MedNEXT
Journal of Medical an Health Sciences

REVIEW ARTICLE

DOI: 10.54448/mdnt23S201

Relationship of the occurrence and main approaches to osteonecrosis of the jaw with the use of bisphosphonates: a concise systematic review

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DOI: https://doi.org/10.54448/mdnt23S201
Received: 12-19-2022; Revised: 03-28-2023; Accepted: 04-01-2023; Published: 04-04-2023; MedNEXT-id: e23S201

Abstract

Introduction: In the setting of bucomaxillo facial surgery, bone tissue is a specialized connective tissue made up of cells and a mineralized extracellular matrix. To reduce the excessive resorption observed in these pathologies, it has been studied more rigorously in pre-clinical and clinical studies to improve anti-resorptive drugs that allow for treating or preventing pathologies of bone metabolism, such as bisphosphonates (BP) and denosumab (DN) as well as some angiogenesis inhibitors, can induce osteonecrosis of the mandible (ONJ). **Objective:** Was to carry out a concise systematic review of the relation of occurrence and main approaches to osteonecrosis of the mandible and/or maxilla with the use of bisphosphonates. **Methods:** The present study was followed by a systematic review model (PRISMA). The search strategy was performed in the PubMed, Cochrane Library, Web of Science and Scopus, and Google Scholar databases. The Cochrane Instrument was used to assess the risk of bias from the included studies. The present study was carried out from December 2022 to January of 2023. **Results and Conclusion:** A total of 108 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed based on the GRADE Instrument and Risk of Bias. A total of 55 articles were fully evaluated and 22 were included and discussed in this study. The American Association of Oral and Maxillofacial Surgeons proposed for the first time its nomenclature "Bisphosphonates Related Osteonecrosis of the Jaws". ONJ is the term used to describe bone cell death when the osteocyte becomes necrotic. Osteonecrosis of the jaws can be considered a severe adverse effect of BP therapy. Osteonecrosis of the jaws induced by the use of antiresorptive drugs commonly occurs in the oral cavity, mainly because the bone tissue is covered and protected only by a thin layer of periosteum and epithelium. Bisphosphonates inhibit RANKL expression, as well as stimulate OPG production by bone marrow cells and osteoblasts, inhibiting the RANK-RANKL interaction. These synergistic actions lead to a decrease in the recruitment of osteoclasts and, consequently, to a reduction in bone resorption.

Keywords: Bisphosphonates. Osteonecrosis. Bone regeneration. Oral and maxillofacial surgery.

Introduction

In the setting of bucomaxillo facial surgery, bone tissue is a specialized connective tissue made up of cells and a mineralized extracellular matrix [1,2]. Under conditions of homeostasis, bone tissue cells, that is, osteoblasts, bone lining cells, osteocytes, and osteoclasts, act in the matrix remodeling process. The balance of bone matrix remodeling and, consequently, bone tissue homeostasis are compromised, for example, in the face of postmenopausal hormonal changes and cases of bone metastases [2].

To reduce the excessive resorption observed in these pathologies, it has been studied more rigorously in pre-clinical and clinical studies to improve anti-resorptive drugs that allow for treating or preventing pathologies of bone metabolism [3-6]. In this sense, anti-resorptive agents, such as bisphosphonates (BP) and denosumab (DN), as well as some angiogenesis inhibitors, can induce osteonecrosis of the mandible

(ONJ). In women, the incidence of ONJ is around 15% at age 50, 30% at age 70, and 40% at age 18-80. Current literature indicates that a complex combination of factors is required to induce ONJ. Several hypotheses about the pathophysiology of ONJ have been previously reported [6].

Thus, according to the American Association of Oral and Maxillofacial Surgeons (AAOMS), the criteria for diagnosing ONJ are the following the presence of exposed bone or fistula for at least 8 weeks, in a patient with a previous or current history of the use of antiresorptive drugs, who did not undergo radiotherapy in the cervicofacial region [7]. In addition to BP and ND, antiangiogenic drugs such as Sunitinib, Sorafenib, and Bevacizumab have been associated with the occurrence of ONJ [7,8].

Bone tissue has significant healing potential, which involves significant interaction between bone and immune system cells [9]. Although fracture healing represents a useful model to investigate endochondral bone healing, intramembranous bone healing models still need to be developed and characterized [10]. The development of provisional immature granulation tissue (7 days) is evident, characterized by marked cell proliferation, angiogenesis, and infiltration of inflammatory cells, associated with growth factors (BMP-2-4-7, TGFβ1, VEGFa), cytokines (TNFα, IL-10), chemokines and receptors (CXCL12, CCL25, CCR5, CXCR4), matrix (Col1a1-2, ITGA4, VTN, MMP1a) and expression of MSC markers (CD105, CD106, OCT4, NANOG, CD34, CD146) [11].

In this sense, the granulation tissue is sequentially replaced by more mature connective tissue (14 days), characterized by the reduction of the inflammatory infiltrate along with the increase in bone formation, marked expression of matrix remodeling enzymes (MMP-2-9), bone formation/maturation, markers and chemokines and receptors associated with healing (CCL2, CCL17, CCR2) [11]. The healing process of the extraction socket is considered complete (21 days) when the dental cavity is filled with trabecular bone with well-defined medullary canals; being the expression of mature bone markers prevalent in this period [12].

In this context, BP such as zoledronic, alendronic, and risedronate acids are a class of drugs used clinically to prevent bone density loss and osteoporosis [13]. Thus, new BP was synthesized for the target of human farnesyl pyrophosphate synthase and human geranylgeranyl pyrophosphate synthase, key enzymes of the mevalonate pathway, and capable of antiproliferative action in several cell lines (PC3, MG63, MC3T3, RAW 264.7, J774A.1, bone marrow cells) involved in bone homeostasis, bone formation, and death. Among sixteen compounds, [1-hydroxy-2-(pyrimidin-2-ylamino)ethane-1,1diyl]bis(phosphoric cid) was effective in reducing PC3 and RAW 264.7 cells. Furthermore, they reduced the number of differentiated osteoclasts similarly to zoledronic acid in the osteoclastogenesis assay [1,13].

In general, the mechanism of action of clodronate and etidronate and alendronate, pamidronate, zoledronate, risedronate, and ibandronate involves the replacement of the oxygen atom by a backbone carbon atom makes the molecule unable to decompose by hydrolysis and binds it tightly to the circulating calcium or calcium from hydroxyapatite crystals in bone [1-3]. Once BP is internalized by osteoclasts, the farnesyl synthetase enzyme of the mevalonate pathway is inhibited. With the interruption or loss of this intracellular metabolic pathway, osteoclastic becomes less efficient in its resorptive activity and, then, undergoes programmed cell death by apoptosis [13].

Thus, antiresorptive agents and angiogenesis inhibitors can induce osteonecrosis of the jaw. However, the exact mechanisms of ONJ are unclear, and definitive treatment strategies have yet to be developed [14]. Only due to this, population aging requires antiresorptive agents and angiogenesis inhibitors, which are increasing worldwide. In this sense, the age and duration of administration of anti-resorptive agents are risks for the development of ONJ [14].

Antiresorptive therapy significantly reduces fracture risk in patients with benign bone disease and skeletal-related events in patients with bone metastases. ONJ is a rare but serious condition that manifests as necrotic bone damage or lesions of the jaws. ONJ has been associated with the use of potent antiresorptive agents [4].

Therefore, the present study aimed to carry out a concise systematic review regarding the relationship between the occurrence and main approaches to osteonecrosis of the mandible and/or maxilla with the use of bisphosphonates.

Methods

Study Design

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

Data Sources

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

Descriptors (MeSH Terms) And Search Strategy

The main descriptors (MeSH Terms) used were *Bisphosphonates. Osteonecrosis. Bone regeneration. Oral and maxillofacial surgery*. The rules of the word PICOS (Patient; Intervention; Control; Outcomes; Study Design) were followed.

Selection Process, Risk of Bias and Quality of Studies

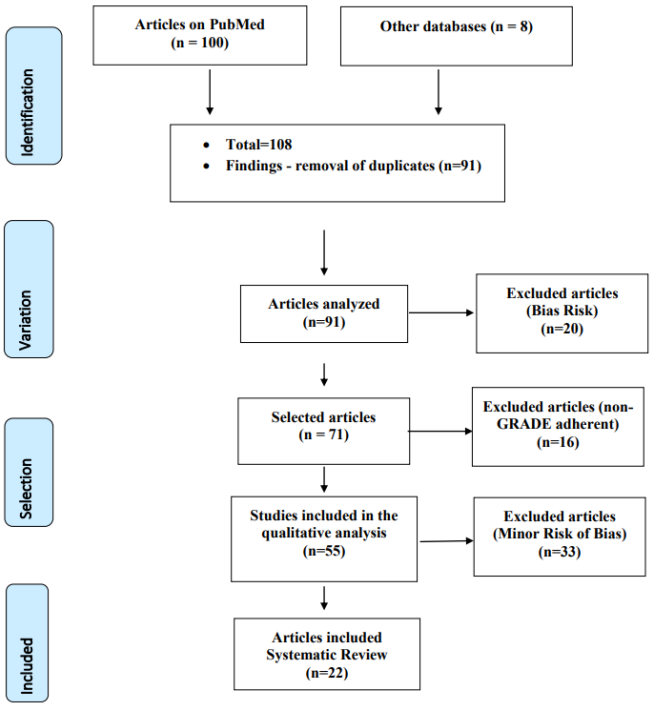
The quality of the studies was based on the GRADE instrument, with randomized controlled clinical studies, prospective controlled clinical studies, and studies of systematic review and meta-analysis listed as the studies with the greatest scientific evidence, and the risk of bias was analyzed according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

Results and Discussion

Summary of Findings

A total of 108 articles were found. Initially, duplicate articles were excluded. After this process, the abstracts were evaluated and a new exclusion was performed based on the GRADE Instrument and Risk of Bias. A total of 55 articles were fully evaluated and 22 were included and discussed in this study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies that were excluded with a high risk of bias (studies with small sample size). Also, 16 studies were excluded because they did not meet the GRADE (**Figure 1**).

Figure 1. Flowchart showing the article selection process.



Major Findings On The Osteonecrosis Of The Jaws

According to Nixon, in 1983, bone necrosis was first described by Professor James Russel, in 1974 [15]. Osteonecrosis of the jaw (ONJ) is defined as exposed bone that fails to heal within 3 months, in the absence of residual or recurrent tumor. The possibility of ONJ was first proposed at the beginning of the 20th century, being considered synonymous with avascular necrosis or aseptic necrosis. Therefore, it is considered bone necrosis caused by obstruction of the blood supply [16].

Initial reports of osteonecrosis of the jaws after administration of bisphosphonates designated this condition as "avascular necrosis of the jaw" or "avascular bone". This fact is due to the similarities of the clinical manifestation of ONJ, caused by radiotherapy and exposure to BP, including the presence of exposed bone with loss of the underlying mucosa. Consequently, the definition of ONJ after radiation therapy (osteoradionecrosis), had been applied similarly to ONJ after the administration of BP [17,18].

In this context, no potential adverse effect of antiresorptive drugs has caused more scientific attention, from professionals working in this field and the like, than osteonecrosis of the jaws, which ranges in severity from small, painless areas of exposed bone, to bone exposure associated with severe pain, sequestration, infection, fistula and pathological fracture of the mandible [16].

The first report of osteonecrosis of the jaws due to the use of bisphosphonates was made by Marx et al in 2003. Already in 2007, a position paper by the American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed for the first time its nomenclature "Bisphosphonates Related Osteonecrosis of the Jaws" (BRONJ). ONJ is the term used to describe bone cell death when the osteocyte becomes necrotic. Necrosis also destroys vascular endothelial cells within the bone tissue, impairing blood flow within it [19,20].

Also, osteonecrosis of the jaws is the term suggested for intra-oral lesions with bone exposure, which simulate dental abscesses or osteomyelitis, in patients submitted to therapy with bisphosphonates and who have not been submitted to radiotherapy in the head and neck region. Osteonecrosis of the jaws can be considered a severe adverse effect of BP therapy [17].

ONJ has also been defined using a variety of terms, including: "bisphosphonateinduced osteonecrosis of the jaw (BIONJ)", "bisphosphonate-associated osteonecrosis of the jaw (BAONJ)", "bisphosphonate-associated osteomyelitis of the jaw (BAOMJ)" and "bisphosphonate-related osteomyelitis of the jaw (BROMJ)" [1,16]. The cited terms were recently denominated by the term "antiresorptive drug-related

osteonecrosis of the jaw (ARONJ)" and currently consolidated as "Medication-related osteonecrosis of the Jaws (MRONJ)" due to clinical reports of osteonecrosis of the jaw related to anti-inflammatory drugs resorptive [2,3].

The main clinical aspects of osteonecrosis of the jaws are areas with bone exposure in the oral cavity, dental mobility, ulcerations and fistulas in the mucosa, exposure of devitalized bone, with a yellowish color with tissue inflammation around the bone exposure, presence of painful and odorous symptoms characteristic [21].

Patients who develop necrosis are aged between 35 and 95 years, with a higher prevalence between 65 and 68 years. Among the risk factors for developing the disease, the dose and frequency administered, the potency of the drug, the route of administration, the duration of treatment, and the half-life of the drug in the bone tissue [1-3].

To confirm the diagnostic hypothesis, imaging tests should be requested, such as panoramic radiography and facial computed tomography. These exams demonstrate the presence of bone sequestration with osteolytic areas associated with surrounding osteoblastic areas and an appearance of bone tissue disorganization, destruction of bone cortices, periosteal reactions, and pathological fractures [4,5].

Besides, osteonecrosis of the jaws induced by the use of antiresorptive drugs commonly occurs in the oral cavity, mainly because the bone tissue is covered and protected only by a thin layer of periosteum and epithelium. Constant stress leads to trauma to the mucosa with bone exposure, which, together with the presence of a large number of bacteria in the oral cavity, makes it prone to infections [5].

The Maxilla and Mandible are the only bones in the human body in contact with the external environment and are always subject to microtrauma due to the presence of teeth, periodontium, and masticatory forces. Furthermore, the alveolar bone has a turnover ten times higher than the long bones [1]. The alveolar bone of the jaws is remodeled daily with a high rate of bone turnover, and the presence of teeth and gingiva provides an easy entrance for bacterial infection. Oral structures are subjected to a wide variety of injuries, which can be physiological, iatrogenic, or inflammatory [21].

Prolonged use of BP can suppress bone turnover with microcrack accumulation, resulting in decreased biomechanics and strength. Blood supply may play a role in MRONJ. With its reduction, it leads to a delay in wound healing due to the antiangiogenic effect [2,3,4,22]. Anti-resorptive drugs can hinder angiogenesis by inhibiting the formation of blood vessels, endothelial cells, fibroblast growth factor, and endothelium. In addition, there is a reduction in proliferation, an increase in apoptosis, and a decrease in capillary formation in endothelial cells, which can cause necrosis [22].

Trauma during dental surgery is a well-recognized predisposing factor for BRONJ, with 60% of cases occurring after oral surgery, including tooth extractions.

However, about 40% of BRONJ cases are not related to invasive dental procedures, probably associated with endodontic and periodontal infections or spontaneous necrosis [3,4].

According to the AAOMS as well as the American Dental Association (ADA) guidelines, tooth extractions in patients on BP should be minimally invasive, with limited manipulation of bones and soft tissues. The mucoperiosteal lining of the dental alveoli is also recommended [5].

The risk of developing BRONJ is also related to the type of bisphosphonate (nitrogenated or not), the form of use (oral 17% or intravenous 83%), and the duration of treatment. Aging can also be a risk factor, associated with an increase in inflammatory diseases, hormonal disorders, oxidative stress, decreased blood flow, and bone turnover [1,2].

In this scenario, the pathogenesis of the disease is certainly associated with many questions about the possible mechanisms underlying the pathophysiology. Five main mechanisms have been proposed, such as impaired remodeling, angiogenesis inhibition, local toxicity, immunomodulation, and local infections [6-8]. Most likely, a combination of these factors facilitates the development of BRONJ. However, the most mentioned hypothesis to explain this mechanism suggests that it is caused by the interruption of bone remodeling and turnover through the inhibition of osteoclasts [22].

There are two main theories about the pathophysiology of BRONJ, based on the action of osteoclasts. The first is "inside-out", in which there is inhibition of osteoclastic activity and marked suppression of bone turnover, together with the physiological propagation of microdamage causing local inflammation. This process leads to bone death within the mandible, with subsequent exposure. As such, bone exposure would be a late event [8,9].

The second "outside-in", which suggests an injury to the oral mucosa, facilitates the entry of bacteria and local infection, which, together with poor bone remodeling, leads to bone death. BRONJ can still result from the combination of these two mechanisms, in addition to hypervascularity which can also play an important role [9].

Bisphosphonates inhibit bone turnover and repair capacity after microaggressions, thus reducing the rate

of epithelial cell proliferation in vitro, exhibiting antiangiogenic properties, and decreasing the production of vascular endothelial growth factor (VEGF) [10,11]. These determine relevant effects on the quality and quantity of bone vascularization, possibly changing the response to trauma and infections [12].

The endothelium can be considered the largest mesocrine organ in the body, producing a wide range of substances of a hormonal nature, with vasoconstrictor and vasodilator functions, as well as important modulators of the coagulation cascade [21,22]. This forms the inner cell layer of blood vessels. It plays an important role in animal physiology, modulating various functions, such as inflammation, coagulation, and local blood flow control [15].

In addition to lining and delimitation functions, the endothelium denotes other relevant functions from a physiological point of view. It works as a semipermeable membrane, regulating the traffic of molecules, as well as presenting functions of synthesis and metabolism of several substances. Its action is mainly reflected in the control of blood flow, the regulation of peripheral vascular resistance, and the modulation of inflammatory and immune responses [1,2,16].

As examples of the biochemical activity of the endothelium, we can refer to the intervention in the metabolism of vasoactive substances, such as angiotensin I and angiotensin II, serotonin, noradrenaline, the inactivation of bradykinin, the formation of prostaglandins, the production of antigens and the intervention, at different levels, in the blood coagulation process, for example, through the production of thrombomodulin [16,17].

Other examples of substances produced by the endothelium can be mentioned prostacyclin and nitric oxide (NO) and several molecules that act by stimulating the formation of new blood vessels, as well as repairing damaged ones [18]. Bisphosphonates also inhibit the transformation of pre-osteoclasts into osteoclasts through bone marrow cells and indirectly via osteoblasts [4]. Normally, osteoblasts are responsible for the recruitment and activation of osteoclasts through the interaction of the "receptor activator of NFk B ligand" (RANKL), being on its surface, with the RANK receptor, always present in the hematopoietic cells precursors of osteoclasts [10,14,22].

RANKL factor receptor activator is a transmembrane and soluble protein produced by osteoblasts. This is located in the cell membrane of osteoclasts and preosteoclasts. To maintain this interaction, osteoblasts also secrete osteoprotegerin (OPG), a soluble receptor, which competes with RANKL for RANK to inhibit osteoclast recruitment and therefore control the osteoblast-osteoclast balance [3,7,19]. Bone resorption increases the results of the RANK / RANKL binding, which stimulates the formation, activity, and survival of osteoclasts [18,22].

Also, osteoprotegerin (OPG) is a naturally occurring soluble signal "Decoy Receptor" for RANKL and inhibits osteoclast activity by binding to RANKL, preventing its interaction with RANK. Both RANKL and OPG are produced by osteoblasts [20]. Therefore, bisphosphonates inhibit RANKL expression, as well as stimulate OPG production by bone marrow cells and osteoblasts, inhibiting the RANK-RANKL interaction. These synergistic actions lead to a decrease in the recruitment of osteoclasts and, consequently, to a reduction in bone resorption [5-7].

Conclusion

The American Association of Oral and Maxillofacial Surgeons proposed for the first time its nomenclature "Bisphosphonates Related Osteonecrosis of the Jaws". ONJ is the term used to describe bone cell death when the osteocyte becomes necrotic. Osteonecrosis of the jaws can be considered a severe adverse effect of BP therapy. Osteonecrosis of the jaws induced by the use of antiresorptive drugs commonly occurs in the oral cavity, mainly because the bone tissue is covered and protected only by a thin layer of periosteum and epithelium. Bisphosphonates inhibit RANKL expression, as well as stimulate OPG production by bone marrow cells and osteoblasts, inhibiting the RANKRANKL interaction. These synergistic actions lead to a decrease in the recruitment of osteoclasts and, consequently, to a reduction in bone resorption.

Acknowledgement
Not applicable.

Funding
Not applicable.

Ethical Approval
Not applicable.

Informed consent
Not applicable.

Data sharing statement
No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

Similarity check
It was applied by Ithenticate@.

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