MedNEXT
Journal of Medical an Health Sciences

REVIEW ARTICLE

DOI: 10.54448/mdnt23S205

Osteonecrosis of the jaw with the use of bisphosphonates and treatment with laser therapy and magnetotherapy: a concise systematic review

Daniele Pedrosa Arede[1], Andresa Silva Beijo[1], Damaris Maria de Paula Martinez[1], Igor Mariotto Beneti[1,2*]

[1] UNORTE - University Center of Northern São Paulo, Dentistry department, São José do Rio Preto, São Paulo, Brazil.
[2] UNIPOS - Post graduate and continuing education, Dentistry department, São José do Rio Preto, São Paulo, Brazil.

*Corresponding author: Dr. Igor Mariotto Beneti.
UNORTE/UNIPOS - Graduate and Postgraduate in Dentistry,
Sao Jose do Rio Preto, Sao Paulo, Brazil.
Email: igor.beneti@globo.com
DOI: https://doi.org/10.54448/mdnt23S205
Received: 01-15-2023; Revised: 03-31-2023; Accepted: 04-10-2023; Published: 04-11-2023; MedNEXT-id: e23S205

Abstract

Introduction: Bisphosphonate-related osteonecrosis of the jaw (BRONJ) has been increasing, mainly as a consequence of the treatment of osteoporosis in elderly women. During bone resorption, bisphosphonates (BP) are taken into osteoclasts and exhibit cytotoxicity, producing a long-lasting anti-bone resorptive effect. several energy-based devices have been used with substantial clinical improvement in the treatment. Devices are widely used in various types of treatment, such as LASER, LED, TEMs, infrared devices, Ultrasound, and radiofrequency, among others. **Objective:** It was to analyze the main findings and weave approaches of scientific evidence of the occurrence of osteonecrosis by the use of bisphosphonates, as well as the possible treatments, highlighting laser therapy and magnetotherapy. **Methods:** The present study was followed by a systematic review model (PRISMA). The search strategy was performed in the PubMed, Cochrane Library, Web of Science and Scopus, and Google Scholar databases. The Cochrane Instrument was used to assess the risk of bias from the included studies. The present study was carried out from December 2022 to March 2023. **Results and Conclusion:** A total of 138 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed based on the GRADE Instrument and Risk of Bias. A total of 58 articles were fully evaluated and 26 were included and discussed in this study. It was concluded that photobiomodulation therapy and magnetotherapy showed safety and efficacy in the treatment of BRONJ, through the reduction of phlogistic signs, faster healing, and reduction of postoperative morbidity. Only four applications of low-intensity laser and magnetotherapy were enough to reduce the inflammatory process in the surgical wound, stimulate the tissue repair process and provide postoperative analgesia.

Keywords: Bisphosphonates. Osteonecrosis. Jaw. Treatments. Laser therapy. Magnetotherapy.

Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) has been increasing, mainly as a consequence of the treatment of osteoporosis in elderly women. During bone resorption, bisphosphonates (BP) are taken into osteoclasts and exhibit cytotoxicity, producing a long-lasting anti-bone resorptive effect. BP is divided into nitrogencontaining BP (N-BP) and non-nitrogen-containing BP (non-N-BP). N-BPs have much stronger anti-bone resorptive effects than non-N-BP, and BRONJ is caused by N-BP. Findings suggest that BRONJ may be induced by mechanisms mediated by phosphate transporters and promoted by infection and that etidronate and clodronate may be useful for preventing and treating BRONJ [1-3].

Bisphosphonates are a class of drugs widely used in several medical specialties [4-8]. Its main property is to inhibit the precipitation of calcium phosphate, decreasing calcification and bone reabsorption, and reducing osteoclastic action by inducing apoptosis of these cells [9-13]. Its prescription was initially restricted to diseases that interfered with bone metabolisms, such as Paget's disease, malignant hypercalcemia, bone metastases, osteolytic lesions, and multiple myeloma. Currently, it has also been widely prescribed for the treatment of osteoporosis and even prophylactically for osteopenia [14].

Within the class of bisphosphonates, there are several drugs with similar action on bone tissue, varying their potency and route of administration. As an example, we can mention Sodium Risedronate, Sodium Etidronate, Zoledronic Acid, and, the one that is most prescribed, for oral use, Sodium Alendronate [14]. Such drugs can cause serious adverse effects in the body, among the most frequent of which can be mentioned: hypocalcemia, impaired kidney function, complications in the digestive tract such as esophageal ulcer, atypical fractures of the femur, atrial/ventricular fibrillation and osteonecrosis of the jaws, the latter being the object of our study [15]. Patients who use this class of medication orally have the lowest prevalence of 0.01% to 0.04% of the occurrence of osteonecrosis, while those who use intravenously are affected between 8% and 12% [16].

However, it has to be reported that the complications, when they occur, are very severe and mutilating, compromising the quality of life of these patients. One of the recent treatments of bone disorders is the use of antiresorptive drugs, including hormone replacement therapy, selective estrogen receptor modulators, bisphosphonates, and denosumab, which reduce the occurrence of pain, pathological fractures, and spinal cord compression [17]. The main property of BP is to inhibit calcium phosphate precipitation, decrease calcification, and bone resorption, and reduce osteoclastic action, by inducing apoptosis of these cells, which reabsorb bone tissue. These have a great affinity with bone tissue, long half-life in bones, inhibiting bone resorption, and can be administered orally or intravenously [2,3,14].

The mechanisms of action of BP in bone metabolism are complex and multifactorial, changing the osteoclastic cytoskeleton, stimulating apoptosis, and mainly reducing the proton pump with alteration of pH and basic acid balance [5,6]. The clinical efficacy of BF increases due to its ability to bind strongly to bone minerals. The initial release of BP occurs by renal excretion or adsorption to bone minerals, extending over weeks to years. During bone resorption, the acidic pH in the resorption gap enhances drug dissociation in bone [7,17].

Furthermore, BP is a synthetic analog of organic pyrophosphates, where the unstable oxygen atom of the central structure (P-O-P) has been replaced by carbon (P-CP), making it more resistant and cannot be broken down by enzymes [18]. BF interferes with chemotaxis and osteoclast attachment to bone along with suppression of osteoclast function. Furthermore, they block the recruitment, activation, and differentiation of osteoclast precursors. They inhibit the proliferation of macrophages, reducing their recruitment and differentiation into osteoclasts, in addition to reducing the number of osteoclasts, altering the cytoskeleton of these cells, depolymerizing the microtubules and retracting the rough membrane, thus hindering their adhesion to the bone [18].

Bisphosphonates have anti-angiogenic effects. As such, impaired vascularity may come to play as one of the terrible factors in the development of osteonecrosis in the jaws. They also act on immunity, resulting in impaired function of myeloid cells, and dendritic cells, and an increase in the number of T cells. These increase the antigenicity of cancer cells as targets and increase adaptive immunity. This impairment of local immunity with a greater infectious tendency may prove to be a key element in osteonecrosis of the jaws [9-11].

In addition, a position paper by the American Association of Oral and Maxillofacial Surgeons (AAOMS) first proposed its nomenclature "Bisphosphonates Related Osteonecrosis of the Jaws" (BRONJ). NO is the term used to describe bone cell death when the osteocyte becomes necrotic. Necrosis also destroys vascular endothelial cells within the bone tissue, impairing blood flow within it [9].

Patients who develop necrosis are aged between 35 and 95 years, with a higher prevalence between 65 and 68 years. Among the risk factors for the development of the disease, we can mention: the dose and frequency administered, the potency of the drug, the route of administration, the duration of the treatment, and the half-life of the drug in the bone tissue [13,17]. To confirm the diagnostic hypothesis, imaging tests should be requested, such as panoramic radiography and facial computed tomography. These exams demonstrate the presence of bone sequestration with osteolytic areas associated with surrounding osteoblastic areas and aspect of bone tissue disorganization, destruction of bone cortices, periosteal reactions, and pathological fractures [17].

In this sense, several energy-based devices have been used with substantial clinical improvement in the treatment, as listed in the medical literature, however with a limited number when applied in clinical studies. In the health area, these devices are widely used in various types of treatment, such as LASER, LED, TEMs, infrared devices, Ultrasound, and radiofrequency, among others. The radiation emitted by the laser device denotes its characteristics, which is a monochromatic, coherent, and collimated wave. Such equipment allows this light energy to interact with specific tissue chromophores (hemoglobin and melanin), which have an affinity for the wavelength of the respective laser light emitted, mainly through absorption [16].

Lasers can be classified according to their power into two large groups High Power Laser (HPL) and Low Power Laser (LPL). The HPL uses energy greater than 5 W, emitting radiation capable of destroying tissue, employing high energy in very short times of around milliseconds to nanoseconds. HPL is widely used for surgical purposes and it acts through various effects, such as photothermal, photomechanical-acoustic, photoionizing, and photoablation. Laser with low power can be divided into 2 groups, according to the respective types of photoreceptors Low-Intensity Laser (LIL), with endogenous action, and Photodynamic Therapy (PDT), acting in the exogenous environment [16].

LPL acts completely differently from HPL, that is, through an effect called photophysical-chemical. This device promotes a photobiomodulation action at the molecular level in cells, tissues, and organs [19]. LIL is when optical radiation interacts with an endogenous photo acceptor and produces cellular/tissue biomodulation. While this interaction occurs, in the presence of molecular O_2, exogenous substances carry out the process of photodynamic therapy (PDT), performing a cytotoxic action on the treated tissue.

Also, in the treatment of photobiomodulation with a low-power laser, there should not be an increase in the temperature of the irradiated tissue. The thermal rise must not exceed 1°C and the power must always be less than 1 Watts. Photobiomodulation may involve two types of tissue action, biostimulation and/or bio-inhibition. The biomodulation action provoked by LPL, depending on the parameters of use (intensity, duration, wavelength, focus size, and optical properties of the target tissue), can cause both positive stimulation (biostimulation) and inhibition (bio-inhibition) in the tissue irradiated target [16,19].

In this regard, LIL wavelengths (600–1000nm) have photobiomodulation properties, such as osteoblast proliferation, collagen formation, facilitating bone regeneration, pain relief, improved wound healing, and nerve repair, in addition to reepithelialization. Inflammation can be characterized as a nonspecific response of the body, the defense against aggressive agents. The inflammatory response begins by trying to isolate the agent and minimize its damage, with a set of vascular, morphological, and biochemical changes in the connective tissue [19].

In this aspect, the mechanisms that explain the occurrence of these observed effects, however, are still not completely clarified, considering the principles that govern the electromagnetic field. Low-frequency pulsed electromagnetic fields are an important physiotherapy tool around the world, as it is a non-invasive, safe, and easy-to-use method. Indicated for the treatment of pain, inflammation, and tissue regeneration. It is possible to infer that, in the biological system and living organisms, BMC are ubiquitous and constantly created by physiological processes (cell movements, ionic fluxes, fluids in circulatory systems, mitochondrial electron transport chain, action potentials in membranes, and thus, onwards [19,20].

In this sense, its main actions are the deviation of particles with electric charge in movement, and the production of currents induced by the piezoelectric effect in bone tissue and collagen. At the cellular level, it normalizes the membrane potential, increases the solubility of substances, and stimulates cellular metabolism [20]. In addition, it produces anti-stress action and promotes acceleration of all repairing phenomena with bio-regenerating, anti-inflammatory and anti-edematous action, without demonstrating side effects. Therefore, biological effects may result from the interaction of these fields with exogenous BMC [20,21]. Therefore, photobiomodulation and magnetotherapy can act positively as adjuvants to the surgical treatment of osteonecrosis of the jaws, induced by the use of sodium alendronate.

Given the above, the present study aimed to analyze the main findings and weave approaches of scientific evidence of the occurrence of osteonecrosis by the use of bisphosphonates, as well as possible treatments, highlighting laser therapy and magnet therapy.

Methods

Study Design

The present study followed a systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and metaanalysis, access available in: http://www.prisma-statement.org/).

Data Sources

The search strategy was performed in the PubMed, Cochrane Library, Web of Science and Scopus, and Google Scholar databases. The present study was carried out from December 2022 to March 2023.

Descriptors (MeSH Terms) And Search Strategy

The main descriptors (MeSH Terms) used were Bisphosphonates. *Osteonecrosis. Jaw. Treatments. Laser therapy. Magnetotherapy*. The rules of the word PICOS (Patient; Intervention; Control; Outcomes; Study Design) were followed.

Selection Process, Risk of Bias and Quality of Studies

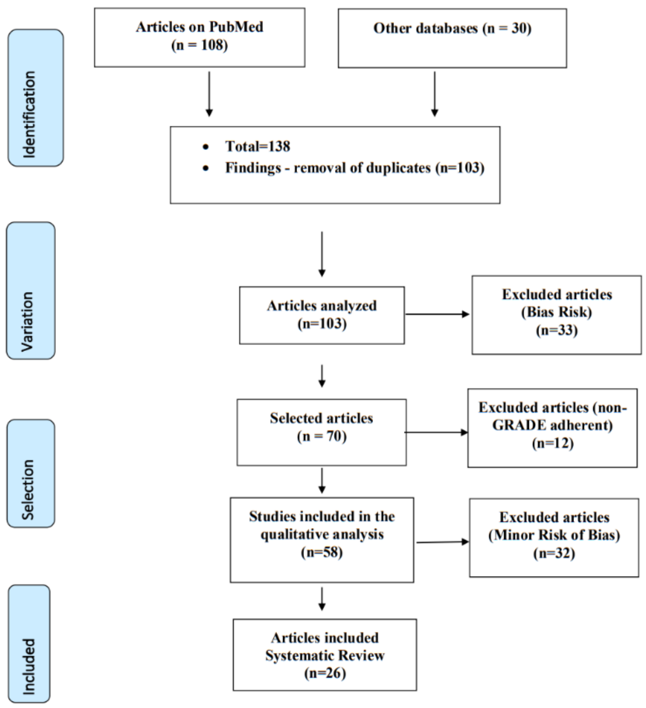
The quality of the studies was based on the GRADE instrument, with randomized controlled clinical studies, prospective controlled clinical studies, and studies of systematic review and meta-analysis listed as the studies with the greatest scientific evidence, and the risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

Summary of Findings

A total of 138 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed based on the GRADE Instrument and Risk of Bias. A total of 58 articles were fully evaluated and 26 were included and discussed in this study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 33 studies that were excluded with a high risk of bias (studies with small sample size). Also, 12 studies were excluded because they did not meet the GRADE (**Figure 1**).

Figure 1. Flowchart showing the article selection process.



Major Findings On The Osteonecrosis Of The Jaws

According to the treatments for bisphosphonate-related osteonecrosis of the jaw (BRONJ), good results with Ozone, PRF, PRP/Debridement/Laser Biostimulation, Laser Surgery and Laser Surgery/Laser Biostimulation stand out. HBO did not obtain good results and was used in only 10 patients. BRONJ is a rare condition in patients with osteoporosis/other pathologies using oral BP. These patients had long exposure time and cumulative doses of BP until the onset of the injury. Cancer patients were exposed to more potent BP administered intravenously, such as pamidronate and zoledronate. These patients had a shorter exposure time until the appearance of the lesion. Conclusions: BRONJ treatment is still under debate and there are promising treatments that need randomized trials with a larger number of patients to confirm their results. Patients using BPs or who will start treatment should be encouraged to undergo preventive dental treatment and maintain good oral hygiene [22].

In this scenario, with the increasing use of Bisphosphonates, against osteoporosis and above all, in cases of menopausal women with osteopenia, proportionally, there has been a greater incidence of the main adverse effect in the maxillomandibular region of these drugs: osteonecrosis of the jaws. The therapy The "gold standard" proposed choice for this disease is surgical treatment. Complications, when present, are very severe and mutilating, greatly impairing the quality of life of these patients. The morbidities are extensive resections, secondary infections, lack of tissue for primary closure, dehiscence, and fistulas, which can evolve into mutilator wounds with serious consequences, such as sepsis [9-12].

In this sense, the literature on photobiomodulation therapy shows effectiveness through the use of low-intensity laser (LIL) and has been increasingly studied. Furthermore, it is a painless, safe, and non-invasive method, when used in adequate dosimetry both in animals and in patients [16,19].

According to the Ministry of Health, osteoporosis is an osteometabolic disease characterized by a decrease in bone mass and destruction of the microarchitecture of bone tissue with increased bone fragility. Its clinical complications include fractures, chronic pain, depression, deformities, loss of independence, and increased mortality. It is estimated that approximately 50% of women and 20% of men aged 50 years or older will suffer an osteoporotic fracture in their lifetime. Among the drugs that reduce osteoporotic fractures, oral bisphosphonates are the first choice drugs in the treatment of osteoporosis [23].

Thus, these drugs can reveal several adverse effects, among them osteonecrosis of the jaws, which affects 0.01% to 0.04% of patients who use the drug orally, however, although complications are rare when they occur they are severe. and mutilating, impairing the quality of life of these individuals [1-4]. According to the AAOMS Guideline, the clinical treatment of Osteonecrosis consists of improving the signs and symptoms, with anti-inflammatories, antibiotic therapy, analgesics, and irrigation with chlorhexidine, which can last for months, aggravating the local conditions.

Surgical treatment, for the removal of necrotic bone and curettage of bone sequestration, has higher success rates than conservative treatment, but with a high rate of recurrence, causing infections, lack of tissue for primary closure, and the need for new resections with facial mutilation [23].

In the search for less invasive treatments for osteonecrosis, Vescovi 2013 et al. [16] developed a new preventive methodology using low-intensity laser after dental extractions in 217 patients treated with BP and only 5 patients observed bone exposure. Magnetotherapy was approved by the FDA and studies have shown the benefits of the electromagnetic field for the treatment of edema, osteoarthritis, wounds, hemodynamic modulation, pain relief, inflammation, tissue regeneration, and bone formation. Being an important tool of Physical Therapy around the world, because it is a non-invasive, safe, and easy-to-use method [20,21].

Weber et al. 2016 [19] found studies demonstrating favorable results with surgical therapy, combined with laser treatment. According to Li et.al. 2020 [24], in a systematic review, observed that there was a significant change in the pain score after LIL and in the assessment of analgesia by VAS, we observed that in the first 7 PO days, the Laser group presented a significant reduction in pain compared to the placebo group and Magneto, a fact that stabilized after 14 days.

Furthermore, Lorenzo-Pouso et al. 2019 [25] in a systematic review suggest that there are currently no markers available to assess BRONJ risk. However, the work indicates that a paradigm shift in bone remodeling, angiogenesis, and endocrine biomarkers could be useful in further research.

According to Vieira 2007 [26], during bone formation, the production of the collagen matrix precedes mineralization. The phase of collagen matrix production coincides with the highest production of alkaline phosphatase, in addition to being more effective for bone formation at the beginning than in the later stages, because in the first stage of bone healing, cellular components are more important and, therefore, more susceptible to the action of the laser. LIL in bone tissue causes an increase in the amount of mRNA used to synthesize type I collagen, which stimulates bone tissue formation and repair.

In this context, lactate dehydrogenase (LDH) is an intracellular enzyme that is present in virtually all body tissues and participates in the process of transforming glucose into energy in animal, plant, and even bacterial cells. LDH is released into the bloodstream when cells are damaged or destroyed, increasing LDH levels in the circulation, and can be detected in a blood test. The highest concentration of this enzyme in the extracellular environment is related to the rupture of the plasmatic membrane and consequent cell death. This fact was not observed in our study in the LIL and MAC groups, with the maintenance of LDH at normal levels [2,3].

Finally, creatine phosphokinase (CPK) is an enzyme found in the heart, brain, skeletal muscle, and many other tissues. CPK catalyzes the conversion of creatine and consumes adenosine triphosphate (ATP) to create creatine phosphocreatine (PCr) and adenosine diphosphate (ADP). This CK enzyme reaction is reversible and thus ATP can be generated from PCr and ADP. In skeletal and cardiac muscle cells, most of the energy is used for muscle contraction. An increased CPK usually indicates muscle damage. The increase was observed only in the placebo Group, in the 12h postoperative period, signaling the process of tissue necrosis, while the LPL and MAC Groups maintained normal levels at all times [2-4].

Conclusion

It was concluded that photobiomodulation therapy and magnetotherapy showed safety and efficacy in the treatment of BRONJ, through the reduction of phlogistic signs, faster healing, and reduction of postoperative morbidity. Only four applications of lowintensity laser and magnetotherapy were enough to reduce the inflammatory process in the surgical wound, stimulate the tissue repair process and provide postoperative analgesia.

Acknowledgement

Not applicable.

Funding

Not applicable.

Ethical Approval

Not applicable.

Informed consent

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

References

1. Endo Y, Funayama H, Yamaguchi K, Monma Y, Yu Z, Deng X, Oizumi T, Shikama Y, Tanaka Y, Okada S, Kim S, Kiyama T, Bando K, Shima K, Suzuki H, Takahashi T. [Basic Studies on the Mechanism, Prevention, and Treatment of Osteonecrosis of the Jaw Induced by Bisphosphonates]. Yakugaku Zasshi. 2020;140(1):63-79. Japanese. doi: 10.1248/yakushi.19-00125.
2. Chien HI, Chen LW, Liu WC, Lin CT, Ho YY, Tsai WH, Yang KC. Bisphosphonate-Related Osteonecrosis of the Jaw. Ann Plast Surg. 2021 Feb 1;86(2S Suppl 1):S78-S83. doi: 10.1097/SAP.0000000000002650.
3. McCadden L, Leonard CG, Primrose WJ. Bisphosphonate-induced osteonecrosis of the ear canal: our experience and a review of the literature. J Laryngol Otol. 2018 Apr;132(4):372-374. doi: 10.1017/S0022215118000324.
4. Sogacheva VV, Syomkin VA. Bisfosfonatnye osteonekrozy chelyustei [Bisphosphonate-related osteonecrosis of the jaws]. Stomatologiia (Mosk). 2022;101(6):85-90. Russian. doi: 10.17116/stomat202210106185.
5. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws-2022 Update. J Oral Maxillofac Surg. 2022 May;80(5):920-943. doi: 10.1016/j.joms.2022.02.008.
6. Anastasilakis AD, Pepe J, Napoli N, Palermo A, Magopoulos C, Khan AA, Zillikens MC, Body JJ. Osteonecrosis of the Jaw and Antiresorptive Agents in Benign and Malignant Diseases: A Critical Review Organized by the ECTS. J Clin Endocrinol Metab. 2022 Apr 19;107(5):1441-1460. doi: 10.1210/clinem/dgab888.
7. Wang M, Wu YF, Girgis CM. Bisphosphonate Drug Holidays: Evidence From Clinical Trials and Real-World Studies. JBMR Plus. 2022 May 24;6(6):e10629. doi: 10.1002/jbm4.10629.
8. Priyadarshini V, Ramachandra SS, Ganganna A. Awareness and Attitude Among Physicians' About Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ): A Cross-sectional study. Curr Drug Saf. 2022 May 14. doi: 10.2174/1574886317666220514160507.
9. Vieira AE, Repeke CE, Ferreira Junior Sde B, Colavite PM, Biguetti CC, Oliveira RC, Assis GF, Taga R, Trombone AP, Garlet GP. Intramembranous bone healing process subsequent to tooth extraction in mice:microcomputedtomography, histomorphometric and molecular characterization. PLoS One. 2015 May 29;10(5):e0128021. doi: 10.1371/journal.pone.0128021. eCollection 2015.
10. Vermeer JA, Renders GA, Everts V. Osteonecrosis of the Jaw-a Bone SiteSpecific Effect of Bisphosphonates. Curr Osteoporos Rep. 2016 Oct;14(5):219- 25. doi: 10.1007/s11914-016-0318-z.
11. Schiodt M, Otto S, Fedele S, Bedogni A, Nicolatou-Galitis O, Guggenberger R, Herlofson BB, Ristow O, Kofod T. Workshop of European Task Force on Medication Related Osteonecrosis of the Jaw.Current challenges. Oral Dis. 2019 Jul 20. doi: 10.1111/odi.13160.
12. Kuroshima S, Sasaki M, Sawase T. Medication-related osteonecrosis of the jaw: A literature review. J Oral Biosci. 2019 Jun;61(2):99-104. doi: 10.1016/j.job.2019.03.005.
13. Goss AN. Osteonecrosis of the jaw and denosumab. Aust Prescr. 2022 Dec;45(6):208-209. doi: 10.18773/austprescr.2022.066.
14. R. Fliefel, M. Tro¨ltzsch, J. Ku¨hnisch, M. Ehrenfeld, S. Otto: Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. Int. J. Oral Maxillofac. Surg. 2015;
15. S Otto, Medication related osteonecrosis of the jaws 2016. ISBN 978-3-662- 43732-2. DOI 0.1007/978-3-662-43733-9. Springer Heidelberg New York Dordrecht London
16. Vescovi, P., Meleti, M., Merigo, E., Manfredi, M., Fornaini, C., Guidotti, R., & Nammour, S. (2013). Case series of 589 tooth extractions in patients under bisphosphonates therapy. Proposal of a clinical protocol supported by Nd: YAG low-level laser therapy. Medicina Oral, Patología Oral Y Cirugía Bucal, 18(4), e680–e685. http://doi.org/10.4317/medoral.18812
17. Otto, Sven. Antiresorptive drug-related osteonecrosis of the jaw (ARONJ)-a guide to research. Eds. Kenneth E. Fleisher, and Risto Kontio. Thieme, 2016, AO Foundation, ISBN: 978-3-905363-10-4, Davos, Switzerland.
18. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa)induced avascular necrosis Treatment strategies and outcomes of BRONJ 579 of the jaws: a growing epidemic. J Oral Maxillofac Surg

2003;61:1115–7.

19. Weber, J. B. B., Camilotti, R. S., & Ponte, M. E. (2016). Efficacy of laser therapy in the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ): a systematic review. Lasers in medical science, 31(6), 1261-1272. DOI 10.1007/s10103-016-1929-4
20. Meyer, P. F., Paiva, A., Cavalcanti, S., da Silva, E. M., da Silva, R. M. V., de Souza Costa, L., & Ronzio, O. A. (2011). Magnetoterapia: é possível este recurso fazer parte da rotina do fisioterapeuta brasileiro?. Arquivos Brasileiros de Ciências da Saúde, 36(1).
21. Silva, R. M. V. D., Xavier, W. J. C., Dantas Neto, R. G., Azevedo, V. M. D., Nascimento, B. J. R. D., Oliveira, J. F. D., & Meyer, P. F. (2016). Efeitos da magnetoterapia no tratamento da dor na osteoartrose de joelho. ConScientiae Saúde, 15(2), 281-287.
22. Ferreira Jr LH Jr, Mendonça Jr KD Jr, Chaves de Souza J, Soares Dos Reis DC, do Carmo Faleiros Veloso Guedes C, de Souza Castro Filice L, Bruzadelli Macedo S, Soares Rocha F. Bisphosphonate-associated osteonecrosis of the jaw. Minerva Dent Oral Sci. 2021 Feb;70(1):49-57. doi: 10.23736/S2724- 6329.20.04306-X.
23. AAOMS AMERICAN ASSOCIATION OF ORAL AND MAXILLOFACIAL SURGEONS POSITION PAPER.Medication-RelatedOsteonecrosisoftheJaw – 2014 Update. Ilinois,abr./2014.http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper.
24. Li FL, Wu CB, Sun HJ, Zhou Q. Effectiveness of laser-assisted treatments for medication-related osteonecrosis of the jaw: a systematic review. Br J Oral Maxillofac Surg. 2020 Apr;58(3):256-267. doi: 10.1016/j.bjoms.2019.12.001.
25. Lorenzo-Pouso, Alejandro I., et al. Biomarkers to predict the onset of biphosphonate-related osteonecrosis of the jaw: A systematic review. Medicina oral, patologia oral y cirugia buccal. 2019, 24.1: e26.
26. Vieira JGH. Diagnóstico laboratorial e monitoramento das doenças osteometabólicas. Jornal Brasileiro de Patologia e Medicina Laboratorial, 2007, 43(2), 75-82.