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BISPHOSPHONATE INDUCED OSTEONECROSIS OF THE JAWS AND CURRENT THERAPIES

Çenelerin Bisfosfonata Bağlı Osteonekrozu ve Güncel Tedaviler

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ABSTRACT

Bisphosphonates are pharmacological agents which are the potent inhibitors of osteoclastic activity. Nowadays, bisphosphonates are used to treat a variety of bone disease or related complications such as metastatic or osteolytic bone disease, hypercalcemia of malignant origin and osteoporosis. Although, bisphosphonates are significantly reduces the skeletal complications of these diseases, they are inevitably cause a specific osteonecrosis characterized by treatment resistant exposed necrotic bone, especially seen in the jaw bones where the bone turnover is high. Currently there is no definitive treatment for this complication induced by the use of bisphosphonates. The search for new treatments methods to prevent the complications that cause patients to become a victim of the economic and social aspects of this situation is still ongoing.

This review is intended to provide information about the chemical structure of bisphosphonates, their mechanisms of action and current diagnosis/treatment methods of the osteonecrosis.

Keywords: Bisphosphonates, malignant diseases, complications, osteonecrosis, treatment options.

ÖZ

Bifosfonatlar osteoklastik aktivitenin güçlü inhibitörü olan farmakolojik ajanlardır. Günümüzde osteolitik kemik hastalığı, malignite kaynaklı hiperkalsemi, metastatik kemik hastalıkları ve osteoporoz gibi birçok farklı kemik hastalığı veya ilişkili komplikasyonun tedavisinde kullanılmaktadırlar. Bifosfonatlar bu hastalıkların iskeletsel komplikasyonlarını önemli ölçüde azaltsa da özellikle yüksek kemik döngüsünün görüldüğü çene kemiklerinde tedaviye dirençli, ekspoze nekrotik kemik ile karakterize özgün bir osteonekroza neden olmaktadırlar. Bifosfonat kullanımına bağlı olarak gelişen bu komplikasyonun henüz kesin bir tedavisi bulunmamaktadır. Hastaların, bu durumun ekonomik ve sosyal yönleri nedeniyle mağdur olmasına sebep olan bu komplikasyonla mücadele etmek için yeni tedavi arayışları hala sürmektedir. Bu derlemede bifosfonatların kimyasal yapıları, etki mekanizmaları ve osteonekrozun güncel tanı /tedavi yöntemleri hakkında bilgi verilmesi amaçlanmıştır.

Anahtar Kelimeler: Bifosfonatlar, malign hastalıklar, komplikasyonlar, osteonekroz, tedavi seçenekleri.

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INTRODUCTION

Bisphosphonates (BPs) are the synthetic analogs of pyrophosphates which are the endogenous regulator of bone mineralization.[1] This pharmacological agents having a strong inhibitory effect on osteoclastic activity were first produced in Germany in the mid-19th century and used in industrial areas, in the prevention of kidney stone formation, in the content of the toothpaste and in obtaining bony gamma graphs in the past.[1-3] However, with changes in the molecular structure the effectiveness of the drug have increased.[2] BPs are currently used in the treatment of many diseases such as breast, prostate and lung cancers associated with bone metastasis, osteogenesis imperfecta, osteoporosis, paget's disease, fibrous dysplasia and multiple myeloma.[4-6]

Chemical structure of the bisphosphonate is similar to inorganic pyrophosphate and the "bis" prefix refers to two phosphonate groups attached to a common carbon atom.[7] Unlike the pyrophosphates, carbon atom is located in the center of bisphosphonates. This difference in molecular structure prevents the hydrolysis of BPs in acidic environments and increases the accumulation of bisphosphonates in the hard and soft tissues.[8] Biological activity of BPs determined by the peripheral chains. According to the nitrogen content in the peripheral chains BPs can be divided into 2 pharmacologic classes as; non-nitrogen-containing (alkaline bisphosphonates) and nitrogen-containing (aminobisphosphonates) BPs (Table 1).[9] Non-nitrogen-containing bisphosphonates are the group of bisphosphonates which have the lowest activity and show their antiresorptive effects by transforming into toxic analog of adenosine triphosphate (ATP) and inducing apoptosis.[10, 11] Antiresorptive activity of nitrogen-containing bisphosphonates involves inhibition of mevalonate pathway which is important for osteoblast function in multiple steps.[2, 10] Mevalonate pathway inhibition results with the failure of prenylation and inability of the Ras, Rho and Rac proteins that regulates the cytoskeleton organization and cell survival to be activated. Thus, intracellular vesicular transport in osteoclasts deteriorate and the resorption process is suppressed.[8, 12, 13]

Table 1. Classification of Bisphosphonates

Drug	Brand name	Generation/Type	Mechanism of action	Route	Indication	Potency
Etidronate	Didronel Disfosfen	1st/NNC	Induces osteoclastic apoptosis	PO, IV	OP, PGD, HMO	1
Clodronate	Bonefos Loron	1st/NNC	Induces osteoclastic apoptosis	PO, IV	OP, PGD	10
Tilduronate	Skelid Tildren	1st/NNC	Induces osteoclastic apoptosis	PO	PGD	10
Neridronate	Nerixia	2nd/ NC-A	Inhibits mevalonate pathway	IM, IV	OI, PGD,CRPS-I	100
Pamidronate	Aredia	2nd/ NC-A	Inhibits mevalonate pathway	IV	OP, HMO, PGD	100
Olpadronate	-	2nd/ NC-A	Inhibits mevalonate pathway	-	EP	500
Alendronate	Fosamax	2nd/ NC-A	Inhibits mevalonate pathway	PO	OP, PG	500
Ibandronate	Boniva	2nd/NC-A	Inhibits mevalonate pathway	PO, IV	OP	1000
Risedronate	Actonel Acral	3rd/NC-H	Inhibits FPS/stabilize conformational changes	PO, IV	OP, PGD, MM, HCM	2000
Zoledronate	Zometa Aclasta	3rd/NC-H	Inhibits FPS/stabilize conformational changes	IV	MM, HCM, MC	10000

NNC: Non nitrogen containing, **NC-A**: Nitrogen containing-alkyl, **NC-H**: Nitrogen containing-heterocyclic, **PO**: Peroral, **IV**: Intravenous, **IM:** Intramuscular**, OP**: Osteoporosis, **PGD**: Paget's disease, **HMO**: Hipercalcemia of malignant origin, **OI**: Osteogenesis imperfecta, **CRPS-I**: Complex regional pain syndrome type I, **MM**: Multiple myeloma, **MC**: Metastatic cancer, **EP**: Experimental purpose, **FPS**: farnesyl pyrophosphate synthase

BPs have particular affinity for hydroxyapatite crystals in areas with high bone turnover. When the bisphosphonate bound to the bone, it can remain stable for approximately 10 years without undergoing hydrolysis.[11, 13, 14] BPs show their activity by inhibiting the development and function of the osteoclasts in molecular, cellular and tissue levels.[15-17] BPs also triggers apoptosis of tumor cells, retarding tumor metastasis by anti-angiogenic properties and inhibit wound healing as well.[18-20]

BPs are drugs with low bioavailability. About 1 % of the drug from the gastrointestinal tract in oral administration and 50 % of the drug in intravenous administration is bound to the bone.[21] Mostly related to the gastrointestinal tract, BPs can cause side effects such as renal toxicity, acute renal failure and hypocalcemia.[6] Also, ocular side effects[22], osteonecrosis[23], esophageal cancer[24], atrial fibrillation[25] and

hepatitis[26] are among the other reported side effects of BPs.

Bisphosphonate-induced osteonecrosis of the jaws (BIONJ) is one of the most serious side effect of bisphosphonates which has defined as the exposed necrotic bone observed in the maxilla and /or mandible at least 8 weeks in the patients who receiving or had been exposed to a bisphosphonate and not had radiation therapy to the craniofacial region.[27] Similar findings of osteonecrosis were first seen in the match factory workers and named as 'Phossy Jaw' in 1899. Convertion of the phosphorus to the potent BPs such as pamidronate and alendronate by the chemical reactions in the body considered as the possible cause of this endemic osteonecrosis. It is reported that although phosphorus vapor in high temperature has a simple chemistry, it converted to the simple BPs when passed through the lungs and combine with the H_2O and either CO_2 and tetrahydrofolate. This simple BPs may have also circulated and combine with either ammonia or any of common amino acids in the respiratory tract such as lysine to produce more potent form of BPs.[28]

BIONJ is observed in the jaw bones rather than the other bones in the skeletal system. It is considered that the main reasons of this are the effect of tooth movement created in the periodontium and the high turn-over in the jawbones.[29] Dixon[30] investigate the remodeling rates in different regions and detected that more remodeling occurs in the alveolar crest than in tibia, in inferior border of mandible and bone in mandibular canal level; 10 times, 5 times and 3-5 times respectively. On the other hand, the microbial environment in the oral cavity, continuous relationship with the environment, susceptibility to trauma and vascularization were all shown among other factors increasing the risk of jaw bone osteonecrosis.[31, 32] In a review conducted by Hughes *et al*.[33] in 1962, it is claimed that the ideal environment for the osteonecrosis originate from the microorganisms and chemicals such as phosphorus together were the jaw bones.

Risk factors that play role in the occurrence of osteonecrosis in the jaw bones due to use of bisphosphonates has been classified as drug related, local and systemic risk factors[34] (Figure 1).

***Osteonecrosis**

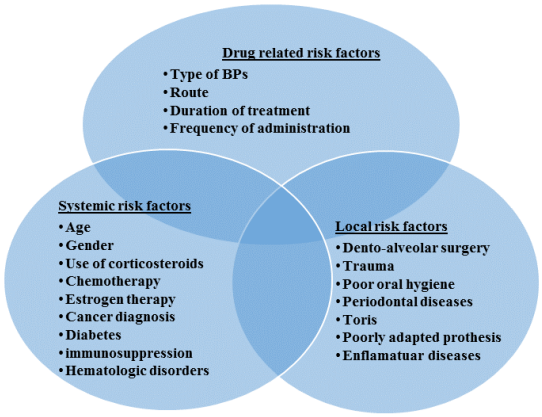

Figure 1. Risk Factors of BIONJ

In 2005 Marx *et al*.[35], in their study to evaluate inducing factors of the 119 cases of osteonecrosis, they found that osteonecrosis reported to occur in 25,2% of the cases spontaneously, 37, 8 % of the cases after tooth extraction, 28,6% of the cases associated with periodontal disease, 11,2% of the cases after periodontal surgery and 0,8% of the cases after apical resection.

The serological biochemical marker used to determine development risk of the osteonecrosis is the serum C-Terminal Telopeptide (CTX) value. CTX is the terminal cross-linked telopeptide of type I collagen which occurs in the cases of increased bone turnover, resulting the fragmentation of the type I collagen by osteoclasts.[36] However, in recent years the radiological detection of periodontal ligament expansion considered more sensitive than serum CTX in predicting the development BIONJ.[37] Also, in a case-control study conducted by Kim *et al*.[36] it is reported that the CTX values did not differ between the patients in the groups of BIONJ and non-BIONJ.

Clinically, BIONJ is characterized by the painful or painless inflammation, purulent drainage, fistula formation and osteolysis or pathologic fractures that may be associated with necrotic bone.[38, 39] Radiologically, non-specific findings of the osteonecrosis were seen in the initial phase but in the late stages sequestration, thickening of lamina dura/alveolar crest and multiple sclerotic areas can observed.[40] In radiological evaluation of BIONJ conventional radiography (panoramic radiography), bone scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) are used.[41-44] Panoramic radiography is useful in the overall evaluation of the jawbones. However, it is not possible to detect changes in bone density depends on osteonecrosis otherwise the bone mineral loss exceed the rate of 30-50 %. Also panoramic radiographs is inadequate to determine the boundaries of necrotic and healthy bones.[45, 46] Technetium-99m-methylene diphosphate bone scintigraphy assessments made by CT was confirmed to be superior to magnetic resonance methods in the diagnosis of osteonecrosis. However, the low resolution of the scintigraphic images and not being able to distinguish malignant lesions with inflammatory stages are the most important disadvantages.[43, 45] CT method is useful to determine the spread of osteonecrosis in both cortical and trabecular bone, its borders and to determine its relationship with neighboring anatomical tissue.[47] MRI techniques is gives detailed information on the presence of more soft tissue involvement.[45, 48]

Prevention and Treatment Strategies in BIONJ

In 2009 American Association of Oral and Maxillofacial Surgeons (AAOMS) has been revised the prevention and treatment strategies (Table 2-3) for patients about to begin bisphosphonate therapy, asymptomatic patients using bisphosphonates and the patients have osteonecrosis.[34]

Table 2: Prevention and treatment strategies in BIONJ

Patients about to begin bisphosphonate therapy	Asymptomatic patients who are undergoing bisphosphonate therapy		Patients with osteonecrosis
	IV	PO	
- A comprehensive oral examination - Elimination of dental pathologies -Providing optimal periodontal/oral health and patient education -Evaluation of prosthesis -Providing the time required for mucosal healing (14-21 days) or adequate healing of the bone after dento-alveolar surgery. -Medical oncologists consultation (for IV BPs)	-Providing optimal oral hygiene -Avoiding traumatic procedures. -Avoiding placement of dental implants - Non-restorable teeth may be kept in the mouth by endodontic treatment of the remaining roots	*-In the patients who have taken oral BPs less than three years:* No alteration or delay in the planned surgery with regular recall *-In the patients who have taking oral BPs less than three years and combined with corticosteroids:* Drug holiday (3 month), providing the time required for osseous healing and utilization of bone turnover marker levels suggested if systemic conditions permit. *-In patients who have received oral bisphosphonates alone or prednisone or other steroid medication more than three years:* Drug holiday (3 month), providing the time required for osseous healing and utilization of bone turnover marker levels suggested if systemic conditions permit.	-Aim: Eliminate pain, control infection, prevent progression of osteonecrosis -Surgical treatment should be delayed (if possible) -Surgery perform in the patients with stage 3 disease or patients with well-defined sequestrum -Areas of necrotic bone that are a constant source of soft tissue irritation should be removed or re-contoured -Elective dentoalveolar surgical procedures should avoided -Symptomatic patients with stage 3 disease may require resection and immediate reconstruction

Table 3: BIONJ Staging and Management

BIONJ Staging and Management (2009 AAOMS) - Current Therapies			
Stage	**Treatment**	**Treatments in Literature**	**Success Rates**
Risk category: Absence of exposed necrotic bone in asymptomatic patients treated with IV and oral BPs	*Not require treatment *Patient education	-	-
Stage 0: Non-specific symptoms or clinical and radiological findings existing without clinical symptoms of exposed necrotic bone	*Management of local factors *Providing oral hygiene *Medical treatment, including the use of antibiotic and analgesic	-	-
Stage 1: The presence of exposed necrotic bone in asymptomatic patients with no evidence of infection	*Antibacterial mouth rinses *Patient education for continuing bisphosphonate treatment *No surgical treatment is indicated	***A)****Pharmacological therapy* ***B)****Pharmacological + surgical therapy* ***C)****Pharmacological + surgical+ platelet rich plasma + laser phototherapy* ***D)****Laser assisted surgery* ***E)****Conventional surgery* ***F)****Antibiotic therapy of minor debridement surgery + HBO* ***G)****Local Debridement or Resective Intervention* ***H)****Resection of necrotic tissues, irrigation with antibiotics, application of L-PRF* ***I)****Surgical treatment with PRP*	**A)**1/3[60], **B)**3/4[60], **C)**1/2[60], **D)**1/1[61], **E)**2/7[61], **F)**3/3[62], **G)**65/108[63] **H)**7/7[64], **I)**1/1[65]
Stage 2: Pain and the clinical signs of infection in patients with exposed necrotic bone	*Symptomatic treatment with oral antibiotics *Antibacterial mouth rinses *Superficial debridement to reduce soft tissue irritation *Pain management	***A)****LLLT applications during the postoperative period in addition to medical and surgical treatment* ***B)****pharmacological + surgical therapy* ***C)****pharmacological plus surgical + platelet rich plasma + laser phototherapy* ***D)****laser assisted surgery* ***E)****Conventional surgery* ***F)****Ultrasonic (piezo) surgery + antibiotics* ***G)****Antibiotic therapy of minor debridement surgery + HBO* ***H)****Local Debridement or Resective Intervention* ***I)****Conservative treatment* ***J)****Resection of all infected tissues, intensive irrigation with antibiotics, application of L-PRF* ***K)****Teriparatide treatment* ***L)****Surgical treatment with PRP* ***M)****Fluorescence-Guided Bone Resection* ***N)****Surgical treatment with ErCrYSGG-laser* ***O)****Segmental mandibulectomy + reconstruction with fibula free flap*	**A)**9/9[66], **B)**0/1[60], **C)**8/9[60], **D)**7/9[61], **E)**3/4[61], **F)**3/4[67], **G)**5/5[62], **H)**127/203[**I)**5/8[68], **J)**18/21[64], **K)**14/15[69], **L)**26/26[65], **M)**13/15[70] **N)**5/5[71], **O)**1/2[72]
Stage 3: Pain, infection and exposed necrotic bone being associated with at least one of the following: *Necrotic bone extending to the lower limit of the alveolar bone that causes pathological fractures *Extraoral fistula, nasal or oroantral communication *Osteolysis extending to the lower limit mandible or sinus	*Antibacterial mouth rinses *Antibiotic therapy and pain control *Surgical debridement/ resection to prevent long-term pain and infection	***A)****LLLT applications during the postoperative period in addition to medical and surgical treatment* ***B)****Resection of necrotic bone followed by PRGF* ***C)****Pharmacological + surgical + platelet rich plasma + laser phototherapy* ***D)****Ultrasonic (piezo) surgery and antibiotics* ***E)****Conventional surgery + pharmacotherapy* ***F)****Combined hyperbaric oxygen (HBO) therapy* ***G)****The use of pedicled buccal fat pad combined with sequestrectomy* ***H)****Local Debridement or Resective Intervention* ***I)*** *Resection of all infected tissues, intensive irrigation with antibiotics, application of L-PRF* ***J)****Surgical resection and immediate osseous microvascular reconstruction* ***K)****Doxycycline fluorescence-guided Er:YAG laser ablation combined with Nd:YAG /diode laser* ***L)****Segmental mandibulectomy and reconstruction with fibula free flap*	**A)**2/2[66], **B)**1/1[73], **C)**3/3[60], **D)**3/4[67], **E)**12/24[74], **F)**4/4[62] **G)**3/3[75], **H)**17/37[63], **I)**18/21[64], **J)**7/7[65], **K)**1/1[76], **L)**4/6[72]

In patients with osteonecrosis conservative treatment, minor surgery, invasive surgery and non-surgical approaches are the current management options.

Conservative Approach

The goal of treatment is controlling pain and secondary infections by preventing the expansion of the necrotic bone to improve the patient's quality of life. Conservative approach is generally indicated for patients in Stage 0, 1 or 2 (Figure 2, 3) stages of BIONJ.[34]

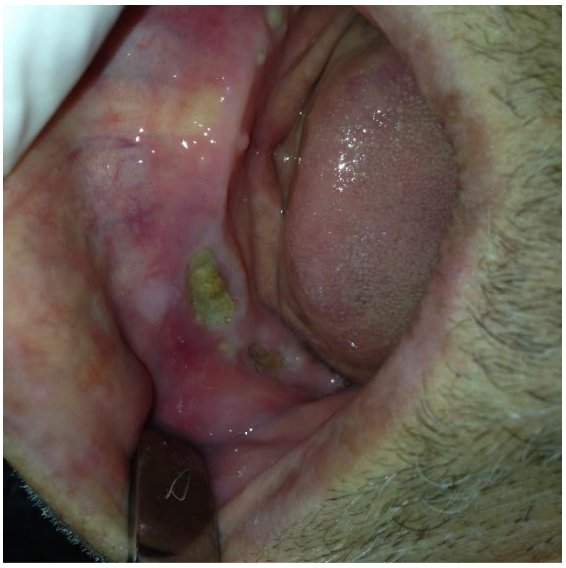

Figure 2. Clinical view of a BIONJ case

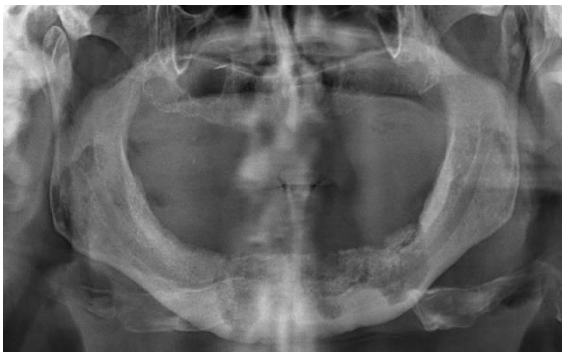

Figure 3. Panoramic view of a BIONJ case

In cases of BIONJ with symptoms of acute infection general approach is palliation of symptoms with antimicrobial chemotherapy. Penicillin or second generation cephalosporins, chlorhexidine rinses, and regular irrigation in the region is the basis of conservative treatment.[49]

Minor Surgery

Minor surgery is appropriate for patients with well limited bone sequestrum. Two different minimally invasive surgical procedures can be defined. Preventive surgery is aimed eliminate concurrent causes further worsen the patient's quality of life and palliative surgery aims to eliminate or alleviate the symptoms and osteonecrotic bone.[50]

Invasive surgery

Stage 3 symptomatic patients may require resection and emergent reconstruction using reconstruction plate or obturator. Candidates for surgery are the patients with Stage III lesions involves painful exposed bone and adjacent soft tissues, acute infection which cannot be treated with oral or IV antibiotics and extra-oral fistula or the cases of pathologic fracture.[51, 52]

Non-Surgical Alternative Treatment Methods in BIONJ

Cellular Mediators

As the Osteonecrosis is a biological degradation it is expected to be useful in treating BIONJ with growth factors. Cellular mediators play an important role in healing of bone and soft tissue defects.[53] Platelet concentrate reported in the literature as a treatment option for osteonecrosis.[54]

Low Level Laser Therapy

Low-level laser therapy (LLLT) is used in the case of BIONJ for supporting the antimicrobial chemotherapy.[55] The result of the study of Stubinger *et al.*[55] performed on 9 patients using Er-YAG laser reported to show uncomplicated postoperative recovery.

Ozone Therapy

Ozone therapy for the management of BIONJ has first reported in the literature in 2006. Rather than being a fundamental treatment, ozone therapy is used as a supportive treatment before and after surgical treatment to improve the patient's quality of life. 90 % improvement has been reported when the use of as ozone as a support to surgery and antibiotic therapy.[56]

Hyperbaric Oxygen Therapy

It is known that the effects of hyperbaric oxygen therapy (HBO) angiogenic. Although, for the treatment of osteoradionecrosis HBO is considered as a definitive treatment option, the effect HBO in the treatment and prevention of the jaw osteonecrosis has not proven yet.[57]

Hormone Treatment

In the treatment of osteonecrosis it is recommended to use of parathyroid hormone (PTH) to increase regeneration of bone. Increased PTH antagonized the effect of bisphosphonate by enhancing the tubular reabsorption of calcium in the bones and by stimulating the adrenal glands for producing 1,25-dihydroxyvitamin D.[58]

Today, there is an obvious trend towards surgical treatment in patients with a diagnosis of BIONJ. In a systematic review which aimed to investigate the efficacy of different therapeutic approaches for BIONJ, It has been shown according to research results that, regardless of the stage of the disease, a major operation or a comprehensive laser-assisted surgery which have recovery rate, respectively, 84 % and 85 % have better results compared with the conservative surgery with an average recovery rate of 75 %. Also, recovery rates for the non-surgical treatments for the combination therapy with the use of LLLT and HBO with antibiotic were found 30% and 52% respectively and recovery rate was found to be 36 % with antibiotic alone.[59]

In conclusion there is no definitive treatment for this drug specific bone necrosis yet. The search for new treatments to combat this condition is still ongoing.

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