Comparison of the Effectiveness of Conservative and Surgical Treatment of Medication-Related Osteonecrosis of the Jaw: a Systematic Review

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ABSTRACT

Objectives: The objective of this systematic review is to evaluate the current knowledge on the effectiveness of conservative and surgical treatment of medication-related osteonecrosis of the jaw.
Material and Methods: MEDLINE (PubMed), ScienceDirect and Cochrane Library search in combination with hand-search of relevant journals was conducted including human studies published in English between January 2017 and February 2023. Studies assessing treatment strategies for medication-related osteonecrosis of the jaw (MRONJ) were included. Quality and risk-of-bias assessment were evaluated by Joanna Briggs Institute (JBI) Risk of Bias tool.
Results: A total of 4227 articles were screened from which 9 studies (7 cohort studies and 2 randomized controlled trials) met the inclusion criteria and were included in the final data synthesis. Two studies evaluate effectiveness of conservative approaches for treating MRONJ, 5 studies evaluate surgical approaches effectiveness, and 2 studies compare between those approaches. The follow-up period ranged from 6 months to 60 months. According to bias assessment, the mean JDI score of the included studies was > 9 ("low risk of bias"). The stage of the disease, the procedure performed on the patient and the results of the treatment were presented.
Conclusions: Surgical therapy seems to be superior to conservative therapy for the management of adverse stages medication-related osteonecrosis of the jaws, while conservative treatment appears to yield good outcomes at asymptomatic patients with early stages of the disease.

Keywords: bisphosphonate-associated osteonecrosis of the jaw; bisphosphonates; conservative treatment; denosumab; oral surgery.

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INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a severe complication that can develop following any kind of surgical operation in the alveolar ridge region. In some cases, it can also develop spontaneously in patients who take antiresorptive or antiangiogenic medications for metabolic disorders [1]. This is most related to the use of bisphosphonates, drugs used to treat a variety of bone diseases, including osteoporosis, Paget's disease of the bone, multiple myeloma, and metastatic cancer [1-5]. Other medications, including denosumab and anti-angiogenic agents, have also been linked to the development of MRONJ [2].

The use of bisphosphonate drugs became popular in the late 20th century for the treatment of many medical conditions associated with abnormalities of bone turnover. However, cases of osteonecrosis associated with bisphosphonates were first described in 2003 [1]. The pathogenesis and explanation of why osteonecrosis primarily affects the jaw skeleton, as well as the best way to treat this complex medical condition, remain controversial [3,4]. Since their discovery in the late 1960s, bisphosphonates have become a very important drug in the treatment of skeletal disorders accompanied by increased bone resorption due to increased osteoclast numbers or activity [6]. These substances have a high affinity for calcium ions, so they are directed to the hydroxyapatite mineral structure of bones, where bisphosphonates are absorbed by active osteoclasts and inhibit the latter's function [7]. As a general medical term, osteonecrosis defines a condition in which bone tissue cells die due to variety of reasons. Osteonecrosis of the jaws, as a specific disease affecting the bone tissues of the jaws, can be conventionally classified as MRONJ, traumatic, nontraumatic, spontaneous osteonecrosis, and osteoradionecrosis [4].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper on 2009 explored the causal link between bisphosphonates and osteonecrosis of the jaw [8]. Bisphosphonate related osteonecrosis of the jaw (BRONJ) or in a terminology, updated in 2014 by AAOMS, MRONJ constitutes a relatively rare but serious medical condition with potentially severe complications. In 2014, AAOMS position paper on MRONJ [9,10], formulated an updated list of clinical criteria for the diagnosis of MRONJ as follows:

- Use of antiresorptive or antiangiogenic medications currently or in the past.
- Exposed bone or bone that can be probed through a maxillofacial intraoral or extraoral fistula that has been present for at least 8 weeks.
- There was no history of jaw radiation therapy or obvious metastatic disease to the jaws.

The AAOMS MRONJ staging system [9] includes 4 distinct clinical stages that are important in selecting the appropriate treatment:

- At risk - there was no evidence of necrotic bone in patients who had received either oral or intravenous bisphosphonates.
- Stage 0 - there was no clinical indication of necrotic bone, but there were other nonspecific clinical findings, radiographic alterations and symptoms.
- Stage 1 - there was exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection. Treatment for stage 1 MRONJ involves discontinuing the offending medication if possible and implementing conservative measures such as antibiotics, pain management and oral hygiene instructions.
- Stage 2 - exposed and necrotic bone, or fistulae that probe to bone, coupled with infection as evidenced by pain and erythema in the exposed bone region, with or without purulent drainage. Treatment for stage 2 MRONJ involves the removal of any loose bone fragments and debridement of the affected area to promote healing. Antibiotics and pain management may also be used as needed.
- Stage 3 - exposed and necrotic bone or a fistula probing to bone in patients suffering from pain, infection, or pathologic fracture. Treatment for stage 3 MRONJ involves more aggressive measures such as surgery to remove the affected bone and reconstruction of the jaw using bone grafts or other materials. Antibiotics and pain management are also used as needed, and the offending medication is usually discontinued.

There is currently no consensus on the optimal treatment strategy for MRONJ. However, two main methods of MRONJ treatment can be distinguished: conservative and surgical. Conservative treatment includes oral hygiene, chlorhexidine mouth rinses, teriparatide medications, and systemic antibiotics to control infection. In more advanced cases, surgical intervention may be necessary, including resection and debridement of necrotic bone, perforation of residual healthy bone, application of soft and hard tissue regeneration material as platelet-rich fibrin (PRF), concentrated growth factor (CGF) and bone morphogenetic protein-2 (BMP-2) [2].

The objective of this systematic review is to evaluate the current knowledge on the effectiveness of conservative and surgical treatment of medication-related osteonecrosis of the jaw.

MATERIAL AND METHODS

Protocol and registration

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews [11].

Focus question

The focus question was developed by using the population, intervention, comparison, and the outcome (PICO) framework, which is presented in Table 1.
The focus question: does conservative therapy alone provide an effective treatment outcome for MRONJ?

Types of publication

The systematic literature review included randomized controlled clinical trials, prospective and retrospective cohort studies, in which authors evaluated the effectiveness of various MRONJ therapies or specific techniques to resolve the condition, as defined in "types of outcome measures" below.

Information sources

The systematic electronic literature search was conducted on MEDLINE (PubMed), ScienceDirect (Elsevier) and Cochrane Library (John Wiley & Sons) databases in combination with hand-search of relevant journals. Additional related publications were found in the electronic "Journal of Oral & Maxillofacial Research", "Journal of Periodontology Search", "Journal of Bone and Mineral Research" and "Journal of International Oral Health".

Types of studies

In this review were included randomized controlled trials (RCTs), prospective or retrospective cohort studies published from January 2017 to February 2023.

Population

Adult individuals diagnosed with MRONJ after taking antiresorptive drugs.

Search strategy

The keywords used for the relevant articles search in the selected databases were: #1 "medication related osteonecrosis jaw" [All Fields] OR "MRONJ" [All Fields] OR "bisphosphonate related osteonecrosis jaw" [All Fields]; #2 "treatment" [All Fields] OR "therapy"; #3 "conservative" [All Fields] OR "surgical" [All Fields]. Search combination performed were #1 AND #2 AND #3. The search was limited to English language. Articles published from January 2017 until February 2023 were searched. The selected clinical studies were initially chosen by the title that matched the research question about treatment methods for treat MRONJ. Then the abstracts of each article were reviewed, and the relevance was examined according to the inclusion criteria. Studies that met all the selection criteria were processed into data expenditure.

Inclusion criteria for the selection

The following inclusion criteria were applied to retrieved bibliographic sources for inclusion in this systematic literature review:

- Time: January 2017 to February 2023.
- Human trial only.
- Language: English.
- Research type: Randomized clinical trials, retrospective and prospective cohort studies.
- Clinical studies with minimum 20 individuals.
- Male and female individuals ≥ 18 years old.

Table 1. PICO guidelines

Patient and population (P)	Adult individuals diagnosed with MRONJ after taking antiresorptive drugs
Intervention (I)	Conservative and surgical treatment for MRONJ
Comparison (C)	Comparison of different MRONJ treatment methods
Outcome (O)	Complete resolution (defined as an absence of symptoms and clinical signs of MRONJ), alterations in bony exposure and mucosal coverage, changes in radiographic lesion extent, recurrence of the condition, presence of pain and quality of life

MRONJ = medication-related osteonecrosis of the jaw.

- Patients in treatment with antiresorptive drugs and develop MRONJ, undergoing conservative or surgical procedures for treatment of MRONJ.
- Staging of MRONJ was performed according to the AAOMS.
- Follow-up period ≥ 6 months.

Exclusion criteria

The following exclusion criteria were applied:
- Excluded designs: reviews, editorials.
- Animal studies, laboratory studies.
- Studies not reporting clinical outcome.
- Patients undergo radiotherapy.
- Pregnant/breastfeeding women.

Data extraction and data items

The data was extracted to previously defined templates according to the aims of the current review. For conservative and surgical treatment of MRONJ, the following data items were extracted from the articles included in this review:
- "Author" - the publication's author was revealed.
- "Year" - reveals the publication year.
- "Study design" - indicates the type of study.
- "Control group" - patients who received nonspecific conservative/surgical treatment.
- "Test group" - patients who received specific conservative/surgical treatment.
- "Mean age" - the average age of the participants in each research group was reported.
- "Stages of MRONJ" - describes patient's status while the study was conducted according to the AAOMS.
- "Recurrence rate" - describes the possibility of recurrence (after treatment).
- "Observation period" - reveals the time in months in which the test and control group patients were followed.
- "Results" - reveals clinical parameters and their values at baseline and after the follow-up period: complete resolution (defined as an absence of symptoms and clinical signs of MRONJ), alterations in bony exposure and mucosal coverage, changes in radiographic lesion extent, recurrence of the condition, presence of pain and quality of life.
- "Conclusions" - short description of each article's conclusions.

Selection process of articles

The selection process began with the identification of articles based on the previously mentioned keywords, followed by an analysis of the titles and abstracts. In the second stage, full-text articles were selected for evaluation. The titles and abstracts of the referred reports were screened separately by two reviewers (R.S. and M.S.). The senior researcher (E.J.) checked for possible inconsistencies and made decisions after consultation with the reviewers. Cohen's kappa coefficient (κ) values for inter-rater reliability were calculated for abstract and title evaluations, selecting 10% of the publications.

Risk of bias

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for randomized controlled trials [12] (Table 2) and JBI Critical Appraisal Checklist for

Table 2. The Joanna Briggs Institute Critical Appraisal Checklist for randomized controlled trials (RCT)

Question number	Defined question
Q1	Was true randomization used for assignment of participants to treatment groups?
Q2	Was allocation to treatment groups concealed?
Q3	Were treatment groups similar at the baseline?
Q4	Were participants blind to treatment assignment?
Q5	Were those delivering treatment blind to treatment assignment?
Q6	Were outcomes assessors blind to treatment assignment?
Q7	Were treatment groups treated identically other than the intervention of interest?
Q8	Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?
Q9	Were participants analysed in the groups to which they were randomized?
Q10	Were outcomes measured in the same way for treatment groups?
Q11	Were outcomes measured in a reliable way?
Q12	Was appropriate statistical analysis used?
Q13	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Table 3. The Joanna Briggs Institute Critical Appraisal Checklist for cohort studies

Question number	Defined question
Q1	Were the two groups similar and recruited from the same population?
Q2	Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Q3	Was the exposure measured in a valid and reliable way?
Q4	Were confounding factors identified?
Q5	Were strategies to deal with confounding factors stated
Q6	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
Q7	Were the outcomes measured in a valid and reliable way?
Q8	Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
Q9	Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
Q10	Were strategies to address incomplete follow-up utilized?
Q11	Was appropriate statistical analysis used?

cohort studies [13] (Table 3) were used to assess the methodological quality of the studies that met the inclusion criteria. "Yes", "no", "unclear", or "not applicable" was given to each criterion. Methodological quality was categorized as follows: "high risk of bias", when the study scored up to 49% of positive answers; "moderate risk of bias", when study scored between 50 and 69% of positive answers; "low risk of bias", when study reached more than 70% of favourable answers.

Synthesis of the results

Selected data were collected and tabulated into the following fields: study; year of publication; study design; population; gender; age; study group; observation period; treatment outcome; results; conclusions.

Statistical analysis

Mendeley® version 2.79 (Elsevier; London, UK) reference manager software was used for article management. The level of agreement between the two raters in selecting abstracts and studies to be read in full text were measured using κ. Meta-analysis was conducted if the included studies were of similar comparison and reporting identical outcome measures.

RESULTS

Study selection

The database search showed 4227 articles in PubMed, ScienceDirect and Cochrane Library. After limited the search to a post-2017 publication date, obtained 2339 articles. After removing 215 duplicate articles there were 2124 articles left. A total of 2108 articles were excluded during the early stage of the screening process due to their irrelevant titles and abstracts; reviews and case studies were also removed during this stage. Sixteen full text articles were assessed for eligibility. Finally, 9 studies [14-22] were included (Figure 1). The level of agreement between the two authors (R.S. and M.S.) in selecting abstracts were measured at $\kappa = 0.92$.

Exclusion of studies

Seven studies [23-29] were eliminated because they did not meet the inclusion criteria: MRONJ not classified according the AAMOS [25-27], less than 20 patients [23,24], animal studies [28,29].

Quality assessment of the included studies

The quality of the included studies is summarized in the Table 4 and 5. All studies were characterized as high quality: two randomized control trials [14,15] were characterized by a JBI score of 11 and 7 cohort studies [16-22] had a mean JBI score of > 9.

Study characteristics

The studies that were included in this review evaluated the effectiveness of conservative and surgical treatment methods in the treatment of MRONJ. Two studies evaluated the effectiveness of conservative methods in the treatment of MRONJ, 5 evaluated the effectiveness of surgical methods, and the remaining 2 studies compared both methods with each other. A total of 472 patients were included in this systematic literature review.

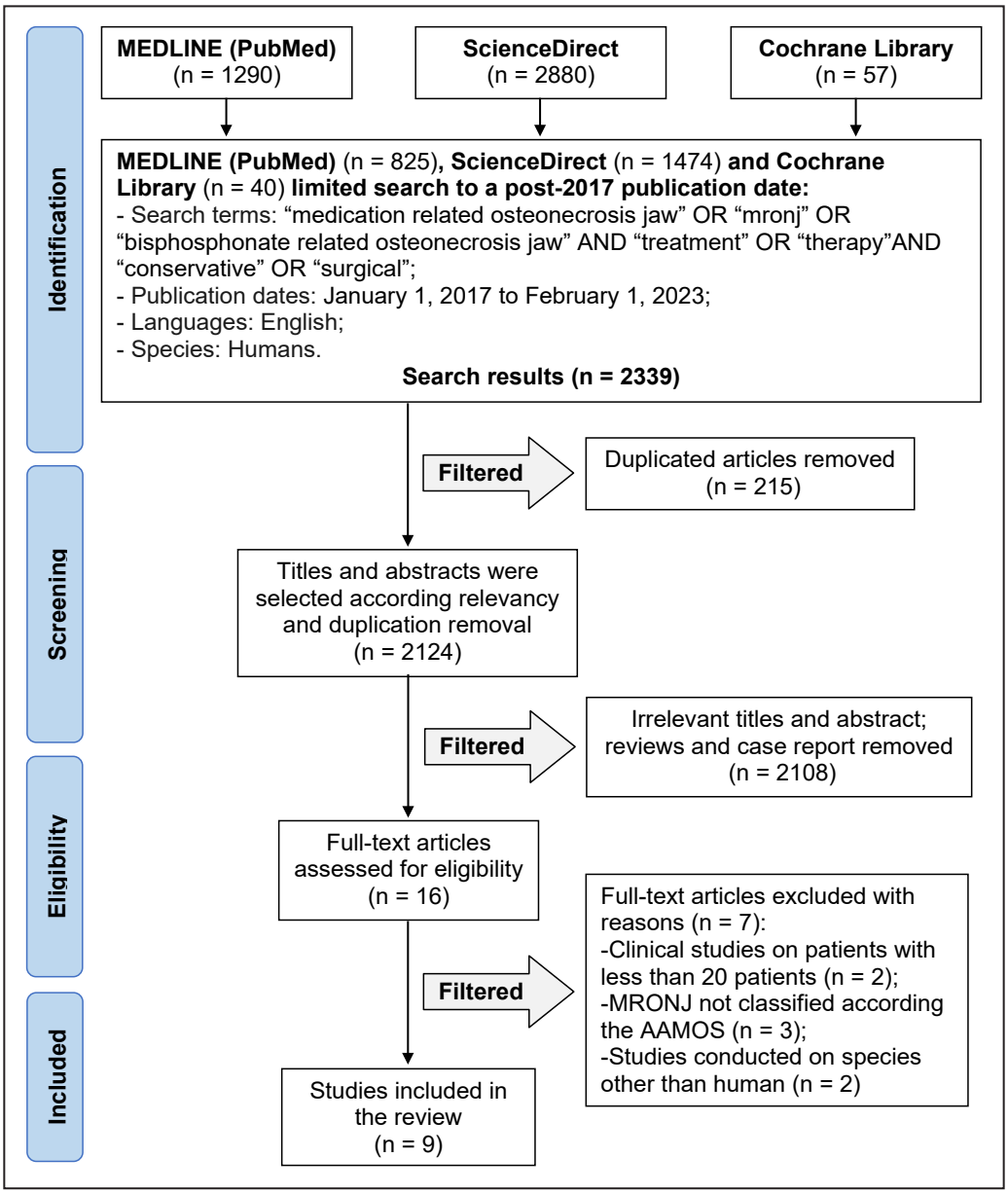

Figure 1. PRISMA flow diagram.

Table 4. Results of randomized controlled trials from The Joanna Briggs Institute Critical Appraisal Checklist

Study	Year of publication	Study design	Checklist													
			Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q11	Q12	Q13
Sim et al. [14]	2020	Randomized control trial	+	+	+	+	+	?	+	?	+	+	+	+	+	+
Yüce et al. [15]	2021	Randomized control trial	+	+	+	?	-	+	+	+	+	+	+	+	+	+

? = unclear; + = yes; - = no.

Characteristics of conservative treatment

A randomized clinical trial by Sim et al. [14], included 34 patients diagnosed with MRONJ after treatment with bisphosphonates or denosumab and treated conservatively (Table 6). The study evaluated the efficiency of teriparatide medication as a therapeutic agent for MRONJ. Patients were divided into two groups according to treatment modalities, including teriparatide subcutaneous injection or not. During the follow-up period, bone density and volume were analysed to evaluate the outcomes. Teriparatide treatment resulted in significantly better resolution of MRONJ lesions compared with placebo injection

Table 5. Results of cohort studies from The Joanna Briggs Institute Critical Appraisal Checklist

Study	Year of publication	Study design	Checklist										
			Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Eguchi et al. [16]	2017	Retrospective cohort study	+	+	+	+	+	+	+	+	+	+	+
Park et al. [17]	2017	Prospective cohort study	+	+	+	+	?	+	+	+	+	?	+
Ristow et al. [18]	2018	Retrospective cohort study	NA	NA	+	+	+	?	+	+	+	+	+
El-Rabbany et al. [19]	2019	Retrospective cohort study	+	+	+	-	-	+	+	+	+	+	+
Guo and Guo [20]	2020	Retrospective cohort study	+	+	+	-	?	+	+	+	+	+	+
Szentpeteri et al. [21]	2020	Retrospective cohort study	-	+	+	+	+	+	+	+	+	+	+
Şahin et al. [22]	2021	Retrospective cohort study	NA	NA	+	+	?	+	+	+	+	+	+

? = unclear; + = yes; - = no; NA = not applicable.

(P = 0.013). In addition, teriparatide was associated with greater bone volume and thus reduced bony defect size to a greater extent in patients after 52 weeks (P = 0.017).

In a retrospective study conducted by Ristow et al. [18], investigated the efficiency of non-surgical conservative treatment stage 1 MRONJ lesions after bisphosphonates or denosumab therapy (Table 6). Seventy-five patients with 92 lesions were treated with antimicrobial mouth rinse three times a day with 0.2% chlorhexidine solution and daily topical application of 1% chlorhexidine gel, no antibiotics were used. In order to execute a controlled manual cleansing of the affected region, follow-up appointments were conducted at least every 4 weeks. Mucosal integrity and absence of infection were analysed to evaluate the outcomes during follow-up period. Mucosal integrity was only obtained in 8 of 92 (8.7%) lesions without signs of residual infection over the entire observational time, whereas 84 of 92 lesions (91.3%) retained an exposed jawbone. Worsening stage occurs in 79.8% of the lesion with no mucosal integrity, indication for surgical procedures was set in 57 lesions.

Characteristics of surgical treatment

In a retrospective study conducted by Guo and Guo [20], presented promising results concerning cortical bone perforation as a therapy for patients with MRONJ after bisphosphonates therapy (Table 7). Twenty-eight patients diagnosed with stage 2 - 3 MRONJ were allocated into 2 groups according to the treatment plan, which was surgical treatment with or without cortical bone perforation. The control group treated with sequestrectomy and curettage while the test group underwent in addition, cortical perforations of the residual healthy bone to allow the infiltration of the adjacent blood supply to the surgical site. During the last 30 months of postoperative follow-up, mucosal coverage and recurrence of exposed bone or fistula at the operated site were analysed to evaluate the outcomes. Mucosal healing was achieved in 8 of 10 (80%) patients from test group, whereas 4 of 18 patients (22.22%) in control group over the entire observational time. The treatment success was significantly greater in the test group (P = 0.005).

Yüce et al. [15] studied 28 osteoporotic patients who had a diagnosis of MRONJ stage 2 or 3 after bisphosphonate therapy (Table 7). The study evaluated the impact of growth factors delivered by CGF on the healing of MRONJ. Patients were randomized into 2 groups to receive surgical treatment with or without CGF incorporation. All the patients underwent dental and periodontal examinations to ensure clinically acceptable oral hygiene and an oral antibiotics 2 weeks before the surgery. The CGF group was treated with topical application of CGF at the surgical site after debridement of necrotic bone, while the control group underwent primary closure without flap mobilization after sequestrectomy and bone curettage. During the 6-month follow-up period, mucosal coverage was examined, with overall mucosal integrity in 11 of 14 (78.6%) patients in the CGF group and 8 of 14 (57.1%) patients in the control group. Data on postoperative healing were not statistically significantly different between groups (P > 0.05).

Table 6. Characteristics of conservative treatment

Study	Population	Gender	Age	Study group	Observation period	Treatment outcome	Results	Conclusions
		Male/female	Years		Months			
Sim et al. [14]	Patients diagnosed with stage 1 - 3 MRONJ underwent subcutaneous teriparatide or placebo injections.	Control: 10/9	Control: 64	Control (n = 19): treated with subcutaneous saline injections	12	Treatment was considered successful if had complete resolution of lesion which assessed by CBCT, 3D Slicer measure change in bone volumes, bone mineral density and F-fluoride PET-CT imaging was performed to measure osteoblastic responses to teriparatide	Control: 33.3% of lesions resolved by 52 weeks	Teriparatide was associated with a greater rate of resolution of MRONJ lesions compared with placebo (P = 0.013)
		Test: 8/7	Test: 64	Test (n = 15): treated with subcutaneous teriparatide 20 mg injection. Total: 47 MRONJ lesions			Test: 45.4% of lesions resolved by 52 weeks	
Ristow et al. [19]	Patients diagnosed with stage 1 MRONJ underwent conservative treatment of MRONJ.	33/42	Male: 67.5 female: 68.9	75 patients with 92 lesions were treated with antimicrobial mouth rinse, 0.2% chlorhexidine solution used three times per day, and 1% chlorhexidine gel applied topically every day	12 - 60	Treatment was considered successful if had complete mucosal coverage without signs of infection	Mucosal coverage: 8 lesions (8.7%). Exposed jaw bone: 84 lesions (91.3%)	Conservative therapy in stage 1 MRONJ leads to a healing in rare cases

MRONJ = medication-related osteonecrosis of the jaw; CBCT = conical-beam computerized tomography; PET-CT = positron emission tomography/computed tomography.

Table 7. Characteristics of surgical treatment

Study	Population	Gender	Age	Study group	Observation period	Treatment outcome	Results	Conclusion
		Male/female	Years					
Yüce et al. [15]	Female osteoporotic patients with stage 2 or 3 MRONJ underwent surgical treatment of MRONJ	Control: 0/14	Control: 73.64 (SD 5.49)	Control (n = 14): treated with sequestrectomy and bone curettage without application of CGF	6 months	Treatment was considered successful if had soft tissue coverage in the surgical site without signs of infection and/or necrotic bone.	Control: 6 healed (42.9%), 8 unhealed (57.1%)	Local application of CGF appears to be an effective approach to the surgical treatment by improving tissue regeneration (P = 0.232)
		Test: 0/14	Test: 73.57 (SD 5.1)	Test (n =14): treated with a local application of CGF on the surgical site after removing the necrotic bone			Test: 11 healed (78.6%), 3 unhealed (21.4%)	
Park et al. [17]	Patients with stage 1 - 3 MRONJ and underwent surgical treatment of MRONJ.	Control: 3/22	75.24	Control (n = 25): surgical debridement of MRONJ lesion followed by application of L-PRF on bony defect	Control: 6 - 26 months	Treatment was considered successful if had mucosal coverage with absence of clinical or radiographical evidence of MRONJ at 4 weeks postoperatively.	- Complete resolution. Control: 9 patients (36%); test: 18 patients (60%). - Delayed resolution. Control: 13 patients (52%); test: 11 patients (36.7%). - No resolution. Control: 3 patients (12%); test: 1 patient (3.3%).	L-PRF with BMP-2 therapy led to beneficial outcomes with complete resolution of the lesions, which were statistically significant when compared to L-PRF therapy alone (P = 0.028)
		Test: 29/1	75.2	Test (n = 30): surgical debridement of MRONJ lesion and application of L-PRF and rhBMP-2 on bony defect	Test: 6 - 31 months			
Guo and Guo [20]	Patients with stage 2 or 3 MRONJ and underwent surgical treatment of MRONJ	Control: 10/8	62.17 (SD 2.8)	Control (n = 18): treated with conventional approach-sequestrectomy and curettage	30 months	Treatment was considered successful if had complete mucosal coverage without bone exposure, fistula and relapse	Control: 4 healed (22.22%), 14 relapse (77.78%)	The test group's rate of treatment success was significantly greater (P = 0.005)
		Test: 6/4	63.5 (SD 3.38)	Test (n = 10): treated with sequestrectomy and curettage with cortical perforations of the residual healthy bone.			Test: 8 healed (80%), 2 relapse (20%)	
Szentpeteri et al. [21]	Patients with stage 2 or 3 MRONJ and underwent surgical treatment of MRONJ	74/27	Control: 63.97	Control (n = 73): surgical open flap debridement of MRONJ lesion	T1 = 1 week; T2 = 2 weeks; T3 = 1 month; T4 = 3 months; T5 = 6 months; T6 = 1 year	Treatment was considered successful if had staging improvement according to the AAOMS, no relapse. Osteonecrosis assessed by X-ray	- Wound healing. Control: 38 cases (58.46%); test: 23 cases (82.14%). - Down-staging. Control: l54 cases (77.14%); test: 100% of cases. - Relapse. Control: 25 cases (65.78%); test: 5 cases (21.73%)	PRF membrane-assisted surgical therapy greatly increased stage improvement and healing rates (P = 0.022) and down staging (P = 0.005) as well as significantly decreased relapse rates (P < 0.001)
			Test: 68.42	Test (n = 28): surgical open flap debridement of MRONJ lesion and defect coverage with 2 PRF membranes.				
Şahin et al. [22]	Patients with stage 2 or 3 MRONJ and underwent surgical treatment of MRONJ	7/14	68.04 (SD 9.82)	Ultrasonic piezoelectric bone surgery was used to remove the necrotic bone. Following debridement, the patient's peripheral blood was centrifuged to obtain L-PRF, which was then administered to the necrotic site	T1 = 1 month; T2 = 3 months; T3 = 6 months; T4 = 12 months	Treatment was considered successful if had complete mucosal, bone covering and the absence of the symptom	T1 = 2 stage III patients had delayed healing. T2, T3, T4 = all patients had complete mucosal healing	The surgical procedure shown yields encouraging results.

MRONJ = medication-related osteonecrosis of the jaw; T = follow-up time; CGF = concentrated growth factor; PRF = platelet-rich fibrin; L-PRF = leukocyte rich and platelet-rich fibrin; BMP-2 = bone morphogenetic protein-2; AAOMS = The American Association of Oral and Maxillofacial Surgeons; SD = standard deviation.

Another retrospective cohort study conducted by Şahin et al. [22], evaluated the effectiveness of some surgical techniques for treatment of MRONJ after bisphosphonates therapy (Table 7). Twenty-one patients diagnosed with stage 2 or stage 3 MRONJ underwent ultrasonic piezoelectric surgical excision of the necrotic area. The patients' peripheral blood was centrifuged to obtain leukocyte and PRF concentrate (L-PRF) and YAG laser for bio stimulation. Evaluation of mucosal coverage without signs of residual infection were assessed 1-month (T1), 3-months (T2), 6-months (T3) and 1-year (T4) after surgery. Amoxicillin/clavulanic acid 1000 mg, metronidazole 500 mg, and 0.12% chlorhexidine mouthwash were administered one week before and two weeks after surgery. In 2 stage 3 patients, healing was delayed 1 month after surgery, and all patients had complete mucosal healing at three months. The surgical method presented in this study yields encouraging results for MRONJ surgical treatment.

Szentpeteri et al. [21] investigated the use of PRF as a therapeutic measure for patient with MRONJ caused by bisphosphonates medication (Table 7). This study included 101 patients diagnosed with stage 2 - 3 MRONJ were allocated into 2 groups according to the treatment plan, including the use of PRF or not. The 2 surgical protocols were evaluated and compared patient recovery, stage improvement, and recurrence. The minimal follow-up duration was one year. A significant difference was observed in favour of the PRF group: better healing of MRONJ lesions ($P = 0.022$), more successful down-staging ($P = 0.005$), and lower relapse rates ($P < 0.001$) compared to the control group.

In a prospective study by Park et al. [17] investigated the combination of bone morphogenetic protein-2 (BMP-2) and leukocyte- and PRF (L-PRF) in the treatment of MRONJ due to previous antiresorptive drug treatment (Table 7). Fifty-five patients were randomized to receive either L-PRF alone or a combination of L-PRF and rhBMP-2 in the bone defect after surgical removal of the necrotic area. Surgical sites were clinically and radiographically examined at 4 and 16 weeks postoperatively for each patient. Clinical examination was performed to determine the existence of exposed bone, mucosal swelling and erythema, purulent drainage, intraoral or extraoral fistula, and/or any pain or discomfort correlated with the surgical site. Eighteen of 30 (60%) patients of test group and 9 of 25 (36%) patients of control group showed complete resolution of the lesion 4 weeks postoperative. L-PRF plus BMP-2 resulted in significantly better healing of MRONJ lesions ($P = 0.028$).

Characteristics of combined treatment

El-Rabbany et al. [19] investigated the effects of surgical and non-surgical treatment of MRONJ after comparing treatment with bisphosphonates and denosumab (Table 8). This study included 78 patients diagnosed with MRONJ who were divided into 2 groups according to the treatment plan. Conservative treatment included 22 patients who received local and/or systemic antibiotics, pentoxifylline, hyperbaric oxygen, and teriparatide. Fifty-six patients classified as surgical treatment group had received conservative therapy in addition to surgical intervention such as debridement, curettage, sequestrectomy, saucerization, and resection. The 2 treatment protocols were evaluated and compared with respect to the absence of pain, open or potential bone during the follow-up period. Overall disease resolution in the surgical group was 39 (70%) compared with 8 (36%) in the non-surgical group. Surgical treatment resulted in significantly better healing of MRONJ lesions compared to non-surgical treatment.

Other retrospective study by Eguchi et al. [16] examined whether surgical or non-surgical treatment improves outcomes for stage 2 MRONJ patients after bisphosphonates and denosumab therapy (Table 8). Fifty-two patients first received non-surgical treatment for at least one month, which included antibacterial mouth rinse, local irrigation, antibiotics and analgesics administration, and professional oral hygiene. At the 1-month follow-up, 28 of 52 patients were treated surgically and 24 remained non-surgically treated, as 18 patients had improved symptoms and 6 patients refused surgical treatment. Surgical treatment comprised necrotic bone removal until bone tissue vascularization was accomplished. Following surgery, antibiotics were given for at least 5 days, and strict follow-up was done at least every 2 weeks. At a 6-month follow-up, the outcomes of both surgical and non-surgical treatments were examined, 'success' is defined as the total elimination of exposed bone without clinical symptoms, and 'failure' is defined as the presence of exposed bone or disease progression. Surgical treatment was performed in 28 patients, of which 25 (89.3%) were successful, and 3 patients (10.7%) were unsuccessful. Conservative treatment was performed on 24 patients and resulted in success for 8 patients (33.3%) and failed in 16 patients (66.7%). Surgical treatment showed statistically better result in compare with conservative treatment ($P < 0.01$).

According to the studies [14-16,18,19,21,22], the most common indications for drug therapy include patients with osteoporosis, breast cancer,

Table 8. Characteristics of combined treatment

Study	Population	Gender	Age	Study group	Observation period	Treatment outcome	Results	Conclusions
		Male/ female	Years		Months			
Eguchi et al. [16]	Patients diagnosed with stage 2 MRONJ and treated with non-surgical or surgical therapy	Surgical: 13/15	Surgical: 72.3 (SD 11.3)	Surgical (n = 28): necrotic bone resection until the bone tissue's vascularization was established	6	Success-complete absence of exposed bone without any clinical symptoms. Failure- bone exposure remaining or disease progress	Surgical: 25 success, 3 failure	In comparison to non-surgical treatment, surgical treatment for stage 2 MRONJ improved efficacy (P < 0.01)
		Non-surgical: 9/15	Non-surgical: 74.8 (SD 10.3)	Non-surgical (n = 24): antibiotics and analgesics, as well as professional oral hygiene management by a dental hygienist			Non-surgical: 8 success, 16 failure	
El-Rabbany et al. [19]	Patients diagnosed with stage 1 - 3 MRONJ and treated with non-surgical or surgical therapy	Surgical: 9/47	Surgical: 79	Surgical (n = 56): debridement, curettage, sequestrectomy, saucerization and resection	Surgical: 15.5	Treatment was considered successful if had absence of pain and absence of exposed or probable bone.	Surgical: 39 healed (70%), 17 unhealed (30%)	Compared to non-surgical therapy, surgical therapy was substantially related with higher odds of resolution
		Non-surgical: 5/17	Non-surgical: 82	Non-surgical (n = 22): local and/or systemic antimicrobial therapy, pentoxifylline, hyperbaric oxygen and teriparatide	Non-surgical: 11		Non-surgical: 8 healed (36%), 14 unhealed (64%)	

MRONJ = medication-related osteonecrosis of the jaw; SD = standard deviation.

multiple myeloma, malignant bone disease and other malignancies (Figure 2). Other cancer includes kidney cell carcinoma, lung carcinoma and bone metastasis [14-16,18,19,21,22].

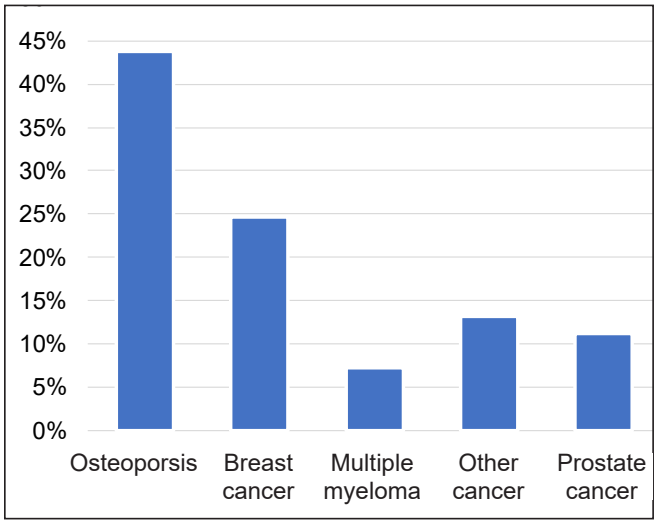

Figure 2. The most common indications for drug therapy [14-16,18,19,21,22].

DISCUSSION

The goal of this systematic literature review was to overview recent studies regarding conservative and surgical treatment methods of MRONJ after antiresorptive therapy and determined if conservative therapy alone yields effective outcome in treatment of MRONJ. The general review was conducted by including recent retrospective, prospective and randomized clinical studies. Of the nine studies included in this systematic literature review, 2 studies evaluated the efficacy of conservative methods in the treatment of MRONJ, 5 studies evaluated the efficacy of surgical methods, and 2 studies compared these methods.

Marx et al. [1] was the first to describe clinical cases of osteonecrosis associated with bisphosphonate medication in 2003 but, to date, the treatment strategy is still controversial, with no consensus regarding a conservative versus a surgical approach [30]. The decision between conservative treatment or surgery is difficult, and it should be taken on an individual basis. According to the AAOMS, the therapeutic goals for patients with MRONJ are to eliminate pain, control soft tissue infection, and minimize the progression or occurrence of bone necrosis. AAOMS also state that conservative treatment is recommended for stages 0 - 2 MRONJ,

although, they recommend that mobile bony sequestrum should be removed to allow for soft tissue recovery. Only stage 3 MRONJ indicated surgical debridement or resection [9]. Conversely, other authors reported improved MRONJ healing rates following surgical interventions. Carlson and Basile [31] reported a 90% success rate in MRONJ patients treated with surgical intervention, with stable mucosal closure maintenance.

Majority of the studies in this systematic literature review revealed that in patients with advance stages of MRONJ, surgical treatment is more effective than non-surgical conservative treatment. The studies of Eguchi et al. [16] and El-Rabbany et al. [19] showed a significant different outcome between conservative and surgical treatment for patients with MRONJ in favour of the surgical approach. In these studies, patients treated with surgery had a significantly higher rate of complete healing compared to patients treated conservatively. Patients defined as surgical in both studies were those who had conservative non-surgical treatment in addition to surgical treatments. The findings of these studies are consistent with those reported in the literature. A recent study [32] found that surgical therapy compared to traditional conservative therapy may be superior in the treatment of MRONJ. This conclusion is corroborated further by recently published retrospective studies demonstrating the efficacy of surgical therapy [33-35]. Incidentally, the study by Ruggiero and Kohn in 2015 [35], assessing predictors of favourable outcomes in patients with MRONJ comes to identical results as this systemic review. Other 5 studies in this systematic literature review concerning diversified surgical approaches treatment for MRONJ expressed relatively positive outcomes. Yüce et al. [15], Park et al. [17], and Szentpeteri et al. [21] investigated the impact of bone and soft tissue regeneration material on bony defect. The application of growth factors is also considered a treatment option because of improving the soft and hard tissue healing. Acting like chemotactic agents, they promote angiogenesis, migration, proliferation, and the differentiation of stem cells from the surrounding mesenchymal tissues into bone forming cells in necrotic bone area [36]. PRF and CGF are autologous preparations derived from the patient's blood through phlebotomy. They release high quantities of growth factors that can help to accelerate and stimulate bone regeneration and tissue healing [37-39]. The use of autologous platelet concentrates (APCs) as an alternative method for the prevention and treatment of MRONJ was developed by Choukroun et al. [40] reported good clinical results [41,42]. PRF application on necrotic bone area showed significant improvement of mucosal healing, down staging, and low relapse rate in the study of Szentpeteri et al. [21], while the results of the study of Yüce et al. [15] showed that the effect of CGF was not significant. In the study made by Park et al. [17], the results showed significance in the use of rhBMP-2 as an adjunctive therapy. rhBMP-2 used as a bone graft which stimulate bone regeneration and widely used in dentistry. Additional study by Kim et al. [43] showed promising result concerning rhBMP-2 application on bony defect by stimulate bone formation. Guo and Guo [20] presented different surgical approach for treating MRONJ by cortical bone perforation to allow infiltration of blood supply to the necrotic site. In patients treated with the cortical bone perforation technique, mucosal coverage and reduction in relapse rates were significantly higher. Danesh-Sani et al. [44] demonstrated that cortical perforation may improve the amount of newly formed bone and accelerate angiogenesis which promote healing in case of bone necrosis. Another surgical technique studied by Şahin et al. [22], who revealed that surgical treatment is more effective than conservative treatment in advanced stages of MRONJ. Surgical treatment with additional surgical tools has been reported. Ultrasonic bone surgery, also known as piezoelectric surgery, has the advantage of enabling less invasive bone cutting without damaging soft tissues. Complete mucosal healing was observed within 3 months postoperatively and no recurrence throughout follow-up period. Surgical treatment is more appropriate in this patient group since conservative treatment has a success record of less than 50% in advanced stages.

By guidelines of AAMOS, conservative non-surgical treatment is recommended, particularly for early stage 1 disease, and for stage 2 disease [9]. Conservative treatment includes maintaining good oral hygiene, visiting the dentist on a regular basis, using chlorhexidine mouthwash, and taking antibiotics. This can assist in the stabilization or improvement of the disease. According to several studies, combining conservative treatment with adjuvant treatments such as hyperbaric oxygen, ozone therapy, or low-intensity laser therapy can result in a higher success rate with positive results [45-47].

There have been many publications in the recent years which have focused on the therapeutic effect of teriparatide in MRONJ cases. Teriparatide is a recombinant human parathyroid hormone which promotes bone turnover by stimulating bone formation with positive balancing in bone metabolism. The use of teriparatide on refractory MRONJ lesions was first described by Harper et al. [48] who observed soft tissue recovery in a patient administered teriparatide

for 3 months. Authors reported that MRONJ lesions resolved after 10 months of daily injections of teriparatide and recommended limiting treatment to 2 years. Similar results have been reported in study made by Sim et al. [14], subcutaneous teriparatide injection seems to yield better result compared to placebo group in patients' stages 1 - 3 MRONJ. However, in patients with advanced stages of MRONJ, there was no appreciable improvement in clinical stage. In contrast, the study conducted by Ristow et al. [18] revealed that conservative treatment for stage 1 MRONJ patients leads to a healing in rare cases. According to the authors, conservative treatment is an appropriate approach for preserving symptoms in patients who are either averse to surgery or whose overall state precludes surgery.

This systematic literature review found that in most studies, conservative therapy alone yields no improvement in patient condition and did not aggravate the condition either. Conservative treatment can be useful for preventing disease progression in patients that are not eligible for surgery and may provide temporary comfort by reducing symptoms and infections, but effective resolution of osteonecrosis should not be expected. Complete surgical removal of the necrotic bone with pre-operative antibiotic therapy, infection management, and softening of the sharp bone edges before mucosal closure is widely regarded as the most appropriate strategy for effective recovery in adverse stages of MRONJ treatment.

This systematic literature review has faced numerous limitations that have a significant impact on its liability. One of the first aims of this study was to analyse the effects of bisphosphonates and other antiresorptive drugs on the periodontium, but due to limited resources, the systematic review of the literature was linked to the aspect of treatment strategies for MRONJ. Furthermore, a small number of studies in the database reported on conservative treatment of MRONJ, whereas a larger database would provide more robust conclusions. Secondary, majority of the included studies have small sample size. A larger sample size of patients would help to improve the study's significance.

CONCLUSIONS

Conservative treatment appears to yield better outcomes at asymptomatic patients with early stages of medication-related osteonecrosis of the jaw, further research is needed to determine the optimal conservative procedures for managing advanced stages.

Most of the included studies revealed that surgical treatment in patients with advanced stages medication-related osteonecrosis of the jaw lead to positive outcome, mainly after surgical removal of necrotic area and application of bone and soft tissues regeneration material.

Surgical treatment is superior to conservative treatment in patients with advance stages of medication-related osteonecrosis of the jaw. In the presented study, patients with advanced medication-related osteonecrosis of the jaw had a positive outcome to surgical therapy combined with conservative treatment, while conservative treatment alone had a positive outcome in patients with early stages of medication-related osteonecrosis of the jaw.

Regular communication and collaboration between dental and medical professionals are crucial in the comprehensive care of patients with medication-related osteonecrosis of the jaw with the goal of providing optimal care for medication-related osteonecrosis of the jaw patients, tailoring the approach to the severity of their condition, and ensuring the best possible clinical outcomes while minimizing the potential for complications.

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