VILNIUS UNIVERSITY
FACULTY OF MEDICINE

GESA CHRISTIN TSCHUCK
Odontology program student

Master's Thesis

Implication of Bisphosphonates in Dental Surgery

Scientific Supervisor: Dr. Asist. Alina Čeabatariūnien

Vilnius

2023

i. Abbreviations

ARD	Antiresorptive drug
BMU	Basic multicellular units
BP	Bisphosphonate
BPs	Bisphosphonates
CT	Computed tomography
HAP	Hydroxyapatite
IV	Intravenous
MRI	Magnetic resonance imaging
MRONJ	Medication-related osteonecrosis of the jaw
N-BPS	Nitrogenous bisphosphonates
NON-N-BPS	Non-nitrogenous bisphosphonates
OPG	Osteoprotegerin
PPi	Pyrophosphate

1. Summary

Bisphosphonates (BPs) have revolutionized the treatment of osteotropic diseases, but their use can lead to a rare but serious side effect termed medication-related osteonecrosis of the jaw (MRONJ). MRONJ can cause exposed bone lesions, resulting in pain, functional impairment, and reduced quality of life. This thesis advocates that interdisciplinary collaboration between healthcare professionals is crucial for effective prevention and management. MRONJ is likely to be underdiagnosed due to the absence of a universal disease code and various study objectives. Careful consideration of risk factors and detection of early radiographic signs of disease development are crucial for better treatment strategies and patient outcomes. Intravenous BPs carry a higher MRONJ risk than oral bisphosphonates. While the treatment effectiveness of drug holidays is not supported by research, antibiotic treatment is widely accepted at all stages of the disease. Conservative surgical treatment is an option for MRONJ at all stages, with early surgical intervention potentially leading to better outcomes. A systematic literature review was conducted to identify articles on bisphosphonates in dental surgery and medication-related osteonecrosis of the jaw, with a standardized data extraction form and thematic analysis of selected 57 out of 2773 initially screened articles based on their titles and abstracts. The aim of this thesis is to explore the intricacies of the implications of BPs in dental surgery, specifically the challenges associated with MRONJ and opportunities for optimizing treatment management. In conclusion, customizing treatment plans to suit the specific circumstances of each patient is essential for maximizing the effectiveness of treatment and reducing the likelihood of complications.

Keywords: Medication-related osteonecrosis of the jaw; Bisphosphonate-related osteonecrosis of the jaw; Bisphosphonates; Side effects; Risk factors; Diagnosis

2. Introduction

Bisphosphonates (BPs) have revolutionized the treatment of osteoporosis and cancer-related conditions, providing patients with effective relief from bone loss and related complications. Despite the generally favorable safety profile of BPs, their use may lead to the development of medication-related osteonecrosis of the jaw (MRONJ), a rare but serious adverse event which is yet to be fully understood in its complexities. MRONJ can present a significant challenge in dental surgery, causing excruciating pain, functional impairment, and a subsequent loss of quality of life for affected patients. However, it is generally regarded as a secondary risk compared to the therapeutic benefits of bisphosphonate therapy for osteotropic diseases.

The topic of MRONJ induced by BPs has become increasingly relevant in the last decade, as evidenced by the significant increase in related biomedical literature. This rise in articles suggests a growing concern in the medical community about this condition and emphasizes the need for continued research and awareness among healthcare professionals.

The aim of this thesis is to explore the intricacies of the implications of BPs in dental surgery, with a specific focus on the challenges associated with MRONJ and opportunities for optimizing treatment management. By doing so, this thesis will provide dental practitioners with valuable insights to better understand the disease, enhance the management of MRONJ, and improve the quality of life for patients undergoing BP treatment. To achieve these aims, this thesis is divided into two parts.

The first part of this thesis focuses on the characteristics of BPs and their use for the treatment of underlying diseases. Specifically, this paper investigates how BPs are used to manage diseases such as osteoporosis or cancer-related diseases and explore their pharmacological mechanisms. By doing so, a detailed understanding of the role BPs play in managing these diseases, and the mechanisms through which they achieve their therapeutic effects is provided. In the second part, the thesis' objectives include a detailed analysis of the side effects of BPs, specifically MRONJ, and their implications in dental surgery. By examining how BPs affect the jawbone and lead to MRONJ, the aim is to provide a better understanding of the disease including its pathophysiology, clinical and radiological appearances, and diagnostic techniques. Additionally, this paper investigates why MRONJ might be underdiagnosed and emphasizes the importance of knowing the risks of developing

this condition. The aim is to provide insights into optimizing patient outcomes for MRONJ by defining treatment goals and examining various management practices. An emphasis is given on the importance of taking into account individual patient factors to achieve optimal outcomes for MRONJ treatment and on the crucial role of interdisciplinary collaboration in ensuring safe and effective management. Specifically, this paper discusses the significance of closely monitoring patients at risk of MRONJ from the beginning of BP therapy and addressing the condition at different stages.

3. Material and Methods

3.1. Search Strategy and Study Selection

Between October 1, 2022, and May 24, 2023, a literature search was conducted on PubMed, which generated a total of 2773 references. In addition, relevant dissertations and articles were searched for using Google to provide additional valid and important information for this thesis. A total of 35 articles were identified and included in the screening process. The search strategy for Google was consistent with that used for the PubMed search, using the same keywords and selection criteria. The screening criteria for these sources were consistent with those used for the PubMed search, including language, date of publication, and quality features.

After removing the duplicates from the initial PubMed search, 1728 results remained. Following screening based on titles and abstracts, 116 articles were retained for further assessment. Of those, 59 articles were excluded due to conflicts of interest, being related to other antiresorptive drugs, or including comorbidities with similar clinical presentations. Ultimately, 57 articles met the inclusion criteria and were included in the review.

A search of articles was carried out using the keywords:

Medication-related osteonecrosis of the jaw; Bisphosphonate-related osteonecrosis of the jaw; Bisphosphonates; Side effects; Risk factors; Diagnosis

The selected keywords were carefully chosen to cover the topic of the master thesis comprehensively and to include a synthesis of the most relevant meanings related to the research topic. These keywords were selected based on their ability to provide the latest and most appropriate knowledge for the research.

3.2. Selection Criteria

Inclusion criteria:

- Full-text articles available
- Language: English or German
- Date of publication: no older than 2013 (with the exception of a few articles)

Inclusion exceptions:

- Articles published before 2013 that incorporated classifications, definitions, or guidelines that were still valid at the time of the literature search

Exclusion criteria:

- No full text available
- Literature written in other languages than English or German
- Articles/ reviews with conflict of interest
- Articles related to other antiresorptive drugs
- Articles include comorbidities with the similar clinical picture

The selection criteria for the reviewed articles were based on quality features. Only articles available in the full text were considered to ensure that no information was missing, potentially affecting the results and outcome of the thesis. To ensure that only the latest available data was included, articles between 2013 and 2023 were chosen. However, articles published before 2013 were also included if they incorporated classifications, definitions, or guidelines that were still valid at the time of the literature search Articles related to other antiresorptive drugs or including comorbidities with similar clinical presentations were excluded from the review.

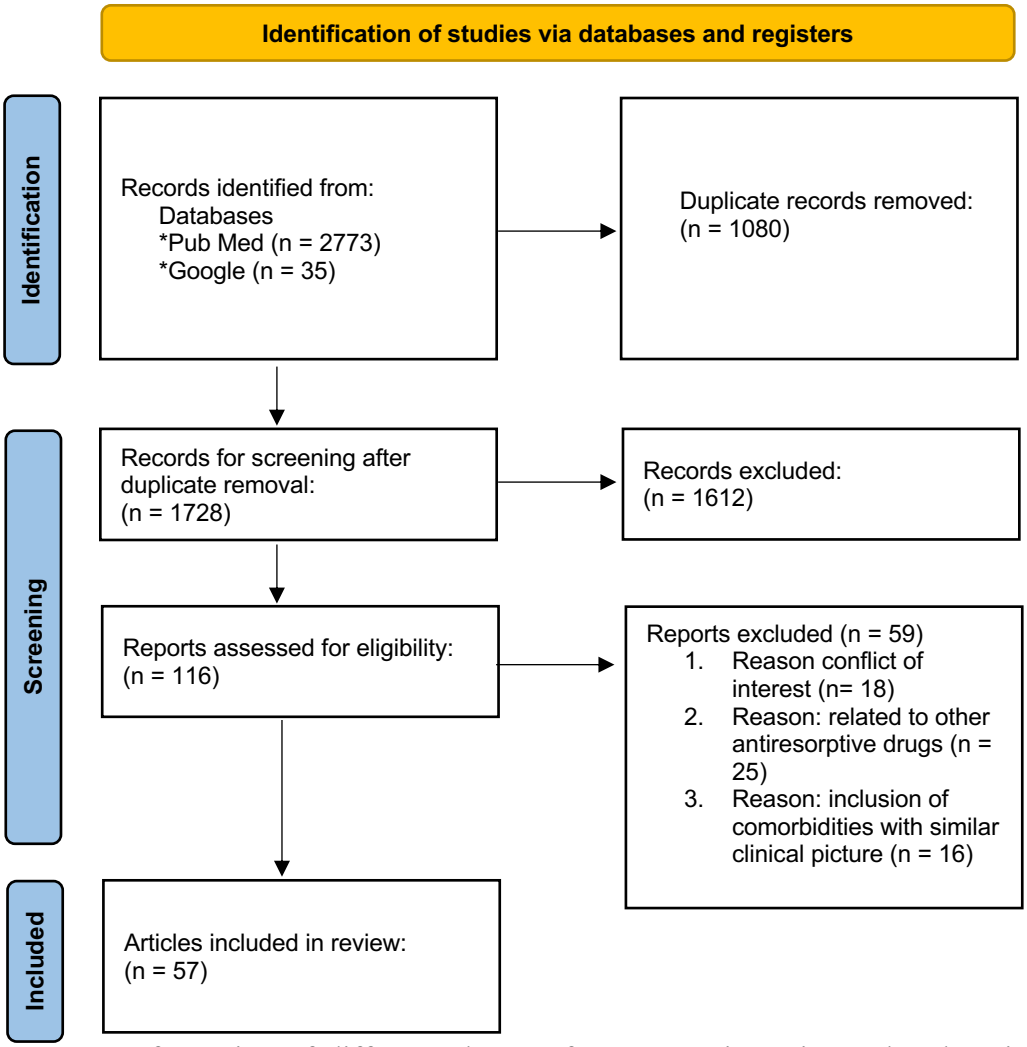

Figure 1. Information of different phases of a systematic review. The chart is based on Prisma 2020 Flow Diagram for new systematic reviews which included searches of databases and registers only (1).

The content of the thesis consists of an explanation of abbreviations, an introduction, a literature review, conclusion. The thesis contains 38 pages, six figures, three tables, and 71 references.

4. History of Bisphosphonates

The first full publication on the biological effect of diphosphonate, later renamed to bisphosphonate (BP), was published 50 years ago. For over 20 years, BPs have been the most widely used antiresorptive drugs (ARD) for managing conditions characterized by imbalances between osteoblast-mediated bone formation and osteoclast-mediated bone degradation, such as osteoporosis and cancer-related conditions, including the prevention of

bone metastatic malignancies (2–9). BPs are now widely studied and distributed drugs, considered the drug of choice for such conditions. Prior to this, in 2003 the first articles on possible “Bisphosphonate-related osteonecrosis of the jaw” were published (2,10,11). In the following period, along with the increasing number of cases, scientific interest in the topic grew. Meanwhile, it became evident that other drug groups were found to be associated with the development of the same clinical picture as induced by BPs. In response, the American Association of Oral and Maxillofacial Surgeons (AAOMS) changed the nomenclature in 2014 from "bisphosphonate-related osteonecrosis of the jaw" (BRONJ) to "medication-related osteonecrosis of the jaw" (MRONJ) to reflect the antiresorptive pharmaceutical denosumab and antiangiogenic therapies (e.g., bevacizumab) which have been recently associated with the condition of MRONJ (12–14). Ongoing research and collaboration among medical professionals are crucial for the safe and effective use of BPs and other medications to treat bone-related diseases.

5. Chemical Structure

BPs are a class of chemically stable compounds that are structurally derived from inorganic pyrophosphate (PPi) (4,15). PPi is a naturally occurring compound that is produced as a by-product of numerous synthetic reactions in the human body and can be detected in various tissues, including blood and urine (15). In 1968, Fleisch identified the role of PPi in preventing the calcification of soft biological tissues by binding to hydroxyapatite (HAP), which are calcium compound crystals, and preventing their dissolution. This discovery sparked the investigation for a structural analogue, which ultimately led to the significant discovery of BPs (16).

BPs closely mimic the structure of PPi, with the main difference being the presence of a central group. While PPi has a P-O-P bond, BPs have a P-C-P bond, which enables them to bind to HAP just as strongly, if not stronger, than PPi. Consequently, BPs are considered excellent targets for bone-related disorders (16). The chemical structure of BPs permits several variations at the C-atom in the position of R1 and R2, which have unique impacts on their physicochemical and pharmacokinetic properties (15,16). Although the R1 group primarily influences BP's affinity towards HAP, the R2 group affects its potency. While the phosphate and hydroxyl group are essential for BPs' affinity to bone, the most critical

determinant is the final component bound to the R2 position, which is responsible for the drug's potency in inhibiting bone resorption (15).

6. Classification and Mechanism of Action

BPs exert their effects on bone metabolism by targeting osteoclasts, leading to a suppression of overall bone turnover (2,3). There are two major groups of BPs, classified based on their distinct molecular mechanisms of action and the presence or absence of a nitrogen substitution, which also plays a crucial role in determining the potency of BPs within each group. The first group comprises the less-potent non-nitrogenous BPs (non-N-BPs), such as etidronate and clodronate (2,4,12,17). Due to their structural similarity to PPi, members of this group can be incorporated into nonhydrolyzable methylene-containing analogues of adenosine triphosphate (ATP) metabolically (16,18). After osteoclast-mediated uptake from the mineral surface of the bone, these non-hydrolyzable ATP analogues accumulate intracellularly within osteoclasts and inhibit multiple ATP-dependent cellular processes, leading to osteoclast apoptosis (4).

The second group of BPs comprises the more potent nitrogenous BPs (N-BPs) (nitrogen-containing R2 side chain), such as pamidronate, alendronate, risedronate, ibandronate, and zoledronate (zoledronic acid) (4,15,16,18). The mechanism of action of N-BPs differs from that of non-N-BPs. N-BPs affect enzymes of the mevalonate pathway by binding to and inhibiting the activity of farnesyl pyrophosphate synthase in osteoclasts (4,16,18). By preventing the production of cholesterol, other sterols, and isoprenoid lipids, the inhibition of these key regulator proteins induces a loss of osteoclastic activity, leading to osteoclast apoptosis (4,18).

6.1. Absorption

In general, BPs are typically not efficiently absorbed in the gastrointestinal tract. Instead, they are distributed throughout the body via the bloodstream, where they can accumulate in bone tissue for many years. Eventually, the BPs are excreted from the body through the kidneys without undergoing any major changes (19). BPs can be administered in different ways, either orally in tablet form, through intravenous (IV) infusions or injections (2,3,17). The intestinal resorption is low, between <1% and 10% and is reduced by simultaneous food

intake, especially calcium. BPs are distributed throughout the body via the bloodstream as complexes bound to albumin. The plasma protein binding of BPs can vary significantly due to differences in the polarity and lipophilicity of their side chains (19,20). In their book, Bartl et al. report that ibandronate has a plasma half-life of 10-16 hours due to its strong binding with albumin at 87%, while zoledronate has a much shorter plasma half-life of only 1-2 hours. About 20-50% of the absorbed amount is stored on the bone surface while the rest is excreted via the kidneys. Moreover, in contrast to blood (1-15 h), the half-life on the bone surface is 150-200 h and in the bone tissue itself, it can exist for many years explaining the long-lasting after-effect of this group of drugs (20). According to Julie Glowacki, Ph.D., BPs have a short circulating half-life of 0.5-2 hours, with rapid uptake into the bone during the first passage. Between 30 and 70% of the absorbed BPs accumulates in the bone, with the remainder excreted in the urine. Glowacki notes that due to the accumulation of BPs in the bone matrix and their removal depending on the turnover of the matrix, they may persist in the matrix for many years, with estimates for endurance in human cancellous bone exceeding 10 years (21). T. John Martin and Vivian Grill note that BPs are quickly absorbed by bone, with a range of 20-80% of the absorbed Bps accumulating at the bone formation and resorption sites. The remaining percentage is rapidly excreted in the urine, resulting in a short half-life of BPs in the circulation of 0.5-2 hours (22). Prasad Narayanan, on the other hand, reports that denosumab has a much longer elimination half-life of 32 days, with a terminal half-life of 5-10 days. Unlike BPs, denosumab does not incorporate into the bone (23).

The long-term bone storage of BPs poses a challenge for dental treatments, which clinicians should bear in mind even if the patient's BP treatment has ended months or years before. While bones loaded with BPs over an extended period can still be resorbed normally, it is unclear whether BPs released during bone regeneration can have clinical efficacy again (20). Ciao-Long Xu et. Al. state that some amount of BPs can be re-embedded in the bone during continued bone formation which results in the assumption that the half-life of BPs in bone is dependent on the bone turnover rate (12).

7. Anatomy of Bone Tissue

The human skeletal system is a dynamic system that serves several important functions (3,24). Primarily, it provides support and structure to the body, while also regulating calcium

and phosphate levels and producing blood cells in conjunction with the kidneys (3). Bone tissue is composed of cells, vessels, and a mineral substance known as HPA (25), with the composition of these components varying depending on the location in the body (24,25).

Cortical bone makes up 80% of bone tissue and is a dense, compact outer layer (25). It has a slow turnover rate, but high resistance, making it essential for skeletal stability (3,24,25). Anatomically, cortical bone consists of small cylinders called osteons, each comprised of concentric layers called lamellae which are made up of organic collagen and inorganic HPA, a calcium phosphate mineral.

The inner part of bone tissue is characterized by a spongy, trabecular pattern known as spongiosa, which represents 20% of the total skeletal mass (25). Spongiosa provides elasticity to the bone and houses bone marrow in the medullary canal where bone cell production takes place. The trabecular pattern allows the skeleton to maintain adequate weight while providing resistance to mechanical stress (3,24). Trabecular bone has a higher turnover rate than cortical bone, playing a major role in bone metabolism (25).

8. Bone Remodeling

The skeletal system is in a constant state of change, known as the "remodeling" (3,24). This active process involves the continuous replacement of old bone tissue with new bone tissue, which is crucial for proper skeletal development and the ability to adapt to individual stresses (24). The process of bone remodeling is orchestrated by specialized bone cells, including osteoclasts and osteoblasts, which are located on the outer surface of the bone (3,26).

Osteoclasts are responsible for the constant degradation of bone tissue, while osteoblasts and osteocytes are accountable for the formation of new bone tissue (3). These cells are temporarily organized in "basic multicellular units" (BMU‘s) located next to each other on the bone surface (26). Within BMUs, equivalent bone degradation and build-up are stimulated, allowing for an efficient bone remodeling (3,26).

In addition to osteoclasts and osteoblasts, BMUs also contain osteocytes and bone lining cells, with bone lining cells forming a circulatory canopy for the BMUs (26). Together, these specialized bone cells and their organization in BMUs play a vital role in maintaining the proper structure and function of the skeletal system through the continuous process of bone remodeling.

The bone remodeling process consists of three distinct phases (26):

1) Initiation of bone resorption by osteoclasts.

Osteoblasts are interconnected with intraosseous osteocytes (26) through a fine canal. While not fully proven, osteocytes could be the main sensor identifying microtrauma in the bone (24). Osteoblasts produce the ligand RANKL, a receptor activator of nuclear factor KB Ligand. RANKL binds to RANK receptors on the surface of nearby monocytes (osteoclast precursors) and induces their differentiation to multinucleated osteoclast cells. RANKL can also activate mature osteoclasts by binding to their RANK receptors directly and initiating their bone resorbing process (27).

2) Transition period from resorption to new bone formation.

Osteoclasts start producing hydrochloride acid (HCI) through which hydroxyapatite crystals dissolve into soluble calcium (Ca 2+) and phosphate ions. These ions are then released into the bloodstream. This change in pH causes hydroxyapatite crystals to detach from the collagenous bone matrix, allowing for the degradation of collagen fibers by proteases and collagenase (26). Osteocytes secrete lysosomal enzymes, mainly collagenase, which digest the organic component of bone, collagen protein, forming pits in the bone surface known as "Howship's lacunae" (27). In return, this resorption process induces osteoblasts to differentiate from mesenchymal cells on neighboring cell surfaces. To keep bone resorption under control, osteoblasts additionally secrete osteoprotegerin (OPG). Imitating RANK receptors, OPG binds to RANKL preventing it from activating RANK receptors and, consequently, slowing down the activation of osteoclasts and inhibiting osteoclastogenesis (26). Once bone degradation is complete, osteoclasts undergo apoptosis to prevent excessive bone resorption (27).

3) Formation phase.

Induced by the resorption process, several growth factors are released from the bone matrix, initiating the recruitment of osteoblasts from bone marrow to the howship lacunae (27). These osteoblasts then begin secreting a non-calcified osteoid seam, mainly composed of collagen, to refill the resorption lacunae. Eventually, the seam is mineralized through the deposition of calcium and phosphate, forming hydroxyapatite crystals (24). By monitoring special bone metabolism parameters in serum and urine, the balance between bone degradation and buildup can be determined (24).

From birth to adulthood, bone mass increases and reaches a point known as "peak bone mass." After puberty, however, bone mass gradually decreases (28). Factors that significantly influence bone density loss include behavioral factors such as alcohol use or smoking, little physical activity, insufficient intake of calcium and vitamin D, and demographic factors such as ethnicity or family-related osteoporosis (29). The equilibrium between bone formation and resorption is also influenced by systemic regulatory factors such as parathyroid hormone, vitamin D, sex hormones, thyroid hormones, calcitonin, as well as various cytokines and growth factors (3). Throughout life, men lose 20-30% of their peak bone mass, while women lose 30-40%, resulting in age-related bone loss known as osteopenia. Since there is no clear boundary between osteopenia and certain bone diseases like osteoporosis, the transition from physiological to pathological bone loss is gradual and should be considered by all practitioners (3).

9. Bone Diseases and Bisphosphonate Treatment

When there is an imbalance between bone degradation and formation, the composition of bone can be altered (24). Excessive bone resorption by osteoclasts without corresponding bone formation by osteoblasts can lead to bone loss and osteoporosis, while excessive bone formation can result in "osteopetrosis" (26). BPs are prescribed to treat metabolic diseases with increased osteoclastic activity, including osteoporosis, Paget's disease, multiple myeloma, and metastasizing malignant primary diseases. BPs play a crucial role in enhancing the quality of life of patients (5–9), reducing pathologically induced fracture rates (30,31) , and alleviating overall pain caused by skeletal metastasis (30) during the treatment. Various studies have shown that patients with osteoporosis, plasmacytoma, breast carcinoma, and prostate carcinoma can significantly improve their quality of life with BPs (5–8). Byun et al. confirmed that BPs can also reduce the incidence of osteoporotic bone fractures (31), while alleviating pain in both men and women to varying degrees (9).

9.1. Bisphosphonates in Osteoporosis

BPs are the most commonly prescribed drug for the treatment of osteoporosis (28), which is among the top ten most prevalent diseases worldwide (31), affecting over 200 million individuals (28). Due to the age-related decline in estrogen levels, postmenopausal women are predominantly affected by osteoporosis (with a women-to-men ratio of 5.7 to 4). BP treatment is effective in counteracting the consequences of osteoporosis, which is characterized by bone tissue degradation, disruption of bone microarchitecture, overall low bone mass, compromised bone strength, and increased risk of fractures (30).

9.2. Bisphosphonates in Oncology

In the field of oncology, the treatment of skeletally metastasizing malignant primary diseases such as multiple myeloma, breast cancer, and prostate cancer has been greatly improved by the use of BPs (33). The prescription rates of BPs have steadily increased, indicating their established therapeutic role in oncology. BPs have demonstrated positive anti-tumor effects, reduced tumor-related bone pain, and lowered fracture risk, making them an indispensable treatment option for bone metastases. However, it is important to note that BP administration may lead to undesirable side effects of MRONJ. Despite this, BPs cannot be discontinued in cases of severe disease progression of malignant tumors with pronounced spread to the skeletal system, as inhibiting skeletal metastasis is crucial. Overall, BP intake enhances the quality of life of patients suffering from plasmacytomas, breast cancer, and prostate cancer (29,30,33).

9.3. Bisphosphonate Treatment Regimes

BP treatment can be administered orally, via injections, or IV. While the relative potency of the individual BP preparations differs significantly, IV administration exhibits a much more effective antiresorptive potency than oral administration explained by a lower intestinal absorption (30). The duration, frequency, and dosage of BP treatment depend on the prescribed active pharmaceutical substance and underlying disease (28,30). However, it is important to note that the risk of developing MRONJ increases with higher doses and longer duration of potent BP treatment (13,14).

Dr. Blank and Dr. Prof. Dr. Gaßmann created a simplified overview of non-nitrogen-containing BPs (non-N-BPs), nitrogen-containing BPs (N-BPs), and denosumab depicted in Table 1, including their active substances, indications, applications, commercially available trade names, and relative potency (34). The table is extended by the relative potency of each BP according to Shaw and Bishop (35). This information may be useful for clinicians in choosing the appropriate BP treatment for their patients (34).

ACTIVE INGREDIENT	INDICATON	APPLIC. ROUTE	R.P.	TRADE NAME
Nitrogenous bisphosphonates:				
Zoledronic acid	Metastasis, plasmacytoma, prevention SC*	i.v.	10000	Zometa®, Aclasta®
Pamidronate	Metastasis, plasmacytoma	i.v.	100	Aredia®, Axidronat®, Pamifos®
Ibandronate	Metastasis, osteoporosis, plasmacytoma, prevention SC*	i.v./ p.o.	500-1000	Bondronat®, Bonviva®
Alendronate	Osteoporosis, M. Paget	p.o.	1000-2000	Fosamax®, Fosavance®
Risedronate	Osteoporosis, M. Paget	p.o.	2000	Actonel®, Acara®
Non-nitrogenous bisphosphonate:				
Etidronate	Osteoporosis, M. Paget	p.o.	1	Etidron®, Didronel®
Clodronate	Metastasis, plasmacytoma	i.v./ p.o.	10	Bonefos®, Clodron®, Ostac®
RANKL-antibody:				
Denosumab	Metastasis, osteoporosis, plasmacytoma, prevention SC*	s.c.		Xgeva®, Prolia®

Table 1. Schematic representation of the most common ARDs on the market as of March 2023. Active pharmaceutical, their approval for the possible indication, administration route, and trade name (34). SC* - prevention of skeletal-related complications in cancer patients without metastasis, R.P. - relative potency (35).

10. Side Effects of Bisphosphonate Treatment

With the accurate use of BPs, their overall clinical benefits outweigh their potential risks and are subsequently considered safe drugs (29). However, there are several possible adverse effects that fall into four categories: acute phase reactions, gastrointestinal side effects,

nephrotoxicity, and MRONJ (10). Oral BPs can cause gastrointestinal side effects such as inflammation, flatulence, and diarrhea, affecting the entire gastrointestinal tract from the lower esophagus to the colon (11). To prevent GIT ulcers, patients are advised to increase their water intake and maintain an upright position before and after taking the medication (10). Acute phase reactions may occur within 24 hours after the initial intravenous administration of nitrogenous BPs, causing fever, limb pain, myalgias, and bone pain (31). Slow administration of intravenous BPs can prevent acute renal failure (10,30). During BP treatment, it is crucial to be aware of the potentially serious condition of MRONJ, which can have significant consequences for dental health. Special interdisciplinary attention should be given to both the prevention and management of this condition (30).

11. Medication-related Osteonecrosis of the Jaw

MRONJ is a side effect that is not yet fully understood and requires differential diagnosis and long-term treatment (30). Lesions appear as non-healing exposed bone in the mouth and severe conditions represent an incentive for their clinical relevance (28,30). MRONJ is commonly reported in patients receiving IV treatment for cancer, and less commonly in those receiving IV BP therapy for osteoporosis, as well as those taking oral BPs (2,10,36). Nevertheless, even to a lesser extent, patients taking oral BPs are at risk too (13). The risk of developing MRONJ generally rises with increased doses and longer duration of potent BP treatment (13,14).

11.1. Diagnosis

Initially, the cause of MRONJ cannot be easily identified due to its clinical similarity to other delayed healing conditions such as osteoradionecrosis, osteomyelitis, bone metastases, and endocrinogenic necrosis of the jaw. To confirm the diagnosis of osteonecrosis and exclude potentially malignant events, a histological tissue examination may also be necessary (11,13,14,17,30,37). It is crucial to distinguish MRONJ from other systemic conditions to achieve successful therapeutic treatment (10,11,13). The AAOMS has presented predefined characteristics for the diagnosis of MRONJ in their most recently published positioning paper from 2022. Accordingly, MRONJ can be considered if all of the following characteristics are present:

1. Previous or current treatment with BPs
2. Non-healing exposed bone in the maxillofacial region that has persisted for more than eight weeks and can be probed through an intraoral or extraoral fistula(e)
3. Absence of previous radiotherapy to the maxillofacial and cervical regions, and non-existence of metastases (13)

In most cases, MRONJ is diagnosed at an advanced stage due to the late onset of symptoms. A precise anamnesis of the patient is necessary to make a correct diagnosis. Therefore, a thorough inspection of the oral cavity and perioral region during regular check-ups is crucial (14,37). However, it is often difficult or impossible to assess the extent of the bony defect under the mucosa by superficial visualization alone. Especially when the necrosis has developed spontaneously without a previous dentoalveolar intervention, the intraoral appearance may not be immediately recognizable or obvious (2,30). Radiographic evaluation through computed tomography (CT) and magnetic resonance imaging (MRI) are essential to detect early soft and hard tissue changes, perform differential diagnosis, and evaluate the extent of the necrosis (14). The imaging procedures will be discussed in more detail later.

11.2. Staging

Several staging systems exist for MRONJ; however, the AAOMS has developed a widely adopted staging system that comprehensively describes all clinical aspects of MRONJ presentation. The AAOMS staging system is currently considered the most relevant system for categorizing MRONJ patients, as it provides options for respective treatment guidelines and helps in predicting treatment outcomes (13).

MRONJ	CLINICAL CONDITION
Risk stage	No evidence of necrotic bone in asymptomatic patients who have been treated with IV or oral BPs. Nonspecific symptoms or clinical and radiographic findings can be present.
Stage 0	No evidence of necrotic bone, but non-specific symptoms or clinical and radiographic findings.
Stage 1	Asymptomatic exposed necrotic bone or fistula that can be probed to the bone. Evidence of soft tissue infection or inflammation. Radiographic findings may be localized in alveolar bone area.

Stage 2	Asymptomatic exposed necrotic bone or fistula that can be probed to the bone. No soft tissue infection or inflammation. Radiographic findings can be localized in alveolar bone area.
Stage 3	Symptomatic exposed necrotic bone or fistula that can be probed to the bone. Evidence of infection. Radiographic findings. Additionally, one or more of the following characteristics are present: - Exposed necrotic bone extending alveolar bone region - Pathological fracture - Extraoral fistula - Oral antral/ oral-nasal communication - Osteolysis extending to the inferior border of the mandible or sinus floor

Table 1. According to the staging system for MRONJ of AAOMS (13)

11.3. Clinical Presentation

If the aforementioned criteria are present, the diagnosis MRONJ can be confirmed. The most significant clinical presentation is an avascular exposed jawbone with no tendency for secondary or spontaneous healing (11). In most cases, MRONJ occurs after dental interventions that affect the bone, such as tooth extraction (13). However, osteonecrosis can also develop spontaneously and may remain asymptomatic and non-specific for months up to years, depending on the extent and location (2,14). The disease may affect the mandible, maxilla, or both jaws, often occurring multifocally (2). The incidence of MRONJ is twice as high in the mandible as in the maxilla (10,11,13,38). The spread of the affected area is non-specific and can range from poorly healing extraction sockets to small, exposed bone areas, massive necrosis of the jaw with sequestrum, or a pronounced soft tissue infection until jaw fracture (2,11,13,14). Characteristically, the affected lesions respond poorly or not at all to local or antibiotic therapies (2).

In the early stages of the disease, symptoms may include non-odontogenic odontalgia, dull, aching jawbone pain that may affect the temporomandibular joint (TMJ), pain in the sinuses, or alteration in the neurosensitivity (13). Altered nerve sensation may be due to compression of the neurovascular bundle. A relatively rare yet possible specific sign of MRONJ is hypo- or anesthesia in the area supplied by the inferior alveolar nerve (Vincent's sign), which can occur at an early stage (2,30). Generally, patients may experience pain ranging from none to severe (2). A typical clinical appearance could be characterized by non-healing extraction sockets with pronounced wound healing disorders that are often resistant to therapy (14). Moreover, intraoral or extraoral swelling may be present, as well as inflamed, ulcerative,

and suppurative soft tissue (14). The differentiation between vital and necrotic bone can be difficult, particularly in the early stages when the clinical picture is often uncharacteristic (30). The necrotic bone may remain asymptomatic for a prolonged time, after which symptoms can develop mainly due to localized inflammation of soft tissues (2,14). The mucosa bordering the defect area can be irritation-free or show granulating marginal walls. The affected bone area often appears white-yellowish (Figure 2) (2).

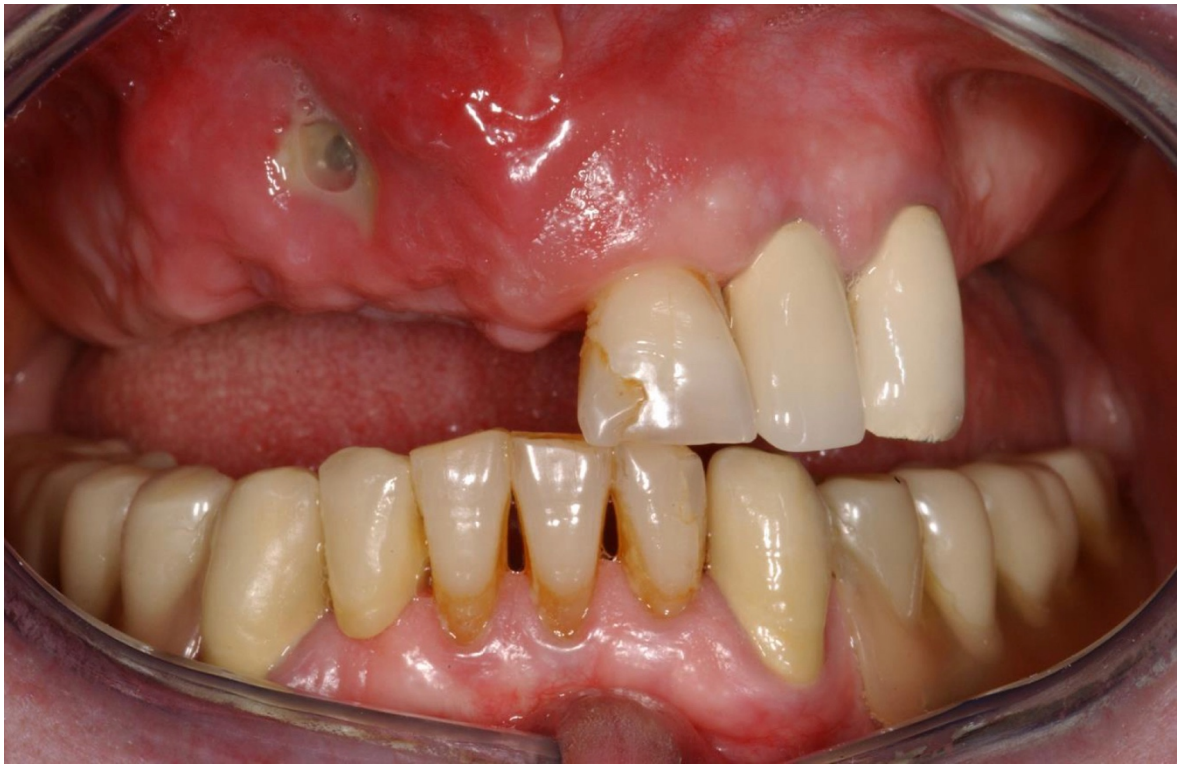

Figure 2. MRONJ of maxilla right side region 12,13. Initial finding; Status after tooth extraction of 11,12,13. 55 years old patient (woman). Underlying disease: breast cancer, drug therapy: Zometa (zoledronic acid) (30).

In many cases, intra-oral lesions superficially appear as rather small. Nevertheless, large areas of necrotic bone may be hidden under the mucosa (shown in Figure 3-5) (30). Moreover, intraoral or extraoral swelling could be present as well as inflamed, ulcerative, and suppurative soft tissues (14). As MRONJ progresses, patients may experience more severe symptoms, such as loosened teeth not caused by periodontal disease, fistulae, or abscess formation (2,13,30). Patients may also complain of halitosis, eating difficulties, and speech disorders (2,30). More advanced cases may involve the progression of exposed bone areas and the formation of sequestra (dead bone fragments), leading to chronic infections, difficulty opening the mouth (trismus), and the loss of jawbone structure. Severe cases may

also result in pathological fractures that require surgical intervention (2,30). Furthermore, if osteonecrosis is localized in the upper jaw, it may involve the maxillary sinuses and lead to maxillary sinusitis or a mouth-antrum connection (2).

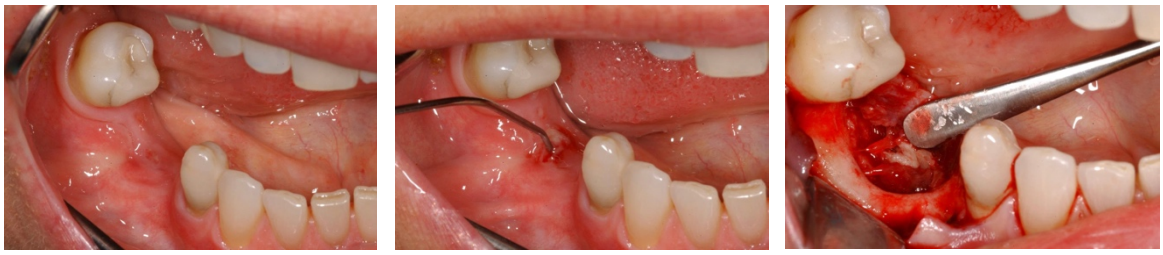

Figure 3-5. MRONJ of lower jaw right side, Regio 45,46; 61 years old patient (women); underlying disease: plasmacytoma, drug therapy: Zometa (zoledronic acid) and Aredia (Pamidronate); initial finding: unspecific appearance (figure 3). Demonstration of fistula (figure 4). Extent of osteolysis (figure 5) (30).

11.4. Radiographic Findings and Imaging Procedures

Radiographically, the appearances of MRONJ vary from no alteration to varying radiolucencies or radio opacities. In the early stages, thickening or even narrowing of the periodontal ligament space can be observed, as well as sclerosis of the lamina dura (2,14,37,39). A systemic literature review led by Prof. Dr. Reinhilde Jacobs investigated early changes visible in imaging modalities, and the authors found that patients in a very early stage of MRONJ development, both in 2D and 3D imaging, showed sclerosis, osteolysis, changes in trabecular alignment, patchy appearing bone structures, thickened lamina dura, persistent extraction sockets, and changes around the mandibular canal (39). Consistent with these findings, M. Gupta et al. and H. Krüger et al. reported morphological changes in the trabecular pattern or as regions of sclerotic bone, cortical thickening, erosions, interruptions as well as sequestrations and pathological fracture (14,37). “Persisting alveolar socket”, a condition where no bone forms after tooth removal, is an explicit indication visualized in x-rays and should draw the clinician’s immediate attention. Thus, even months after tooth extraction or tooth loss, the cortical walls of the alveoli remain intact without showing any signs of bony thinning or progressive destruction due to osteolysis (2,14,30,37).

In their retrospective study Cordoso et al. evaluated panoramic radiographs of 35 patients diagnosed with MORNJ. More frequent affection of the mandible compared to maxilla was observed. A significant difference of prevalence in genders could not be assessed as well as

no major connection between the duration of BP treatment and the number of lesions. Furthermore, in general, bone sclerosis was the most frequent finding followed by osteolysis and thickening of lamina dura. According to stage two, the most radiographic finding was diffuse bone sclerosis whereas in stage 3 predominantly it was cortical bone erosions, thickening of the inferior alveolar nerve canal and pathological fracture. Cordoso et al. concluded "the higher the clinical staging, the greater the severity of the bone alteration" and stated that panoramic radiographic examination is a beneficial observational tool for patients under antiresorptive therapy (40).

In addition to conventional radiographs, CT scans, and digital volume tomography (DVT) scans can give three-dimensional information about the extent of the lesion and therefore constitute a very helpful investigative instrument for dentists, especially for diagnosis, therapy, and surgery planning (2,14,37). However, even with CT, clear objectification of the necrosis borders is not possible (2). Other imaging methods include magnetic resonance imaging (MRI), nuclear imaging, and bone scintigraphy (2,14).

Evaluation of osseous changes in MRI shows the same results as visible in CT (13). MRI offers the possibility to detect bone marrow oedema and soft tissue changes surrounding the lesion, which can be early symptoms of bone ischemia or necrosis (2). According to Prof. Dr. Reinhilde Jacobs et al., three-dimensional imaging better visualized periradicular radiolucencies, crater-like defects, thickened mandibular cortical bone, bone sequestrum, and irregularities in the osseous cortical bone. However, no association between bony changes in early onset and the development course of MRONJ could be detected (39).

Depending on lesion progression and impact on vascularity, bone scintigraphy has a high sensitivity for the detection of early-stage disease and ischemic osteonecrosis. Osteonecrotic regions could be precisely displayed by increased radiolucencies around the affected areas shown by increased perfusion and blood pool (14).

The presence of both osteolysis and osteosclerosis at a site has been found to increase the risk for the development of MRONJ following tooth extraction in that area (13,14). Therefore, when teeth exhibit periapical lesions or pre-existing noticeable radiographic changes, it is important to carefully evaluate the need for surgical intervention in order to minimize the risk of complications related to MRONJ (41). In these cases, the use of three-

dimensional imaging can be beneficial, as it can accurately detect the presence of sequestra, both forming and already formed, and initiate early treatment intervention (14,37).

Since MRONJ can often manifest asymptomatically, dental clinicians must remain vigilant of early onset symptoms and utilize appropriate screening tools to detect the early developmental signs of the condition. Detecting MRONJ in its early stages is critical to prevent further disease progression and reduce the need for invasive surgical procedures. Therefore, dental clinicians should consider using three-dimensional imaging techniques at all stages, including the identification of early signs, diagnosis, and surgery planning.

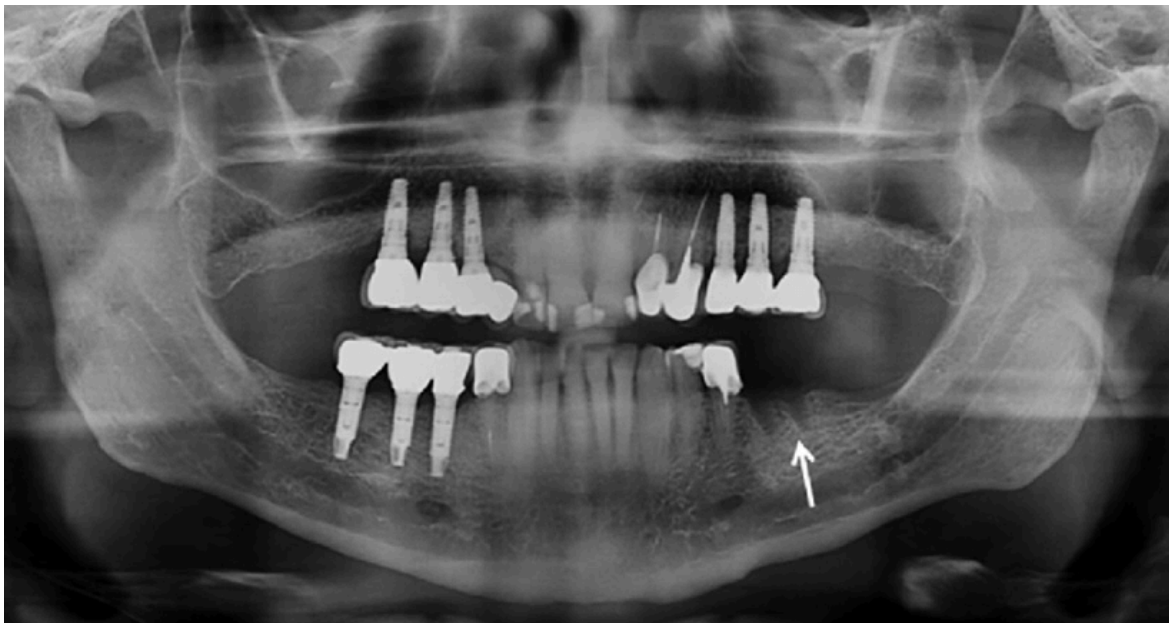

Figure 6. Panoramic radiograph visualizing nonhealing extraction sockets region 36 (arrow) 12 months after tooth extraction. Patient associated with IV BP therapy (42).

12. Pathophysiology

A multifactorial complex of causes is assumed for the risk and development of MRONJ. In recent years, various disease patterns have been discussed, whereby the question of the triggering factor for the specific development of osteonecrosis in the jawbone has not yet been conclusively clarified (13,43). The available scientific data led to the following pathogenesis proposals.

12.1. Alteration of Bone Turnover of Jaw

Since MRONJ has so far been reported almost exclusively in the jawbone, the question arises as to why BPs accumulate in higher concentrations in the jawbone than in any other parts of the skeleton (2). The high bone remodeling rate of the jaws (for example ten times more than in the tibia (38)) is the most commonly mentioned reason for the increased uptake of BPs. Additionally, the jawbone has higher levels of calcium and collagen, which attract BPs to a greater extent (10,13,38,44). Moreover, the increased vascularization and bone remodeling processes in the lamina dura due to physiological tooth movement, tooth loss, and constant chewing loads also contribute to the higher uptake of BPs (2,13,38).

Bone metabolism, which is initiated through osteoclast-mediated bone resorption, can be altered by the apoptosis of osteoclasts, decreased blood flow, and bone cell necrosis induced by ARDs. BPs are ARDs that directly affect the formation, differentiation, and function of osteoclasts, leading to a reduction in the rate of bone turnover (2,10,13,44). As non-functional osteoclasts can be seen in the surrounding tissues of necrotic bone lesions in patients treated with BPs, the hypothesis of bone remodeling reduction is further emphasized (2). The suppression and reduction of bone remodeling processes lead to altered mineralization and an increase of microfractures (2,10,38). Subsequently, demanded by the continuation of the remodeling process for example by tooth extraction, more BP accumulates resulting in no bone resorption and no following bone formation, leading to the presence of necrotic bone. Thereupon the overlying bone and soft tissues become deprived from their blood supply and gradually dismantle, provoking parts of clinically exposed bone (38). The consequence of the over-suppression of bone turnover leads to compromised jaw healing in response to normal physiological microdamage (e.g., occlusion) and iatrogenic events (e.g., tooth extraction) (17).

12.2. Inhibition of Angiogenesis

To explain the development of jaw necrosis, some authors assume a locally disturbed blood supply which is crucial for tissue health and survival (2,10). BPs, especially zoledronic acid, can have direct inhibiting effects on angiogenesis in vitro and in vivo (10). Additionally, animal studies have shown a decrease in vascularity at sites of MRONJ and a reduction in the number of microvessels during the early stages of bone healing (45). The use of BPs in

the early and late stages of MRONJ results in a reduction of overall vascularity due to decreased arterial and venous areas of periodontal tissues. Furthermore, proper angiogenesis required for healing after a tooth extraction is inhibited (13).

12.3. Infection

The close relationship between the teeth and jawbone provides a route for microorganisms and other inflammatory agents to enter the bone, a situation not found in any other anatomical location in the human body (30). Although most studies report tooth extraction as the major inciting event for MRONJ development, most extracted teeth had pre-existing periodontal or periapical disease thus increasing the risk for the development of MRONJ (44,46). Nevertheless, pre-existing dental infection is not a guarantee for developing osteonecrotic lesions (13).

The presence of inflammatory cytokines, especially at MRONJ lesion site, supports the role of inflammation, and thus associations between the presence of biofilm and poor oral hygiene are associated with the development of MRONJ (13). Moreover, existing considerations assume that bone coated with BPs, especially amino-BPs, increases bacterial adhesion, resulting in bone necrosis and osteomyelitis (12). As various researchers reported, microbial biofilms play a role in etiopathogenesis, with specific staining for bacteria which typically reveals actinomyces. However, further studies are necessary to validate these findings, as actinomyces are commonly found in the oral cavity and may be a consequence of the lesion itself instead of the initiator (10,44). Furthermore, local changes in pH caused by dentoalveolar infection or surgery are discussed for being the cause or enhancing the development of MRONJ (2,18).

12.4. Impact on soft Tissues

The accumulation of BP in the jawbone can have a direct toxic effect on the covering mucosa (2). Regarding the impact on soft tissues, some researchers state that BPs have a proapoptotic effect on the keratinocytes of the gastrointestinal tract and the oral cavity. Furthermore, the proliferation of mucosal cells, as well as wound healing, is inhibited or delayed. Studies have found negative effects on gingival fibroblasts, osteoblasts, and osteosarcoma cells. They found a reduced production of extracellular proteins after administration of BPs (10). Açil

et al. also observed cytotoxic effects on these cell lines under the administration of zoledronate, pamidronate, and alendronate (47). Furthermore, BP released from the bone can impair the function and proliferation of epithelial and immune cells of the soft tissue (2).

Since the jawbone is only separated from the oral cavity by a thin layer of mucosa, microorganisms can penetrate more easily. The proximity of the jawbone to the oral cavity, separated only by a thin layer of mucosa, provides an easy entry port for microorganisms. Since the oral cavity is a natural habitat for bacteria, it is easier for bacteria to spread to the nearby bone tissue, which can facilitate the spread of infection (2,10). As a result, any injuries to the mucosa, whether caused by surgical interventions, prostheses pressure points or traumatic ingestion, could provide the oral microflora with unhindered access to penetrate the bone (2).

12.5. Multifactorial

As more knowledge is gained, it is becoming evident that a multifactorial hypothesis is required to explain the pathogenesis of MRONJ. Patients with coexisting illnesses such as diabetes, compromised immunity, rheumatoid arthritis, as well as patients suffering from metastatic or primary bone malignancies, and patients on medications are at significantly higher risk for developing MRONJ, regardless of whether they are taking BPs or not (13,44). Additionally, higher incidences of MRONJ have been reported in patients with multiple myeloma receiving multiple chemotherapeutic agents (13). Pharmaceuticals such as steroids and cytostatic agents can have an impact on wound healing and interfere with epithelialization (48).

Although the exact cause of MRONJ is not yet fully understood, various articles suggest that genetic predisposition may be a contributing factor to its risk and development. However, it is essential to note that MRONJ is likely the result of a combination of factors, as proposed by the multifactorial hypothesis. Further investigation is required to understand how genetics and environmental factors contribute to the development of MRONJ (13,14).

13. Epidemiology and Risk Factors

The incidence and prevalence of MRONJ is difficult to define due to two main factors. Firstly, the same diagnostic code is often used for multiple diseases, making it challenging to obtain clear insights into the incidence of MRONJ. Secondly, studies on the topic use different variables, making it challenging to provide accurate statistics.

In terms of diagnosis codes, it is important to note that different disease codes for MORNJ exist around the world. For instance, in the United States, the website ICD10data.com, which is a free reference website designed for the fast lookup of all current American ICD-10-CM (diagnosis) and ICD-10-PCS (procedure) medical billing codes, lists different codes for different diseases for example osteonecrosis due to drugs (MRONJ) (M87.180), Osteomyelitis (M86.9), Periostitis of jaws (M27.2), and Alveolitis of jaws (M27.3) (49). In both Germany (50) and Lithuania, the same disease code (K10.2) is used to record cases of MRONJ along with several other inflammatory conditions of the jaws, including osteomyelitis, periostitis, and osteoradionecrosis. Using the same code for different conditions can make it difficult to distinguish MRONJ cases from other conditions with the same code, resulting in inaccurate reporting of MRONJ incidence and prevalence. This is complicated by differences in diagnosis codes across countries, which can hinder accurate statistics. Improvements in disease coding practices are necessary to ensure accurate monitoring and reporting of MRONJ cases in these countries.

Several studies have investigated the incidence and prevalence of MRONJ in patients receiving bisphosphonate therapy but based on different objectives. These objectives include various individual factors, such as the characteristics of BP therapy (e.g., treatment duration, administration route), local site conditions (e.g., oral hygiene, tooth extractions), and systemic factors (e.g., concomitant diseases and medications). Additionally, some studies group together populations using BPs, denosumab and other ARDs, leading to inaccurate results. The complex interplay of various factors makes it a difficult task to accurately assess the epidemiology of MRONJ, including its incidence and prevalence.

13.1. Risk Factors

To attain the best treatment results for patients, it might be recommended to perform a thorough evaluation of their individual risk factors and create a customized risk profile for each patient. This approach is especially crucial as these risk factors can substantially enhance the chances of developing MRONJ and consideration can significantly enhance patient outcomes. The risk of developing MRONJ is subject to several factors and can be classified into three categories: drug-related (BP therapy), local, and systemic.

13.2. Bisphosphonate Therapy

The potency and duration of BP therapy are crucial factors that influence the development of MRONJ. Especially a higher cumulative dose and longer treatment duration, as well as taking different BPs simultaneously, increase the incidence of the disease (10,11,44,45). Based on their systematic review, Anastasilakis et al. concluded that the use of ARDs poses a higher risk of MRONJ in patients with advanced malignancies compared to those with benign bone diseases. This is due to the higher doses and more frequent administration BP administration, especially when combined with other risk factors (e.g., concomitant diseases and medicaments) (51).

Since high cumulative doses are usually reached with IV administration, MRONJ predominantly occurs in patients receiving intravenous bisphosphonate therapy for malignant diseases (19,45), However, reports also exist of incidences in patients taking less potent BPs orally (44). For instance, Ruggiero et al. state that the risk for developing MRONJ in osteoporosis patients treated with oral or IV BPs ranges from 0.02% to 0.05%. The AAOMS suggests that the probability of MRONJ occurrence in cancer patients receiving BP treatment is less than 5%, though the risk ranges from 0 to 18%. The varying follow-up durations, ranging from one to ten years, account for the significant difference in estimates. (13). Studies have shown that the risk of developing MRONJ increases from 1% after the first year to 13%, and in some cases, up to 20%, after four years of BP therapy (45). Cases have been reported for the high-potency BPs pamidronate and especially zoledronate (19,44) in patients with metastatic carcinoma (44% breast carcinoma, 15% prostate carcinoma) and multiple myeloma (33%) during long-term therapy with high doses. In contrast, the incidence was ten times lower with the use of ibandronate (19).

13.3. Local Risk Factors

Local risk factors that can increase the risk of developing MRONJ include both dental and surgical interventions. Procedures such as teeth extraction, implantation, periodontal surgeries, or bone grafting can easily lead to osteonecrotic events under the use of BP therapy (10,13). In addition, neglected oral hygiene, pre-existing periodontal diseases, teeth with apical lesions (44,46) and improperly fitting dentures significantly elevate the risk for developing MRONJ (13,17). As a result of the close proximity of anatomical structures, infections can easily spread (2,13). According to Manfredi et al., a multicenter prospective cohort study involving oral BP-treated patients, severe periodontal disease, tooth extraction, and starting the preventive dental program after the beginning of zoledronate therapy were significant risk factors associated with the development of MRONJ. The study found that 17 out of 156 patients (10.89%) developed osteonecrosis during the study period (52). Mücke et al. identified invasive dental procedures and dental infections as the most significant risk factors for MRONJ. Their conclusion emphasizes the importance of eliminating potential risk factors that could lead to invasive dental procedures and establishing proper oral hygiene before initiating BP treatment to prevent MRONJ (52). Furthermore, multiple studies have reported that MRONJ is twice as likely to occur in the mandible than in the maxilla (10,11,13,38).

13.4. Systemic Risks and concomitant Factors

Several systemic factors increase the likelihood of developing MRONJ, including age, gender, and behavioral factors (e.g., obesity, tobacco, alcohol intake, and genetic predisposition (13,14,16,19,44). In addition to underlying diseases like osteoporosis or cancer, comorbidities such as systemic diseases like diabetes mellitus, rheumatoid arthritis, conditions with low hemoglobin or calcium levels, and hyperlipidemia are also highly likely to increase the risk of developing osteonecrotic lesions (2,14,44). Moreover, concomitant disease treatments and medications, including chemotherapy, renal dialysis, or corticosteroids are significant risk factors for the development of MRONJ (13, 47). According to Kawahara et al., managing uncontrolled systemic diseases that increase the risk of developing MRONJ is crucial before initiating BP therapy. The date of antiresorptive therapy initiation should be determined by physicians after consulting with dentists regarding necessary dental treatments (54).

By combining these risk profiles, important insights can be gained regarding the occurrence of MRONJ and how it may develop based on various interacting factors. However, it is important to recognize that these figures might not fully capture the true epidemiology of MRONJ, as the condition is frequently underdiagnosed owing to the absence of a universal disease code, varying study objectives and inclusion of individual factors. Consequently, more research is needed to comprehensively grasp the scope of the condition and to establish effective prevention and treatment approaches.

14. Treatment Management

14.1. Treatment Goals

It is important to note that the annotation sheets for BP drugs, including but not limited to Prolia, Zometa, Bondronat, and Pamifos, suggest consulting with a dentist before and during treatment, utilizing conditional language such as "should" or "may". However, considering the grave risk of MRONJ, it may be appropriate to use more assertive language in these recommendations. It is imperative for dental professionals, patients, and other healthcare providers involved to remain vigilant and take proactive measures to detect and address any possible symptoms of this condition. Hence, the primary goals of MRONJ treatment are to prevent its occurrence, prioritize the treatment of the underlying disease, and preserve patients' quality of life (13). Therefore, it is crucial to prioritize the treatment of the underlying disease to ensure that cancer patients receive necessary oncological treatments and that patients with osteoporosis receive ongoing support for their bone health. Patients' quality of life should be raised by proper patient education and reassurance, control of pain, prevention of secondary infection, lesion extension, and development of new necrotic areas as well as fragility fractures (13,55). Treatment strategies should consider not only the potency of the BPs but also individual patient factors (13,44). As a dental practitioner, preventing osteonecrotic events should always be a top priority while taking into account the patient's overall health.

15. Prophylaxis and Preventive Measurements

A clear distinction should be made between prophylaxis, measures counteracting oral pathologies before the start of BP therapy, and prevention, measures during ongoing BP therapy.

15.1. Prophylaxis

Interdisciplinary awareness and cooperation, particularly among colleagues who prescribe bisphosphonates - such as oncologists, internists, orthopaedists, general practitioners, and other physicians involved in the treatment - should be given high priority (13). A multi-professional team, including the dentist, is necessary to develop proper interdisciplinary treatment plans and reduce the risk of side effects.

Prophylaxis measures encompass comprehensive patient education concerning the treatment regimen and the significance of oral hygiene, as well as a thorough risk assessment prior to the initiation of BP therapy (38,55). Investigations conducted by Ripamonti et al. show a significant reduction in MRONJ event rates in oncology patients of 1.3% respectively, with prophylactic measures alone compared to 3,2% respectively, without prophylactic measures (46). In the effort to prevent MRONJ, it is crucial to conduct a physical and radiographic examination prior to the initiation of antiresorptive therapy, as well as to gather information about the patient's medical history. Therefore, under an agreement between the dentist and involved specialists, the initiation of BP therapy should be delayed until the patient's dental health status is optimized (13,44). It should be kept in mind that patients receiving BP treatment for malignant diseases are at higher risks for the development of MRONJ. Therefore, there is greater flexibility in terms of the urgency of optimizing oral health for osteoporosis patients, who usually receive less potent oral BPs (13). In general, it is recommended to improve oral hygiene and periodontal status of the patient, extract teeth that are not worth preserving, perform necessary elective dentoalveolar surgery, treat active carious lesions and treatable periapical inflammation before initiation of BP therapy (13,19,46). Additionally, prostheses should be checked for possible pressure points. Subsequently, the patient should be enrolled in a personalized recall program, depending on his individual risks, to counteract possible inflammatory processes in time. The patient

should be taught that promoting factors such as smoking, and alcohol consumption should be avoided (10).

15.2. Prevention

Prevention includes measures during ongoing BP therapy whether the patient is asymptomatic or already presents with signs of osteonecrosis. In this regard, the dentist must be precisely informed about the medical history, including details on the drug (name, route of administration, dosage, intake frequency), its indication, and any other concomitant medication or diseases (30,38). A patient taking BPs who visits the dental office must be closely evaluated for signs of MRONJ development. An accurate individual risk assessment should be performed using information from the patient's medical history, physical examination, and imaging scans. If the examination does not reveal pathologies, the dentist should inform the patient about their individual risks, and educate the patient about the importance of oral health and preventive measures for staying asymptomatic (14).

16. Asymptomatic patients receiving oral Bisphosphonates

Although the risk of developing MRONJ from oral bisphosphonates is relatively low, it is still important to take precautions. Patients undergoing BP therapy for osteoporosis may be able to undergo more invasive dental treatments (e.g., tooth extractions or implantation) and elective dental surgery with proper management and monitoring (13). As implantation becomes an increasingly popular treatment option, it's important to consider the varying success rates of implant placement in patients taking oral BP according to different studies (13,44,56–59). A systematic review, conducted by Gelazius et al., on implant placement in patients receiving oral BPs and IV BPs revealed that implant placement in patients receiving oral BPs is generally safe, if good care is implemented before and after the surgery. Furthermore, it has been suggested that the duration of oral BP use does not affect the success rate of implants or the development of necrosis (56). In general, the occurrence of implant-related necrosis (MRONJ) can be categorized as early, triggered by implant surgery, or late, triggered by the presence of the implant. Giovannacci et al. state that both the placement of implants and the presence of the implant itself presents a possible risk factor for the development of implant-related necrosis (57). Kwon et al. concluded acceleration of MRONJ lesions during and after BP therapy (58). According to Ulrike Hilscher, implant

insertion is one possible trigger for microorganisms that may lead to osteonecrotic events. Therefore, it is crucial to carefully consider the indication for the procedure and differentiate between medically necessary and elective implantations, considering the patients individual risks (30).

While the chances of developing MRONJ due to oral BP therapy are relatively low, the lack of substantial clinical research makes it difficult to provide clear treatment guidelines or recommendations for patients currently taking oral BPs. Nevertheless, patients should always be informed of the potential low but existing risks of delayed bone healing, infection or implant failure (13,44).

17. Asymptomatic Patients receiving intravenous Bisphosphonates

For patients receiving high potent BPs for cancer reasons, good oral hygiene and dental care are crucial in preventing dental problems that can otherwise contribute to the development of malignancies or may require surgical intervention (10,14). Patients should maintain their oral health and adhere to their recall program. To reduce the risk of bone damage, it is generally recommended to avoid procedures that directly impact the bones. Before any procedure, the patient and their dentist should discuss the risks, treatment options, and alternatives. Depending on the treatment, additional interdisciplinary consultation may be necessary (10,13,14,44).

When it comes to non-restorable teeth, there are treatment options with a lower risk of developing osteonecrotic lesions. One potential treatment option involves removing the tooth crown and undergoing endodontic treatment of the remaining roots (34,44). Diegritz et al. emphasize the key role of non-surgical endodontics in the care of patients undergoing antiresorptive therapy. According to their scientific paper, root canal treatment or revision is a reasonable alternative to surgical interventions (extraction, root tip resection), even if tooth preservation may appear questionable in some respect (46). To minimize the risk of adverse effects and ensure optimal health maintenance for oncology patients receiving frequent, high-dose bisphosphonate treatment such as zoledronic acid or pamidronate, Gupta et al. recommend avoiding dental implant placement when patients receive BPs four to twelve times per year (14). Based on current data, implant placement in patients receiving BPs for cancer-related reasons is highly contraindicated due to the high risk of developing MRONJ

(13,38,44,55,57–59). When treating patients taking high-potency BPs, it's important to exercise caution and explore less invasive treatment options to reduce the risk of osteonecrotic events while also considering the patient's quality of life.

18. Treatment for symptomatic Patients

The objective of treating individuals diagnosed with MRONJ is to halt the progression or onset of bone necrosis, alleviate pain, manage infections in both soft and hard tissues, and restore function (13,55). The treatment options for MRONJ include two major options, conservative or surgical treatment, while also a combination of both, with the addition of adjuvant therapies can be considered. While the literature and the AAOMS generally recommend an appropriate therapy that varies depending on the stage of the disease (as shown in Table 3), there is currently no standardized treatment protocol or clear boundary between treatment options (13). Thus, the treatment strategy, regardless of whether it incorporates non-surgical or surgical techniques, should be personalized based on the specific needs, potential risks, and situation of each patient. Radiographic imaging is essential for proper MRONJ lesion evaluation, diagnosis, and treatment planning in all stages. Interdisciplinary collaboration with treating physicians is universally recognized as an important component in all treatment approaches for managing MRONJ (13,14).

18.1. Conservative Therapy

Conservative treatment of MRONJ aims to alleviate pain and halt the progression of the disease. Treatment should not be delayed, even if patients are not experiencing symptoms, as the condition can still worsen. Conservative measures include management of oral conditions to maintain good oral hygiene and establish proper oral health (13,14,30,44). In addition, local measures such as antimicrobial mouthwashes and rinses with agents like chlorhexidine 0.12% and hydrogen peroxide can be used, as well as systemic agents like antibiotics, anti-inflammatory agents, antifungal agents, and analgesics. (13,14,37,38).

Regular dental check-ups are generally recommended for "at risk" patients without clinical or radiological signs of MRONJ, with recommended intervals of every year, six months, or three months, depending on the patient's individual risk factors (60). For stage 0 patients, conservative treatment involves systemic antibiotics and pain control as needed to prevent

disease progression (61). Patients with radiological abnormalities but no symptoms should be monitored every 8 weeks (60).

Stage 1 and stage 2 MRONJ treatment typically involves a conservative approach, focusing on local antibacterial rinses and monitoring with the goal of achieving soft tissue healing within eight weeks. According to AlDhalaan et al., in stage 2 patients a conservative approach to treating MRONJ involves combating inflammation using antibiotics and antimicrobial mouthwashes (61). To select an appropriate medication, it is recommended to conduct an antibiogram and examine microbial cultures in the biofilm of the necrotic area, as noted by Ruggiero et al. (55).

In order to minimize the risk of complications and ensure effective treatment for MRONJ, it is recommended to avoid surgical debridement as an initial treatment for stage 1, even when there is exposed bone present. Instead, it is advised to monitor the healing progress for a period of eight weeks. If no improvement is observed during this time, surgical debridement may be considered according to the guidelines for stage 2, which includes debridement of necrotic tissue, to eliminate any loose necrotic bone fragments and reduce soft tissue irritation (62). Scheduling periodic clinical follow-up examinations are indispensable to effectively monitor disease progression and adjust treatment as needed (10,13,30,38,44,60,62). Rugani suggests that conservative treatment should aim to alleviate acute symptoms for a minimum of two weeks, with four subsequent visits to the dentist or surgeon during this period (60).

18.2. Surgical Therapy

In the advanced stages of MRONJ, when conservative treatments have proven ineffective, it is important to consider surgical therapy, which has been shown to deliver high success rates (2,13,30,38). Surgical treatments for the disease vary depending on its stage, ranging from local surgical repairs that involve removing the infected bone and adequately closing the oral mucosa, to more extensive procedures that may require the loss of entire sections of the jaw and subsequent reconstruction under general anaesthesia (13,14,60,63).

Local debridement is typically carried out using minimal trauma techniques and is frequently conducted with the use of local anaesthesia. Surgical treatment in general involves:

- Removal of necrotic bone and mobile fragments
- Smoothing of any bone edges for jawbone correction
- Tension-free primary wound closure

(13,14,30,44,62,64).

To ensure the complete removal of necrotic bone and address any tertiary complications, such as existing jaw fractures, surgical treatment is recommended. As recommended by the AAOMS, both segmental or marginal resection of the mandible and partial maxillectomy have been identified as effective methods for managing MRONJ (13). Prior to resective surgery, it is crucial to use radiographic imaging to evaluate the extent of the lesion with precision and to appropriately plan the reconstruction of any resected portions of the jaw. If surgical repair is performed, it is recommended to take samples for histopathological analysis for differential diagnosis (37).

To summarize, while treating patients with MRONJ according to their diagnosis and stage is essential, it is equally crucial to consider individual factors such as age, gender, and underlying medical conditions to develop a patient-specific treatment plan. Therefore, implementing patient-tailored approaches is necessary to provide effective and personalized care to each patient.

18.3. Conservative vs. surgical Treatment and adjuvant Treatment Options

The initial treatment approach for patients with MRONJ should be based on the stage of the disease. However, patient-tailored approaches are necessary to account for specific factors such as age, gender and underlying medical conditions. (30,60). Non-surgical approaches can be beneficial in all stages, particularly in patients with significant comorbidities that make surgery less feasible (13,60). However, it's important to note that a conservative approach that focuses on symptom relief may be preferred for some patients, but it may not address the underlying cause of the condition. Therefore, if conservative treatment is not effective in achieving the desired outcome or showing any signs of progress, surgical approaches should be considered based on the potential benefits and risks to the patient

(13,60,65). Several studies have demonstrated that early surgical intervention for MRONJ can yield positive outcomes, while surgical interventions, in general, have been found to have higher success rates in all stages compared to conservative treatment (13,62,64,65).

To improve patient outcomes, other therapeutic approaches can be combined with alternative treatment options for MRONJ, such as hyperbaric oxygen, bone marrow stem cell intralesional transplantation, platelet-derived growth factor, and low-level laser therapy. However, given the limited data available on the use of these alternative treatment options, further research is needed to standardize their administration and optimize their clinical efficacy for MRONJ management. (10,13,14,62,64).

19. Drug Holiday

Due to the accumulation of BPs in the body caused by prolonged use of the drug, it is worth considering taking a break, known as a "drug holiday" from the medication before and after surgical interventions. The potential of drug holiday as a treatment option for the prevention of MRONJ has gained interest among dental professionals. However, it should be noted that the evidence for their effectiveness is outweighed by the evidence against it, and further research is needed to determine the overall efficacy and optimal duration of such breaks (41,58,63,66–68).

Morishita et al. studied the effects of temporary discontinuation of antiresorptive agents for 90, 120, or 180 days on the management of MRONJ and found that it had no positive impact on treatment outcomes. The study suggests that early surgical intervention is recommended as the preferred approach instead of a drug holiday (63). Ottesen et al.'s systematic review of high-dose ARD holidays for cancer patients undergoing dental surgery or tooth extraction found inconclusive evidence of their effectiveness due to different variables and observations in the available data. However, one study that met their requirements concluded that a drug holiday was not effective (41). Furthermore, a prospective in vivo study by Wang-yong et al. found that an eight-week drug holiday in osteoporotic rats did not prevent the occurrence of MRONJ-like lesions after dental extractions (66). Consistent with these findings, Aboalela et al.'s systematic review concluded that high dose antiresorptive drug ARD holiday is not effective for preventing MRONJ after tooth extraction (67).

On the other hand, a study conducted by Kim et al. focused on the effectiveness of a drug holiday in the management of MRONJ. The study included 54 MRONJ patients, 21 of whom were surgically managed with debridement or sequestrectomy, and 33 were conservatively managed using antibiotics. The results showed that a longer drug holiday did not improve symptoms in conservative management, while surgical management resulted in a good prognosis. On the other hand, they found that the duration of a drug holiday to be a prognostic factor in the surgical management group, with at least 4 months needed to prevent a poor prognosis (59). Moreover, a study by Hayashida found that discontinuing BPs during nonsurgical treatment significantly increased the cure rate in osteoporosis patients and was associated with a better treatment outcome in patients with malignant tumors, although not statistically significant. However, drug holidays did not improve outcomes in patients with either osteoporosis or malignant tumors who underwent surgical therapy (68).

The efficacy of drug holidays in preventing MRONJ is a contentious issue, and the current evidence suggests that the benefits are outweighed by the potential risks. While some studies have reported slightly enhanced positive outcomes with conservative or surgical approaches, it remains unclear whether a drug holiday, such as a 4-month pause in BP treatment, can be safely implemented without adversely affecting the patient's quality of life. It is critical to consult with the treating specialist before considering any surgical interventions and to carefully weigh the timing of BP cessation and resumption to ensure the best possible outcome for the patient's overall health.

20. Antibiotic Treatment

Antibiotic treatment during MRONJ management is widely recognized as crucial among dental professionals. BP therapy may cause osteonecrosis in previously asymptomatic patients and patients with a history of MRONJ following surgical procedures. Research has consistently demonstrated the crucial role of systemic antibiotic prophylaxis in achieving successful treatment outcomes, including the prevention of osteonecrosis, infection, and recurrence, as well as the promotion of healing (2,13,38,44,62,69). Antibiotic prophylaxis is commonly used in patients with and without previous MRONJ who are undergoing treatment with oral or IV BPs. The most frequently prescribed antibiotics for prophylaxis include penicillin, amoxicillin, amoxicillin/clavulanic acid, metronidazole, and/or a combination thereof (38,44,62,69). If a patient has an allergy to penicillin or amoxicillin,

alternative antibiotics such as erythromycin, clindamycin, or lincomycin may be prescribed instead (44,69). Zirk et al. conducted a retrospective study aimed at investigating the clinical course of patients diagnosed with stage II and III MRONJ. The study emphasized the critical role of antibiotics in the treatment of MRONJ, with ampicillin/sulbactam and clindamycin being the most frequently prescribed antibiotics. The group receiving ampicillin/sulbactam exhibited a significant reduction in the need for subsequent interventions, which highlights the importance of a suitable antibiotic regimen in preventing the recurrence of MRONJ in advanced stages. The study concluded that clindamycin is no longer a viable option for initial perioperative antibiotic treatment in patients with MRONJ stages II and III, and instead recommended piperacillin/tazobactam due to its broad-spectrum activity against gram-positive, gram-negative, and anaerobic bacteria compared to clindamycin (70). These findings underscore the critical role of appropriate antibiotic selection in effectively managing MRONJ.

Although there is no standardized treatment duration or consensus on the use of antibiotics during surgical procedures involving patients receiving oral or IV BPs, many authors recommend initiating antibiotic therapy at least one day prior to surgery and continuing systemic antibiotic therapy for about a week after the procedure to improve postoperative care (13,38,44,64,69).

Antibiotic therapy is a crucial part of conservative and surgical management for patients, whether asymptomatic or presenting MRONJ, to reduce symptomatology and prevent worsening. Although multiple studies have examined the use of antibiotics for prophylactic therapy in patients receiving oral or IV BPs, the absence of clinical data and randomized controlled trials presents a challenge in establishing a standardized treatment protocol that can be applied universally. Hence, it is crucial to take into account the individual patient's circumstances (clinical presentation, response to treatment, severity of the disease) when determining the most appropriate antibiotic, dosage, and duration.

MRONJ STAGE	THERAPEUTIC STRATEGIES
Risk stage	No treatment is indicated. Patient education. Good oral hygiene with re-examinations at least every six months.
Stage 0	Systemic treatment, including pain medication and antibiotic administration.
Stage 1	Antibacterial mouthwash. Quarterly check-ups. Patient education and regular review of the indications for continued bisphosphonate administration. Antibiotic treatment if patient's conditions is difficult.
Stage 2	Symptomatic treatment with oral antibiotics and antibacterial mouthwash. Pain management. Debridement of necrotic tissue to prevent soft tissue irritation and control infection. Common follow-ups with oral hygiene and re-evaluation of necrotic bone.
Stage 3	Antibacterial mouthwash. Broad-spectrum antibiotics. Pain management. Surgical removal of necrotic tissue or resection for long-term relief from infection and pain.

Table 3. Therapeutic approaches according to the respective stages of MRONJ (9,10,13,71).

21. Conclusion

In conclusion, this thesis has explored the implications of bisphosphonates in dental surgery, with a particular focus on medication-related osteonecrosis of the jaw. Through a comprehensive review of the literature, insights were gained into the challenges associated with the impact of bisphosphonates on dental surgery, including its pathophysiology, clinical and radiological diagnostics, and therapeutic approaches.

Despite being considered a secondary side effect, medication-related osteonecrosis of the jaw can seriously affect patients. Given the complexities involved in the management of medication-related osteonecrosis of the jaw, a proactive interdisciplinary approach that involves all medical specialists has been demonstrated to be crucial to raise awareness of the adverse effects of bisphosphonate treatment and to ensure holistic care during treatment. To achieve this, healthcare providers and drug companies should use assertive language in bisphosphonate drug recommendations to raise awareness and prevent the potential development of this condition.

The research findings suggest that it can be challenging to report the incidence and prevalence rate of medication-related osteonecrosis of the jaw accurately. To ensure accurate monitoring and reporting of such cases, it is essential to improve disease coding practices.

It was discovered, that in developing treatment plans for medication-related osteonecrosis of the jaw, dental specialists must carefully create an individual risk profile for each patient, including taking into consideration the characteristics of bisphosphonate treatment, and local and systemic factors. The risk of medication-related osteonecrosis of the jaw is greatly influenced by the choice of bisphosphonate treatment. Intravenous bisphosphonates used for cancer patients carry a higher risk of medication-related osteonecrosis of the jaw development than oral bisphosphonates used for osteoporosis, which require less stringent management. Attention should be given to early radiographic changes, such as osteolysis, osteosclerosis, thickening of the lamina dura, and persistent extraction sockets. Furthermore, it is highly advisable to incorporate the advantages of 2D and 3D radiographic modalities for diagnostic purposes and surgical planning. Research has shown that conservative treatment approaches can be utilized at all stages of medication-related osteonecrosis of the jaw, while early surgical intervention may lead to more successful outcomes and less invasive treatments. However, it has been found that the selected treatment depends on several factors and cannot be applied one to one from guidelines such as of American Association of Oral and Maxillofacial Surgeons guidelines.

Despite contrasting findings, the current research does not support the concept of drug holidays, and further investigation is required to assess their efficacy, duration, and safety. In contrast, antibiotic treatment is widely accepted as a highly effective treatment approach at all stages.

In conclusion, as the literature on medication-related osteonecrosis of jaws treatment is characterized by opposing findings and varying methodologies, this thesis argues that it is crucial to tailor treatment plans to the individual patient's unique circumstances to optimize effective treatment and minimize the risk of complications. Therefore, this thesis provides valuable insight into the importance of considering individual factors in the context of medication-related osteonecrosis of the jaw treatment. Further research is needed to fully understand the complex factors at play in the development and treatment of medication-related osteonecrosis of the jaw and to develop evidence-based treatment guidelines for clinicians to follow.

22. Sources

1. PRISMA [Internet]. [cited 2023 Apr 25]. Available from: http://www.prisma-statement.org/PRISMAStatement/FlowDiagram

2. Schreyer C. Bisphosphonat-assoziierte Kiefernekrosen: Risikofaktoren und klinische Präsentation.

3. Ziebart T. Untersuchung der Beeinflussung von Bisphosphonaten auf die Vitabilität der an der Wundheilung beteiligten Zellen in vitro [Internet]. Johannes Gutenberg-Universität Mainz; 2009 [cited 2023 Mar 12]. Available from: https://openscience.ub.uni-mainz.de/handle/20.500.12030/1596

4. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. 2008 Sep;83(9):1032–45.

5. Hadji P, Ziller V, Gamerdinger D, Spieler W, Articus K, Baier M, et al. Quality of life and health status with zoledronic acid and generic alendronate--a secondary analysis of the Rapid Onset and Sustained Efficacy (ROSE) study in postmenopausal women with low bone mass. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2012 Jul;23(7):2043–51.

6. Wardley A, Davidson N, Barrett-Lee P, Hong A, Mansi J, Dodwell D, et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. Br J Cancer. 2005 May 23;92(10):1869–76.

7. Khan MA, Partin AW. Bisphosphonates in Metastatic Prostate Cancer. Rev Urol. 2003;5(3):204–6.

8. Berenson JR, Hillner BE, Kyle RA, Anderson K, Lipton A, Yee GC, et al. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. J Clin Oncol Off J Am Soc Clin Oncol. 2002 Sep 1;20(17):3719–36.

9. Obermayer-Pietsch B, Foessl I, Dimai H. Langfristige Therapiekonzepte bei OsteoporoseLong-term treatment concepts for osteoporosis. Internist. 2021 Mar 12;62.

10. Mia-Leena Arndt. Charakterisierung der Entzündungsreaktion und Apoptosemechanismen bei der Bisphosphonatassoziierten Osteonekrose des Kiefers zur Therapieoptimierung. Christian-Albrechts-Universität zu Kiel; 2018.

11. Enssle A. Patienten mit einer Bisphosphonat – assoziierten Kiefernekrose – Eine psychometrische Evaluation [Internet]. Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU); 2017 [cited 2023 Mar 12]. Available from: https://opus4.kobv.de/opus4-fau/frontdoor/index/index/docId/9030

12. Xu XL, Gou WL, Wang AY, Wang Y, Guo QY, Lu Q, et al. Basic research and clinical applications of bisphosphonates in bone disease: what have we learned over the last 40 years? J Transl Med. 2013 Dec 11;11:303.

13. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws-2022 Update. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg. 2022 May;80(5):920–43.

14. Gupta M, Gupta N. Bisphosphonate Related Jaw Osteonecrosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2023 Mar 12]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK534771/

15. Ganapathy N, Gokulnathan S, Balan N, Maheswaran T, Venkatesan null. Bisphosphonates: An update. J Pharm Bioallied Sci. 2012 Aug;4(Suppl 2):S410-413.

16. Barbosa JS, Almeida Paz FA, Braga SS. Bisphosphonates, Old Friends of Bones and New Trends in Clinics. J Med Chem. 2021 Feb 11;64(3):1260–82.

17. Borromeo G, Tsao CE, Darby I, Ebeling P. A review of the clinical implications of bisphosphonates in dentistry. Aust Dent J. 2011 Mar 1;56:2–9.

18. Russell RGG. Bisphosphonates: from bench to bedside. Ann N Y Acad Sci. 2006 Apr;1068:367–401.

19. Bartl R, Bartl C, Gradinger R. Einsatz der Bisphosphonate in der Orthopädie und Unfallchirurgie. Orthop. 2008 Jun 1;37(6):595–614.

20.Bartl R, Bartl C, Ward A. Bisphosphonates in Medical Practice: Actions, Side Effects, and Practical Advice. Springer; 2007.

21.Glowacki JPhD. BISPHOSPHONATES AND BONE.

22.Martin TJ, Grill V. Bisphosphonates - mechanisms of action. Aust Prescr [Internet]. 2000 Jun 1 [cited 2023 Apr 13];23(6). Available from: https://www.nps.org.au/australian-prescriber/articles/bisphosphonates-mechanisms-of-action

23.Narayanan P. Denosumab: A comprehensive review. South Asian J Cancer. 2013;2(4):272–7.

24.E. Neumann, Prof. Dr. G. Schett. Knochenstoffwechsel. Molekulare Mechanismen. springermedizin.de [Internet]. 2007 [cited 2023 Mar 12];Zeitschrift für Rheumatologie. Ausgabe 4/2007. Available from: https://www.springermedizin.de/knochenstoffwechsel/8385444

25.Hadjidakis DJ, Androulakis II. Bone remodeling. Ann N Y Acad Sci. 2006 Dec;1092:385–96.

26.Florencio-Silva R, Sasso GR da S, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. BioMed Res Int. 2015;2015:421746.

27.Rucci N. Molecular biology of bone remodelling. Clin Cases Miner Bone Metab. 2008;5(1):49–56.

28.Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. Eur J Rheumatol. 2017 Mar;4(1):46–56.

29.Kuźnik A, Październiok-Holewa A, Jewula P, Kuźnik N. Bisphosphonates-much more than only drugs for bone diseases. Eur J Pharmacol. 2020 Jan 5;866:172773.

30.Hilscher U. Bisphosphonat-assoziierte Osteonekrosen der Kiefer: potentielle medikamentöse Risikofaktoren.

31.Byun JH, Jang S, Lee S, Park S, Yoon HK, Yoon BH, et al. The Efficacy of Bisphosphonates for Prevention of Osteoporotic Fracture: An Update Meta-analysis. J Bone Metab. 2017 Feb;24(1):37–49.

32.Bundesselbsthilfeverband für Osteoporose e.V. (BfO). Bundesselbsthilfeverband Osteoporos e.V. [cited 2023 Mar 12]. Available from: https://www.osteoporose-deutschland.de/

33.Body JJ, Mancini I. Bisphosphonates for cancer patients: why, how, and when? Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2002 Jul;10(5):399–407.

34.Dr. Julia Blank, Prof Dr. Gaßmann. Antiresorptive Medikamente. Bedeutung bei parodontologischen Therapien. ZWP ONLINE [Internet]. 2018;Prophylaxe. Available from: https://www.zwp-online.info/fachgebiete/prophylaxe/grundlagen/antiresorptive-medikamente-die-bedeutung-bei-parodontologischen-therapien

35.Shaw NJ, Bishop NJ. Bisphosphonate treatment of bone disease. Arch Dis Child. 2005 May;90(5):494–9.

36.Ottesen C, Schiodt M, Jensen SS, Kofod T, Gotfredsen K. Tooth extractions in patients with cancer receiving high-dose antiresorptive medication: a randomized clinical feasibility trial of drug holiday versus drug continuation. Oral Surg Oral Med Oral Pathol Oral Radiol. 2022 Feb;133(2):165–73.

37.M. Krüger, Mainz, M. Hautmann, Regensburg A. Bartella, Aachen, B. Al-Nawas, Mainz, K.A. Grötz, Wiesbaden. S2k-Leitlinie: Infizierte Osteoradionekrose (IORN) der Kiefer. AWMF Online Portal Wissienschaftlichen Med [Internet]. 2018; Available from: https://register.awmf.org/assets/guidelines/007-046l_S2k_Infizierte-Osteoradionekrose-der-Kiefer-IORN_2018-02.pdf

38.Singh M, Gonegandla GS. Bisphosphonate-Induced Osteonecrosis of the Jaws (BIONJ). J Maxillofac Oral Surg. 2020 Jun;19(2):162–7.

39.Moreno-Rabié C, Gaêta-Araujo H, Oliveira-Santos C, Politis C, Jacobs R. Early imaging signs of the use of antiresorptive medication and MRONJ: a systematic review. Clin Oral Investig. 2020 Sep;24(9):2973–89.

40.Cardoso CL, Barros CA, Curra C, Fernandes LMP da SR, Franzolin S de OB, Júnior JSF, et al. Radiographic Findings in Patients with Medication-Related Osteonecrosis of the Jaw. Int J Dent. 2017;2017:3190301.

41.Ottesen C, Schiodt M, Gotfredsen K. Efficacy of a high-dose antiresorptive drug holiday to reduce the risk of medication-related osteonecrosis of the jaw (MRONJ): A systematic review. Heliyon. 2020 Apr;6(4):e03795.

42.Faria K, Ribeiro AC, Brandão T, da Silva W, Lopes M, Pereira J, et al. Radiographic patterns of multiple myeloma in the jawbones of patients treated with intravenous bisphosphonates. J Am Dent Assoc. 2018 May 1;149:382–91.

43.He L, Sun X, Liu Z, Qiu Y, Niu Y. Pathogenesis and multidisciplinary management of medication-related osteonecrosis of the jaw. Int J Oral Sci. 2020 Oct 21;12(1):30.

44.Gupta S, Gupta H, Mandhyan D, Srivastava S. Bisphophonates related osteonecrosis of the jaw. Natl J Maxillofac Surg. 2013;4(2):151–8.

45.Staehler P. Risikofaktoren für das Auftreten einer MRONJ bei Patienten mit oralen Implantaten. 2019;

46.Ripamonti CI, Maniezzo M, Campa T, Fagnoni E, Brunelli C, Saibene G, et al. Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. Ann Oncol Off J Eur Soc Med Oncol. 2009 Jan;20(1):137–45.

47.Açil Y, Möller B, Niehoff P, Rachko K, Gassling V, Wiltfang J, et al. The cytotoxic effects of three different bisphosphonates in-vitro on human gingival fibroblasts, osteoblasts and osteogenic sarcoma cells. J Cranio-Maxillo-fac Surg Off Publ Eur Assoc Cranio-Maxillo-fac Surg. 2012 Dec;40(8):e229-235.

48.Russell RGG. Bisphosphonates: the first 40 years. Bone. 2011 Jul;49(1):2–19.

49.The Web's Free 2023 ICD-10-CM/PCS Medical Coding Reference [Internet]. [cited 2023 Apr 19]. Available from: https://www.icd10data.com/

50.ICD-10-GM-2023 Code Suche [Internet]. [cited 2023 Apr 19]. Available from: https://www.icd-code.de/

51.Anastasilakis AD, Pepe J, Napoli N, Palermo A, Magopoulos C, Khan AA, et al. Osteonecrosis of the Jaw and Antiresorptive Agents in Benign and Malignant Diseases: A Critical Review Organized by the ECTS. J Clin Endocrinol Metab. 2022 Apr 19;107(5):1441–60.

52.Manfredi M, Mergoni G, Goldoni M, Salvagni S, Merigo E, Meleti M, et al. A 5-year retrospective longitudinal study on the incidence and the risk factors of osteonecrosis of the jaws in patients treated with zoledronic acid for bone metastases from solid tumors. Med Oral Patol Oral Cir Bucal. 2017 May;22(3):ee42-e348.

53.Mücke T, Krestan CR, Mitchell DA, Kirschke JS, Wutzl A. Bisphosphonate and Medication-Related Osteonecrosis of the Jaw: A Review. Semin Musculoskelet Radiol. 2016 Jul;20(3):305–14.

54.Kawahara M, Kuroshima S, Sawase T. Clinical considerations for medication-related osteonecrosis of the jaw: a comprehensive literature review. Int J Implant Dent. 2021 May 14;7:47.

55.Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg. 2014 Oct;72(10):1938–56.

56.Gelazius R, Poskevicius L, Sakavicius D, Grimuta V, Juodzbalys G. Dental Implant Placement in Patients on Bisphosphonate Therapy: a Systematic Review. J Oral Maxillofac Res. 2018;9(3):e2.

57.Giovannacci I, Meleti M, Manfredi M, Mortellaro C, Greco Lucchina A, Bonanini M, et al. Medication-Related Osteonecrosis of the Jaw Around Dental Implants: Implant Surgery-Triggered or Implant Presence-Triggered Osteonecrosis? J Craniofac Surg. 2016 May;27(3):697–701.

58.Kwon TG, Lee CO, Park JW, Choi SY, Rijal G, Shin HI. Osteonecrosis associated with dental implants in patients undergoing bisphosphonate treatment. Clin Oral Implants Res. 2014 May;25(5):632–40.

59.Holzinger D, Seemann R, Matoni N, Ewers R, Millesi W, Wutzl A. Effect of dental implants on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg. 2014 Oct;72(10):1937.e1-8.

60.Rugani, Petra; Dr. med. dent. Evaluierung verschiedener Behandlungsstrategien von Bisphosphonat-assoziierter Osteonekrose der Kieferknochen – Erstellung eines Behandlungskonzeptes [Internet]. Universitätsklinik für Zahnmedizin und Mundgesundheit; Available from: https://online.medunigraz.at/mug_online/wbAbs.showThesis?pThesisNr=37900&pOrgNr=1&pPersNr=51707

61.AlDhalaan NA, BaQais A, Al-Omar A. Medication-related Osteonecrosis of the Jaw: A Review. Cureus. 12(2):e6944.

62.Eguchi T, Kanai I, Basugi A, Miyata Y, Inoue M, Hamada Y. The assessment of surgical and non-surgical treatment of stage II medication-related osteonecrosis of the jaw. Med Oral Patol Oral Cir Bucal. 2017 Nov;22(6):e788–95.

63.Morishita K, Soutome S, Otsuru M, Hayashida S, Murata M, Sasaki M, et al. Relationship between drug holiday of the antiresorptive agents and surgical outcome of medication-related osteonecrosis of the jaw in osteoporosis patients. Sci Rep. 2022 Jul 7;12(1):11545.

64.Marcianò A, Rubino E, Peditto M, Mauceri R, Oteri G. Oral Surgical Management of Bone and Soft Tissues in MRONJ Treatment: A Decisional Tree. Life Basel Switz. 2020 Jun 29;10(7):99.

65.Ristow O, Rückschloß T, Müller M, Berger M, Kargus S, Pautke C, et al. Is the conservative non-surgical management of medication-related osteonecrosis of the jaw an appropriate treatment option for early stages? A long-term single-center cohort study. J Cranio-Maxillo-fac Surg Off Publ Eur Assoc Cranio-Maxillo-fac Surg. 2019 Mar;47(3):491–9.

66.Zhu W yong, Yang W fa, Wang L, Lan X, Tao Z ying, Guo J, et al. The effect of drug holiday on preventing medication-related osteonecrosis of the jaw in osteoporotic rat model. J Orthop Transl. 2023 Mar 1;39:55–62.

67.Aboalela AA, Farook FF, Alqahtani AS, Almousa MA, Alanazi RT, Almohammadi DS. The Effect of Antiresorptive Drug Holidays on Medication-Related Osteonecrosis of the Jaw: A Systematic Review and Meta-Analysis. Cureus. 2022 Oct;14(10):e30485.

68.Hayashida S, Yanamoto S, Fujita S, Hasegawa T, Komori T, Kojima Y, et al. Drug holiday clinical relevance verification for antiresorptive agents in medication-related osteonecrosis cases of the jaw. J Bone Miner Metab. 2020 Jan 1;38(1):126–34.

69.Bermúdez-Bejarano EB, Serrera-Figallo MÁ, Gutiérrez-Corrales A, Romero-Ruiz MM, Castillo-de-Oyagüe R, Gutiérrez-Pérez JL, et al. Prophylaxis and antibiotic therapy in management protocols of patients treated with oral and intravenous bisphosphonates. J Clin Exp Dent. 2017 Jan 1;9(1):e141–9.

70.Zirk M, Kreppel M, Buller J, Pristup J, Peters F, Dreiseidler T, et al. The impact of surgical intervention and antibiotics on MRONJ stage II and III – Retrospective study. J Cranio-Maxillofac Surg. 2017 Aug 1;45(8):1183–9.

71.Dr. med. Dr. dent. Christian Diegritz. Vermeidung von medikamenten-assoziierten Kiefernekrosen in der Endodontie. Quintessenz Verl-GmbH [Internet]. 2019 [cited 2023 Mar 12];Quintessenz Zahnmedizin(Endodontie). Available from: https://www.quintessence-publishing.com/deu/de/news/zahnmedizin/endodontie/vermeidung-von-medikamentenassoziierten-kiefernekrosen-in-der-endodontie