José Pedro Mateus Fernandes

The effectiveness of teriparatide in the treatment of medication-related osteonecrosis of the jaw: Narrative review

Faculty of Health Sciences

Fernando Pessoa University

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Dissertation presented to Fernando Pessoa University

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ABSTRACT

Introduction: Drug-related osteonecrosis of the jaw is a rare complication; however, it can be debilitating. There was a need to study teriparatide in the treatment of drug related osteonecrosis of the jaw (MRONJ) due to lack of efficacy of conventional treatment.

Aim: To compile the currently existing studies in order to evaluate the efficacy of teriparatide in the treatment of MRONJ.

Materials and Methods: An electronic search was conducted, through online databases, such as MedLine (PubMed), On-Line Knowledge Library (B-On) and Cochrane Library. The keywords defined were "Teriparatide", "Medication-related osteonecrosis of the jaw", “osteonecrosis”, and “treatment” combined between them using the bolean connector AND. Only articles in English and Portuguese between the year 2017 and 2023 conducted only in humans, were taken into account. Forty-six articles were found, of which thirty-eight were excluded after applying the previously defined exclusion criteria. We included eight of the articles found.

Results: The results demonstrated efficacy in the use of teriparatide, especially when it is used concomitantly with antibiotic therapy. Individuals undergoing treatment with teriparatide associated with another therapeutic modality are more likely to have complete resolution of osteonecrosis when compared to individuals using teriparatide alone. Antibiotic associated with teriparatide therapy is, however, the most effective therapeutic modality in the treatment of MRONJ.

Conclusion: Although all the studies are promising, the scientific evidence is still lacking, making the level of confidence low. More studies will be needed to safely conclude that the use of teriparatide is factually advantageous.

Key words: "Teriparatide", " Medication-related osteonecrosis of the jaw”, “osteonecrosis”, “treatment”

RESUMO

Introdução: A osteonecrose da mandíbula relacionada a medicamentos é uma complicação rara; no entanto, pode ser debilitante. Houve necessidade de estudar a teriparatida no tratamento da osteonecrose da mandíbula relacionada a medicamentos (MRONJ) devido à falta de eficácia do tratamento convencional.

Objetivo: Compilar os estudos atualmente existentes para avaliar a eficácia da teriparatida no tratamento da MRONJ.

Materiais e Métodos: Foi realizada uma busca eletrônica, através de bases de dados online, como MedLine (PubMed), On-Line Knowledge Library (B-On) e Cochrane Library. As palavras-chave definidas foram “Teriparatida”, “Osteonecrose da mandíbula relacionada à medicamentos”, “osteonecrose” e “tratamento” combinadas entre si por meio do conector boleano AND. Foram considerados apenas artigos em inglês e português entre o ano de 2017 e 2023, realizado em humanos. Foram encontrados quarenta e seis artigos, dos quais trinta e oito foram excluídos após aplicação dos critérios de exclusão previamente definidos. Incluímos oito dos artigos encontrados.

Resultados: Os resultados demonstraram eficácia no uso da teriparatida, principalmente quando utilizada concomitantemente à antibioticoterapia. Indivíduos em tratamento com teriparatida associada a outra modalidade terapêutica apresentam maior probabilidade de resolução completa da osteonecrose quando comparados a indivíduos em uso isolado de teriparatida. A terapia associada a antibióticos é, no entanto, a modalidade terapêutica mais eficaz no tratamento da MRONJ.

Conclusão: Embora todos os estudos sejam promissores, ainda faltam evidências científicas, tornando o nível de confiança baixo. Mais estudos serão necessários para concluir com segurança que o uso da teriparatida é factualmente vantajoso.

Palavras-chave: "Teriparatida", " Osteonecrose da mandíbula relacionada à medicamentos”, “Osteonecrose”, “Tratamento”

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Throughout these six years, there were several people who, in some way, made it run the best way possible. In a path of learning and overcoming, I finish proudly saying that beyond the completion of the course, resilience and the will to be better tomorrow than today won.

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ABBREVIATIONS AND ACRONYMS LIST

AAOMS American Association of Oral and Maxillofacial Surgeons

µg/day Micrograms per day

ASBMR American Society for Bone and Mineral Research

BRONJ Bisphosphonate Related Osteonecrosis of the jaw

CBCT Cone Beam Computed Tomography

CI Confidence Interval

CT Computed Tomography

CTXs Carboxy-terminal type 1 collagen crosslinks

FDA Food and Drug Administration

IU International Unit

IV Intravenous

LLLT Low Level Laser Therapy

Kg Kilogram

Mg Miligram

mg/day Miligrams per day

MRONJ Medication Related Osteonecrosis of the jaw

OHIP-14 Oral Health Impact Profile 14

PET-CT Positron Emission Tomography Computed Tomography

PICO Population, Intervention, Comparison, Outcome

PRISMA Preferred Reporting Items for Systematic Reviews and Meta Analyses

P1NP Procollagen Type 1 N-Terminal Propeptide

PTH Parathyroid hormone

PTH (1-84) Parathyroid hormone aminoacids 1-84

RANKL Receptor Activator of Nuclear Factor Kappa-B Ligand

rhPTH (1-34) Recombinant human parathyroid hormone aminoacids1-34

VEGF Vascular Endothelial Growth Factor

% Percentage

I.INTRODUCTION

Bone metabolism is a dynamic and complex process that occurs continuously throughout our lives, constantly renewing, with formation and resorption occurring simultaneously in different areas of the skeleton. This process of bone remodeling is necessary for the maintenance of healthy bone and for bone adaptation to the mechanical demands of the body The regulation of bone metabolism is done through a balance between osteogenesis (bone formation) and osteolysis (bone reabsorption), both processes are controlled by specific cells. In particular, osteocytes, osteoblasts and osteoclasts. (Xiao *et al*., 2016, Hadjidakis and Androulakis, 2006)

Osteocytes are osteoblasts trapped in the bone matrix that still produce matrix proteins, but with decreased metabolic activity. These have cellular prolongations that form a network of canalicles in the bone matrix. The exact function of osteocytes is not yet fully understood, but it is likely that they are involved in bone remodeling in order to respond to bone tissue tension and recruiting osteoclasts to sites where bone resorption occurs. On the other hand, osteoblasts are cells responsible for bone formation during osteogenesis, these are derived from mesenchymal stem cells, which are undifferentiated traveling cells that have the ability to differentiate into various types of other cells, including osteoblasts. Bone formation occurs in three phases, production of organic matrix (osteoid), maturation of the organic matrix (phosphorylation) and mineralization (precipitation). The osteoblasts produce the osteoid matrix, rich in collagen, which undergoes maturation and deposition of minerals, becoming rigid and mineralized. The rate of collagen synthesis decreases as mineralization continues resulting in the formation of the mature bone. The balance between matrix production and mineralization is essential for proper bone health. Osteoclasts are responsible for the resorption of the bone. They are large multinucleated cells (up to 100 mm in diameter) derived from hematopoietic mononuclear cells. Osteoclasts reabsorb bone by releasing acids and enzymes that dissolve the inorganic matrix and organic matrix of bone, releasing calcium and other minerals into the bloodstream. In addition to cells, bone metabolism is regulated by various chemicals, such as hormones, growth factors, and cytokines. In the case of PTH, for example, it is

produced by the parathyroid glands, increases bone reabsorption, stimulating the activity of osteoclasts and the release of calcium from bone to blood. Vitamin D, which is activated in the skin and kidneys in response to sunlight exposure, is important for intestinal absorption of calcium and both regulates bone metabolism. Other hormones, such as estrogen, testosterone, and growth hormone, also play an important role in the regulation of bone metabolism. (Xiao *et al*., 2016, Hadjidakis and Androulakis, 2006, Limones *et al*., 2020)

Medication-related osteonecrosis of the jaw (MRONJ) is a rare potentially severe reaction and involves progressive destruction of the bone of the jaw or jaws. This is associated with significant morbidity and negatively affects quality of life. It is an adverse reaction associated with certain drugs, commonly used in the treatment of neoplasms and osteoporosis, namely related to bisphosphonates, denosumab and angiogenesis-inhibiting agents (denosumab, axitinib, bevacizumab). This involves the progressive destruction of bone in the mandible and/or maxilla. This adverse reaction is closely related to the type of drug, route of administration, the dosage, and the duration of treatment. (Beth-Tasdogan *et al.*, 2022, Limones *et al*., 2020)

Although the first cases of MRONJ were reported 20 years ago, the pathophysiological mechanism is still not fully understood. It is believed to be a multifactorial condition resulting from a combination of local and systemic effects as well as individual patient risk factors, but several hypotheses have been proposed. Osteonecrosis of the jaw is so named, since it occurs in about 65% of cases in the jaw, due to its low vascularity and consequently lower healing capacity. (El-Rabbany *et al*., 2017, Kawahara *et al*., 2021)

Suppression of osteoclastic activity, inhibition of angiogenesis, infection/inflammation and soft tissue toxicity, all play a significant role in the occurrence of MRONJ. Antiresorptive agents such as bisphosphonates and denosumab inhibit osteoclast function and may lead to decreased bone remodeling and reabsorption. Inhibition of angiogenesis may adversely affect bone regeneration and healing ability after bone damage. Infection and inflammation may play an important role in the progress of MRONJ. The presence of bacteria in the oral cavity can lead to a secondary infection in the affected area which

worsens the condition. Soft tissue toxicity caused by bisphosphonates origins decreased keratinocyte proliferation, which eventually can lead to bone exposure. Trauma or intra-oral invasive procedures may be associated with this toxicity and induce MRONJ. (Ruggiero *et al*., 2014, El-Rabbany *et al.*, 2017)

There are, as in everything, individual risk factors for each patient. They can be related to age and medical history: advanced age, presence of chronic diseases (such as diabetes, and pre-existing bone disease) , prolonged use of anti-resorptive agents, and related to oral cavity status and lifestyle: unsatisfactory dental hygiene, periodontal disease, use of unfitted of dentures or smoking. Certain dental procedures, which can influence/worsen the physiopathology of MRONJ associated to each patient. (Anabtawi *et al.*, 2021, Ruggiero *et al*., 2014, El-Rabbany *et al.*, 2017, Dunphy *et al.*, 2020)

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has defined that for a case to be considered MRONJ it must meet the following requirements:

- History of use of antiresorptive therapies or use of angiogenesis inhibitors,
- Presence of an area of exposed bone in the maxillofacial region that does not heal within 8 weeks even with appropriate care,
- Absence of a history of radiation therapy in the area, or absence of malignant tumours to the maxillofacial region. (Ruggiero *et al*., 2014, Cerrato *et al*., 2021)

Bisphosphonates are a class of drugs widely used in the treatment of certain bone diseases, such as osteoporosis and metastatic bone neoplasia. Denosumab is a monoclonal antibody that acts as an inhibitor of Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), a protein involved in the regulation of bone resorption. As such both of these drugs, are used to treat osteoporosis and prevent bone complications in metastatic bone cancer. In turn, angiogenesis inhibitors, like denosumab, are drugs often used in certain types of cancer, acting by inhibiting the growth of new blood vessels in tumours. (Goker *et al.*, 2021, Migliorati *et al*., 2019)

Bisphosphonates are osteotropic agents with antiresorptive activity and present many therapeutic indications, as mentioned above, are commonly used in the treatment and

prevention of osteoporosis, as well as Paget's disease, multiple hypercalcaemia assoaciated to neoplasia. Bisphosphonates bind to bone hydroxypatite and inhibit the activity of osteoclasts, the cells that reabsorb the bones. Thus, there is a reduction in bone turnover, which results in an increase in bone mineral density and a reduction in serum calcium. Bisphosphonates exhibit a long bone retention time, causing even in the absence of bisphosphonates withdraw their effects to be felt. There are two classes of bisphosphonates: low oral risk (alendronic acid, clodronic acid, ethhydronic acid, ibandronic acid and risedronic acid) and intravenous (ibandonic acid and zoledronic acid) and those of high risk intravenous. (Beth-Tasdogan *et al*., 2022, Ohbayashi et al., 2020, Cerrato *et al.*, 2021)

Denosumab is a potent antireabsorvent agent and is used to treat osteoporosis in postmenopausal women and men at high risk of fracture. It should be administered once every six months at a dose of 60 mg. This drug is also used to prevent bone complications in adults with solid tumour bone metastases and to treat a type of bone neoplasm called giant cell bone tumour. Denosumab is a monoclonal antibody that is designed to bind to an antigen called RANKL. By inhibiting RANKL, denosumab reduces the formation and activity of osteoclasts. (Beth-Tasdogan *et al*., 2022, Sim *et al.*, 2020)

Antiangiogenic agents are increasingly used as antineoplastic medicines to treat renal cell carcinomas, gastrointestinal tumours and other solid tumours. These drugs interfere in the formation of new blood vessels by inhibiting angiogenesis signaling cascades, such as signaling of vascular endothelial growth factor (VEGF) (bevacizumab and aflibercept), mechanistic target of rapamycin signaling (temsirolimus and everolimus) or tyrosine kinase signaling (gefitinib, erlotinib, sorafenib). MRONJ is a known and rare side effect of these agents, possibly resulting from their interaction with wound healing or differentiation and survival of osteoclasts. The FDA (Food and Drug Administration) included drug safety warnings on the labels of bevacizumab, aflibercept and sunitinib to raise awareness of the development of MRONJ. (Beth-Tasdogan *et al*., 2022, Dos Santos Ferreira *et al.*, 2021)

Initially this condition was called bisphosphonate-related osteonecrosis of the jaw (BRONJ), since at the time, investigators believed that these were the only class of medicines that caused osteonecrosis of the jaw. Already in 2014, the Special Committee of the AAOMS, proposed the amendment of the BRONJ nomenclature for MRONJ, and this change was justified to cover the increase of cases related to osteonecrosis. Bisphosphonates are commonly used to treat various conditions, including osteoporosis, latent hypercalcemia associated with breast cancer and multiple myeloma. It was only later found that the appearance of this condition was due not only to the use of bisphosphonates but also to the use of angiogenesis inhibitors and the use of denosumab. Failure of the height treatment led to new research including hyperbaric oxygen therapy, platelet-rich plasma, low frequency laser irradiation and the use of teriparatide. The present narrative review is based on evaluating the efficacy of teriparatide in the treatment of MRONJ. (Beth-Tasdogan *et al*., 2022)

The estimated risk of MRONJ is between 1 in 10,000 and 1 in 100,000 patient-years, with the reported incidence of MRONJ being higher in patients receiving high doses of antiresorptive agents. Despite being a rare condition, the frequency of MRONJ is highly variable and depends on several factors, such as the type of drug used, the indication of treatment (cancer versus osteoporosis), the dosage administered and the duration of treatment. There are certain studies and analyses of these same data that indicate that the incidence of MRONJ in patients with cancers exposed to intravenous zoledronic acid varies from 0.3 to 5%. In the case of denosumab, another drug used to treat cancer and osteoporosis, the risk of MRONJ varies between 0.7 and 1.9%. In parallel, in people with osteoporosis receiving lower doses of bisphosphonates or denosumab, the incidence of MRONJ is considerably lower. In individuals with osteoporosis treated with bisphosphonates or denosumab, the risk of developing MRONJ is approximately 100 times lower than the risk observed in cancer patients. While there is a less clear association between antiangiogenic medicinal products and the development of MRONJ. According to analytical data from the FDA Adverse Event Reporting System database suggest that antiangiogenic medicinal products are associated with a lower risk of MRONJ compared to bisphosphonates administered intravenously. (Beth-Tasdogan *et al*., 2022; Sim *et al.* 2020)

The diagnosis of MRONJ should be differential with other forms of osteonecrosis and other previously defined clinical conditions. As in any diagnosis, it is necessary to take into account the clinical history, clinical exam, and imaging examinations. It is of high importance to know all the medications taken in the last years, their duration and dosage, as well as the route of administration. Bearing in mind that the use of certain medications leads to the appearance of MRONJ, as mentioned above. As a rule, MRONJ has great repercussions both on the quality of life of patients and on health resources. Patients with MRONJ usually have signs and symptoms that include pain, swelling, fistulas intra and extraoral, erythematous or ulcerated soft tissue, associated with bone exposure that in serious cases can lead to pathological fractures. As mentioned above, the predominance of this disease in the jaw is highlighted due to low vascularization of the disease. The dominant cause of MRONJ is bone injury associated with decreased ability to heal. The standard treatment always passes through the minimization of symptoms, and again it is to be emphasized that it may be surgical or non-surgical. Panoramic radiography, with its limitations and computed tomography (CT) can be used to assess the extent of the lesion, presence of bone sequestrum, and the relationship with adjacent structures. Once all the data has been collected, other conditions associated with the same signs and symptoms presented should be excluded (such as infections such as sinusitis, alveolar osteitis, gingivitis/periodontitis, periapical pathology and some forms of cemento-osseous dysplasia, or malignant tumours, and other bone diseases). Although it does not mention histological criteria in determining the diagnosis, these end up being clinically relevant and frequent for the diagnosis. Although histological criteria are not mentioned, they are most of the times highly relevant for final diagnosis. (Khan *et al*., 2015, Ruggiero, 2015, Mohamed El-Rabbany *et al*. 2017, Campisi *et al.,*2020)

The AAOMS and ASBMR (American Society for Bone and Mineral Research) recommend the classification of MRONJ into four stages. This staging system should be performed after diagnosis, since when appropriate with clinical symptoms and radiographic findings, it serves as a guide in the treatment strategies for the specific case.
- Stage 0 is characterized by a lack of clinical evidence of osteonecrosis, but with a history

of drug use associated with MRONJ and therefore may present symptoms such as pain, swelling, or infection in the maxillofacial region.

- Stage 1 osteonecrosis occurs, usually asymptomatic, with the mucosa intact and no signs of infection. However, there may be exposure of the alveolar bone during dental procedures.
- Stage 2 is characterized by the presence of infection
- Stage 3 is characterized by the presence of osteonecrosis associated with severe symptoms, including severe pain, recurrent infection, cutaneous fistulas or purulent drainage, with bone involvement that extends beyond the maxillofacial region, such as nerve involvement, orbit, sinus of the face, or pathological fractures. (Beth-Tasdogan *et al.*, 2017, Anabtawi *et al.*, 2021)

Treatment of MRONJ involves infection control, decreased progression of necrosis and promotion of tissue healing. If MRONJ occurs while the patient is on high dose bisphosphonates or denosumab, the continuation of therapy should be discussed considering the severity and evolution of MRONJ, the burden and activity of the cancer disease, and patient health status and health status. As for treatment, there are two treatment options, conservative and surgical, being the later performed when the conservative therapies are not achieving good results. The conservative approach includes adequate oral hygiene, treatment of dental problems, use of oral antiseptics and, if necessary, antibiotic therapy. The surgical approach is recommended when conservative measures are not effective, surgical treatment consists of removal of necrotic bone and proper tissue closure. (Nicolatou-Galitis et al., 2019, Beth-Tasdogan *et al*.,2022, (Mohamed *et al*., 2022, Govaerts *et al*., 2020)

Teriparatide (rhPTH (1-34)) was developed by the pharmaceutical company Eli Lilly and Company, it is a synthetic analog of parathyroid hormone (PTH 1-84), with an amino acid sequence identical to the first 34 amino acids of the natural hormone. Teriparatide was conceived on the rationale that intermittent administration of PTH could have an anabolic effect on bone, thereby stimulating bone formation and reducing the risk of osteoporotic fractures. Pre-clinical studies demonstrated the potential of this approach, and teriparatide

was approved by the FDA in 2001 as the first osteoanabolic agent to treat severe osteoporosis. (Krege *et al*., 2022, Govaerts *et al.*, 2020, Chiba *et al*., 2022)

Teriparatide is administered by subcutaneous injection into the abdominal wall or anterior thigh at a daily dose of 20 micrograms. The maximum duration of teriparatide use is limited to 2 years. During treatment patients should receive vitamin D and calcium supplementation. The mechanism of action is based on its similarity to parathyroid hormone (PTH), which is produced naturally by the body. Teriparatide binds to and activates the PTH cell receptors. The main effect of teriparatide is to stimulate bone formation, this stimulation occurs through several mechanisms, being to increase osteoblast activity and decrease osteoclast activity. In addition, also has effects on calcium and phosphate metabolism, increasing intestinal absorption of calcium and reducing renal excretion of calcium and phosphate. (Vall and Parma,2023, Chiba *et al.*,2022, Wang *et al*., 2017) (Figure 1 p37)

Teriparatide is a well tolerated drug with mild and transient side effects such as nausea, headache and dizziness. Changes in calcium metabolism such as hypercalcaemia and hypercalciuria are common, but usually do not cause serious problems. The most worrying adverse effect is the theoretical risk of developing osteosarcoma, however, this risk is considered minimal and insignificant in humans, and the use of teriparatide is limited to 2 years of use. Teriparatide must not be used in patients who have known hispersensibility to the active substance or to any excipient of the medicinal product. In addition, it is not recommended in patients with untreated underlying metabolic bone disease, such as uncontrolled hypercalcaemia, primary hyperparathyroidism or other metabolic diseases, or in paediatric and young patients with open epiphyses. On the other hand, it is important to take some precaution in the use of teriparatide in patients with previous history of bone radiotherapy or treatment with antineoplastic medicinal products, since there is a theoretical risk of developing increased osteosarcoma. (Vall and Parmar, 2023, Chiba *et al.*, 2022)

Conventional therapies have proved to be shortcoming when treating MRONJ, new therapeutic options in the treatment of MRONJ. This dissertation aims to evaluate the results regarding the use of Teriparatide when treating medication related osteonecrosis of the jaws, aiming to answer the following question:

"Is teriparatide an effective therapeutic option for the treatment of MRONJ?" and " Is teriparatide safe for treating MRONJ?"

I.I MATERIALS AND METHODS

The aim of this narrative review is to answer the clinical question referred above, based on the keyword defined previously. For the development of the research question PICO strategy was used (Table 1, p10) and PRISMA diagram (Figure 2, p38) methodology for article selection was used. (Huttin *et al*., 2015; Moher *et al*., 2009)

The search was done using an online database, MedLine (PubMed), On-Line Knowledge Library (B-On) and Cochrane Library databases using the predefined key words "Teriparatide", "Medication-related osteonecrosis of the jaw", "osteonecrosis", and "treatment" combined between them using the boolean connector AND.

The article included were clinical trials, meta-analyses, randomized controlled trials and systematic reviews with the time frame of publication being the past 6 years (2017-2023) Exclusion criteria were languages other than Portuguese and English and articles that were not fully available for free consultation. (Table 2, p10)

Table 1: Strategy Population, Intervention, Comparison, Outcome (PICO) for question formulation

Population	Patients over 18 years old, both gender with MRONJ
Intervencion	Teriparatide
Comparison	MRONJ treated with teriparatide or without
Outcomes	Teriparatide used for the treatment of MRONJ should improve normal disease course

Table 2: Defining inclusion criteria and exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
2017-2023	Articles Without free access
Clinical Trial	Languege other English and Portuguese
Meta-Analysis	
Randomized Controlled Trial	
Systematic Review	
Cases Report	
Review	

The analysis of the articles to include in this review was carried out by two (J.F.) and (F.O), the results obtained were discussed after the inclusion / exclusion criteria were applied and after analyzing each article by the title, abstract and by reading the full text, reaching the number of 8 articles.

II.DEVELOPMENT

II.I RESULTS

Completed the integrative search phase resulted 8 articles looked upon the use of teriparatide for the treatment of MRONJ. That are summarized in figure 1 to better understand the current literature available regrading, the different objectives, materials and methods, adverse effects and results. Conclusions will be described, compared and discussed later. The characteristics of each study are summarized in the attached tables. (Table 3 pp 39-42 and Table 4 p43)

2.1.1 M. Mohamed. *et al*. (2022)

This is a case report in which a specific case was studied. The case involves the presentation of an 81-year-old lady with severe osteoporosis and ischemic heart disease. She has been taking alendronic acid 70 mg weekly for about 3 years since tooth extraction. She manifested the following symptoms: non-healing sites, facial pain and erythema, maxillary sinus with smelly discharge. The diagnosis was MRONJ stage 3 confirmed by orthopantomography and computed tomography. She had no history of osteosarcoma or local radiotherapy. For 14 days, she underwent conventional therapy which included: debridement limited to the exposed bone, long-term antibiotics and chlorhexidine washing of the exposed areas, despite this, her clinical condition worsened. He was vitamin D deficient which was immediately corrected. P1NP and CTX were within normal values, therefore, treatment with teriparatide 20 μg/day subcutaneously for a period of 2 years was suggested.

At the end of 2 months, there was full soft tissue coverage of the intraoral lesion, the fistula was covered by healthy oral mucosa and did not require further debridement. The levels of the markers, P1NP and CTX were unchanged. With this, there was a possibility to undergo surgical closure of the fistula. In the end, the lady had successful therapy which led to an increase in appetite and gradual weight gain.

With the study of this case, it was possible to identify the potential of using teriparatide in the treatment of MRONJ, as teriparatide increases the production of T cells, thus increasing the production of osteoblasts RANKL causing an increase in osteogenesis and increased recruitment of osteoclasts. These cells, as mentioned above, are essential in the healing process and act as a prerequisite for the anabolic effect of teriparatide on osteoblasts. Teriparatide induces an anabolic window essential for bone formation and positive bone balance.

2.1.2 Beth-Tasdogan. *et al*. (2022)

The aim of this systematic review is to evaluate the effects of interventions versus no treatment, placebo or control on MRONJ prophylaxis in people exposed to anti-reabsortive or anti-angiogenic drugs. The objective was also to evaluate the benefit-risk relationship of surgical and non-surgical interventions, whether combined or not. Treatment of MRONJ involves infection control, decreased progression of necrosis and promotion of tissue healing.

Treatment may be subdivided into non-surgical treatment and surgical treatment. Non-surgical treatment may involve oral use of pentoxyphylin and vitamin E (alpha-tocopherol) in addition to antimicrobial therapy. Another option will be the use of hyperbaric oxygen, which involves the use of pure oxygen in a pressurized room or tube and topical ozone therapy to improve healing. The use of low frequency laser therapy (LLLT) is also seen as a promising adjuvant treatment. The use of platelet-rich plasma is suggested to improve the healing of postoperative wounds. This is commonly used in the gel formulation, formed by the combination of platelet-rich plasma, thrombin and calcium chloride. Normally, this gel contains more fibrogen, platelets and growth factors compared to a blood sample. In addition, the bone can be restored by the use of teriparatide, which as mentioned above is a recombinant hormone of parathyroid. This is approved for the treatment of osteoporosis, but is often used off label in the healing of fractures and dental stability. Another therapeutic option is the use of human recombinant morphogenic proteins, since they have the ability to induce osteogenesis, improving healing. An absorbable collagen sponge is used which is impregnated with these proteins

and is placed at the site of the bone defect. On the other hand, surgical treatments include sequestrectomy, debridement, resection, immediate reconstruction and further extraction of teeth within the exposed necrotic bone. Current medical treatment involves the use of local or systemic antibiotics and cheeks with antiseptic fluids, notably with chlorine-hexidine, or both, and surgical debridement or resection.

Surveys were conducted in four bibliographic databases by June 16, 2021, included 13 articles, out of a total of 1668 participants, of which 8 participants were new additions, compared to the initial study. Five of the randomized clinical trials evaluated the different possible interventions for MRONJ prevention. One of the randomized clinical trials compared standard care with regular dental examinations at three-month intervals and preventive treatments, which included pre-dental antibiotics and the use of wound closure techniques, which in turn prevented exposure and contamination of bone. This last trial was done using male patients with prostate cancer treated with zoledronic acid. The result was positive as it appears that this intervention led to a decrease in the risk of MRONJ. On the other hand, the dentoalveolar surgery was considered an event predisposing to the development of MRONJ, that is, five of the randomized clinical trials evaluated several measures to be taken in the prevention of post-operative MRONJ. These studies evaluated and compared the administration of enriched plasma with growth factors in post-extraction alveol, standardized medical and surgical care versus isolated standardized medical and surgical care. They also evaluated the delicate surgery and closure by primary intent versus non-traumatic dental avulsion and closure by secondary intent.

In relation to the treatment of MRONJ, eight of the randomized clinical trials evaluated the different therapeutic options by determining the cure rate of MRONJ for each of the options. One randomized clinical trial looked at hyperbaric oxygen treatment beyond standard care, including the use of antiseptic collutories, topical and/or systemic antibiotics and surgery and compared the results with the isolated use of hyperbaric oxygen. Another randomized clinical trial compared autofluorescence with tetracycline fluorescence guided sequestrectomy for MRONJ surgical treatment for a period of one year. The cure rate of MRONJ was not significantly different when compared to autofluorescence surgery and conventional bone surgery. Three randomized clinical trials

investigated the effect of the use of growth factors and platelet concentrates on the healing rate of MRONJ. They evaluated the effects of platelet-rich fibrin after surgery versus isolated surgery. They also evaluated bone morphogenic protein 2 associated with platelet-rich fibrin versus isolated platelet-rich fibrin. Only two randomized clinical trials focused on the use of teriparatide in MRONJ patients. The largest study involved 700 participants and the smallest study involved only 13 participants. Most of the participants were women. All studies except 2 included participants treated with bisphosphonates. Two of the trials were based on pharmacological treatment with teriparatide, one of them used 20 micrograms/day and had 33 participants, while the second trial used a dose of 56 micrograms/week and had 12 participants. The purpose of these trials was to compare teriparatide therapies to 20 micrograms vs conventional treatment. On the other hand, the efficacy of teriparatide at 56 micrograms/week with teriparatide at 20 micrograms/day was evaluated. The duration of treatment was the same for both doses and lasted for a period of six months. All participants were supplemented with vitamin D and calcium.
As mentioned above, teriparatide stimulates osteoblasts to increase bone density when used intermittently.

In this study, the results after administration of injectable teriparatide at a dose of 20 micrograms per day were compared with the results after administration of a saline solution (placebo), belonging to the control group. All the patients suffered from MRONJ at different stages. The primary events were defined as clinical and radiological resolution of MRONJ lesions. These were evaluated by oral examination and CBT imaging. The secondary events were defined as improvement of the MRONJ stage with change in the size of the MRONJ lesion and improvement of the quality of life. Bone mineral density and osteoblastic response were biochemically measured using the P1NP marker and using PET-CT imaging.

The results were also evaluated after comparing the administration of daily teriparatide (20 micrograms) versus weekly administration (56.5 micrograms) in addition to the standard treatment. All participants had MRONJ at different stages.Defined by the change in clinical stage of MRONJ after 6 months of treatment, changes in bone metabolism (using bone scintillography), changes in bone formation percentage in MRONJ osteolysis

and measurement of bone rotation markers. However, any of the results had very low scientific evidence.

Having said that, the available evidence is insufficient to claim or refute a benefit of any of the interventions studied for the treatment of MRONJ. However the bone can be restored by teriparatide, by stimulation of osteoblasts in the increase in bone density, as mentioned above.

2.1.3 L Dos Santos Ferreira *et al.* (2021)

The purpose of this systematic review was to combine the available data from MRONJ cases treated with teriparatide and to assess the actual efficacy of teriparatide. This study provided information that could improve the understanding of the effects of teriparatide, allowing physicians and clinicians to make more informed decisions. The concomitant use of teriparatide with antibiotic therapy is expected to be an effective protocol. Teriparatide, as mentioned above, is a molecule that makes up the first 34 amino acids of intact PTH. Its action occurs through intermittent stimulation of the PTH1 receptor in osteoblasts and their pathways, which in turn generate greater bone anabolic activity when compared to the catabolic activity generated. Other studies have shown that its action increases bone volume and reduces the size of the bone defect in 80% of subjects who underwent MRONJ treatment. This is a systematic review in meta analysis of observational and clinical studies of the efficacy of therapy with teriparatide in patients with MRONJ. This study was based on a survey of six different databases (PubMed, Web of Science, Scopus, Ovid, Embase and LILACS) during December 2020. Subsequently, descriptive analyses of MRONJ clinical-demographic data were performed. This revision was drawn up on the basis of PRISMA guidelines. The eligibility criteria have been defined in advance. Poisson Progression was used for statistical data analysis to evaluate the total resolution rate of MRONJ when using teriparatide. For final analysis only 111 subjects from the 26 studies were included.

With this study in meta analysis it can be found that 73% of the subjects with osteonecrosis involves the jaw, and the average time of evolution corresponds to five months. It was also found that the most common cause of MRONJ is dental extraction, although other triggering factors such as implant placement and periodontitis can be identified. Osteoporosis was the main reason for the use of anti-resorptive drugs, and the most commonly used are undoubtedly bisphosphonates, with the possibility of using denosumab, a monoclonal antibody. In addition, it was found that the use of anti-resorptive drugs promotes more time-consuming healing after surgical procedure. The average duration of use of these medicinal products was 52.8 months for bisphosphonates and 4 months for denosumab. It was also found that the most prevalent stage with 68 cases corresponded to stage 2 of the MRONJ. For administration of 20 μg/day of teriparatide subcutaneously may be used for approximately 18 months and not more than 24 months. However, the duration of treatment depends on the prescriber. In the present systematic review, the mean duration of treatment was approximately 7 months and 59.5% of patients had a total resolution of established MRONJ lesions. About 7.2% of patients showed a partial or total resolution of the established lesions and 20.7% of patients showed no improvement. More prolonged administration is associated with a greater benefit with regard to injury healing. It was found that short-term teriparatide along with antibiotherapy may be a reasonable treatment in the initial cure of lesions. In addition to this beneficial combination, other therapeutic options such as teriparatide in isolate (32 cases, 28.8%), teriparatide associated with conservative therapy (54 cases, 48.7%), teriparatide associated with surgery and conservative therapy (12 cases, 10.8%) and teriparatide associated with laser therapy (1 case, 0.9%) were also considered.

Another conclusion was that although certain comorbidities are associated with the development of MRONJ, namely chronic use of corticosteroids, chemotherapy and diabetes mellitus, these do not directly affect the total resolution of lesions when using teriparatide subcutaneously. This does not mean that there are no comorbidities that directly affect the resolution of the same, this evidence although it may be true should always be interpreted with some care. It is necessary to consider the sub notification of systemic agents. Although no other comorbidities have been mentioned due to their lack of relevance, problems such as hypertension, rheumatoid arthritis, smoking habit, alcohol

consumption, hypercholesteremia, cardiovascular disease, gastrointestinal disease and renal failure are also highlighted.

It was also found that patients who were treated with teriparatide associated with other therapeutic modalities were 1,210 times more likely to present total resolution of osteonecrosis. These therapeutic modalities mainly included antibiotherapy, surgical approach and laserterapy mentioned above. With this systematic review it was found that the probability of total lesions resolution depended directly on the MRONJ stage. After this, it was found that patients with stage 1 of MRONJ were 1,185 more likely to achieve total MRONJ resolution when compared to patients with stage 3 of MRONJ.

Patients who concomitantly performed anti-resorptive therapies and teriparatide were evaluated to understand the efficacy of teriparatide when using other drugs.

With the increasing aging of the population, there is a greater proportion of patients exposed to anti-resorptive drugs. Since all comorbidities described as being the most common (chronic use of corticosteroids, chemotherapy and diabetes mellitus) are closely related to aging. In this respect, based on the overall results of this study, teriparatide therapy in combination with another therapeutic modality may be effective in the treatment of MRONJ, noting that the results are more promising when using teriparatide and other agents concomitantly when, of course, compared to using teriparatide alone.

The results of this systematic review have a limit since there is only one randomized study evaluating the use of teriparatide in the treatment of MRONJ. Data on other comorbidities, duration of treatment and study of certain serological parameters are also missing. Another failure to point out is the lack of study of the role of genetic susceptibility of each individual.

2.1.4 F. Goker *et al.* (2021)

As previously mentioned, there are several therapeutic alternatives in the treatment of MRONJ, from the most conservative to the most invasive treatments, namely regarding

surgical procedures. The present systematic review is based on evaluating the effective therapeutic options available for the treatment of this condition. After that, the therapeutic options will be compared. Any improvements in the healing of hard and soft tissues, any decrease in the incidence of complications or any beneficial effects on the quality of life of patients have been taken into account.

This systematic review included research in different databases, such as Medline, Scopus and Cochrane. The research included only clinical studies in humans. Keywords and inclusion/exclusion criteria have been defined in advance. Articles have been researched addressing different therapeutic agents, ranging from platelet concentrates, teriparatide, hyperbaric oxygen, laserterapy, ozone applications and surgical procedures. 118 articles were used, 15 articles studying the effect of platelet concentrate, 4 articles studied the effect of teriparatide, 10 articles studied the effect of laserterapy, 3 articles studied the effect of hyperbaric oxygen, 2 articles studied the effect of ozone applications, 9 articles were based on the use of conservative protocols and, finally, 75 articles studied surgical interventions with MRONJ treatment. One of the evaluation criteria defined was improved healing of the treated site.

Bisphosphonates are the most commonly used class in the treatment of bone diseases, including osteoporosis, and are also primarily responsible for the development of MRONJ. These lesions are known for necrotic lesions of the bone. In addition to this class, also denosumab, a monoclonal antibody was associated with this condition The etiology of MRONJ is still unknown, although there are several hypotheses. Treatment involves minimizing the progression or occurrence of osteonecrosis, eliminating pain, controlling infection and improving the patient's quality of life. At an early stage of the disease, initial stages, the treatment undergoes conservative measures (adequate oral hygiene, cheeks with chlorhexidine at 0.12% and antibiotics), mentioned above. Surgical interventions are avoided whenever possible, at least at an early stage. At a more advanced stage, treatment will include surgical debridement or resection and will be considered more invasive. There are several adjuvant therapies proposed by the literature, including the use of teriparatide. The success of the therapy involves increasing bone

density and healing of soft tissues in different surgical procedures. However, there is no standard therapeutic strategy.

The surgical recession was the most tested treatment protocol, several retail options with promising results have been reported, highlighting the mucoperiosteal and mucoperiosteal retailing associated with double layer closure with oral fat retail and shutter rehabilitation, mouthfeel cushion, microvascular free slashes, surgery associated with reconstruction of soft parts with local myofascial retail, nasolabial rectangles vs mucoperiosteal closure, pediculated oral fat combined with sequestrectomy, comparison of local mucoperosteal retailers with milo-hyoid retailers and reconstruction with vascularized fibula retailing of the jaw. In addition, fluorescence-guided surgery and piezoelectric surgery were evaluated for necrotic bone recession, which demonstrated beneficial results. On the other hand, low frequency laser therapy was considered the fastest and least invasive surgery with the most comfortable post-operative healing process. The use of teriparatide has been described with an extremely useful method for resolving established MRONJ lesions.

Systemic antibiotics are considered part of standard therapy after surgical procedures; however, their effectiveness is limited by low penetration rate at the site of infection and impaired blood supply. The recommended antibiotic is bactericide, inexpensive and without major side effects. According to AAOMS the treatment modality of MRONJ should always be conservative and therefore surgical procedures should be avoided. However, there are systematic revisions that consider surgical treatment more effective than non-surgical treatment. According to this systematic review there is a heterogeneity of surgical options. In short, with this systematic review it was possible to conclude that treatments involving surgical procedures are more effective than those not involving surgical procedures, since there is better resolution/healing of bone defects associated with MRONJ. In this case, it was realized that the surgical procedures could be done at any stage of the disease, since they prevent the natural progression of the disease. It was realized that when non-surgical treatments were used, even in early stages, the rate of healing was low. Teriparatide has been beneficial when, especially associated with the use of oral antibiotics, such as doxycycline after surgical procedure. Systemic use of

teriparatide and antibiotics has been reported as an effective way to treat necrotic lesions. Surgical interventions may not be sufficient to achieve long-term wound closure. In any case, this decision is made by the prescriber and should take into account the overall conditions of the patient concerned.

2.1.5 M. Anabtawi *et al.* (2021)

This study took into account radiological, histopathological and serological parameters to assess the efficacy of treatments. Electronic databases (PubMed, Embase and Scopus) were used for this review and articles from April 2005 to April 2020 were considered. After the search, only seventeen of the articles were used taking into account the inclusion criteria.

The first case of MRONJ treated with teriparatide, as mentioned in this review, was reported in 2007. In this study, 94 patients were found to have MRONJ and were initially treated with teriparatide. Three of the patients treated with teriparatide dropped out of treatment prematurely and therefore the reported results involved only 91 patients. The average age of the participants was 76. More than 50% of the participants were female. About 88 participants took oral bisphosphonates, including alendronate, risedronate, ibandronate, pamidronate, or minodronate. The remaining 6 patients made intravenous anti-resorptive drugs. These medications were administered in the treatment of primary and secondary osteoporosis. Cases of spontaneous development of MRONJ have also been reported, often associated with a surgical, traumatic and infectious process. These included extractions, non-surgical endodontic treatment, dental implant placement surgery, trauma-causing misfit prostheses and periodontal disease. The different articles presented different treatment strategies and under different conditions. Doses and frequencies of treatment with teriparatide varied, as in some teriparatide was taken daily and in others it was taken at weekly or monthly intervals. The longest duration of treatment with teriparatide was 26 years. According to this article, the most common anatomical site in the development of MRONJ is the jaw, and of the 94 articles, 68 confirmed the development of MRONJ in the jaw and only 15 confirmed the development of jaw disease. The remaining articles confirmed the development at both anatomical sites

and/or did not specify the site. Most patients were diagnosed with MRONJ at stage 2 and 3, only one patient was diagnosed with MRONJ stage 1. Response to treatment was assessed using clinical markers. On the other hand, the response to the treatment of MRONJ by teriparatide was also evaluated by radiological and biochemical means.

This results in this paper, found that teriparatide treatment should not be given for longer than two years as there is a high risk of osteosarcoma. In 12 studies, antiresorptive treatment was stopped before the start of teriparatide treatment and the other 5 studies did not specify whether treatment was stopped or not. Across the studies, clinical improvement was seen in 32 patients (35%), complete resolution in 50 patients (55%), no improvement in 2 patients (2%), stabilized disease in 6 patients (7%) and worsening of the clinical situation in 1 patient (1%). Clinical outcomes included: improvement of pain, absence of purulent content, infection, healing of fistulas, reduction of bone exposure area, among others.

Of the 17 studies, only 3 reported treatment-related complications with teriparatide. In one of these 24-month studies, five patients (17%) discontinued treatment due to adverse side effects. A case of a patient who developed arthritis after being given teriparatide has also been mentioned, causing the patient to stop treatment after 12 days. Another patient had nausea which caused treatment to be discontinued after 3 months. In another study, it was found that 2 out of 10 patients (20%) left the study, as they had facial and lower limb oedema, as well as nausea and vomiting. These effects would have come after 3 days. In addition, there was a case of arthralgia in the knee and another patient left treatment. There was also a report of psychological problems in a total of four patients treated with teriparatide.

With the increasing ageing population, patients are more likely to have multiple comorbidities and be polymedicated, which in turn can complicate the treatment of MRONJ, reducing therapeutic options and making surgical procedures inappropriate. MRONJ is a complex process that can negatively affect the patient's quality of life, and its pathophysiology is still poorly understood. Teriparatide, as a PTH analog, was approved by the FDA in 2017 in the treatment of osteoporosis and has been studied in the treatment of MRONJ. However, this review highlights the lack of high-quality evidence

on the use of PTH analog in the treatment of MRONJ, as the literature is composed of reduced cases and case series. In most of the articles, teriparatide was being used as an adjunctive treatment which made it difficult to verify the efficacy of teriparatide and whether the improvements described were indeed associated with the use of PTH analog or its association with other therapeutic modalities. In essence, the treatment of MRONJ using teriparatide is under strict prescription. The available literature does not provide sufficient evidence to determine the efficacy of teriparatide in MRONJ, mainly due to the lack of high-quality studies. In addition, there is a high risk of bias, which in turn makes it difficult to determine the efficacy of teriparatide and its effects in the medium and long term. However, the use of teriparatide, according to the authors, may be a viable option for the treatment of MRONJ in intractable patients or who may not be submitted to surgical treatment. Therefore, in the future, randomized clinical trials in larger cohorts with long-term follow-up should be carried out in order to study the efficacy and safety of teriparatide in the treatment of MRONJ, only in this way will it be possible to recast the guidelines for the treatment of MRONJ.

2.1.6 Sim *et al.* (2020)

This is a double-blind, randomized, controlled study involving 34 participants aged 18 years or older diagnosed with MRONJ. Participants were previously treated with bisphosphonates or denosumab. The diagnosis of MRONJ was confirmed by a dental physician specializing in the treatment of MRONJ. Those with a history of previous craniofacial radiotherapy, hypercalcemia, hyperparathyroidism, or severe renal failure were excluded from the study. That said, these study allowed to evaluate the efficacy and safety of healing of MRONJ lesions established by subcutaneous administration of teriparatide.

Study participants were randomly divided into two groups, the teriparatide group, which received daily subcutaneous injections of teriparatide 20 μg for 8 weeks with 15 participants, and the placebo group, which received saline injections with 19 participants. Both groups also received oral calcium carbonate supplementation, 600 mg once a day

and vitamin D, 1,000 IU once a day, in addition to standard clinical treatment for MRONJ, the latter including antiseptic mouthrinses, antibiotic therapy, and limited surgical debridement. Participants were randomly assigned to the different treatment groups based on the duration of MRONJ diagnosis, less than 12 months and 12 months or more. During the visits, a qualified dentist examined the participants to determine the clinical stage of MRONJ and assess the resolution of each individual lesion.

Cone beam computerized tomography (CBCT) scans were performed for several weeks in order to assess the radiological resolution of MRONJ. Participants' quality of life was assessed by completing Oral Health Impact Profile 14 (OHIP-14) questionnaires. In addition, fluorine positron emission tomography/computed tomography (PET-CT) was performed at weeks 0 and 8 to measure osteoblastic responses to teriparatide. At each visit, a blood sample was collected from each fasting participant in the morning to perform analyses of bone remodeling markers carboxy-terminal type 1 collagen crosslinks (CTXs) and procollagen type 1 N-propeptide (P1NP) and standard biochemical tests, including calcium and parathyroid hormone levels.

The incidence of adverse effects reported include gastrointestinal symptoms, musculoskeletal pain and injection site reactions. These were compared between groups and most were classified as mild adverse effects. Three serious adverse effects were subsequently reported in each of the groups, with one death in the placebo group. In addition, a patient in the placebo group was diagnosed with a new malignancy. In the teriparatide group there was no worsening of pre-existing malignancies nor the development of new malignancies.

It was possible to support the role of teriparatide in MRONJ treatment, this being important as current recommendations and guidelines in the management of MRONJ are constantly called into question due to lack of quality data. The effect of teriparatide is due to increased osteoblastic activity at the site of lesions, resulting in a reduction in the volume of the bone defect and possibly better mucosal coverage and resolution. The anabolic effect in reducing the volume of the bone effect is proven by the placebo controlled study. Teriparatide was associated with a clinically significant increase in the

P1NP marker in 85.7% of the participants. Fluor PET-CT radiological examination further demonstrated an increased uptake within the jaw, between the fluoride and hydroxyapatite. The anabolic mechanism is associated with potential concerns, namely in stimulating cell proliferation within the bone, which in turn leads to exacerbation of malignant bone disease or recurrence in patients who have been successfully treated and are in remission. Teriparatide therapy should be limited to 24 cumulative months as it has been associated with osteosarcoma in preclinical studies. On the other hand, there is no causal relationship between teriparatide and osteosarcoma in humans in post-marketing surveillance. In any case, as mentioned above, during this study the participants had minimal exposure to teriparatide, received only injections for eight weeks, and therefore the theoretical risk of developing osteosarcoma would be extremely low. The resolution rate of MRONJ is 33.3% over one year in the placebo group and is consistent with published data. It also highlights the costly chronicity of the condition and the need for proven therapies to promote the cure of MRONJ. MRONJ remains a widely feared and potentially debilitating consequence of antiresorptive therapy. In short, for eight weeks the administration of teriparatide injections once daily improves the resolution rate of MRONJ lesions and therefore represents an effective and safe option in the treatment of MRONJ. Despite the promising results, it should be borne in mind that the experimental sample is reduced, which in turn causes the negative results to be conservative and the adverse effect rate to be lower than expected.

2.1.7 Y. Ohbayashi *et al*. (2020)

The objective of this systematic review was to evaluate the efficacy of teriparatide in the treatment of MRONJ in patients with osteoporosis and to compare the differences in clinical outcomes following daily vs weekly teriparatide administration.

A number of 13 patients were enrolled and were randomly subdivided into two groups: teriparatide 56 micrograms/week and teriparatide 20 micrograms/day, the results were evaluated for 6 months. Exclusion criteria included: hypercalcemia complication, high risk of osteosarcoma, bone neoplasm, metabolic bone disease, pregnancy or breast-feeding and severe complication such as neoplasm, heart disease, liver disease and kidney

failure. Patients received conventional therapy plus intensive antibiotherapy according to the MRONJ stage plus intensive antibiotherapy as needed. The duration of treatment with antibiotherapy varies between 1 and 18 months. When the clinical presentation is acute, intravenous antibiotics followed by a variable period of oral antibiotherapy were administered. For prolonged or relapsing infection during treatment of 6 months the dose schedule of antibiotherapy was adjusted according to antibiogram results (microbiologic analysis). After giving up one patient, the groups had 6 patients each. Changes in clinical stage of MRONJ, bone metabolism, bone formation percentage and bone remodeling markers were evaluated.

Examinations were performed that included panoramic radiography, computed tomography, bone scintology, microbiology testing and chemical analysis that included bone remodeling markers.

Teriparatide as a drug with anabolic action has been shown to be effective in preventing fractures by vertebral and non-vertebral fragility. The use of this drug in combination with other MRONJ therapies has been considered highly useful in uncontrolled trials. As mentioned above, daily or weekly injections may be made. The quantity and quality of bone metabolism markers differ according to the frequency of administration. With daily injections, serum concentrations of the marker P1NP patients increased rapidly and remained significantly elevated throughout the treatment period. On the other hand, following weekly administration of teriparatide, osteocalcin levels increased by 4 weeks of treatment, decreased by 24 weeks and remained constant for 48 weeks.

Treatment of MRONJ with teriparatide led to partial remission or complete remission in five of the patients in the daily group and three of the patients in the weekly group. There was a significant improvement in MRONJ stages in all patients. In the daily group the improvements were more evident when compared to the weekly group. This study is the first comparative study of clinical results when teriparatide is used at different frequencies. The results were promising.

The anabolic effect of PTH is due to its ability to promote bone anabolism by stimulating aerobic glucose via insulin-like growth factor signaling. PTH stimulates osteoblastic activity, osteoblastic differentiation and bone coating cells, and mitigates osteoblastic apoptosis. Teriparatide showed potential in the treatment of MRONJ. 7 of the 8 MRONJ patients treated with teriparatide daily for 4 to 24 months showed clinical improvement, improvements in lesions of 6 patients were also reported within 1 to 3 months of treatment, marginal resection was also described in 2 patients, segmentary resection in a patient, decortication in a patient and sequestrectomy also in a patient. In addition, some authors have found that patients who have never started glycocorticoids or chemotherapy have reached one or two stages of disease improvement or complete cure.

As mentioned above, MRONJ is a side effect of the treatment of osteoporosis with bisphosphonates. The frequency of MRONJ in these patients is 0.001 to 0.01%. Teriparatide has been approved for the treatment of patients with osteoporosis at high risk of fracture, including postmenopausal women, men with primary or secondary hypogonadism, and men and women with glycocorticoid-induced osteoporosis. Unlike bisphosphonates, teriparatide preferentially stimulates osteoblasts to produce new bone tissue causing an increase in bone mass and strength.

Authors used for MRONJ, the treatment with teriparatide associated with conventional treatment in female patients with MRONJ led to partial remission or complete remission in 83.3% of patients in the daily group and 50% of patients in the weekly group. Five of these patients were treated with glycocorticoids and did not undergo invasive surgery other than sequestrectomy. All patients improved significantly and when compared both groups did not present significant differences in bone metabolism, bone formation percentage or bone renewal markers. However, the clinical efficacy of weekly teriparatide injections has not been confirmed. In this study, MRONJ stages improved significantly before and after treatment with conventional treatment-associated teriparatide. It was found that there was a significant increase in the daily group of bone remodeling markers, notably with regard to P1NP and osteocalcin which increased in the first 3 months and decreased at 6 months. All other bone remodeling markers did not undergo significant changes after comparison of both groups. Six months after initiation of treatment the clinical results of the weekly group were similar to the daily group.

The present study presents several limitations taking into account the size of the sample as it may be concerned to detect significant differences between the daily and weekly groups. In addition, the study was only done over six months, which results in few results, as different durations of treatment with teriparatide leads to different results.

2.1.8 Mohamed El-Rabbany *et al.* (2017)

This systematic review article, the authors systematically evaluated the effectiveness of various treatment modalities used in MRONJ, given that evidence is still scarce. The authors conducted a comprehensive search in MedLine, Embase, Cochrane and Scopus. They considered 13 studies which included randomized controlled trials, non-randomized controlled trials and cohort studies.

Treatment is mainly symptomatic and is divided into surgical and non-surgical treatment. Non-surgical therapies include: local and/or systemic antibiotic therapy, cessation of anti-resorptive or anti-angiogenic therapy, hyperbaric oxygen therapy, low intensity laser therapy, ozone therapy, teriparatide, pentoxifylline and tocopherol. In particular, teriparatide was compared with plasma rich in growth factors. Surgical treatment can be classified into conservative and aggressive. Surgical therapy when compared to non-surgical therapy may result in higher rates of resolution of MRONJ. Although they also carry higher risks. Further studies should be done to understand whether conservative surgery is more or less beneficial compared to aggressive surgery. Local antibiotic therapy with or without systemic antibiotic therapy associated with surgical treatment was found to have greater advantages in complete resolution of the disease. According to the authors, hyperbaric oxygen therapy does not treat but supplements, as it is associated with increasing rates of improvement in the treatment group. However, more studies will be needed before conclusive statements can be made about many of the treatment strategies for MRONJ. The effectiveness of other therapies is still poorly understood.

II. DISCUSSION

The MRONJ has great repercussions both on the quality of life of the patient and on health resources, as mentioned above. Patients with MRONJ usually have signs and symptoms that include pain, swelling, exposed bone sequestration, fistulas, erythematous or ulcerated soft tissue, and pathological fractures. This situation mostly affects the mandibular bone, the most common cause being the trauma associated with the decreased ability to heal. The current treatment is divided into conventional or surgical. Conventional treatment includes: local or systemic antibiotherapy, cessation of anti-resorptive or angiogenic therapy, hyperbaric oxygen therapy, low-intensity laserterapy, teriparatide, ozonotherapy, pentoxylin and tocopherol (vitamin E).

In this dissertation different types of articles were used since the efficacy of teriparatide in the treatment of MRONJ is something that has been studied in recent years but does not yet have sufficient clinical trials. The purpose of this dissertation is to provide information that can improve the understanding of the effects of teriparatide.

The Sim *et al* study was the first and only randomized placebo-controlled study to demonstrate the efficacy of MRONJ therapy and to support the role of teriparatide in the treatment of established MRONJ. According to Sim *et al,* teriparatide improves the resolution rate of MRONJ lesions and represents an effective and safe treatment. Teriparatide was associated with a higher lesion resolution rate, with 45.5% of lesions resolved within 52 weeks compared to 33.3% of lesions in the placebo group. At week 52 there was a reduction in bone defects resulting from the increase in bone volume. As for side effects, these do not vary significantly between groups. The most common were nausea, anorexia and musculoskeletal pain. Teriparatide use is associated with a 30% increase in CTX at week 8. The only significant predictor of MRONJ resolution was the low gingival index, which represents an indicator of good oral hygiene. At the time of the existence of other comorbidities, the resolution of MRONJ lesions was less prone, however, this characteristic was not statistically significant. Also, Dos Santos Ferreira *et al*, found that the concomitant use of glycocorticoids and the presence of Diabetes

Mellitus do not directly influence the lesion resolution rate. Therefore, statistically, the existence of comorbidities does not affect their resolution.

Once again, there was agreement between Sim *et al.* and Dos Santos Ferreira *et al.* the patients who were treated with teriparatide associated with other therapeutic modalities were 1,210 times more likely to present total resolution of osteonecrosis. Since the treatment commonly used involves the combination of topical and oral antibiotics, cheeks with antiseptic substances and surgical treatment, also mentioned in the identified articles. It was found that the probability of total lesions resolution depends directly on the MRONJ stage. That is, patients in stage 1 of MRONJ are 1,185 more likely to achieve total MRONJ resolution when compared to patients with stage 3 of MRONJ.

According to Dos Santos Ferreira *et al*, the existence of other comorbidities does not directly affect the total resolution of lesions when using teriparatide subcutaneously. This does not mean that there are no comorbidities that directly affect the resolution of the same, this evidence may, however, be true, should be taken into account with some care, being to highlight some of the most common comorbidities: hypertension, rheumatoid arthritis, smoking habit, alcohol consumption, hypercholesteremia, cardiovascular disease, gastrointestinal disease and renal failure.

As mentioned above, AAOMS argues that the treatment of MRONJ should always be conservative and therefore surgical procedures should be avoided. However, surgical treatment is more effective than non-surgical treatment. Having said that, and in order to avoid surgical intervention, Goker *et al*. it also shows the importance of associating antibiotic therapy with teriparatide. Only in this way will the results be more effective. Systemic use of teriparatide and antibiotics has been reported as an effective way to treat necrotic lesions since surgical interventions may not be sufficient to achieve a long-term closure of the wound. Having said that, Dos Santos Ferreira *et al.* may also conclude that the combination of teriparatide with other therapeutic agents is beneficial and has more promising effects with regard to the treatment of MRONJ compared to the use of teriparatide alone.

According to Goker *et al*. the success of the therapy is due to increased bone density and healing of soft tissues in different surgical procedures. On the other hand, Goker *et al.* concluded that all treatments that include more beneficial ssurgical procedures take into account that they improve the resolution/healing of bone defects associated with the pathology. It was realized that any surgical procedure could be done at any stage of the MRONJ preventing normal progression of the same. in any case this decision will always pass through the prescriber.

According to M. Anabtawi *et al.,* there was a clinical improvement in 32 patients (35%), a complete resolution in 50 patients (55%), no improvement in 2 patients (2%), stabilized disease in 6 patients (7%) and worsening of the clinical situation in one patient (1%). Clinical results included improvement of pain, absence of purulent content, i.e. infection, better healing of fistulae and reduction of bone exposure area. Like all the other authors mentioned above, they also concluded that the best therapeutic option would be the combination of teriparatide with topical and/or systemic antibiotherapy, not least because the efficacy of antibiotherapy is dependent on the antibiotic's penetration capacity at the site of infection and blood flow.

Whether M. Anabtawi *et al.* as Dos Santos Ferreira *et al.* agreed that with the increasing aging of the population, patients are more likely to exhibit multiple comorbidities and therefore be polymedicated. This, in turn, can complicate the treatment of MRONJ and reduce therapeutic options by making surgical procedures inappropriate. Also M. Anabtawi *et al.* highlighted the concomitant use of teriparatide and other therapeutic agents/procedures. As in all previously reported studies, it does not present sufficient evidence to determine the efficacy of teriparatide in MRONJ. Since there is a high risk of bias, this in turn makes it difficult to determine the efficacy of teriparatide and its effects in the medium and long term.

According to M. Mohamed *et al.* the potential of teriparatide use, again associated with other therapeutic modalities, could be identified. However, there was a significant improvement in symptoms in the specific case of study. Teriparatide increased T-cell production, causing it to also increase the production of RANKL osteoblasts, which in

turn leads to an increase in osteogenesis and increased recruitment of osteoclasts. These are essential in the healing process and function as a prerequisite for the anabolic effect of teriparatide on osteoblasts. After 2 months, there was a full coverage of the soft tissues of the intra-oral lesion, the fistula was completely coated by the healthy oral mucosa and did not need further debridement. In relation to marker levels, P1NP and CTX have not changed. Having said that, there was the possibility of undergoing the surgical closure of the fistula. Finally, the woman succeeded in the therapy which caused an increase in appetite and gradual weight gain. M. Mohamed *et al.* realized that teriparatide induces an essential anabolic window to bone formation and positive bone balance. This effect was also described by Sim *et al.* and is at the basis of the teriparatide mechanism of action.

All authors agreed that wherever possible it should be opted for non-surgical treatment, considering that it is less invasive. In any case, it should be stressed again that surgical treatment is more efficient. They also agreed that treatment whether invasive or conservative should be started as early as possible at the time of diagnosis. Treatment is always symptomatic and varies from patient to patient. The decision will always be made by the prescribing clinician.

Based on what is mentioned by Mohamed El-Rabbany *et al*. there are therapeutic modalities that should be adjusted to the diagnosis. Mohamed El-Rabbany *et al.* refers to different therapeutic modalities and allows the combination of different modalities, again included teriparatide. Mohamed El-Rabbany *et al*. makes it clear that local antibiotherapy with or without associated systemic antibiotherapy has greater advantages with respect to complete resolution of MRONJ. In relation to teriparatide, it does not show much progress, but it bets on new trials so that new scientific evidence of high quality can be obtained. Having said that, there is another point of agreement between the authors. However, further studies will be needed in order to obtain conclusive statements on many of MRONJ's treatment strategies.

According to Natalie H Beth-Tasdogan. *et al.* teriparatide may have been beneficial in restoring bone, again, as mentioned by M. Mohamed *et al.* by activation of osteoblasts leading to increased bone density. In any case, there is no high-quality scientific evidence.

Both studies (20 micrograms/day or 56 micrograms/week) showed a low or very low degree of evidence quality. This means that confidence in the effect estimate is limited and the true effect may be substantially different or that confidence is reduced and the actual effect is likely to be substantially different from the estimate, respectively.

According to Natalie H Beth-Tasdogan. *et al*. teriparatide is approved for the treatment of osteoporosis but is often used off label in fracture healing and dental stability. Teriparatide stimulates osteoblasts to increase bone density when used intermittently. The available evidence is insufficient to claim or refute a benefit of any of the interventions studied for the treatment of MRONJ. However the bone can be restored by teriparatide, by stimulation of osteoblasts in the increase of bone density.

Besides the other authors, also Natalie H Beth-Tasdogan. *et al*. distinguishes treatment in non-surgical treatment and surgical treatment. The bone can be restored by the use of teriparatide. The available evidence remains insufficient to claim or refute a benefit of any of the interventions studied for the treatment of MRONJ. However the bone can be restored by teriparatide, by stimulation of osteoblasts in the increase in bone density, as already mentioned by other authors.

In agreement to Y. Ohbayashi *et al. ,* Natalie H Beth-Tasdogan. *et al*. also agrees that teriparatide as a drug with anabolic action, has shown a beneficial effect in the prevention of fractures by vertebral and non-vertebral fragility. Its use in combination with other MRONJ therapies has been considered to be of great use in uncontrolled trials and all authors seem to agree with this statement. As mentioned above, daily or weekly injections may be made. The quantity and quality of bone metabolism markers differ according to the frequency of administration. With daily injections, serum concentrations of the P1NP marker increased rapidly and remained significantly high throughout the treatment period. Y. Ohbayashi *et al* confirmed a significant improvement in MRONJ stages in all patients, however, in the daily group the improvements were more evident when compared to the weekly group. The anabolic effect of PTH is due to its ability to promote bone anabolism by stimulating aerobic glucose via insulin-like growth factor signaling. In turn, PTH stimulates osteoblastic activity, osteoblastic differentiation and bone coating

cells, as well as mitigating osteoblastic apoptosis. According to Y. Ohbayashi *et al* treatment with teriparatide associated with conventional treatment in female patients with MRONJ led to partial remission or complete remission in 83.3% of patients in the daily group and 50% of patients in the weekly group.

According to Natalie H Beth-Tasdogan. *et al*.and Y. Ohbayashi *et al.,* ensuring that daily use of teriparatide was beneficial in relation to weekly use. In addition, there was a significant improvement in MRONJ stages before and after treatment with teriparatide associated with conventional treatment.

All authors Known side effects include nausea and vomiting, dizziness, hypercalcemia and hypersensitivity reactions. But the major problem with using teriparatide for more than two years, according to the authors, is the theoretical risk of osteosarcoma. In addition, there are long and medium-term effects that have not been identified due to a lack of studies. So, the safety of using teriparatide is based on its short-term use.

Therefore, and taking into account the analyzed papaers, teriparatide is an effective therapeutic option for the treatment of MRONJ. Although, like any other study mentioned above, it has limitations taking into account the size of the sample as it may cause the detection of significant differences between the daily and weekly groups. Another problem is, basically, the short duration of treatments, longer treatments lead to results with greater confidence.

III.CONCLUSION

MRONJ is rare but truty debilitating condition and its physiopathological mechanism is not fully understood, making it a challange to treat.

Treatment involves elimination of pain and infection control, with the aim of stopping disease progression. It may or may not be conservative. However, most authors consider surgical treatment invasive but more effective in cases of extended disease. MRONJ can be treated through different therapeutic strategies and subcutaneous teriparatide has been suggested and studied in the treatment of MRONJ over the years.

Teriparatide is a recombinant fragment of PTH and has shown therapeutic benefit when associated with other therapeutic modalities. Its concomitant use with local and systemic antibiotherapy should be highlighted. This can be used daily or weekly at different doses. This drug is approved for the treatment of osteoporosis. With daily administration there is a more significant increase in P1NP and consecutively an increase in bone mass, which by activation of osteoblasts leads to an improvement in bone healing.

However, the overall quality of evidence is low with a potential risk of bias, making it difficult to determine the efficacy of teriparatide in the treatment of MRONJ. The great limitation was always the small number of the sample and the limited duration of treatment. Therefore, further clinical trials will be needed in the future, to assess efficacy and safety in order to be considered for treating MRONJ.

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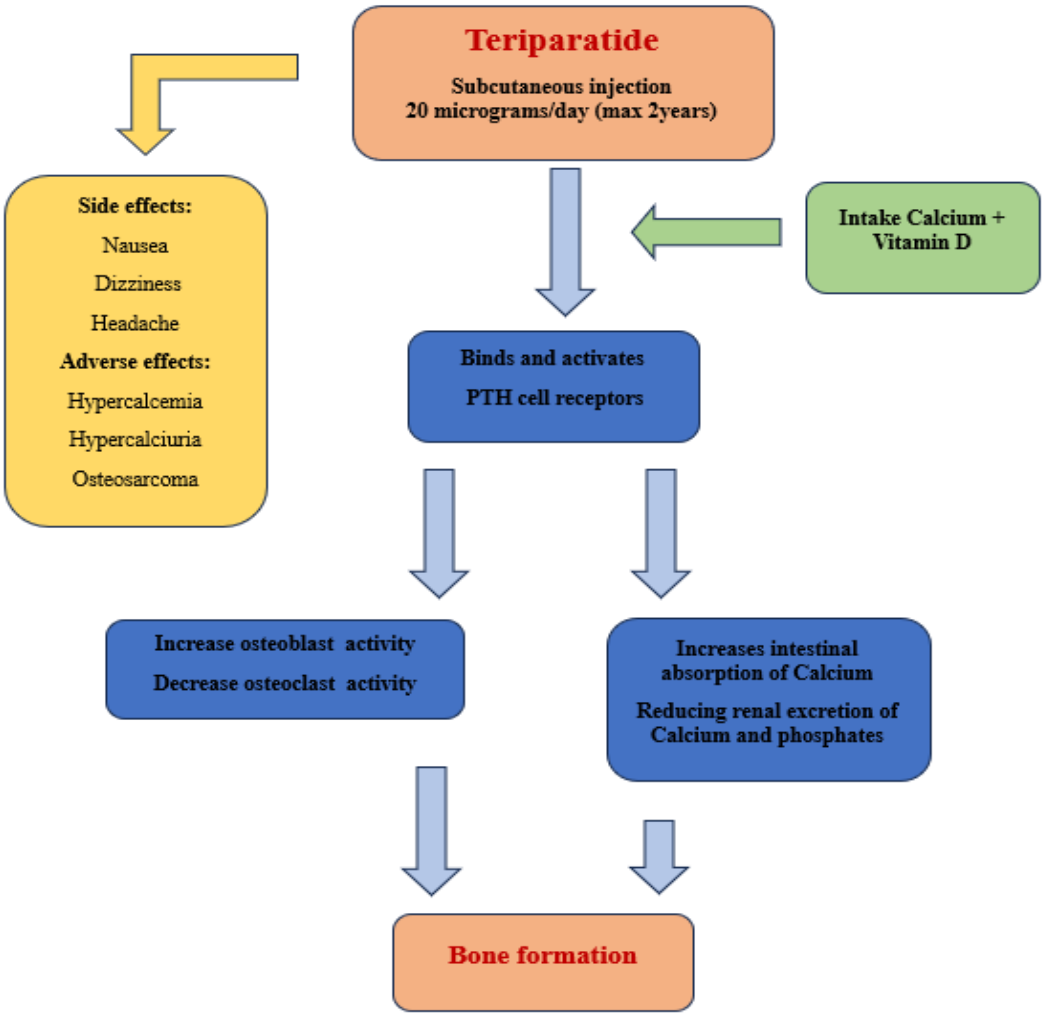
V.ATTACHMENTS

Figure 1: Resumed teriparatide mechanism of action leading to bone formation



Legend: PTH: Parathyroid hormone

Figure 2: PRISMA Diagram

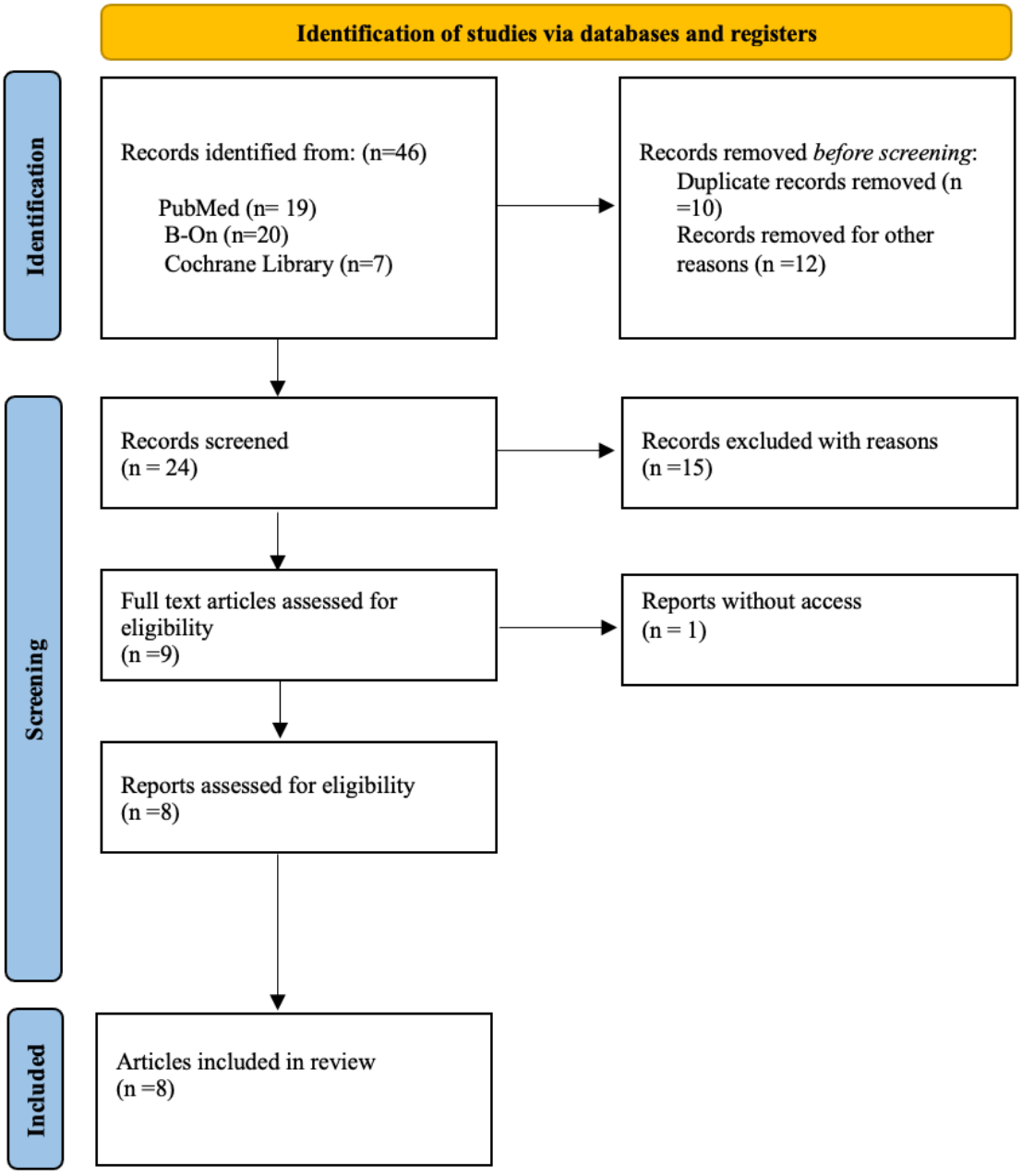


Table 3: Resumed characteristics of each study

AUTHORS	Nº OF PARTICIPANTS	TYPE OF STUDY	MEDICATION CAUSED MRONJ	TREATMENT	OUTCOMES
M. Mohamed. *et al*. (2022)	1	Case Report	Alendronato 70 mg	14 months, teriparatide 20 μg/day subcutaneously for a period of 2 years	• Full soft tissue coverage of the intraoral lesion • Fistula covered by healthy oral mucosa and did not need further debridement; • Increased appetite • Gradual weight gain.
Natalie H Beth-Tasdogan. *Et al*. (2022)	1668	Systemic Review	N/A	All but 2 studies included participants treated with bisphosphonates. Two of the trials were based on pharmacological treatment with teriparatide, one of which used 20 micrograms/day and included 33 participants, while the second trial used a dosage of 56 micrograms/week and included 12 participants.	• Teriparatide stimulates osteoblasts • This stimulation leads to an increase in bone density.

AUTHORS	Nº OF PARTICIPANTS	TYPE OF STUDY	MEDICATION CAUSED MRONJ	TREATMENT	OUTCOMES
Dos Santos Ferreira *et al.* (2021)	For final analysis 111 individuals.	Systematic Review	N/A	20 μg/day teriparatide subcutaneously	• 59.5% of patients had a complete resolution of established MRONJ lesions
F. Goker *et al.* (2021)	6182 Participants	Systematic Review	N/A	• Different therapeutic agents ranging from platelet concentrates, teriparatide, hyperbaric oxygen, lasetherapy, ozone applications and surgical procedures.	• Teriparatide combined with oral antibiotics such as doxycycline after surgery. • Concomitant and systemic therapy improved necrotic lesions. • Surgical interventions may not be sufficient for long-term wound closure.

AUTHORS	Nº OF PARTICIPANTS	TYPE OF STUDY	MEDICATION CAUSED MRONJ	TREATMENT	OUTCOMES
Sim *et al.* (2020)	34	Double-blind, randomized, controlled trial	Previously treated with bisphosphonates or denosumab.	• 20 μg/day teriparatide subcutaneously vs placebo (salt injection)	• Increased osteoblastic activity at the lesion site • Reduction in bone defect volume • Possible improvement in mucosa coverage and resolution. • Teriparatide associated with a clinically significant increase in the marker P1NP in 85.7% of participants. • Fluor PET-CT radiologic examination also demonstrated increased uptake within the mandible, between the flurette and hydroxyapatite.
M. Anabtawi *et al.* (2020)	94	Systemic Review	Previously treated with bisphosphonates	• Doses and frequencies of treatment with teriparatide varied, (some teriparatide was taken daily and in others it was taken at weekly or monthly intervals).	• Clinical improvement in 32 patients (35%) • Complete resolution in 50 patients (55%) • No improvement in 2 patients (2%) • Stabilized disease in 6 patients (7%) Worsening of the clinical situation in 1 patient (1%).

AUTHORS	Nº OF PARTICIPANTS	TYPE OF STUDY	MEDICATION CAUSED MRONJ	TREATMENT	OUTCOMES
Y. Ohbayashi e*t al*. (2020)	13	Systematic Review	Previously treated with bisphosphonates	• Teriparatide 56 micrograms/week VS Teriparatide 20 micrograms/day, for 6 months.	• Treatment with teriparatide resulted in partial remission or complete remission in five of the patients (daily group) and three of the patients (weekly group). • There was a significant improvement in MRONJ stages in all patients. • Daily group showed more improvements
Mohamed El-Rabbany *et al.* (2017)	13 studies which included randomized controlled trials, non-randomized controlled trials and cohort studies.	Systematic review	Previously treated with bisphosphonates, denosumab and antiangiogenic agents	• Various therapies have been studied	• There are many options for MRONJ treatment but is important more studies for more available conclusions.

Legend: Mg: Milligrams; **µg/day :** micrograms per day; **N/A:** Not Available; **MRONJ:** Medication Related Osteonecrosis of the Ja

Table 4: Demographic characterization of included studies

AUTHORS	STUDY TYPE	NUMBER OF PARTICIPANTS	AGE
M. Mohamed. *et al*. (2022)	Case Report	1	81
Beth-Tasdogan. *et al*. (2022)	Systemic Review	1668	N/A
L Dos Santos Ferreira *et al.* (2021)	Systematic Review	111 (26 Studies)	76 mean
Goker *et al.* (2021)	Systematic Review	118 participants (7 studies) Study 1: 583 Study 2: 4282 Study 3:108 Study 4: 72 Study 5: 632 Study 6: 57 Study 7: 448	24-88
M. Anabtawi *et al.* (2021)	Systematic Review	94	76 mean
Sim *et al.* (2020)	Double-blind, randomized, controlled trial	34	18 years or >18 years
Y. Ohbayashi *et al*. (2020)	Systematic Review	13	50 years or > 50 years
Mohamed El-Rabbany *et al.* (2017)	Systematic Review	13 studies	18 years or >18 years (62-73)

Legend: N/A: Not Available;

Table 5: Medication related to the case of osteonecrosis of the jaw in each study.

AUTHORS	DOSAGE / ADMINISTRATION ROUTE	USED FOR TREATMENT OF	GROUP OF DRUG
M. Mohamed. *et al*. (2022)	70mg/ Weekly N/A	Osteoporosis	**BIPHOSPHONATES**
Beth-Tasdogan. *et al*. (2022)	IV administration	Osteoporosis (in postmenopausal women or men with high fracture risk)	**BIPHOSPHONATES**
L Dos Santos Ferreira *et al.* (2021)	IV administration Oral administration	Osteoporosis Malignant Neoplasm Osteopenia	**BIPHOSPHONATES** **DENOSUMAB**
Goker *et al.* (2021)	N/A	N/A	**BIPHOSPHONATES** **DENOSUMAB** **ANTIANGIOGENIC AGENTS**
M. Anabtawi *et al.* (2021)	IV administration Oral administration	Osteoporosis	**BIPHOSPHONATES**

AUTHORS	DOSAGE / ADMINISTRATION ROUTE	USED FOR TREATMENT OF	GROUP OF DRUG
Sim *et al.* (2020)	N/A	Malignant Bone disease Myeloma Breast Cancer Prostate Cancer Osteoporosis	**BIPHOSPHONATES** **DENOSUMAB**
Y. Ohbayashi *et al*. (2020)	N/A	Osteoporosis	**BIPHOSPHONATES**
Mohamed El-Rabbany *et al.* (2017)	N/A	N/A	**BIPHOSPHONATES** **DENOSUMAB** **ANTIANGIOGENIC AGENTS**

Legend: IV: Intravenous; **MRONJ:** Medication Related Osteonecrosis of the Jaw; **Mg:** Milligrams; **N/A:** Not Available