Rita Sanjiva Sinai Cacodcar

.

Surgical treatment of drug induced osteonecrosis of the jaws: a systematic review

Universidade Fernando Pessoa

Faculdade de Ciências da Saúde

Porto, 2020

Rita Sanjiva Sinai Cacodcar

Surgical treatment of drug induced osteonecrosis of the jaws: a systematic review

Universidade Fernando Pessoa

Faculdade de Ciências da Saúde

Porto, 2020

Rita Sanjiva Sinai Cacodcar

"Work presented to the University Fernando Pessoa as part of the requirements to obtain the Master of Dental Medicine degree ".

_____

Rita Sanjiva Sinai Cacodcar

ABSTRACT

Introduction: The growing number of osteonecrosis of the jaws cases associated with antiresorptive/antiangiogenic therapies is significant. The surgical treatment is still widely discussed.

Objective: Evaluate how effective is the surgical therapy in the treatment of drug-induced osteonecrosis of the jaws.

Methodology: PubMed and B-on, with English MESH terms, limited on humans and published between 2015-2019.

Results: Of the 1478 articles found, 16 met the eligibility criteria. Total of 809 patients, 531 were females (65.9%), mean age was 70.47 years, and the follow-up range from 3-164 months. Surgical treatment had 84,06% of success. Highest results observed when patients were treated with laser-assisted surgery (87,50%).

Conclusions: Surgical treatment in combination with antibiotic therapy, can present extremely beneficial results. Laser approach showed to be the most effective in promoting long-lasting palliative care, with resolution of pain and infection.

Keywords: *"Diphosphonates"; "Osteonecrosis"; "Bisphosphonate associated osteonecrosis of the jaw"; "Jaws"; "Antiresorptive drugs"*

RESUMO

Introdução: O aumento de casos de osteonecrose dos maxilares associados a terapias anti-reabsortivas/antiangiogênicas é preocupante. O tratamento cirúrgico é ainda amplamente discutido.

Objetivo: Avaliar a eficácia do tratamento cirúrgico da osteonecrose maxilar, induzida por medicação.

Materiais e métodos: PubMed e B-on, com termos MESH em inglês, limitados a humanos e publicados entre 2015-2019.

Resultados: Dos 1478 artigos encontrados, 16 preencheram os critérios de elegibilidade. Do total de 809 pacientes, 531 eram do sexo feminino (65,9%), a idade média foi 70.47 anos e o follow-up 3-164 meses. O tratamento cirúrgico teve 84,06% de sucesso. Foram obtidos resultados mais altos, quando tratados com cirurgia assistida por laser (87,50%).

Conclusões: O tratamento cirúrgico associado à antibioticoterapia pode apresentar resultados extremamente benéficos. A abordagem a laser mostrou-se a mais eficaz na promoção de cuidados paliativos duradouros com resolução de dor e infeção.

Palavras-chave: "Difosfonatos"; "Osteonecrose"; “Osteonecrose mandibular associada ao bisfosfonato”; "Maxilas”; "Medicações anti-reabsortivas”

AGRADECIMENTOS

Aos meus pais e irmãos, por todo o suporte e valores transmitidos, por permitirem formar-me e ter conquistado mais uma etapa, tão importante na minha vida. Sem vocês nada disto seria possível.

Ao meu orientador, Dr. Pedro Ferreira Trancoso, foi uma honra trabalhar consigo. Expresso a minha profunda gratidão por toda a confiança depositada, e por toda a paciência, foi um pilar indispensável ao longo de todo o processo, que desde cedo se revelou trabalhoso e exigente.

À minha grande amiga e binómia Rita Almeida, por 5 anos inesquecíveis. Viemos de Faro com uma mala de sonhos, é gratificante olhar para trás e ver o quanto crescemos e o quão melhor foi, do que planeávamos com apenas 16 anos. O que sonhámos, o que vivemos e o que alcançámos. Retornamos mais juntas ainda, e com a certeza que é só o inicio.

A todos os meus amigos, pelo apoio e lealdade ao longo destes anos.

Ao Dr. Renato Morales Jóias, Dra. Renata Pilli Jóias, a todo o corpo docente e funcionários, da Universidade Metodista de São Paulo, que no período de 6 meses me receberam de braços abertos e contribuíram para um intercambio tão enriquecedor.

E por fim, mas não menos importante, não posso deixar de agradecer a Universidade Fernando Pessoa, e a todo o corpo docente, por me terem acolhido e proporcionado um percurso académico tão marcante.

A todos, um muito obrigada!

INDEX

LIST OF TABLES:

LIST OF FIGURES:

LIST OF ABBREVIATIONS:

AAOMS - American Association of Oral and Maxillofacial Surgeons

ARONJ - Antiresorptive drug related osteonecrosis of the jaw

BFF - Buccal fat flap

BP - Bisphosphonates

BMP - Bone morphogenetic protein

BRONJ - Bisphosphonate-related osteonecrosis of the jaw

FDG - Fluorodeoxyglucose

HBO - Hyperbaric oxygen therapy

LLLT - Low-level laser therapy

MRONJ - Medication related osteonecrosis of the jaw

MMF - Mylohyoideus muscle flap

PRF – Platelet Rich Fibrin

PRP - Platelet Rich Plasma

VEGF – Vascular Endothelial Growth Factor

I – INTRODUCTION

Bisphosphonates (BPs) which are used mainly in the treatment of patients with osteoporosis, malignant hypercalcemia, multiple myeloma, or to avoid and control bone metastases, may cause osteonecrosis of the jaw. (Lopes *et al.*, 2015).

The term "*bisphosphonate-related osteonecrosis of the jaw* (BRONJ)" has recently changed to "*medication-related osteonecrosis of the jaw* (MRONJ)". The *American Association of Oral and Maxillofacial Surgeons* (AAOMS) suggested this change, due to the growing number of maxillary and mandibular osteonecrosis related not only to BPs, but also to other antiangiogenic and antiresorptive agents, such as denosumab (Ruggiero *et al.*, 2014).

The AAOMS position document modified the definition of MRONJ from the 2009 paper (Ruggiero, 2009). Now, patients may have the disease if they present all the following conditions: a) previous treatment with antiresorptive or antiangiogenic agents; b) presence of necrotic bone exposure or intra- or extra-oral fistulization for over 8 weeks without remission; and c) no evidence of radiotherapy or diseases metastasizing to the head and neck region (Ruggiero *et al.*, 2014).

The first reports of MRONJ were published in 2003 (Marx *et al.*, 2003). Although the entire pathophysiology of MRONJ has not yet been fully clarified, a few hypotheses were proposed considering this disease to be multifactorial.

BPs are powerful inhibitors of osteoclastic activity leading to suppression of bone turnover. They also have anti-angiogenic properties, activate T-cells, have direct tumoricidal effects and it is clear as well that infection, trauma and reduced vascularity play important roles (Clézardin, 2013). Denosumab is an antibody against RANK-ligand that also leads to inhibition of osteoclastic activity, strengthening the hypothesis that osteoclast inhibition and suppression of bone turnover, plays a central role in the etiopathogenesis (Kyrgidis e Toulis, 2011).

In the 2014 position paper, AAOMS categorized the risk factors for osteonecrosis of the jaw as drug-related, genetic, systemic, local or demographic (Ruggiero *et al.*, 2014).

The clinical appearance of MRONJ can vary extensively. Over the years, several classifications have been published, although the AAOMS staging system is the most

frequently used. According to the clinical appearance, the AAOMS defined four different stages. **Stage 0** No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms; **Stage 1** Asymptomatic lesions with bone exposure in absence of signs of infection - patients should control the infection of exposed bone with antimicrobial rinses (Chlorhexidine 0,12%); **Stage 2** Bone exposure with pain, infection, and swelling in the area of lesion; **Stage 3** Bone exposure, pain, inflammation, maxillary sinus involvement, cutaneous fistulas, and pathological fractures (Bodem *et al.*, 2016).

There's still great controversy regarding the most adequate treatment for MRONJ. However, the consensus on the main goal of the treatment remains undisputed. Of great importance, is to control infection, to slow the disease progression, and to promote soft and hard tissue healing.

The success rates of surgical and non-surgical treatments are variable. The non-surgical treatments embrace the use of systemic antibiotic therapy and oral antiseptic rinses, sometimes combined with hyperbaric oxygen therapy and low-level laser therapy. The surgical treatments proposed in the literature are divided into conservative approaches such as bone debridement, sequestrectomy, or more aggressive therapies such as resection of affected bone and jawbone reconstruction, if deemed necessary (Mauceri *et al.*, 2018).

Although the need for surgical treatment for stage 3 is widely accepted, there are still controversies. In addition, there are also different recommendations for the surgical treatment of stage 2 MRONJ, because it remains difficult to obtain surgical margins that are free from disease while removing all the necrotic bone (Bodem *et al.*, 2016).

Currently, surgical treatment remains questionable. My personal interest in this topic arose out of the fact that worldwide, several cases of osteonecrosis of jaw are presented in clinical practice, being mistakenly categorized in the wrong AAOMS clinical stage and subsequently receiving the inappropriate treatment.

1.1 – Aim

The aim of this study is to conduct a systematic review, to understand the real efficacy of the surgical treatment of osteonecrosis of the jaws induced by drugs. Additionally, evaluation and comparison of the success rate of different surgical procedures was done. This systematic search was carried out in PubMed and B-on.

The research question was formulated using the PICOS statement (P) patients or population; (I) intervention; (C) comparator or control group; (O) outcome; (S) study design

"How effective is surgical treatment of drug-induced osteonecrosis of the jaws?"

II – DEVELOPMENT

2.1 – Materials and methods

The present systematic review was based on the PRISMA® (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement published in 2009 (Liberati *et al.*, 2009).

The search was carried out by two authors, using primary databases PubMed and B-on, covering the period of 5 years, with no restrictions on language. The last electronic search was conducted on 28 November 2019. The references were processed using Mendeley.

The PICOS strategy was used for the research question construction: (P) patients or population: patients with MRONJ; (I) intervention: surgical approach; (C) comparator or control group: other treatment; (O) outcome: improvement or complete healing of MRONJ; (S) study design: intervention studies

The search strategy used both Medical Subject Headings terms (MeSH) and free-text words, combined with the Boolean connectors "AND" and "OR", as described below:

Table 1: The search strategy

PubMed	((((("biphosphonates/therapeutic use"[mesh]) and ("bisphosphonate-associated osteone-crosis of the jaw/surgery"[mesh] or "bisphosphonate-associated osteonecrosis of the jaw/therapy"[mesh])) and (jaws))
B-on	bisphosphonates AND osteonecrosis AND jaws AND bronj OR aronj AND treatment

After eliminating duplications, the potential titles and abstracts were filtered, the articles screened, and the eligibility process was carried out based on the following inclusion and exclusion criteria (Table2).

Table 2: Inclusion and exclusion criteria adopted in the systematic review

Inclusion criteria	Exclusion criteria
Intervention studies	Studies that did not report an intervention
Conducted in humans	Animal studies
Studies not older than 5 years	Older than 5 years
Follow up period of at least 3 months	Without follow-up or with one lasting less than 3 months
Surgical treatments	Non-surgical treatment

Articles that did not meet the inclusion and exclusion criteria were excluded from the analysis. Although studies usually follow certain criteria, there is no standardization in the methodology; therefore, studies are prone to bias, due to the differences in the selection and allocation of the samples, in the measurement of the analyzed variables or in the reading of the results.

The risk of bias can be assessed with the help of the Cochrane Collaboration tool, developed by a group of experts to identify the variables in each included study (Higgins *et al.*, 2011). However, the tool proved not to be adequate since the gross majority of results lacked important information relevant to the review, contributing to a risk of bias.

A more suitable scale, Newcastle-Ottawa (NOS), was then found. The scale consists of eight sections covering three areas: (1) patient selection; (2) comparability of the two branches of the study; and (3) results assessment (Lo, Mertz e Loeb, 2014).

2.2 – Surgical Therapy

According to the evidence, that exposed bone with irregular margins and formed sequestrations increase the risk of inflammation and infection and should therefore be eliminated, surgical therapy is subdivided in two different approaches, conservative surgery and extensive surgery (Longo *et al.*, 2014; Rupel *et al.*, 2014).

It is defined as conservative surgical approach when there is removal of necrotic bone (sequestrectomy) and / or superficial surgical debridement of necrotic bone combined with oral antibiotics and chlorhexidine rinses. It could be associated with adjuvant therapies such as the use of *Platelet Rich Plasma* (PRP). Local curettage, despite allowing reduction, but not the total elimination of necrotic bone, has been shown to be advantageous in decreasing sharp bone margins that traumatize soft tissues (Vescovi *et al.*, 2014; Ristow *et al.*, 2015).

When used in surgery, lasers have excellent potential. It can provide ablation of bone tissue, with minimal risk of thermal injury of adjacent tissues. In addition, it has bactericidal, detoxification and bio-stimulating effects that may increase bone regeneration and help wound healing after surgery (Baek *et al.*, 2015; Zeitouni *et al.*, 2017).

In those patients in which previous treatment has failed or in very advanced cases of MRONJ, a marginal or segmental jaw bone resection is indicated. The associated resection is surgically extensive, aiming to eliminate all the necrotic tissue until viable margins with blood are attained, leaving only healthy bone. Moreover, marginal resections include the resection of the affected alveolar processes. These approaches are often performed under general anesthesia (Bedogni *et al.,* 2011).

Favia *et al.,* 2018 advocates the inclusion of a minimum of one centimeter of viable bone with the preservation of noble structures, vessels and cortical bone to improve re-ossification and healing.

The segmental resection of maxillary bone aims at removing a segment of the mandible, preventing the progression of necrosis, being recommended only for severe cases due to the associated high levels of morbidity and decreased quality of life (Dimopoulos *et al.*, 2006; Rupel *et al.*, 2014). This type of surgery could be further enhanced by the use of fluorescent guides to detect bone margins (Rupel *et al.*, 2014; Favia *et al.*, 2018).

A mucosal incision must be made in order to promote a tension-free mucoperiosteous covering in the area of bone exposure (Rugani *et al.*, 2015; Ristow *et al.*, 2019). The reconstruction of bone defects to achieve complete healing and protect the affected site, can be achieved through the surgical use of local or distant flaps, such as microvascular and oral fat tissue. The use of such flaps leads to increased satisfactory results in terms of the quality of life of the patient (Ristow *et al.*, 2018).

In comparison with the unaffected areas, necrotic bone is typically darker, yellowish and due to the decrease in porosity, it is lighter and surrounded by areas of sclerosis, which are harder and vascularized. In order to enhance the success of removing necrotic bone, surgeons have access to different methods to determine bone margins. Certain diagnostic radiological devices assist in this identification, such as computed tomography (Vescovi *et al.*, 2014; Ristow *et al.*, 2015; Fleisher *et al.*, 2016).

2.3 – Results

The PRISMA flow diagram of the screening and selection process is demonstrated in Fig. 1. Initially, a total of 1478 articles were identified in the PubMed and B-on databases. From these results, 560 records were obtained after the removal of duplicates. Moreover, 513 articles were excluded based on the titles and abstracts. Therefore, 47 records were screened and after the eligibility process, 31 records were excluded based on the inclusion and exclusion criteria. In the end, 16 fulfilled the inclusion criteria and were selected for qualitative analysis.

Among the 16 selected studies, 10 were retrospective studies, 4 were prospective studies, and two were case series. All manuscripts were published between 2015- 2019.

A total of 809 patients were evaluated, of which 531 were females (65,9%), 206 were males (25,3%), and 72 were missing information (8,69%). The mean age of these patients was 70,47 years and the follow-up ranges were from 3 to 164 months.

The groups compared in this study varied, but all of them received surgical therapy as treatment for MRONJ (Table 3), which can be categorized into three different surgical approaches: conservative, extensive and laser surgery.

Studies and results are reported in tables 3-4 and the laser characteristics in table 5.

Fig 1: PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) flow diagram of the screening and selection process.

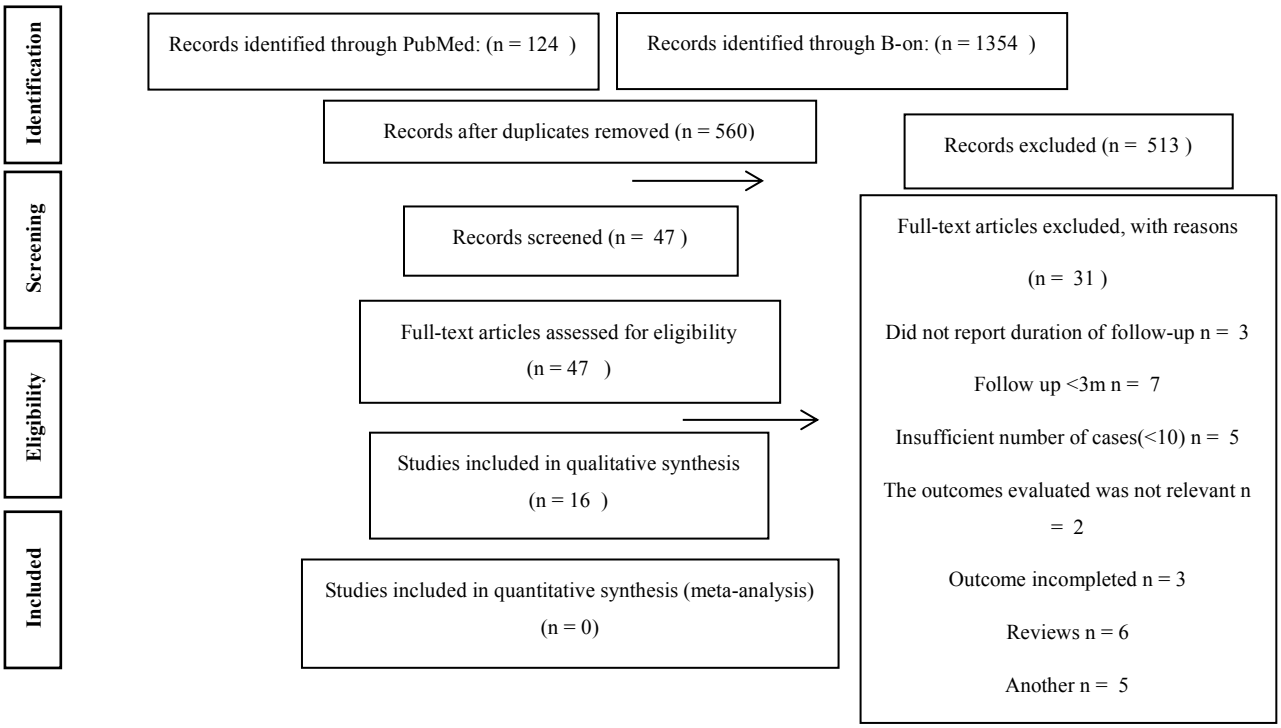

Table 3: Summary of the characteristics of the included studies

Authors Year	Patients	Mean age	Antiresorptive taken	AAOMS stage	Site of lesion	Risk of bias	Type of Treatment
(Giudice et al., 2018)	24 23	74.7±6.5	DENO 47	II 27; III 2 0	Mand 49; Max 12	8	**A** Remove necrotic bone+PRF **B** Remove necrotic bone+suture
(Park, Kim e Kim, 2017)	55	75.24 75.20	ALE 30; RIS 7; PAM 3; ZOL 1; IBA 6,BIS 8	I 8; II 43; III 4	Mand 37; Max 16; Both 2	8	**A** Sequestromy+curretage+debridment+PRF **B**Sequestromy+curretage+debridment+PRF+BMP
(Aljohani *et al.*, 2018)	3 31 22	70±9	ZOL 21; ALE 2; PAM 2; IBA 2; ZOL+PAM 4; DENO 2	0 3; I 5; II 48; III 10	Mand 43; Max 17; Both 3	6	**A** Non surgical **B**Complete surgical removal of necroticbone, smoothening of sharp bony edges, and plastic coverage **C** Fluorescence guided surgery
(Nisi *et al.*, 2018)	53	71.9±10.2	ALE 45; IBA 5; RIS 3	I 7; II 39; III 7	Mand 39; Max 12	6	Sequestrectomy, debridement with rotating or piezoelectric instruments
(Nisi *et al.*, 2016)	120	67	ZOL 97; ALE 17; IBA 3; RIS 3	I 26; II 77; III 26	NA	6	Sequestrectomy, debridement of softtissue, and curettage of bone. Anyresidual sequestra were removed to ensure healing by first intention.
(Ristow *et al.*, 2018)	87	66.25±9.58	BIS 42; DENO 33; BIS+DENO 12	I 40; II 44; III 20	Mandible 68; Maxilla 30	8	**A** Conventionalsurgery+MMF flap **B** Conventionalsurgery+BFFflap
(Ristow *et al.*, 2017)	41	71.80±9.4	BIS 32; BIS+DENO 8	I 4; II 41; III 6	Mand 33; Max 18	8	**A** Auto-fluorescence guided surgery **B** Tetracycline guided surgery
(Nørholt e Hartlev, 2016)	15	68.5	ALE 5; IBA 1; PAM 1; DENO 4; ZOL 4	II 13; III 2	Mand 11; Max 3; Both 1	7	Remove necrotic bone with piezoelectric device +smooth edges+PRF
(Pichardo, Kuijpers e van Merkesteyn, 2016)	74	67.9	ZOL10; PAM 23; .ALE 30; RIS 9; IBAN 1	II 22; III 52	Mand 11; Max 58; Both 5	7	Sequestrectomy, thorough surgical removal and saucerization of the non-vital bone up to bleeding bone margins, and closing primary defect in layers
(Lopes *et al.*, 2015)	33	65.6±10.6	ZOL 22; PAM 3; ZOL+PAM 5; ALE 2; ALE+ZOL 1	II 37; III 9	Mand 24; Max 6	5	Extensive sequestrectomy and bonyresection up to bleeding margins, withsmoothening of sharp edges, and meticulous wound closure
(Fleisher et al., 2016)	31	64	ZOL 14; PAM 1; ZOL+PAM 3; DENO 10; DENO+BIS 3	II 31; III 2	NA	7	Surgical resection with FDG + mucoperiosteal flap + HBO
(Bodem *et al.*, 2016)	39	72±9	ZOL 39	II 23; III 24	Mand 34; Max 13	7	Resection + sharp bone + mucoperiosteal flap
(Caldroney *et al.*, 2017)	11	65.8	ZOL 7; PAM 2; ALE 1; DENO+ZOL1	III 11	Mand 11	5	Broad resection and microvascular flap reconstruction:7 Fibula freeflaps, 4 Scapular free flaps
(Favia et al., 2017)	82 24	**A**70.2 **B** 71	**A** BIS 88; DENO 13; BIS+DENO 6 **B** BIS 15; DENO 7; BIS+DENO 1	**A** I 9; II 61; III 37 **B** I 2; II 4; III 18	**A** Mand 73; Max 34 **B** Mand 12; Max 12	7	**A** Extensive bony resection up to viable and bleeding margins + mucoperiosteal flap **B** Antiseptic mouth rinse(chlorhexidine), periodic dentalchecks, systemic antibiotic administration Monthly LLLT, superficial sequestrectomy
(Merigo *et al.*, 2018)	21	74	ZOL 12; ALE 8; NR 1	I 2, II 15; III 4	Mand 15; Max 6	6	PMD(Mectron,Italy) remove necrotic bone;Er:YAG laser vapor necrotic bone; Diode laser for biomodulation; PRP
(Mauceri *et al*., 2018)	10	75,2±5,94	ZOL 9; ZOL+IBA 1	II 6;III 4	Mand 9; Max 1	5	Er,Cr:YSGG laser debridement and sequestrectomy of the necrotic bone+ PRP +Tension-free soft tissue closure

ZOL: zoledronic; RIS: risedronate; IBAN: ibandronate; ALE: alendronate; PAM: pamidronate; DENO: denosumab; BIS: bisphosphonate

Table 4: Summary of the results of the included studies

Authors Year	Type of treatment	Antibiotic	Follow-up	Outcome
(Giudice et al., 2018)	Conservative surgery	yes	12	**A** CH n=23 **23/24(95.8%)** **B** CH n=21 **21/23((91.3%)**
(Park, Kim e Kim, 2017)	Conservative surgery	yes	6	**A** CH n=9; PH n=13; NH n=3 **9/25(36%)** **B** CH n=18; PH n=11; NH n=1 **18/30(60%)**
(Aljohani *et al.*, 2018)	Non surgical Conservative surgery Extensive surgery	yes	3.48	**A** CH=2; NH=1 **2/3 (66.66%)** CH n=21; PH n=5; NH n=4; L n=7 **21/31(67.7 %)** **B** CH n=17; PH n=1; NH n=4 **17/22(77.3%)**
(Nisi *et al.*, 2018)	Conservative surgery	yes	6	PH n=107; NH n=20; W n=1 **107/128(83%)**
(Nisi *et al.*, 2016)	Conservative surgery	yes	24	CH n=45, PH n=8 **45/53(91.8%)**
(Ristow *et al.*, 2018)	Conservative surgery	yes	4-8	**A** CH n=44; PH n=6 **44/50 (88%)** **B** CH n=27; PH n= 2 **27/29 (93.1%)**
(Ristow *et al.*, 2017)	Extensive surgery	yes	24	**A** CH n=20; NH n=2 **20/22(94%)** **B** CH n=18; NH n=1 **18/19(89%)**
(Nørholt e Hartlev, 2016)	Extensive surgery	yes	7-20	CH n=14; R n=1 **14/15(93%)**
(Pichardo, Kuijpers e van Merkesteyn, 2016)	Extensive surgery	yes	6-96	CH n=69; NH n=5 **69/74(93.2%)**
(Lopes *et al.*, 2015)	Extensive surgery	yes	10	CH n=40; PH n=3; NH n=3(W n=1) **40/43(87%)**
(Fleisher et al., 2016)	Extensive surgery	yes	3-38	CH n=25; NH n=8 25/33**(75.75%)**
(Bodem *et al.*, 2016)	Extensive surgery	yes	4-12	CH n=24; PH n=11; NH n=12 **24/47(51%)**
(Caldroney *et al.*, 2017)	Extensive surgery	yes	25	CH n=11 **11/11(100%)**
(Favia et al., 2017)	Extensive surgery Non surgical	yes	12-28	**A** CH n=102; PH n=5 **102/107(95.3%)** **B** NH=24
(Merigo *et al.*, 2018)	Laser surgery	yes	5-164	CH n = 20;R n=1 **20/21(95%)**
(Mauceri *et al.*, 2018)	Laser surgery	yes	15 days,one month,three,six,twelve months follow-up period	CH n=3; CI n=8; NEB n=6;CSI n=5; NCSI n=2 **8/10 (80%)**

CH: complete healing; PH: partial healing; NH: not healing; W: worse; R: recurrence; CI: clinical improvement; NEB: non-exposed bone; CIS: clinical symptoms improvement; NCSI: non clinical symptoms improvement

Table 5: Characteristics of the laser equipment's in the laser approach

Authors	Laser character	Power (mW)	Energy density(J/cm)	Time of radiation
(Merigo *et al.*, 2018)	Er:YAGlaser: 200mJ, 20 Hz;Diode lase:continuous mode 808nm	Er:YAGlaser: NA;Diodelaser :1000	Er:YAGlaser:39.80; Diodelaser:21231	Er:YAGlaser: once during surgery; Diode laser: the first session just after suturing, the subsequent ones were 2 times/week until suture removal
(Mauceri *et al.*, 2018)	2780nm,20Hz	0-6000	NA	Er:YAGlaser:during the surgical intervention

It was observed that bisphosphonates were the medication most used (81,57%), followed by denosumab (14,5%) and a small percentage used both (3,88%). The drug treatment was administered IV in 217 patients (57,7%) and the mean duration of drug therapy was 38,19 months. Zoledronate was responsible for the majority of MRONJ cases accounting for 42,16%, alendronate 17,54%, then denosumab 14,53%, pamidronate 4,38%, risedronate 2,75%, and ibandronate 2,38%. In some patients the type of bisphosphonate was not specified (23,18%). A combination of the aforementioned drugs was also found to be responsible: zoledronate and pamidronate (1,50%); zoledronate and ibandronate (0,125%), and zoledronate and alendronate (0,125%).

The three most common indications for antiresorptive or antiangiogenic treatment were breast cancer (38,8%), osteoporosis (16,9%) and prostate cancer (24,4%).

Some studies also reported the respective stage of MRONJ (I, II, and III), according to Ruggiero (2014). The most prevalent stage described in the studies was stage II (59,46%), followed by stage III (28,66%) and stage I (11,5%).

The authors evaluated the affected sites by MRONJ. The data obtained showed that the majority of the lesions were found in the mandible (64,4%) and to a lesser extent in the maxilla (32,69%). It was also observed that lesions were found in both jaws in 2,88% of patients.

The table 6 shows the evaluation of the risk of bias of the selected studies using the Newcastle-Ottawa Scale. The included studies appeared to have a low to moderate risk of bias.

2.3.1 – Conservative surgical approach

All the studies considered (Nisi *et al.*, 2016, 2018; Park, Kim e Kim, 2017; Aljohani *et al.*, 2018; Giudice *et al.*, 2018; Ristow *et al.*, 2018), showed healing rates of over 60%, with the exception of one study (Park, Kim e Kim, 2017).

The healing rates using *Platelet Rich Fibrin* (PRF), are relatively controversial. Although Giudice *et al.*, 2018, reported good outcomes (94,4%), Park, Kim e Kim, 2017 reported low rates (36%). Posteriorly, Park, Kim e Kim, 2017 used the addition of *bone morphogenetic protein-2* (BMP), leading to increased success rates of 60%. Three studies (Nisi *et al.*, 2016, 2018; Giudice *et al.*, 2018), used only conservative surgery and reported a healing rate of 83,45%.

Even higher success rates were observed when conservative surgery was performed adding *Mylohyoideus Muscle Flaps* (MMFs) (83%) or *Buccal Fat Flaps* (BFF) (93,1%) (Ristow *et al.*, 2018). Total healing rate after conservative surgical approaches was 79,97%.

2.3.2 – Extensive surgical approach

Although in a study, one of the patients got worse (Lopes et al., 2015), the other selected studies reported high success rates (Bodem *et al.*, 2016; Fleisher *et al.*, 2016; Nørholt e Hartlev, 2016; Pichardo, Kuijpers e van Merkesteyn, 2016; Caldroney *et al.*, 2017; Ristow *et al.*, 2017; Aljohani *et al.*, 2018; Favia *et al.*, 2018).

The addition of *Hyperbaric Oxygen therapy* (HBO) and piezoelectric devices provided good results (Fleisher *et al.*, 2016; Nørholt e Hartlev, 2016). Further approaches with high healing outcome (86,76%) were fluorescent and auto-fluorescent guided bone resection (Ristow *et al.*, 2017; Aljohani *et al.*, 2018) and the use of PRF, to enhance healing after surgery (93%) (Nørholt e Hartlev, 2016). Total healing rate after extensive surgical approaches was 84,72%.

2.3.3 – Laser surgery approach

Maureci *et al.,* 2018 and Merigo *et al.,* 2018, utilized high-intensity laser surgery (ErCrYSGG and Er:YAG lasers) to perform ablation of necrotic tissue obtaining therefore bloody viable margins, providing high healing rates, ranging from 80% to 95%. Merigo *et al.,* 2018, used adjuvant *Low-Level Laser Therapy* (LLLT), due to its high affinity of absorption by water and hydroxyapatite leading to better results (95%). Both studies also made use of PRP. Total healing rate after laser surgical approaches was 87,5%.

III – DISCUSSION

Systematic reviews are invaluable tools, aimed at answering clinical topics, especially controversial ones, based on the best scientific evidence available (Marques, 2018).

The management of MRONJ remains a controversial topic. Some authors argue that patients should undergo palliative therapy instead of seeking complete cure through more aggressive interventions, as they reported that surgical treatment ultimately would not be

able to provide complete cure for the osteonecrosis. Over the years, recent studies have tried to prove the opposite and proposed other types of treatment approaches (Marx *et al.*, 2003; Magopoulos *et al.*, 2007; Scoletta *et al.*, 2010).

Since conservative therapy is only effective at minimize symptoms rather than curing completely the condition, surgical approaches are the only method for achieving long lasting mucosal healing in MRONJ patients. The aim of this systematic review was to assess the efficacy of different surgical treatments for MRONJ.

Some studies reported that the type of bisphosphonates may play a role in the development of MRONJ. Of special importance are BPs containing nitrogen like pamidronate and zoledronate, with the latter being associated with a higher risk than pamidronate (Marx *et al.*, 2003; Ruggiero *et al.*, 2004; Dimopoulos *et al.*, 2006). Coincidently, it was observed that the medications most used by the patients, zoledronate (42,16%) and pamidronate (17,54%), were also those associated with a higher risk.

The mean duration of drug therapy, was 38,19 months; this is a crucial factor for the development of MRONJ. It has been proposed that the development of MRONJ requires a long period of exposure (Ruggiero *et al.*, 2014).

Recent studies suggest that IV bisphosphonates are more likely to develop MRONJ than oral ones (Marx *et al.*, 2003; Bamias *et al.*, 2020). This is in accordance with the present review, which showed that 57,7% of BRONJ lesions developed following IV BPs use.

The large number of female patients affected by BRONJ in the studies may be pure coincidence, as they tend to take more oral BPs than male patients, due to osteoporosis and rheumatoid arthritis, diseases that are more common in women (Conte-neto *et al.*, 2011). In accordance with this review, it was found a high prevalence of BRONJ among women (65,9%).

The mandible (64,4%) was more affected than the maxilla (32,69%). This could be attributed to the decreased vascularity of the mandible (Fliefel *et al.*, 2015).

Despite all the controversies, there is consensus in the use of surgery in those cases characterized by chronic exposure of necrotic bone, since it can interfere with wound healing and naturally is infected (Rugani *et al.*, 2015).

There was clinical heterogeneity among the studies, which is not surprising given the significant number of interventions available and the considerable variations in

techniques applied, which made it difficult to draw deep conclusions. Therefore, the main limitation of the present review is the restriction of statistics to qualitative analysis only. Nevertheless, the risk of bias has been reduced through quality assessment procedures with the Newcastle-Ottawa Scale (NOS).

Favia *et al.*, 2018, demonstrated that the use of a conservative approach in combination with LLLT did not lead to complete healing of lesions, with most of them just remaining stable. It should be taken into account that only Favia *et al.*, 2018 evaluated conservative surgery, and that this study only included 21 patients. Currently, the recommended treatment for all MRONJ stages includes antibiotics, antiseptic mouth rinses and periodical dental checkups (Ruggiero *et al.*, 2014; Bodem *et al.*, 2016).

It was evident from the data collected, that the conservative surgical approach provided better results than a purely non-surgical conservative approach. In the patients treated with conservative surgery, 79,97% achieved full healing.

A total of 403 patients were managed through minimally invasive surgical approach by using sequestrectomy, curettage, debridement, or smoothening of bone, with or without flaps (Nisi *et al.*, 2016, 2018; Park, Kim e Kim, 2017; Aljohani *et al.*, 2018; Giudice *et al.*, 2018; Ristow *et al.*, 2018).

Park, Kim e Kim, 2017, after studying the use of Leucocyte-Platelet Rich Fibrin (L-PRF) matrix, noted its slow dissolution, which allows for a progressive release of platelet-derived growth factors and cytokines. Moreover, the leucocytes within L-PRF act as an anti-infectious agent with a role in immune regulation and produced large amounts of *vascular endothelial growth factor* (VEGF). This enabled an accelerated successful healing of epithelial wounds, improved tissue vascularization and enhanced soft tissue regeneration.

Giudice *et al.*, 2018, demonstrated similar results when utilizing the L-PRF matrix with conventional surgery. Additionally, mucosal healing and perceived quality of life were evaluated. A long-term follow-up evaluation showed no statistical differences between the PRF and non-PRF groups in terms of mucosal healing and absence of infection, but the short-term follow-up showed significant improvement in terms of quality of life in the PRF group, due to the accelerated healing. In this new era of significant medical advancements, such biological therapies can be viable treatment options of numerous skeletal conditions as an alternative or adjuvant for resection or bone grafts.

Despite this, the use of L-PRF alone is still disputed. A new therapy for MRONJ, based on the adjuvant application of L-PRF simultaneously with bone morphogenetic protein-2 (BMP-2), which stimulates not only soft tissue healing but also osseous, has been discussed.

Park, Kim e Kim, 2017, investigated if such combination would contribute to a higher success in the surgical treatment of osteonecrosis by comparing the outcome of healing of these lesions in two groups of patients: the L-PRF and the L-PRF+BMP-2. This study demonstrated a significant positive outcome in the resolution of the disease in the L-PRF+ BMP-2 group (60%) compared to the first group (36%). The healing pattern of the second group was more accelerated. The reason behind this may be that BMP-2 exhibits a reversal effect on the over suppression of bone remodeling in MRONJ, through a biphasic function of osteoclast activation and differentiation.

Mauceri *et al.*, 2018 and Merigo *et al.*, 2018 verified that the use of laser-assisted surgery, plus platelet rich plasma in the treatment of MRONJ achieved a significant rate of clinical improvement or healing (87,5%). The use of laser technology for BRONJ treatment and its beneficial effects on tissue healing has been widely investigated in the last years.

Laser (Er:YAG) may represent a useful option in the treatment of MRONJ. It acts by vaporizing necrotic bone as well as bio-modulating both soft and hard tissues, due to its affinity to water and hydroxyapatite. Laser technology enables a clean and precise ablation of bone without the use of conventional rotary cutting tools, thus limiting adverse effects. This generates minimal injury of surrounding bone and soft tissues, while producing an ablative surface conducive to cell attachment, allowing faster bone healing (Vescovi *et al.*, 2010, 2012).

The lack of vascularization represents one of the major factors in the pathogenesis of BRONJ. To counter it, Platelet Rich Plasma (PRP) is largely used in postsurgical wound healing. After the surgical ablation of necrotic bone and the decontamination of the surgical site, PRP stimulates the release of numerous growth factors. These growth factors promote cell chemotaxis, proliferation and differentiation which stimulate angiogenesis, bone and mucosal healing leading to deposition of new extracellular matrix (Lopez-Jornet *et al.*, 2016).

Merigo *et al.*, 2018 combined the effect of Er:YAG laser with the bio-modulating properties of a diode laser (808 nm). LLLT approach, which is completely safe and

comfortable for the patient, may help complete mucosal healing through the stimulation of keratinocytes, osteoblasts and endothelial cells. The laser diode increased the healing from 80% to 95%.

However, these studies provided only the rates of clinical improvement or healing and did not compare laser-assisted surgery with traditional, conservative or extend surgery. This review, therefore, can only evaluate laser-assisted surgery qualitatively rather than quantitatively.

Extensive surgical approach was the most commonly used method for the management of BRONJ, yielding good outcomes in patients (84,72%). This approach provided superior results compared to the healing rate achieved with the conventional surgical approach (79,97%) but inferior results compared with the laser surgery approach (87,5%). This finding suggested that extensive bone resection up to the bleeding margins was more effective than a sequestrectomy, with or without the use of L-PRF, for obtaining full mucosal healing in MRONJ, but it was less effective than laser surgery.

Invasive surgery with microvascular flap reconstruction yielded even better results. Caldroney *et al*., 2017, documented excellent outcomes in treating patients affected by MRONJ. Since 2008, microvascular flap reconstruction of the jaw has been documented as a viable option for MRONJ. However, this type of extensive surgery carries a risk of severe morbidity. Three patients developed persistent wound related complications (27%) after surgery.

Aljohani *et al.*, 2018, reported a very high success rate (92%) in MRONJ patients using mandibular segmental resection and partial maxillectomy with the purpose of securing clean margins with healthy bone.

Fleisher *et al.*, 2016, observed that low-risk *fluorodeoxyglucose* (FDG) PET-CT findings predicted successful healing in surgeries above the mandibular canal. The mechanism behind the loss of autofluorescence in necrotic bone is uncertain. It is probably correlated to alterations in the calcified part of the bone. Ristow *et al.*, 2017, attributed this phenomenon to the loss of collagen in necrotic areas.

The complete removal of necrotic bone is naturally the main objective. Therefore, to enhance the results, Pautke *et al.,* 2009, considered the incorporation of fluorescence-

guided bone surgery, which enables a clearer visualization of the transition between necrotic and non-necrotic bone during the surgical procedure.

It is particularly difficult to measure the outcomes of different MRONJ therapies for two reasons: First, the definition of therapy success has not been universally defined, and particular studies that favor non-surgical therapy, often consider non-deterioration of the patient as a success. Second, only few studies have, up to today, compared the therapy outcomes of medical and surgical treatment in a controlled clinical manner.

Overall, a very high success rate with the sequential use of novelty high-tech devices was verified throughout the different stages of treatment of MRONJ. Experimental therapies enable faster and less invasive surgeries, with a more comfortable postoperative healing process and may represent a new and original approach to the treatment of this condition.

IV – CONCLUSION

The present review allowed to conclude that surgical treatment in combination with antibiotic therapy, can present extremely beneficial results. The laser approach has shown to be effective in promoting long-lasting palliative care with resolution of pain and infection.

Opinions converge on the multifactorial nature of MRONJ pathophysiology, however, there is still a long way to go to understand which mechanisms are really involved in its development. As mentioned, there is a number of factors that can increase the risk of developing the disease and that should always be taken into account when establishing a therapy with these drugs.

From the point of view of future research, it is important to focus on relevant issues, namely the comparison between invasive versus more conservative surgical approaches and the choice between surgical versus non-surgical therapy protocols. Lack of such data prevents the study results from being statistically significant excluding therefore the possibility of doing a meta-analysis.

On the other hand, it is also important to further evaluate the effects of the adjuvant therapies mentioned above and to evaluate the effect of other less studied alternative therapies. Furthermore, it is of great importance to ensure that future studies are as bias-free as possible through blind or double-blind trials, particularly regarding the evaluation of results.

XV – ANNEXES

Table 6: Risk of bias of the studies included in the review, evaluated using the Newcastle-Ottawa Scale

First author,year, andreference	(a1) Representiveness of exposed cohort / Is the case definition adequate?	(a2) Selection of non exposed cohort / Representativeness of the cases	(a3) Ascertainment of provided treatment/ Selection of Controls	(a4) Absence of outcome of interest at start of study/ Definition of Controls	(b) Comparablity of the cohort/ Comparability of cases and controls on the basis of the design or analysis	(c1) Adequacy of assessment/ Ascertainment of exposure	(c2) Length of follow up/ Same method of ascertainment for cases and controls	(c3) Imcomplete outcome data/ Non-Response Rate	Overall risk of bias
(Merigo *et al.*, 2018)	★		★	★		★	★	★	6
(Mauceri *et al.*, 2018)	★		★	★		★		★	5
(Park, Kim e Kim, 2017)	★	★	★	★	★	★	★	★	8
(Ristow *et al.*, 2018)	★	★	★	★	★	★	★	★	8
(Nørholt e Hartlev, 2016)	★	★	★	★		★	★	★	7
(Pichardo, Kuijpers e van Merkesteyn, 2016)	★	★	★	★		★	★	★	7
(Aljohani *et al.*, 2018)	★		★	★	★	★	★		6
(Lopes *et al.*, 2015)	★		★	★		★	★		5
(Nisi *et al.*, 2016a)	★		★	★		★	★	★	6
(Caldroney *et al.*, 2017)	★		★	★		★	★		5
(Nisi *et al.*, 2016b)	★		★	★		★	★	★	6
(Giudice *et al.*, 2018)	★	★	★	★	★	★	★	★	8
(Bodem *et al.*, 2016)	★	★	★	★		★	★	★	7
(Favia *et al.*, 2018)	★		★	★	★	★	★	★	7
(Ristow *et al.*, 2017)	★	★	★	★	★	★	★	★	8
(Ristow *et al.*, 2018)	★	★	★	★	★	★	★	★	8
(Fleisher *et al.*, 2016)	★	★	★	★		★	★	★	7

VI – REFERENCES

Aljohani, S. *et al.* (2018). Osteonecrosis of the jaw in patients treated with denosumab: A multicenter case series. *Journal of Cranio-Maxillofacial Surgery*, 46(9), pp. 1515–1525.

Bamias, A. *et al.* (2020). Osteonecrosis of the Jaw in Cancer After Treatment With Bisphosphonates : Incidence and Risk Factors, 23(34).

Bodem, J. P. *et al.* (2016). Surgical management of bisphosphonate-related osteonecrosis of the jaw stages II and III. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. Mosby Inc., 121(4), pp. 367–372.

Caldroney, S. *et al.* (2017). Surgical resection and vascularized bone reconstruction in advanced stage medication-related osteonecrosis of the jaw. *International Journal of Oral and Maxillofacial Surgery*. Churchill Livingstone, 46(7), pp. 871–876.

Clézardin, P. (2013). Mechanisms of action of bisphosphonates in oncology: a scientific concept evolving from antiresorptive to anticancer activities. *BoneKEy Reports*, 2(FEBRUARY), pp. 1–7.

Conte-neto, N. *et al.* (2011). Oral bisphosphonate-related osteonecrosis of the jaws in rheumatoid arthritis patients : a critical discussion and two case reports. *Head & Face Medicine*. BioMed Central Ltd, 7(1), p. 7.

Dimopoulos, M. A. *et al.* (2006). increased risk after treatment with zoledronic acid Fe rra ta St or ti Fo u nd at Fe rra ta St or ti Fo u. *Haematologica*, 91(1), pp. 968–971.

Favia, G. *et al.* (2018). Medication-related osteonecrosis of the jaw: Surgical or non-surgical treatment? *Oral Diseases*, 24(1–2), pp. 238–242.

Fleisher, K. E. *et al.* (2016). Does Fluorodeoxyglucose Positron Emission Tomography With Computed Tomography Facilitate Treatment of Medication-Related Osteonecrosis of the Jaw? *Journal of Oral and Maxillofacial Surgery*. W.B. Saunders, 74(5), pp. 945–958.

Fliefel, R. *et al.* (2015). Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: A systematic review. *International Journal of Oral and Maxillofacial Surgery*. Churchill Livingstone, pp. 568–585.

Giudice, A. *et al.* (2018). Can platelet-rich fibrin improve healing after surgical treatment of medication-related osteonecrosis of the jaw? A pilot study. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. Mosby Inc., 126(5), pp. 390–403.

Higgins, J. P. T. *et al.* (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Online)*, 343(7829), pp. 1–9.

Kyrgidis, A. e Toulis, K. A. (2011). Denosumab-related osteonecrosis of the jaws. *Osteoporosis International*, 22(1), pp. 369–370.

Liberati, A. *et al.* (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Medicine*, 6(7).

Lo, C. K. L., Mertz, D. e Loeb, M. (2014). Newcastle-Ottawa Scale: Comparing reviewers' to authors' assessments. *BMC Medical Research Methodology*. BMC Medical Research Methodology, 14(1), pp. 1–5.

Longo, F. *et al.* (2014). Platelet rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw: Personal experience and review of the literature. *International Journal of Dentistry*, 2014.

Lopes, R. N. *et al.* (2015). Surgical Therapy for Bisphosphonate-Related Osteonecrosis of the Jaw: Six-Year Experience of a Single Institution. *Journal of Oral and Maxillofacial Surgery*, 73(7), pp. 1288–1295.

Lopez-Jornet, P. *et al.* (2016). Medication-related osteonecrosis of the jaw: Is autologous platelet concentrate application effective for prevention and treatment? A systematic review. *Journal of Cranio-Maxillofacial Surgery*. Elsevier Ltd, 44(8), pp. 1067–1072.

Magopoulos, C. *et al.* (2007). Osteonecrosis of the jaws due to bisphosphonate use. A review of 60 cases and treatment proposals. *American Journal of Otolaryngology - Head and Neck Medicine and Surgery*, 28(3), pp. 158–163.

Marques, J. (2018). Revisões sistemáticas: O que São e para que Servem. *VIA revista*, 3(4), p. 51.

Marx, R. E. *et al.* (2003). Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. *Journal of Oral and Maxillofacial Surgery*, 63(11), pp. 1567–1575.

Mauceri, R. *et al.* (2018). Conservative Surgical Treatment of Bisphosphonate-Related Osteonecrosis of the Jaw with Er,Cr:YSGG Laser and Platelet-Rich Plasma: A Longitudinal Study. *BioMed Research International*, 2018, pp. 10–12.

Mücke, T. *et al.* (2016). Free flap reconstruction for patients with bisphosphonate related osteonecrosis of the jaws after mandibulectomy. *Journal of Cranio-Maxillofacial Surgery*. Churchill Livingstone, 44(2), pp. 142–147.

Nisi, M. *et al.* (2016). Conservative surgical management of patients with bisphosphonate-related osteonecrosis of the jaws: a series of 120 patients. *British Journal of Oral and Maxillofacial Surgery*. Churchill Livingstone, 54(8), pp. 930–935.

Nisi, M. *et al.* (2018). Conservative surgical treatment of medication related osteonecrosis of the jaw (MRONJ) lesions in patients affected by osteoporosis exposed to oral bisphosphonates: 24 months follow-up. *Journal of Cranio-Maxillofacial Surgery*. Churchill Livingstone, 46(7), pp. 1153–1158.

Nørholt, S. E. e Hartlev, J. (2016). Surgical treatment of osteonecrosis of the jaw with the use of platelet-rich fibrin: a prospective study of 15 patients. *International Journal of Oral and Maxillofacial Surgery*, 45(10), pp. 1256–1260.

Park, J. H., Kim, J. W. e Kim, S. J. (2017). Does the Addition of Bone Morphogenetic Protein 2 to Platelet-Rich Fibrin Improve Healing After Treatment for Medication-Related Osteonecrosis of the Jaw? *Journal of Oral and Maxillofacial Surgery*. American Association of Oral and Maxillofacial Surgeons, 75(6), pp. 1176–1184.

Pichardo, S. E. C., Kuijpers, S. C. C. e van Merkesteyn, J. P. R. (2016). Bisphosphonate-related osteonecrosis of the jaws: Cohort study of surgical treatment results in seventy-four stage II/III patients. *Journal of Cranio-Maxillofacial Surgery*. Churchill Livingstone, 44(9), pp. 1216–1220.

Pichardo, S. E. C. e van Merkesteyn, J. P. P. R. R. (2016). Evaluation of a surgical treatment of denosumab-related osteonecrosis of the jaws. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. Mosby Inc., 122(3), pp. 272–278.

Ristow, O. *et al.* (2015). Treatment perspectives for medication-related osteonecrosis of the jaw (MRONJ). *Journal of Cranio-Maxillofacial Surgery*. Churchill Livingstone, pp. 290–293.

Ristow, O. *et al.* (2017). Comparison of auto-fluorescence and tetracycline fluorescence for guided bone surgery of medication-related osteonecrosis of the jaw: a randomized controlled feasibility study. *International Journal of Oral and Maxillofacial Surgery*. Churchill Livingstone, 46(2), pp. 157–166.

Ristow, O. *et al.* (2018). Double-layer closure techniques after bone surgery of medication-related osteonecrosis of the jaw – A single center cohort study. *Journal of Cranio-Maxillofacial Surgery*. Elsevier Ltd, 46(5), pp. 815–824.

Ristow, O. *et al.* (2019). Is the conservative non-surgical management of medication-related osteonecrosis of the jaw an appropriate treatment option for early stages? A long-term single-center cohort study. *Journal of Cranio-Maxillofacial Surgery*, 47(3), pp. 491–499.

Rugani, P. *et al.* (2015). Stage-related treatment concept of medication-related osteonecrosis of the jaw—a case series. *Clinical Oral Investigations*. Springer Verlag, 19(6), pp. 1329–1338.

Ruggiero, S. L. *et al.* (2004). Osteonecrosis of the Jaws Associated with the Use of Bisphosphonates: A Review of 63 Cases. *Journal of Oral and Maxillofacial Surgery*, 62(5), pp. 527–534.

Ruggiero, S. L. *et al.* (2014). American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw — 2014 Update. *Journal of Oral Maxillofacial Surgery*. American Association of Oral and Maxillofacial Surgeons, 72(10), pp. 1938–1956.

Rupel, K. *et al.* (2014). A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRRupel, K., Ottaviani, G., Gobbo, M., Contardo, L., Tirelli, G., Vescovi, P., … Biasotto, M. (2014). A systematic review of therapeutical approaches in b. *Oral oncology*. Elsevier Ltd, 50(11), pp. 1049–1057.

Scoletta, M. *et al.* (2010). Treatment outcomes in patients with bisphosphonate-related osteonecrosis of the jaws: A prospective study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and*

Endodontology. Elsevier Inc., 110(1), pp. 46–53.

Vescovi, P. *et al.* (2010). Surgical approach with Er: YAG laser on osteonecrosis of the jaws (ONJ) in patients under bisphosphonate therapy (BPT). *Lasers in Medical Science*, 25(1), pp. 101–113.

Vescovi, P. *et al.* (2012). Surgical approach and laser applications in BRONJ osteoporotic and cancer patients. *Journal of Osteoporosis*, 2012.

Vescovi, P. *et al.* (2014). Conservative surgical management of stage i bisphosphonate-related osteonecrosis of the jaw. *International Journal of Dentistry*, 2014.