

# Treatment of medication-related osteonecrosis of the jaw (MRONJ). A systematic review

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**Abstract. – OBJECTIVE:** Medication-related osteonecrosis of the jaw (MRONJ) is a severe drug-related side effect mostly seen in the maxillofacial region of patients under current or previous treatment with antiresorptive and/or antiangiogenic agents. There is a wide range of treatment options explained in literature for the management of this condition, from conservative treatments to surgical procedures of various levels of invasiveness, which are sometimes supplemented with adjunctive therapies. The present systematic review aimed at evaluating the treatment options of MRONJ in terms of successful outcomes.

**MATERIALS AND METHODS:** Medline, Scopus, and Cochrane databases were searched. The search was limited to clinical studies involving human subjects with at least 3 cases. There was no other limitation for language, publication date, and study design for the articles to be included. A hand search of the bibliographies of identified articles was also performed. The evaluation criterion was an improvement in the healing of the treated site after treatment procedures.

**RESULTS:** After evaluation of the full text of the articles, 118 articles were selected for evaluation (15 platelet concentrates, 4 teriparatide, 10 laser therapy, 3 hyperbaric oxygen, 2 ozone applications, 9 conservative protocols, and 75 surgical interventions articles). The evaluated articles reported positive improvements in healing/staging of the osteonecrosis sites.

**CONCLUSIONS:** Due to the low evidence level and the limited sample size of the studies included, the results of this review must be cautiously interpreted. However, they can be suggestive for evaluating the possible benefits of these treatment options in MRONJ management. Further prospective comparative studies with a large sample size are urgently needed to confirm the results.

*Key Words:*

Bisphosphonates, MRONJ, BRONJ, MRONJ treatment, PTH, Laser therapy, Platelet concentrates, HBO, Ozone therapy, Oral surgery.

## Introduction

Bisphosphonates (BPs) are the most famous major class of drugs for the treatment of bone diseases<sup>1</sup>. Since their discovery in the 1960s, BPs are widely used in patients with various conditions affecting bone tissue (such as osteoporosis and similar diseases)<sup>1</sup>.

In spite of the successful action of BPs therapy in controlling these conditions, various reports have presented necrotic bone exposures in patients receiving BPs<sup>2-4</sup>. The first researcher in literature who described bisphosphonate-related osteonecrosis of the jaw (BRONJ) was Robert Marx as “BP-related adverse event characterized by the presence of necrotic bone in the maxillofacial area, with or without exposed bone, that does not heal within eight weeks, in patients with no oral cancer and no radiation therapy to the craniofacial region”<sup>2</sup>.

Additionally, several cases of ONJ in patients not under BPs therapy but using other antiresorptive agents (like denosumab) or antiangiogenic medications (bevacizumab, sunitinib, carbozantinib) were described. Currently, in 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended to change the initial definition of BRONJ to medication-related osteonecrosis of the jaw (MRONJ)<sup>5</sup>. According to AAOMS update in 2014, MRONJ was defined as “Area of exposed or probable bone in the maxillofacial region with no resolution for longer than 8 weeks in patients treated with an antiresorptive or an antiangiogenic agent and with no history of radiation therapy to the to the head and neck region”<sup>5</sup>.

## Treatment Strategies of MRONJ

The etiopathogenesis of MRONJ is still unknown, although the hypotheses are usually focused on the drug’s mechanism of action and

the risk factors that can lead to osteonecrosis<sup>6</sup>. There is no gold standard therapy defined in the literature, and the treatment of MRONJ is generally very challenging<sup>3,7,8</sup>. Treatment strategies are mainly focused on minimizing the progression or occurrence of bone necrosis, eliminating pain, controlling infection, and optimizing the quality of life of the patient<sup>3,5,7,8</sup>. In the initial stages, the treatment mostly focuses on conservative measures, such as oral hygiene, 0.12% chlorhexidine mouthwashes, and antibiotics. Surgical interventions are avoided whenever possible to prevent additional surgical sites that may result in areas of exposed necrotic bone<sup>5</sup>. For patients with established MRONJ at advanced stages, surgical interventions, such as surgical debridement or resection are considered more appropriate. A number of adjunctive therapies were proposed in the literature with beneficial results. Different biological agents, among which autologous platelet concentrates, recombinant growth and differentiation factors, parathyroid hormone (PTH, teriparatide) and low-level laser therapy (LLLT), hyperbaric oxygen therapy (HBO), and ozone therapy have been successfully used to enhance bone and soft tissue healing in different surgical procedures<sup>9</sup>.

The primary aim of this systematic review was to evaluate and compare the treatment options reported in the literature for the management of MRONJ in patients under current or previous antiresorptive and/or antiangiogenic drug treatment. Any improvements in hard and soft tissue healing, any decrease in the incidence of complications, any beneficial effects on patients' quality of life were taken into consideration.

## Materials and Methods

### Search Strategy

The following databases were searched electronically: PubMed (<http://www.ncbi.nlm.nih.gov/sites/pubmed>), Scopus (<http://www.scopus.com>), and Cochrane Central Register of Controlled Trials (CENTRAL). An additional electronic search was performed for Grey literature databases: HealthInfonet (<http://www.healthinfonet.ecu.edu.au>), Closing the Gap Clearinghouse (<http://www.aihw.gov.au/closingthegap>) and OpenGrey (<http://www.opengrey.eu>).

The search string was composed of the following terms, used alone or in combination through Boolean operators OR and AND: "BRONJ",

"MRONJ", "bisphosphonate", "denosumab", "bevacizumab", "sunitinib", "carbozantanim", "antiresorptive agents", "antiresorptive therapy", "antiangiogenic agents", "osteoporosis", "osteonecrosis", "maxilla", "mandible", "platelet-rich plasma", "platelet concentrates", "platelet growth factors", "platelet-rich fibrin", "PRP", "PRGF", "PRF", "Platelet-Derived Growth Factor", "PDGF", "bone morphogenetic proteins", "BMP-2", "BMP-7", "recombinant factors", "parathyroid hormone", "PTH", "teriparatide", "statin", "Low level laser therapy", "Hyperbaric oxygen Therapy (HBO)", "Ozone therapy", "Growth differentiation factor", "oral surgery", "extraction socket", "tooth extraction".

In addition, all the issues of the following journals since 2000 were hand-searched: *British Journal of Oral and Maxillofacial Surgery*, *International Journal of Oral and Maxillofacial Surgery*, *Journal of Oral and Maxillofacial Surgery*, *Oral Oncology*, *Oral Surgery*, *Oral Medicine*, *Oral Pathology*, and *Oral Radiology*. The reference list of the reviews and of the included studies was also checked manually for possible studies that were not identified through the electronic search.

### Inclusion and Exclusion Criteria

- Clinical results of treatments for MRONJ/BRONJ patients (either retrospective or prospective clinical trials) and case reports with at least 3 patients were included.
- No restrictions were set regarding the language and the year of publication.
- Animal studies, review articles, and technical notes were excluded.
- In cases of multiple publications of the same authors using the same pool of patients, the most recent article with the longer follow-up and the larger sample size was taken into consideration.

### Selection of the Studies

Initially, the collected articles were assessed by two independent reviewers (MDF and FG) in order to check if they met all inclusion criteria. In case of disagreement, the case was discussed, and a joint decision was taken. The concordance between reviewers was assessed by means of the Cohen's Kappa coefficient. The reason for exclusion for excluded articles was recorded. The methodological quality of the articles and suitability for inclusion in a meta-analysis was also evaluated. Data were extracted by MDF and FG,

independently using an *ad hoc* data collection form.

### **Data Collection**

The AAOMS MRONJ staging was used<sup>5</sup>. The following data was collected from each included article:

Study design, study setting (university, hospital, private practice), support of a sponsor, sample size, patients gender and age, smokers or no smoker, type, dosage and administration route of antiresorptive drug taken, reason for treatment, dosage, duration of treatment at surgery, type of adjunctive biological agent used, oral surgery procedure, site (maxilla or mandible), outcome variable used to evaluate treatment success, follow-up duration, complications, adverse events, post-surgical onset/recurrence of MRONJ. The evaluation criterion for the studies was “*improvement in the healing/staging of MRONJ after treatment*”.

### **Risk-of-Bias Assessment**

The following methodological parameters were recorded to evaluate the risk-of-bias: clear definition of inclusion and exclusion criteria, clear definition of outcomes assessment and success criteria, number of surgeons involved, completeness of the outcome data reported, recall rate (adequate if dropout <20%), sample size (adequate if sample size >20), and length of the follow-up period (adequate if follow-up period ≥2 years), and the random sequence generation method and allocation concealment (in randomized studies).

Low risk-of-bias: In cases when all parameters were considered adequate.

High risk-of-bias: In cases when one or more of the parameters were considered inadequate,

Moderate risk-of-bias: In cases when at least one unclear and no inadequate items.

### **Statistical Analysis**

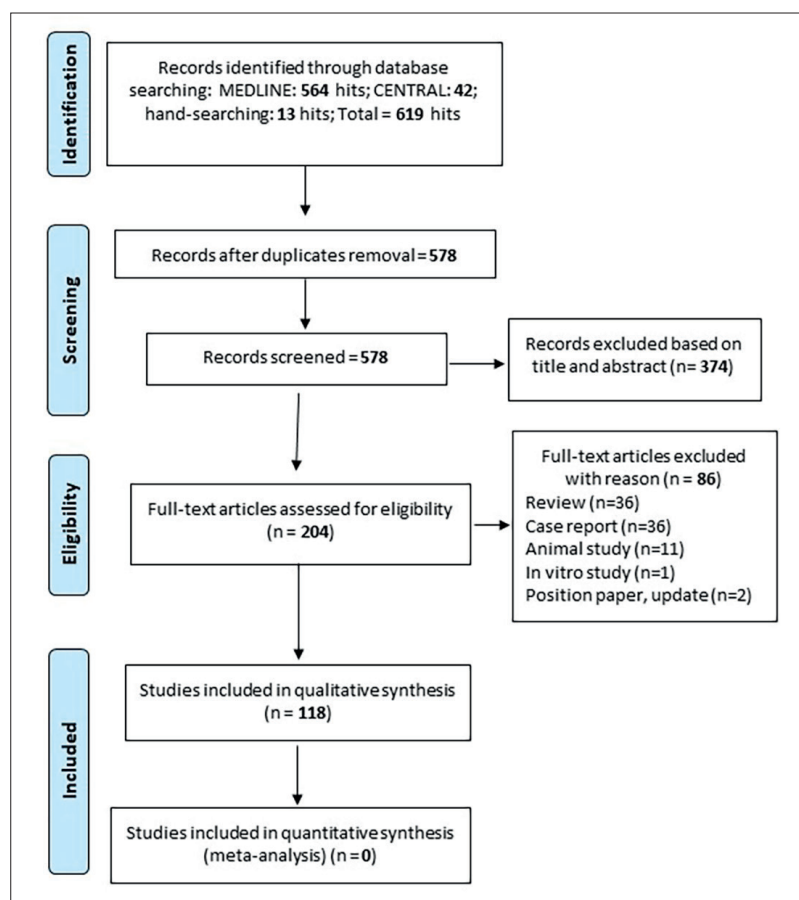
Descriptive statistics of the included case series studies were done by summarizing the total number of cases treated with each surgical approach and the percentage of successful cases with healing and without post-surgical complications. For studies reporting comparison between cases treated with and without additional procedures, the estimates of the effects of such procedures were expressed as odds ratio (OR) together with 95% confidence intervals. The statistical evaluation was conducted considering both the surgical site and the patient as

the analysis unit, whenever possible. When two or more studies presented similar comparisons (using the same protocol in similar patient groups, with similar follow-up), a meta-analysis was performed, and ORs were combined using a fixed-effects model (Mantel-Haenszel method). The software RevMan (Review Manager Version 5.3, 2014; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used to estimate the mean difference in the primary outcome between groups. The effect of location (maxilla vs. mandible), gender, antiresorptive drug administration route on the incidence of adverse events were also evaluated.  $p=0.05$  was considered as the significance level. When meta-analysis was not feasible due to the absence of studies with similar features, only qualitative analysis was done, and the outcomes were presented in a narrative way.

## **Results**

The last electronic search was performed on 15/09/2020. The flowchart summarizing the screening process is presented in Figure 1. The electronic search yielded a total of 564 articles. 13 additional articles were found by hand-searching. After a first screening of the titles and abstracts, a total of 204 articles reporting results of clinical studies on patients under antiresorptive therapy that underwent oral surgery procedures in combination with the use of biological agents were selected. After evaluation of the full text of these articles, 86 of them were excluded. As a result, a total of 118 articles were selected for evaluation (15 articles about platelet concentrates, 4 articles on teriparatide (PTH) applications, 10 articles about laser therapy, 3 hyperbaric oxygen, 2 ozone, 9 conservative protocol articles, and 75 articles on diversity of surgical interventions). In [Supplementary Table I](#), therapy characteristics and outcomes of the include studies are listed. Data regarding general characteristics and sample features of the included studies are reported in [Supplementary Table II](#) and [Supplementary Table III](#), respectively.

According to the results of this review, PRP/PRGF/L-PRP (as adjunctive therapy to surgical resection) is one of the most popular treatment modalities. Local applications of PRP/PRGF/L-PRP resulted in improvements of healing at the necrotic defect site for MRONJ/BRONJ patients<sup>10-23</sup>.



**Figure 1.** Flowchart of the article selection process.

It is evident that surgical interventions for surgical resection of the necrotic tissues were the most tested treatment protocol in MRONJ/BRONJ patients<sup>24-98</sup>. A diversity of flap options were reported by several authors with promising results (mucoperiosteal flap and mucoperiosteal flap + double-layer closure with buccal fat pad flap (BFPF) & rehabilitation with obturators<sup>24</sup>, buccal fat pad flap<sup>25</sup>, microvascular free flaps<sup>32</sup>, surgery + soft tissue reconstruction using a local myofascial flap<sup>57</sup>, nasolabial flaps vs. mucoperiosteal closure<sup>58</sup>, pedicled buccal fat pad combined with sequestrectomy<sup>44</sup>, comparison of local mucoperiosteal flaps with mylohyoid flaps<sup>65</sup>, vascularized fibula flap reconstruction of the mandible<sup>69</sup>).

Fluorescence guided surgery<sup>45,72,73,79,89</sup> and piezo-electric surgery<sup>27-28</sup> were evaluated for the resection of necrotic bone with beneficial results.

As an adjunctive option or as an alternative to surgery, ozone<sup>99,100</sup>, HBO, laser therapy applications<sup>101-103</sup> were evaluated with favorable outcomes. Laser therapy with Er:YAG or LLLT (low light laser therapy) was found advantageous,

as faster and less invasive surgery with a more comfortable postoperative healing process<sup>104-113</sup>. Systemic intake of teriparatide (PTH) was tested and was reported as a useful method in the resolution of MRONJ/BRONJ lesions<sup>114-117</sup>. The use of PTH together with a local application of recombinant human Bone Morphogenic Growth Factor 2 (rhBMP-2) was also investigated. The regeneration ratio was reported as significantly greater than control groups<sup>114</sup>.

Conservative non-surgical protocols were tested (in order to minimize the risk of relapse with the extension of the areas of bone exposure and aggravation of the symptoms) and were found beneficial<sup>118-126</sup> except one report<sup>123</sup>. Antibiotic regimen, in addition to conservative modalities, was reported as an effective way of controlling infection in MRONJ/BRONJ patients<sup>118,120,122,125</sup>.

According to the results after the evaluation, all of the studies reported had positive results and/or improvement in the necrotic defect site. There was just one study reporting a negative result<sup>123</sup>. In that study, conservative non-surgi-

cal therapy in MRONJ stage I resulted in a low healing rate, and the authors advised early and consequent surgical interventions throughout all stages of the disease to prevent progress<sup>123</sup>.

## Discussion

The therapy of BRONJ is a challenging problem, and according to the AAOMS report updated in 2014, the main treatment objectives for patients with an established diagnosis of MRONJ are to eliminate pain, control infection, and minimize the progression or occurrence of bone necrosis<sup>5</sup>. Although treatment recommendations exist by several authors, there is no consensus regarding the most appropriate standard treatment strategy for MRONJ<sup>120</sup>.

Systemic antibiotics are considered as a part of the standard therapy after surgical procedures, but their efficacy can be limited due to a low penetration rate at the site of infection and impaired blood supply<sup>127</sup>. Generally, the appropriate antibiotic for MRONJ is recommended as bactericidal, economic, and without any side effects<sup>128</sup>.

According to the AAOMS report, the treatment modality should always be conservative and elective surgical procedures should be avoided. The new surgical sites may become additional areas of exposed necrotic bone and present a risk of relapse with the extension of the areas of bone exposure and aggravation of the symptoms<sup>120,129</sup>. However, there are many studies<sup>24-98</sup> and systematic reviews<sup>8,130,131</sup>, suggesting that surgical treatment is more effective than non-surgical treatment in patients with MRONJ. Various authors compared surgical and non-surgical conservative protocols<sup>38-40,49,81,90</sup>. Additionally, according to the results of this systematic review, there is a great heterogeneity of the surgical options. Almost all of the studies highlighted the beneficial effects of the surgical protocols that are reported. In conclusion, most of the researchers reported better MRONJ/BRONJ defect resolution/healing in patients that had surgical interventions compared with patients that were treated with more conservative protocols.

Although conservative/selective surgical debridement is the treatment of choice in advanced MRONJ stages, the visualization of the borders of osteonecrosis represents a problem. Recently, fluorescence-guided bone resection was introduced in order to determine the extent of debridement. For this purpose, preoperative doxycycline was

administered that can be detected by a fluorescent light source. The ability to discriminate between necrotic and viable bone regions, in turn, allowed the precise intraoperative identification of the margins of necrotic bone for resection<sup>72,73</sup>. Autofluorescence/tetracycline fluorescence-guided surgery was also tested for the resection of necrotic bone<sup>45,72,73,79,89</sup>. These types of non-aggressive approaches permitted the removal of all necrotic bone, avoided damage to adjacent healthy bone, and resulted in fewer recurrences<sup>45,72,73,79,89</sup>. Additionally, as a less aggressive method, piezo-electric surgery was evaluated and reported as a valuable option in surgical interventions in cases of MRONJ/BRONJ<sup>27,28,100</sup>.

Following surgical interventions and complete debridement of necrotic bone, another challenge is the need for a water-tight closure of the defect, in order to minimize the risk of microbial contamination of the wounds and the exposed bone<sup>65,66</sup>. Following the resection of the necrotic soft and hard tissues, for the closure of the defect site, a diversity of flap options were proposed with promising results (mucoperiosteal flap and mucoperiosteal flap + double-layer closure with buccal fat pad flap (BFPF) and rehabilitation with obturators<sup>24</sup>, buccal fat pad flap<sup>25</sup>, microvascular free flaps<sup>32</sup>, resective surgery and soft tissue reconstruction using a local myofascial flap<sup>57</sup>, nasolabial flap vs. mucoperiosteal flap closure<sup>58</sup>, pedicled buccal fat pad combined with sequestrectomy<sup>44</sup>, comparison of local mucoperiosteal flaps with mylohyoid flaps<sup>65</sup>, vascularized fibula flap<sup>69</sup>, local myofascial flap<sup>58</sup>, buccal fat flap<sup>25,44,80</sup>, mucoperiosteal flap<sup>65</sup>, fibula free flap<sup>85</sup>). However, there are no randomized controlled studies investigating whether non-surgical or surgical treatment provides the best treatment outcome. Due to this fact, the role of surgery in the management of MRONJ remains controversial<sup>49</sup>.

According to the results of this study, it is clear that each treatment protocol has beneficial effects on the healing of necrotic defects. There was just one study that reported negative results<sup>123</sup>. However, that negative report was in accordance with the other studies. Negative results were found for conservative non-surgical therapy in MRONJ stage I with a low healing rate. As a result, it was concluded that early and consequent surgical advances should be performed throughout all stages of the disease to prevent progress<sup>123</sup>.

To enhance the outcomes of the surgical interventions, several adjunctive therapies, such as

PTH<sup>114-117</sup>/laser therapy<sup>104-113</sup>/Hyperbaric Oxygen Therapy (HBO)<sup>101-103</sup>/Ozone therapy<sup>99,100</sup>/Platelet concentrates<sup>10-23</sup> were proposed in the literature by different study groups with similarly successful results. PRP/PRGF/L-PRP as an adjunctive therapy<sup>10-23</sup> was tested with faster and more comfortable postoperative healing. Laser therapy<sup>104-113</sup> and ozone procedure<sup>99,100</sup> was found advantageous. The systemic use of teriparatide<sup>114-117</sup> and antibiotics<sup>118,120,122,125</sup> was reported as an effective way in the management of necrotic lesions.

According to the opinion of the authors of this present report, surgical interventions with/without adjunctive treatment protocols seems to be effective in downgrading/healing MRONJ/BRONJ lesions in all stages; however, surgical interventions might not be sufficient in receiving a long-term wound closure<sup>55</sup>. Anyway, the decision on the most appropriate modality treatment should be patient-specific and should be based on patient-specific factors such as: health status, age, stage of the MRONJ, and location of necrotic tissues.

The main limitations of this study are the diversity of the protocols and success criteria that were set by the authors. There is a great heterogeneity of evaluating techniques, success criteria, and inclusion criteria. The results were presented in a different way; some authors evaluated the improvement in healing, while others complete resolution or improvement in BRONJ stages. Many authors reported positive results, although most of them were not statistically significant. Some of the articles concluded that the treatment modality applied might be feasible for BRONJ/MRONJ defects. Additionally, there was a great variety of the study protocols that were reported for timing/sample size/treatment duration/follow-up period/study type. It is true that researchers seek to perform original research, meaning to investigate materials and techniques that have never been evaluated before by others. Authors, instead of repeating modalities already tested by others, tend to report variations of the different protocols. By doing this, researchers also increase the chances to publish in valuable scientific journals. On the other hand, in order to be accepted worldwide by the scientific community, any clinical protocol needs to be validated by confirmatory studies performed by different research groups. Only when similar results are obtained in different clinical settings using the same protocol, the latter can be considered reliable and predictable.

## Conclusions

The results of this review, though largely based on low-evidence level studies, suggest that adjunctive therapies to oral surgery procedures may have beneficial effects for preventing the occurrence and recurrence of MRONJ. Scarce evidence was found regarding the effect of therapies on MRONJ treatment and prevention. However, it was the common conclusion that surgical interventions should always be in minimum measures, and caution should always be paid, especially in the case of oncologic patients. The main focus should be optimizing the quality of life of the patient.

There is still no consensus regarding the gold standard treatment strategy for MRONJ. Major surgery option is especially indicated for patients who suffer from advanced MRONJ stages. In the early stages, non-surgical treatment or selective surgery seems to be an appropriate alternative. Nevertheless, more studies are needed to clarify the definite significance and extend of surgical interventions.

We hope that our findings might stimulate researchers to perform additional case-control studies and, possibly, randomized studies with a large sample size in order to confirm the beneficial effects of biological agents in the management of MRONJ.

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## Conflict of Interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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## Authors' Contribution

F.G., M.D.F., Fr.G. and E.G. conceived and designed the analysis. Databases were searched and data was collected by F.G., and M.D.F. All the authors contributed on analysis and interpretation of data for the work. F.G. drafted the work and wrote the manuscript with input from all authors. F.G., M.D.F., Fr.G., L.F., and E.G. revised the work critically for intellectual content. Integrity of the work was appropriately investigated and resolved by F.G., M.D.F., Fr.G., L.F., and E.G. All authors contributed and approved equally to the final version of the manuscript.

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