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Regenerative and surgical strategies for medication-related osteonecrosis of the jaw (MRONJ): a systematic review

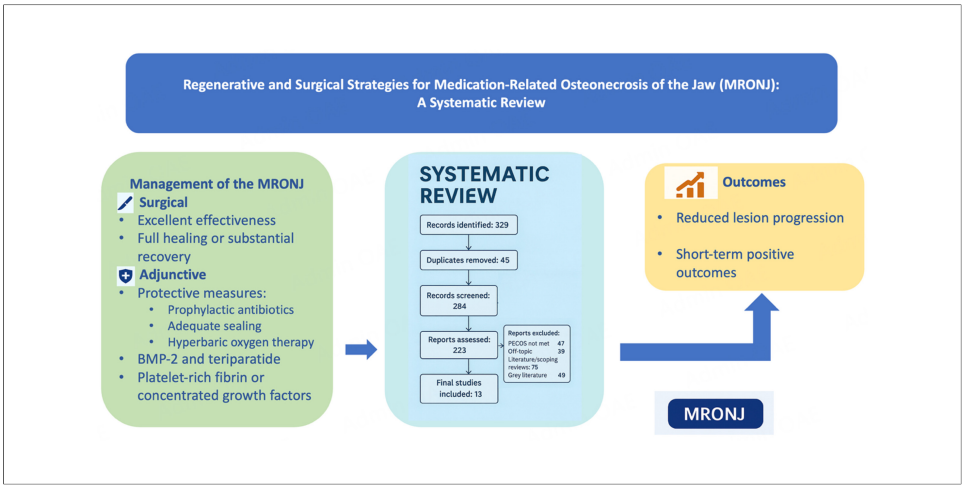
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Keywords:
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Abstract

Aim: Medication-related osteonecrosis of the jaw (MRONJ) challenges clinicians with its complex pathology and high risk of complications.

Methods: We searched seven databases - PubMed, Scopus, Web of Science, Cochrane Library, Embase, CINAHL, and Google Scholar - and adapted the search strings for each database to optimize retrieval of relevant studies. We then systematically reviewed the included studies to identify the most effective treatments for promoting MRONJ healing.

Results: A total of 329 records were identified through database searches across seven electronic databases. After removal of 45 duplicates, 284 records were screened. Following title and abstract screening and full-text assessment, 13 studies met the eligibility criteria and were included in the qualitative synthesis. The included studies consisted primarily of randomized controlled trials and retrospective cohort studies investigating

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surgical, pharmacological, and adjunctive therapeutic strategies for MRONJ management. Risk-of-bias assessment using the RoB 2.0 and ROBINS-I (Risk of Bias in Non-randomised Studies - of Interventions) tools showed that most studies presented low to moderate risk of bias, although some methodological concerns were identified. Surgical interventions were commonly associated with improved clinical healing, while adjunctive therapies such as bone morphogenetic protein-2 and teriparatide showed promising outcomes in selected cases. Follow-up periods ranged from 1 month to 2 years, and outcome measures included clinical, radiological, and histological evaluations.

Conclusion: MRONJ treatment is diverse and multifaceted. Such inferences were made to varying degrees in previous investigations, illustrating the limitations for clinical use, revealing the need for further studies to clarify both the efficacy and optimal use of the interventions in diverse clinical settings.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) has recently captured interest due to its increasing prevalence as well as its poorly defined etiology. It is an extremely disabling disorder that causes severe pain and is associated with impaired oral function in affected individuals[1,2]. It is commonly characterized as the exposed or necrotic jawbone, often due to long-term treatment by bisphosphonates, other antiresorptive agents, and anti-angiogenic drugs that are usually used for osteoporosis, malignancy, or rheumatoid arthritis[3]. MRONJ pathogenesis is multifactorial and mediated through a variety of molecular, cellular, and biomechanical mechanisms that disrupt the homeostatic integrity of bone and favor the formation of osteonecrotic lesions[4,5].

The mandible is highly sensitive to the pharmacodynamic actions of these medications as bone resorption is suppressed. Nevertheless, the precise etiology of MRONJ pathways continues to be unknown[6,7]. MRONJ typically presents with pain, inflammation, and bone exposure, which significantly affects quality of life and often requires aggressive surgical interventions[8].

Certain anatomical and physiological features make the jaw particularly prone to the negative impact of these drugs. This propensity is associated with the high vascularity and frequent bone remodeling of the alveolar process and periodontium, due to the mechanical stress of chewing[2,7]. MRONJ is thought to result from disturbances in bone remodeling, impaired angiogenesis, microtrauma, impaired immune function, or the presence of inflammation or infection[9].

The American Society for Bone and Mineral Research and the American Association of Oral and Maxillofacial Surgeons define MRONJ based on the following criteria: (i) current or prior treatment with antiresorptive or antiangiogenic agents; (ii) exposed or necrotic bone in the maxillofacial region persisting for more than eight weeks; (iii) no history of radiation therapy to the jaws; and (iv) absence of metastatic disease in the jawbones[2,10]. Treatment modalities should be individualized according to the stage of MRONJ, since early lesions may be managed conservatively, whereas surgery may be required for advanced lesions[11]. The duration of drug treatment and temporary interruptions ("drug holidays") play an essential role in lesion management and healing[12]. MRONJ has four stages based on clinical features. Stage 0 includes non-exposed, prodromal disease, while stages 1 through 3 involve exposed bone, with or without infection, and increasing severity, including pathological fractures, fistulae, and osteolysis reaching the mandibular border or sinus floor[11-13]. Despite the lack of research into the pathogenesis, there are relatively few available evidence-based

therapy indications for MRONJ[11,14]. The present systematic review presents the most recent evidence-based medical treatment approaches for MRONJ, focusing on the effectiveness of strategies aimed at regenerating bone and new tissue. Data from randomized controlled trials and observational studies were compiled to assess the effectiveness of interventions for promoting MRONJ healing using the Population, Exposure, Comparison, Outcome, Study Design (PECOS) framework.

METHODS

Eligibility criteria

The PECOS framework was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guidelines [Figure 1][15]:

• **Population (P):** Patients diagnosed with MRONJ at any stage (early, moderate and advanced).

• **Exposure (E):** Therapeutic interventions - surgical, pharmacological, or adjunctive - intended to promote bone healing and soft tissue regeneration in MRONJ.

• **Comparator (C):** Standard care, placebo, or alternative interventions.

• **Outcome (O):** Evidence of bone and soft tissue healing assessed through clinical, radiological, and histological outcomes, as well as measures of pain reduction and recurrence.

• **Study design (S):** Randomized controlled trials, non-randomized clinical trials, cohort studies, and case series with a minimum of ten patients.

A summary of the inclusion and exclusion criteria is presented in Table 1.

Database search plan

A thorough systematic search was undertaken on seven databases: PubMed, Scopus, Web of Science, Cochrane Library, Embase, CINAHL, and Google Scholar. Google Scholar was included to retrieve grey literature and studies not indexed in the other databases, despite its limitations regarding the quality of literature. The search strategies employed MeSH terms [Table 2]. The search was limited to English-language publications published within the last 20 years (January 2005-January 2025) to ensure contemporary relevance and feasibility of analysis. The final literature search was completed on January 5, 2025.

Although grey literature was retrieved during the search process, it was excluded during the screening phase according to the predefined exclusion criteria.

Data extraction protocol

Both authors independently extracted data using a structured extraction form. Variables included study details (author, year, geographic location), participant information (sample size, age, gender), treatment modalities, MRONJ severity, treatment and follow-up period, evaluation methods (clinical, radiological, histological), and primary outcomes. Any discrepancies were resolved through discussion or referral to a third person. Cohen's kappa was calculated to assess inter-rater reliability for study inclusion in this systematic review.

Bias analysis strategy

Risk of bias in non-randomized studies was assessed using the ROBINS-I (Risk Of Bias In Non-randomised

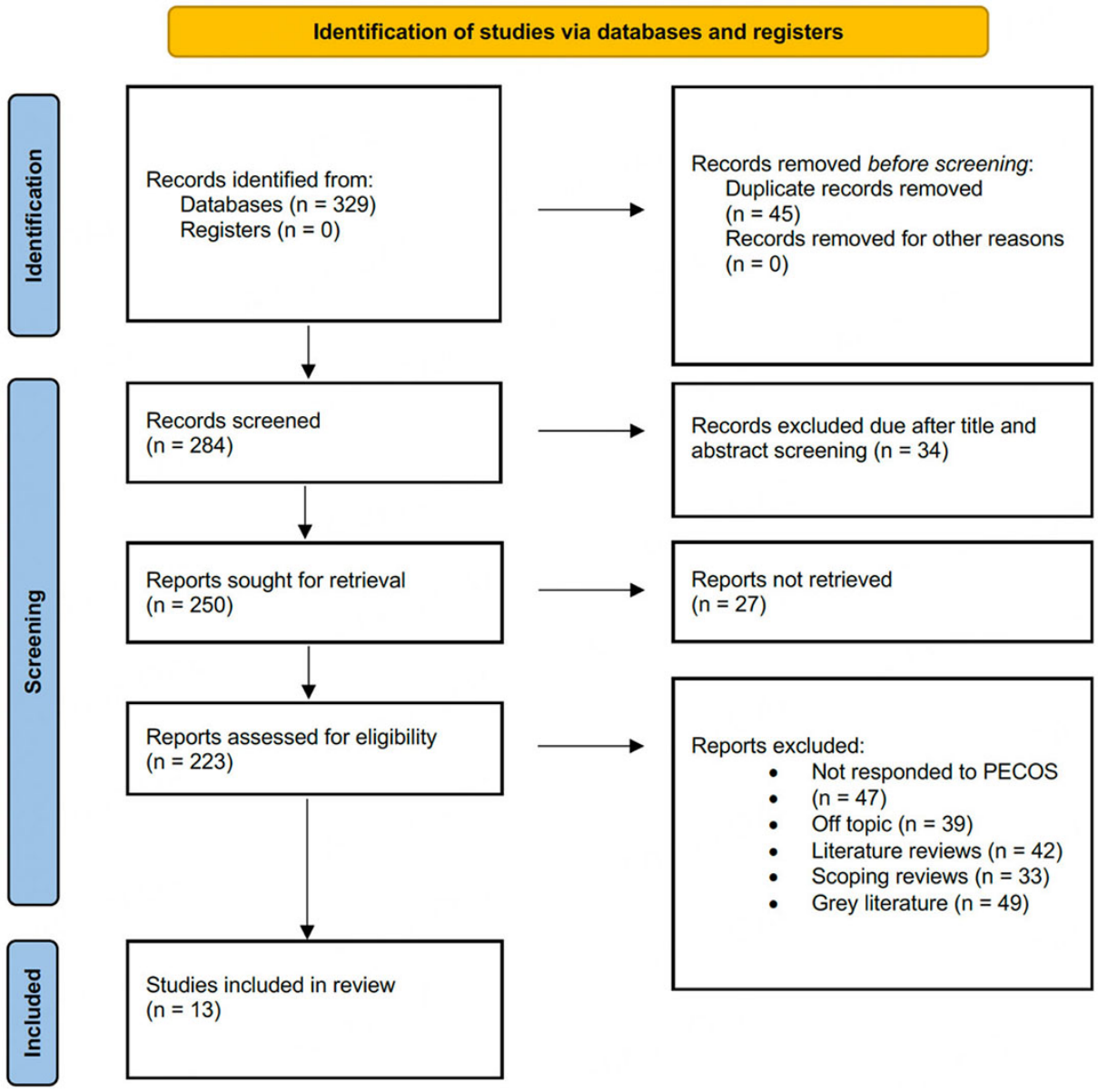


Figure 1. Description of the different stages of article selection process for the review (PRISMA FLOWCHART).

Table 1. Inclusion and exclusion criteria for the review

Inclusion criteria	Exclusion criteria
Studies investigating therapeutic interventions for MRONJ healing	Title and abstrct Studies not focused on MRONJ healing
Studies involving human participants	Animal studies, in vitro studies, or reviews
Studies published in English language	Studies published in languages other than English
RCTs, retrospective/cohort studies	Case reports, literature reviews, grey literature
Studies with a clear description of the therapeutic intervention and outcome measures	Studies with incomplete or unclear descriptions of the therapeutic intervention or outcome measures
Studies published within the last 20 years (2005-2025)	

Studies - of Interventions) tool[16], while the Cochrane's Risk of Bias 2 Tool (RoB 2) 2.0[17] was applied to randomized controlled trials. Two reviewers independently evaluated the risk of bias; disagreements were

Table 2. Search strings/phrases used across the different databases

Database	Search string
PubMed	((("osteonecrosis of the jaw"[MeSH]) OR ("medication-related osteonecrosis of the jaw"[All Fields])) AND (("healing"[MeSH]) OR ("bone regeneration"[MeSH])) AND (("therapy"[MeSH]) OR ("intervention"[MeSH]))
Scopus	("osteonecrosis of the jaw" OR "medication-related osteonecrosis of the jaw") AND ("healing" OR "bone regeneration") AND ("therapy" OR "intervention")
Web of Science	(("osteonecrosis of the jaw" OR "medication-related osteonecrosis of the jaw") AND ("healing" OR "bone regeneration")) AND ("therapy" OR "intervention")
Cochrane Library	("osteonecrosis of the jaw" OR "medication-related osteonecrosis of the jaw") AND ("healing" OR "bone regeneration") AND ("therapy" OR "intervention")
Embase	(("osteonecrosis of the jaw"/exp) OR ("medication-related osteonecrosis of the jaw"/exp)) AND (("healing"/exp) OR ("bone regeneration"/exp)) AND (("therapy"/exp) OR ("intervention"/exp))
CINAHL	(("osteonecrosis of the jaw" OR "medication-related osteonecrosis of the jaw") AND ("healing" OR "bone regeneration")) AND ("therapy" OR "intervention")
Google Scholar	("osteonecrosis of the jaw" OR "medication-related osteonecrosis of the jaw") AND ("healing" OR "bone regeneration") AND ("therapy" OR "intervention")

resolved through consensus or third-party adjudication. Inter-reviewer agreement, assessed using Cohen's kappa, was 0.87, indicating strong concordance.

RESULTS

Trial inclusion process

In total 329 records were identified from database searches, and no records from the trial registries were found. After the elimination of 45 duplicate entries, 284 records remained for screening. After title and abstract screening, 250 articles were considered eligible for full-text assessment. However, 27 full-text articles could not be retrieved, leading to 223 studies considered eligible. The primary reasons for exclusion were studies not meeting PECOS criteria (n = 47), off-topic articles (n = 39), literature reviews (n = 42), scoping reviews (n = 33), and grey literature (n = 49). After applying all exclusion criteria, 13 studies[18-30] met the eligibility requirements and were included in the final analysis.

Assessed levels of bias

Risk of bias was classified as low, moderate, or high, based on the domain-specific criteria outlined in the Cochrane RoB 2.0 tool (for randomized trials) and the ROBINS-I tool (for non-randomized studies). Each domain - such as confounding (D1) and participant selection (D2) - was independently assessed by two reviewers, with the overall risk of bias determined by the highest level of concern in any domain.

Most studies[18,20,23,24,26] were rated as having a low overall risk of bias [Figure 2], while some[19,25,30] presented moderate concerns, and one study[28] was classified as having moderate risk of bias [Figure 3]. In detail, the studies by Freiberger *et al.*[18], Mozzati *et al.*[20], Park *et al.*[23], Poxleitner *et al.*[24], and Sahin *et al.*[26] showed a low risk of bias across all domains. Giudice *et al.*[19], Ristow *et al.*[25], and Yüce *et al.*[30] demonstrated concerns in multiple domains. Soutome *et al.*[28] had a moderate overall risk of bias, while Mücke *et al.*[21] exhibited a high risk specifically in domain D4, and Ohbayashi *et al.*[22] showed some concern in domain D5. Sim *et al.*[27] and Varoni *et al.*[29] demonstrated low risk in most domains, although minor concerns were noted in domains D5 and D7, respectively.

Baseline characteristics observed

Table 3 presents the trials included in this review[18-30] and their respective outcome assessments. The trials by Freiberger *et al.*[18] and Giudice *et al.*[19] had a slight majority of female participants, with 44%:56% and 42%:58%, respectively. In direct contrast, Mozzati *et al.*[20] reported marked imbalance, at 4%:96% and 2%:98% male:female (M:F) ratios for Protocols A and B, respectively. This marked gender imbalance could be due to

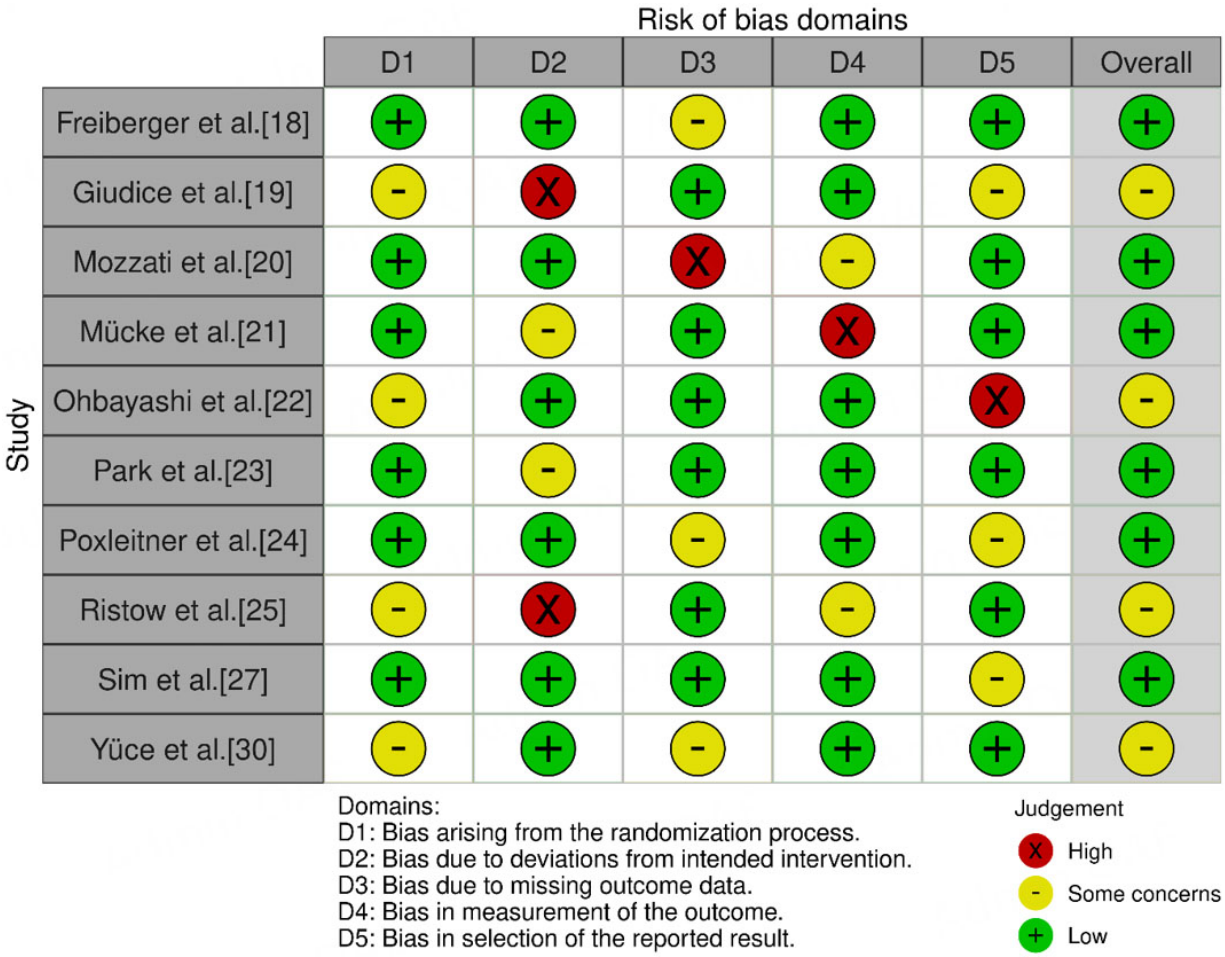


Figure 2. Bias assessed using RoB 2.0 tool.

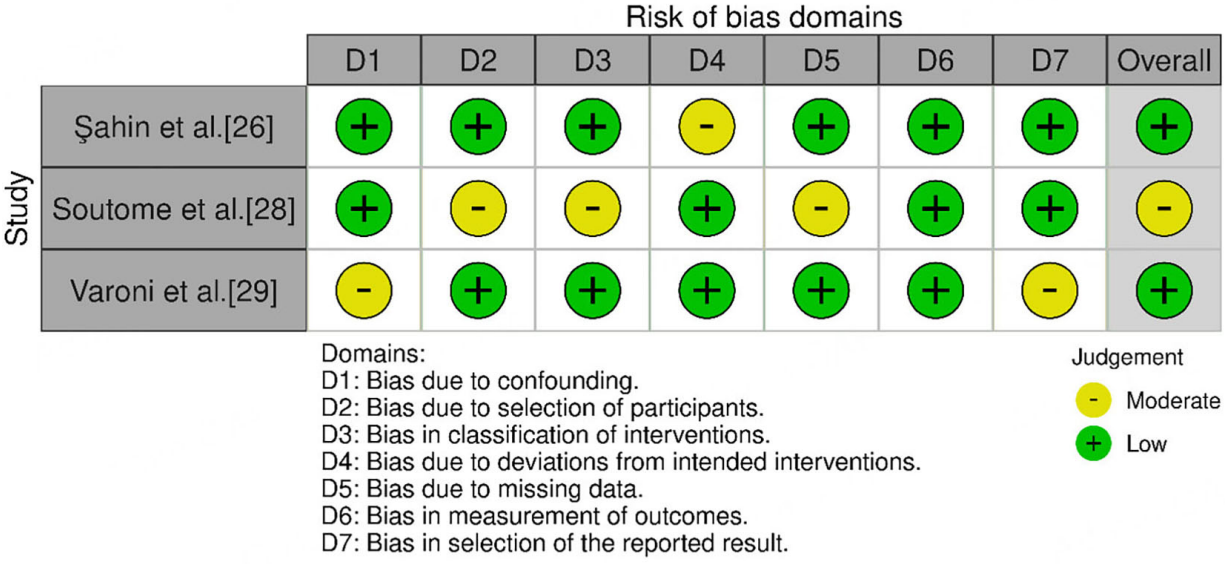


Figure 3. Bias assessed using ROBINS-I tool.

Table 3. Studies included in the review and their observed assessments

Study	Year	Design/Sample	Intervention	Follow-up	Primary outcome	Key findings
Surgical interventions						
Freiberger *et al.*[18]	2012	RCT, 49	HBO *vs.* standard care	2 years	Lesion size, pain	HBO improved lesions (68%) and faster pain relief
Mozzati *et al.*[20]	2013	RCT, 700	Protocol A *vs.* Protocol B	12-72 month	Post-op MRONJ incidence	Both protocols effective; Protocol B preferred (less trauma)
Mücke *et al.*[21]	2016	RCT, 253	Standard care *vs.* prophylactic antibiotics + tension-free closure	2-4 years	MRONJ incidence/year	Group B reduced MRONJ incidence by 82%
Sahin *et al.*[26]	2022	Retrospective, 21	Ultrasonic surgery + L-PRF + Nd:YAG laser	1-12 month	Mucosal healing	100% success; 2 delayed healing cases
Soutome *et al.*[28]	2021	Retrospective, 38	Segmental/marginal mandibulectomy	1-3+ month	Healing	55.3% complete healing; PR type influences outcome
Varoni *et al.*[29]	2021	Retrospective, 35	Antibiotics, pentoxifylline, tocopherol + sequestrectomy	24 month	Healing, recurrence	92% long-term healing; 30% recurrence
Adjunctive/pharmacological interventions						
Giudice *et al.*[19]	2018	RCT, 47	PRF *vs.* standard care	1 year	Mucosal integrity	PRF improved short-term mucosal integrity (T1 only)
Ohbayashi *et al.*[22]	2020	RCT, 13	Weekly *vs.* daily TPTD	6 month	MRONJ stage	Daily TPTD showed better improvement
Park *et al.*[23]	2017	RCT, 55	L-PRF *vs.* L-PRF + rhBMP-2	6 month	Healing	BMP-2 addition improved resolution (75% vs. 48%)
Poxleitner *et al.*[24]	2020	RCT, 77	Post-extraction primary closure *vs.* PRF clot	90 days	Mucosal coverage	No significant difference between groups
Ristow *et al.*[25]	2020	RCT, 160	Epiperiosteal *vs.* subperiosteal closure	≥ 6 month	MRONJ prevention	Comparable success rates
Sim *et al.*[27]	2020	RCT, 34	Teriparatide *vs.* placebo	1 year	MRONJ staging	Teriparatide improved lesion resolution
Yüce *et al.*[30]	2021	RCT, 28	CGF *vs.* control	6 month	Soft tissue healing	No significant benefit of CGF

the specific population sampled in that protocol (e.g., postmenopausal women with osteoporosis). Among the available data, Mücke *et al.*[21] included only male participants, and Ohbayashi *et al.*[22] included only female participants. Park *et al.*[23] reported an almost equal distribution: 57%:43%, and 43%:57% M:F in the Leukocyte- and Platelet-Rich Fibrin (L-PRF) and L-PRF + rhBMP-2 (recombinant human bone morphogenetic protein-2) groups, respectively. Poxleitner *et al.*[24] found a majority of females: 0%:100% and 3%:97% M:F in Groups A and B, respectively. The other studies presented various M:F ratios, ranging between 7:14 (reported by Sahin *et al.*[26]) and 53:47 (reported by Sim *et al.*[27]). Sample sizes differed between 13 participants in the study of Ohbayashi *et al.*[22] and 700 participants in the study of Mozzati *et al.*[20]. Most of the sample sizes included between 30 and 100 subjects.

Interventions and groups assessed

The study objectives differed: some focused on the prevention of MRONJ, including those conducted by Freiberger *et al.*[18], Mozzati *et al.*[20], Park *et al.*[23], Poxleitner *et al.*[24], and Sahin *et al.*[26]; whereas others - Giudice *et al.*[19], Mücke *et al.*[21], Ohbayashi *et al.*[22], Ristow *et al.*[25], Sim *et al.*[27], Soutome *et al.*[28], Varoni *et al.*[29], and Yüce *et al.*[30] - investigated treatment strategies for patients with MRONJ. With respect to study design, the majority were prospective randomized controlled trials (RCTs), including studies by Freiberger *et al.*[18], Mozzati *et al.*[20], Park *et al.*[23], Poxleitner *et al.*[24], Ristow *et al.*[25], and Sim *et al.*[27]; several were retrospective cohort studies, such as those by Giudice *et al.*[19], Ohbayashi *et al.*[22], Soutome *et al.*[28], and Varoni *et al.*[29]; and only one was a multicenter RCT, reported by Yüce *et al.*[30].

Interventions for MRONJ varied across studies. Hyperbaric oxygen (HBO) therapy was investigated in the study by Freiberger *et al.*[18], while platelet-rich fibrin (PRF) was evaluated in studies by Mozzati *et al.*[20], Park *et al.*[23], and Poxleitner *et al.*[24]. rhBMP-2 was also assessed in the study by Park *et al.*[23]. Surgical approaches were explored as well, including ultrasonic piezoelectric bone surgery, as reported by Sahin *et al.*[26], and segmental or marginal mandibulectomy, as in the study by Varoni *et al.*[29]. Control groups differed across studies: some used standard care, as reported by Freiberger *et al.*[18] and Mozzati *et al.*[20]; others employed placebo treatments, as reported by Sim *et al.*[27] and Yüce *et al.*[30]; in addition, non-PRF placement was used as a control in the study by Mozzati *et al.*[20], and no concentrated growth factor (CGF) placement served as the control in the work of Yüce *et al.*[30].

Results observed

The follow-up periods ranged from 1 month[28] to 2 years[18], with varying intervals in between. The outcome measures also differed across studies, reflecting the variations in objectives and interventions.

Freiberger *et al.*[18] reported a statistically significant improvement in the HBO group following treatment; 68% of patients improved, with a mean time to improvement of 39.7 weeks. Giudice *et al.*[19] found that the PRF group showed significant variations in mucosal integrity, absence of infection, and pain only at T1. Mozzati *et al.*[20] reported 100% success in both groups. Conversely, Mücke *et al.*[21] concluded that Group B showed a highly significant reduction in MRONJ incidence, with an observed risk of 82%.

Ohbayashi *et al.*[22] reported significant improvement in MRONJ stage for the daily teriparatide (TPTD) group. Park *et al.*[23] observed a significantly higher complete resolution rate in the L-PRF + rhBMP-2 group compared to the L-PRF group (75.2% *vs.* 48%, $P = 0.028$). Poxleitner *et al.*[24] reported no statistically significant between-group differences. Ristow *et al.*[25] reported successful healing in 100% of cases; however, two patients showed delayed healing.

Sahin *et al.*[26] demonstrated that a combined approach of surgical debridement and adjunctive teriparatide significantly improved bone healing in patients with MRONJ. Sim *et al.*[27] reported a complete healing rate of 55.3%, with poor outcomes influenced by platelet reactivity (PR) patterns. Soutome *et al.*[28] reported a long-term healing rate of 92%, though the recurrence rate was 30.4%. Varoni *et al.*[29] found no significant differences in postoperative healing between groups. For Yüce *et al.*[30], specific outcome measures were not clearly extractable.

DISCUSSION

Converging and diverging findings on MRONJ treatment strategies were observed during comparison with the included studies. As we see, surgical procedures are effective therapeutic approaches to MRONJ in numerous studies. Mozzati *et al.*[20] and Ristow *et al.*[25] presented consistent results, with Mozzati *et al.*[20] preferring Protocol B for less trauma to soft and hard tissues. Similarly, Sahin *et al.*[26] showed success using

the surgical protocol for advanced MRONJ. Collectively, this would indicate that surgery may prove to be particularly beneficial in patients with high-stage MRONJ. Nevertheless, the modest sample sizes in these analyses limit the available evidence, and the need for larger, well-powered clinical trials is identified.

Another group of studies supports the use of adjunctive therapies to enhance MRONJ treatment outcomes. Park *et al.*[23] demonstrated an enhanced healing in the presence of bone morphogenetic protein 2 (BMP-2) and Sim *et al.*[27] also proposed that teriparatide, possibly used as an effective therapeutic agent, may be potentially useful in MRONJ treatment. These findings imply that adjunctive therapy with adjuvant therapies such as BMP-2 and teriparatide can also be effective in increasing success rates in the treatment of MRONJ. However, Yüce *et al.*[30] identified no benefit from CGF, thus, the effect of adjunctive treatments may be based on patient characteristics, disease stage or treatment protocol.

In contrast, in numerous studies, outcomes suggested findings that varied from most others. Freiberger *et al.*[18] suggested that HBO treatment could serve as a promising adjunct to, or alternative for, surgical approaches in MRONJ. Giudice *et al.*[19] stated that PRF enhanced immediate healing while long-term efficacy of PRF compared to other treatments has not yet been established. Finally, Mücke *et al.*[21] demonstrated that antibiotic prophylaxis combined with tension-free wound closure significantly decreased MRONJ incidence. Similar preventive approaches were also investigated in studies by Poxleitner *et al.*[24] and Yüce *et al.*[30], although their results were more heterogeneous.

Notably, Yüce *et al.*[30] found that CGF did not significantly improve soft tissue repair in MRONJ, a result that contradicts the findings from other adjunctive therapies. These results may have limited generalizability, as they are specific to the patient population and clinical setting of the study. Ohbayashi *et al.*[22] and Varoni *et al.*[29] presented results which are difficult to directly compare, and looked at novel treatments including daily teriparatide treatment, with combined pharmacological-surgical protocols, respectively. Several non-randomized studies showed moderate to high risk of bias, leading to caution in translation to clinical practice.

Studies by Mozzati *et al.*[20], Ristow *et al.*[25], and Sahin *et al.*[26] share a common focus on evaluating the effectiveness of surgical interventions in treating MRONJ. Similarly, Park *et al.*[23] and Sim *et al.*[27] both investigated the role of adjuvant therapies - BMP-2 and teriparatide, respectively - in MRONJ treatment. The remaining studies varied considerably in design and focus, examining diverse methods for both prevention and treatment of MRONJ.

In cases of early-stage MRONJ, patients are often asymptomatic with minimal bone exposure and conservative/noninvasive treatment protocols have been proposed as a reasonable alternative[2]. The problem is that these patients are often poor candidates for long-term antibiotic use due to advanced age, previous prolonged chemotherapy regimens, or metastatic bone disease. While local or systemic antibiotic therapy may alleviate symptoms, this relief is often short-lived; recurrences occur on average every three weeks[31], leading researchers to seek alternative treatment modalities. Conservative management might alleviate the symptoms and infections in the short run, but one must not forget that osteonecrosis is not going to be cured by these methods[32]. However, if there is exposed necrotic bone, then conservative management fails because the bone tissue is dead and therefore can never be restored to its former state.

The decision to discontinue medications prior to surgical intervention for MRONJ remains a topic of debate[33]. A recent systematic review and meta-analysis found that patients with multiple myeloma or osteoporosis who underwent a "drug holiday" from alendronate, ibandronate, or zoledronate exhibited a higher prevalence of complete recovery[34]. On the other hand, some researchers argue that withdrawal of

these drugs is unnecessary due to the long half-life of bisphosphonates (approximately 11 years), which are sequestered in bone hydroxyapatite crystals. There is also a concern that drug discontinuation may exacerbate underlying conditions, such as bone pain or skeletal weakness.

Similar to our findings, Beth-Tasdogan *et al.*[35] conducted a systematic review to assess interventions for the prophylaxis and treatment of MRONJ. Including only RCTs, however, they made the conclusion that the certainty of existing evidence was low or very low. Our review demonstrated this and found that evidence for MRONJ interventions remains limited and of low quality. Similarly, Kawahara *et al.*[36] described a systematic literature review to produce updated recommendations for dental treatment which would be directed to avoid the onset of MRONJ. Their findings emphasized the importance of producing clinical guidelines from scientific evidence; they mirrored our own findings that high-quality evidence is a requisite for clinical practice.

Kuroshima *et al.*[37] conducted this review to summarize the current knowledge and theories on MRONJ from clinical perspective and basic science perspective. The study included MRONJ definition, epidemiology, causative drugs, histopathology, and pathophysiology. Likewise, our work explored MRONJ epidemiology, pathophysiology and risk factors. Similarly, AlRowis *et al.*[38] performed a review of the literature to identify diagnostic criteria and risk factors of MRONJ. They also discussed its pathophysiology, preventive methods, and treatments. Their review had covered the commonality across epidemiology, diagnostic criteria, risk factors, pathogenesis and therapeutic management. As there is high heterogeneity in interventions and outcome measures as well as follow-up periods across the included studies, a meta-analysis was not possible and a qualitative assessment was thus conducted solely.

Limitations

Our results should be interpreted in the context of several limitations. Variability in study design and population may have contributed to heterogeneity in the findings, limiting the ability to perform a meta-analysis. Moreover, only a few studies were available investigating specific interventions such as add-on therapies, which could limit the extent to which the findings can be generalized. Publication bias is also a consideration as this review is based entirely on published literature. Similarly, there were limitations with respect to differences in follow-up periods and outcome measures, but both were included to prevent a significant loss of the body of available literature.

Clinical recommendations

Based on our findings, several recommendations were made for managing MRONJ. Oral surgeons, oncologists and other health professionals must take a comprehensive multidisciplinary approach to ensure optimal treatment outcomes. For the more advanced stages of MRONJ, surgical procedures such as debridement and resection are indicated. Prophylactic measures should be properly defined, with tension-free wound closure. Adjuvants are shown to possess promising therapeutic potential, especially bone morphogenetic protein-2 and teriparatide. Care must be tailored to patients' individual disease stage and history. Finally, future research will need to determine more definitively the degree to which these interventions are both effective and best implemented depending on the clinical case and also to formulate evidence-based guidelines in managing MRONJ.

CONCLUSION

Based on this review, surgical interventions appear most successful for advanced-stage MRONJ, while BMP-2 and teriparatide have shown efficacy in promoting healing in some cases. Prophylactic measures, such as antibiotics and tension-free wound closure, may reduce the risk of MRONJ in high-risk populations.

However, well-designed, multicenter studies are needed to establish optimal treatment protocols for the various stages of MRONJ.

DECLARATIONS

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Authors' contributions

Conceptualized and designed the study: Veeraraghavan VP, Minervini G
Drafted the manuscript: Veeraraghavan VP, Piccolo S
Data analysis: Fiorito N, Minervini G, Russo D
Conducted the literature search and data collection: Uzuncibuk H, Fiorito N
Prepared the figures and tables: Uzuncibuk H, Fiorito N, Marrapodi MM, Russo D
Contributed to literature selection, quality evaluation, and manuscript revision: Cervino G, Minervini G
All authors reviewed and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the authors used DeepL Translate for language checking/grammar correction. After its use, the authors thoroughly reviewed, verified, and revised all content to ensure accuracy and originality. The authors take full responsibility for the integrity and final content of the published article.

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None.

Conflicts of interest

Minervini G and Marrapodi MM serve as Junior Editorial Board Members of the *Journal of Cancer Metastasis and Treatment*. They had no involvement in the editorial process of this manuscript, including reviewer selection, handling, or decision-making, while the other authors have declared that they have no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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