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Article

OSTEONECROSIS OF THE JAWS. ANALYSIS OF RISK FACTORS AND DENTAL MANAGEMENT STRATEGIES- PART II

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ABSTRACT

Introduction: Medication-related osteonecrosis of the jaw (MRONJ) presents a significant clinical challenge due to the increasing use of anti-resorptive drugs. Characterized by exposed necrotic bone, pain, and infection, MRONJ requires a multidisciplinary approach. This review aims to synthesize current evidence and emerging innovations in the surgical and medical management of MRONJ. *Materials and Methods:* A critical review of the existing scientific literature on MRONJ was conducted, using electronic databases such as PubMed, Scopus, and Google Scholar. Extracted information was organized by thematic categories, synthesized, and critically analyzed for a comprehensive overview. *Discussion:* The surgical protocol involves careful preoperative evaluation, professional oral hygiene, and the use of antiseptic mouthwashes. Surgical techniques range from debridement and curettage to aggressive resection, with the aim of completely removing necrotic tissue. New protocols integrate laser photobiomodulation, platelet-rich plasma, and deferoxamine to promote tissue regeneration. Suspension of anti-resorptive therapy, in agreement with the attending physician, is crucial. Treatment can be surgical and non-surgical. *Conclusions:* Optimal management of MRONJ requires a personalized, multidisciplinary approach. Implementing preventive protocols, early diagnosis, and adopting updated treatments, combining conservative and surgical strategies, are key to reducing the incidence of MRONJ and improving the quality of life for affected patients.

KEYWORDS: *MRONJ, bisphosphonate, regenerative therapy, oral surgery, therapeutic innovation*

INTRODUCTION

The management of medication-related osteonecrosis of the jaw (MRONJ) has become an increasingly important focus within oral and maxillofacial surgery and related medical fields, due to the widespread use of antiresorptive agents such as bisphosphonates and denosumab, as well as other targeted therapies (1). Characterized by exposed necrotic bone in the maxillofacial region that persists for more than eight weeks and is often associated with pain, infection, and impaired healing, MRONJ represents a significant clinical challenge that affects patients' quality of life and complicates various dental and surgical procedures (2). Over the years, our understanding of MRONJ has evolved from viewing it primarily as a surgical problem to recognizing its multifactorial pathogenesis involving impaired bone remodeling, vascular

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damage, and inflammatory processes, which necessitates a multidisciplinary approach to treatment (3). Several studies have highlighted the fundamental role of cells (4) and cytokines (5) in the pathogenesis of oral and intestinal inflammation (6) and in cancer development for diagnosis (7-9). Traditional conservative therapies, focused on antimicrobial management and symptom control, have been integrated and, in many cases, replaced by increasingly sophisticated surgical interventions aimed at removing necrotic tissue and promoting regeneration. Advances in imaging, digital workflow planning, and minimally invasive surgical techniques have paved the way for more precise and effective treatments (10). In addition to conventional surgical and pharmacological methods, recent developments have introduced innovative additional therapies that utilize regenerative medicine, laser biostimulation, and bioengineering strategies. Techniques such as laser photobiomodulation, platelet-rich plasma, deferoxamine, hyperbaric oxygen therapy, and the application of growth factors like BMP-2 are increasingly integrated into treatment protocols to stimulate tissue regeneration, reduce inflammation, and improve healing outcomes (11). Additionally, emerging approaches involving biomaterials such as human amniotic membranes and nanoscale drug delivery systems offer promising future directions in the fight against MRONJ (12). This review aims to synthesize current evidence and emerging innovations in the surgical and medical management of MRONJ, highlighting protocols for preoperative planning, surgical techniques, and adjuvant therapies. By understanding these evolving strategies, clinicians can better adapt treatment plans, reduce morbidity, and improve the prognosis for patients affected by this debilitating condition.

MATERIALS AND METHODS

This review article was created through a critical search and analysis of the existing scientific literature on drug-induced osteonecrosis of the jaw (MRONJ). Electronic databases such as PubMed, Scopus, and Google Scholar were consulted to identify relevant published articles, using specific keywords such as mandibular osteonecrosis, drug-induced mandibular osteonecrosis, pharmacological treatment of mandibular osteonecrosis, and surgical treatment of mandibular osteonecrosis. Clinical studies, reviews, and case reports relevant to the aetiology, risk factors, diagnosis, prevention, and treatment of MRONJ were included, excluding irrelevant articles. The extracted information was organized into thematic categories (definition, mechanisms, drugs, risk factors, clinical aspects, prevention, biomarkers), synthesized, and critically analysed for a comprehensive overview, with attention to gaps and controversies and an assessment of methodological quality.

DISCUSSION

Surgical protocol

After conducting a thorough clinical evaluation and analyzing the patient's medical history, if it is decided to proceed with surgery to remove an infectious focus, it is essential to follow a strict protocol. In cases of MRONJ requiring extensive resections, preoperative planning is essential to guide reconstruction and prosthetic rehabilitation. To this end, advanced digital workflows can be employed. The use of digital facebows has demonstrated high precision in vitro, facilitating the creation of accurate diagnostic models and surgical guides (13,14). Before the intervention, it is necessary to undergo a thorough professional oral hygiene session, preferably two or three weeks before the operation, to eliminate any infectious foci that could complicate the postoperative period. It is also important to use a 0.2% alcohol-free chlorhexidine mouthwash, which should be used a few weeks before the procedure and also one minute before the procedure, to reduce the bacterial load. Surgically, it is necessary to close with first intention sutures, and during the procedure, one should try to keep the intervention as minimally invasive as possible, avoiding trauma and attempting to remove granulation tissue with minimal invasiveness. Immediately afterwards, the area is washed with antibacterial solutions for about two minutes to further reduce the presence of bacteria (15). Regarding antibiotic prophylaxis, specific regimens are generally recommended, although there is no single uniform protocol; Commonly, penicillins such as amoxicillin (1 gramme three times a day), with or without clavulanic acid, are used in combination with metronidazole (500 mg three times a day) to cover a wide range of bacteria. In case of penicillin allergy, alternatives such as erythromycin, clindamycin, or ciprofloxacin can be used, with dosages and administration times adjusted based on the presence or absence of suppuration at the treatment site. If there are no infections or pus formation, the antibiotic can be started the day before the procedure and continued for about 7-10 days; If there are signs of suppuration, it should be started about a week before extraction and continued for 7-10 days.

New Protocols to Reduce Risk

Recently, thanks to significant advancements in medical technology, new surgical protocols have emerged that utilize laser photobiomodulation (Nd:YAG, diode laser), the use of non-transfusional blood components (such as PRP), and the use of deferoxamine.

Platelet-rich plasma (PRP) is an autologous concentration of platelets obtained by centrifuging the patient's blood, also containing inflammatory cells such as monocytes and neutrophils, and rich in proteins with growth factors like PDGF, TGF-β, VEGF, and EGF. These elements promote recruitment, cell proliferation, and the formation of new blood vessels, contributing to tissue regeneration and healing processes (16,17).

Laser Photobiomodulation in oral surgery helps reduce pain and inflammation and promotes wound healing by improving cellular activity and altering the permeability of cell membranes. It works by increasing the hyperpolarization state of nerve endings, thus inhibiting pain transmission to the central nervous system and reducing the activity of mediators such as prostaglandins, interleukins, tumour necrosis factor, and cyclooxygenase (18).

Deferoxamine (DFO) is a medication used in iron poisoning and to accelerate the healing of pathological fractures after radiotherapy, as it inhibits the enzyme prolyl hydroxylase, promoting the formation of new blood vessels through the stimulation of VEGF. Experimental studies, including those on rodents, suggest that local application of DFO via gelatin sponges can improve bone regeneration, promote neovascularization, and offer protection against MRONJ, accelerating healing after tooth extraction (19).

Suspension of therapy

The therapy suspension strategy aims to reduce the accumulation of anti-resorptive drugs at the surgical site, promoting an improvement in healing conditions. In the case of bisphosphonates, their long half-life can prolong their effects on bone even after a single administration, particularly in cancer patients with bone metastases or multiple myeloma. For this reason, it is recommended to discontinue them at least one week before surgery and to stop therapy for at least three months, depending on clinical conditions, in close consultation with the treating physician (15). For denosumab, which has a short and dose-dependent half-life, discontinuation should occur at least 21 days before invasive procedures, with therapy able to be resumed after 4-6 weeks (20). If the treatment is aimed at osteometabolic disorders, such as Prolia, it is recommended to perform the procedures at least 3 weeks after the last administration and to resume the medication at least one month after the surgery, preferably after the fifth month from the last dose if not urgent. Anti-angiogenic drugs, such as Bevacizumab, also benefit from preoperative suspensions (21). It is advisable to discontinue them at least 5-8 weeks before surgery to allow for complete elimination from the body and reduce the antiangiogenic effect, minimizing the risk of complications and improving the chances of optimal healing. The drug should be resumed at least 28 days after the surgery. For tyrosine kinase or m-TOR inhibitors, which have a known half-life, it is suggested that invasive procedures be performed at least one week after the last administration (22).

Treatment

When we talk about the treatment of medication-related osteonecrosis of the jaw, we are faced with two possible therapeutic options: surgical therapy and non-surgical therapy.

Non-surgical therapy

Non-surgical therapy primarily focusses on the use of medications to control the infectious process and alleviate pain, with the aim of slowing the progression of the disease and stabilizing its symptoms. This approach proves particularly effective in the early stages of the disease, while it is less useful in the advanced stages. This class of therapy includes a subset of treatments. Pharmacological pain management is a fundamental component, as the pain can be intense and persistent, significantly limiting the patient's quality of life. In such cases, the use of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, or ketamine is recommended, to be administered under the supervision of specialists to avoid the risk of toxicity (23). At the same time, antiseptic therapy is used with mouthwashes containing chlorhexidine digluconate, available in 0.12% alcohol-free concentrations or 0.20% containing alcohol. It is recommended to use these mouthwashes for a maximum of two weeks, preferably one week before and one week after any surgical procedure, to reduce bacterial load and prevent complications. In patients for whom surgical treatment is not possible, or in cases of refractory MRONJ, maintenance therapy with chlorhexidine twice daily for one month can be used. Alternatively, to chlorhexidine, other disinfectants such as hydrogen peroxide or baking soda solution can be used (24). Antibiotic therapy plays a key role in managing the infection that characterizes this condition. However, the exclusive use of antibiotics is not sufficient to completely resolve the problem, but it proves useful in controlling infectious exacerbations or in patients with complications that prevent more invasive treatments.

The typical therapeutic strategy involves a combination of penicillins and metronidazole, administered for 7-14 days. In case of allergy to these molecules, alternatives such as erythromycin, clindamycin, or ciprofloxacin are chosen.

Surgical therapy

Therapeutic strategies for drug-induced osteonecrosis of the jaw have changed over time due to the accumulation of new knowledge and clinical experience, leading to an increasing recognition of the importance of surgical therapy. For many years, this method was considered a second-line option, reserved primarily for the most severe forms or those unresponsive to conservative treatments. However, in recent years, numerous experts have suggested considering surgery even in the early stages of the disease, with the aim of stopping its progression as soon as possible. Numerous studies show that the surgical approach can achieve better results compared to conservative therapies, as it allows for the complete removal of necrotic tissue, promoting the formation of healthy tissue and thus accelerating bone healing. It is essential to completely and safely remove the necrotic tissue, precisely defining the margins of the lesion's extent through both intraoperative assessments and preoperative radiological examinations. During the procedure, observing bone bleeding is a common method for identifying viable bone, while a fluorescent lamp can also be used, which exploits the different fluorescence between viable bone and necrotic bone (25,26). Surgical treatment for MRONJ includes various techniques such as debridement, curettage, sequestrectomy, and resection, with or without microvascular reconstruction. According to the literature, bone curettage without extension and sequestrectomy are considered part of conservative surgical treatment, while a more extensive or complete resection of the necrotic lesion, with or without microvascular reconstruction, is classified as aggressive surgical treatment (27).

i. Conservative surgical treatment: The main objective of conservative treatment is the complete removal of necrotic tissue, extending as far as possible towards the surrounding tissue which, macroscopically and radiographically, appears healthy and well-vascularized. It is essential to avoid interrupting the continuity of the mandibular body and extending into the paranasal sinuses. The treatment concludes with the repositioning and suturing of the mucosal flaps, closing by first intention to prevent bacterial entry and promote healing.
ii. Bone curettage: This treatment involves the removal of necrotic bone tissue until a bleeding bone surface is reached, followed by the complete closure of the defect through the mobilization of a mucoperiosteal flap. This procedure is performed under local anesthesia and can be carried out using rotary burs or less invasive instruments like sonic instruments. It is important to emphasize that during curettage, the necrotic tissue should not yet be completely separated from the surrounding viable bone; Otherwise, it would be a sequestrectomy. To promote a good outcome, osteoplasty of the bone surface can also be performed to eliminate residual roughness and facilitate site closure (28).
iii. Sequestrectomy: allows for the removal of the sequestrum, a necrotic portion that separates spontaneously from healthy bone and is expelled naturally or through surgery. The procedure involves the removal of necrotic tissue affecting the alveolar process, followed by osteoplasty and closure with a mucoperiosteal flap (29).
iv. Aggressive surgical treatment: Resective surgery represents the most invasive and radical strategy. The goal is to remove all the diseased bone tissue until healthy and viable tissue is reached. It is essential to perform marginal osteoplasty, utilizing full-thickness flap mobilization to ensure primary intention closure of the defect. The difference between resection techniques lies in the fact that marginal resection preserves the continuity of the bone segment, removing only the block of necrotic tissue, while segmental resection involves the interruption of the bone segment. To preserve alveolar bone volume and support the implant site, various studies have described innovative surgical techniques for alveolar ridge preservation with immediate dental implant placement (30,31), while others have focused on the effectiveness of electrolytic cleaning and regenerative therapy in the treatment of peri-implantitis (32). Moreover, employing innovative graft biomaterials has been shown to positively influence implant survival rates in regenerated sites (33). The standard procedure for treating the mandible is mandibulectomy, which unfortunately always results in a loss of facial symmetry and occlusion. It is widely accepted that when a full-thickness defect is created in the mandible, it is important to immediately reconstruct the bone continuity to restore facial shape and ensure the best functional recovery. Following mandibulectomy, the reconstruction of mandibular integrity can be achieved through the use of a titanium plate to replace the removed bone, anatomical replicas of the mandible, or alternatively, through the use of vascularized bone flaps (34).

Additional therapies

The evolution of therapeutic strategies for managing MRONJ has led to greater emphasis on the use of innovative and multimodal approaches.

Among these, treatment with teriparatide has shown promise, thanks to the short-term benefits observed in clinical trials. This recombinant human protein, consisting of the 1-34 portion of parathyroid hormone (rhPTH 1-34), is the only FDA-approved anabolic therapy for the treatment of severe osteoporosis. Its action promotes osteoblastic activity, stimulating the formation of new bone tissue and improving radiographic signs of healing. Although the hormone can have both anabolic and catabolic effects on bone, intermittent exposure stimulates its formation, contributing to increased bone mass and offering a promising therapeutic context even in cases of MRONJ, with potential reparative effects on maxillary bone defects (35).

In both surgical and conservative settings, the use of low-intensity laser has been successfully recognized as an effective complementary treatment in both the medical and surgical management of MRONJ. Different laser wavelengths have demonstrated a biostimulating effect, improving repair processes and promoting bone growth, osteoblast mitotic activity, and the development of blood and lymphatic vessels. Studies have indicated that LLLT (Low-Level Laser Therapy) promotes bone healing in traumatic areas and increases mineralization during regeneration processes, stimulating the activity and differentiation of osteoblasts. Additionally, it has been observed that laser biostimulation could also be beneficial in the treatment of "early" forms of MRONJ, offering a safe, minimally invasive, and well-tolerated therapeutic option. In conservative surgery, the laser can target necrotic bone, vaporizing it until healthy bone is reached. In these cases, the Er:YAG laser (2,940 nm) is used, a laser that gently penetrates only 0.1 mm, ensuring a highly conservative and precise treatment is performed (36,37). Instead, for adequate implant therapy, an innovative technique called the "Hybrid Funnel Technique" has recently been proposed, which aims to optimize implant site preparation by minimizing trauma and preserving local vascularization. A pilot study explored the effectiveness of this technique, suggesting potential benefits in terms of osseointegration and soft tissue healing (38). It is important to note that implant surface microtopography can play a crucial role in the success of osseointegration. Recent studies have demonstrated that laser microtopographies can promote osteoblast proliferation and bone deposition, potentially improving long-term implant outcomes (39).

Another strategy to use is hyperbaric oxygen therapy and ozone therapy, which are two complementary therapies frequently employed as neoadjuvant or adjuvant interventions in the treatment of advanced mandibular osteonecrosis, particularly in cases where bone healing is compromised and invasive surgical procedures, such as maxillary resections or microvascular reconstructions, are not indicated or are contraindicated. Various scientific evidence suggests that these approaches could offer significant benefits, improving the chances of resolution and recovery in patients affected by this complex condition. Hyperbaric oxygen therapy involves inhaling pure oxygen in pressurized chambers where the air pressure exceeds atmospheric pressure (40,41). This non-invasive treatment causes an increase in reactive nitrogen and oxygen species, which promote the production of substrates necessary for the enzyme nitric oxide synthase. These mediators play a crucial role in bone metabolism by modulating the activity of osteoclasts and osteoblasts. Specifically, nitric oxide is produced constitutively by both the latter and the former, and its role in the bone process is characterized by dual effects depending on the concentrations. At moderate levels, nitric oxide promotes bone turnover, contributing to the replacement of old bone tissue with new and reducing bone resorption, thus facilitating the restoration of physiological balance. However, at higher concentrations, its role becomes more complex and can be detrimental, promoting inflammatory processes in bone tissue and contributing to the progression of conditions like osteoporosis. An excessive increase in this reactive species can also inhibit the formation of new bone tissue, interfering with the regeneration and repair of damaged tissues. Reactive oxygen species (ROS), produced during hyperbaric oxygen therapy, appear to positively influence bone homeostasis by modulating the expression of key factors such as RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand) and osteoprotegerin. This regulation promotes the controlled differentiation of osteoclasts, contributing to an optimal balance between bone formation and resorption and reducing the risk of pathological conditions such as osteopetrosis, which is often present in animal models of osteonecrosis. An emerging hypothesis suggests that ROS generated during hyperbaric oxygen (HBO) treatment may exert a beneficial effect by suppressing osteoclast activity and promoting bone healing processes, thanks to the modulation of the local environment and the stimulation of tissue regeneration. Several studies showed how inflammatory processes (42,43) around teeth (44,45), novel dental implant, regenerated maxillary sites with biomaterials (46), derived from biofilm adhesion and bacterial colonization (42), promote hard and soft tissues pathogenesis (43) as bone loss, gingivitis, periodontitis, carcinogenesis, (47,48) mucositis and peri-implantitis related to the immune-cells genetic and cytokines cascade activation. (42,43,49) These effects, although still under investigation, open up interesting therapeutic prospects for the use of this technology in complex cases of osteonecrosis, where the primary goal is to promote bone repair and recovery

through a biochemical action that enhances the natural tissue response (50). Ozone therapy has shown promising results in the treatment of MRONJ, acting as an effective biostimulation method to enhance the repair processes in the affected area. This therapy is known for its ability to hinder the growth of microorganisms (bacteria, fungi, and viruses), stimulate blood circulation, and increase the amount of oxygen in tissues. Additionally, ozone can help reduce pain and improve local immune activity. Ozone application can be done through two main methods: insufflations obtained with special equipment or through the use of ozonated oil. Studies in the literature suggest that this therapy promotes neoangiogenesis and stimulates the immune system, facilitating the formation of granulation tissue that demarcates the area of bone necrosis and contributes to the healing of the tissues involved (15). The use of BMP-2 (bone morphogenetic protein-2) represents a promising therapeutic option in the treatment of MRONJ. Originally approved by the Food and Drug Administration (FDA) for applications such as maxillary sinus augmentation and alveolar preservation, the recombinant form of human BMP-2 (rhBMP-2) has been shown to possess broader osteoinductive properties. Given the excessive suppression of bone remodeling typical of MRONJ, it is hypothesized that BMPs can stimulate the formation of new bone tissue and promote the healing process. Studies on post-sequestrectomy sites treated with rhBMP-2/ACS have demonstrated a significant increase in bone regeneration, suggesting effective potential in treating the condition, although official FDA approval is still lacking at this time. This therapy is expected to play a significant role in the future as well (51).

A final innovative strategy involves the use of human amniotic membrane, rich in epithelial and mesenchymal stromal cells, along with various growth factors such as EGF, FGF, and TGF. This membrane is distinguished by its biocompatibility, permeability, stability, elasticity, and reabsorbability. It has antimicrobial, anti-inflammatory, antifibrotic, and analgesic effects, and has been shown to promote neovascularization, encouraging the formation of new blood vessels and supporting epithelial regrowth and wound healing. The presence of metalloproteinase inhibitors and reduced immunogenicity, due to low expression of human leukocyte antigens (HLAs), make it a material of great interest as a support in the prevention and treatment of bisphosphonate-associated osteonecrosis of the jaw (52). Finally, research is focusing on controlled-release systems for anti-inflammatory drugs, such as those based on nanoscale polymeric hybrids, which could offer advantages in local inflammation control. These systems aim to release the drug in a targeted manner, minimizing systemic side effects (53).

CONCLUSIONS

Drug-induced osteonecrosis of the jaw (MRONJ) requires a thorough understanding of the causes, risk factors, and available treatment options. Conservative therapies, such as pharmacological management of pain and infection, are useful in the initial stages, but are often insufficient to resolve the pathology. Surgical intervention, ranging from curettage to aggressive resection, has proven effective in removing necrotic tissue and promoting bone healing. Innovative protocols that integrate laser photobiomodulation, the use of PRP, and deferoxamine administration show promising results in improving vascularization and tissue regeneration. Targeted suspension of pharmacological therapy, in agreement with the attending physician, is crucial to reduce the accumulation of anti-resorptive drugs at the surgical site. Ultimately, optimal management of MRONJ requires a personalized multidisciplinary approach that takes into account the patient's individual risk assessment, the specific characteristics of the lesion, and the response to therapies. Implementing preventive protocols, early diagnosis, and adopting updated treatments, combining conservative and surgical strategies, are key to reducing the incidence of MRONJ and improving the quality of life for affected patients.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Ruggiero SL, et al. "Management of osteonecrosis of the jaws: a systematic review and international consensus." Oral Oncology. 2014;50(3):239-246.
2. Khan AA, Morrison A, Hanley DA, et al. Bisphosphonate-related osteonecrosis of the jaw: position of the American Association of Oral and Maxillofacial Surgeons. J Oral Maxillofac Surg. 2015;73(11):1977-1991.
3. Shah PS, et al. "Evolving management strategies in bisphosphonate-related osteonecrosis of the jaw." Current Oncology Reports. 2020;22(6):57.

4. Lauritano D, Mastrangelo F, D'Ovidio C, et al. Activation of Mast Cells by Neuropeptides: The Role of Pro-Inflammatory and Anti-Inflammatory Cytokines. Int J Mol Sci. 2023;24(5):4811. doi:10.3390/ijms24054811.
5. Tettamanti L, Kritas SK, Gallenga CE, et al. IL-33 mediates allergy through mast cell activation: Potential inhibitory effect of certain cytokines. J Biol Regul Homeost Agents. 2018;32(5):1061-1065.
6. Conti P, Caraffa A, Ronconi G, et al. Impact of mast cells in mucosal immunity of intestinal inflammation: Inhibitory effect of IL-37. Eur J Pharmacol. 2018;818:294-299. doi:10.1016/j.ejphar.2017.09.044.
7. Minetti E, Palermo A, Ferrante F, et al. Autologous tooth graft after endodontically treated used for socket preservation: a multicenter clinical study. Appl Sci. 2019;9(24):5396. doi:10.3390/app9245396.
8. Pomella S, Melaiu O, Dri M, Martelli M, Gargari M, Barillari G. Effects of Angiogenic Factors on the Epithelial-to-Mesenchymal Transition and Their Impact on the Onset and Progression of Oral Squamous Cell Carcinoma: An Overview. Cells. 2024;13(15):1294. doi:10.3390/cells13151294.
9. Carinci F, Arcelli D, Lo Muzio L, Francioso F, Valentini D, Evangelisti R, Volinia S, D'Angelo A, Meroni G, Zollo M, Pastore A, Ionna F, Mastrangelo F, Conti P, Tetè S. Molecular classification of nodal metastasis in primary larynx squamous cell carcinoma. Transl Res. 2007;150(4):233-245. doi:10.1016/j.trsl.2007.03.011
10. Bagan JV, et al. "Osteonecrosis of the jaw related to bisphosphonate therapy: clinical guidelines and management." Journal of Clinical Medicine. 2022;11(10):2902.
11. Grigolato R, et al. "Laser therapy in the management of osteonecrosis of the jaw: review of the literature." Photomedicine and Laser Surgery. 2017;35(9):468-475.
12. Meloni S, et al. "Regenerative approaches in the management of medication-related osteonecrosis of the jaw." Biomedicines. 2021;9(10):1438.
13. Raffone C, Gianfreda F, Antonacci D, Pompeo MG, Bollero P, Canullo L. Chairside virtual patient protocol. Part 3: In vitro accuracy of a digital facebow. J Dent. 2023;137:104622. doi:10.1016/j.jdent.2023.104622.
14. Gianfreda F, Pesce P, Marcano E, Pistilli V, Bollero P, Canullo L. Clinical Outcome of Fully Digital Workflow for Single-Implant-Supported Crowns: A Retrospective Clinical Study. Dent J (Basel). 2022;10(8):139. doi:10.3390/dj10080139.
15. Campisi G, Bedogni A, Fusco V; Società Italiana di Chirurgia Maxillo-Facciale; Società di Patologia e Medicina Orale. Clinical and therapeutic recommendations on medication-related osteonecrosis of the jaw (ONJ) and its prevention. New Digital Press; 2020. ISBN: 9788855091473.
16. Franchini M, et al. The use of platelet-rich plasma in oral surgery: a systematic review and meta-analysis. Blood Transfus. 2019;17(3):357-367.
17. Miranda M, Gianfreda F, Rosa A, et al. Treatment of Oral Mucositis Using Platelet-Rich-Fibrin: A Retrospective Study on Oncological Patients. J Craniofac Surg. 2023;34(5):1527-1529. doi:10.1097/SCS.0000000000009450.
18. Hosseinpour S, Tunér J, Fekrazad R. Photobiomodulation in Oral Surgery: A Review. Photobiomodul Photomed Laser Surg. 2019;37(12):814-825. doi:10.1089/photob.2019.4712.
19. Yalcin-Ülker GM, Günbatan M, Duygu G, Soluk-Tekkesin M, Özcakir-Tomruk C. Could Local Application of Hypoxia Inducible Factor 1-α Enhancer Deferoxamine Be Promising for Preventing of Medication-Related Osteonecrosis of the Jaw?. Biomedicines. 2023;11(3):758. doi:10.3390/biomedicines11030758.
20. Sølling AS, Tsourdi E, Harsløf T, Langdahl BL. Denosumab discontinuation. Curr Osteoporos Rep. 2023;21(1):95-103. doi:10.1007/s11914-022-00771-6.
21. Serra E, Paolantonio M, Spoto G, Mastrangelo F, Tetè S, Dolci M. Bevacizumab-related osteneocrosis of the jaw. Int J Immunopathol Pharmacol. 2009;22(4):1121-1123. doi:10.1177/039463200902200429
22. Pimolbutr K, Porter S, Fedele S. Osteonecrosis of the Jaw Associated with Antiangiogenics in Antiresorptive-Naïve Patient: A Comprehensive Review of the Literature. Biomed Res Int. 2018;2018:8071579. doi:10.1155/2018/8071579.
23. Jackson K, Ashby M, Martin P, Pisasale M, Brumley D, Hayes B. "Burst" ketamine for refractory cancer pain: an open-label audit of 39 patients. J Pain Symptom Manage. 2001;22(4):834-842. doi:10.1016/s0885-3924(01)00340-2.

24. Shahraki M, Khazaei AH, Hakimi S, Hasheminasab M, Haradasht SA. Effect of chlorhexidine, povidone-iodine, and hydrogen peroxide irrigation on pain and swelling after mandibular third molar surgery: randomized controlled trial. Int J Oral Maxillofac Surg. 2025;54(7):677-683. doi:10.1016/j.ijom.2025.01.021
25. Lesclous P, Grabar S, Abi Najm S, et al. Relevance of surgical management of patients affected by bisphosphonate-associated osteonecrosis of the jaws. A prospective clinical and radiological study. Clin Oral Investig. 2014;18(2):391-399. doi:10.1007/s00784-013-0979-2.
26. Pautke C. Treatment of medication-related osteonecrosis of the jaw. In: Medication-Related Osteonecrosis of the Jaws. Springer Berlin Heidelberg; 2015:79-91. doi:10.1007/978-3-662-43733-9_7.
27. On SW, Cho SW, Byun SH, Yang BE. Various Therapeutic Methods for the Treatment of Medication-Related Osteonecrosis of the Jaw (MRONJ) and Their Limitations: A Narrative Review on New Molecular and Cellular Therapeutic Approaches. Antioxidants (Basel). 2021;10(5):680. doi:10.3390/antiox10050680.
28. El-Rabbany M, Lam DK, Shah PS, Azarpazhooh A. Surgical Management of Medication-Related Osteonecrosis of the Jaw Is Associated With Improved Disease Resolution: A Retrospective Cohort Study. J Oral Maxillofac Surg. 2019;77(9):1816-1822. doi:10.1016/j.joms.2019.03.040.
29. Nisi M, La Ferla F, Karapetsa D, et al. Conservative surgical management of patients with bisphosphonate-related osteonecrosis of the jaws: a series of 120 patients. Br J Oral Maxillofac Surg. 2016;54(8):930-935. doi:10.1016/j.bjoms.2016.06.015.
30. Grassi A, Monica D, Minetti E, et al. Innovative Alveolar Ridge Preservation Surgical Technique with Immediate Dental Implant Placement: A Retrospective Case Report of 1-Year Follow-Up. Eur J Dent. 2024;18(1):408-414. doi:10.1055/s-0043-1772676.
31. Mastrangelo F, Gastaldi G, Vinci R, et al. Immediate Postextractive Implants With and Without Bone Graft: 3-year Follow-up Results From a Multicenter Controlled Randomized Trial. Implant Dent. 2018;27(6):638-645. doi:10.1097/ID.0000000000000816.
32. Gianfreda F, Punzo A, Pistilli V, et al. Electrolytic Cleaning and Regenerative Therapy of Peri-implantitis in the Esthetic Area: A Case Report. Eur J Dent. 2022;16(4):950-956. doi:10.1055/s-0042-1750773.
33. Minetti E, Celko M, Contessi M, et al. Implants Survival Rate in Regenerated Sites with Innovative Graft Biomaterials: 1 Year Follow-Up. Materials (Basel). 2021;14(18):5292. doi:10.3390/ma14185292.
34. Bedogni A., Bettini G., Ferronato G., Fusetti S., Saia G. Replacement of fractured reconstruction plate with customized mandible implant: A novel technique. Laryngoscope 2014;124(2):401–4. Doi: 10.1002/lary.24230
35. Kwon Y-D, Kim D-Y. Role of teriparatide in medication-related osteonecrosis of the jaws (MRONJ). Dent J (Basel). 2016;4(1):41.
36. Inchingolo A, et al. MRONJ treatment strategies: a systematic review and two case reports. Appl Sci. 2023;13(8):4370.
37. Vescovi, P., Manfredi, M. & Merigo, E. Adjuvant Treatment Options in the Management of Medication-Related Osteonecrosis of the Jaw. in Medication- Related Osteonecrosis of the Jaws 103–109 (Springer Berlin Heidelberg, Ber-lin, Heidelberg, 2015). doi:10.1007/978-3-662-43733-9_9.
38. Canullo L, Iacono R, Pires Godoy E, et al. Hybrid Funnel Technique: A Novel Approach for Implant Site Preparation: A Pilot Study. Dent J (Basel). 2022;10(9):157. doi:10.3390/dj10090157.
39. Mastrangelo F, Quaresima R, Canullo L, Scarano A, Muzio LL, Piattelli A. Effects of Novel Laser Dental Implant Microtopography on Human Osteoblast Proliferation and Bone Deposition. Int J Oral Maxillofac Implants. 2020;35(2):320-329. doi:10.11607/jomi.7606.
40. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O, Peter JU. Interventions for managing medication-related osteonecrosis of the jaw. Cochrane Database Syst Rev. 2022;7(7):CD012432. doi:10.1002/14651858.CD012432.pub3.
41. El-Rabbany M, Sgro A, Lam DK, Shah PS, Azarpazhooh A. Effectiveness of treatments for medication-related osteonecrosis of the jaw: a systematic review and meta-analysis. J Am Dent Assoc. 2017;148(7):584-594.e2. doi:10.1016/j.adaj.2017.04.002.
42. Conti P, Caraffa A, Ronconi G, et al. Impact of mast cells in mucosal immunity of intestinal inflammation: Inhibitory effect of IL-37. Eur J Pharmacol. 2018;818:294-299. doi:10.1016/j.ejphar.2017.09.044
43. Conti P, Caraffa A, Ronconi G, et al. Mast cells participate in allograft rejection: can IL-37 play an inhibitory role? Inflamm Res. 2018;67(9):747-755. doi:10.1007/s00011-018-1166-3
44. Mastrangelo F, Dedola A, Cattoni F, et al. Etiological periodontal treatment with and without low-level laser therapy on IL-1β level in gingival crevicular fluid: an in vivo multicentric pilot study. J Biol Regul Homeost Agents. 2018;32(2):425-431.

45. Tetè S, Mastrangelo F, Traini T, et al. A macro- and nanostructure evaluation of a novel dental implant. Implant Dent. 2008;17(3):309-20. doi: 10.1097/ID.0b013e318182d494.
46. Minetti E, Palermo A, Ferrante F, et al. Autologous Tooth Graft after Endodontical Treated Used for Socket Preservation: A Multicenter Clinical Study. Applied Sciences. 2019; 9(24):5396. https://doi.org/10.3390/app9245396
47. Carinci F, Arcelli D, Lo Muzio L, et al. Molecular classification of nodal metastasis in primary larynx squamous cell carcinoma. Transl Res. 2007;150(4):233-245. doi:10.1016/j.trsl.2007.03.011
48. Lo Muzio L, Tetè S, Mastrangelo F, et al. A novel mutation of gene CBFA1/RUNX2 in cleidocranial dysplasia. Ann Clin Lab Sci. 2007;37(2):115-20.
49. Tranasi M, Sberna MT, Zizzari V, et al. Microarray evaluation of age-related changes in human dental pulp. J Endod. 2009;35(9):1211-7. doi: 10.1016/j.joen.2009.05.026.
50. Sacco R, et al. A systematic review of oxygen therapy for the management of medication-related osteonecrosis of the jaw (MRONJ). Appl Sci. 2019;9(3):1026.
51. Min SH, Kang NE, Song SI, Lee JK. Regenerative effect of recombinant human bone morphogenetic protein-2/absorbable collagen sponge (rhBMP-2/ACS) after sequestrectomy of medication-related osteonecrosis of the jaw (MRONJ). J Korean Assoc Oral Maxillofac Surg. 2020;46(3):191-196. doi:10.5125/jkaoms.2020.46.3.191.
52. Sacco R, Akintola O, Sacco N, et al. The Use of Human Amniotic Membrane (hAM) as a Treatment Strategy of Medication-Related Osteonecrosis of the Jaw (MRONJ): A Systematic Review and Meta-Analysis of the Literature. Medicina (Kaunas). 2023;59(5):968. doi:10.3390/medicina59050968.
53. Sammartino G, Marenzi G, Tammaro L, et al. Anti-inflammatory drug incorporation into polymeric nano-hybrids for local controlled release. Int J Immunopathol Pharmacol. 2005;18(3 Suppl):55-62.