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BİSPHOSPHONATES IN DENTİSTRY

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REVİEW

Abstract

Bisphosphonates are widely used in a variety of conditions, particularly in postmenopausal women to prevent age-related osteoporosis and associated fractures. They are also used to treat malignant hypercalcemia, Paget's disease, and to prevent bone metastases from cancers such as lung, prostate, and colon cancer. However, a significant side effect of bisphosphonate therapy is the potential for bone tissue necrosis.

Bisphosphonate-induced osteonecrosis of the jaw (BIONJ) is a particularly common complication in patients receiving bisphosphonate therapy. This condition primarily affects the maxilla and mandible, areas that undergo bone remodeling at a higher rate than other sites in the skeleton. The clinical presentation of BIONJ can be highly variable, ranging from localized, non-healing bone lesions to extensive areas of exposed necrotic bone. This variability in presentation presents significant challenges for diagnosis and management in the dental office.

Given the prevalence of bisphosphonate use and the associated risks, dentists must exercise caution when treating patients on these medications. For patients diagnosed with BIONJ, it is essential that dental treatment plans are developed in close collaboration with relevant medical specialists. Ideally, comprehensive dental treatment should be completed prior to initiation of bisphosphonate therapy to minimize the risk of complications.

The purpose of this study is to review and present current treatment modalities for patients on bisphosphonate therapy, focusing on both the systemic and local effects of these drugs. By synthesizing the most recent literature, this study aims to provide evidence-based guidelines for dental practitioners managing patients who are either currently taking bisphosphonates or have a history of bisphosphonate use.

Key Words: Bisphosphonates, osteonecrosis, dental management, BIONJ

Introduction

Bisphosphonates are widely used drugs for the treatment of various bone diseases (1,2). They are particularly favored in postmenopausal women for the prevention of age-related osteoporosis and associated fractures. They are also used to treat malignant hypercalcemia, Paget's disease (3,4), and to prevent bone metastases from cancers such as lung, prostate, and colon cancer (5-7).

The mechanism of action of these drugs is based on their function as synthetic analogues of endogenous inorganic pyrophosphates that regulate bone metabolism (1,2). They primarily inhibit osteoclast metabolism, thereby reducing bone resorption. These properties make them valuable in the treatment of a variety of bone-related disorders (3,4). Bisphosphonates are classified into two groups: nitrogen-containing and non-nitrogen-containing, with the nitrogen-containing group being more effective on osteoclasts (8).

However, the use of bisphosphonates in dental practice can lead to complications, most notably bisphosphonate-induced osteonecrosis of the jaw (BIONJ). This condition presents unique challenges for dental practitioners managing patients on bisphosphonate therapy (1,5).

Given the widespread use of bisphosphonates and the potential for serious oral complications, it is critical for dental professionals to understand how to effectively manage patients on bisphosphonate therapy.

The purpose of this study is to review and present current treatment modalities for patients on bisphosphonate therapy, focusing on both the systemic and local effects of these drugs. By synthesizing the most recent literature, we aim to provide evidence-based guidelines for dental practitioners managing patients who are either currently taking bisphosphonates or have a history of bisphosphonate use.

Mechanism of action and pharmacokinetics of bisphosphonates

The primary biological action of all bisphosphonates is to inhibit bone resorption, thereby reducing bone turnover and regeneration. Bisphosphonates bind to hydroxyapatite crystals in bone and are removed only by acid dissolution by osteoclasts. During normal bone remodeling,

osteoclasts resorb bone and internalize bisphosphonates, leading to osteoclast death (9). This process results in the disruption of key bone-inducing proteins, including bone morphogenetic protein (BMP) and insulin-like growth factors (IGFs), preventing the removal of old bone and inhibiting the formation of new osteoid. As a result, old bone persists beyond its programmed lifespan, leading to hypermineralization and the characteristic effects of bisphosphonate toxicityc (9,10).

Osteoblasts and osteoclasts influence each other through differential and inhibitory feedback mechanisms during bone resorption. Osteoblasts release BMP, IGF-1 and IGF-2, which are potentiated and promote osteoblast differentiation to regenerate resorbed bone. However, the balance between bone resorption and formation is critical; if resorption exceeds new bone formation, it can lead to fractures and weakness. Osteoblasts regulate this process by secreting osteoprotegerin (OPG), which competes with Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) to modulate osteoclast activity (Fig. 1) (10).

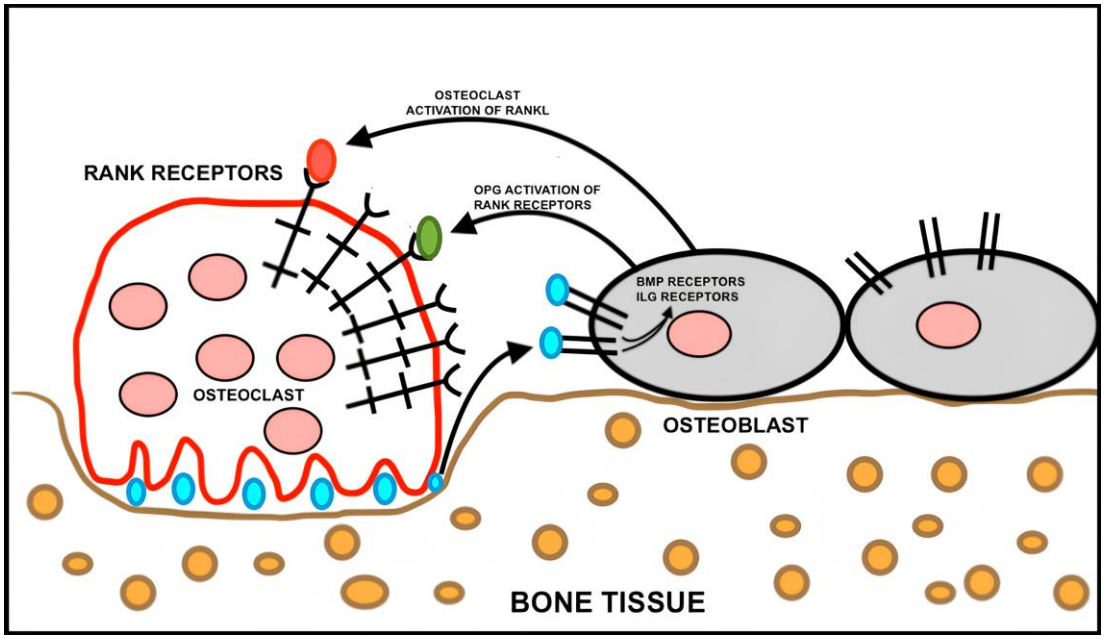

Figure1. Mechanism by which osteoblasts and osteoclasts act on each other (Marx RE 10).

This complex interplay between osteoblasts and osteoclasts underlies the bone remodeling cycle, and bisphosphonates may disrupt this balance through their effects on osteoclast metabolism.

Indications for use of bisphosphonates

1. Cancers and bone metastases

Cancer itself can resorb bone by secreting RANKL and other osteoclast stimulating factors (11,12). When activated by pathological processes such as cancer, osteoclasts cannot distinguish this stimulation from physiological responses. Cancer can induce bone resorption through the secretion of cytokines that activate osteoclasts. This process disrupts normal bone remodeling and creates space for tumor growth, leading to severe bone pain, fractures, and potential loss of bone integrity. Bisphosphonates can mitigate these effects by reducing osteoclast activity and thereby limiting the extent of bone destruction and associated complications. (Fig. 2) (9,13).

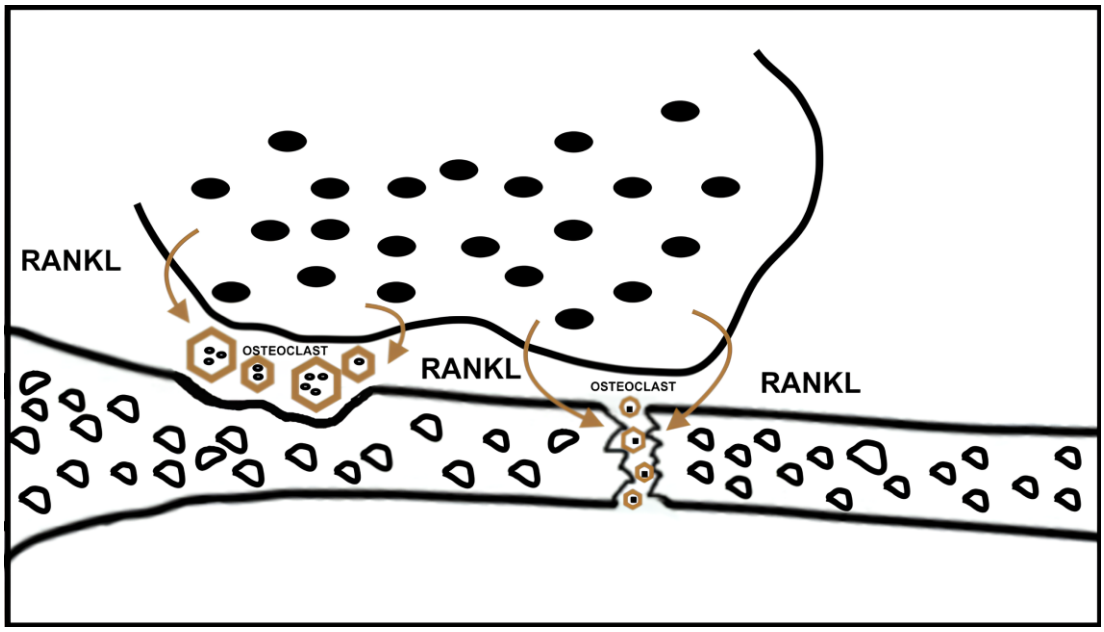

Figure 2. Mechanism of bone metastasis of cancers (9).

Bisphosphonates such as pamidronate and zoledronate, reduce the osteoclast population, thereby preventing metastasis independent of RANKL or other osteoclast-activating factors secreted by cancers. Although not primarily anticancer agents, bisphosphonates have significantly improved the duration and quality of life of patients with metastatic cancer in the bone (11,12). This benefit has often overshadowed the potential complications of osteonecrosis associated with these drugs. Currently, patients with multiple myeloma, metastatic breast cancer, metastatic prostate cancer and other cancers benefit from bisphosphonate therapy.

2. Hypercalcemia in malignancies

Intravenous bisphosphonates are most used to treat hypercalcemia associated with small cell lung cancer, multiple myeloma, prostate cancer and, less commonly, oropharyngeal squamous cell carcinoma (6,14,15).

Hypercalcemia in cancer patients can result from two primary mechanisms: Parathyroid hormone-like peptide secretion into the bloodstream and RANKL-like protein release. Bisphosphonates are effective in treating hypercalcemia by targeting these mechanisms and inhibiting bone resorption.

Pamidronate is indicated as a single dose for the treatment of hypercalcemia, administered either orally or intravenously (16). Studies have shown that in hypercalcemia due to oropharyngeal malignancy, a 4mg dose of zoledronic acid (Zometa) can reduce serum calcium levels from over 17mg/dl to the normal range (8.5-11.5mg/dl) within 24 hours. This rapid normalization of hypercalcemia and associated symptoms demonstrates the potent inhibitory effect of intravenous bisphosphonates on osteoclast activity (10).

3.Paget's disease

Paget's disease is characterized by a significant disruption of the bone remodeling cycle. This condition leads to severe alterations in bone resorption and apposition, which decreases compressive strength, increases vascularity, and often results in bone pain and elevated serum alkaline phosphatase levels.

Paget's disease primarily affects adults over the age of 40 and has been effectively treated with bisphosphonates (4). These drugs are successful in relieving bone pain, reducing bone turnover, and normalizing alkaline phosphatase levels. Among bisphosphonates, etidronate (Didronel) and tiludronate (Skelid) are the most commonly prescribed, although all bisphosphonates have shown efficacy in treating Paget's disease. Importantly, bisphosphonates used for Paget's disease have not been associated with osteonecrosis (10).

4. Osteoporosis

Osteoporosis is a common bone disease affecting adults over the age of 45, with increased incidence and severity in postmenopausal women. The condition is characterized by increased

fibrous adipose tissue in the bone marrow, resulting in decreased trabecular bone density and a more porous bone structure. Clinically, it results in reduced resistance to compression, vertebral compression fractures, and an increased risk of fractures from minor trauma or spontaneously. Bisphosphonates are important in the treatment and prevention of osteoporosis by inhibiting bone resorption and binding to hydroxyapatite crystals in bone (16-19). Common oral bisphosphonates prescribed for osteoporosis include alendronate, risedronate, and ibandronate (20).

Bisphosphonate-induced osteonecrosis of the jaw (BIONJ)

BIONJ is a distinct condition characterized by exposed bone in the maxilla or mandible that persists for more than 8 weeks in patients with a history of bisphosphonate use and no prior radiation to the jaw. It can occur spontaneously or following invasive dental procedures such as tooth extraction, periodontal surgery, apical resection, or dental implant placement (5,19). BIONJ has only been observed in the jaw, not in other skeletal regions, although long-term alendronate use has been associated with femur fractures (21,22). Osteonecrosis usually begins in the alveolar bone and may extend to the ramus or basal bone of the jaw (5). Subclinical radiographic signs may include sclerosis or loss of the lamina dura and widening of the periodontal space. Incidence rates are reported to be 60% in the mandible, 30% in the maxilla, and 10% in both jaws, reflecting the blood supply characteristics of these areas (1). Special attention should be paid to the alveolar process, as this is where exposed bone typically first appears in BIONJ cases.

1. Oral bisphosphonate-induced osteonecrosis of the jaw

The development of BIONJ is influenced by several factors, including the route of administration and the type and dose of bisphosphonate used. Osteonecrosis induced by oral bisphosphonates differs from that induced by intravenous administration in three important ways (23,24).

A longer duration of bisphosphonate use is usually required for bone exposure to occur, and when it does occur, the exposure is generally smaller and less symptomatic. Discontinuation of

oral bisphosphonates often leads to gradual improvement and spontaneous healing within 6-12 months, with increased responsiveness to local debridement (10).

2. BIONJ from the use of bisphosphonates in intravenous

The incidence of BIONJ is closely related to the potency, duration and frequency of the specific bisphosphonate used. For example, zoledronic acid (Zometa), the most potent bisphosphonate, can lead to bone exposure within 3-12 months when administered at the recommended monthly dose of 4mg (10).

It's important to note that osteonecrosis in patients taking bisphosphonates can occur in unexposed areas of the jaw or other parts of the skeleton. The American Association of Oral and Maxillofacial Surgeons (AAOMS) defines such cases as 'stage 0 bisphosphonate-induced osteonecrosis (25).

Marx (25) and the AAOMS have revised their staging system, recognizing that pain, previously a key criterion, is more indicative of secondary infection than osteonecrosis itself. The new staging system focuses on clinical assessment of the extent of bone necrosis and radiographic assessment of bone involvement:

Stage 0: No exposed bone in the jaw or other skeletal areas.
Stage 1: Exposed bone in one quadrant or less, without alveolar osteolysis or sinus involvement (Fig. 3).

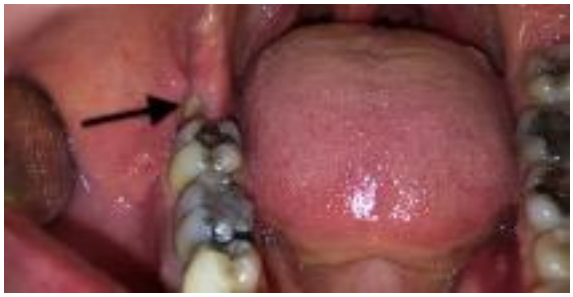

Figure 3. BIONJ Stage 1

Stage 2: Exposed bone in two or more quadrants, without alveolar osteolysis or sinus involvement (Fig. 4).

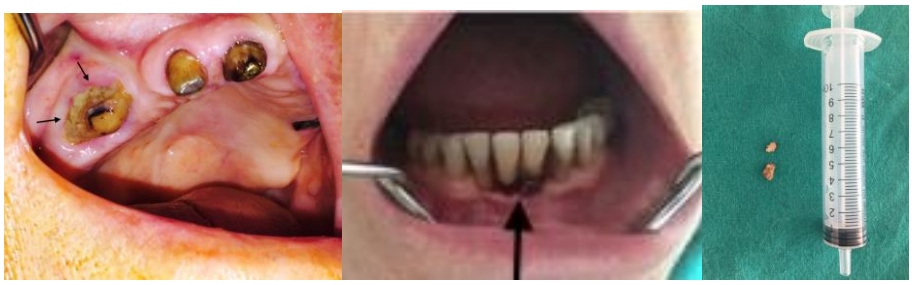

Figure 4. BIONJ Stage 2

Stage 3: Presence of alveolar osteolysis, pathologic fracture, skin fistula or sinus involvement (Fig. 5).

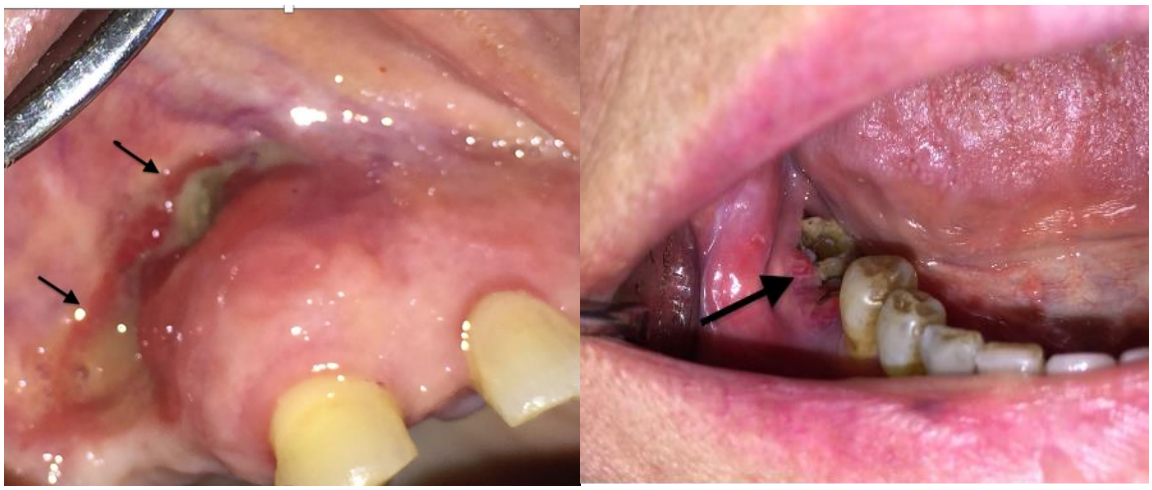

Figure 5. BIONJ Stage 3

Prevention, treatment and management of BIONJ

In stage 0 BIONJ patients, preventive measures are critical. These include elimination of existing inflammatory dental pathology, extraction of periodontally unsalvageable teeth, caries control, periodontal care, and planning for fixed or removable dentures. In addition, impacted teeth not associated with the oral environment should not be extracted and multilobulated tori should be removed.

In Stage-1, Stage-2 and selected Stage-3 cases, treatment focuses on controlling secondary infection, relieving pain and restoring function. Local debridement is generally ineffective and can result in large areas of exposed bone and is therefore not recommended in cases of intravenous BIONJ. The primary goals in these cases are to control pain and limit the spread of

secondary infection and exposed bone. These goals are typically achieved with bactericidal agents such as chlorhexidine and antibiotics (10).

1. A typical antibiotic regimen

-Rinse mouth with 0.12% chlorhexidine mouthrinse three times daily. Prolonged use of chlorhexidine may cause taste disturbance, staining of hard tissues and alteration of the normal oral flora.
-Quinolones (e.g., levofloxacin) should not be used for more than two weeks due to their chondrotoxic effects.
-Azithromycin should not be used for more than two weeks to avoid elevation of liver enzymes.
-Lincosamides, such as clindamycin, have excellent bone penetration and are used for osteomyelitis. However, clindamycin is ineffective against Eikenella, Moraxella and Actinomyces species, which may cause secondary infections in BIONJ. This regimen is used to treat secondary infections, which are often recurrent (9).

2. Advanced treatment for Stage-3 BIONJ

For Stage-3 patients with pathologic fractures or recurrent flares, more extensive surgery may be required. In the maxilla, resection may include hemimaxillectomy with debridement of the infected sinus membrane. Small defects after hemimaxillectomy can be closed with buccal fat transfer, while larger defects may require a temporal muscle flap. Otherwise, a maxillary obturator will be required to manage the oroantral-nasal relationship. By implementing these preventive measures and treatment strategies, the management of BIONJ can be optimized to improve patient outcomes and quality of life (10).

Hyperbaric oxygen therapy (HBOT) is an effective approach to the prevention and treatment of osteonecrosis of the jaw. Osteonecrosis caused by radiation therapy reduces the number and type of cells that help bone heal. The irradiated area becomes hypoxic, with the hypoxia concentrated mainly in the center of the tissue. Oxygen activates the remaining cells in this area and promotes rapid healing. With BIONJ, osteoclast death and impaired bone remodeling occur because of direct chemical toxicity to the osteoclasts rather than physical injury as seen with radiation therapy. Therefore, oxygen therapy is generally not considered beneficial for BIONJ.

However, laser therapy and platelet-rich plasma (PRP) have been reported to be effective in the treatment of BIONJ (26,27).

3. Prevalence and affected areas

Studies suggest that 31% of BIONJ cases involve asymptomatic bone exposure, while 69% involve both bone exposure and pain. The mandible is involved in 68% of cases, the maxilla in 28%, and both jaws in 4%. The molar region is most commonly involved, accounting for 88% of cases, with the maxillary molar region accounting for 65.5% and the mandibular molar region accounting for 22.5%. This predisposition in the molar region is due to the natural occlusal force as well as the compressive forces exerted by crown-bridge restorations or removable dentures on the bone formation cycle (23).

4. Management of bone exposure

Once bone is exposed, it is likely to be permanent, even if intravenous bisphosphonate therapy is discontinued or local debridement is performed. Most attempts at local debridement result in additional bone exposure. Therefore, treatment should focus on symptom control and limiting the spread of the disease by non-surgical means. Preventive measures should be taken before starting bisphosphonate therapy. Abscessed, unrestorable, and periodontally unsalvageable teeth should be extracted to allow time for the bone healing before starting therapy (10).

Research has shown that 25% of osteonecrosis cases develop spontaneously, while 75% result from invasive dental procedures. In a study by Marx et al, osteonecrosis following invasive procedures was attributed to tooth extraction (36%), unrestored caries (16.5%), advanced periodontal disease (17.1%), failed root canal treatment (2.6%), dental implant placement (2.6%), and apical resection (0.7%). Since 75% of cases are due to surgical dental trauma, uncontrolled occlusal trauma, or inflammatory dental disease, the most effective strategy to prevent BIONJ is to avoid the need for invasive dental surgery after initiation of bisphosphonate therapy and to eliminate inflammatory dental pathology (23).

When managing the dental health of patients receiving bisphosphonate therapy, priority should be given to caries control, tooth restoration, root canal therapy, and periodontal surgery. After these treatments, fixed or removable dentures and conventional tissue-supported full dentures

may be considered. Dental implants are unsuitable for these patients because bisphosphonates disrupt the bone remodeling cycle necessary for implant osseointegration. Studies have shown that implant treatment often fails in patients using intravenous bisphosphonates, suggesting that prosthetic restorations should be considered only after treatment with BIONJ (28).

Although routine prophylaxis is not required for noninvasive procedures, it is recommended for invasive dental procedures in patients receiving intravenous bisphosphonates due to their high risk of infection, such as those with metastatic cancer. Bisphosphonate therapy should not be deferred in patients who require noninvasive procedures such as dental cleaning, fluoridation, restorations, or dentures.

Patients receiving bisphosphonate therapy should be thoroughly informed about the effects of the drug and the potential risk of developing osteonecrosis in the future. Clear communication of these risks will help patients make informed decisions and take necessary precautions to maintain their oral health (10).

Dental procedures and the use of bisphosphonates

Oral bisphosphonates are generally less likely to cause osteonecrosis than intravenous bisphosphonates. However, certain precautions and protocols are still needed for patients on oral bisphosphonate therapy, especially those undergoing dental procedures.

For patients who have been taking oral bisphosphonates for less than two years and are at risk for osteonecrosis, the following steps are recommended:

1. Take a drug holiday: A six-month drug holiday should be initiated.
2. Measure C-terminal telopeptide-X (CTX): At the end of the six months, measure the serum CTX level.

- If the CTX level is less than 100 pg/mL, postpone the planned surgical procedure and extend the drug-free period for an additional three months.
- If the CTX level is between 100-150 pg/mL, the planned surgery can proceed, but the risk of osteonecrosis remains low.

3. Postoperative protocol: After surgery and a three-month recovery period, bisphosphonate therapy may be resumed (9,29)

For patients who have been taking oral bisphosphonates for more than three years but are not currently at risk for osteonecrosis, the following protocol should be followed:

1.Drug Interruption: Interrupt bisphosphonate use for three months if CTX level is greater than 150 pg/mL.
2.Surgery: Perform necessary surgery.
3.Postoperative protocol: After three months of recovery, resume bisphosphonate therapy.

It is critical that all decisions regarding discontinuation of bisphosphonate therapy be made by the prescribing physician. Dentists should work closely with the patient's physician to determine the best course of action.

In cases where symptomatic treatment is ineffective and emergency treatment is required (e.g., extraction of an infected tooth, pain relief, or abscess drainage), the risk of osteonecrosis can be accepted. However, the patient must be informed of the potential complications and informed consent should be obtained before proceeding with any emergency procedures. By following these guidelines, dental professionals can help minimize the risk of osteonecrosis in patients undergoing bisphosphonate therapy while ensuring that necessary dental treatments are performed safely (10).

This study highlights the need for further studies to address unresolved questions and controversies regarding bisphosphonates in dentistry. Research should focus on the long-term effects of bisphosphonates, the mechanisms leading to BIONJ, and the genetic factors contributing to its development. In addition, research into the efficacy of different bisphosphonate formulations and their interactions with other drugs used in dentistry could optimize treatment protocols and improve patient outcomes.

Conclusion

The primary goal in the management of BIONJ is to control secondary infections and prevent progression of osteonecrosis. Dentists play a critical role in this process by providing comprehensive oral care prior to bisphosphonate therapy and by educating patients about the risks and the importance of oral hygiene and regular dental examinations.

Non-invasive treatments such as antibiotics and chlorhexidine mouthwash are recommended, while invasive procedures should be avoided. Preventive care is essential given the difficulties in treating established BIONJ. For patients taking bisphosphonates, careful risk assessment should guide treatment decisions. Emerging treatments such as laser therapy and PRP show potential and require further research.

A multidisciplinary approach involving dentists, oral surgeons, and physicians is essential. By focusing on prevention, appropriate treatments, and ongoing monitoring, the risk of BIONJ can be minimized, leading to better patient outcomes.

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FIGURE LEGENDS

Figure1. Mechanism by which osteoblasts and osteoclasts act on each other (Marx RE 10).

Figure 2. Mechanism of bone metastasis of cancers (9).

Figure 3. BIONJ Stage 1

Figure 4. BIONJ Stage 2

Figure 5. BIONJ Stage 3