1 mg/kg) for the last 2 wk. The other group received saline only (VEH). At the end of treatment, the upper right second molars were extracted and bone defects were created in the tibia and mandible. After extraction, half of each group (ALN/DEX and control) received daily injections of PTH (80 μg/kg) for 2 wk; the other half received saline. Euthanasia: 2 wk after extractions	Administration of ALN from OVX, twice weekly (0.8 mg/kg) for 12 wk, and DEX daily (1 mg/kg) for the last 2 wk. The other group received only saline (VEH). After tooth extraction, half of each group (ALN/DEX and control) received daily injections of PTH (80 μg/kg) for 2 wk; the other half received saline	ALN/DEX treatment is associated with open necrotic wounds in the mandible, but it did not compromise healing or prevent bone filling in tibial defects. PTH therapy prevented the formation of necrotic lesions in the mandible and favored the regeneration of tibial defects. PTH use was associated with the preservation of osteocyte viability in bone wounds in the mandible and tibia	Wound healing was impaired in the mandible of rats treated with the ALN/DEX combination, and PTH therapy rescued necrotic lesions. This suggests that PTH therapy can be used to prevent ONJ in patients treated with the combination therapy

(continued)

Table 2. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Dayisoylu et al. (2013)[59]	To evaluate the effectiveness of adjunctive PTH injections in managing MRONJ following tooth extraction after chronic bisphosphonate administration	36 female Sprague-Dawley rats (*Rattus norvegicus*)	Group I (Control): injected IP sterile saline (SS) 3×/wk for 8 wk. Group II (ZOL-only): injected IP (ZOL; 0.1 mg/kg) 3×/wk for 8 wk. Group III (ZOL + Extraction): ZOL + molar extraction +8-wk recovery. Group IV (ZOL + Extraction + PTH): ZOL + extraction + PTH (30 μg/kg/d) for 8 wk	30 μg/kg/d PTH analog (Forsteo1, teriparatide 250 mg/mL, 3 mL injectable, Lilly, Turkey) was injected s.c. for 8 wk. Controls: ZA-only and extraction-only groups to isolate PTH effects. Endpoint: Histomorphometric analysis of OBs, OCs, FBs, and MRONJ incidence	MRONJ incidence: Group III (ZOL + Extraction): 66% MRONJ (ulceration, necrosis). Group IV (ZOL + Extraction + PTH): 22% MRONJ ($p < .01$). Cellular activity: OBs: higher in PTH group (279.23 ± 74.29) vs ZOL-only (84.14 ± 66.37; $p < .01$). OCs: Increased in PTH group (4.34 ± 3.65) vs ZOL-only (1.26 ± 0.47; $p < .01$). Inflammation: severe in group III (100% grade 2) vs mild in PTH group (66.6% grade 2, 22.2% grade 0). Mucosal healing: 77% complete epithelialization in PTH group vs 0% in group III. Clinical implication: Adjunctive PTH may mitigate MRONJ in high-risk patients, but further studies are needed to optimize dosing and evaluate long-term safety (eg, osteosarcoma risk)	Although significant improvements in bone healing were observed in the PTH group, more studies are needed to evaluate this treatment

Abbreviations: ALN: alendronate; DEX: dexamethasone; FBs: fibroblasts; GC: gelatamp control; hPTH: human PTH; IC: injection control; iPTH: intermittent PTH; MRONJ: medication-related osteonecrosis of the jaws; OBs: osteoblasts; OCs: osteoclasts; ONJ: osteonecrosis of the jaw; OVX: bilateral ovariectomy; OVZ-Z: ovariectomized rats administered zoledronate; OVZ-ZP: ovariectomized rats administered zoledronate and PTH after implant installation; TG: teriparatide gelatapam; TI: teriparatide injection; TPD: teriparatide; ZA: zoledronic acid; ZOL: zoledronate.

Table 3. Characteristics of the included studies using ceramic-based biomaterials to prevent MRONJ.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Guo et al. (2025)[99]	Develop a Mg nanocomposite hydrogel to enhance mandible regeneration in MRONJ by addressing angiogenesis, infection, and inflammation and minipigs	Female Sprague Dawley rats (12 wk old)	MRONJ was induced in rats using ZOL (0.3 mg/kg) for 12 continuous weeks. Mandible defects were created and treated with Mg hydrogel. Minipigs were used for feasibility testing	Mg hydrogel was injected into defects. It released Mg^{2+}, promoted type H vessel formation, and modulated the immune microenvironment	PBM hydrogel improved bone regeneration, angiogenesis, and stem cell recruitment. It reduced inflammation and pathogenic bacteria in MRONJ rats. In minipigs, it enhanced bone formation and integration	The Mg hydrogel is a promising injectable bone substitute for MRONJ, addressing multiple pathological factors (impaired healing, infection, inflammation), and demonstrating feasibility in large-animal models
Pellicano et al. (2024)[102]	Assess the preventive effects of bioactive glass and pericardial membrane on MRONJ in a rat model	26 Male Wistar *Rattus norvegicus* albinus rats (9 wk old)	Treated with IP with ZOL (200 μg/kg) for 4 wk, post-tooth extraction, are divided into groups: saline, ZOL, ZOL + membrane, saline + membrane, ZOL + bioglass + membrane and saline + membrane + bioglass. Evaluated over 8 wk	Application of pericardial membrane alone or with F18 bioglass post-tooth extraction	Bioglass + membrane prevented osteonecrosis, osteolysis, and abscess formation. ZOL alone caused severe bone loss	Combination of bioglass and pericardial membrane effectively prevents MRONJ in preclinical models
Funayama et al. (2023)[77]	Assess β-TCP's role in preventing MRONJ by adsorbing ZOL and promoting socket healing	48 male Sprague-Dawley rats treated with high-dose ZOL	Rats received ZOL (1.2 mg/kg) for 2 wk, molars extracted, and sockets filled with β-TCP or left empty. Evaluated at 1, 4, and 8 wk, divided into groups: control and β-TCP	β-TCP (0.01 g) placed in extraction sockets	β-TCP reduced ZOL deposition in connective tissue (2.2 ng vs 4.9 ng in controls). Improved mucosal coverage, bone healing, and reduced necrotic bone. Autophagy-related proteins (Atg9a, ULK-3) were upregulated in β-TCP group	β-TCP absorbed ZOL, reduced local BP concentration, and prevented MRONJ by enhancing autophagy and bone healing
Sacco et al. (2022)[98]	Evaluate HADOX as a preventive strategy for MRONJ in rats treated with bisphosphonates	35 Female Wistar rats	Rats divided into 7 groups: HADOX, HA, and sham groups with varying ZOL doses (4%, 8%). Tooth extraction performed after 4 wk of ZOL treatment Groups: G1 - HA 4% ZOL, G2 - HA 8% ZOL, G3 - HADOX 4% ZOL, G4 - HADOX 8% ZOL, G5 - sham 4% ZOL, G6 - sham 8% ZOL, and G7 - sham NaCl	HADOX or HA applied to extraction sockets. Euthanasia after 28 d for histological analysis	HADOX increased NFB and reduced inflammation compared to HA. Biomaterial retention was higher in HADOX groups	HADOX promotes bone healing and reduces inflammation, making it a potential preventive strategy for MRONJ
Zhu et al. (2022)[100]	To investigate whether biodegradable magnesium (Mg)-based implants could prevent MRONJ by promoting angiogenesis	50 male Sprague Dawley rats (8 wk old)	Rats received once-weekly IP of ZOL (130 μg/kg) and DEX (3.8 mg/kg), for 5 wk, dental extraction and mandibular bone defect creation, followed by implant placement, divided into 6 groups: saline + Ti implant; ZOL + Ti (implant); ZOL + Mg (implant); ZOL + Mg + SU5416 (Mg implant + VEGFR-2 inhibitor for 8 wk), ZOL + Mg + BIBN (Mg implant + CGRP receptor antagonist for 2 wk) and ZOL + Mg + SU5416 + BIBN (Mg implant + VEGFR-2 inhibitor for 8 wk and CGRP receptor antagonist for 2 wk) Euthanasia 8 wk after surgery	Local implantation of biodegradable Mg or Ti rods in the mandible. Some groups received were co-treated with VEGFR-2 inhibitor (SU5416) and/or CGRP receptor antagonist (BIBN)	Mg implants reduced MRONJ-like lesion incidence (from 100% in BP + Ti to 50% in BP + Mg); promoted new bone formation; increased VEGFA and CGRP expression. Inhibiting VEGFR-2 and CGRP receptors reversed the beneficial effects of Mg	Mg implants alleviated MRONJ-like lesion development by promoting angiogenesis via VEGF- and CGRP-mediated pathways. Mg devices have translational potential as internal fixation materials for patients at risk of MRONJ

(continued)

Table 3. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Tanaka et al. (2021)[80]	Evaluate BMP-2/β-TCP's potential in preventing/treating alveolar bone necrosis in MRONJ-like mice	C57BL/6 J mice (8-12 wk old females)	A combined administration CY (150 mg/kg) and ZOL (0.05 mg/kg) were injected, respectively, SC and IP, twice a week for 3 wk, divided into groups: prevention model: CY/ZOL pre- and post-tooth extraction and treatment model: CY/ZOL pre-extraction, suspended post-BMP-2/β-TCP transplantation	BMP-2/β-TCP transplanted into tooth sockets	BMP-2/β-TCP reduced necrotic bone and increased BMP (prevention model). Improved bone quality in both models	BMP-2/β-TCP is a promising therapy for MRONJ prevention and treatment
Mikai et al. (2020)[79]	Assess BMP-2/β-TCP transplantation for preventing/treating MRONJ-like lesions in mice	Female C57BL/6 J mice (8-12 wk old)	A combined administration CY (150 mg/kg) and ZOL (0.05 mg/kg) were injected, respectively, SC and IP, twice a week for 3 wk. BMP-2/β-TCP was transplanted into the tooth extraction sockets, divided into groups: prevention: immediately post-extraction and treatment: 2 wk post-extraction (with curettage). Evaluated at 4 wk post-transplantation	Local transplantation of BMP-2 adsorbed onto β-TCP into tooth extraction sockets	Prevention: partial bone formation and reduced necrosis. Treatment: complete bone regeneration reduced empty lacunae, and increased osteopontin expression. No significant angiogenesis changes	BMP-2/β-TCP promotes bone regeneration in MRONJ, with stronger effects in treatment than prevention, suggesting clinical potential for MRONJ management
Paulo et al. (2020)[97]	Investigate if BCP ceramics can prevent MRONJ by limiting zoledronate toxicity in extraction sites	35 female Wistar rats (16 and 18 wk)	Chronic ZOL (0.1 mg/kg) administration IP 3 times a week, tooth extraction, BCP application in sockets, divided into groups: control 14, ZOL 14, control 21, ZOL 21, and ZOL/BCP	BCP granules (75% HA, 25% β-TCP) placed in extraction sockets	BCP improved healing, reduced bone exposure, and normalized bone density. Nuclear medicine showed reduced ZOL uptake in BCP-treated rats	BCP ceramics limit ZOL toxicity and may prevent MRONJ by adsorbing bisphosphonates
Su et al. (2020)[78]	Investigating BBG in MRONJ prevention	Mouse model + cell lines female Sprague-Dawley rats (3 wk old)	Rats in the experimental group were IP with ZOL (125 μg/kg) DEX (5 mg/kg) for 4 wk. Rats in the control group was IP with an equal volume of saline for 4 wk, extraction + BBG in vivo/in vitro, divided into groups: control, ZOL, BBG and ZOL + BBG	BBG locally applied	BBG restored angiogenesis and osteogenesis. The BRONJ lesions were satisfactorily repaired and BMD, bone volume/tissue volume, trabecula number, OCN-positive cells, and CD31-positive cells were increased in the BBG-treated groups compared with saline-treated groups	Exposure of BMSCs and HUVECs to BBG restores osteogenesis and angiogenesis inhibited by zoledronate. BBG prevented MRONJ by promoting tissue regeneration
de Almeida et al. (2018)[101]	Assess the efficacy and safety of HA scaffolds in preventing MRONJ	48 male Wistar rats (45 ± 3 d)	ZOL administration (0.6 mg/kg) for 3 times, tooth extraction and scaffold implantation performed, divided into 4 subgroups: control, ZOL, ZOL + scaffold 0.2 and ZOL + scaffold 0.6	For the fixation of the scaffold in the cleft, a bioadhesive buccal gel was used	Scaffolds reduced osteonecrosis and improved bone healing. Some hematological changes observed but normalized over time	HA scaffolds are effective and safe for preventing MRONJ

Abbreviations: Atg9a: autophagy-related protein 9A; BBG: borate bioactive glass; BCP: biphasic calcium phosphates; BP: release bisphosphonates; BMSCs: BM mesenchymal cells; β-TCP: beta-tricalcium phosphate; CGRP: calcitonin gene-related peptide; CY: cyclophosphamide; DEX: dexamethasone; HA: hydroxyapatite; HADOX: hydroxyapatite loaded with doxycycline; HUVECs: human umbilical vein endothelial cells; Mg: magnesium; MRONJ: medication-related osteonecrosis of the jaw; NFB: newly formed bone; sham: without graft biomaterial; Ti: titanium; ULK3: serine/threonine-protein; ZOL: zoledronate.

Table 4. Characteristics of the included studies using stem cell-based therapies to prevent MRONJ.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Shi et al. (2025)[33]	To investigate the preventive effects of the PRP/Bio-Oss granules composite on MRONJ	18 female Sprague-Dawley rats	Rats treated with ZOL (0.1 mg/kg, by IP injections 3x/wk, 12 wk); all rats underwent molar extractions and bone defect creation at wk 4, divided into groups: control group: empty defect, Bio-Oss group: defect filled with Bio-Oss granules and composite group: defect filled with PRP + Bio-Oss composite Euthanasia at 8 wk post-surgery	PRP gel combined with Bio-Oss granules the defect sites were filled with 10 mg of Bio-Oss granules and 12 mg of a PRP/Bio-Oss granules composite applied into bone defects immediately after extraction	Composite group had 0% bone exposure, highest BMD and BV/TV, lowest % of empty osteocyte lacunae. Superior soft and hard tissue healing vs Bio-Oss or control groups (which had 83.3% and 66.7% bone exposure, respectively)	PRP/Bio-Oss composite effectively prevented MRONJ in BPs-treated rats by enhancing angiogenesis, osteogenesis, and soft tissue healing. Promising strategy for high-risk patients
Cao et al. (2025)[107]	Investigate the role of lymphangiogenesis in MRONJ and evaluate IGF-1-loaded hydrogel for prevention	40 female Sprague-Dawley rats (8 wk old)	Rats treated with ZOL (0.2 mg/kg by IP injections) and DEX (2 mg/kg) for 8 wk, followed by molar extraction. IGF-1 delivered via hydrogel or injection, divided into groups: CG, IGF-1-CGGP, and CGGP	IGF-1-loaded chitosan/gelatin/β-glycerol phosphate hydrogel applied to extraction sockets	IGF-1 restored PI3K/AKT pathway, enhanced angiogenesis/lymphangiogenesis, and prevented MRONJ-like lesions. Hydrogel outperformed injections	IGF-1 via hydrogel is a promising strategy for MRONJ prevention by restoring vascular and lymphatic function
Kurokawa et al. (2025)[106]	Evaluate bFGF application to prevent MRONJ post-tooth extraction in rats	24 female Sprague-Dawley rats (10 wk old)	Rats treated with ZOL (60 μg/kg, i.v. injections) were randomly divided into: control group: HPC and test group: bFGF-HPC	0.3% bFGF +3% HPC or HPC applied to extraction sockets	MRONJ incidence: 8.3% (bFGF) vs 100% (control). Increased angiogenesis and bone formation	Local bFGF application effectively prevents MRONJ by enhancing tissue healing
Zheng et al. (2024)[112]	Explore mechanisms of ADSC-derived exosomes in preventing MRONJ by focusing on macrophage M1 polarization and pyroptosis	C57BL/6 N male mice (6-8 wk old)	Was administrated IP ZOL (1 mg/kg) once a day, and the tooth extraction was extracted after 2 wk. The mice were randomly assigned to 4 groups: CG, ZOL, hydrogel, and Exo (100 μg/mL, 2-3 μL)	ADSC-derived exosomes (100 μg/mL) locally injected into extraction site	Exosomes accelerated wound healing, reduced M1 polarization, and suppressed pyroptosis via NF-κB/NLRP3/IL-1β axis	ADSC-derived exosomes prevent MRONJ by inhibiting macrophage pyroptosis and inflammation
Dong et al. (2024)[113]	To investigate the impact and mechanisms of ADSCs in preventing MRONJ by activating autophagy and inhibiting apoptosis in gingival epithelium	Male C57BL/6 N mice (6 wk old)	Mice received ZOL (1 μg/mg) IP injections, followed by tooth extraction, divided into 3 groups: CG, MRONJ (ZOL-treated), and ADSC treated	ADSCs (1×10^6 cells in PBS) were injected i.v. after tooth extraction. Autophagy (LC3, SQSTM1) and apoptosis (Cleaved-CASP3) in gingival epithelium were examined	ADSC promoted gingival epithelium migration and new bone formation. ADSC restored impaired autophagic flux (reduced LC3/SQSTM1) and decreased apoptosis in gingival epithelium. ADSC-CM rescued autophagosome-lysosome fusion in vitro. Reduced TUNEL+ cells in ADSC-treated mice	ADSC prevents MRONJ by activating autophagic flux and inhibiting apoptosis in gingival epithelium, suggesting a novel stem cell-based therapy
Tao et al. (2024)[34]	Investigate the preventive effect of Hep/GelMA-PRF hydrogel on MRONJ	48 female Sprague-Dawley rats (8 wk old)	MRONJ rat model induced by ZOL (125 μg/kg) IP injections 2 times weekly and DEX (5 mg/kg) 1 time weekly, followed by tooth extraction, divided into 3 groups: ZOL, Hep/GelMA and Hep/GelMA-PRF	Hep/GelMA-PRF hydrogel applied to extraction sockets	Improved bone regeneration and reduced necrosis. Upregulated osteogenic markers (OCN, Col I, BMP-2). Reduced inflammation	Hep/GelMA-PRF hydrogel prevents MRONJ by promoting osteogenesis and controlling growth factor release, induce osteogenic differentiation, reduce inflammation, and keep a stable microenvironment for tissue repair

(continued)

Table 4. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Nishimaki et al. (2024)[148]	Investigate MSC sheets to prevent MRONJ triggered by titanium implants in rats	24 male Sprague-Dawley rats (8 wk old)	Rats administered ZOL (66 μg/kg) and DEX (5 mg/kg) s.c. 3 times per week for 7 wk, divided into 3 groups: VEH group (sterile saline injection without drugs), CG MSC sheet (−) only the titanium plate was covered with soft tissue, and the mandibular skin was sutured without cell sheet grafting and MSC sheet co-grafted	Allogeneic BM-derived MSC sheets co-grafted with titanium implants	Reduced bone necrosis and empty lacunae in MSC sheet (+) group. No significant difference in BV/TV. TRAP staining revealed a decreased number of TRAP-positive cells in areas with a large number of empty lacunae in the MSC sheet (−) group	MSC sheets may prevent MRONJ by reducing necrosis and improving bone health
Kaminogo et al. (2024)[116]	Evaluate DPSC-CM in preventing MRONJ and its relationship with Wnt signaling	Male C57BL6J mice (8 wk old)	MRONJ model: anti-RANKL Ab (250 μg) + CYP (150 mg/kg) twice weekly. DPSC-CM administered post-extraction, divided into groups: CG, DEMEM, and DPSC-CM	DPSC-CM (atelocollagen scaffold) applied to extraction sockets	DPSC-CM enhanced osteogenesis, reduced inflammation, and improved Wnt signaling (↑β-catenin, ↓Dkk-1)	DPSC-CM prevents MRONJ by modulating Wnt signaling and promoting bone healing
Etemadi et al. (2023)[149]	Assess the preventive effects of L-PRF on MRONJ following dental extraction in rats	28 male Wistar rats	Rats administered IP injections of ZOL (0.06 mg/kg) for 4 wk, evaluated at 4 wk post-extraction, divided into groups: saline (control), ZOL (positive control), and L-PRF (case) groups. Split-mouth design: L-PRF applied to 1 extraction socket in ZOL treated rats	L-PRF gel placed in extraction sockets post-extraction	L-PRF reduced osteonecrosis centers by 41.67% and inflammation severity. No significant change in blood vessel density or fibroblast count	L-PRF may prevent MRONJ by reducing osteonecrosis and inflammation, but further studies are needed
Zheng et al. (2023)[111]	Investigate if MSCs-derived exosomes prevent MRONJ via IL-1RA-mediated anti-inflammatory effects	C57BL/6 N male mice (6-8 wk old)	Mice ZOL (1 mg/kg IP injections) administered for 4 wk; tooth extraction at 2 wk, divided into groups: CG treated with a VEH and PBS, ZOL treated with ZOL and PBS, hydrogel treated with ZOL, and hydrogel and EXO treated with ZOL, and hydrogel-injected post-extraction	MSCs-derived exosomes (with/without IL-1RA knockdown) in hydrogel applied to sockets	Exosomes promoted gingival healing, reduced IL-1β/TNF-α, and increased IL-1RA. IL-1RA-deficient exosomes impaired healing and bone regeneration	MSCs-derived exosomes prevent MRONJ via IL-1RA-mediated anti-inflammatory effects
Sadat-Ali et al. (2022)[150]	To evaluate the efficacy of ABMDO and A-Heal in treating MRONJ in rats	30 female Wistar rats (≥3 mo old)	All rats in Groups I-III were given IV ZOL (80 μg/kg) once a week for 4 wk and maxillary molar extraction. Treatments were administered for 12 wk post-extraction, divided into groups: group ABMDO treatment, group A-Heal treatment, and group saline (control) Outcomes assessed via CT scans and histopathology at 4 wk post-treatment	Group 1: Local injection of 2 million osteoblasts in 0.5 mL at MRONJ site Group 2: Topical A-Heal (5 mg/kg) applied 3x/wk for 3 wk. Group 3: Saline placebo	Radiology (CT): Groups 1 & 2 showed osteosclerosis, calcifications, and soft-tissue healing; Group 3 had bone erosion and ulceration Histology: groups 1 & 2 exhibited reactive bone formation; Group 2 had the highest vascular proliferation (factor VIII an endothelial cell marker). Group 3 showed cartilage proliferation, inflammation, and poor healing	Both ABMDO and A-Heal promoted MRONJ healing in rats, with A-Heal demonstrating superior angiogenic effects. The study supports further trials in larger animals and humans
Sarkarat et al. (2022)[151]	Evaluate HA and ACS in reducing BRONJ post-extraction	40 male Wistar rats (2 mo old)	Rats administered ZOL (0.04 mg/kg) injections IV for 5 wk. Molar extraction with socket treatments, divided into groups: HA, ACS, HA + ACS, and CG	Socket filled with HA, ACS, or HA + ACS post-extraction	HA + ACS reduced empty lacunae and increased live bone. HA alone showed higher eosinophil counts (allergic reaction). ACS alone improved vascularization early	HA + ACS is effective in promoting bone healing and reducing BRONJ signs. HA alone may trigger immune responses
Kaibuchi et al. (2022)[108]	Investigate efficacy of MSC sheet therapy for MRONJ	Rats and beagle dogs with MRONJ-like lesions	Allogeneic MSC sheets transplanted into MRONJ models. Evaluated healing, angiogenesis, and bone metabolism	MSC sheets derived from BM (rats) and adipose tissue (dogs)	Healing of bone exposure, increased neovascularization, and osteoclast activity in treated groups	MSC sheets promote healing via angiogenesis, bone metabolism, and immunomodulation. Clinical trials planned

(continued)

Table 4. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Jamalpour et al. (2022)[152]	Compare surgical therapy, PBM, A-PRF, and L-PRF for MRONJ management	60 male Wistar rats	Rats administered of ZOL (0.06 mg/kg) injections IP; tooth extraction; MRONJ lesions treated with combinations of therapies, divided into groups: CG surgery alone, Surg alone, Surg + PBM, Surg + APRF, Surg + LPRF, Surg + APRF + PBM, and Surg + LPRF + PBM	In groups PBM was performed using an diode laser (808 nm; 500 mW; 1.4 J/energy 5 J/cm^2; 120 s) on first, third, fifth, seventh, and 10th postoperative days. In groups A-PRF, or L-PRF, 2 mL of blood was collected from the retro-orbital sinus into the specified sterile tubes using a capillary pipette (plain glass-based vacuum tube for A-PRF and glass-coated plastic tube for L-PRF	A-PRF and L-PRF treatment resulted in significant improvements in clinical, histological, and radiographical parameters compared to the CG. The PBM also decreased wound dimensions, and the number of empty lacunae compared to the CG. Surg + APRF + PBM and Surg + LPRF + PBM were the only groups that presented a significantly higher mean number of osteocytes	Combined PBM and A-PRF or L-PRF therapies optimize MRONJ healing and bone regeneration
Sharma et al. (2021)[153]	To assess the efficacy of a gelatin HA hydrogel loaded with VEGF in preventing MRONJ by counteracting the anti-angiogenic effects of ZOL	24 female Sprague Dawley rats (10-12 wk old)	Rats administered IP of ZOL (198 μg/kg) once a week, tooth extraction and defect creation. Healing was assessed for 4 wk post-surgery, divided into groups: no-gel CG, gel-alone (HA hydrogel), and VEGF-gel (hydrogel + VEGF)	Local implantation of a gelatin-hyaluronic acid hydrogel loaded with VEGF (200 ng) extraction sockets. VEGF release kinetics were evaluated in vitro.	VEGF-gel significantly reduced osteonecrosis and inflammatory infiltrate compared to no-gel and gel-alone groups. VEGF-gel increased vascularity (vWF and CD105 expression) and neovascularization. Gene expression of vascular and bone markers was upregulated, and systemic VEGF levels increased	Local delivery of VEGF via a hydrogel prevents MRONJ by restoring angiogenesis, reducing inflammation, and improving bone healing. This approach offers a clinically viable strategy for MRONJ prevention
Huang et al. (2021)[117]	Evaluate the effects of sEV-AT on MRONJ-like lesions in rats by promoting angiogenesis	35 female SD rats (8 wk old)	Rats treated with ZOL (66 μg/kg) and DEX (5 mg/kg) 3 times per week for 4 wk, tooth extraction performed after 2 wk, divided into 3 groups: CG, ZOL + DEX, and sEV-AT	Intravenous sEV-AT every 3 d post-extraction	sEV-AT reduced MRONJ-like lesions, promoted soft tissue healing, increased bone volume, and enhanced angiogenesis	sEV-AT prevents MRONJ by promoting angiogenesis and tissue regeneration
Kushiro et al. (2021)[154]	Examine the preventive effect of locally administered DPSC-CM on MRONJ in ZOL treated rats	Male Wistar rats (8 wk old)	Rats treated with ZOL (160 μg/kg) for 3 wk, then tooth extraction, divided into groups according to the material used: Collagen beads + CM and Gelatin sponge + CM, control group collagen beads + PBS, gelatin sponge + PBS, and non-administration	DPSC-CM delivered via atelocollagen or gelatin sponges. Sacrifice after 1 wk for analysis	Atelocollagen + DPSC-CM reduced bone exposure and empty lacunae, increased VEGF-positive cells	Local DPSC-CM with atelocollagen may prevent MRONJ by promoting mucosal healing and angiogenesis
Yang et al. (2021)[75]	Investigate therapeutic effects of hUC-MSCs on MRONJ in vitro and in vivo	Female Sprague-Dawley rats	Rats treated with ZOL (66 μg/kg/wk) and DEX (5 mg/kg) s.c. for 4 wk. Two weeks after s.c. injection, maxillary molars were extracted, divided into groups: CG, BPs-treated and hUC-MSC. In vitro: Co-culture of rBM-derived cells with hUC-MSCs. In vivo: hUC-MSCs transfused i.v.	Intravenous transfusion of hUC-MSCs (1 × 10^6 cells)	Reduced BP-induced cytotoxicity and inflammation. Increased bone regeneration markers (RUNX2, OSX, BMP-2). Normalized RANKL/OPG ratio. Improved mucosal healing and reduced osteonecrosis in vivo	hUC-MSCs show therapeutic potential for MRONJ via anti-inflammatory and bone-regenerative effects

(continued)

Table 4. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Gao et al. (2021)[104]	Assess PDGF-BB's therapeutic effects on MRONJ by enhancing angiogenesis and osteogenesis	30 female Sprague-Dawley rats (6-8 wk old)	Rats treated with ZOL (200 μg/kg) + DEX (5 mg/kg) for 16 wk, followed by molar extraction. PDGF-BB delivered via fibrin sealant post-debridement, divided into groups: CG (saline) and MRONJ	Fibrin sealant with 100 ng/mL PDGF-BB applied to extraction sockets	PDGF-BB increased angiogenesis, osteogenesis, and healing (80% success vs 30% control)	PDGF-BB rescues impaired bone healing in MRONJ by restoring coupling of angiogenesis and osteogenesis
Razmara et al. (2021)[103]	Investigate the efficacy of collagen scaffold alone and PRP-collagen scaffold in preventing ZOL induced MRONJ in rats	17 male Wistar rats (mean age of 10 wk)	Rats treated with ZOL (0.06 mg/kg/wk for 4 wk). Bilateral tooth extraction of mandibular first molars; divided into 3 groups: scaffold + PRP + suture, scaffold + suture, and CG suture only. Sacrificed 8 wk for evaluation	PRP-enriched collagen scaffold or collagen scaffold alone applied post-extraction	PRP + scaffold group showed higher BMD, osteoblast count, and new bone formation. Reduced osteonecrosis and inflammation compared to scaffold-alone and control groups	PRP-enriched collagen scaffold is effective in preventing MRONJ by enhancing bone formation and reducing necrosis and inflammation
Rodriguez-Lozano et al. (2020)[155]	Evaluate allogeneic BM-MSC transplantation in MRONJ prevention	30 female Wistar rats (8-12 wk old)	Rats treated with ZOL (0.1 mg/kg) administered injections IP, for 3 times per week, for 9 wk in extraction sockets, divided into 2 groups: BM-MSCs/β-TCP and CG saline/β-TCP	BM-MSCs seeded on β-TCP implanted in sockets	BM-MSC group had no MRONJ cases (vs 33% in control), increased osteoclasts, and bone formation	BM-MSC may prevent MRONJ by enhancing bone remodeling and reducing necrosis
Doppelt et al. (2020)[156]	Evaluate EPCs to treat MRONJ	10 female and male Lewis rats (13 wk old)	Rats treated with s.c. injection of ZOL (7.5 μg/kg) + DEX (1 mg/kg) once a week for 11 wk, tooth extraction + EPC treatment, divided into groups: CG, ZOL, DEX, and ZOL + DEX	EPCs injected locally	Improved wound healing and vascularization	EPCs promote healing via paracrine effects
Watanabe et al. (2020)[74]	To investigate whether MSC-EVs can prevent MRONJ by suppressing cellular senescence and promoting wound healing	81 female Wistar/ST rats (9 wk old)	Rats treated with ZOL (35 μg/kg) once a week for 3 wk and DEX (1 mg/kg) IP injected every day for 3 wk, divided into groups: CG without injecting ZOL and DEX, ZOL + saline, and ZOL + EVs. In vivo: Rat BRONJ model with tooth extraction. In vitro: ZOL-treated BM cells, fibroblasts, osteoclasts, and cancer cells	MSC-EVs injected i.v. (30 μg/0.5 mL) the day after tooth extraction	MSC-EVs reduced cellular senescence markers (p21, pRB) and SASP factors (IL-6, IL-8, MMP1, MMP3) Promoted wound healing and angiogenesis in vivo. No effect on osteoclast apoptosis or cancer cell proliferation	MSC-EVs prevent MRONJ by suppressing cellular senescence and promoting wound healing without interfering with ZOL's anti-resorptive effects
Kuroshima et al. (2019)[115]	Examine the effects of QQ-controlled PBMNCs on reducing MRONJ-like lesions in mice, focusing on wound healing and angiogenesis	62 female C57BL/6 J mice (8-12 wk old)	Treated with ZOL (0.05 mg/kg) and CY (150 mg/kg) twice and once a week before and after tooth extraction, respectively, divided into groups: CG (VEH control), CY/ZA-CG therapy, and CY/ZA + QQ-PBMNC therapy. Evaluated at 72 h and 2 wk	Systemic transplantation of QQ-PBMNCs (20 000 cells/mouse) post-extraction	QQ-PBMNCs improved soft tissue healing (collagen production, reduced PBMNs) and angiogenesis. Partial improvement in osseous healing. No adverse effects on BM	QQ-PBMNC transplantation reduces MRONJ-like lesions by improving soft tissue healing and angiogenesis, offering a potential therapeutic strategy
Tamari et al. (2019)[114]	To investigate the role of EPCs in healing MRONJ lesions by addressing impaired vascularization and soft tissue healing caused by ZOL and DEX	50 male and female Lewis inbred rats (13 wk)	Treated s.c. injection of one of the following, once a week for 11 wk with ZOL (7.5 μg/kg) and DEX (1 mg/kg), tooth extraction was performed at wk 3, divided into groups: CG (saline), ZOL, DEX, ZOL + DEX. Healing was assessed for 8 wk post-extraction	Local injection of early or late EPCs, MSCs, or culture medium into MRONJ-like lesions. EPCs were derived from human blood and characterized for CD31, CD34, and KDR expression	EPCs healed 13/14 MRONJ lesions, compared to 2/7 with MSCs and 2/6 with culture medium. EPCs increased serum and tissue VEGF levels, reduced necrotic bone area, and improved epithelial and fibroblast function. Minimal EPC engraftment suggested a paracrine healing mechanism	EPCs effectively healed MRONJ lesions by enhancing vascularization and soft tissue function, primarily through paracrine mechanisms. This study supports EPCs as a novel treatment for MRONJ

(continued)

Table 4. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Alonso-Rodriguez et al. (2019)[118]	Analyze effects of ADSCs in a BRONJ-like murine model	38 female Wistar rats (8 wk old)	Rats treated injection IP with ZOL (0.1 mg/kg) 3 times per week for 9 wk, molar extraction followed by ADSC application, divided into groups: CG and ADSC	Local application of ADSCs (1×10^6 cells) into extraction sockets	Greater new bone formation in ADSCs-treated group. No difference in osteonecrosis incidence between groups	ADSCs enhance bone formation in MRONJ-like conditions, suggesting potential for prevention/treatment
Toro et al. (2019)[157]	Evaluate autologous PRP for preventing MRONJ post-tooth extraction	28 Senile Wistar *Rattus norvegicus* rats (20 mo)	The drug treatment was initiated 1 d after ligature installation and lasted 7 wk with ZOL (100 μg/kg), divided into groups: CG, CG-PRP, ZOL, and ZOL-PRP post-extraction	PRP (125 μL) applied to extraction sites	PRP restored bone formation and reduced necrosis. Lower inflammation and higher VEGF/BMP2/4 expression in PRP groups	PRP is a safe and effective preventive therapy for MRONJ, restoring tissue repair capacity compromised by ZOL
Brierly et al. (2019)[76]	Assess the efficacy of star PEG-RGD-heparin hydrogel with BMP-2 to prevent MRONJ after tooth extraction in ZOL-treated rats	24 Sprague-Dawley rats (aged between 63–67 d)	Two doses of ZOL (0.1 mg/kg, IV), tooth extraction, hydrogel ± BMP-2 implantation, divided into groups: group (1) Defects were then left empty, group (2) implanted with hydrogels without rhBMP, or group 3. implanted with hydrogels with BMP-2	Hydrogel with BMP-2 (5 μg) placed in extraction sockets	Increased bone formation and osteocyte density with BMP-2 hydrogel. Reduced osteonecrosis features compared to empty sockets	BMP-2 hydrogel promotes bone regeneration and may prevent MRONJ
Imada et al. (2019)[105]	Prevent BRONJ post-tooth extraction using bFGF-loaded gelatin hydrogel	43 female Sprague-Dawley rats (10 wk old)	All rats received 2 IV injections of ZOL (60 μg/kg) once per week for a period of 2 wk. Rats randomized into groups: CG, CG (hydrogel alone), and bFGF. Evaluated at 3 and 8 wk	bFGF-containing gelatin hydrogel applied to extraction sockets	0% osteonecrosis in bFGF group vs 85.7%-100% in controls. Enhanced mucosal healing and bone formation	bFGF hydrogel prevents BRONJ by promoting wound healing and bone regeneration
Cardoso et al. (2019)[158]	Investigate the use of PRP on tooth extraction sites in rats treated with ZOL	30 male Albinus Wistar rats	Rats received IV injections of ZOL (0.035 mg/kg) for 8 wk, followed by tooth extraction. Divided into 2 groups: G1 (PRP after resection) and G2 (resection only). Evaluated on 14, 28, and 42 d	PRP application post-resection vs resection alone	G1 showed greater bone formation, vascularization, and VEGF expression at 28 and 42 d. No significant difference in microCT	PRP improves bone repair and vascularization in MRONJ
Ogata et al. (2018)[110]	Assess cytokine mixtures mimicking MSC secretomes for MRONJ treatment	Wistar/ST male rats (5 wk old)	Rats received by ZOL (35 μg/kg) and DEX (1 mg/kg), divided into groups: CG (non-treatment), DMEM, MSC-CM, cytokine mix (MIV), MSC-CM-depleted MIV	Intravenous injection of MSC-CM or MIV (MCP-1, IGF-1, VEGF)	MIV improved bone healing, osteoclast function, and soft tissue coverage (66%-67% healing vs controls)	Cytokine mixtures offer a standardized, cell-free alternative for MRONJ treatment
Oh and Kim (2017)[159]	Evaluate collagen sponge and BMP-2 for preventing MRONJ in rats	20 female Sprague-Dawley rats (10 wk old)	Rats received IP injections by ZOL (0,1 mg/kg) for 8 wk, followed by tooth extraction, divided into groups: CG (no treatment) and experimental (collagen sponge ± BMP-2) Evaluated for 8 wk	Collagen sponge ± BMP-2 applied to extraction sockets	Reduced MRONJ incidence (30% with collagen, 20% with collagen + BMP vs 80%-90% in controls). Improved bone density and healing	Collagen sponge ± BMP may reduce MRONJ incidence
Kaibuchi et al. (2016)[73]	To evaluate the therapeutic potential of MSC sheets in treating MRONJ in a rat model	39 female Sprague-Dawley rats (4 wk old)	Treated with ZOL (66 μg/kg) and DEX (5 mg/kg) 3x/wk for 4 wk, followed by tooth extraction, divided into groups: CG (untreated) and BP-treated: MSC sheet transplant, MSC IV injection, and no-transplant control. Outcome measures: wound healing, bone exposure, micro-CT, histology, immunohistochemistry	MSC sheet group: 1 MSC sheet (1.5×10^6 cells) transplanted into extraction socket. MSC IV group: 1.5×10^6 MSCs injected via tail vein. Control group: No cell transplant	MSC sheet group: 12.5% bone exposure (vs 80% control, 100% IV); enhanced angiogenesis (106 ± 9.6 vessels/mm^2 vs 40 ± 5.3 control); reduced empty osteocyte lacunae (31% vs 84% control); increased osteoclast activity (25.7 ± 3.4 cells/mm^2 vs 6.3 ± 4.5 control)	MSC sheet transplantation significantly improved wound healing and angiogenesis in BRONJ rats, outperforming IV injection. Local MSC delivery is a promising alternative for BRONJ treatment

(continued)

Table 4. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Matsuura et al. (2016)[160]	Investigate the therapeutic MSC in treating MRONJ-like lesions in mice, focusing on interactions between diseased and control MSC	49 male C57BL/6 N mice (6 wk old)	Treated IV with ZOL (125 μg/kg) and DEX (10 mg/kg) twice a week via the tail vein, divided into groups: CG, ZOL, and ZOL + MSC groups. Diseased MSCs (d-MSCs) and control MSCs (c-MSCs) were compared. Coculture experiments to study mitochondrial exchange	Systemic administration of MSCs. Coculture of d-MSCs and c-MSCs to study mitochondrial transfer	d-MSCs showed impaired differentiation and proliferation. c-MSCs restored wound healing and reduced inflammation. Mitochondrial exchange between c-MSCs and d-MSCs was observed, suggesting a therapeutic mechanism	MSC therapy for MRONJ involves mitochondrial exchange between transplanted and host MSC, restoring cellular function
Barba-Recreo et al. (2015)[82]	To compare the effectiveness of various potential preventive treatments for MRONJ after dental extractions in ZOL treated rats, focusing on the local application of ADSCs, with or without stimulation by BMP-2 and PRP	56 male Wistar rats *R norvegicus* (8 wk old)	Intervention: 9 wk of ZOL (0.1 mg/kg IP 3×/wk) + molar extractions in wk 8, divided into groups (n = 13-15/group): group 1 (Flap): mucoperiosteal flap coverage post-extraction, group 2 (PRP): PRP clot + flap, group 3 (ADSCs + PRP): allogeneic ADSCs (1×10^6 cells) in PRP clot + flap and group 4 (ADSCs + BMP-2 + PRP): ADSCs pre-cultured with BMP-2 + PRP + flap. Endpoint: histologic/radiographic analysis at 7 d post-extraction	ADSCsD Mechanism: immunomodulation, osteogenic/angiogenic cytokine secretion (eg, VEGF, HGF). PRP mechanism: growth factor release (PDGF, TGF-β) to enhance wound healing BMP-2 role: osteogenic differentiation of ADSC Key variables: osteonecrosis incidence, osteoclast density, bone remodeling, vascularity	Osteonecrosis incidence: - Group 1 (Flap): 46%. - Group 2 (PRP): 54%. - Group 3 (ADSCs + PRP): 20% (p = .007 vs non-ASC groups). - Group 4 (ADSCs + BMP-2 + PRP): 8%. Osteoclast density: higher in ADSCs groups (9.0 ± 3.3 vs 7.3 ± 3.2 osteoclasts/field; p = .045). Bone remodeling: enhanced in ADSCs groups (score 2.9 ± 0.8 vs 2.3 ± 0.9; p = .024). Vascularity: no significant intergroup differences (p > .05)	ADSCs efficacy: ADSC-based therapies reduced MRONJ incidence by 72% and enhanced bone turnover, likely via immunomodulation and osteoclast activation. Synergistic effects: PRP improved ADSCs retention, while BMP-2 further optimized osteogenesis (8% MRONJ incidence in Group 4) Clinical implication: local ADSCs /PRP/ BMP-2combinations may prevent MRONJ in high-risk patients, warranting clinical trials
Ogata et al. (2015)[109]	Evaluate the therapeutic effects of conditioned media from MSCs (MSC-CM) in a rat MRONJ-like model	Male Wistar/ST rats (7 wk old)	Treated with ZOL (35 μg/kg/wk) and DEX (1 mg/kg/d) for 2 wk, maxillary molars extracted; rats divided into: CG (non-treatment), DMEM (−), and MSC-CM groups. Sacrificed at 2 wk post-injection	Intravenous injection of MSC-CM (1 mL) post-MRONJ induction	MSC-CM group showed complete mucosal healing, new bone formation, and increased osteoclast activity. Reduced necrotic bone volume compared to controls	MSC-CM promotes bone regeneration and healing in MRONJ through paracrine effects, offering a potential therapeutic strategy
Sarkarat et al. (2014)[161]	Evaluate PRP effects on ZOL induced MRONJ in rats	7 female rats	Rats received ZOL (0.04 mg/kg) for 5 wk, followed by molar extraction, divided into groups: CG and experimental (PRP injected) into 1 socket per rat	PRP injected post-extraction. Assessed epithelialization, angiogenesis, and bone regeneration	PRP increased vital bone (75.83% vs 48.33% in control) but no significant differences in epithelialization or angiogenesis	PRP may enhance osseous regeneration in MRONJ, but long-term efficacy requires further study

Abbreviations: A-Heal: angiogenesis factor; A-PRF: advanced platelet-rich fibrin; ABMDO: autologous BM-derived osteoblasts; ACS: absorbable collagen sponge; ADSCs: adipose-derived stromal cells; bFGF: basic FGF; BM-MSCs: BM-derived mesenchymal stem cells; BV/TV: bone volume fraction; β-TCP: β-tricalcium phosphate; CG: control group; CGGP: chitosan/gelatin/β-glycerol phosphate; Col I: type collagen I; CY: cyclophosphamide; DPSC-CM: dental pulp stem cell-conditioned medium; DPSC-CM: dental pulp stem cell conditioned media; DEX: dexamethasone; EPCs: endothelial progenitor cells; EVs: extracellular vesicles; GelMA: methacrylated gelatin; HA: hyaluronic acid; HepMA: methacrylated heparin; HPC: hydroxypropyl cellulose; hUC-MSCs: human umbilical cord-derived mesenchymal stem cells; IGF-1: insulin-like growth factor; IL-1RA: IL-1 receptor antagonist; L-PRF: leukocyte- and platelet-rich fibrin; MRONJ: medication-related osteonecrosis of the jaws; MCP: monocyte chemoattractant protein; MSCs: mesenchymal stromal cell; MSC-CM: secretomes in conditioned media from human; OCN: osteocalcin; PBM: photobiomodulation; PBS: phosphate buffer saline; PDGF-BB: platelet-derived growth factor-BB; PRP: platelet-rich plasma; PRF: platelet-rich fibrin; Surg: surgical resection; QQ: quality and quantity; rBM: rat BM; SASP: senescence-associated secretory phenotype; sEV-AT: small extracellular vesicles derived from adipose tissue; TRAP: tartrate-resistant acid phosphatase; ZOL: zoledronate.

Table 5. Characteristics of the included studies using ozone-based therapies to prevent MRONJ.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Delanora et al. (2025)[119]	Evaluate systemic OZ effects on MRONJ healing in senescent rats, focusing on bone and soft tissue repair	28 senescent female Wistar rats (18 mo old)	Rats received ZOL (100 μg/kg) or saline every 3 d for 7 wk, with OZ (0.7 mg/kg) post-extraction, divided into groups: SAL, SAL+OZ, ZOL, and ZOL + OZ	Systemic OZ IP every 2 d for 4 wk post-extraction	ZOL + OZ showed improved bone healing, reduced non-vital bone, and modulated inflammation vs ZOL Increased VEGF and OCN expression in ZOL + OZ Reduced TNF-α and IL-1β levels with ozone	OZ enhances bone and soft tissue healing in MRONJ by promoting angiogenesis and reducing inflammation, suggesting clinical potential
Pereira-Silva et al. (2024)[81]	Compare OZ as prevention/treatment of MRONJ	40 male Wistar rats (3 mo old)	Administering 04 applications of ZOL (0.035 mg/kg), extraction and received an OZ/oxygen mixture at a dose of (0.7 mg/kg) daily, administered by the IP route, divided into groups: SAL, ZOL, POG, TOG, and TPOG	OZ IP every 2 d (pre, post, or both) in the prevention and treatment group TPOG	TOG and POG had better bone repair than TPOG	OZ modulated alveolar bone repair in animals treated with ZOL, mainly after surgery trauma, leading to bone formation as healing tissue
Silva et al. (2024)[120]	To determine the ideal concentration of ozonized sunflower oil (OZ) to prevent and modulate zoledronate-induced mandibular osteonecrosis (MRONJ) in senescent rats	35 female Wistar rats, 18 mo old (senescent model)	Rats were divided into 5 groups: SAL (saline control), ZOL (zoledronate), ZOL + OZ500 (ozonized oil 500 mEq/kg), ZOL + OZ600 (ozonized oil 600 mEq/kg), and ZOL + OZ700 (ozonized oil 700 mEq/kg). Zoledronate (100 μg/kg) was administered i.p. every 3 d for 7 wk. After 3 wk, the lower first molar was extracted, followed by local OZ therapy at baseline, day 2, and day 4 post-extraction	Local application of ozonized sunflower oil at 500, 600, or 700 mEq/kg into the extraction socket in rats treated with zoledronate	The ZOL + OZ600 group showed the highest bone volume (BV) and neoformed bone tissue (NFBT) compared to other groups ($p < .05$). All OZ groups had significantly less non-vital bone tissue (NVBT) than the ZOL group ($p < .05$). No signs of infection or systemic toxicity were observed	Ozonized oil at concentrations of 500, 600, and 700 mEq/kg prevented MRONJ and promoted tissue healing in senescent rats treated with zoledronate. The 600 mEq/kg concentration was the most effective in enhancing bone formation and may be considered the optimal dose for clinical translation
Monteiro et al. (2021)[121]	Evaluate ozonated oil for MRONJ prevention	12 male Wistar rats (2 mo old)	Each rat received an IV of ZOL (0.04 mg/kg) in the caudal vein once a week for 5 wk, extraction + ozonated oil for 10 min/d during 3 d, divided into groups: group 1 - the clotted socket was maintained, group 2 - the socket was treated with ozonated	Ozonated oil in socket	Less necrotic bone in treated group	Suggest that ozonated oil might prevent MRONJ-like lesions at tooth extraction sites in rats submitted to a disease induction protocol
Liu et al. (2019)[122]	Assess if immediate HBO post-extraction ameliorates MRONJ in rats	40 female Sprague Dawley rats (5 wk ages)	Both groups received the 4 injections ZOL (7.5 μg/kg) and DEX (1 mg/kg) SC daily, divided into 4 groups: 0, 2, 4, or 7 injections SC of ZOL + DEX. Second experiment, the HBO (2.5 ATA, 100% O_2 for 90 min/d for 5 d) applied post-extraction	HBO immediately after extraction	HBO reduced lesion size and number in 4-injection group. Histology showed reduced inflammation and epithelial coverage	Immediate HBO effectively decreases MRONJ development
Silva et al (2017)[162]	To investigate the effect of hyperbaric oxygen (HBO) therapy on tooth extraction sites in bisphosphonate-treated rats	35 female Wistar rats (*Rattus norvegicus*), 140 d old	The rats were treated with ZA, subjected to tooth extractions, and allocated to groups: 7 d of HBO, 14 d of HBO, 7 d of control, and 14 d of control. The tooth extraction sites were analyzed by histomorphometry and immunohistochemistry. The 7-d HBO group was euthanized after 7 d of treatment, and the 14-d HBO group after 14 d of HBO. The control groups, which received ZA without HBO, were euthanized simultaneously with the respective HBO groups, resulting in the 7- and 14-d control groups	ZA was administered i.p. at a dose of 0.6 mg/kg weekly, for a total of 5 applications. After 45 d, the 3 upper right molars were extracted under i.p. anesthesia. Forty-five days after the extractions, a clinical evaluation was performed and HBO therapy was initiated. Test group 1 (HBO, 7 d) received daily sessions for 7 d, and test group 2 (HBO, 14 d) received daily sessions for 14 d	HBO had no significant impact on exposed bone volume at 7 or 14 d. In H&E analysis, the 14-d HBO group had lower nonvital bone compared to controls and the 7-d HBO group. At 7 d, HBO significantly reduced the expression of VEGF, RANKL, BMP-2, and OPG compared to the control group, while at 14 d, no significant differences were observed in these variables	HBT may reduce the presence of non-vital bone microscopically observed in tooth extraction sites of rats treated with bisphosphonates, possibly demonstrating a dose-dependent effect

Abbreviations: ATA: atmospheres absolute; DEX: dexamethasone; HBO: hyperbaric oxygen; H&E: hematoxylin and eosin; IV: i.v. injection; MRONJ: medication-related osteonecrosis of the jaws; O_2: oxygen; OCN: osteocalcin; OPG: osteoprotegerin; OZ: ozone therapy; POG: prevention; SAL: negative control; TPOG: prevention and treatment; TOG: after extraction; ZA: zoledronic acid; ZOL: zoledronate.

Table 6. Characteristics of the included studies using other-based therapies to prevent MRONJ.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Jin et al. (2025)[129]	Explore betaine's role in rescuing BP-impaired BMSCs function and alleviating MRONJ via m6A-METTL3-dependent mechanisms	36 male Sprague Dawley rats	Rats treated injection IP by ZOL (0.1 mg/kg) for 6 wk, divided into groups: CG (saline), ZOL, and ZOL + betaine. In vitro: BP-treated BMSCs ± betaine. In vivo: MRONJ rats ± betaine supplementation. m6A methylation, SAM levels, and osteogenic markers assessed	Betaine (2% w/v in drinking water) for BRONJ rats; 10 mM betaine for BMSCs	Betaine restored m6A methylation, SAM levels, and osteogenic differentiation in BP-treated BMSCs. In vivo, betaine reduced bone necrosis and improved healing	Betaine rescues BP-impaired BMSCs via m6A-METTL3, offering a potential therapeutic strategy for MRONJ
Topan et al. (2025)[123]	Evaluate royal jelly (RJ) efficacy in managing MRONJ in rats	60 female Wistar rats (8 wk old)	Rats treated injection IP by ZOl (0.1 mg/kg) every 3 d for 8 wk, divided into 5 groups: CG, BP (ZOL), RJ, treatment (RJ post-surgery), preventive (RJ pre-surgery). Tooth extraction + alveolar defect	Oral RJ (100 mg/kg/d) pre- or post-surgery. BP administered i.p.	RJ groups showed improved bone healing (micro-CT), reduced IL-1β/TNF-α levels, and enhanced soft/hard tissue healing	RJ may be effective as a therapeutic or preventive agent for MRONJ
de Almeida et al. (2025)[124]	Evaluate the ability of omega-3 to modulate tissue response in MRONJ, focusing on histopathological and immunohistochemical parameters	44 female *Rattus norvegicus*, albinus Wistar rats (4 mo old)	Bilateral ovariectomy, ZOL (100 μg/kg) or VEH (saline) treatment, experimental periodontitis, tooth extraction, omega-3 supplementation, divided into groups: CG, ZOL, CG + omega-3, and ZOL + omega-3	Daily dietary supplementation with omega-3 (40 mg/kg; salmon-derived, 60% EPA, 40% DHA) via gastric gavage	Omega-3 reduced non-vital bone tissue (NVBT) and inflammation in ZOL-treated rats. Improved epithelial and connective tissue structure. No significant change in osteoclast/osteoblast activity	Omega-3 supplementation attenuates MRONJ severity by reducing inflammation and NVBT
Hadad et al. (2025)[70]	Test 10% DBG on MRONJ prevention	72 male *R norvegicus* albinus Wistar rats (3 mo old)	Rats treated with ZOL (35 μg/kg) were administered i.v., divided into groups: CG (saline), ZOL, and DOXI gel post-extraction	Local 10% DBG	Higher vital bone %, ↑ bone markers in DOXI group	Local DOXI gel improved bone healing and prevented MRONJ
Du et al. (2025)[130]	To explore the preventive effects of PRO on MRONJ) by promoting osteogenesis in vitro and in vivo	40 male C57BL/6 mice (8 wk old)	Rats treated were administered IP with ZOL (μg/kg) twice a week, before tooth extraction, divided into 4 groups: control, ZOL, PRO, and ZOL-PRO. In vitro: BMSCs treated with ZOL and PRO to assess proliferation and osteogenic differentiation	PRO (20 mg/kg, IP) was administered before and after tooth extraction in ZOL-treated mice. Osteogenic markers (ALP, BMP2, RUNX2) and apoptosis (TUNEL) were analyzed	PRO enhanced BMSCs proliferation and osteogenic differentiation. PRO reduced osteonecrosis and improved bone formation in ZOL-treated mice. Increased BMP2+, RUNX2+, and ALP+ cells in PRO groups. Reduced TUNEL+ apoptosis in ZOL-PRO group	PRO prevents BRONJ by enhancing osteogenesis and reducing apoptosis, offering a potential therapeutic strategy via β-adrenergic signaling modulation
Soundia et al. (2024)[49]	Characterize macrophage polarization during early MRONJ development and explore the role of rosiglitazone in reducing MRONJ burden	66 male C57BL/6 J mice (6 wk old)	Mice received ZOL (200 μg/kg) or saline, with ligature-induced periodontal disease. Rosiglitazone was administered to some groups, divided into groups: CG, CG + Rosiglitazone ZOL, ZOL+ Rosiglitazone. Analyzed at 1, 2, 4, and 5 wk post-ligature	Rosiglitazone (PPAR-g activator) to shift macrophage polarization from M1 to M2	M1 macrophage polarization was dominant in zoledronate-treated mice. Rosiglitazone reversed M1/M2 ratio, reduced osteonecrosis, and decreased bone exposure	M1 macrophages contribute to early MRONJ development. Rosiglitazone may mitigate MRONJ by promoting M2 polarization and reducing inflammation

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Table 6. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Costa de Sousa et al. (2024)[141]	Investigate the effect of PAb gel on bone necrosis in a MRONJ rat model	54 female Wistar rats (12 wk old)	Rats received ZOL (0.1 mg/kg) IP 3 wk for 9 wk, followed by molar extraction, divided into groups: CG (saline + placebo gel), ZOL (ZOL + placebo gel), and PAb (ZOL + 1% PAb gel)	PAb gel applied to dental alveolus post-extraction. Evaluated mucosal healing, osteocyte viability, bone sequestration, and Wnt signaling	PAb gel improved mucosal healing, increased viable osteocytes, reduced empty lacunae, and enhanced bone remodeling via Wnt signaling. Improved bone quality (collagen, mineralization)	PAb gel mitigates MRONJ by stimulating bone remodeling and improving bone quality, showing promise as a therapeutic tool
Gürses et al. (2024)[163]	Evaluate the efficacy of ME in preventing MRONJ in rats	36 male Wistar rats (6 mo old)	Rats treated with ZOL (0.1 mg/kg) 3 times a week. Tooth extraction performed after 6 wk of ZA administration, divided into 3 groups: CG, ZOL, ZOLA + ME	ME (100 mg/kg) administered 1 wk pre- and 4 wk post-extraction	ME reduced bone exposure, improved epithelialization, and decreased osteoclast detachment	ME shows potential for preventing MRONJ but is not a complete solution
Lemos et al. (2024)[131]	To evaluate the efficacy of digoxin (an RORγt inhibitor) in attenuating MRONJ in a rat model induced by ZOL	40 male Wistar rats (8-12 wk old)	Rats treated with ZOL (0.20 mg/kg, IV) and subjected to tooth extraction, divided into groups: CG (saline), positive control (ZOL only), and 3 test groups (ZOL + digoxin at 1, 2, or 4 mg/kg). Tooth extraction: day 42; euthanasia on day 70. Outcome measures: radiographic analysis, histomorphometry, immunohistochemistry (IL-17, TNF-α, etc.), western blot (RORγt), and femur mechanical testing	Digoxin groups: oral gavage at 1, 2, or 4 mg/kg, 3x/wk. ZOL administration: IV on days 0, 7, 14, and 49	Digoxin (2-4 mg/kg): reduced radiolucency, inflammatory cells, empty osteocyte lacunae, and apoptotic osteoclasts; downregulated IL-17, TNF-α, IL-6, RANKL, and NFκB; reversed RORγt expression; improved femur mechanical properties but increased renal/cardiac toxicity at higher doses	Digoxin attenuated MRONJ by inhibiting the Th17/IL-17 pathway via RORγt blockade, suggesting IL-17 as a therapeutic target. Higher doses showed efficacy but posed systemic toxicity risks
Cantorán-Castillo et al. (2024)[142]	To establish a novel rat model of MRONJ by combining bisphosphonate treatment, oral surgery, and bacterial inoculation, and to evaluate the potential preventive effects of GuaDex or antibiotics	24 male Wistar rats (8 wk old)	Rats divided into 4 groups: groups 1-3 received weekly IV ZOL (1 mg/kg) for 4 wk before and 2 wk after osteotomy. Osteotomy + bacterial inoculation (*S. gordonii*). Treatments administered on day 8	Group 1: GuaDex injection into osteotomy socket. Group 2: IM clindamycin. Group 3: IM saline (CG positive control). Group 4: IM saline (CG negative control, no ZOL/bacteria)	GuaDex group: 0% MRONJ incidence (vs 83% in positive controls); active bone regeneration: osteoblast proliferation, vascularization, and absence of bacterial colonization; elevated serum calcium (+46% vs controls), and reduced ALP (110.52 IU/L vs 126.20 IU/L in positive controls). Clindamycin group: 80% early MRONJ, avascular necrosis, and bacterial persistence. Positive control: MRONJ lesions, inflammatory infiltrates, and defective healing	GuaDex demonstrated dual efficacy in: (1) Preventing MRONJ via antimicrobial action against *S. gordonii*. Stimulating osteogenesis through enhanced osteoblast activity and vascularization. Clinical implication: local polyguanidine therapy may offer a superior alternative to systemic antibiotics for MRONJ prophylaxis
Isleyen et al. (2024)[32]	To evaluate the effect of SEL administration on the prevention of MRONJ in an animal model	48 male Wistar rats (12 wk old)	Rats treated with ZOL (0.06 mg/kg) for 5 wk, except saline group. All rats underwent extraction of left mandibular molars at wk 5, randomly assigned into 4 groups: CG (saline, negative control; ZOL (positive control), SEL preop + ZOL (selenium before extraction), and ZOL + SEL postop (selenium after extraction). Euthanasia at wk 9	SEL (0.3 mg/kg) was administered daily for 15 d either before or after tooth extraction	Postoperative SEL significantly improved new bone formation, increased OCN and osteoblast count, and reduced necrotic bone area. Preoperative SEL improved angiogenesis and connective tissue formation, but was less effective in bone parameters	Selenium administration had preventive effects against MRONJ. Postoperative SEL was more effective in enhancing bone healing; preoperative SEL may benefit soft tissue healing. SEL shows promise as a preventive agent for MRONJ

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Table 6. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Zhu et al. (2023)[134]	To evaluate whether a ZOL drug holiday can help prevent MRONJ following tooth extractions in an osteoporotic animal model	20 female Sprague-Dawley rats (8 mo old)	Rats underwent bilateral ovariectomy. All animals received ZOL (80 g/kg) weekly for 8 wk. Divided into 2 groups: CG: dental extraction immediately after ZOL and DH: 8-wk drug holiday after ZOL, then dental extraction evaluated 8 wk post-extraction	ZOL drug holiday for 8 wk prior to tooth extraction in DH group; control group continued without holiday	Drug holiday restored osteoclastic activity (↑ TRAP+ cells, ↑ CTX-I serum levels); however, it did not reduce incidence of MRONJ-like lesions. No worsening of osteoporotic parameters was observed	An 8-wk drug holiday partially recovered bone turnover but did not prevent MRONJ development. Longer holidays or combined strategies may be required. No adverse effects on systemic bone health were seen
Inoue et al. (2023)[164]	Evaluate the synergistic effect of systemic risedronate and local TERPY (NO donor) on peri-implant bone repair in osteoporotic rats	72 female Wistar rats (3 mo old)	The rats were divided into experimental groups according to the type of systemic disorder, diet, and drug treatment (sham, OVX + HD, and OVX + HD + RIS), and also into subgroups according to the type of implant to be installed (CONV, TERPY 10 μM, and TERPY 100 μM). Biomechanical and molecular analyses post-implantation. ovariectomy + high-fat diet)	Systemic risedronate + TERPY-coated implants (10 μM or 100 μM)	TE10 improved bone repair in OVX + HD; risedronate enhanced OPG expression and reduced RANKL. TERPY at 10 μM promoted osteogenesis and angiogenesis	TERPY at low concentration (10 μM) enhances peri-implant bone repair, especially in osteoporotic conditions, synergizing with risedronate
Mroczek et al. (2023)[138]	Evaluate sildenafil as prophylaxis for MRONJ	30 males Wistar rats (90 d old)	Rats treated IP administered with ZOL (0.1 mg/kg) twice a week + extraction ± sildenafil, divided into groups: CG saline, ZOL, and ZOL sildenafil	Oral sildenafil (dose not specified)	Reduced bone exposure and necrosis	Sildenafil may be protective via angiogenesis and anti-inflammatory pathways
Duygu et al. (2023)[137]	Investigate the prophylactic effect of systemic EPO on MRONJ after tooth extraction in ZOL treated rats	36 female Sprague Dawley rats (12 wk old)	Rats treated IP injections with ZOL (0.1 mg/kg) was conducted 3 times a week for 8 wk, divided into 6 groups: group 1: CG and group EPO received IP of saline pre- and/or post-extraction. Rats in groups III and VI of ZOL	EPO administered i.p. Sacrifice at 16 wk for histological and immunohistochemical analysis	EPO pre- and post-extraction increased VEGF expression and bone formation, reducing necrosis	Systemic EPO, especially when administered pre- and post-extraction, may prevent MRONJ by enhancing angiogenesis and bone healing
Pan et al. (2023)[165]	Evaluate dietary nitrate's effects on MRONJ-like lesions by reducing monocyte necrosis and inflammation in mice	Female C57BL/6 J mice (8 wk old)	Mice received ZOL (600 μg/kg, IV) and tooth extraction. Dietary nitrate (4 mM sodium nitrate) was administered pre- and post-extraction, divided into groups: CG (no ZOL), ZA-only, and ZOL + nitrate. Evaluated at 1 and 5 wk post-extraction	Dietary nitrate supplementation in drinking water	Nitrate increased plasma NO levels, reduced monocyte necroptosis, and improved bone healing. Decreased pro-inflammatory cytokines, (TNF-α, IL-6) enhanced osteoclast activity, and bone remodeling	Dietary nitrate mitigates MRONJ by reducing monocyte necrosis and inflammation, offering a preventive/therapeutic option

(continued)

Table 6. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Yalcin-Ülker et al. (2023)[136]	Investigate the prophylactic effect of DFO on MRONJ by assessing bone healing and HIF-1α levels	36 female Sprague Dawley rats (12 wk old)	Rats received zoledronic acid (ZA) for 8 wk to induce MRONJ. DFO was applied locally into extraction sockets with GS carriers. Groups: control, GS, GS/DFO, ZOL, ZOL-GS, ZOL-GS/DFO	Local application of DFO (5.2 μg/7.8 μL) with GS into extraction sockets	New bone formation rates were higher in ZOL-GS and ZOL-GS/DFO groups but not significantly. HIF-1α levels were significantly higher in DFO-treated groups. Necrosis was absent in DFO-treated ZOL groups	DFO may prophylactically improve bone healing in MRONJ by elevating HIF-1α, but further studies are needed to confirm its efficacy
Vitale et al. (2023)[125]	Assess resveratrol in MRONJ prevention	50 adults female Wistar rats	Rats underwent OVX bilateral. RES (10 mg/kg) and placebo ZOL (0.1 mg/kg) was prepared using PBS and was administered IP twice weekly, divided into groups: non OVX surgery (placebo), surgery OVX (placebo), OVX + RS, OVX + ZOL (placebo), and OVX + RES + ZOL	Oral RES (10 mg/kg/d) were administrated daily by gavage for 140 d	RES improved bone architecture and healing	RES shows promise but not fully protective
de Sousa et al. (2022)[69]	Evaluate atorvastatin's effect on ZOL induced osteonecrosis of the jaw (MRONJ) in rats	Female Wistar rats (12 wk old)	Rats treated with ZOL (0.1 mg/kg) 3 d a week for 9 wk + tooth extraction, divided into 4 groups: CG (saline), ZOL, Atorvastatin pre- or post-extraction. Evaluated at day 77	Atorvastatin (27 mg/kg) administered before or after tooth extraction	Atorvastatin improved mucosal healing, reduced osteocyte death, and bone sequestration. Modulated inflammation ($\downarrow$TNF-α, IL-1β). Activated Wnt pathway	Atorvastatin prevents and treats ZOL-induced MRONJ via anti-inflammatory and bone anabolic effects
Gkouveris et al. (2022)[72]	Investigate HMGB1/RAGE signaling in osteocyte death during MRONJ pathogenesis	C57BL6J male mice (4 wk old)	Rats treated with ZOL (200 μg/kg) 2 times weekly + ligature-induced periodontitis + HMGB1/RAGE inhibitors administered, divided into groups: CG, CG-Inhibitors, ZOL, and ZOL-Inhibitors	Tanshinone IIA (10 mg/kg) and RAGE antagonist peptide (3 mg/kg) i.p.	HMGB1/RAGE inhibition reduced osteonecrosis and bone exposure. Cytoplasmic HMGB1 increased in osteocytes	HMGB1-RAGE pathway is a therapeutic target for MRONJ prevention
Soma et al. (2022)[166]	Investigate prevention of MRONJ induced by tooth extraction in zoledronate-treated mice using active vitamin D analogs, anti-inflammatory agents, or antibiotics	Female C57BL/6 mice (8 wk old)	Mice received zoledronate for 2 wk before tooth extraction, followed by 6 wk of continued treatment. Co-administered active vitamin D analogs, anti-inflammatory drugs, or antibiotics	$1,25(OH)_2D_3$ or ED71 (active vitamin D analogs), low-profen (anti-inflammatory), meloxicam (anti-inflammatory), or amoxicillin (antibiotic)	Active vitamin D analogs, anti-inflammatory agents, and antibiotics significantly reduced MRONJ incidence, osteocyte apoptosis, and inflammatory cytokine levels	MRONJ prevention is possible without discontinuing zoledronate by targeting inflammation or infection with active vitamin D, anti-inflammatory agents, or antibiotics
Delfrate et al. (2022)[167]	To evaluate the effectiveness of pentoxifylline and α-tocopherol in the prevention or treatment of MRONJ	60 adult male Wistar rats	Rats treated IP administration of ZOL (0.1 mg/kg) twice a week for 12 wk, divided into groups: 6 groups ($n = 10$/group): prevention: CG (saline), BP-prev (ZOL), BP/PT-prev (ZOL + pentoxifylline + α-tocopherol); treatment: CG (saline), BP-treat (ZOL), BP/PT-treat (ZOL + pentoxifylline + α-tocopherol). All animals had molar extraction at wk 6	Pentoxifylline (50 mg/kg/d) + α-tocopherol (80 mg/kg/d) either: prophylactically (wk 5-12) or as treatment (wk 12-16, after ZOL discontinuation)	Treatment group (BP/PT-treat) showed 50% reduction in osteonecrosis incidence, improved bone vascularization, reduced necrotic bone area, and increased osteocyte number and alveolar bone repair. Prevention group (BP/PT-prev) showed only a slight reduction in necrotic area, with no significant protective effect	Pentoxifylline + α-tocopherol was not effective as a preventive measure when administered with ZA. However, it showed therapeutic benefits when applied after bisphosphonate discontinuation, likely by enhancing angiogenesis and osteogenesis

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Table 6. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Sanda et al. (2022)[140]	Evaluate FS on MRONJ healing	18 female Wistar rats (4 wk old)	Rats treated with ZOL (66 μg/kg) and DEX (5 mg/kg) s.c. 3 times a week. Single FS injection (1 or 10 mg/kg) at MRONJ site 2 wk post-extraction, divided into experiment 1 groups: ZOL + DEX and CG or experiment 2 groups: CG (saline), FS a low concentration, and FS a high concentration Evaluated for 4 wk	Local FS injection (1 or 10 mg/kg) post-MRONJ onset	FS reduced necrotic bone area, improved epithelial closure, and increased new bone formation. Higher dose (10 mg/kg) was more effective	Topical FS promotes MRONJ healing by reducing necrosis and enhancing bone formation
Matsunaka et al. (2022)[168]	Investigate BD in MRONJ-like lesions	21 female Wistar rats (4 wk old)	The rats in all groups were injected with ZOL (66 μg/kg) and DEX (5 mg/kg) s.c. 3 times a week, extraction, then BD injection, divided into groups: MRONJ, BD concentrations, a low dose (0.13 mg/kg) and BD a high dose (1.3 mg/kg)	Local BD injection (low/high dose)	BD enhanced wound closure and reduced necrosis	BD may suppress inflammation and promote healing
Castillo et al. (2021)[146]	Investigate if controlling/preventing periodontitis reduces MRONJ occurrence in rice rats treated with ZOL	75 male rice rats (4 wk old)	Rats treated with ZOL (80 μg/kg), divided into 5 groups: STD diet ± ZOL ± PC, SF diet ± ZOL	STD diet ± ZOL ± bi-weekly PC. SF diet (high soluble fiber) ± ZOL	PCs reduced MRONJ prevalence from 50% to 7% in ZOL-treated rats. SF diet prevented MRONJ and periodontitis	Periodontal maintenance and dietary soluble fiber reduce MRONJ risk by mitigating periodontitis
Soundia et al. (2021)[71]	Determine if local RANKL delivery improves extraction socket healing in bisphosphonate-treated rats	30 Wistar-Han rats (7 wk old)	Rats treated injected IP with ZOL (66 μg/kg) once a week, with extraction sockets treated with RANKL or water, divided into groups: receiving saline CG and CG-RANKL or ZOL and ZOL-RANKL or water	Local RANKL application via collagen tapes in extraction sockets Continued ZOL administration	RANKL improved socket healing and reduced osteonecrosis in ZOL-treated rats Increased osteoclast numbers and attachment	Local RANKL enhances osteoclast activity and socket healing without discontinuing bisphosphonates
Hadaya et al. (2021)[135]	Investigate the effect of antiresorptive discontinuation (ZOL and OPG-Fc) on MRONJ development and resolution in 2 settings: pre-tooth extraction and post-MRONJ establishment	Male Wistar Han rats (2 mo old)	Rats treated with ZOL. Two experiments: (1) Discontinuation before tooth extraction; (2) Discontinuation after ONJ establishment. μCT, histologic, and clinical assessments	ZOL or OPG-Fc discontinuation ("drug holiday") prior to extraction or after MRONJ induction	OPG-Fc discontinuation before extraction reduced MRONJ burden; ZOL discontinuation had no effect. Neither drug improved MRONJ resolution post-establishment	Antiresorptive discontinuation efficacy depends on drug type and timing. OPG-Fc discontinuation before extraction may reduce MRONJ risk, but discontinuation post-MRONJ does not aid healing
Nakagawa et al. (2021)[169]	Investigate metformin's effect on preventing MRONJ-like lesions in ZOL/DEX-treated rats	Male Wistar rats (4 wk old)	Rats treated s.c. with ZOL (0.1 mg/kg) + DEX (1 mg/kg) twice a week, tooth extraction, divided into 4 groups: CG, ZD (ZOL + DEX), Ins + ZD (ZOL + DEX + insulin), Met + ZD (ZOL + DEX + metformin's. Evaluated at 4 wk post-extraction	Metformin (250 mg/kg) or insulin (4-6 IU) co-administered with ZOL/DEX	Metformin improved socket healing and reduced osteonecrosis. No change in GluOC levels. Increased osteoclasts in ZD group	Metformin may protect against MRONJ-like lesions by improving glucose metabolism and bone healing

(continued)

Table 6. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Movahedian Attar et al. (2020)[126]	To evaluate the protective role of RSV against osteonecrosis after tooth extraction in rats treated with bisphosphonates	39 male *R norvegicus* Wistar rats (9-11 wk old)	Groups ($n = 13$/group): (1) ZOL/DEX: ZOL (200 μg/kg/d s.c. injection) + DEX dexamethasone (1 mg/kg/d s.c. injection) for 14 d (2) ZOL/DEX/RSV: ZOL/DEX + resveratrol (10 mg/kg/d s.c. injection) for 14 d (3) CG: no drug treatment Intervention: extraction of maxillary first and second molars Endpoint: histological analysis at 14 d post-extraction for osteonecrosis, inflammation, vascularity, and bone formation	Dose/route: 10 mg/kg/d s.c. (based on prior evidence of pro-angiogenic effects at this dose). Control groups: ZOL/DEX to induce BRONJ-like lesions; untreated controls for baseline healing	Osteonecrosis incidence: ZOL/DEX: 84.6% (11/13 rats; vs ZOL/DEX/RSV) ZOL/DEX/RSV: 15.4% (2/13 rats) Control: 23.1% (3/11 rats vs ZOL/DEX). Histological outcomes: new bone formation: no significant difference between ZOL/DEX (49.2% ± 9.6) and ZOL/DEX/RSV (48.6% ± 6.0) Inflammation/vascularity: no significant intergroup differences, though RSV group showed trends toward reduced inflammation	RSV efficacy: significant reduction in osteonecrosis incidence (69.2% decrease vs ZOL/DEX likely due to antioxidant protection against ZOL-induced soft tissue damage and ROS-mediated DNA injury Clinical implication: RSV may serve as a prophylactic adjunct in high-risk patients undergoing ZOL therapy, but further studies are needed to optimize dosing and evaluate long-term safety
Zhao et al. (2020)[132]	To explore the potential of tFNAs in treating MRONJ by promoting angiogenesis and M2 macrophage polarization	30 Male Wistar rats (8 wk old)	Rats treated IP injected by ZOL (125 μg/kg) and DEX (5 mg/kg) twice a week for 5 wk, divided into groups: CG, ZOL, ZOL + tFNAs. In vivo: rat BRONJ model with tooth extraction. In vitro: ZOL-treated HUVECs and RAW264.7 macrophages	tFNAs injected IP (10 nM, 100 μL) daily for 1 wk after tooth extraction	tFNAs enhanced angiogenesis by upregulating VEGFA, VEGFR2, and MMPs. Promoted M2 macrophage polarization and reduced M1 polarization. Improved wound healing and bone repair in vivo	tFNAs promote BRONJ treatment by enhancing angiogenesis and M2 macrophage polarization, offering a novel therapeutic strategy
Yadegari et al. (2020)[127]	Study melatonin's role in preventing MRONJ	30 male Wistar rats (12 wk old)	Rats treated IP injected by ZOL (0.1 mg/kg) 3 times a week for 4 wk, Tooth extraction after 4 wk, 3 groups: CG (saline), ZOL and ZOL + melatonin	Oral melatonin (5 mg/kg/d) for 3 wk alongside ZOL	Melatonin reduced osteonecrosis (70% vs 90% in ZOL group) but decreased osteoclasts/fibroblasts	Melatonin may mitigate ZOL side effects, but further research is needed
Adachi et al. (2020)[139]	To evaluate the preventive effect of locally injected FS on the development of MRONJ-like lesions in a rat model treated with ZOL and DEX	30 female Wistar rats (4 wk old)	Rats treated with ZOL (66 μg/kg) and DEX (5 mg/kg) were administered 3 times a week, divided into groups: CG (no treatment), MRONJ (ZOL + DEX), and MRONJ treated with FS at low (0.1 mg/kg), medium (1.0 mg/kg), or high (10 mg/kg) doses. Tooth extraction was performed at wk 2, and fluvastatin was injected locally. Healing was assessed for 2 wk post-extraction	Single local injection of FS at the extraction site immediately after tooth extraction. FS was dissolved in saline and administered at 3 concentrations	FS (medium and high doses) significantly reduced necrotic bone exposure and improved epithelial continuity. High-dose FS reduced necrotic bone area and ratio, and increased bone volume fraction. FS promoted angiogenesis and bone formation	Local injection of fluvastatin at the time of tooth extraction can prevent MRONJ-like lesions by promoting bone and soft tissue healing, reducing necrosis, and enhancing angiogenesis
Tamaki et al. (2020)[133]	Investigate the effects of anti-RANKL Ab cessation on MRONJ-like lesions and macrophage polarization in mice	94 female C57BL/6 J mice (8 wk old)	Mice received chemotherapy CY (150 mg/kg) and anti-RANKL mAb with tooth extraction. mAb was discontinued after 3 wk to assess healing. Groups: CY/mAb continuation (CY/mAb-C) vs discontinuation (CY/mAb-D). Evaluated at 2 and 4 wk post-extraction	Discontinuation of anti-RANKL mAb after inducing MRONJ-like lesions	mAb cessation improved soft tissue healing and increased M2 macrophages. No change in angiogenesis/lymphangiogenesis. Dynamic M1-to-M2 macrophage shift promoted healing	Anti-RANKL Ab cessation promotes MRONJ healing via macrophage polarization shift, suggesting a potential therapeutic strategy

(continued)

Table 6. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Hidaka et al. (2019)[145]	To develop a rat model of MRONJ by combining tooth extraction in alendronate-treated, OVX rats with localized *P. gingivalis* administration to mimic periodontitis	35 aged OVX female Wistar rats	5 groups ($n = 7$/group): (1) CG (2) Pg (*P. gingivalis* infection only) (3) ALN (alendronate (35 mg/k, only) (4) ALN + Pg (5) ALN + Pg + LIPUS All rats had right maxillary first molar surgically removed at 12 wk post-OVX	Daily application of LIPUS to tooth sockets for 20 min/d, 5 d/wk for 4 wk (ALN + Pg + LIPUS group)	ALN + Pg rats had delayed healing, alveolar bone loss, and reduced BMD. LIPUS prevented these outcomes, restored mRNA levels of regenerative markers (eg, RANKL, VEGF, IL-6), and improved blood flow and epithelial closure	LIPUS prevented MRONJ-like symptoms in rats pretreated with alendronate and exposed to periodontitis. It exerted both local and systemic regenerative effects. LIPUS shows promise as a non-invasive preventive therapy for MRONJ
Hokugo et al. (2019)[144]	To evaluate the efficacy of a "rescue" BP in displacing pre-adsorbed ZOL to prevent osteonecrosis and improve extraction socket healing in mice	Female C57BL/6 J mice (7-10 wk old)	Mice received systemic ZOL, followed by local or systemic administration of low-potency BPs (AF647-ZOL, MHDP, ETI). Extraction socket healing was evaluated via micro-CT, histology (H&E, TRAP staining), and fluorescence imaging	Local intra-oral injection of low-potency BPs (AF647-ZOL, MHDP, ETI) prior to tooth extraction. Systemic IV injection of MHDP was also tested. BP displacement was quantified via fluorescence imaging	Local lpBP (MHDP, ETI) reduced osteonecrosis by 80% and improved socket healing. Systemic lpBP (MHDP) showed partial efficacy (50% reduction). BP displacement was confirmed in vivo via fluorescence imaging. lpBP normalized gingival inflammation and epithelial hyperplasia	Local application of lpBP displaces legacy ZOL in jawbone, preventing osteonecrosis and improving extraction socket healing. This approach may benefit patients requiring continued BP therapy for primary diseases
Elsayed et al. (2018)[143]	Investigate the role of matrix-bound bisphosphonates in MRONJ and test EDTA chelation as a preventive strategy	20 female Sprague-Dawley rats (10-12 mo old)	Rats treated with IV ZOL (80 ug/kg) for 13 wk, followed by bilateral molar extraction. Unilateral EDTA treatment post-extraction, divided into groups: CG (EDTA), CG (saline), ZOL (EDTA), and ZOL (saline)	Topical 17% EDTA applied to extraction sites for 10 min	EDTA chelation improved mucosal healing, reduced osteonecrosis, and rescued osteoclast function	Matrix-bound bisphosphonates contribute to MRONJ; EDTA chelation prevents osteonecrosis by restoring osteoclast activity
Liu et al. (2018)[128]	Investigate the effects of icariin on wound healing and MRONJ prevention in rats treated with ZOL and DEX	30 female Sprague Dawley strain rats (8 wk old)	Rats treated IP injected with ZOL (0.2 mg/kg) and DEX (2 mg/kg) were injected once a week for 8 wk, divided into 5 groups: CG (saline), ZD, ZD + LICA, ZD + MICA, and ZD + HICA. Tooth extraction was performed after OVX and drug administration	Icariin administered intragastrically post-extraction	Icariin improved wound healing and VEGF expression but did not reduce MRONJ incidence. Osteoclast activity was modulated	Icariin promotes healing but does not prevent MRONJ. Effects are dose dependent
Koneski et al. (2018)[170]	To evaluate the in vivo effects of GGOH on the development of BRONJ	30 male Wistar rats	Rats were divided into 3 groups: EG1, EG2, and a CG. On the third week all animals underwent extraction of the lower right first molars	Rats from EG1 and EG2 were treated with 0,06 mg/kg ZA i.p. weekly in a duration of 5 wk, while CG received saline ip. The rats from EG2 received a local solution of GGOH in concentration of 5 mM in the socket every day after the tooth extraction	EG2 showed significantly improved wound healing and tissue proliferation. EG2 significantly differed from EG1 and CG for the presence of microscopical osteonecrosis. Regarding to the number of empty lacunes without osteocytes and the level of necrosis, all groups demonstrated significant differences	GGOH in a form of local solution may be a promising option for prevention and treatment of BRONJ

(continued)

Table 6. Continued.

Author (year)	Objectives	Animal model	Experimental design	Treatment approach	Main results	Conclusions
Yalcin-Ulker et al. (2017)[171]	To investigate the prophylactic effect of PTX on MRONJ	33 female Sprague-Dawley rats (12 wk old)	ZOL (0.1 mg/kg) 3x/wk IP for 8 wk, divided into 5 groups: CG, saline + PTX, ZOL + saline, ZOL + PTX, and ZOOL + PTX + PTX (before and after extraction) left mandibular second molar extracted; animals sacrificed after 8 wk	PTX administered either post-extraction PTX: 50 mg/kg/d IP for 3 wk (ZOL/PTX) or both pre- and post-extraction (ZOL/PTX/PTX)	PTX given only after extraction (ZOL/PTX) did not significantly improve inflammation or bone healing; PTX given before and after extraction (ZOL/PTX/PTX) significantly improved bone healing, reduced inflammation, increased vascularization, and regeneration	PTX has prophylactic and therapeutic effects if given before and after tooth extraction. It can positively modulate inflammation and enhance healing in MRONJ models, but post-extraction use alone is not effective
Oliveira et al. (2017)[172]	To evaluate the effects of DEX and NIM on BRONJ in rats	80 male Wistar rats	Rats treated IV administration of 3 consecutive doses of ZOL (0.2 mg/kg). Ten groups: CG (saline IV + gavage: saline, DEX 0.04, DEX 0.4, DEX 4, or NIM) • MRONJ (ZOL IV + molar extraction + gavage: saline, DEX 0.04, DEX 0.4, DEX 4, or NIM) ZA: 0.2 mg/kg IV × 3 doses +1 post-extraction dose	DEX (0.04, 0.4, 4 mg/kg) or NIM (10.3 mg/kg) administered weekly by gavage before each ZOL infusion	None of the anti-inflammatory treatments prevented MRONJ signs. DEX increased bacterial colonies and inflammatory infiltrate. NIM reduced neutrophil infiltration but did not prevent necrosis	Anti-inflammatory therapy with DEX or NIM did not prevent MRONJ development. DEX attenuated leukocytosis but worsened local inflammation. NIM reduced neutrophil recruitment but did not alter necrosis severity
Mada et al. (2017)[173]	To evaluate the effects of green tea intake and ZA i.v. therapy on teeth socket repair	Sixty male albinus Wistar rats	Rats were divided into 4 groups: CG, IV 0.9% SS, GT-1% green tea in drinking water and IV SS, BP-IV BP, and BP + GT-IV BP and 1% green tea. After 10 wk, right upper molars were extracted and the green tea started to be offered for GT and BP + GT. After 7, 14, and 28 d the animals were euthanized	0.035 mg/kg of BP was administered every 2 wk	Lack of socket repair in BP and BP + GT groups and significant increase of polimorphonuclear leukocytes at day 28. The association of BP and GT caused a disturbance in OPG/RANKL system and retarded Runx-2 labeling. Although strong TRAP labeling was observed, most of the positive cells in BP and BP + GT groups were not located on bone surface	Socket healing of rats treated with BP and regular drinking green tea presented no relevant differences in comparison to those treated with BP alone
Zhao et al. (2012)[174]	To evaluate whether (99)Tc-MDP can effectively reduce estrogen deficiency-induced bone loss while presenting a lower risk of BRONJ	Female C3H/HeJ strain mice and C57BL/6 J mice (8 wk old)	Experimental groups: Tc-MDP or ZOL was administrated i.v. 2 wk post-OVX for 2 wk. Mice were killed 5 wk after OVX; received i.v. ZOL (125 μg/kg, twice per week) with or without DEX	(99)Tc-MDP (125 μg/kg, twice each week) with or without DEX (5 mg/kg, twice each week) via the tail vein	OVX mice treated with (99)Tc-MDP showed significantly improved BMD and trabecular bone volume by inhibiting osteoclasts and enhancing the osteogenic differentiation of BM mesenchymal stem cells	(99)Tc-MDP therapy may be a promising approach in the treatment of osteoporosis with less risk of causing BRONJ
Oizumi et al. (2010)[175]	Effects of etidronate on the inflammatory and necrotic actions of ZOL and on ABREs of various NBPs including ZOL	Female mice (6-7 wk of age)	NBP solution was injected s.c. into the right and left pinnas (inside) near the root of the ear (20 μL each ear)	Etidronate at 8, 16, and 100 mmol/L	Etidronate co-injection reduced ZOL-induced inflammation, necrosis, and tissue retention. Decreased the ABRE of zoledronate and other NBPs, even when administered 16 h later. The etidronate reduced previously bound ZOL in bone	Etidronate may inhibit NBP entry into inflammatory or necrotic cells, block their binding to bone, eliminate or replace accumulated NBPs, and thereby help prevent or treat NBP-related jaw osteonecrosis

Abbreviations: (99)Tc-MDP: Technetium-99 conjugated with methylene diphosphonate; ABREs: anti-bone-resorptive effects; ALAN: alendronate; ALP: alkaline phosphatase; BD: benidipine; BMSCs: BM mesenchymal cells; BP: bisphosphonate; BRONJ: Bisphosphonate-related osteonecrosis of the jaws; CA: citric acid; CG: control group; CY: cyclophosphamide; DEX: dexamethasone; DFO: deferoxamine; DH: drug holiday; DOXI: doxycycline; stromal cells; EG1: experimental groups 1; EG2: experimental group 2; EP: experimental periodontitis; EPO: erythropoietin; FS: fluvastatin; GGOH: geranylgeraniol; GS: gelatin sponge; GT: green tea; GuaDex: polyguanidine; HIF-1α: hypoxia-inducible factor 1-alpha; HMGB1: high mobility group box 1; LIPUS: low-intensity pulsed ultrasound; lpBP: low potency; mAb: antibody; ME: methenolone enanthate; MRONJ: medication-related osteonecrosis of the jaws; NBPs: nitrogen-containing bisphosphonates; NIM: nimesulide; NVBT: non-vital bone tissue; OVX: ovariectomy; PAb: polysacharide of *Agaricus blazei*; PC: periodontal cleaning; PRO: propranolol; PTX: pentoxifylline; RJ: royal jelly; RSV: resveratrol; RUNX2: RUNX2; SAM: S-adenosyl methionine; SEL: selenium; SF: soluble fiber; SS: saline solution; STD: standard diet; tFNAs: tetrahedral framework nucleic acids; ZA: zoledronic acid; ZOL: zoledronate.

irradiation was associated with enhanced expression of regenerative proteins such as osteocalcin (OCN), as observed by Mergoni et al.[92] further supporting its role in bone anabolism.

Hormone-based therapies for MRONJ prevention and treatment

A total of 14 preclinical studies investigating hormone-based strategies, predominantly centered on PTH and its synthetic analog teriparatide (TPD), demonstrated varying degrees of success in preventing or ameliorating MRONJ in rat and rice rat models (Table 2). This section to represent the spectrum of PTH and TPD applications in MRONJ models, encompassing preventive and therapeutic designs, systemic vs local delivery, and dose- and time-dependent protocols, thereby capturing the diversity of experimental approaches reported in the literature.

These studies evaluated different administration routes (systemic, local, and sustained-release), dosing regimens (single vs intermittent), treatment timing (pre-, peri-, or post-operative), and animal models (including ovariectomized and senile rats). Across the board, TPD-based interventions were consistently associated with improved bone healing, increased osteocyte viability, enhanced angiogenesis, and reduced osteonecrotic lesions.

PTH stimulates new bone growth by increasing osteoblast survival and number through several key pathways: it upregulates pro-osteoblastogenic growth factors like IGF1 and FGF2, it inhibits the bone-resorbing Wnt-antagonist sclerostin to activate the Wnt/ß-catenin pathway, and it increases the expression and activity of the Runx2 transcription factor, all of which promote osteoblast activity.[93] Teriparatide is a recombinant fragment of human PTH and a potent osteoanabolic agent. The drug has undergone multiple clinical trials that proved its safety and efficacy for the treatment of osteoporosis. The described TPD mechanism involves activating Wnt signaling in osteoblasts, a pathway that promotes bone-building cell differentiation and activity, leading to increased BMD and strength to heal necrotic bone in MRONJ. This anabolic effect creates a positive bone balance, improving bone microarchitecture and accelerating the resolution of MRONJ lesions compared to treatments like placebo.[94]

PTH and teriparatide as preventive interventions

A number of studies explored the preventive potential of TPD when administered prior to or around the time of tooth extraction in bisphosphonate-treated animals. Zandi et al.[57] demonstrated that short-term perioperative administration of teriparatide (20 μg/kg/d for 4 wk) significantly reduced the incidence of bone exposure and necrotic lesions, regardless of whether treatment was initiated pre- or post-extraction. In both protocols, TPD-treated groups exhibited significantly fewer empty lacunae and greater osteocyte density compared to controls, confirming the capacity of TPD to preserve bone vitality.

Similarly, Park et al.[67] demonstrated that daily administration of TPD (20 μg/kg) for 4 wk in ovariectomized, ZOL-treated rats improved trabecular bone parameters and reduced MRONJ-like lesions, associated with decreased inflammation and enhanced bone formation, supporting the efficacy of TPD under osteoporotic conditions analogous to those in postmenopausal women. Jung et al.[63] investigated the temporal effects of TPD, comparing pre- and post-operative administration. Although neither timing produced significant clinical improvements, histological analysis revealed that pre-operative TPD significantly reduced the number of empty osteocytic lacunae and increased vascularization compared to post-operative treatment or controls, suggesting that timing may influence microscopic bone healing even when gross clinical outcomes are unchanged. It is crucial to highlight that TPD is approved exclusively for patients with osteoporosis, including postmenopausal women at high risk of fracture, men with primary or hypogonadal osteoporosis, and individuals with glucocorticoid-induced osteoporosis. Importantly, TPD is contraindicated in patients with bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, Paget's disease, or prior radiation therapy to the skeleton, due to concerns about safety and lack of evidence in these populations. The AAOMS Position Paper[7] does not provide specific recommendations regarding the use of teriparatide in MRONJ management and interpretation, and its application should therefore be interpreted with caution.

Hormonal interventions for established MRONJ lesions

Multiple studies focused on the therapeutic role of TPD and related compounds after the onset of MRONJ-like lesions. Castillo et al.[58] used a rice rat model with pre-established lesions and found that intermittent PTH treatment (40 μg/kg, 3x/wk) reduced MRONJ prevalence from 93% to 27%, increased bone turnover, and promoted mucosal repair.

Liu et al.[56] directly compared the effects of teriparatide and icariin in ovariectomized rats with MRONJ. Both agents improved healing parameters, icariin reduced soft tissue wound area while teriparatide significantly decreased necrotic bone and increased RANKL expression, a marker of bone remodeling. Importantly, both treatments elevated BMP-2 expression, indicating shared osteogenic pathways. Zandi et al.[68] conducted a dose- and time-dependent analysis of teriparatide treatment. They found that doses of 10-20 μg/kg/d significantly enhanced clinical and histological recovery in a stage-dependent manner, with negligible benefits observed at 2 μg/kg/d. Notably, extending treatment duration from 4 to 8 wk conferred no additional therapeutic benefit, indicating a possible plateau effect in efficacy. Ersan et al.[60] provided further support for teriparatide's therapeutic potential. In their study, daily administration of TPD (30 μg/kg) for 28 d post-extraction resulted in increased BMD, reduced osteonecrosis, and normalization of osteoclast activity compared to bisphosphonate-treated controls.

Local and sustained-release hormonal delivery systems

Innovative approaches to hormone delivery were also evaluated. Etemadi et al.[62] compared local injection and gelatin sponge (gelatamp) delivery of teriparatide. Both methods enhanced bone remodeling and reduced necrosis, though local injection yielded superior outcomes, emphasizing the importance of bioavailability and retention time at the surgical site. Erten Taysi et al.[61] tested a chitosan microsphere/poloxamer gel system for localized delivery of human PTH (hPTH). Both single and repeated injections effectively reduced necrotic

areas and stimulated new bone formation. Notably, single-dose microspheres performed comparably to repeated injections, suggesting a viable strategy for enhancing patient compliance.

Histological evaluations across studies consistently demonstrated beneficial effects of PTH/TPD on bone cell populations and vascularization. For example, Dayisoylu et al.[59] reported that adjunctive PTH treatment significantly increased osteoblast and osteoclast numbers while reducing inflammation and epithelial discontinuities. Bisphosphonate-related osteonecrosis of the jaws incidence decreased from 66% to 22% with PTH intervention. Osteoblast counts were markedly higher in treated animals (279.23 ± 74.29) compared to ZOL-only groups (84.14 ± 66.37; $p < .01$), and mucosal healing was complete in 77% of the PTH-treated group. Similarly, Jung et al.[63] observed a significant increase in blood vessel density in the pre-operative TPD group ($p = .002$), aligning with enhanced angiogenesis, a critical element in MRONJ resolution. These microscopic improvements often preceded or occurred independently of clinical changes, underlining the importance of tissue-level assessments in preclinical models.

Ceramic-based biomaterials in the prevention and management of MRONJ

Ten preclinical studies explored the potential of bioactive ceramic materials, including β-TCP, hydroxyapatite (HA), biphasic calcium phosphate (BCP), BMP-2-loaded ceramics, and borate-based bioactive glasses, as preventive or therapeutic interventions for MRONJ (Table 3). These studies used various rodent models of MRONJ, induced by bisphosphonates (mostly ZOL), sometimes in combination with immunosuppressive agents such as cyclophosphamide. Across all studies, ceramic materials improved alveolar socket healing, reduced inflammation and necrosis, and in some cases adsorbed zoledronate locally, contributing to lower tissue drug concentrations and reduced toxicity.

Ceramic-based biomaterials have been used in MRONJ prevention/treatment by providing a 3D scaffold that supports bone regeneration, promoting the attachment, growth, and differentiation of BM stromal cells (BMSCs). These bioactive scaffolds, often made from materials like HA and β-TCP, mimic the body's natural bone composition and create an osteoconductive environment that encourages new bone formation.[95,96]

β-TCP and Zoledronate adsorption

Funayama et al.[77] demonstrated that β-TCP, when placed in extraction sockets of rats treated with high-dose ZOL, significantly reduced local drug deposition. Zoledronate levels in soft connective tissues were lower in the β-TCP group (2.2 ng) compared to untreated controls (4.9 ng). Histologically, β-TCP enhanced mucosal re-epithelialization, decreased necrotic bone, and promoted bone formation. These benefits were mechanistically associated with increased expression of autophagy-related proteins such as Atg9a and LC-3, suggesting a novel protective mechanism through cellular clearance pathways.

In a similar study, Paulo et al.[97] used BCP, composed of 75% HA and 25% β-TCP, to fill extraction sockets. BCP limited ZOL accumulation at the surgical site, as confirmed by nuclear medicine imaging. Treated animals showed better bone density, reduced bone exposure, and improved socket healing. These findings support the use of calcium phosphate-based ceramics as bisphosphonate scavengers at extraction sites to minimize drug-induced cytotoxicity.

Functionalized ceramics for anti-inflammatory and osteogenic support

Sacco et al.[98] evaluated a functionalized biomaterial, HA doped with doxycycline (HADOX), as a dual-acting scaffold providing both structural support and anti-inflammatory effects. In rats treated with ZOL, HADOX increased newly formed bone (NFB), and reduced local inflammation compared to HA alone. The biomaterial demonstrated strong tissue integration and prolonged retention in vivo, likely contributing to its sustained therapeutic effect. This study highlights the benefit of loading ceramics with anti-inflammatory agents for added functional gain in MRONJ prevention.

BMP-2-enhanced ceramics for bone regeneration

Two studies, by Mikai et al.[79] and Tanaka et al.[80] focused on the combination of BMP-2 and β-TCP to restore bone structure in MRONJ-like lesions. Mikai et al.[79] evaluated both preventive and therapeutic protocols in mice treated with ZOL and cyclophosphamide. In the prevention model, BMP-2/β-TCP applied at the time of tooth extraction led to partial bone regeneration and reduced necrosis. In the treatment model (BMP-2/β-TCP applied 2 wk post-extraction following surgical debridement), animals exhibited complete socket healing, reduced empty lacunae, and enhanced osteopontin expression, demonstrating superior bone remodeling. Although angiogenesis was not significantly altered, the regenerative capacity of BMP-2/β-TCP was pronounced. Tanaka et al.[80] confirmed these findings in a similar MRONJ-like model. The BMP-2/β-TCP composite improved BMD and bone quality in both prevention and treatment protocols, underscoring its versatile applicability. These studies position BMP-2-functionalized ceramics as strong candidates for both prophylactic and regenerative interventions in MRONJ.

Borate-based bioactive glasses

Su et al.[78] introduced borate bioactive glass (BBG) as a regenerative scaffold with pro-angiogenic and osteogenic properties. In a mouse model of MRONJ induced by ZOL, BBG enhanced soft and hard tissue healing by stimulating angiogenesis and osteogenesis. In vitro experiments corroborated the in vivo results, showing increased endothelial cell proliferation and osteoblast differentiation. These dual effects are particularly relevant in MRONJ, where both vascular compromise and bone necrosis are key pathophysiologic features.

Bioactive materials and scaffold-based therapies

Guo et al.[99] developed a magnesium-based nanocomposite hydrogel (PBM) that, when injected into mandibular defects, significantly enhanced angiogenesis, type H vessel formation, immune modulation, and stem cell recruitment in both rats and minipigs. This hydrogel promoted bone regeneration while reducing inflammation and bacterial colonization. Similarly, Zhu et al.[100] reported that biodegradable magnesium implants reduced the incidence of MRONJ-like lesions in rats and enhanced bone formation through the activation of VEGF- and CGRP-mediated pathways. The protective effect

was reversed when specific inhibitors of VEGF or CGRP signaling were co-administered. In another approach, de Almeida et al.[101] showed that HA scaffolds improved bone healing and reduced necrotic areas in rats treated with bisphosphonates, with minimal systemic toxicity. Pellicano et al.[102] further demonstrated that combining pericardial membranes with bioactive glass prevented osteonecrosis and bone abscess formation in a zoledronate-treated rat model.

Biologics

Preclinical research has extensively explored the potential of biological agents, including platelet concentrates, growth factors, MSCs, exosomes, and bioengineered hydrogels, to prevent MRONJ. These studies collectively demonstrate significant improvements in mucosal healing, bone regeneration, angiogenesis, and inflammation modulation in animal models, offering promising therapeutic strategies for clinical translation (Table 4).

Platelet concentrates and growth factor-based strategies

Platelet-derived therapies, such as PRP, leukocyte- and platelet-rich fibrin (L-PRF), and advanced PRF (A-PRF), have consistently reduced osteonecrosis, bone exposure, and inflammatory infiltration in MRONJ models. Indeed, PRP can help prevent MRONJ by accelerating bone cell proliferation, due to the concentrated growth factors released by activated platelets. These growth factors stimulate the migration and proliferation of MSCs, which then differentiate into new bone tissue, accelerating the bone healing and repair process at the extraction site. For instance, Shi et al.[33] demonstrated that a PRP/Bio-Oss composite completely prevented bone exposure in rats treated with ZOL, achieving superior BMD and bone volume fraction (BV/TV) compared to Bio-Oss alone or untreated controls. Similarly, Razmara et al.[103] reported that PRP-enriched collagen scaffolds enhanced bone formation and reduced osteonecrosis by increasing osteoblast activity and vascularization.

Growth factor-based strategies have also shown remarkable efficacy. Gao et al.[104] found that PDGF-BB delivered via fibrin sealant restored angiogenesis and osteogenesis, achieving an 80% success rate in preventing MRONJ compared to 30% in controls. Imada et al.[105] and Kurokawa et al.[106] demonstrated that bFGF-loaded hydrogels reduced osteonecrosis incidence to 0% and 8.3%, respectively, by enhancing mucosal healing and bone regeneration. Additionally, Cao et al.[107] showed that IGF-1-loaded hydrogels promoted lymphangiogenesis and angiogenesis via PI3K/AKT pathway activation, offering a novel mechanism for MRONJ prevention.

Mesenchymal stem cells and conditioned media

Mesenchymal stem cells-based therapies, including BM-derived (BM-MSCs), adipose-derived (ADSCs), and umbilical cord-derived (hUC-MSCs) stem cells, offer therapeutic potential for preventing MRONJ by secreting paracrine factors and extracellular vesicles (EVs) including exosomes. These factors promote gingival wound healing, enhance angiogenesis, reduce inflammation, and regulate bone remodeling. Mesenchymal stem cells-derived exosomes, in particular, are a promising cell-free therapy that accelerates tooth socket healing and regenerates bone by affecting macrophage polarization, inhibiting cell senescence, and influencing osteoclast activity. Kaibuchi et al.[73,108] reported that locally transplanted MSC sheets significantly improved wound healing and angiogenesis, reducing osteonecrosis incidence to 12.5% compared to 80%-100% in controls. Similarly, Yang et al.[75] found that i.v. hUC-MSCs normalized the RANKL/OPG ratio, enhanced osteogenic markers (RUNX2, BMP-2), and reduced inflammation in BRONJ rats.

Mesenchymal stem cells-conditioned media (MSC-CM) and secretome-mimicking cytokine cocktails have emerged as cell-free alternatives. Ogata et al.[109,110] demonstrated that MSC-CM and a cytokine mixture (MCP-1, IGF-1, VEGF) improved bone healing and soft tissue coverage approximately 65%, suggesting paracrine-mediated regeneration. Watanabe et al.[74] further showed that MSC-derived EVs (MSC-EVs) suppressed cellular senescence markers (p21, pRB) and inflammatory cytokines (IL-6, IL-8), promoting wound healing without interfering with ZA's anti-resorptive effects.

Exosome-based therapies

Exosomes derived from MSCs have shown potent immunomodulatory and regenerative properties. The therapeutic approach reduces harmful inflammation by shifting macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, while also inhibiting cell death (pyroptosis), potentially by blocking the NF-κB/NLRP3/IL-1β pathway. This strategy aims to control the balance of macrophages, a critical factor in many inflammatory diseases, by suppressing M1-driven inflammation and promoting tissue repair mediated by M2 macrophages. Zheng et al.[111,112] demonstrated that ADSC-derived exosomes reduced M1 macrophage polarization and pyroptosis via NF-κB/NLRP3/IL-1β axis suppression, while IL-1RA-enriched exosomes enhanced gingival healing and bone regeneration. Similarly, Dong et al.[113] reported that ADSC exosomes restored autophagic flux (reduced LC3/SQSTM1) and decreased apoptosis in gingival epithelium, highlighting their role in tissue homeostasis.

Stem cell-derived conditioned media and cytokine cocktails

Dental pulp stem cell-conditioned medium (DPSC-CM) and MSC secretome mimics have shown promise in MRONJ prevention. Similarly, to platelet concentrates and growth factor-based strategies, DPSC-CM and MSC secretomes therapies reduce inflammation, stimulate the regeneration of blood vessels (angiogenesis) and bone tissue, and promote the expression of growth factors and bone-healing molecules, making them a promising cell-free alternative to stem cell transplantation for preventing MRONJ. Kushiro et al.[154] found that DPSC-CM delivered via atelocollagen sponges reduced bone exposure and increased VEGF-positive cells, promoting mucosal healing. Ogata et al.[110] further validated that cytokine cocktails mimicking MSC secretomes (MIV) enhanced osteoclast function and soft tissue regeneration, offering a standardized, scalable therapeutic approach.

Autologous cell and biomaterial combinations

Combining autologous cells with biomaterials has yielded synergistic effects. Barba-Recreo et al.[82] reported that ASCs + PRP + BMP-2 reduced BRONJ incidence to 8%, outperforming PRP or flap coverage alone. Shi et al.[33] and Brierly

et al.[76] demonstrated that PRP/Bio-Oss and rhBMP-2 hydrogels, respectively, enhanced osteocyte density and bone formation while reducing necrosis. Tao et al.[34] further showed that Hep/GelMA-PRF hydrogels upregulated osteogenic markers (OCN, Col I, BMP-2) and reduced inflammation, underscoring the benefits of growth factor-controlled release systems.

Endothelial progenitor cells and PBMCs

Endothelial progenitor cells (EPCs) and quality-controlled PBMCs (QQ-PBMNCs) have demonstrated strong angiogenic potential. Tamari et al.[114] found that EPCs healed 13/14 MRONJ lesions by increasing VEGF levels and reducing necrotic bone area, primarily via paracrine mechanisms. Kuroshima et al.[115] reported that QQ-PBMNCs improved soft tissue healing and angiogenesis without adverse effects on BM, suggesting clinical translatability.

Stem cell-derived and secretome-based therapies

Conditioned media from dental pulp stem cells (DPSC-CM), as shown by Kaminogo et al.[116] enhanced osteogenesis, modulated Wnt signaling, and decreased inflammation in a DRONJ (denosumab-related osteonecrosis of the jaws) mouse model. Huang et al.[117] reported that adipose-derived extracellular vesicles (sEV-AT) administered systemically promoted angiogenesis, improved soft tissue healing, and significantly reduced the extent of BRONJ lesions. Alonso-Rodriguez et al.[118] observed that local application of ASCs improved bone formation in bisphosphonate-treated rats, though osteonecrosis incidence remained unchanged.

Ozone and oxygen-based therapies for MRONJ prevention and treatment

A small but growing body of preclinical research has investigated the role of ozone-based and hyperbaric oxygen (HBO) therapies in the prevention and management of MRONJ. These therapies work by promoting tissue oxygenation, enhancing circulation, modulating inflammation, and stimulating bone and soft tissue repair, with some studies reporting significant improvements in wound healing and bone regeneration in various animal models (Table 5).

Delanora et al.[119] assessed the effects of systemic ozone therapy on MRONJ healing in senescent rats. In this study, 18-mo-old female Wistar rats were treated with ZOL or saline for 7 wk prior to molar extraction. Rats receiving systemic ozone therapy (0.7 mg/kg i.p. every 48 h for 4 wk post-extraction) showed significant improvements in bone and soft tissue healing compared to ZOL-only controls. Specifically, ozone therapy led to reduced non-vital bone, increased expression of VEGF and OCN, and decreased levels of pro-inflammatory cytokines TNF-α and IL-1β. These results suggest that ozone may mitigate MRONJ by modulating the inflammatory response and promoting angiogenesis.

Pereira-Silva et al.[81] compared the timing of systemic ozone administration, before, after, or both before and after tooth extraction, in a ZOL-treated rat model. The study revealed that ozone therapy administered after extraction resulted in the most favorable bone healing outcomes. Both postextraction treatment-only (TOG) and prevention-only (POG) ozone groups showed improved repair relative to untreated controls, but TOG exhibited the most pronounced histological and microstructural bone regeneration, underscoring the importance of timing in therapeutic efficacy.

Silva et al.[120] evaluated the ideal concentration of ozonized oil in the alveolar socket healing following tooth extraction. Clinical evaluation 28 d after tooth extraction revealed that the saline group (SAL) exhibited normal socket healing, while the ZOL presented with bone exposure and incomplete mucosal coverage, indicative of MRONJ. In contrast, the groups treated with ozonized oil (OZ500, OZ600, OZ700) displayed delayed but complete mucosal healing, with no evidence of bone exposure or infection. All ozonized oil-treated groups demonstrated significant increases in bone formation (NFBT) compared to the ZOL group. Collectively, these results suggest that local application of ozonized sunflower oil, particularly at a concentration of 600 mEq/kg, effectively prevents MRONJ development and promotes bone regeneration in senescent rats undergoing ZOL therapy.

Monteiro et al.[121] investigated the local application of ozonated oil directly into extraction sockets of ZOL-treated rats. Their findings demonstrated a significant reduction in necrotic bone area in the treated group compared to controls, suggesting that topically applied ozonated oil may serve as a protective strategy against MRONJ development. Finally, Liu et al.[122] evaluated the preventive potential of immediate HBO therapy following tooth extraction in a rat model receiving varying doses of ZOL and DEX. HBO was administered daily (2.5 ATA, 100% O_2 for 90 min) for 5 consecutive days immediately post-extraction. The most significant reductions in lesion size and number were observed in rats that received 4 bisphosphonate injections. Histological analysis revealed improved epithelial coverage and decreased inflammatory infiltrates in HBO-treated animals, supporting its use as a non-invasive prophylactic intervention.

Together, these studies suggest that ozone-based therapies, whether administered systemically or locally, may have significant potential in reducing MRONJ severity or preventing lesion development. The observed benefits appear to be mediated through enhanced angiogenesis, reduced inflammation, and improved bone regeneration. Although HBO has shown efficacy in osteoradionecrosis, clinical studies in MRONJ patients have not consistently supported its use. Further research is needed to refine the optimal dose, timing, and delivery mode to maximize clinical efficacy.

Other strategies to prevent MRONJ

A broad spectrum of strategies has been evaluated in preclinical models to prevent or mitigate MRONJ. These studies target multiple aspects of MRONJ pathogenesis, including impaired bone remodeling, chronic inflammation, defective angiogenesis, microbial infection, and immune dysregulation. The interventions can be grouped into categories based on their mechanisms of action: natural compounds, pharmacological modulators, stem cell-derived therapies, immunoregulatory agents, antioxidant/angiogenic factors, local antimicrobials, statins, physical therapies, and antiresorptive discontinuation protocols. The summary of several studies across this category is shown in Table 6.

Natural compounds and nutritional interventions

Several naturally derived compounds have shown therapeutic promise. Topan et al.[123] demonstrated that royal jelly (RJ),

administered orally either before or after dental extractions, improved bone and soft tissue healing, enhanced microarchitectural integrity, and reduced the expression of inflammatory cytokines. Likewise, de Almeida et al.[124] found that omega-3 supplementation, rich in EPA and DHA, significantly reduced necrotic bone and inflammation in a ZOL-treated, ovariectomized rat model. Resveratrol was tested by Vitale et al.[125] and Movahedian Attar et al.[126]; both studies found it significantly lowered the incidence of osteonecrosis, although its effect on bone regeneration was inconsistent. Melatonin, evaluated by Yadegari et al.[127] reduced necrosis but showed limited effects on osteoclast and fibroblast activity. Icariin, investigated by Liu et al.[128] enhanced soft tissue healing and VEGF expression but failed to reduce MRONJ incidence, suggesting dose-dependent limitations.

Pharmacological modulators of Osteogenesis and inflammation

Betaine[129] reversed bisphosphonate-induced impairment of BM stromal cells by restoring m6A methylation and SAM levels, enhancing osteogenic differentiation, and reducing necrosis in vivo. Propranolol,[130] a β-adrenergic antagonist, promoted osteogenesis and reduced apoptosis in bisphosphonate-exposed mice, improving bone healing through upregulation of BMP2, ALP, and RUNX2. Rosiglitazone,[49] a PPAR-γ agonist, shifted macrophage polarization from pro-inflammatory M1 to reparative M2 phenotype, decreasing osteonecrosis and bone exposure. Lemos et al.[131] demonstrated that digoxin attenuated MRONJ by downregulating the IL-17/RORγt axis, reducing inflammation and osteonecrosis, although higher doses were associated with systemic toxicity.

Immunoregulatory, molecular targeted interventions, and antiresorptive discontinuation and drug holidays

Zhao et al.[132] demonstrated that tetrahedral framework nucleic acids (tFNAs) enhanced angiogenesis and induced M2 macrophage polarization, promoting tissue regeneration and bone healing. The study by Gkouveris et al.[72] demonstrated inhibition of the HMGB1-RAGE signaling axis, resulting in decreased osteonecrosis and reduced bone exposure in ZOL-treated mice. Soundia et al.[71] showed that local delivery of RANKL restored osteoclast function and improved socket healing, even under ongoing bisphosphonate administration. Tamaki et al.[133] found that discontinuation of anti-RANKL Ab therapy promoted a macrophage shift from M1 to M2, leading to improved soft tissue healing and reduced lesion burden. Zhu et al.[134] investigated an 8-wk bisphosphonate drug holiday before tooth extraction, which partially restored bone turnover markers but failed to significantly reduce MRONJ incidence. Hadaya et al.[135] found that discontinuation of the anti-RANKL agent OPG-Fc before extraction reduced MRONJ burden, whereas zoledronate discontinuation or drug withdrawal after lesion onset did not improve healing. de Molon et al.[36] demonstrated that OPG-Fc, a RANK-L inhibitor, but not ZOL drug withdrawn reverses features of osteonecrosis in a mouse model.

Antioxidant and Angiogenic therapies

Yalcin-Ülker et al.[136] found that local application of deferoxamine (DFO), a hypoxia-inducible factor-1α (HIF-1α) stabilizer, increased angiogenic signaling and reduced bone necrosis. Duygu et al.[137] showed that systemic erythropoietin (EPO) administration before and after extraction enhanced vascularization and reduced lesion severity. Sildenafil, as reported by Mroczek et al.[138] improved angiogenesis and reduced necrosis through NO-mediated pathways. Local application of fluvastatin, studied by Adachi et al.[139] and Sanda et al.[140] improved epithelialization and bone formation in a dose-dependent manner.

Local antimicrobial and anti-inflammatory strategies

Hadad et al.[70] demonstrated that local application of 10% DBG improved bone healing and reduced osteonecrosis in a ZOL-induced MRONJ model. Costa de Sousa et al.[141] showed that a gel containing polysaccharides from *Agaricus blazei* reduced bone necrosis, enhanced osteocyte viability, and activated Wnt signaling. In a model incorporating bacterial inoculation, Cantorán-Castillo et al.[142] reported that polyguanidine (GuaDex) application fully prevented MRONJ development and stimulated osteoblast proliferation and angiogenesis, outperforming systemic clindamycin. Elsayed et al.[143] demonstrated that topical EDTA chelation removed matrix-bound bisphosphonates, restored osteoclast function, and improved mucosal healing. Hokugo et al.[144] showed that local application of low-potency bisphosphonates displaced previously adsorbed zoledronate in jawbone and significantly improved healing outcomes.

Systemic and local statin therapies

de Sousa et al.[69] showed that atorvastatin, when administered systemically either before or after dental extraction, modulated inflammatory markers (TNF-α, IL-1β), activated the Wnt pathway, and improved mucosal and bone healing in MRONJ rats. Fluvastatin, evaluated by Sanda et al.[140] exerted similar effects when locally administered, reducing necrotic bone and promoting angiogenesis.

Physical modalities and supportive care

Hidaka et al.[145] demonstrated that low-intensity pulsed ultrasound (LIPUS) prevented MRONJ-like lesions in rats exposed to alendronate and *Porphyromonas gingivalis*. Low-intensity pulsed ultrasound promoted vascular regeneration, enhanced gene expression of RANKL and VEGF, and restored bone remodeling. Castillo et al.[146] reported that periodontal maintenance therapy and a high-soluble fiber diet significantly reduced MRONJ incidence in rice rats treated with bisphosphonates, highlighting the importance of controlling local risk factors.

Concluding remarks and future directions

Over the last 2 decades, animal research has significantly advanced our understanding of MRONJ and provided a valuable foundation for exploring preventive and therapeutic strategies.[7,9,11] Numerous interventions, including laser and PBM therapies, aPDT, pharmacological modulators, biologics, biomaterials, and natural compounds, have shown promising outcomes. Collectively, these approaches have demonstrated the capacity to reduce necrotic bone, improve soft tissue healing, enhance angiogenesis, and modulate inflammatory responses. However, despite the optimism raised by these

findings, the translation of such preclinical successes into meaningful clinical applications remains elusive.[9,11]

One of the most pressing limitations lies in the disparity between the clinical context in which MRONJ most frequently arises and the experimental conditions typically used in animal studies. From a systemic disease perspective, most rodent studies are performed on healthy animals. In the clinical reality however, MRONJ patients are often patients with primary or metastatic bone malignancy and are treated with antiresorptives often in combination with chemotherapy, antiangiogenics, corticosteroids, and other systemic therapies that profoundly affect bone and immune homeostasis. Similarly, for osteoporotic patients, the systemic disease affects bone homeostasis and alters tissue healing. In addition, systemic comorbidities, such as diabetes or autoimmune disease further complicate the clinical reality. From a local disease perspective, the majority of rodent studies utilize extraction of healthy teeth to induce local trauma, while in the clinical setting extractions are performed when teeth are so severely affected by dental disease (caries, periodontal disease or periapical disease) that cannot be rescued by conservative treatment. Finally, antiresorptives in rodent models are administered more frequently and at suprapharmacologic doses to generate high frequency and severity of MRONJ for sufficient statistical power. However, these treatment regimens do not parallel the clinical reality.

The suitability of mouse and rat oral tissues paralleling that of their human counterparts poses an additional complexity. Rodent models, while invaluable for mechanistic exploration, cannot fully recapitulate the structural and biological complexity of the human oral cavity.[24,28,30] The jawbone is uniquely characterized by its thin mucosa, rich vascularization, and constant exposure to microbial challenge, features that are only partially represented in rodents. Rodent bone is lamellar and lacks osteons, the fundamental structural unit of human cortical bone. Moreover, the cortical bone in humans is considerably wider than in rodents, which may increase vulnerability to MRONJ onset and hinder treatment success. Utilizing animal models that more closely mimic human tissue architecture, including mucosal, vascular, and bone structures, would provide a more faithful platform for testing interventions. The use of larger animals such as minipigs, sheep, or dogs, which more closely replicate human oral anatomy, bone remodeling dynamics, and microbiota, should bridge the gap between rodent studies and clinical reality. Although such models pose ethical and financial challenges, they may be indispensable for addressing translational uncertainties that cannot be resolved in rodents [1-3, 9-11].

The greatest obstacle of MRONJ rodent models is the complete lack of standardization in experimental approaches. There is great variability in the published literature involving the age and sex of the animals, the location (maxilla vs mandible, dentate vs non-dentate areas, first vs second molar, etc.), the local instigating factor (extraction vs dental disease vs surgical trauma), the antiresorptive dosing and administration route, the experimental time courses for disease establishment and healing, and the establishment of objective clinic, radiographic and histologic measures that reflect disease presence and burden. Without commonly accepted experimental approaches and assessments, results from various studies are virtually impossible to compare and contrast [1-3, 9-11].

A multipronged approach needs to be followed to transition translational findings in the clinical setting (Figure 4).

a) Of utmost importance is the establishment of objective experimental measures for assessment of disease burden.
b) Continued discovery of fundamental biological processes that underlie MRONJ pathogenesis and of pharmacological or interventional therapies that can ameliorate disease burden will offer alternative approaches to manage the disease.
c) In rodent models, direct head-to-head comparisons of diverse preventive and therapeutic strategies in the same experimental setting will allow identification of the most effective strategies. Given the multifactorial nature of the disease, it is unlikely that a single universal treatment will suffice. Combination of treatments that address multiple aspects of disease mechanisms (Figure 2) will likely be more effective.
d) Mono- or multi-therapies with consistently favorable outcomes should transition to larger animal models (sheep or mini-pigs) with more relevant functional, physiologic and structural biology to humans. Here, therapies that are already used for management of other disease could find immediate application. Yet, novel therapies could provide significant breakthroughs despite their longer implementation process.
e) Ultimately, Phases I, II, and III clinical trials will evaluate safety and dosage, assess effectiveness, compare with existing treatments, establish side effects and provide evidence for regulatory approval and implementation.

Looking forward, artificial intelligence (AI) holds significant potential to address some of the translational and methodological challenges highlighted in this review. Machine learning and other AI-driven approaches can aid in integrating heterogeneous datasets from preclinical and clinical studies, enabling more accurate identification of predictive biomarkers and therapeutic targets. Artificial intelligence algorithms may also enhance experimental design by simulating disease progression, optimizing treatment protocols, and predicting treatment outcomes, thus reducing variability and increasing reproducibility. Furthermore, AI can support the standardization of outcome measures across laboratories and clinical settings, helping to harmonize data reporting and improve comparability. Ultimately, leveraging AI could accelerate the translation of promising adjunctive therapies from bench to bedside, streamline decision-making, and improve personalized patient care in MRONJ management.

Conclusion

In conclusion, while the preclinical literature on MRONJ prevention and treatment has expanded rapidly and yielded valuable insights, significant gaps remain before these findings can be applied in clinical practice. The complexity of MRONJ pathogenesis, the limitations of current animal models, the heterogeneity of preclinical study designs, and the lack of standardization in experimental methodology and disease assessment represent formidable obstacles. However, by embracing methodological rigor, mechanistic exploration, and patient-centered translation, the field is well positioned to move from promising experimental outcomes toward evidence-based clinical strategies. Reducing the incidence and morbidity of MRONJ will likely require not only innovation in preventive and therapeutic approaches

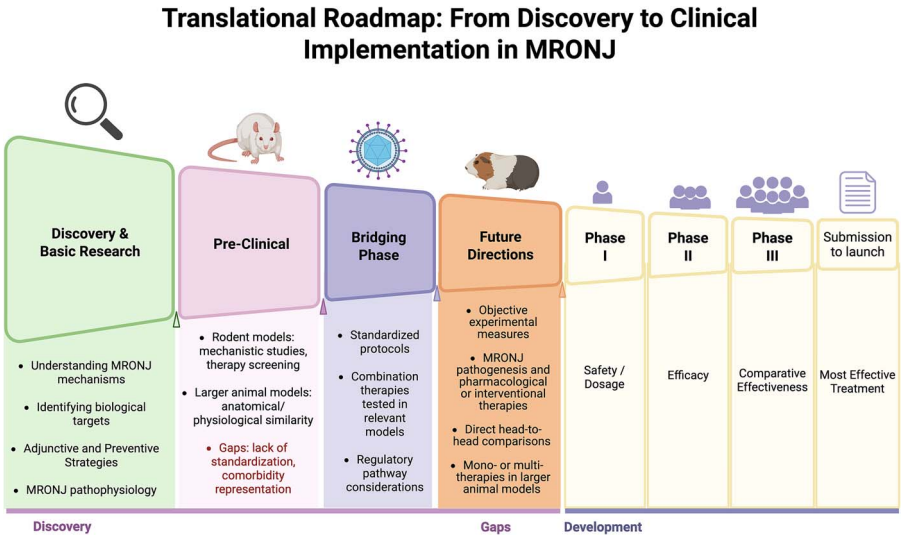

Figure 4. This figure illustrates the sequential phases required to translate research findings into clinical practice for medication-related osteonecrosis of the jaw (MRONJ). The roadmap is divided into 3 main segments: discovery, gaps, and development, highlighting the continuum from basic research to clinical application. Discovery & Basic Research (green): this initial stage focuses on understanding the mechanisms underlying MRONJ, identifying biological targets, and exploring adjunctive and preventive strategies. Studies at this phase aim to elucidate MRONJ pathophysiology to inform therapeutic development; pre-clinical (purple): pre-clinical research involves the use of rodent models, mechanistic studies, and early proof-of-concept evaluations to assess therapy efficacy and safety under controlled experimental conditions. It also includes the evaluation of adjunctive strategies using animal models. A major challenge identified here is the lack of standardization and reproducibility across experimental protocols; bridging phase (blue): this phase addresses the translation of pre-clinical findings into protocols suitable for human trials. It emphasizes the need for standardized experimental protocols, rigorous safety and efficacy testing, and strategies to ensure reproducibility. The ultimate goal is to bridge the gap between laboratory discoveries and clinical interventions; future directions (orange): this section outlines emerging priorities, including the development of objective and reproducible MRONJ phenotyping systems, optimization of preclinical models to mimic human pathology, and strategies to improve translational validity. Focus areas include identifying optimal dosing regimens, refining interventions for MRONJ prevention, and developing biomarkers to monitor treatment response; clinical development (yellow): the clinical development pathway includes phase I (safety and dosage), phase II (efficacy), and phase III (comparative effectiveness) trials, culminating in submission for regulatory approval and clinical implementation. These steps ensure that interventions meet rigorous safety, efficacy, and effectiveness standards before being adopted into clinical practice. The roadmap highlights critical gaps, such as standardization and reproducibility, that need to be addressed to accelerate progress from discovery to implementation. Created with BioRender.com (License Number: FL292C873C).

but also a fundamental reorientation toward integrated, individualized care. Bridging the gap from bench to bedside will demand close collaboration among basic scientists, clinicians, and regulatory authorities, as well as a commitment to standardization and transparency in preclinical research. Only through such concerted efforts will the promise of preclinical discoveries be realized in improved outcomes for patients living with or at risk of MRONJ.

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Conflicts of interest

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Data availability

No original data were used in this manuscript.

References

1. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw: 2014 update. *J Oral Maxillofac Surg*. 2014;72(10):1938-1956. https://doi.org/10.1016/j.joms.2014.04.031
2. Yoneda T. Bisphosphonate-related osteonecrosis of the jaw-after a decade has passed. *Clin Calcium*. 2014;24(3):407-415
3. Yoneda T, Hagino H, Sugimoto T, et al. Bisphosphonate-related osteonecrosis of the jaw: position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons. *J Bone Miner Metab*. 2010;28(4):365-383. https://doi.org/10.1007/s00774-010-0162-7
4. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg*. 2004;62(5):527-534. https://doi.org/10.1016/j.joms.2004.02.004
5. Marx RE. Pamidronate (Aredia) and zoledronate (zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003;61(9):1115-1117. https://doi.org/10.1016/s0278-2391(03)00720-1
6. Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo SB. Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper. *J Am Dent Assoc*. 2005;136(12):1658-1668. https://doi.org/10.14219/jada.archive.2005.0108
7. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on medication-related osteonecrosis of the jaws: 2022 update. *J Oral Maxillofac Surg*. 2022;80(5):920-943. https://doi.org/10.1016/j.joms.2022.02.008
8. Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Ann Oncol*. 2012;23(5):1341-1347. https://doi.org/10.1093/annonc/mdr435
9. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res*. 2015;30(1):3-23. https://doi.org/10.1002/jbmr.2405
10. Aghaloo T, Hazboun R, Tetradis S. Pathophysiology of osteonecrosis of the jaws. *Oral Maxillofac Surg Clin North Am*. 2015;27(4):489-496. https://doi.org/10.1016/j.coms.2015.06.001
11. Tetradis S, Allen MR, Ruggiero SL. Pathophysiology of medication-related osteonecrosis of the jaw: a minireview. *JBMR Plus*. 2023;7(8):e10785. https://doi.org/10.1002/jbm4.10785
12. Allen MR, Burr DB. The pathogenesis of bisphosphonate-related osteonecrosis of the jaw: so many hypotheses, so few data. *J Oral Maxillofac Surg*. 2009;67(5):61-70. https://doi.org/10.1016/j.joms.2009.01.007
13. Fliefel R, Troltzsch M, Kuhnisch J, Ehrenfeld M, Otto S. Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. *Int J Oral Maxillofac Surg*. 2015;44(5):568-585. https://doi.org/10.1016/j.ijom.2015.01.026
14. Tsao C, Darby I, Ebeling PR, et al. Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. *J Oral Maxillofac Surg*. 2013;71(8):1360-1366. https://doi.org/10.1016/j.joms.2013.02.016
15. Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int*. 2008;19(6):733-759. https://doi.org/10.1007/s00198-007-0540-8
16. Khan AA, Morrison A, Kendler DL, et al. Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the international task force on ONJ. *J Clin Densitom*. 2017;20(1):8-24. https://doi.org/10.1016/j.jocd.2016.09.005
17. Khan A, Morrison A, Cheung A, Hashem W, Compston J. Osteonecrosis of the jaw (ONJ): diagnosis and management in 2015. *Osteoporos Int*. 2016;27(3):853-859. https://doi.org/10.1007/s00198-015-3335-3
18. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O, Peter JU. Interventions for managing medication-related osteonecrosis of the jaw. *Cochrane Database Syst Rev*. 2022;2022(7):CD012432. https://doi.org/10.1002/14651858.CD012432.pub3
19. Ruan HJ, Li MY, Zhang ZY, Ma HL, He Y. Medication-related osteonecrosis of the jaw: a retrospective single center study of recurrence-related factors after surgical treatment. *Clin Oral Investig*. 2024;28(10):549. https://doi.org/10.1007/s00784-024-05911-z
20. Sonis ST, Watkins BA, Lyng GD, Lerman MA, Anderson KC. Bony changes in the jaws of rats treated with zoledronic acid and dexamethasone before dental extractions mimic bisphosphonate-related osteonecrosis in cancer patients. *Oral Oncol*. 2009;45(2):164-172. https://doi.org/10.1016/j.oraloncology.2008.04.013
21. Aghaloo TL, Felsenfeld AL, Tetradis S. Osteonecrosis of the jaw in a patient on denosumab. *J Oral Maxillofac Surg*. 2010;68(5):959-963. https://doi.org/10.1016/j.joms.2009.10.010
22. Aghaloo TL, Cheong S, Bezouglaia O, et al. RANKL inhibitors induce osteonecrosis of the jaw in mice with periapical disease. *J Bone Miner Res*. 2014;29(4):843-854. https://doi.org/10.1002/jbmr.2097
23. Aghaloo TL, Kang B, Sung EC, et al. Periodontal disease and bisphosphonates induce osteonecrosis of the jaws in the rat. *J Bone Miner Res*. 2011;26(8):1871-1882. https://doi.org/10.1002/jbmr.379
24. Aguirre JI, Castillo EJ, Kimmel DB. Preclinical models of medication-related osteonecrosis of the jaw (MRONJ). *Bone*. 2021;153(12):116184. https://doi.org/10.1016/j.bone.2021.116184
25. de Molon RS, Cheong S, Bezouglaia O, et al. Spontaneous osteonecrosis of the jaws in the maxilla of mice on antiresorptive treatment: a novel ONJ mouse model. *Bone*. 2014;68(11):11-19. https://doi.org/10.1016/j.bone.2014.07.027
26. Kang B, Cheong S, Chaichanasakul T, et al. Periapical disease and bisphosphonates induce osteonecrosis of the jaws in mice. *J Bone Miner Res*. 2013;28(7):1631-1640. https://doi.org/10.1002/jbmr.1894
27. Soundia A, Hadaya D, Esfandi N, et al. Osteonecrosis of the jaws (ONJ) in mice after extraction of teeth with periradicular disease. *Bone*. 2016;90(9):133-141. https://doi.org/10.1016/j.bone.2016.06.011
28. Yan R, Jiang R, Hu L, Deng Y, Wen J, Jiang X. Establishment and assessment of rodent models of medication-related osteonecrosis of the jaw (MRONJ). *Int J Oral Sci*. 2022;14(1):41. https://doi.org/10.1038/s41368-022-00182-4
29. Bae EB, Kim MY, Ji S, et al. Anti-VEGF neutralizing antibody delays osteomucosal healing by reducing collagen formation in mice. *Sci Rep*. 2025;15(1):36903. https://doi.org/10.1038/s41598-025-20840-x
30. Hadad H, Matheus HR, Pai SI, Souza FA, Guastaldi FPS. Rodents as an animal model for studying tooth extraction-related medication-related osteonecrosis of the jaw: assessment of outcomes. *Arch Oral Biol*. 2024;159(3):105875. https://doi.org/10.1016/j.archoralbio.2023.105875
31. Hanada D, Mochizuki M, Nakahara T, Tanaka A. Novel standardized method for inducing medication-related osteonecrosis of the jaw in rats and precise quantitative assessment of pathological outcomes. *Odontology*. 2025;113(4):1415-1426. https://doi.org/10.1007/s10266-025-01076-7

32. Isleyen M, Cina M, Asci H, Ilhan I, Oguz YR. The preventive effect of preoperative and postoperative selenium on the medication-related osteonecrosis of the jaw: an animal study in rats. *J Oral Maxillofac Surg*. 2024;82(7):828-839. https://doi.org/10.1016/j.joms.2024.03.026
33. Shi K, Xu Y, Chen Z, et al. Preventive effect of platelet-rich plasma/Bio-Oss granules composite on medication-related osteonecrosis of the jaw in a rat model. *J Dent*. 2025;158(7):105802. https://doi.org/10.1016/j.jdent.2025.105802
34. Tao L, Gao Y, Li Y, et al. The preventive effect of photocrosslinked Hep/GelMA hydrogel loaded with PRF on MRONJ. *BMC Oral Health*. 2024;24(1):1010. https://doi.org/10.1186/s12903-024-04792-8
35. de Molon RS, Hsu C, Bezouglaia O, et al. Rheumatoid arthritis exacerbates the severity of osteonecrosis of the jaws (ONJ) in mice. A randomized, prospective, controlled animal study. *J Bone Miner Res*. 2016;31(8):1596-1607. https://doi.org/10.1002/jbmr.2827
36. de Molon RS, Shimamoto H, Bezouglaia O, et al. OPG-Fc but not zoledronic acid discontinuation reverses osteonecrosis of the jaws (ONJ) in mice. *J Bone Miner Res*. 2015;30(9):1627-1640. https://doi.org/10.1002/jbmr.2490
37. Kuroshima S, Sasaki M, Murata H, Sawase T. Medication-related osteonecrosis of the jaw-like lesions in rodents: a comprehensive systematic review and meta-analysis. *Gerodontology*. 2019;36(4):313-324. https://doi.org/10.1111/ger.12416
38. Surboyo MDC, El Fadhlallah PM, Sato-Yamada Y, et al. The effects of zoledronate administration routes on the reproducibility of BRONJ in rodent models: a systematic review. *Bone*. 2025;199(10):117563. https://doi.org/10.1016/j.bone.2025.117563
39. Holtmann H, Lommen J, Kubler NR, et al. Pathogenesis of medication-related osteonecrosis of the jaw: a comparative study of in vivo and in vitro trials. *J Int Med Res*. 2018;46(10, 10):4277-4296. https://doi.org/10.1177/0300060518788987
40. Rao NJ, Yu RQ, Wang JY, Helm A, Zheng LW. Effect of periapical diseases in development of MRONJ in immunocompromised mouse model. *Biomed Res Int*. 2019;2019(9):1-10. https://doi.org/10.1155/2019/1271492
41. Kim T, Kim S, Song M, et al. Removal of pre-existing periodontal inflammatory condition before tooth extraction ameliorates medication-related osteonecrosis of the jaw-like lesion in mice. *Am J Pathol*. 2018;188(10, 10):2318-2327. https://doi.org/10.1016/j.ajpath.2018.06.019
42. Otto S, Pautke C, Martin Jurado O, et al. Further development of the MRONJ minipig large animal model. *J Craniomaxillofac Surg*. 2017;45(9):1503-1514. https://doi.org/10.1016/j.jcms.2017.07.002
43. Curra C, Cardoso CL, Ferreira OJ, et al. Medication-related osteonecrosis of the jaw. Introduction of a new modified experimental model. *Acta Cir Bras*. 2016;31(5):308-313. https://doi.org/10.1590/S0102-865020160050000003
44. Kolpakova ME, Zubareva AA, Artamonova TD, et al. Experimental model of osteonecrosis of the jaw in rats treated with zoledronic acid. *Br J Oral Maxillofac Surg*. 2017;55(2):156-159. https://doi.org/10.1016/j.bjoms.2016.10.006
45. Hoefert S, Eufinger H. Relevance of a prolonged preoperative antibiotic regime in the treatment of bisphosphonate-related osteonecrosis of the jaw. *J Oral Maxillofac Surg*. 2011;69(2):362-380. https://doi.org/10.1016/j.joms.2010.06.200
46. Mawardi H, Giro G, Kajiya M, et al. A role of oral bacteria in bisphosphonate-induced osteonecrosis of the jaw. *J Dent Res*. 2011;90(11, 11):1339-1345. https://doi.org/10.1177/0022034511420430
47. Soundia A, Hadaya D, Esfandi N, et al. Zoledronate impairs socket healing after extraction of teeth with experimental periodontitis. *J Dent Res*. 2018;97(3):312-320. https://doi.org/10.1177/0022034517732770
48. Morita M, Iwasaki R, Sato Y, et al. Elevation of pro-inflammatory cytokine levels following anti-resorptive drug treatment is required for osteonecrosis development in infectious osteomyelitis. *Sci Rep*. 2017;7(4):46322. https://doi.org/10.1038/srep46322
49. Soundia A, Elzakra N, Hadaya D, et al. Macrophage polarization during MRONJ development in mice. *J Dent Res*. 2024;103(9):899-907. https://doi.org/10.1177/00220345241258990
50. Zhang Q, Atsuta I, Liu S, et al. IL-17-mediated M1/M2 macrophage alteration contributes to pathogenesis of bisphosphonate-related osteonecrosis of the jaws. *Clin Cancer Res*. 2013;19(12):3176-3188. https://doi.org/10.1158/1078-0432.CCR-13-0042
51. Ervolino E, Olivo MB, Toro LF, et al. Effectiveness of antimicrobial photodynamic therapy mediated by butyl toluidine blue in preventing medication-related osteonecrosis of the jaws in rats. *Photodiagn Photodyn Ther*. 2022;40(12):103172. https://doi.org/10.1016/j.pdpdt.2022.103172
52. Ozalp O, Goksu O, Toru HS, Altay MA, Sindel A. Comparing the effects of low-level laser therapy and gaseous ozone as a preventive measure on medication-related osteonecrosis of the jaws following tooth extraction: a rat model. *Eur J Med Res*. 2024;29(1):359. https://doi.org/10.1186/s40001-024-01907-3
53. Zheng Y, Dong X, Chen S, et al. Low-level laser therapy prevents medication-related osteonecrosis of the jaw-like lesions via IL-1RA-mediated primary gingival wound healing. *BMC Oral Health*. 2023;23(1):14. https://doi.org/10.1186/s12903-022-02678-1
54. Ayhan M, Gedik B, Kalelioglu EE, et al. Comparison of the effects of four laser wavelengths on medication-related osteonecrosis of the jaw (MRONJ) in a murine model: an in vivo photobiomodulation study. *Int J Med Sci*. 2024;21(15):2959-2973. https://doi.org/10.7150/ijms.93224
55. Pontes JCX, Figueiredo LS, Lima WJM, et al. Photodynamic therapy repairs medication-related osteonecrosis of the jaw by reducing NF-kB protein in rats. *J Appl Oral Sci*. 2024;32:e20230447. https://doi.org/10.1590/1678-7757-2023-0447
56. Liu J, Mattheos N, Deng C, et al. Management of medication-related osteonecrosis of jaw: comparison between icariin and teriparatide in a rat model. *J Periodontol*. 2021;92(1):149-158. https://doi.org/10.1002/JPER.19-0620
57. Zandi M, Dehghan A, Mohammadi-Mofrad A, Amini P, Vahdatinia F. Short-term perioperative teriparatide therapy for the prevention of medication-related osteonecrosis of the jaw: a randomized, controlled preclinical study in rats. *J Craniomaxillofac Surg*. 2017;45(2):275-280. https://doi.org/10.1016/j.jcms.2016.12.010
58. Castillo EJ, Jiron JM, Croft CS, et al. Intermittent parathyroid hormone enhances the healing of medication-related osteonecrosis of the jaw lesions in rice rats. *Front Med (Lausanne)*. 2023;10(6):1179350. https://doi.org/10.3389/fmed.2023.1179350
59. Dayisoylu EH, Senel FC, Ungor C, et al. The effects of adjunctive parathyroid hormone injection on bisphosphonate-related osteonecrosis of the jaws: an animal study. *Int J Oral Maxillofac Surg*. 2013;42(11, 11):1475-1480. https://doi.org/10.1016/j.ijom.2013.05.001
60. Ersan N, van Ruijven LJ, Bronckers AL, Olgac V, Ilguy D, Everts V. Teriparatide and the treatment of bisphosphonate-related osteonecrosis of the jaw: a rat model. *Dentomaxillofac Radiol*. 2014;43(1):20130144. https://doi.org/10.1259/dmfr.20130144
61. Erten, Taysi A, Cevher E, Sessevmez M, Olgac V, Mert Taysi N, Atalay B. The efficacy of sustained-release chitosan microspheres containing recombinant human parathyroid hormone on MRONJ. *Braz Oral Res*. 2019;33:e086. https://doi.org/10.1590/1807-3107bor-2019.vol33.0086
62. Etemadi SM, Teimoori F, Sehat M, Razavi SM, Tajmiri G. Local single-dose teriparatide administration for BRONJ

prevention: insights from a rat model study. *J Maxillofac Oral Surg*. 2024;23(6):1500-1507. https://doi.org/10.1007/s12663-024-02301-6
63. Jung J, Shim GJ, Kim M, et al. Effect and timing of parathyroid hormone analog administration for preventing medication-related osteonecrosis of the jaws in a murine model. *J Craniomaxillofac Surg*. 2021;49(8):719-725. https://doi.org/10.1016/j.jcms.2021.02.023
64. Keskinruzgar A, Bozdag Z, Aras MH, Demir T, Yolcu U, Cetiner S. Histopathological effects of teriparatide in medication-related osteonecrosis of the jaw: an animal study. *J Oral Maxillofac Surg*. 2016;74(1):68-78. https://doi.org/10.1016/j.joms.2015.07.005
65. Kuroshima S, Entezami P, McCauley LK, Yamashita J. Early effects of parathyroid hormone on bisphosphonate/steroid-associated compromised osseous wound healing. *Osteoporos Int*. 2014;25(3):1141-1150. https://doi.org/10.1007/s00198-013-2570-8
66. Park JY, Heo HA, Park S, Pyo SW. Enhancement of peri-implant bone formation via parathyroid hormone administration in a rat model at risk for medication-related osteonecrosis of the jaw. *J Periodontal Implant Sci*. 2020;50(2):121-131. https://doi.org/10.5051/jpis.2020.50.2.121
67. Park KM, Lee N, Kim J, Kim HS, Park W. Preventive effect of teriparatide on medication-related osteonecrosis of the jaw in rats. *Sci Rep*. 2023;13(1):15518. https://doi.org/10.1038/s41598-023-42607-y
68. Zandi M, Dehghan A, Zandipoor N, Amini P, Doulati S. Effect of different doses and durations of teriparatide therapy on resolution of medication-related osteonecrosis of the jaw: a randomized, controlled preclinical study in rats. *J Craniomaxillofac Surg*. 2018;46(3):466-472. https://doi.org/10.1016/j.jcms.2017.12.027
69. de Sousa VC, Sousa FRN, Vasconcelos RF, et al. Atorvastatin reduces zoledronic acid-induced osteonecrosis of the jaws of rats. *Bone*. 2022;164(11):116523. https://doi.org/10.1016/j.bone.2022.116523
70. Hadad H, de Jesus LK, Pereira-Silva M, et al. The role of a local application of 10% doxycycline gel in the prevention of medication-related osteonecrosis of the jaw in rats. *Clin Oral Investig*. 2025;29(4):205. https://doi.org/10.1007/s00784-025-06279-4
71. Soundia A, Hadaya D, Chau Y, et al. Local RANKL delivery improves socket healing in bisphosphonate treated rats. *Bone*. 2021;148(7):115945. https://doi.org/10.1016/j.bone.2021.115945
72. Gkouveris I, Hadaya D, Elzakra N, et al. Inhibition of HMGB1/RAGE signaling reduces the incidence of medication-related osteonecrosis of the jaw (MRONJ) in mice. *J Bone Miner Res*. 2022;37(9):1775-1786. https://doi.org/10.1002/jbmr.4637
73. Kaibuchi N, Iwata T, Yamato M, Okano T, Ando T. Multipotent mesenchymal stromal cell sheet therapy for bisphosphonate-related osteonecrosis of the jaw in a rat model. *Acta Biomater*. 2016;42(7):400-410. https://doi.org/10.1016/j.actbio.2016.06.022
74. Watanabe J, Sakai K, Urata Y, Toyama N, Nakamichi E, Hibi H. Extracellular vesicles of stem cells to prevent BRONJ. *J Dent Res*. 2020;99(5):552-560. https://doi.org/10.1177/0022034520906793
75. Yang G, Kim YN, Kim H, Lee BK. Effect of human umbilical cord matrix-derived mesenchymal stem cells on bisphosphonate-related osteonecrosis of the jaw. *Tissue Eng Regen Med*. 2021;18(6):975-988. https://doi.org/10.1007/s13770-021-00372-x
76. Brierly GI, Ren J, Baldwin J, et al. Investigation of sustained BMP delivery in the prevention of medication-related osteonecrosis of the jaw (MRONJ) in a rat model. *Macromol Biosci*. 2019;19(11,11):e1900226. https://doi.org/10.1002/mabi.201900226
77. Funayama N, Yagyuu T, Imada M, Ueyama Y, Nakagawa Y, Kirita T. Impact of beta-tricalcium phosphate on preventing tooth extraction-triggered bisphosphonate-related osteonecrosis of the jaw in rats. *Sci Rep*. 2023;13(1):16032. https://doi.org/10.1038/s41598-023-43315-3
78. Su Z, Li J, Bai X, et al. Borate bioactive glass prevents zoledronate-induced osteonecrosis of the jaw by restoring osteogenesis and angiogenesis. *Oral Dis*. 2020;26(8):1706-1717. https://doi.org/10.1111/odi.13436
79. Mikai A, Ono M, Tosa I, et al. BMP-2/beta-TCP local delivery for bone regeneration in MRONJ-like mouse model. *Int J Mol Sci*. 2020;21(19):7028. https://doi.org/10.3390/ijms21197028
80. Tanaka Y, Aung KT, Ono M, et al. Suppression of bone necrosis around tooth extraction socket in a MRONJ-like mouse model by E-rhBMP-2 containing artificial bone graft administration. *Int J Mol Sci*. 2021;22(23):12823. https://doi.org/10.3390/ijms222312823
81. Pereira-Silva M, Hadad H, de Jesus LK, et al. Ozone therapy effect in medication-related osteonecrosis of the jaw as prevention or treatment: microtomographic, confocal laser microscopy and histomorphometric analysis. *Clin Oral Investig*. 2024;28(2):151. https://doi.org/10.1007/s00784-024-05547-z
82. Barba-Recreo P, Pardo DC, de Vera JL, Georgiev-Hristov T, et al. Adipose-derived stem cells and platelet-rich plasma for preventive treatment of bisphosphonate-related osteonecrosis of the jaw in a murine model. *J Craniomaxillofac Surg*. 2015;43(7):1161-1168. https://doi.org/10.1016/j.jcms.2015.04.026
83. Hadad H, Kawamata de Jesus L, Piquera Santos AF, et al. Beta tricalcium phosphate, either alone or in combination with antimicrobial photodynamic therapy or doxycycline, prevents medication-related osteonecrosis of the jaw. *Sci Rep*. 2022;12(1):16510. https://doi.org/10.1038/s41598-022-20128-4
84. Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. *J Photochem Photobiol B*. 1999;49(1):1-17. https://doi.org/10.1016/S1011-1344(98)00219-X
85. Passarella S, Karu T. Absorption of monochromatic and narrow band radiation in the visible and near IR by both mitochondrial and non-mitochondrial photoacceptors results in photobiomodulation. *J Photochem Photobiol B*. 2014;140(11):344-358. https://doi.org/10.1016/j.jphotobiol.2014.07.021
86. Poyton RO, Ball KA. Therapeutic photobiomodulation: nitric oxide and a novel function of mitochondrial cytochrome c oxidase. *Discov Med*. 2011;11(57):154-159
87. Statkievicz C, Toro LF, de Mello-Neto JM, et al. Photomodulation multiple sessions as a promising preventive therapy for medication-related osteonecrosis of the jaws after tooth extraction in rats. *J Photochem Photobiol B*. 2018;184(7):7-17. https://doi.org/10.1016/j.jphotobiol.2018.05.004
88. Weber JBB, Camilotti RS, Jasper J, Casagrande LCO, Maito F. Effect of low-level laser therapy on tissue repair after dental extraction in rats administered zoledronic acid and dexamethasone. *J Biomed Opt*. 2017;22(5):058001. https://doi.org/10.1117/1.JBO.22.5.058001
89. Silva PGB, Praxedes Neto R, Lima LA, et al. Photodynamic therapy and photobiomodulation therapy in zoledronic acid-induced osteonecrosis in rats. *Photodiagn Photodyn Ther*. 2022;38(6):102889. https://doi.org/10.1016/j.pdpdt.2022.102889
90. Sarkarat F, Modarresi A, Chiniforush N, Yazdanparast L, Rakhshan V. Efficacy of photodynamic therapy in minimizing bisphosphonate-related osteonecrosis of the jaws after dental extraction: a preliminary animal study. *J Oral Maxillofac Surg*. 2019;77(2):307-314. https://doi.org/10.1016/j.joms.2018.09.036
91. Ervolino E, Statkievicz C, Toro LF, et al. Antimicrobial photodynamic therapy improves the alveolar repair process and prevents the occurrence of osteonecrosis of the jaws after tooth extraction in senile rats treated with zoledronate. *Bone*. 2019;120(3):101-113. https://doi.org/10.1016/j.bone.2018.10.014

92. Mergoni G, Vescovi P, Sala R, et al. The effect of laser therapy on the expression of osteocalcin and osteopontin after tooth extraction in rats treated with zoledronate and dexamethasone. *Support Care Cancer*. 2016;24(2):807-813. https://doi.org/10.1007/s00520-015-2847-x
93. Jilka RL. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. *Bone*. 2007;40(6):1434-1446. https://doi.org/10.1016/j.bone.2007.03.017
94. Dempster DW, Cosman F, Kurland ES, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res*. 2001;16(10, 10):1846-1853. https://doi.org/10.1359/jbmr.2001.16.10.1846
95. Dong X, He L, Zang X, et al. Adipose-derived stem cells promote bone coupling in bisphosphonate-related osteonecrosis of the jaw by TGF-beta1. *Front Cell Dev Biol*. 2021;9(5):639590. https://doi.org/10.3389/fcell.2021.639590
96. Wang J, Qi X, Zhou Y, et al. Stabilization of Bio-Oss((R)) particulates using photocurable hydrogel to enhance bone regeneration by regulating macrophage polarization. *Front Bioeng Biotechnol*. 2023;11(6):1183594. https://doi.org/10.3389/fbioe.2023.1183594
97. Paulo S, Laranjo M, Paula A, et al. Calcium phosphate ceramics can prevent bisphosphonate-related osteonecrosis of the jaw. *Materials (Basel)*. 2020;13(8):1955. https://doi.org/10.3390/ma13081955
98. Sacco R, Sartoretto SC, de Brito Resende RF, et al. The use of hydroxyapatite loaded with doxycycline (HADOX) in dentoalveolar surgery as a risk-reduction therapeutic protocol in subjects treated with different bisphosphonate dosages. *Medicina (Kaunas)*. 2022;59(1):46. https://doi.org/10.3390/medicina59010046
99. Guo J, Yao H, Chang L, et al. Magnesium nanocomposite hydrogel reverses the pathologies to enhance mandible regeneration. *Adv Mater*. 2025;37(2):e2312920. https://doi.org/10.1002/adma.202312920
100. Zhu WY, Guo J, Yang WF, et al. Biodegradable magnesium implant enhances angiogenesis and alleviates medication-related osteonecrosis of the jaw in rats. *J Orthop Translat*. 2022;33(3):153-161. https://doi.org/10.1016/j.jot.2022.03.004
101. de Almeida AD, Leite FG, Chaud MV, et al. Safety and efficacy of hydroxyapatite scaffold in the prevention of jaw osteonecrosis in vivo. *J Biomed Mater Res B Appl Biomater*. 2018;106(5):1799-1808. https://doi.org/10.1002/jbm.b.33995
102. Pellicano AA, Benites BM, Paschoa AFN, et al. Mitigating jaw osteonecrosis: bioactive glass and pericardial membrane combination in a rat model. *Front Oncol*. 2024;14(5):1348118. https://doi.org/10.3389/fonc.2024.1348118
103. Razmara F, Bayat M, Shirian S, et al. Application of a collagen scaffold saturated with platelet-rich plasma in prevention of bisphosphonate-related osteonecrosis of the jaw in the rat animal model. *Heliyon*. 2021;7(5):e06930. https://doi.org/10.1016/j.heliyon.2021.e06930
104. Gao SY, Lin RB, Huang SH, et al. PDGF-BB exhibited therapeutic effects on rat model of bisphosphonate-related osteonecrosis of the jaw by enhancing angiogenesis and osteogenesis. *Bone*. 2021;144(3):115117. https://doi.org/10.1016/j.bone.2019.115117
105. Imada M, Yagyuu T, Ueyama Y, et al. Prevention of tooth extraction-triggered bisphosphonate-related osteonecrosis of the jaws with basic fibroblast growth factor: an experimental study in rats. *PLoS One*. 2019;14(2):e0211928. https://doi.org/10.1371/journal.pone.0211928
106. Kurokawa S, Yagyuu T, Funayama N, Imada M, Kirita T. Prevention of bisphosphonate-related osteonecrosis of the jaw with basic fibroblast growth factor: an experimental study in rats. *Odontology*. 2025;113(2):1427-1435. https://doi.org/10.1007/s10266-025-01073-w
107. Cao Z, Zhao C, Hu L, et al. Biomaterial-based lymphangiogenesis-enhanced therapeutic strategy for robustly-integrated medication-related osteonecrosis of jaw prevention. *ACS Appl Mater Interfaces*. 2025;17(25):36315-36333. https://doi.org/10.1021/acsami.5c02812
108. Kaibuchi N, Iwata T, Koga YK, Okamoto T. Novel cell therapy using mesenchymal stromal cell sheets for medication-related osteonecrosis of the jaw. *Front Bioeng Biotechnol*. 2022;10(5):902349. https://doi.org/10.3389/fbioe.2022.902349
109. Ogata K, Katagiri W, Osugi M, et al. Evaluation of the therapeutic effects of conditioned media from mesenchymal stem cells in a rat bisphosphonate-related osteonecrosis of the jaw-like model. *Bone*. 2015;74(5):95-105. https://doi.org/10.1016/j.bone.2015.01.011
110. Ogata K, Matsumura M, Moriyama M, Katagiri W, Hibi H, Nakamura S. Cytokine mixtures mimicking secretomes from mesenchymal stem cells improve medication-related osteonecrosis of the jaw in a rat model. *JBMR Plus*. 2018;2(2):69-80. https://doi.org/10.1002/jbm4.10013
111. Zheng Y, Dong X, Wang X, et al. Exosomes derived from adipose tissue-derived mesenchymal stromal cells prevent medication-related osteonecrosis of the jaw through IL-1RA. *Int J Mol Sci*. 2023;24(10):8694. https://doi.org/10.3390/ijms24108694
112. Zheng Y, Wang X, He Y, Chen S, He L, Zhang Y. Exosomes from adipose-derived mesenchymal stromal cells prevent medication-related osteonecrosis of the jaw by inhibiting macrophage M1 polarization and pyroptosis. *Int J Nanomedicine*. 2024;19(11):12675-12693. https://doi.org/10.2147/IJN.S482849
113. Dong X, Chen S, He Y, Zhang Y. Prevention of medication-related osteonecrosis of the jaw in mice by adipose-derived stem cells associated with activated autophagic flux. *J Dent Sci*. 2024;19(4):2106-2113. https://doi.org/10.1016/j.jds.2024.05.003
114. Tamari T, Elimelech R, Cohen G, et al. Endothelial progenitor cells inhibit jaw osteonecrosis in a rat model: a major adverse effect of bisphosphonate therapy. *Sci Rep*. 2019;9(1):18896. https://doi.org/10.1038/s41598-019-55383-5
115. Kuroshima S, Nakajima K, Sasaki M, et al. Systemic administration of quality- and quantity-controlled PBMNCs reduces bisphosphonate-related osteonecrosis of jaw-like lesions in mice. *Stem Cell Res Ther*. 2019;10(1):209. https://doi.org/10.1186/s13287-019-1308-8
116. Kaminogo K, Yamaguchi S, Chen H, et al. Preventive effects of dental pulp stem cell-conditioned media on anti-RANKL antibody-related osteonecrosis of the jaw. *Calcif Tissue Int*. 2024;115(2):185-195. https://doi.org/10.1007/s00223-024-01232-1
117. Huang J, Wang L, Tian W. Small extracellular vesicles derived from adipose tissue prevent bisphosphonate-related osteonecrosis of the jaw by promoting angiogenesis. *Int J Nanomedicine*. 2021;16(5):3161-3172. https://doi.org/10.2147/IJN.S305361
118. Alonso-Rodriguez E, Gonzalez-Martin-Moro J, Cebrian-Carretero JL, et al. Bisphosphonate-related osteonecrosis. Application of adipose-derived stem cells in an experimental murine model. *Med Oral Patol Oral Cir Bucal*. 2019;24(4):e529-e536. https://doi.org/10.4317/medoral.22959
119. Delanora LA, de Lima Neto TJ, da Rocha TE, et al. Systemic ozone therapy improves oral hard and soft tissue healing in medication-related osteonecrosis of the jaw (MRONJ): a study in senescent female rats. *Biomedicines*. 2025;13(5):1248. https://doi.org/10.3390/biomedicines13051248
120. Silva MC, Delamura IF, de Sa Simon ME, et al. Is there an ideal concentration of ozonized oil for the prevention and modulation of zoledronate-induced mandibular osteonecrosis? A study on senescent rats. *J Funct Biomater*. 2024;15(12):353. https://doi.org/10.3390/jfb15120353
121. Monteiro CGJ, Vieira EM, Emerick C, et al. Ozonated oil effect for prevention of medication-related osteonecrosis of the jaw (MRONJ) in rats undergoing zoledronic acid therapy. *Clin Oral Investig*. 2021;25(12, 12):6653-6659. https://doi.org/10.1007/s00784-021-03951-3

122. Liu SS, Lin TY, Fu E, et al. Immediate hyperbaric oxygen after tooth extraction ameliorates bisphosphonate-related osteonecrotic lesion in rats. *J Periodontol*. 2019;90(12, 12):1449-1456. https://doi.org/10.1002/JPER.18-0761
123. Topan C, Bilge S, Demirbas AE, Agyuz G, Kara A. Royal jelly as a therapeutic intervention in medication-related osteonecrosis of the jaw (MRONJ): an animal model study. *J Oral Pathol Med*. 2025;54(4):232-240. https://doi.org/10.1111/jop.13627
124. de Almeida JM, Turini HD, Matheus HR, et al. Omega-3 attenuates the severity of medication-related osteonecrosis of the jaws in rats treated with zoledronate. *PLoS One*. 2025;20(3):e0320413. https://doi.org/10.1371/journal.pone.0320413
125. Vitale M, Correa MG, Ervolino E, et al. Resveratrol for preventing medication-related osteonecrosis of the jaws in rats. *Oral Dis*. 2024;30(3):1462-1474. https://doi.org/10.1111/odi.14544
126. Movahedian Attar B, Razavi SM, Daneshmand M, Davoudi A. Protective effects of resveratrol against osteonecrosis at the extraction site in bisphosphonate-treated rats. *Int J Oral Maxillofac Surg*. 2020;49(11, 11):1518-1522. https://doi.org/10.1016/j.ijom.2020.02.019
127. Yadegari A, Aminzadeh A, Seyyedkhamesi S, Aminian M. The effect of melatonin on prevention of bisphosphonate-related osteonecrosis of the jaw: an animal study in rats. *J Korean Assoc Oral Maxillofac Surg*. 2020;46(4):266-274. https://doi.org/10.5125/jkaoms.2020.46.4.266
128. Liu J, Mattheos N, Su C, et al. The effects of icariin on wound healing of extraction sites with administration of zoledronic and dexamethasone: a rat model study. *J Oral Pathol Med*. 2018;47(2):198-205. https://doi.org/10.1111/jop.12659
129. Jin Y, Song J, Diao Z, Han X, Fan Z. Betaine alleviates bisphosphonate-related osteonecrosis of the jaw by rescuing BMSCs function in an m6A-METTL3-dependent manner. *Int J Mol Sci*. 2025;26(11):5233. https://doi.org/10.3390/ijms26115233
130. Du Q, Wang Q, Wang Y, Zhao C, Pan J. Beta-adrenergic receptor antagonist propranolol prevents bisphosphonate-related osteonecrosis of the jaw by promoting osteogenesis. *J Dent Sci*. 2025;20(1):539-552. https://doi.org/10.1016/j.jds.2024.04.016
131. Lemos JVM, Martins JOL, Machado LC, et al. Digoxin attenuates bisphosphonate related osteonecrosis of the jaws by RORgammat-dependent Th17 response in male rats. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2024;138(6):781-793. https://doi.org/10.1016/j.oooo.2024.08.013
132. Zhao D, Cui W, Liu M, et al. Tetrahedral framework nucleic acid promotes the treatment of bisphosphonate-related osteonecrosis of the jaws by promoting angiogenesis and M2 polarization. *ACS Appl Mater Interfaces*. 2020;12(40):44508-44522. https://doi.org/10.1021/acsami.0c13839
133. Tamaki S, Kuroshima S, Hayano H, et al. Dynamic polarization shifting from M1 to M2 macrophages in reduced osteonecrosis of the jaw-like lesions by cessation of anti-RANKL antibody in mice. *Bone*. 2020;141(12):115560. https://doi.org/10.1016/j.bone.2020.115560
134. Zhu WY, Yang WF, Wang L, et al. The effect of drug holiday on preventing medication-related osteonecrosis of the jaw in osteoporotic rat model. *J Orthop Translat*. 2023;39(3):55-62. https://doi.org/10.1016/j.jot.2022.12.006
135. Hadaya D, Soundia A, Gkouveris I, et al. Antiresorptive-type and discontinuation-timing affect ONJ burden. *J Dent Res*. 2021;100(7):746-753. https://doi.org/10.1177/0022034520986804
136. Yalcin-Ulker GM, Gunbatan M, Duygu G, Soluk-Tekkesin M, Ozcakir-Tomruk C. Could local application of hypoxia inducible factor 1-alpha enhancer deferoxamine be promising for preventing of medication-related osteonecrosis of the jaw? *Biomedicines*. 2023;11(3):758. https://doi.org/10.3390/biomedicines11030758
137. Duygu G, Yalcin-Ulker GM, Gunbatan M, Soluk-Tekkesin M, Ozcakir-Tomruk C. Evaluation of preventive role of systemically applied erythropoietin after tooth extraction in a bisphosphonate-induced MRONJ model. *Medicina (Kaunas)*. 2023;59(6):1059. https://doi.org/10.3390/medicina59061059
138. Mroczek T, Delfrate G, Mecca LEA, et al. Sildenafil reduces bisphosphonate-induced jaw osteonecrosis in rats. *Clin Oral Investig*. 2023;27(5):2437-2448. https://doi.org/10.1007/s00784-023-04890-x
139. Adachi N, Ayukawa Y, Yasunami N, et al. Preventive effect of fluvastatin on the development of medication-related osteonecrosis of the jaw. *Sci Rep*. 2020;10(1):5620. https://doi.org/10.1038/s41598-020-61724-6
140. Sanda K, Ayukawa Y, Yasunami N, et al. Therapeutic effect of fluvastatin on medication-related osteonecrosis of the jaw. *J Periodontol*. 2022;93(6):837-846. https://doi.org/10.1002/JPER.21-0294
141. Costa de Sousa V, Nunes Sousa FR, Felipe Vasconcelos R, et al. Polysacharide of *Agaricus blazei* gel mitigates bone necrosis in model of the jaws related to bisphosphonate via Wnt signaling. *Sci Rep*. 2024;14(1):8215. https://doi.org/10.1038/s41598-024-58445-5
142. Cantoran-Castillo A, Beltran-Salinas B, Antunez-Trevino JM, et al. Preventing bisphosphonate induced osteonecrosis of the jaw with a polyguanidine conjugate (GuaDex): a promising new approach. *Bone*. 2024;187(10):117211. https://doi.org/10.1016/j.bone.2024.117211
143. Elsayed R, Abraham P, Awad ME, et al. Removal of matrix-bound zoledronate prevents post-extraction osteonecrosis of the jaw by rescuing osteoclast function. *Bone*. 2018;110(5):141-149. https://doi.org/10.1016/j.bone.2018.01.030
144. Hokugo A, Kanayama K, Sun S, et al. Rescue bisphosphonate treatment of alveolar bone improves extraction socket healing and reduces osteonecrosis in zoledronate-treated mice. *Bone*. 2019;123(6):115-128. https://doi.org/10.1016/j.bone.2019.03.027
145. Hidaka K, Mikuni-Takagaki Y, Wada-Takahashi S, et al. Low-intensity pulsed ultrasound prevents development of bisphosphonate-related osteonecrosis of the jaw-like pathophysiology in a rat model. *Ultrasound Med Biol*. 2019;45(7):1721-1732. https://doi.org/10.1016/j.ultrasmedbio.2019.02.015
146. Castillo EJ, Messer JG, Abraham AM, et al. Preventing or controlling periodontitis reduces the occurrence of osteonecrosis of the jaw (ONJ) in rice rats (*Oryzomys palustris*). *Bone*. 2021;145(4):115866. https://doi.org/10.1016/j.bone.2021.115866
147. Gol EB, Ozkan N, Bereket C, Onger ME. Extracorporeal shock-wave therapy or low-level laser therapy: which is more effective in bone healing in bisphosphonate treatment? *J Craniofac Surg*. 2020;31(7):2043-2048. https://doi.org/10.1097/SCS.0000000000006506
148. Nishimaki K, Kaibuchi N, Washio K, Yamato M. Application of mesenchymal stromal cell sheets to prevent medication-related osteonecrosis of the jaw with titanium implants in rats. *Odontology*. 2024;112(3):938-949. https://doi.org/10.1007/s10266-024-00900-w
149. Etemadi SM, Shooshtarian F, Tajmiri G, Sehat M. Histopathological assessment of the preventive effect of leukocyte-platelet-rich fibrin on bisphosphonate-related osteonecrosis of the jaw following dental extraction: an animal study. *Heliyon*. 2023;9(7):e17792. https://doi.org/10.1016/j.heliyon.2023.e17792
150. Sadat-Ali M, AlMasoud NA, Hegazi TM, et al. Treatment of bisphosphonate induced osteonecrosis of jaw in rats using an angiogenesis factor (A-heal) and ABMDO (autologous bone marrow derived osteoblasts). *Saudi Dent J*. 2022;34(2):100-106. https://doi.org/10.1016/j.sdentj.2021.12.006
151. Sarkarat F, Modarresi A, Riyahi A, Mortazavi P, Tabandeh F, Rakhshan V. Efficacy of hyaluronic acid, absorbable collagen sponge, and their combination in minimizing bisphosphonate-related osteonecrosis of the jaws (BRONJ) after dental

extraction: a preliminary animal histomorphometric study. *Maxillofac Plast Reconstr Surg*. 2022;44(1):8. https://doi.org/10.1186/s40902-022-00337-7
152. Jamalpour MR, Shahabi S, Baghestani M, Shokri A, Jamshidi S, Khazaei S. Complementarity of surgical therapy, photobiomodulation, A-PRF and L-PRF for management of medication-related osteonecrosis of the jaw (MRONJ): an animal study. *BMC Oral Health*. 2022;22(1):241. https://doi.org/10.1186/s12903-022-02275-2
153. Sharma D, Hamlet S, Vaquette C, Petcu EB, Ramamurthy P, Ivanovski S. Local delivery of hydrogel encapsulated vascular endothelial growth factor for the prevention of medication-related osteonecrosis of the jaw. *Sci Rep*. 2021;11(1):23371. https://doi.org/10.1038/s41598-021-02637-w
154. Kushiro H, Takahashi H, Tanaka A. Effects of the prevention of medication-related osteonecrosis of the jaw by local administration of a dental pulp stem cell-conditioned medium to the rat tooth extraction socket. *Odontology*. 2021;109(4):836-844. https://doi.org/10.1007/s10266-021-00607-2
155. Rodriguez-Lozano FJ, Onate-Sanchez R, Gonzalvez-Garcia M, et al. Allogeneic bone marrow mesenchymal stem cell transplantation in tooth extractions sites ameliorates the incidence of osteonecrotic jaw-like lesions in zoledronic acid-treated rats. *J Clin Med*. 2020;9(6):1649. https://doi.org/10.3390/jcm9061649
156. Doppelt O, Cohen G, Tamari T, Elimelech R, Sabbah N, Zigdon-Giladi H. Endothelial progenitors increase vascularization and improve fibroblasts function that prevent medication-related osteonecrosis of the jaw. *Oral Dis*. 2020;26(7):1523-1531. https://doi.org/10.1111/odi.13412
157. Toro LF, de Mello-Neto JM, Santos F, et al. Application of autologous platelet-rich plasma on tooth extraction site prevents occurence of medication-related osteonecrosis of the jaws in rats. *Sci Rep*. 2019;9(1):22. https://doi.org/10.1038/s41598-018-37063-y
158. Cardoso CL, Curra C, Curi MM, et al. Treatment of bisphosphonate-related osteonecrosis using platelet-rich plasma: microtomographic, microscopic, and immunohistochemical analyses. *Braz Oral Res*. 2019;33:e050. https://doi.org/10.1590/1807-3107bor-2019.vol33.0050
159. Oh JS, Kim SG. Collagen sponge and rhBMP-2 improve socket healing in rats treated with zoledronic acid. *Braz Oral Res*. 2017;31(0):e99. https://doi.org/10.1590/1807-3107bor-2017.vol31.0099
160. Matsuura Y, Atsuta I, Ayukawa Y, et al. Therapeutic interactions between mesenchymal stem cells for healing medication-related osteonecrosis of the jaw. *Stem Cell Res Ther*. 2016;7(1):119. https://doi.org/10.1186/s13287-016-0367-3
161. Sarkarat F, Kalantar Motamedi MH, Jahanbani J, Sepehri D, Kahali R, Nematollahi Z. Platelet-rich plasma in treatment of zoledronic acid-induced bisphosphonate-related osteonecrosis of the jaws. *Trauma Mon*. 2014;19(2):e17196. https://doi.org/10.5812/traumamon.17196
162. Silva ML, Tasso L, Azambuja AA, et al. Effect of hyperbaric oxygen therapy on tooth extraction sites in rats subjected to bisphosphonate therapy-histomorphometric and immunohistochemical analysis. *Clin Oral Investig*. 2017;21(1):199-210. https://doi.org/10.1007/s00784-016-1778-3
163. Gurses G, Sur E, Cengiz ZO, Korez MK. Evaluation of methenolone enanthate efficacy in preventing MRONJ: a randomized trial on rats. *J Oral Pathol Med*. 2024;53(8):530-537. https://doi.org/10.1111/jop.13574
164. Inoue BKN, Paludetto LV, Monteiro NG, et al. Synergic action of systemic risedronate and local rutherpy in peri-implantar repair of ovariectomized rats: biomechanical and molecular analysis. *Int J Mol Sci*. 2023;24(22):16153. https://doi.org/10.3390/ijms242216153
165. Pan W, Gu J, Xu S, et al. Dietary nitrate improves jaw bone remodelling in zoledronate-treated mice. *Cell Prolif*. 2023;56(7):e13395. https://doi.org/10.1111/cpr.13395
166. Soma T, Iwasaki R, Sato Y, et al. Osteonecrosis development by tooth extraction in zoledronate treated mice is inhibited by active vitamin D analogues, anti-inflammatory agents or antibiotics. *Sci Rep*. 2022;12(1):19. https://doi.org/10.1038/s41598-021-03966-6
167. Delfrate G, Mroczek T, Mecca LEA, et al. Effect of pentoxifylline and alpha-tocopherol on medication-related osteonecrosis of the jaw in rats: before and after dental extraction. *Arch Oral Biol*. 2022;137(5):105397. https://doi.org/10.1016/j.archoralbio.2022.105397
168. Matsunaka K, Imai M, Sanda K, et al. Therapeutic effect of benidipine on medication-related osteonecrosis of the jaw. *Pharmaceuticals (Basel)*. 2022;15(8):1020. https://doi.org/10.3390/ph15081020
169. Nakagawa T, Tsuka S, Aonuma F, et al. Effects of metformin on the prevention of bisphosphonate-related osteonecrosis of the jaw-like lesions in rats. *J Prosthodont Res*. 2021;65(2):219-224. https://doi.org/10.2186/jpr.JPOR_2019_629
170. Koneski F, Popovic-Monevska D, Gjorgoski I, et al. In vivo effects of geranylgeraniol on the development of bisphosphonate-related osteonecrosis of the jaws. *J Craniomaxillofac Surg*. 2018;46(2):230-236. https://doi.org/10.1016/j.jcms.2017.11.007
171. Yalcin-Ulker GM, Cumbul A, Duygu-Capar G, Uslu U, Sencift K. Preventive effect of phosphodiesterase inhibitor pentoxifylline against medication-related osteonecrosis of the jaw: an animal study. *J Oral Maxillofac Surg*. 2017;75(11, 11):2354-2368. https://doi.org/10.1016/j.joms.2017.04.017
172. Oliveira CC, Barros Silva PG, Ferreira AEC Jr, et al. Effects of dexamethasone and nimesulide on bisphosphonate-related osteonecrosis of the jaw: an experimental study. *Arch Oral Biol*. 2017;83(11):317-326. https://doi.org/10.1016/j.archoralbio.2017.08.016
173. Mada EY, Santos AC, Fonseca AC, et al. Effects of green tea and bisphosphonate association on dental socket repair of rats. *Arch Oral Biol*. 2017;75(3):1-7. https://doi.org/10.1016/j.archoralbio.2016.12.001
174. Zhao Y, Wang L, Liu Y, et al. Technetium-99 conjugated with methylene diphosphonate ameliorates ovariectomy-induced osteoporotic phenotype without causing osteonecrosis in the jaw. *Calcif Tissue Int*. 2012;91(6):400-408. https://doi.org/10.1007/s00223-012-9649-7
175. Oizumi T, Funayama H, Yamaguchi K, et al. Inhibition of necrotic actions of nitrogen-containing bisphosphonates (NBPs) and their elimination from bone by etidronate (a non-NBP): a proposal for possible utilization of etidronate as a substitution drug for NBPs. *J Oral Maxillofac Surg*. 2010;68(5):1043-1054. https://doi.org/10.1016/j.joms.2009.08.027

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