

# Emerging therapeutic strategies for medication-related osteonecrosis of the jaw: From microenvironmental modulation to precision medicine (Review)

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**Abstract.** Medication-related osteonecrosis of the jaw (MRONJ) is a challenging complication associated primarily with antiresorptive and antiangiogenic therapies. Its pathogenesis involves a complex interplay of impaired bone remodeling, angiogenesis, inflammation and infection, immune regulation and soft tissue healing. Established management includes conservative care, antimicrobial and symptomatic treatment when indicated and surgical intervention, however clinical outcomes remain variable. The present review aimed to summarize pharmacological, regenerative, biomaterial-based and physical or adjunctive strategies targeting the pathological microenvironment of MRONJ, with emphasis on their mechanisms of action and clinical evidence. The present review also examines the potential role of precision medicine in individualized risk assessment and treatment. Teriparatide, pentoxifylline/tocopherol, autologous platelet concentrates and human amniotic membrane have varying degrees of clinical support, although evidence remains limited or heterogeneous for several approaches. By contrast, geranylgeraniol, hydrogels, most mesenchymal stromal cell-based or cell-derived

strategies, natural products and melatonin are supported predominantly by preclinical or limited clinical evidence. Other adjunctive approaches, including hyperbaric oxygen, ozone therapy, photobiomodulation, laser-assisted surgery and antimicrobial photodynamic therapy, require further validation. Overall, these strategies may complement established management, but their clinical readiness varies. Standardized clinical studies and integration of multidimensional patient data may facilitate more robust evaluation and individualized MRONJ management.

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## 1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a severe oral and maxillofacial complication associated with the use of antiresorptive and antiangiogenic agents (Fig. 1). According to the American Association of Oral and Maxillofacial Surgeons, the diagnosis of MRONJ requires all three of the following criteria: i) Current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications; ii) exposed bone or bone that can be probed through an intra-oral or extraoral fistula in the maxillofacial region that has persisted for >8 weeks; and iii) no history of radiation therapy or metastatic disease to the jaws (1). With the widespread use of bisphosphonates, denosumab and antiangiogenic agents in the management of conditions such as bone metastasis and osteoporosis, increasing clinical attention has been directed toward MRONJ (2,3). These medication classes act through different biological pathways: Bisphosphonates suppress

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osteoclast-mediated bone resorption, denosumab inhibits RANKL/RANK signaling and antiangiogenic agents interfere with vascular signaling (1,4). The clinical context of antiresorptive therapy differs between patients with malignant diseases and those with osteoporosis (5). Higher dose and/or more frequent regimens are typically used in patients with malignant diseases, whereas lower dose regimens are typically used for osteoporosis (5). Differences in the underlying disease, medication exposure and concomitant therapies may consequently influence the risk and clinical manifestation of MRONJ. The pathogenesis of MRONJ remains incompletely understood. Accumulating evidence indicates that its initiation and progression are associated with disruption of the local pathological microenvironment (1,4). This disruption involves interrelated processes, including suppressed bone remodeling, impaired vascular supply, dysregulated immune responses, microbial infection and inflammation and soft tissue toxicity (4).

Management of MRONJ is individualized according to disease stage, symptoms, lesion extent and the patient overall condition. Conservative management includes maintenance of oral hygiene, local antimicrobial care, pain control and systemic antibiotics when clinically indicated (1). Surgical treatment is an important component of MRONJ management and may range from debridement and sequestrectomy to more extensive resection, depending on the extent of the lesion (6). Treatment planning may require coordination between dental or oral and maxillofacial specialists and physicians responsible for the underlying disease and MRONJ-associated medication therapy. Nevertheless, surgical management presents challenges. Determining the appropriate resection margin for necrotic bone can be difficult, while extensive debridement may result in substantial soft tissue and osseous defects. Surgical morbidity may be greater in medically compromised patients or those with multiple comorbidities (7). Current pharmacological management is primarily directed toward infection control and symptom relief, whereas options that directly target the pathological processes underlying MRONJ remain limited (8).

The multifactorial nature of MRONJ has prompted increasing interest in therapeutic strategies targeting different components of its pathological microenvironment (9-11). Current research encompasses pharmacological therapy, regenerative approaches, biomaterial-based strategies and physical or adjunctive intervention, addressing key pathological processes underlying MRONJ, including dysregulated bone remodeling, vascular dysfunction, aberrant inflammatory and immune response, microbial involvement and defective tissue repair (9,11). These advances have expanded the therapeutic landscape of MRONJ, but differences remain among intervention strategies in terms of clinical indication, strength of evidence and translational maturity (10,11). Moreover, the relative contribution of these pathological processes may vary between patients, influenced by heterogeneity in underlying disease, medication exposure, individual susceptibility and clinical characteristics, further complicating therapeutic decision-making (3,5).

The present review examines therapeutic strategies for MRONJ within the framework of microenvironment

modulation, their biological rationale, supporting evidence, clinical applicability and current limitations. At the same time, interpatient heterogeneity in disease characteristics and therapeutic responses has fueled growing interest in more individualized approaches to MRONJ management (12-15). Integrating clinical, pharmacological, imaging, microbiological and molecular information may facilitate more precise risk stratification and tailored preventive and therapeutic strategies. The present review further considers the potential role of precision medicine in advancing individualized MRONJ management (Fig. 2).

## 2. Literature search strategy

A structured literature search was conducted. PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Web of Science Core Collection (<https://www.webofscience.com/wos/woscc/basic-search>) were searched for English-language articles published from January 2010 to March 2026. The final search was performed on March 31, 2026. The search strategy combined disease-related terms, including 'medication-related osteonecrosis of the jaw', 'MRONJ', 'bisphosphonate-related osteonecrosis of the jaw', 'BRONJ' and 'osteonecrosis of the jaw', with terms related to treatment and clinical management, including 'treatment', 'therapy', 'management', 'prevention', 'therapeutic strategy', 'surgery', 'adjunctive therapy', 'regenerative medicine', 'bone regeneration', 'tissue regeneration', 'drug therapy', 'cell therapy' and 'biomaterial'. Additional terms representing the major therapeutic approaches discussed in this review included 'teriparatide', 'pentoxyfylline', 'tocopherol', 'geranylgeraniol', 'platelet-rich plasma', 'platelet-rich fibrin', 'autologous platelet concentrate', 'mesenchymal stem cell', 'hydrogel', 'human amniotic membrane', 'hyperbaric oxygen therapy', 'ozone therapy', 'photobiomodulation', 'laser therapy', 'antimicrobial photodynamic therapy', 'precision medicine', 'risk prediction', 'machine learning', 'genetic susceptibility' and 'biomarker'. These terms were used individually or in combinations according to the topic being searched. The reference lists of relevant reviews and key primary studies were screened to identify additional eligible publications. Landmark studies published before 2010 were also included to provide historical context for the development of specific therapeutic approaches.

Publications relevant to the prevention, treatment or adjunctive management of MRONJ were considered. Eligible evidence included randomized and non-randomized clinical trials, prospective and retrospective observational studies, case series and reports, systematic reviews and meta-analyses, as well as preclinical *in vivo* and *in vitro* studies when clinical evidence was limited or mechanistic information was required. Studies focusing exclusively on osteoradionecrosis or osteonecrosis unrelated to medication exposure were excluded unless they provided mechanistic or therapeutic information directly relevant to MRONJ. Priority was given to primary studies, recent evidence and studies providing clinically or mechanistically relevant information. No formal meta-analysis or quantitative risk-of-bias assessment was performed. Preclinical, observational and interventional clinical evidence was interpreted according to the respective study design and

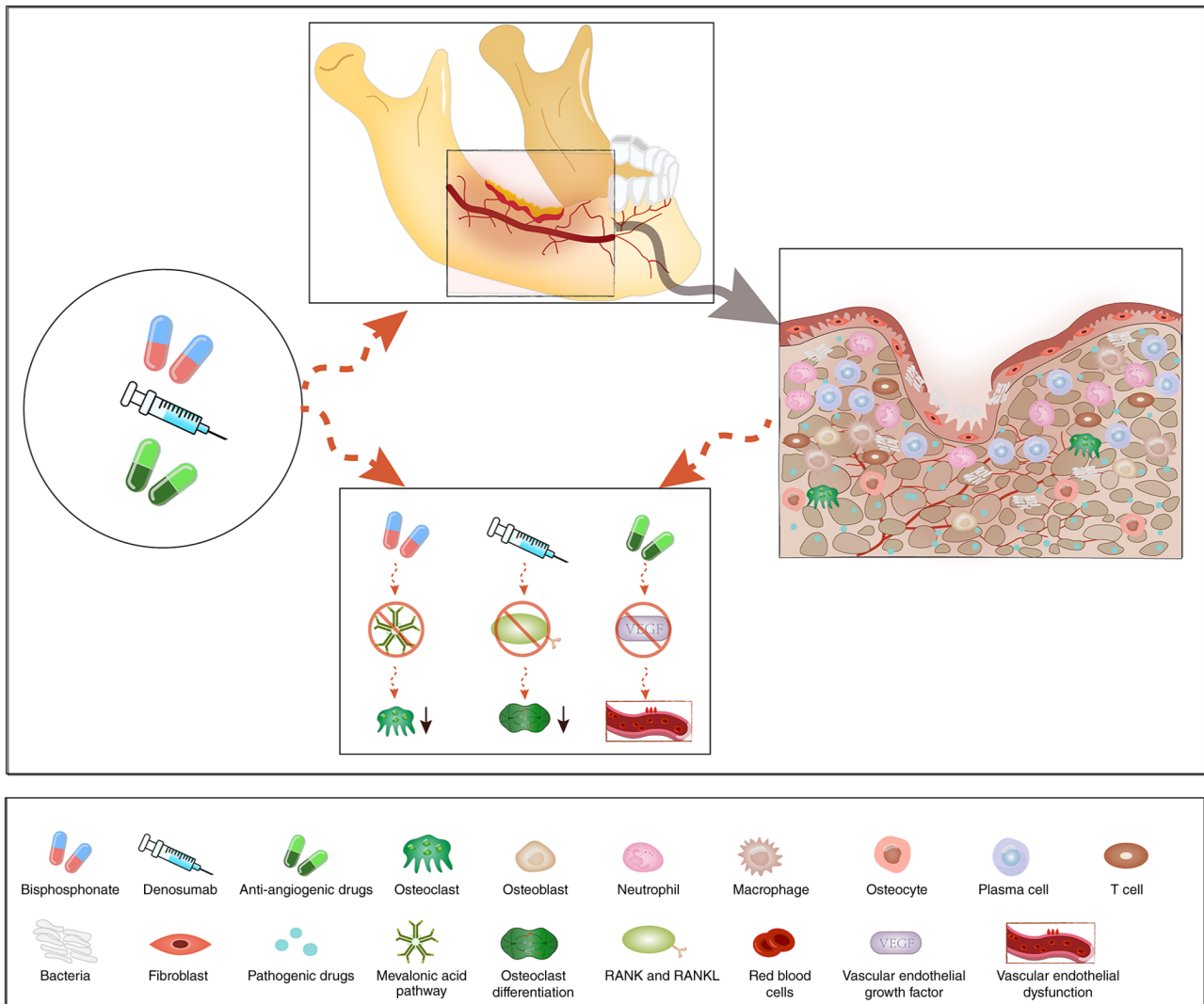


Figure 1. Overview of MRONJ. Medication classes associated with the development of MRONJ include bisphosphonates, denosumab and antiangiogenic agents. Diagnostic criteria for MRONJ include current or previous exposure to antiresorptive therapy, alone or in combination with immune-modulating or antiangiogenic agents; exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that persists for >8 weeks; and no history of radiation therapy to the jaw or obvious metastatic disease involving the jaw. Necrotic bone is characterized by non-viable osteocytes and empty lacunae, with reduced or absent osteoblastic and osteoclastic activity. The surrounding tissue may exhibit infiltration by inflammatory cells, including lymphocytes, plasma cells, neutrophils and macrophages, together with fibroblast proliferation, bacterial colonization and inflammatory or purulent exudate. Principal pathogenic mechanisms associated with bisphosphonates, denosumab and antiangiogenic agents include suppressed bone remodeling, impaired angiogenesis, infection and inflammation, and soft tissue toxicity. MRONJ, medication-related osteonecrosis of the jaw.

level of evidence to avoid equating findings derived from different evidence hierarchies.

### 3. Modulation of the MRONJ microenvironment

Therapeutic strategies for MRONJ target distinct but interconnected components of its pathological microenvironment (9-11). Systemic modulation of bone metabolism focuses on restoring bone remodeling balance, whereas regenerative strategies aim to promote angiogenesis and tissue repair (9,10) (Fig. 3). Bioactive materials provide platforms for local delivery and regenerative support, while physical and adjunctive therapy (Fig. 4) targets tissue oxygenation, microbial control and wound healing (9-11). These strategies are not mutually exclusive and may have complementary roles in staged or multimodal management (10) (Table I).

#### Systemic modulation of bone metabolism

*Teriparatide (TPTD)*. TPTD is a recombinant active fragment of human parathyroid hormone comprising amino acids 1-34 and is used in the treatment of osteoporosis (16). When administered intermittently, TPTD stimulates both osteoblast and osteoclast activity, thereby enhancing bone remodeling (17). In addition, TPTD upregulates the expression of growth factors such as vascular endothelial growth factor, which may contribute to a local microenvironment conducive to bone repair (18).

Harper and Fung (19) provided an early clinical report of intermittent low-dose parathyroid hormone therapy in bisphosphonate-associated osteonecrosis of the mandible, suggesting the potential of anabolic stimulation in jawbone healing. Subsequent evidence has included both preclinical and clinical studies (20-23). In a zoledronic acid-associated MRONJ model in rice rats, Castillo *et al* (20) demonstrated that intermittent

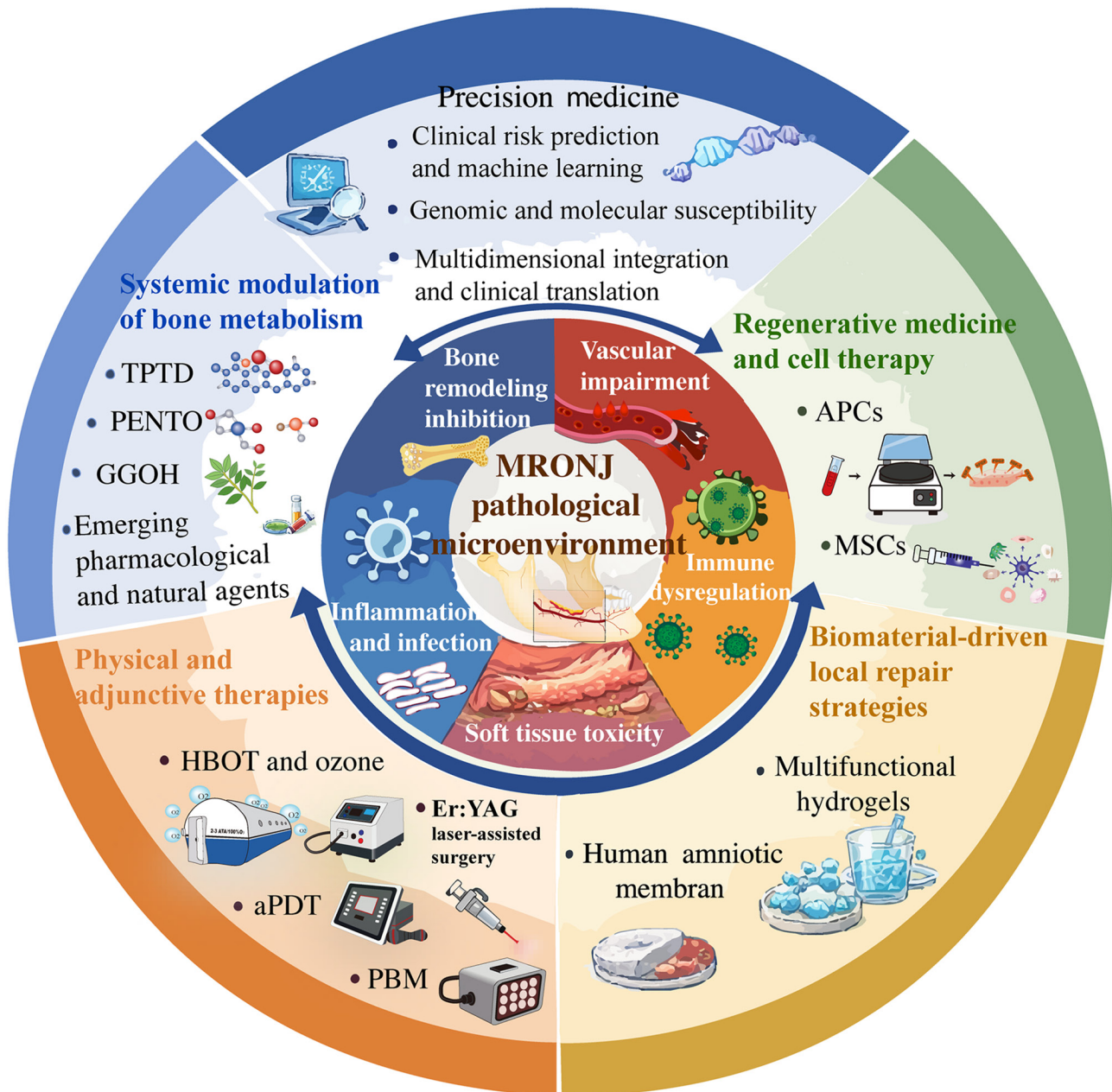


Figure 2. Pathological microenvironment and therapeutic strategies for MRONJ. The development of MRONJ is associated with a complex pathological microenvironment characterized by suppressed bone remodeling, impaired angiogenesis, infection and inflammation and soft tissue toxicity. Therapeutic strategies aim to modulate these pathological processes through multiple mechanisms. Precision medicine approaches may support individualized risk assessment, prevention and treatment. MRONJ, medication-related osteonecrosis of the jaw; APC, autologous platelet concentrate; MSC, mesenchymal stem cell; HBOT, hyperbaric oxygen therapy; Er:YAG, erbium-doped yttrium aluminum garnet; aPDT, antimicrobial photodynamic therapy; PBM, photobiomodulation; TPTD, teriparatide; PENTO, pentoxifylline and tocopherol; GGOH, geranylgeraniol.

parathyroid hormone treatment enhances lesion healing, providing preclinical support for its osteoregenerative effects. A systematic review and meta-analysis of 26 publications involving 111 MRONJ cases reported complete resolution in 59.5% of patients receiving TPTD monotherapy and suggested a higher likelihood of complete resolution when TPTD was combined with other types of therapy, including surgery, antibiotic therapy and laser therapy, although the evidence base consisted largely of case reports and small clinical series (21). Kim *et al* (22) described two cases in which adjunctive TPTD combined with surgical treatment resulted in complete clinical and radiographic resolution. Importantly, Sim *et al* (23)

conducted a randomized placebo-controlled trial of TPTD in patients with MRONJ and reported a significantly greater rate of lesion resolution with TPTD than with placebo. In the aforementioned trial, TPTD was administered at 20  $\mu\text{g}/\text{day}$  for 8 weeks, however, the optimal treatment duration for MRONJ remains to be established (23). Collectively, these findings support TPTD as a potential adjunctive treatment for selected patients, although patient selection, underlying disease, indication for antiresorptive therapy, treatment duration and relevant precautions warrant consideration.

TPTD may be associated with adverse effects, including nausea and transient alterations in calcium metabolism (18).

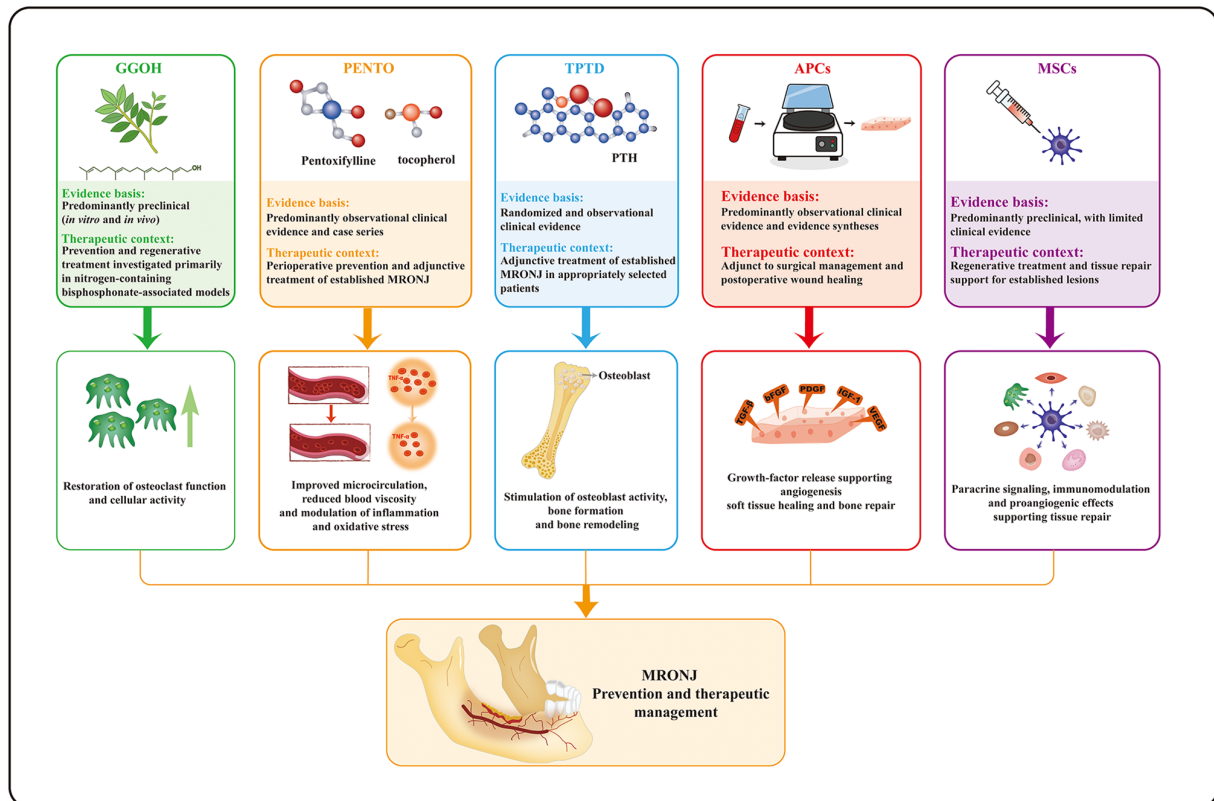


Figure 3. Pharmacological and regenerative strategies investigated for MRONJ, including GGOH, PENTO, TPTD, APCs and MSC-based therapy. GGOH, geranylgeraniol; PENTO, pentoxifylline and tocopherol; TPTD, teriparatide; APC, autologous platelet concentrate; MSC, mesenchymal stem cell; MRONJ, medication-related osteonecrosis of the jaw; bFGF, basic fibroblast growth factor; PDGF, platelet-derived growth factor; PTH, parathyroid hormone; IGF, insulin-like growth factor.

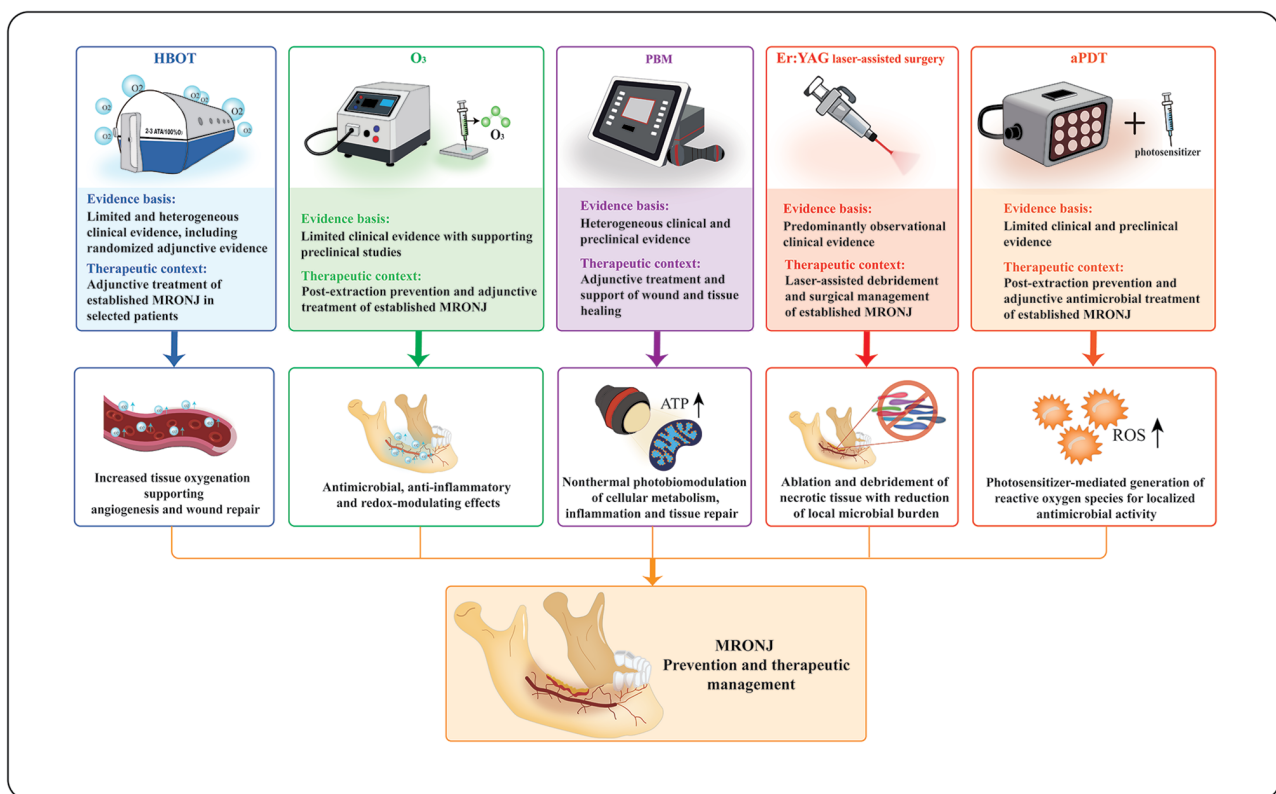


Figure 4. Physical and adjunctive therapeutic approaches for MRONJ, including HBOT, ozone therapy, PBM, Er:YAG laser-assisted surgery and aPDT. HBOT, hyperbaric oxygen therapy; PBM, photobiomodulation; Er:YAG, erbium-doped yttrium aluminum garnet; aPDT, antimicrobial photodynamic therapy; MRONJ, medication-related osteonecrosis of the jaw; ROS, reactive oxygen species.

Table I. Therapeutic strategies for MRONJ.

## A, Systemic modulation of bone metabolism

| Therapy                       | Primary mechanism                                                                                                          | Key findings                                                                                                                                                                              | Advantages and limitations                                                                                                                                                                                                                                                           | Evidence basis                                                                                                              | Intended use                                                                                                                                         | (Refs.) |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Teriparatide                  | Restores coupled bone remodeling and supports angiogenesis and bone repair through intermittent PTH signaling              | Clinical studies, including a placebo-controlled randomized trial, suggest improved lesion resolution and bone healing in selected patients                                               | Systemic anabolic effect with stronger clinical evidence; patient selection is key, MRONJ-specific optimal treatment duration remains uncertain, relevant contraindications and precautions must be considered                                                                       | Randomized clinical evidence, case reports, systematic review/meta-analysis, supporting preclinical <i>in vivo</i> evidence | Adjunctive treatment of established MRONJ in appropriately selected patients, particularly those with osteoporosis                                   | (16-23) |
| Pentoxifylline and tocopherol | Improves microcirculation and modulates inflammation, oxidative stress and fibrosis                                        | Prophylactic in patients undergoing tooth extraction. In a therapeutic study of 43 patients with MRONJ at different stages, 46% achieved complete remission                               | Non-invasive and generally well tolerated; protocols and treatment duration vary, therapeutic response may be slow and evidence for advanced disease remains limited. Evidence from osteoradionecrosis should not be directly extrapolated to MRONJ                                  | Observational clinical evidence and case series                                                                             | Prevention around dentoalveolar procedures in at-risk patients and non-surgical or adjunctive treatment of established MRONJ                         | (24-31) |
| GGOH                          | Restores protein prenylation disrupted by nitrogen-containing bisphosphonate-mediated inhibition of the mevalonate pathway | Preclinical studies using local delivery systems report restoration of osteoclast function, attenuation of bisphosphonate-associated cell injury and improved healing-associated response | Mechanistically targeted to nitrogen-containing bisphosphonates and suitable for local delivery; relevance to other medication classes remains uncertain. Potential interference with intended bisphosphonate effects and concentration-dependent cytotoxicity require consideration | Preclinical <i>in vitro</i> and <i>in vivo</i> ; primarily bisphosphonate-specific                                          | Local prevention and regenerative treatment of nitrogen-containing bisphosphonate-associated jaw osteonecrosis investigated at the preclinical level | (32-40) |

Table I. Continued.

A, Systemic modulation of bone metabolism

| Therapy                                                        | Primary mechanism                                                                                     | Key findings                                                                                                                                                                                                                  | Advantages and limitations                                                                                                                            | Evidence basis                                                                        | Intended use                                                                                                              | (Refs.)    |
|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|------------|
| Anabolic modulation (AASs)                                     | Promote anabolic bone response and may enhance osteogenic signaling and tissue repair                 | Methenolone enanthate decreases osteonecrotic changes in a bisphosphonate-associated rat model                                                                                                                                | Potential anabolic support for bone repair; evidence remains preclinical and adverse effects associated with prolonged AAS exposure limit translation | Preclinical <i>in vivo</i> evidence with supporting experimental mechanistic evidence | Prevention or attenuation of bisphosphonate-associated jaw osteonecrosis investigated at the preclinical level            | (41,48-50) |
| Antioxidant and bone-modulatory approaches (RSV and melatonin) | Modulate oxidative stress and inflammation and support bone homeostasis and remodeling                | RSV improves bone formation indices and attenuated osteonecrotic changes in bisphosphonate-associated models. Melatonin improves bone remodeling and decreases osteonecrotic changes in a zoledronic acid-induced BRONJ model | Target oxidative and inflammatory components of disease; efficacy and safety in patients with MRONJ remain unestablished                              | Preclinical <i>in vivo</i>                                                            | Prevention or attenuation of bisphosphonate-associated osteonecrotic changes investigated at the preclinical level        | (42-44,47) |
| Bioactive natural products (Tualang honey and RJ)              | Antimicrobial, anti-inflammatory and tissue-protective effects supporting soft and hard tissue repair | Tualang honey with hydroxyapatite attenuates pamidronate-associated fibroblast toxicity <i>in vitro</i> ; RJ improves soft and hard tissue healing in a bisphosphonate-associated rat model                                   | Potentially accessible bioactive agents, but active components, optimal dosing and clinical efficacy remain undefined                                 | Preclinical <i>in vitro</i> and <i>in vivo</i>                                        | Cytoprotection and regenerative support for bisphosphonate-associated tissue injury investigated at the preclinical level | (45,46)    |

B, Regenerative medicine and cell therapy

| Therapy | Primary mechanism                        | Key findings                 | Advantages and limitations        | Evidence basis               | Intended use                     | (Refs.)              |
|---------|------------------------------------------|------------------------------|-----------------------------------|------------------------------|----------------------------------|----------------------|
| PRP     | Provides platelet-derived growth factors | Case series report favorable | Autologous and readily integrated | Case series with broader APC | Adjunct to surgical treatment of | (51-54,62, 63,67-71) |

Table I. Continued.

## B, Regenerative medicine and cell therapy

| Therapy                                     | Primary mechanism                                                                                                                                    | Key findings                                                                                                                                                        | Advantages and limitations                                                                                                                                                | Evidence basis                                                                    | Intended use                                                                       | (Refs.)                     |
|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------|
|                                             | and cytokines that support angiogenesis, soft tissue repair and bone healing                                                                         | healing when PRP is combined with bone resection; systematic reviews have evaluated PRP/APCs as adjunctive strategies                                               | with surgery; notable heterogeneity in preparation, surgical protocol, patient population and outcome definitions limits comparison                                       | systematic review                                                                 | established MRONJ                                                                  |                             |
| PRF/L-PRF                                   | Provides a fibrin scaffold with platelets and leukocytes and supports sustained release of bioactive factors                                         | Prospective and retrospective studies report favorable healing when PRF/L-PRF is combined with surgery                                                              | Simple autologous preparation and fibrin scaffold; outcomes affected by centrifugation protocol, patient factors, surgical technique and disease characteristics          | Prospective and retrospective clinical evidence                                   | Adjunct to surgical treatment and postoperative wound healing in established MRONJ | (51,54-56, 62,64-71, 73-75) |
| CGF/i-PRF                                   | Concentrated platelets, fibrin and growth factors support angiogenesis and tissue regeneration; injectable preparations facilitate local delivery    | MRONJ-specific clinical evidence is limited primarily to CGF, including a case series with long-term follow-up; i-PRF is supported by broader regenerative evidence | Flexible local application but MRONJ-specific clinical evidence is limited and preparation protocols remain heterogeneous                                                 | Limited CGF clinical evidence with broader review/experimental evidence for i-PRF | Adjunctive regenerative support during surgical management of established MRONJ    | (57-61,72)                  |
| MSC-based cell therapy                      | Primarily acts through paracrine, immunomodulatory, proangiogenic and regenerative signaling rather than sustained direct osteogenic differentiation | Preclinical studies show improved angiogenesis, immune regulation and bone repair; limited clinical reports suggest potential benefit                               | Multimodal regenerative potential but cell sourcing, expansion, viability, delivery, manufacturing and regulatory requirements limit translation                          | Preclinical <i>in vivo</i> evidence with limited clinical evidence                | Regenerative treatment of established lesions and support of tissue repair         | (76-83,85)                  |
| MSC-derived extracellular vesicles/exosomes | Deliver paracrine bioactive cargo that modulates inflammation, angiogenesis and tissue repair without viable cell transplantation                    | Preclinical studies report improved vascularization, immune regulation and bone regeneration in medication-associated jaw osteonecrosis models                      | Cell-free approach may avoid limitations of viable cell transplantation; isolation, characterization, dosing, storage and manufacturing standardization remain unresolved | Preclinical <i>in vivo</i>                                                        | Prevention and regenerative repair investigated at the preclinical level           | (86-88)                     |

Table I. Continued.

C, Biomaterial-driven local repair strategies

| Therapy                                                 | Primary mechanism                                                                                                                         | Key findings                                                                                                                                                                                   | Advantages and limitations                                                                                                                                                   | Evidence basis                                                                                                                    | Intended use                                                                                                                     | (Refs.)        |
|---------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|----------------|
| Immunomodulatory, angiogenic and regenerative hydrogels | Modulate the local inflammatory/regenerative microenvironment and promote angiogenesis, osteogenesis and structural regeneration          | Improved mucosal and bone healing; magnesium-based hydrogel promotes mandibular regeneration following debridement, while VEGF delivery decreases osteonecrotic changes following extraction   | Integrates microenvironmental regulation with vascular and bone regeneration; evidence is predominantly preclinical and bisphosphonate-associated                            | Preclinical <i>in vivo</i> evidence from bisphosphonate-associated models                                                         | Prevention, treatment of experimental lesions and post-debridement regenerative reconstruction, depending on the hydrogel system | (89-92)        |
| Cell and bioactive-factor delivery hydrogels            | Local delivery of cells and osteogenic factors within a three-dimensional regenerative scaffold, with mechanical support where applicable | Improved soft tissue healing and bone reconstruction in experimentally established medication-associated jaw osteonecrosis lesions                                                             | Combines local cell/factor delivery with structural support; cell-containing systems complicate sterilization, storage, manufacturing, scalability and regulation            | Preclinical <i>in vivo</i>                                                                                                        | Regenerative treatment of experimentally established lesions                                                                     | (89,93, 94)    |
| Controlled release and preventive hydrogels             | Sustained local release of bioactive factors or therapeutic agents, with antimicrobial and cytoprotective functions                       | Hep/GelMA-PRF improve osteomucosal healing and decrease post-extraction osteonecrotic changes; clindamycin/GGOH show combined antimicrobial and cytoprotective effects <i>in vitro</i>         | Enables localized sustained delivery; oral retention, degradation, sterilization, manufacturing reproducibility and long-term biosafety require further evaluation           | Preclinical, including <i>in vivo</i> preventive and <i>in vitro</i> drug delivery studies; predominantly bisphosphonate-specific | Post-extraction prevention and localized preventive drug delivery investigated at the preclinical level                          | (89,92, 95,96) |
| Human amniotic membrane                                 | Provides a biological scaffold with anti-inflammatory, antifibrotic, proangiogenic and wound healing properties                           | Small clinical studies report favorable mucosal healing and surgical outcomes; systematic review/meta-analysis findings are encouraging but based on heterogeneous protocols and small studies | Biocompatible biological scaffold and potential surgical adjunct; processing, preservation, donor screening, storage, orientation, fixation and regulatory requirements vary | Small observational/comparative clinical studies, pilot studies, systematic review/meta-analysis                                  | Adjunct to surgical treatment for wound coverage and postoperative soft tissue healing                                           | (99-105)       |

Table I. Continued.

## D, Physical and adjunctive therapy

| Therapy                       | Primary mechanism                                                                                                               | Key findings                                                                                                                                                                                                                   | Advantages and limitations                                                                                                                                                          | Evidence basis                                                                                               | Intended use                                                                                                 | (Refs.)       |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|---------------|
| Hyperbaric oxygen therapy     | Increases tissue oxygenation and may support angiogenesis, infection control and wound repair                                   | Clinical studies, including randomized adjunctive evidence, suggest improvement in lesion status and pain-related outcomes, but a definitive complete-healing benefit has not been established                                 | Non-invasive adjunct, but requires specialized facilities and repeated sessions; treatment burden, contraindications, adverse effects and optimal patient selection remain concerns | Limited randomized clinical evidence, observational/ case-based evidence, systematic review                  | Adjunctive treatment of established MRONJ/ BRONJ in selected patients                                        | (106-113)     |
| Ozone therapy                 | Antimicrobial, anti-inflammatory and redox-modulating effects                                                                   | Local O <sub>2</sub> -O <sub>3</sub> infiltration has been investigated in established MRONJ, while randomized clinical evidence is available for post-extraction prevention; ozonized oil has supporting preclinical evidence | Multiple formulations and delivery routes differ in dosing and safety; protocol heterogeneity and limited MRONJ-specific evidence for certain routes restrict interpretation        | Randomized preventive clinical evidence, limited case series, supporting preclinical <i>in vivo</i> evidence | Post-extraction prevention and adjunctive treatment of established MRONJ, depending on the delivery approach | (114-118)     |
| PBM                           | Non-thermal photochemical modulation of cell metabolism, inflammation, angiogenesis and tissue repair                           | Heterogeneous clinical and preclinical studies report improved mucosal healing, pain control, and bone-associated outcomes, particularly when PBM is used with conventional treatment                                          | Non-invasive and repeatable; heterogeneity in wavelength, fluence, power, exposure duration and treatment schedules limits reproducibility and comparison                           | Preclinical and heterogeneous clinical evidence, including retrospective and prospective studies             | Adjunctive treatment of established MRONJ and support of postoperative wound healing                         | (119-123)     |
| Er:YAG laser-assisted surgery | Ablation and debridement of necrotic tissue through laser-tissue interaction, with potential decrease of local microbial burden | Clinical series report favorable outcomes when Er:YAG is incorporated into surgical or multimodal treatment, including patients with stage I-III disease                                                                       | Precise tissue ablation with limited thermal damage when appropriately used; evidence is largely observational and treatment parameters vary                                        | Observational clinical evidence, including retrospective and prospective clinical studies                    | Laser-assisted surgical debridement or ablation of established MRONJ                                         | (121,124-127) |

Table I. Continued.

D, Physical and adjunctive therapy

| Therapy                            | Primary mechanism                                                                                             | Key findings                                                                                                                                                                           | Advantages and limitations                                                                                                                                                                                              | Evidence basis                                                                                                  | Intended use                                                                           | (Refs.)   |
|------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------|
| Antimicrobial photodynamic therapy | Photosensitizer activation by light in the presence of oxygen generates ROS with local antimicrobial activity | Preventive preclinical and small clinical studies report decreased osteonecrotic changes; therapeutic evidence consists primarily of case reports and small multimodal clinical series | Local antimicrobial action with limited systemic exposure; efficacy depends on photosensitizer, wavelength, fluence, oxygen availability, biofilm characteristics and treatment protocol. Tissue penetration is limited | Limited clinical and experimental evidence, including preventive preclinical studies and small clinical reports | Post-extraction prevention and adjunctive antimicrobial treatment of established MRONJ | (128-135) |

AAS, androgen-anabolic steroid; APC, autologous platelet concentrate; aPDT, antimicrobial photodynamic therapy; BRONJ, bisphosphonate-related osteonecrosis of the jaw; CGF, concentrated growth factor; Er:YAG, erbium-doped yttrium aluminum garnet; GelMA, gelatin methacryloyl; GGOH, geranylgeraniol; hAM, human amniotic membrane; HBOT, hyperbaric oxygen therapy; Hep, heparin; i-PRF, injectable platelet-rich fibrin; L-PRF, leukocyte-rich platelet-rich fibrin; MRONJ, medication-related osteonecrosis of the jaw; MSC, mesenchymal stem cell; O<sub>2</sub>-O<sub>3</sub>, oxygen-ozone; PBM, photobiomodulation; PENTO, pentoxifylline and tocopherol; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; PTH, parathyroid hormone; RJ, royal jelly; ROS, reactive oxygen species; RSV, resveratrol; TPTD, teriparatide; VEGF, vascular endothelial growth factor.

Its use in patients with MRONJ requires careful patient selection and risk assessment. TPTD should be used cautiously in individuals with disorders of calcium metabolism and typically avoided in patients with an elevated baseline risk of osteosarcoma. This population includes individuals with bone metastasis, a history of skeletal malignancy or prior skeletal radiation therapy (18). The primary indication for antiresorptive therapy should be considered, as patients receiving antiresorptive agents for osteoporosis differ clinically from those receiving high-dose therapy for malignant bone disease. Use of TPTD in MRONJ should be individualized based on the underlying disease, extent of skeletal involvement and overall risk-benefit profile (18,23).

**Pentoxifylline (PTX) and tocopherol (PENTO).** PTX, a methylxanthine derivative, is primarily used to improve microcirculation in patients with peripheral vascular disease (24). PTX improves erythrocyte deformability, thereby facilitating microvascular perfusion (25). Beyond its hemorheological effects, PTX exerts immunomodulatory and anti-inflammatory effects, which may contribute to reduced scar formation (26,27). Tocopherol, a form of vitamin E, exhibits antioxidant properties and may promote angiogenesis by increasing the levels of pro-angiogenic growth factors (28).

PENTO was initially studied extensively for radiation-associated tissue injury, particularly osteoradionecrosis, and its use has been explored in MRONJ (24,28). To the best of our knowledge, clinical evidence regarding PENTO in MRONJ remains limited and includes both prophylactic and therapeutic

studies (28-31). Evidence derived from osteoradionecrosis should not be directly extrapolated to MRONJ because the two conditions differ in their underlying etiology and pathophysiology (24,28). In a case series of 17 patients with cancer receiving intravenous bisphosphonates who underwent a total of 32 tooth extractions, Magalhães *et al* (29) evaluated PENTO as a prophylactic approach administered before and after extraction. Stage I MRONJ developed in three patients (17.6%), corresponding to 3/32 extraction sites (9.4%), and healing was reported in all three cases (29). Słowik *et al* (30) evaluated daily PENTO therapy in 43 patients with MRONJ at different disease stages, with 46% achieving complete remission. De Moraes *et al* (31) summarized the PENTO regimens used for osteoradionecrosis and MRONJ, with PTX doses ranging from 400 to 1,200 mg/day and tocopherol doses from 400 to 1,200 IU/day, highlighting notable heterogeneity in the dosing regimens (31).

Despite its non-invasive nature and generally favorable tolerability, the clinical role of PENTO in MRONJ remains ill-defined (30,31). Treatment courses are typically prolonged and substantial inter-study variability in dosing regimens and treatment duration hinders the development of standardized clinical protocols (30,31). Potential adverse effects, including an increased bleeding risk associated with PTX, warrant consideration, particularly with prolonged treatment (27,31). Further controlled studies are needed to identify patient subgroups most likely to benefit from PENTO and to define the optimal timing and duration of PENTO therapy.

*Geranylgeraniol (GGOH)*. GGOH occurs naturally in various plant-derived sources, microorganisms and animal tissues, including annatto (*Bixa orellana*), sunflower oil, olive oil and tomatoes (32,33). Endogenous GGOH is generated via the mevalonate pathway through dephosphorylation of geranylgeranyl pyrophosphate (34). As a downstream metabolite of this pathway, GGOH bypasses the inhibitory effect of nitrogen-containing bisphosphonates on farnesyl pyrophosphate synthase, thereby restoring protein prenylation and improving osteoclast function (34,35). GGOH has therefore been proposed as a functional antagonist of nitrogen-containing bisphosphonates (23). GGOH has been investigated primarily as a potential strategy for bisphosphonate-related osteonecrosis of the jaw (BRONJ), particularly in experimental models involving nitrogen-containing bisphosphonates (36–39). To facilitate localized and sustained delivery of GGOH, it is incorporated into biomaterials such as bone cement and collagen membranes. In a preclinical model, Feldman *et al* (36) evaluated GGOH incorporated into bone cement pellets and reported restoration of osteoclast viability and resorptive function in bisphosphonate-treated osteoclasts *in vitro*, together with improved early bone healing in the GGOH-treated side compared with the control side in a rat model. *In vitro*, Manzano-Moreno *et al* (37) investigated GGOH-loaded biomimetic collagen membranes and demonstrated that GGOH supplementation counteracts the adverse effects of zoledronate on osteoblast-like cells. In a mouse model, Otto *et al* (38) reported that GGOH attenuates zoledronate-induced impairment of angiogenesis. Similarly, Chen *et al* (39) showed that GGOH restored macrophage efferocytosis impaired by zoledronic acid and improves bone healing in a BRONJ mouse model. Collectively, these findings support the potential of GGOH as a therapeutic strategy for nitrogen-containing bisphosphonate-associated MRONJ. However, its applicability to denosumab- or antiangiogenic agent-associated MRONJ remains unclear, as these agents act through mechanisms distinct from those underlying the effects of GGOH (34). GGOH may interfere with the therapeutic effects of bisphosphonates used in the management of tumors and osteoporosis. Therefore, its use should be considered in the context of the underlying disease and available alternative therapies. In addition, high doses of GGOH may exert cytotoxic effects on gingival fibroblasts and bone cells (35,40).

*Pharmacological and natural agents*. Emerging pharmacological and natural agents have been investigated as potential therapeutic approaches for MRONJ, including those that do not directly target antiresorptive mechanisms (41–46). These agents may exert indirect therapeutic effects by modulating the local microenvironment and supporting tissue repair (41–47).

*Anabolic modulation*. Anabolic modulation is an experimental approach to promote bone repair through mechanisms distinct from those of antiresorptive therapy. Androgen-anabolic steroids (AASs) exert skeletal anabolic actions and are associated with increased bone formation (48). Preclinical findings indicate that androgen-related modulation may influence the osteogenic activity of mesenchymal stem cells (MSCs) (49). Gürses *et al* (41) reported that methenolone enanthate

decreases bone exposure and histopathological abnormality associated with MRONJ in a bisphosphonate-treated rat model. However, the evidence remains preclinical and the adverse effects associated with prolonged AAS exposure may limit their translational potential (50).

*Antioxidant and bone-modulatory agents*. Resveratrol (RSV) is a phyto-oestrogen with antioxidative and anti-inflammatory properties that may support bone homeostasis through modulation of oxidative stress and inflammation (47). Attar *et al* (42) reported that RSV improved bone-formation indices and reduced osteonecrosis at extraction sites in bisphosphonate-treated rats. Vitale *et al* (43) similarly found that RSV attenuates, rather than completely prevents, osteonecrotic changes in a zoledronic acid-associated rat model. Melatonin represents another bone-modulatory agent with antioxidant properties. Yadegari *et al* (44) evaluated melatonin in a zoledronic acid-induced BRONJ rat model and reported a decreased incidence of osteonecrosis, although osteonecrosis remained more frequent than in the control group. To the best of our knowledge, evidence for RSV and melatonin remains preclinical and their efficacy and safety in patients with MRONJ have not been established.

*Bioactive natural products*. Bioactive natural products have been investigated as potential adjunctive approaches for MRONJ management because of their antimicrobial, anti-inflammatory and tissue-protective properties: Fauzi *et al* (45) reported that the combination of Tualang honey and hydroxyapatite partially attenuates pamidronate-induced fibroblast toxicity and preserves cell viability *in vitro*. Topan *et al* (46) assessed the therapeutic potential of royal jelly, a complex mixture of bioactive constituents, in a bisphosphonate-associated MRONJ rat model and reported improved soft and hard tissue healing. These findings remain experimental, and further research is needed to determine their potential for clinical application.

#### *Regenerative medicine and cell therapy*

*Autologous platelet concentrates (APCs)*. APCs are platelet-rich products prepared by centrifugation of autologous blood and comprise preparations with distinct biological characteristics and physical properties (51). Among the commonly used preparations, platelet-rich plasma (PRP) is typically obtained as a plasma concentrate and commonly requires anticoagulation and activation (52–55). By contrast, platelet-rich fibrin (PRF) is prepared without anticoagulants and forms a three-dimensional fibrin matrix that entraps platelets, leukocytes and bioactive factors (51,54–55). Leukocyte-rich PRF (L-PRF) is a solid PRF preparation characterized by a leukocyte-containing fibrin network (55,56), while concentrated growth factor (CGF) is produced using a specific variable speed centrifugation protocol that generates a dense fibrin-rich matrix (51,54,57,58). Injectable PRF (i-PRF) is obtained using lower speed, shorter centrifugation and remains injectable before fibrin polymerization, facilitating its application to irregular defects or combination with other biomaterials (59–61). These differences in centrifugation parameters, cell distribution, fibrin architecture and physical form can influence the retention and release kinetics of platelet-derived bioactive

factors. These factors support soft and hard tissue repair by modulating osteogenic activity, collagen production, inflammatory response and angiogenesis (62).

Clinical evidence for APCs in MRONJ is derived primarily from small prospective or retrospective observational studies and case series, with most preparations used as adjuncts to surgical treatment (63-71). Early reports described the use of PRP in three patients with bisphosphonate-associated osteonecrosis, as well as the application of L-PRF during surgical management (63,64). Clinical studies investigating PRF-based approaches report generally favorable postoperative healing outcomes (65,66). Systematic reviews have evaluated APCs as adjunctive strategies, but interpretation is limited by heterogeneity in APC preparation, surgical protocol, patient characteristics and outcome definitions (67-71). Among APC preparations, clinical evidence for CGF remains scarce: Dipalma *et al* (72) reported no recurrence during a 60-month follow-up of six patients treated with a combination of CGF and piezosurgery.

Overall, current clinical evidence suggests APCs may be useful as adjuncts to surgical management rather than as independently established treatments for MRONJ (67-71). Direct cross-study comparison of healing or success rates is not reliable because of variability in APC preparation protocols, surgical procedures, disease stages, patient characteristics, follow-up duration and outcome definitions across studies (73-75). Such heterogeneity limits reliable assessment of the comparative efficacy of PRP, PRF/L-PRF, CGF and i-PRF. To the best of our knowledge, adequately powered randomized comparative trials using standardized preparation protocols and outcome definitions are lacking.

**MSC-based therapy.** MSCs have been widely investigated in regenerative medicine because of their multilineage potential and ability to modulate inflammation and angiogenesis (76-78). Beyond their differentiation potential, MSCs secrete cytokines, growth factors and other paracrine mediators that can regulate immune responses, angiogenesis and endogenous tissue repair (76). Increasing evidence suggests these paracrine, immunomodulatory and proangiogenic effects are major contributors to MSC-mediated tissue regeneration, rather than sustained direct differentiation of transplanted cells into bone-forming cells (77,79).

Bone marrow-derived MSCs (BMSCs) and adipose-derived MSCs (ADSCs) are commonly investigated MSC sources for regenerative and cell-based therapeutic applications (78). BMSCs possess notable osteogenic potential, whereas ADSCs are relatively accessible and exhibit favorable proliferative capacity *in vitro* (80). Nevertheless, the biological characteristics and regenerative capacity of MSCs vary depending on their tissue source and culture conditions.

**MSC transplantation and cell sheet approaches.** The majority of available evidence supporting MSC-based therapy for MRONJ is derived from preclinical investigations (78,81-84). Kikui *et al* (81) demonstrated therapeutic effects of MSC administration in a zoledronate/dexamethasone-induced BRONJ-like mouse model, with immunomodulatory effects and improved bone healing (81). Cell sheet technology has been explored as a means of maintaining MSCs within a structured extracellular matrix and enhancing local tissue repair: Kaibuchi *et al* (82)

summarized preclinical findings from rat and canine bisphosphonate-associated models, in which local MSC sheet transplantation promoted mucosal and bone healing; these findings warrant further investigation of cell sheet approaches for MRONJ.

MSC-based approaches have also been investigated in combination with PCs: Limited clinical reports have documented mucosal healing and bone regeneration following administration of MSC-containing preparations combined with PRP or PRF, although the small sample sizes and multimodal treatment regimens preclude definitive attribution of these outcomes to MSC therapy (83,84). However, the clinical translation of MSC-based approaches is limited by cell harvesting and expansion, manufacturing complexity, high cost and patient selection. Autologous BMSCs may not represent a viable option for certain patients with hematological malignancy, particularly those with multiple myeloma-associated MRONJ (78,85).

**MSC-derived exosomes.** MSC-derived exosomes are potential mediators of tissue repair and regeneration. These nanoscale extracellular vesicles carry proteins, lipids and regulatory nucleic acids that can modulate intercellular signaling and contribute to tissue repair (86). Dong *et al* (87) evaluated exosomes derived from ADSCs in a preclinical MRONJ model and reported enhanced gingival healing and bone remodeling, together with decreased lesion development (87). Evidence is limited to preclinical studies, and further research is needed to establish standardized protocols for exosome isolation, characterization, dosing and storage before clinical translation (88).

#### *Biomaterial-driven local repair strategies*

**Hydrogels.** Hydrogels are a class of bioactive material that mimic the hydrated environment of soft tissue and provide a three-dimensional matrix for cell survival and nutrient transport, while facilitating local retention and controlled release of bioactive molecules (89). These properties support their application in drug delivery, tissue engineering and wound healing. Hydrogel-based strategies for MRONJ have been investigated predominantly at the preclinical level, with many models involving bisphosphonate exposure (90-96). Current designs focus on microenvironment regulation, angiogenesis and osteogenesis, mechanical support, delivery of cells and bioactive factors and sustained local release (90-96).

**Immunomodulation, angiogenesis and structural regeneration.** One notable hydrogel-based strategy is to regulate the local microenvironment while promoting vascular and bone regeneration. Costa de Sousa *et al* (90) evaluated an *Agaricus blazei* polysaccharide gel in a BRONJ model and found that local delivery increases type I collagen production and promotes mucosal healing, accompanied by activation of Wnt signaling and improved bone remodeling. Guo *et al* (91) developed a magnesium-based nanocomposite hydrogel for mandibular reconstruction following debridement, which provides mechanical support, promotes type H vessel formation, activates Osterix-positive osteoprogenitors and modulates the inflammatory and infectious microenvironment, thereby supporting mandibular regeneration.

Angiogenic regulation has also been explored as a preventive strategy: Sharma *et al* (92) assessed a VEGF-loaded hydrogel in zoledronic acid-treated rats following tooth

extraction and demonstrated that sustained local VEGF delivery enhances angiogenesis and lymphangiogenesis while decreasing osteonecrotic changes. These findings suggest hydrogel-mediated vascular and microenvironmental regulation may have applications in both prevention and regenerative repair, depending on the timing and design of the intervention.

**Cell and bioactive factor delivery.** A second strategy uses hydrogel scaffolds as local delivery platforms for regenerative cells and osteogenic factors. Tu *et al* (93) established MRONJ-like maxillary defects in rats treated with zoledronic acid and dexamethasone and evaluated a gelatin methacryloyl (GelMA)/polydopamine hydrogel containing alveolar mucosa-derived stem cells and parathyroid hormone. The composite hydrogel promoted soft tissue healing and bone regeneration at the defect sites (93). Ning *et al* (94) developed a microfiber-reinforced low-acyl gellan gum hydrogel incorporating rat ADSCs and bone morphogenetic protein-2 and tested its therapeutic potential in established rat MRONJ lesions. This engineered hydrogel combined mechanical reinforcement with localized delivery of stem cells and osteogenic factors, thereby promoting mucosal recovery and bone reconstruction (94).

Together, the aforementioned studies support the potential of cell-laden hydrogel systems to provide both structural support and a localized regenerative environment for the repair of established MRONJ lesions. Nevertheless, available evidence remains limited to preclinical studies and further clinical studies are needed to determine their safety and therapeutic efficacy.

**Controlled release and preventive delivery.** Controlled local release is particularly relevant to preventive hydrogel strategies as it can prolong the local availability of bioactive factors at high-risk sites and thereby support the early tissue-healing environment during the period when MRONJ may develop (95). Tao *et al* (95) developed a photocrosslinked heparin/GelMA hydrogel loaded with PRF and assessed its performance in a rat MRONJ model established using zoledronic acid and dexamethasone administration followed by tooth extraction. The hydrogel was placed directly into the extraction socket, where it exhibited relatively slow degradation and reached swelling equilibrium, with its swelling ratio stabilizing within 24 h, while enabling continuous release of PRF-derived growth factors for >4 weeks. This strategy promoted osteomucosal healing and decreased osteonecrotic changes following tooth extraction (95).

Antimicrobial and cytoprotective functions can be incorporated into preventive delivery systems. Sungkhaphan *et al* (96) constructed an *in vitro* clindamycin/GGOH-loaded hydrogel system for the prevention of bisphosphonate-associated osteonecrosis. This hydrogel provided sustained drug release and antibacterial activity and attenuated zoledronate-induced cytotoxicity (96).

Collectively, the applications of hydrogel systems vary across stages of MRONJ development and management. Preventive applications focus on local delivery before or immediately following a triggering procedure (92,95,96), whereas regenerative strategies target established experimental lesions (90,93,94) or reconstruction following surgical debridement (91). Accordingly, hydrogel formulations incorporate combinations of functions, including

immunomodulation, antimicrobial activity, angiogenesis, osteogenesis, cell delivery, mechanical support and controlled release.

**Translational challenges.** Despite their versatility, hydrogel-based systems face barriers to clinical translation. In the oral cavity, implanted materials are exposed to saliva, microorganisms and repeated mechanical loading, making local retention and mechanical stability key considerations for clinical application (89). Material degradation kinetics must also be controlled to maintain structural integrity and delivery functions throughout the therapeutic period while ensuring appropriate degradation and clearance (89,97).

Sterilization represents a challenge, especially for hydrogels containing cells, proteins, growth factors or other bioactive components (97). Increasing material complexity raises concerns regarding manufacturing reproducibility, batch consistency, scalability, storage stability and quality control (97). Combination products that integrate biomaterial scaffolds with therapeutic agents, cells or biological factors may be subject to more complex regulatory requirements (97). Long-term local and systemic biosafety, including the effects of degradation by-products and interactions with the oral microbiota, remains to be assessed. Most hydrogel evidence relevant to MRONJ remains preclinical and many experimental models are based specifically on bisphosphonate exposure (90-95). Standardized studies under clinically relevant oral conditions and clinical investigations are therefore needed to determine their translational potential.

**Human amniotic membrane (hAM).** hAM is a naturally derived bioactive material obtained from placental tissue. It exhibits low immunogenicity and good biocompatibility and contains a rich extracellular matrix enriched with collagen, laminin, fibronectin and multiple growth factors (98). These biological properties contribute to epithelialization, modulation of inflammatory responses and attenuation of scar formation (98).

In MRONJ, the biological properties of hAM may address multiple pathological alterations within the local disease microenvironment (98,99). hAM may alleviate local inflammation by modulating pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6 (98,99). As a biological barrier and native extracellular matrix scaffold, hAM may support mucosal coverage and tissue integration (99). Its angiogenic and antifibrotic properties contribute to wound healing and tissue repair (99). Clinical evidence for hAM in MRONJ is derived largely from small clinical studies and evidence syntheses (100-103). Çanakçı *et al* (100) reported preliminary outcomes following hAM transplantation in patients with stage II MRONJ, reporting a healing rate of 85%. In a case-control study, Ragazzo *et al* (101) compared surgical treatment with and without local hAM application and observed favorable postoperative outcomes in the hAM group. Odet *et al* (102) conducted a pilot study evaluating cryopreserved hAM in patients with stage II-III MRONJ and reported encouraging clinical outcomes. A systematic review and meta-analysis including 91 patients reported an overall surgical success rate of 91.2% following hAM application (103). Nevertheless, this pooled estimate should be interpreted cautiously because of the limited sample size, heterogeneity in treatment protocols and differences in study designs.

The biological and handling properties of hAM are partly determined by its processing and preservation. Fresh hAM retains native tissue components but has a short storage period and presents logistical challenges (99). By contrast, frozen or cryopreserved membranes allow longer storage under controlled low temperature conditions, although these preservation procedures may affect cell viability and alter biological properties, such as the retention of growth factors and extracellular matrix components (99). Dehydrated or lyophilized membranes offer greater storage stability and easier handling; nevertheless, processing may alter tissue structure and the content of bioactive components (104). These differences should be considered when comparing clinical outcomes across studies using different hAM preparation protocols.

Successful clinical translation of hAM relies on standardized protocols for donor screening, tissue processing, storage and surgical handling. In the MRONJ pilot study by Odet *et al* (102), cryopreserved hAM was placed between the bone and mucosa, with a resorbable collagen sponge used in selected cases to facilitate graft handling and stabilization. Due to the inherent fragility of hAM, graft fixation and wound closure strategies may need to be adapted to the characteristics of the surgical defect (102). Furthermore, donor eligibility, tissue processing, storage and release of hAM grafts are subject to tissue-banking requirements intended to ensure the safety, quality and traceability of donated tissues, as well as applicable regulatory requirements, which may vary across jurisdictions (105).

Overall, hAM represents a promising adjunct to surgical management of MRONJ, facilitating wound coverage and postoperative soft tissue healing rather than serving as an established stand-alone therapy. Although current clinical findings are encouraging, limited sample sizes, heterogeneous surgical protocols and variations in hAM preparation methods limit definitive conclusions (100-103). Larger prospective comparative studies using standardized membrane processing and application protocols are warranted to define its clinical efficacy, safety and appropriate indications in MRONJ management.

#### *Physical and adjunctive therapy*

**Hyperbaric oxygen therapy (HBOT).** HBOT increases tissue oxygen tension under elevated atmospheric pressure, which may modulate inflammation, oxidative stress, angiogenesis and wound repair (106). To date, clinical evidence for HBOT in MRONJ remains limited and heterogeneous: Available systematic reviews and clinical studies report variable healing outcomes when HBOT was delivered as an adjunct to conventional treatment, however, the overall quality of evidence was low and no definitive therapeutic benefit has been established (107-110). In a randomized controlled trial, Freiburger *et al* (111) evaluated HBOT as an adjunctive therapy combined with surgical intervention and antibiotic administration in patients with BRONJ. The HBOT group showed a higher overall improvement rate and more rapid pain reduction, together with a shorter time to improvement; however, no significant intergroup difference was observed in complete gingival healing (111). The aforementioned study was insufficiently powered to draw definitive conclusions regarding HBOT efficacy (111).

HBOT requires specialized facilities and repeated treatment sessions, which imposes considerable clinical and practical burdens on patients. Barotrauma and other oxygen- or pressure-associated adverse effects have been reported in patients undergoing HBOT (112,113). Treatment eligibility should be determined following assessment of contraindications and the patient overall condition. Given the limited and heterogeneous evidence and uncertainty regarding optimal patient selection, HBOT may be considered as an adjunctive option in selected patients rather than a routine treatment for MRONJ.

**Ozone therapy.** Ozone therapy has shown promising antimicrobial, anti-inflammatory and redox-modulating effects (114,115). Ozone can be delivered via various formulations and routes, including gaseous O<sub>2</sub>-O<sub>3</sub> mixtures, ozonated water and oil and local tissue infiltration, as well as systemic approaches such as autohemotherapy (114). These modalities differ in ozone concentration, delivery method, tissue exposure and safety profiles and should not be considered interchangeable.

Clinical evidence supporting the use of ozone therapy for MRONJ remains sparse: Di Fede *et al* (116) investigated O<sub>2</sub>-O<sub>3</sub> mucosal infiltration in seven patients with stage II MRONJ who were considered unsuitable for surgery and reported favorable mucosal healing outcomes. However, the small uncontrolled case series limits conclusions regarding efficacy. At the preclinical level, Silva *et al* (117) evaluated the effects of different concentrations of ozonized oil in a zole-dronate-induced mandibular osteonecrosis model in senescent rats. All ozone-treated groups exhibited decreased non-vital bone, with the 600 milliequivalents/kg concentration showing the greatest bone volume and new bone formation (117). O<sub>2</sub>-O<sub>3</sub> infiltration has also been investigated for MRONJ prevention: In a randomized, open-label phase II trial involving 117 patients at risk of MRONJ who underwent tooth extraction, Di Fede *et al* (118) reported improved wound healing scores during the inflammatory and proliferative phases following adjunctive O<sub>2</sub>-O<sub>3</sub> infiltration. This supports the potential preventive role of ozone therapy rather than its efficacy in treating established MRONJ lesions. Overall, differences in ozone formulation, concentration, administration route, treatment frequency and clinical setting limit direct comparison of outcomes across studies, while MRONJ-specific evidence for certain ozone modalities, particularly ozonated water and systemic autohemotherapy, remains insufficient.

#### *Photonic therapy*

**Photobiomodulation (PBM).** PBM uses low-intensity light irradiation to induce non-thermal biological responses. PBM modulates mitochondrial function and ATP synthesis, thereby influencing inflammatory signaling, angiogenesis and tissue repair (119). These biological effects depend on irradiation parameters, including wavelength, output power or irradiance, fluence, pulse characteristics, exposure duration, treatment frequency and irradiation technique (120).

Current clinical investigations have primarily evaluated PBM as an adjunct to conventional management (120-122). In a clinical study, Vescovi *et al* (121) analyzed 190 patients with BRONJ, with 166 treated sites managed using medical and surgical protocols with or without low-level laser therapy.

Neodymium-doped yttrium aluminum garnet (Nd:YAG) irradiation was used for low-level laser therapy at 1.25 W and 15 Hz. Among the 97 surgically treated sites, 78 (80.4%) achieved complete mucosal healing (121). However, the use of multiple treatment combinations, including antibiotic therapy, conventional or erbium-doped yttrium aluminum garnet (Er:YAG)-assisted surgery, and low-level laser therapy, limits the ability to determine the independent contribution of PBM. In addition, the aforementioned study was restricted to bisphosphonate-associated osteonecrosis, limiting the generalizability of its findings. Michalak *et al* (122) evaluated PBM in 31 patients with MRONJ, including 14 patients with stage I and 17 with stage II-III disease; 10 patients had osteoporosis, whereas 21 were receiving cancer treatment. PBM was delivered using a 635 nm diode laser at 100 mW in continuous-wave mode, with four irradiation sites treated for 20 sec/site. Clinical improvement was observed during follow-up, although the absence of an untreated control group and heterogeneity in disease stage and patient characteristics limit definitive conclusions regarding efficacy (122). At the preclinical level, Ayhan *et al* (123) compared PBM at 405, 445, 660 and 808 nm in a bisphosphonate-associated model and reported wavelength-dependent differences in clinical, radiological and histological responses (123). These findings indicate that treatment outcomes may vary according to the irradiation protocol.

Notable heterogeneity exists across PBM studies, including variations in wavelength, power, fluence, exposure duration, pulse mode, treatment frequency, irradiation site, combined therapeutic strategies and outcome definitions, limiting cross-study comparisons and reproducibility (119,120). Standardized reporting of irradiation parameters and treatment protocols is needed to define the clinical role and appropriate application of PBM in MRONJ management.

**Laser-assisted surgical debridement and ablation.** Er:YAG laser irradiation at 2,940 nm is strongly absorbed by water and hydroxyapatite, enabling controlled ablation of mineralized tissue with limited thermal injury to adjacent structures (124). These characteristics support its use for necrotic bone removal and conservative surgical debridement in MRONJ.

Clinical evidence was reported by Vescovi *et al* (121) in 190 patients with BRONJ, including 166 treated sites. Er:YAG-assisted surgery was performed by bone resection or vaporization using variable settings ranging from 250 mJ at 20 Hz to 300 mJ at 30 Hz. Surgical treatment resulted in complete mucosal healing in 78 of 97 sites (80.4%) and favorable outcomes were reported following Er:YAG-assisted conservative surgery. Notably, the aforementioned study involved different treatment combinations and was limited to bisphosphonate-associated disease, which restricts direct comparison between Er:YAG and conventional surgical approaches. Porcaro *et al* (125) included 57 patients with stage I-III MRONJ who were treated using five protocols, including medical therapy, conventional surgery, ozone therapy, Er:YAG-assisted surgery and combined ozone/Er:YAG treatment. Patients were followed for  $\geq 12$  months and favorable healing outcomes were reported in protocols incorporating Er:YAG. However, the case series design, heterogeneous treatment regimens and relatively small subgroups limit definitive assessment of the independent contribution of Er:YAG.

Er:YAG has been incorporated into multimodal treatment of advanced disease. Vescovi *et al* (126) reported a patient with stage III MRONJ associated with denosumab treatment for metastatic breast cancer who underwent piezoelectric surgery combined with Er:YAG bone ablation and postoperative Nd:YAG PBM (126). Complete mucosal healing without recurrence was maintained during long-term follow-up. Although the aforementioned study demonstrates the feasibility of combining laser-assisted surgery with other modalities in advanced MRONJ, the single case design does not permit assessment of the individual contribution of Er:YAG.

Overall, available clinical studies (121,125,126) report favorable outcomes with Er:YAG-assisted surgical protocols, but differences in medication exposure, disease stage, surgical technique, laser parameters, concomitant intervention and outcome definitions limit direct comparison across studies. Systematic reviews have similarly highlighted heterogeneity in laser-assisted and autofluorescence-guided surgical protocols (119,127). Further comparative clinical studies using standardized surgical and laser parameters are warranted.

**Antimicrobial photodynamic therapy (aPDT).** aPDT exerts localized antimicrobial activity by combining a photosensitizer, light of an appropriate wavelength and molecular oxygen to generate reactive oxygen species (128). Unlike PBM, which induces non-thermal biological modulation, aPDT targets microorganisms primarily through photosensitizer-mediated oxidative reactions. Its antimicrobial effect is influenced by multiple treatment parameters, including photosensitizer type and concentration, pre-irradiation incubation time, wavelength, fluence, oxygen availability and treatment frequency (129,130). Biofilm characteristics, including composition, density and extracellular matrix may further affect photosensitizer penetration and microbial susceptibility to aPDT (129).

In a preclinical bisphosphonate-associated rat model, Ervolino *et al* (128) assessed the preventive efficacy of butyl toluidine blue-mediated aPDT and reported a decreased incidence of MRONJ-like osteonecrotic lesions. However, clinical evidence remains limited: Poli *et al* (131) described a preventive case series involving 11 non-oncological patients with osteoporosis who were receiving non-intravenous antiresorptive therapy and underwent dentoalveolar surgery. Methylene blue-based aPDT was applied using a  $660 \pm 10$  nm diode laser at 100 mW following extraction and surgical debridement; no clinical or radiographic evidence of MRONJ was observed during the 6-month follow-up (131). Nevertheless, the absence of a control group, small sample size and additional interventions, including surgical closure and subsequent PBM, limit attribution of the favorable outcomes specifically to aPDT.

aPDT has been reported as an adjunct in the treatment of established MRONJ, although current clinical evidence consists primarily of case reports and small series (132). For example, Schussel *et al* (133) described a surgically ineligible patient with BRONJ who was managed with a multimodal regimen comprising aPDT, antibiotics and PENTO and showed decreased pain, resolution of infection and a decrease in bone exposure during follow-up. However, the multimodal treatment approach limits the ability to determine the independent therapeutic contribution of aPDT.

The clinical efficacy of aPDT is constrained by limited light penetration and decreased availability of photosensitizers and

oxygen within mature or deep-seated biofilms. Accordingly, treatment parameters cannot be readily extrapolated across different photosensitizers, light sources, biofilm conditions or clinical settings. Experimental studies have shown that hypoxic microenvironments diminish the antimicrobial efficacy of photodynamic treatment and microorganisms embedded in multispecies biofilms may respond differently from planktonic counterparts (134,135). Further clinical studies with standardized reporting of photosensitizer concentration, incubation time, wavelength, fluence, treatment frequency and microbiological or clinical outcomes are warranted.

#### 4. Precision medicine in MRONJ

Interindividual variability serves a key role in the onset and progression of MRONJ, as only certain patients exposed to antiresorptive and antiangiogenic medications develop MRONJ (3). Clinical heterogeneity provides a rationale for risk-stratified therapeutic strategies that integrate clinical characteristics, medication exposure, molecular features and other patient-specific factors. Precision medicine aims to integrate this multidimensional information with omics technologies and computational tools to refine individualized risk assessment and inform tailored MRONJ management (136). However, precision medicine approaches in MRONJ remain predominantly at the exploratory or model development stage and their clinical validity and translational utility have yet to be established.

*Clinical risk prediction and machine learning.* Machine learning approaches have recently been investigated for MRONJ risk prediction: Warin *et al* (137) retrospectively analyzed electronic medical records from 5,305 patients receiving antiresorptive therapy, among whom 81 developed MRONJ (1.5%). Using demographic, medical, pharmacological, laboratory and dental variables, the aforementioned study developed and compared six machine learning algorithms (137). The best-performing model achieved an accuracy of 0.95 and an area under the receiver operating characteristic curve (AUC) ranging from 0.89 to 0.90. However, the low number of MRONJ events relative to the overall cohort and the single-center retrospective design warrant caution when interpreting model performance.

In a retrospective study, Kwack and Park (138) evaluated automated machine learning models in 340 female patients with osteoporosis aged  $\geq 55$  years who received antiresorptive therapy and underwent tooth extraction or implant treatment. Gradient boosting achieved an AUC of 0.8283 in the training set and 0.7526 in the independent test set, with medication duration, patient age, number of operated teeth and surgical site identified as influential variables. These findings support the feasibility of multivariable machine learning-based MRONJ risk prediction, although existing models remain insufficiently validated for routine clinical use.

To facilitate the clinical translation of predictive models, standardized approaches to model development, validation and outcome reporting are needed. Key considerations include model discrimination and calibration, management of class imbalance and overfitting, missing data handling and performance evaluation in independent external cohorts.

External validation is key given inter-cohort variability in patient characteristics, underlying disease, antiresorptive indication and dose, dental procedure and healthcare settings. Furthermore, high discriminatory performance alone does not establish clinical utility. Before integration into routine clinical workflows, predictive models should demonstrate the ability to inform individualized decision-making, including the intensity of dental surveillance, timing of invasive dental procedures and implementation of risk-stratified preventive measures (139).

*Genomic and molecular susceptibility.* Molecular and genomic studies (140-143) have identified multiple candidate molecular signatures potentially associated with susceptibility to jaw osteonecrosis, but these findings represent different levels of evidence. Balachandran *et al* (140) performed an integrated bioinformatics analysis of BRONJ and identified seven candidate hub genes, including fibronectin 1, *TNF*, Jun proto-oncogene AP-1 transcription factor subunit, signal transducer and activator of transcription 3, actin  $\beta$ , glyceraldehyde-3-phosphate dehydrogenase and protein tyrosine phosphatase receptor type C (140). Notably, these genes should be regarded as exploratory molecular candidates rather than validated biomarkers, as they were identified through *in silico* analyses and require independent biological and clinical validation.

Nicoletti *et al* (141) conducted a pharmacogenetic genome-wide association study and identified an association between RNA binding motif single stranded interacting protein 3 and bisphosphonate-induced osteonecrosis of the jaw. The initial genome-wide analysis included 30 cases and 17 treatment-tolerant controls, with additional genetically matched population controls incorporated in subsequent analyses. The limited sample size and study population restrict the generalizability of the initial genetic findings. Yang *et al* (142) identified a chromosome 8 locus associated with MRONJ and validated the lead single-nucleotide polymorphism rs2736308 in an osteoporosis cohort; the locus is linked to B lymphoid tyrosine kinase, cathepsin B and farnesyl-diphosphate farnesyltransferase 1. Although these findings provide evidence for genetic susceptibility to MRONJ, the identified genomic loci cannot by themselves be considered clinically validated biomarkers. Genetic susceptibility may interact with the pathological processes that characterize the MRONJ microenvironment. For example, polymorphisms in VEGF/VEGFA, a key regulator of angiogenesis, are associated with BRONJ susceptibility (143). Together with previously reported candidate genes implicated in inflammatory, immune and bone-remodeling pathways (140,142), these findings suggest interindividual molecular variation may influence biological responses relevant to the local microenvironment. However, these associations remain exploratory and do not establish definitive causal mechanisms underlying MRONJ pathogenesis. Independent replication across diverse populations, prospective evaluation and demonstration of incremental predictive value beyond established clinical risk factors are needed before genetic profiling can be incorporated into routine MRONJ risk stratification and clinical management.

*Multidimensional integration and clinical translation.* Medication exposure is a key component of individualized MRONJ risk assessment. Antiresorptive treatment parameters, including treatment duration, cumulative exposure, drug class and dose and therapeutic indication, should be considered with underlying disease and other patient-associated factors (144). In particular, patients receiving high-dose antiresorptive therapy for malignancy have distinct risk profiles from those receiving lower dose therapy for osteoporosis. Dental assessment and risk-stratified management should be performed before and during antiresorptive treatment (1,145).

Future precision-medicine frameworks for MRONJ should integrate multiple complementary domains rather than relying on isolated biomarkers or single-algorithm prediction tools. Clinical variables may include age, comorbidities, immune status, oral hygiene and previous dental disease; pharmacological variables may include drug class, dose, route, duration and cumulative exposure; imaging may characterize local bone and soft tissue changes; microbiological information may reflect the local infectious environment; and genomic or molecular data may provide information on individual susceptibility. Integration of these multidimensional datasets into rigorously validated predictive models may enable personalized risk stratification and inform tailored preventive surveillance and treatment planning. However, the independent contribution and incremental value of each domain remain to be established.

Several practical barriers limit this transition. Genomic and molecular testing incurs additional cost and may not be equally accessible across healthcare settings, while the collection of genomic and longitudinal clinical data raises privacy and data governance concerns. Machine learning prediction algorithms may also reflect biases in training cohorts, potentially limiting generalizability when applied to different ethnic populations, geographical regions or patient subgroups with oncological or osteoporotic indications. Additional challenges include limited model interpretability and technical barriers to integrating predictive tools into electronic health record systems and routine dental-medical workflows (146). Clinically viable prediction tools should demonstrate tangible benefits in preventive and therapeutic decision-making and improve patient outcomes, rather than merely achieving high statistical predictive performance.

## 5. Discussion and conclusion

MRONJ is increasingly recognized as a heterogeneous disorder rather than a single pathological entity with a uniform therapeutic response, which shapes the interpretation of emerging intervention strategies (2,4,6,7). Several approaches, including TPTD, PENTO, APCs and hAM, have yielded preliminary clinical support in selected settings, but the available studies are generally limited by small sample sizes, heterogeneous protocols and inconsistent outcome definitions (21,23,30,31,67,103). By contrast, GGOH, hydrogels, most MSC-based or cell-derived approaches, melatonin and natural products are predominantly confined to preclinical investigation (34,36,44–46,78,83,87,91,93). While their mechanistic rationales are well-substantiated by experimental findings, robust clinical validation is lacking to confirm translational efficacy. Collectively,

these emerging modalities should be regarded as promising complementary tools to optimize established MRONJ management, rather than substitutes for conservative care, antimicrobial management when indicated and appropriate surgical intervention.

Future progress is unlikely to depend on a single optimal therapy. Given the multifactorial nature of MRONJ, emerging strategies may need to address multiple pathological processes through complementary mechanisms, including modulation of inflammation, angiogenesis, bone remodeling, infection and soft tissue repair. However, greater biological complexity does not necessarily translate into greater clinical value. Multifunctional systems, such as hydrogels and cell-based platforms, introduce challenges in reproducibility, manufacturing, storage, regulatory classification and long-term safety. The central question is therefore shifting from whether a treatment can modify a pathological pathway to whether it produces a reproducible and clinically meaningful benefit in a defined patient population.

This transition also links microenvironment-directed therapy with precision medicine. The same intervention is unlikely to have comparable effects across patients with different underlying diseases, medication classes, cumulative exposures, oral conditions and disease stages. Differences among bisphosphonates, denosumab and antiangiogenic agents should also be considered when evaluating therapeutic strategies and decisions regarding medication interruption. Future MRONJ management may require integration of clinical characteristics, pharmacological exposure, imaging features, microbiological information and validated molecular markers to refine risk stratification and treatment selection. At present, however, machine learning models, genomic associations and bioinformatics-derived candidates remain investigational and should not be treated as clinically validated decision tools. Their clinical value depends on external validation, calibration, interpretability and demonstrated impact on preventive or therapeutic decision-making. Prospective multicenter studies with standardized outcome definitions, appropriate controls, detailed treatment-parameter reporting, stage-specific analyses and long-term follow-up are needed to determine which approaches provide clinically meaningful benefits, for which patients and at what stage of MRONJ management.

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## Availability of data and materials

Not applicable.

## Authors' contributions

XLZ conceived the study and wrote and edited the manuscript. XZZ and JJJ conceived the study and edited the manuscript. CYL, LWL, QH and TYC edited the manuscript. QTZ conceived the study. JYL edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

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Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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