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Osteonecrosis of the jaw as a result of bisphosphonate therapy for osteoporosis and the success of dental implantation – a review of current scientific evidence

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Abstract

Introduction: Bisphosphonates and other antiresorptive drugs are the basis of pharmacotherapy for osteoporosis and cancerous diseases affecting the bones. Despite their high clinical efficacy, a growing number of scientific reports indicate a risk of osteonecrosis of the jaw (ONJ), especially in patients receiving intravenous and long-term treatment. Due to the increasing frequency of dental implant use and the 延长 ing average life expectancy of patients, the relationship between antiresorptive therapy and the success of implantation has become an important clinical issue. Understanding the mechanisms of ONJ development, risk factors, and current treatment guidelines is crucial to ensuring the safety of patients undergoing implant procedures.

Purpose of work: The aim of this paper is to present the current state of knowledge on the relationship between bisphosphonate therapy for osteoporosis and the risk of osteonecrosis of the jaw in the context of implant procedures. The study aims to discuss the mechanisms of

action of bisphosphonates, factors predisposing to MRONJ, clinical course and treatment principles, as well as to review current recommendations for patient eligibility for implant procedures.

Materials and methods: An analysis of research papers available on PubMed and Google Scholar was undertaken using the following keywords: bisphosphonates; osteoporosis; MRONJ; medication-related osteonecrosis of the jaw; osteonecrosis; jawbone necrosis; antiresorptive therapy; dental implants; implantology; osseointegration.

Results: Analysis of current research confirms that the use of bisphosphonates, especially in intravenous form and in long-term therapy, significantly increases the risk of developing osteonecrosis of the jaw (ONJ), which may affect the success of dental implantation. In patients treated orally, this risk is lower, but not completely eliminated, especially after several years of therapy. The highest number of implant failures was reported in the lateral segments of the mandible and maxilla and in patients with existing inflammation, such as peri-implantitis, which may be a factor initiating MRONJ. Most studies indicate that implantation in patients taking oral bisphosphonates is possible but requires individual risk assessment and close monitoring. In patients treated with intravenous bisphosphonates, implantation is associated with a significantly higher risk of complications.

Keywords: Bisphosphonates; MRONJ; osteoporosis; implantology; osteonecrosis of the jaw; antiresorptive drugs; peri-implantitis; osseointegration.

OSTEOPOROSIS – INTRODUCTION

Osteoporosis is a chronic, systemic disease of the skeletal system in which bone mineral density decreases and microarchitecture is disrupted. These changes lead to weakened skeletal strength and increased susceptibility to fractures. [1] Although the diagnosis of osteoporosis is based primarily on the measurement of bone mineral density – a key parameter determining bone strength – its clinical significance stems from the occurrence of fractures. It is worth noting that the likelihood of fractures is influenced by a wide range of factors, many of which are not directly related to the condition of the bone tissue itself. [2,3,4] Although the diagnosis of osteoporosis is based primarily on the measurement of bone mineral density (BMD), which is a key indicator of skeletal strength, the actual clinical significance of the disease stems from the occurrence of fractures. It should be emphasised that the likelihood of their occurrence is influenced by many factors not directly related to the condition of bone tissue. The most commonly observed locations of osteoporosis-related fractures include the spine, hip joint,

distal radius and proximal humerus. In postmenopausal women, the risk of fracture in one of these areas is higher than the likelihood of developing breast cancer (approximately 12%). In Western European countries, the total chance of fracture in any of these areas exceeds 40%, which is comparable to the risk of developing ischaemic heart disease. [5] Fractures in the proximal end of the femur are associated with sudden onset of severe pain and significant functional impairment and almost always require hospital treatment. The recovery process is lengthy and full function is often not possible, meaning that some patients require long-term institutional care. Vertebral fractures can also cause acute pain and functional impairment, but they are often asymptomatic or oligosymptomatic. They tend to recur, and the degree of disability increases with the number of fractures suffered. In turn, injuries to the distal radius are associated with significant pain and temporary limb dysfunction, but the prognosis for recovery is generally favourable.

TREATMENT OF OSTEOPOROSIS – PHARMACOLOGICAL AND NON-PHARMACOLOGICAL

Non-pharmacological treatment includes:

- Regular physical activity – including weight-bearing exercises, resistance training and balance exercises; this has a beneficial effect on bone mineral density and reduces the risk of falls;
- Avoiding immobilisation – prolonged inactivity accelerates bone loss;
- Quitting smoking – nicotine disrupts bone metabolism and increases the risk of fractures;
- Limiting alcohol consumption – excessive consumption has a negative effect on bones and promotes falls;
- Calcium – the recommended intake is usually 1000-1200 mg/day (from diet or supplements);
- Vitamin D – supplementation aimed at maintaining a 25(OH)D concentration above 30 ng/ml, which supports mineralisation and reduces the risk of falls;
- Protein – adequate intake (1-1.2 g/kg body weight/day) improves muscle function and supports bone regeneration;

- Balance and proprioception training;
- Correction of visual impairments;
- Modification of the home environment (removal of barriers, improvement of lighting);
- Appropriate treatment of neurological and cardiac conditions that contribute to falls.

Pharmacological treatment of osteoporosis involves two main groups of drugs: antiresorptive drugs (inhibiting bone loss) and anabolic drugs (stimulating bone formation). The most commonly used antiresorptive drugs are: bisphosphonates – these are the first-line treatment for most patients. This group is divided into three main generations.
The **first generation** includes: etidronate and clodronate;
The **second generation** includes: tiludronate, pamidronate and alendronate;
The **third generation** includes: risendronate, ibandronate and zolendronate.
Bisphosphonates remain a key group of drugs used in the treatment of osteoporosis. The anti-fracture effect of bisphosphonates results from their multifaceted action. Studies have shown that these drugs increase bone mineral density and reduce the risk of fractures both within and outside the spine. [6,7,8,9] Despite the emergence of new therapeutic strategies, these drugs remain the cornerstone of pharmacotherapy. Recent research has focused primarily on developing dosing regimens that allow for less frequent administration (e.g., weekly, monthly or every few months) to increase treatment comfort and improve compliance. [10,11,12,13] Bisphosphonates have a strong antiresorptive effect by inhibiting osteoclast function and inducing their apoptosis, and additionally have an indirect effect on reducing osteoblast activity. [14] Bisphosphonates also affect the process of bone formation, limiting the surface area of new bone by reducing the frequency of bone remodelling cycle activation. [15] The effect on bone formation is less than that on resorption inhibition, but ultimately leads to an increase in bone mineral density (BMD). The duration of the effect of bisphosphonates depends on their potency, the dose administered, the intervals between doses and the rate of bone remodelling. [16]

Currently, bisphosphonates are primarily used in the prevention and treatment of bone metastases through [17]:

- Inhibition of bone resorption by limiting osteoclast activity and shortening their survival time;
- Inhibition of cancer cell proliferation and acceleration of their apoptosis;
- Slowing down the migration of cancer cells to the bone matrix;
- Treating osteoporosis by reducing the rate of bone turnover and shifting the metabolic balance of bone in favour of bone formation, leading to a gradual increase in bone mass, especially in the spine and pelvis;
- Diagnostic tests, such as bone scintigraphy, where bisphosphonates are used as markers to assess bone metabolism.

Adverse clinical symptoms associated with bisphosphonate treatment may include:

- Osteonecrosis of the jaw – According to a literature review by Woo et al., most cases of this complication (94%) occurred in patients receiving high doses of intravenous bisphosphonates, mainly zoledronic acid and pamidronate. [18] When mandibular osteonecrosis is diagnosed, treatment is mainly based on conservative methods, including the use of antiseptic mouthwashes, antibacterial therapy and, if necessary, limited surgical debridement, which in most cases results in a cure. [19]. In addition, the strong antiangiogenic properties of antiresorptive drugs lead to a significant reduction in the vascularisation of the jawbones during periods of rapid metabolic growth, when the demand for blood supply is increased. [17]
- Atrial fibrillation - In patients receiving intravenous zoledronic acid once a year, a statistically significant increase in the incidence of severe episodes of atrial fibrillation, defined as events resulting in hospitalisation, temporary incapacity for work or assessed as life-threatening, has been observed. [20]
- Hypocalcaemia - Hypocalcaemia following bisphosphonate use occurs most commonly after intravenous administration and may affect patients with high osteoclastic bone resorption activity, such as those with Paget's disease. [21]
- Acute inflammatory reaction - Acute inflammatory reactions occur in 10-30% of patients receiving their first infusion of nitrogen bisphosphonates. They usually manifest as transient fever, muscle, joint and head pain, and flu-like symptoms. It is believed that these acute phase symptoms result from the secretion of pro-inflammatory cytokines by peripheral Tγβ lymphocytes. [22]

- Excessive bone turnover - bisphosphonates suppress osteoclast activity, raising concerns that long-term therapy with these drugs may lead to so-called ‘bone freezing’, manifested by excessive inhibition of bone remodelling, impaired microfracture repair capacity and increased bone fragility. An increased incidence of microfractures has been reported in studies on dogs treated with high doses of bisphosphonates. [23]
- Severe musculoskeletal pain - most oral and intravenous bisphosphonate preparations indicate musculoskeletal pain as a possible side effect, and the US FDA recently issued a warning emphasising that severe and debilitating musculoskeletal pain can occur at any time during bisphosphonate therapy. [24]

DRUG NECROSIS OF THE JAWBONE – MRONJ

Antiresorptive drugs, by inhibiting the proliferation of squamous epithelial cells, slow down the healing of damage to the oral mucosa, which normally protects the jawbones. As a result, a gateway for infection in the bone is created, which can lead to the development of bisphosphonate-associated osteonecrosis of the jaw. Bisphosphonate-associated osteonecrosis of the jaw is defined as the presence of an exposed, necrotic bone fragment in the maxillofacial region that does not heal for at least 8 weeks in a patient who is currently or has previously taken bisphosphonates, with no prior radiotherapy to the head and/or neck. There is complete agreement that the highest risk of this complication is in patients receiving intravenous antiresorptive drugs used long-term in cancer therapy, primarily pamidronate and zoledronate. Oral bisphosphonates, such as alendronate, risedronate and clodronate, used in both cancer and osteoporosis treatment, are associated with a lower risk of developing osteonecrosis of the jaw, but do not eliminate it completely. [17] The annual incidence of MRONJ is higher in patients receiving high doses of antiresorptive therapy (2,305.8 cases per 100,000 people) compared to those receiving low doses (132.5 cases per 100,000 people). Among people who do not use antiresorptive drugs, the incidence of osteonecrosis of the jaw is much lower, at only 5.1 cases per 100,000 people. [17] The annual incidence of MRONJ is higher in patients receiving high doses of antiresorptive therapy (2,305.8 cases per 100,000 people) compared to those receiving low doses (132.5 cases per 100,000 people). Among individuals who do not use antiresorptive drugs, the incidence of osteonecrosis of the jaw is significantly lower, at only 5.1 cases per 100,000 individuals. [25] Numerous other studies have also demonstrated a relationship between the occurrence of MRONJ and bisphosphonate therapy. [26,27,28]

The diagnosis of MRONJ is made when three criteria are met [29]:

1. The presence of exposed bone in the maxillofacial region persisting for more than 8 weeks.
2. No previous radiotherapy and no confirmed cancer metastases in the head and neck region.
3. Current use or previous treatment with antiresorptive drugs or angiogenesis inhibitors.

It is worth noting that MRONJ can develop as a result of soft tissue damage in the bone area and as a consequence of primary or secondary bacterial infection. The most commonly isolated microorganism in these infections is Actinomyces spp. The particular predisposition of the jaw bones to osteonecrosis results from the high level of bone remodelling – in the alveolar bone of the mandible, it is about ten times higher than in long bones, which increases susceptibility to the development of drug-induced necrosis.

In addition, excessive pressure from dental prostheses can exacerbate bone remodelling, increasing the sensitivity of the bone to drugs. Bisphosphonates released from the bone have a direct cytotoxic effect on soft tissues, reducing their resistance to mechanical trauma and bacterial and fungal invasion. Inhibition of fibroblast and keratinocyte activity also contributes to mucosal integrity disorders, which promotes the development of necrotic changes. [29]

Risk factors for MRONJ:

- Use of stronger bisphosphonates (especially newer generation preparations). The route of administration is also important – intravenous treatment is associated with a significantly higher risk of developing osteonecrosis (0.8–1.2%) compared to oral therapy, where the percentage is only 0.01–0.04%. The risk of complications increases further with the use of high doses and prolonged treatment, especially exceeding three years.
- Local conditions that increase the risk of MRONJ include any procedures that interfere with the alveolar bone, such as tooth extractions, implantations or endodontic and periodontal surgery that disrupt the continuity of the bone tissue. An additional aggravating factor is inflammation within the oral cavity and accompanying conditions, including periodontal abscesses and periapical lesions.
- Anatomical factors: lesions are more common in the maxilla than in the mandible (2:1).

- Demographic and systemic factors, including advanced age, Caucasian race, and general diseases such as diabetes or long-term glucocorticosteroid therapy. The general condition of the body, including postmenopausal status and reduced body weight, also plays an important role. [29]

The symptoms of MRONJ include:

- Exposed bone within the jaws;
- Localised pain;
- Soft tissue swelling;
- Signs of gingivitis;
- Increased mobility of previously stable teeth. [29]

We distinguish between three stages of bone necrosis.

Level of advancement	**Diagnosis**	**Treatment**
Grade 0	No signs of osteonecrosis are found in clinical examinations, but the patient may experience non-specific symptoms or ambiguous changes visible in radiological examinations.	Treatment includes local therapy along with the elimination of local risk factors, such as caries or periodontal disease. If necessary, pain relief and appropriately selected antibiotic therapy are implemented.
Grade 1	Visible exposed necrotic bone, with the patient remaining asymptomatic and showing no clinical signs of infection.	The use of oral rinses with antibacterial properties, such as a 0.12% chlorhexidine solution, is not recommended. Surgical treatment should also not be used in this case.
Grade 2	A visible area of necrotic, exposed bone accompanied by pain and clear clinical symptoms of infection.	Treatment includes antibacterial mouth rinses and appropriate antibiotic therapy. Most pathogens are penicillin-sensitive, while alternatives

		such as quinolones, metronidazole, clindamycin, doxycycline or erythromycin are used in penicillin-allergic patients. In resistant cases, prolonged intravenous combination antibiotic therapy may be required.
Grade 3	An exposed, necrotic bone fragment accompanied by pain and infection. Necrosis may extend beyond the alveolar process, potentially leading to pathological fractures, fistulas, or communication with the sinus or nasal cavity.	The procedure involves surgical debridement or resection combined with appropriately selected antibiotic therapy. Treatment of advanced forms of MRONJ or cases showing no improvement despite conservative therapy should be carried out in hospital.

To support the healing process of the extraction socket in patients using bisphosphonates and suffering from MRONJ, the use of platelet-rich fibrin (PRF) may be beneficial. The numerous growth factors present in PRF stimulate angiogenesis and contribute to the acceleration of bone tissue regeneration.

According to the guidelines developed by the Working Group of the Polish Dental Association and the National Antibiotic Protection Programme on the rational use of antibiotics in dentistry, routine antibiotic prophylaxis is recommended in patients taking bisphosphonates, denosumab or bevacizumab, if the planned procedure involves the bone structures of the jaws (including tooth extractions, alveolar surgery, endodontic procedures with surgical elements, or periodontal procedures). Prophylaxis begins the day before the procedure and continues for the next three days, which corresponds to a short-term treatment regimen.

In the presence of additional factors increasing the risk of osteonecrosis of the jaw, such as zoledronic acid therapy, intravenous administration of bisphosphonates, long-term use of these drugs (≥3 years) or previous episodes of inflammation or osteonecrosis , it is recommended to consider extending antibiotic therapy for up to 14 days as part of long-term prophylaxis.

These recommendations indicate amoxicillin with clavulanic acid as the first-choice drug: in adults at a dose of 1000 mg (875 mg + 125 mg) every 12 hours, and in children at a dose of (45 mg + 6.4 mg)/kg b.w. per day in two divided doses. In patients with hypersensitivity to β-lactam antibiotics, the recommended alternative is clindamycin administered to adults at a dose of 300 mg every 8 hours and to children at a dose of 8–16 mg/kg b.w. per day in 3–4 divided doses.
The treatment of MRONJ can be complicated and time-consuming, which emphasises the importance of determining the optimal timing for dental implant placement in patients planning to undergo antiresorptive therapy or who have a family history of osteoporosis. Proper planning of the procedure is crucial for improving implant outcomes and minimising the risk of complications. A significant challenge in dental care for patients taking antiresorptive drugs remains the insufficient awareness of doctors regarding the impact of these drugs on the development of jawbone necrosis. [30,31] Dental implants require a proper osseointegration process, but the use of antiresorptive drugs may limit bone turnover, potentially disrupting implant integration with the bone.

DENTAL IMPLANTATION

With the growing importance of implantology, numerous studies have been conducted to analyse the impact of various factors, including osteoporosis, on implant survival rates. [32] This has prompted various dental associations to develop guidelines to support dentists in the care of patients taking antiresorptive drugs:

- The European Federation of Periodontology (EFP) recommends avoiding implant placement in patients taking bisphosphonates or denosumab due to the increased risk of developing MRONJ. [33]
- In turn, the American Dental Association (ADA) indicates that in patients with non-malignant diseases undergoing antiresorptive therapy, it is possible to continue the treatment plan, provided that factors such as the drug administration schedule and duration of therapy are carefully analysed. However, in patients with malignant diseases, dental implant placement during antiresorptive therapy is contraindicated. [34]
- The National Health Service (NHS) indicates that patients receiving intravenous bisphosphonates are generally not recommended candidates for implant treatment due to the increased risk of osteonecrosis. However, individuals taking oral bisphosphonates for a short period of time have a lower risk of this complication. The risk of MRONJ

and the management of patients who start anti-resorptive therapy after implantation and full osseointegration remains unclear. [35]

Reports indicate that the presence or location of dental implants may provoke the development of MRONJ, especially in patients treated with intravenous bisphosphonates [36,37,38]. Studies documenting the occurrence of MRONJ in patients using oral bisphosphonates have also been published [39,40,41]. On the other hand, some authors [38,42,43] have not observed an increased risk of implant failure in patients taking oral bisphosphonates. Two studies (Goss [44] and Massaad [45]) presented data on the severity of MRONJ in a total of 15 dental implants. Of these, 12 failed implants were classified as stage 2 MRONJ, while 3 implants were classified as stage 3. The other studies did not report the degree of MRONJ for failed implants. Jacobsen [46] and Lazarovici [47] showed that dental implants placed in the posterior maxilla are associated with a higher risk of maxillary osteonecrosis. Studies by Seki et al. [48] indicate that peri-implantitis may act as a trigger for the development of MRONJ [49], even when the implant is already fully integrated with the bone. Inflammation and bone loss around the implant, characteristic of peri-implantitis, may create conditions conducive to the development of MRONJ. It should be emphasised that MRONJ occurs mainly within the dental implant and not in adjacent tissues, as confirmed by observations made by Pogrel and colleagues. [50] In most systematic reviews, dental implant failures occurred mainly in patients who had received intravenous bisphosphonates for more than 50 months. The most common site of implant failure was the posterior mandible, followed by the posterior maxilla. [51,52,53] In order to reduce the incidence of MRONJ, patients should be informed about potential risk factors. A study by Anitua et al. [53] showed that poorly fitting dentures, including implant-supported dentures, may also be a factor in the development of MRONJ in patients with dental implants.

Conclusions: Bisphosphonate therapy, especially intravenous preparations used in oncology, significantly increases the risk of osteonecrosis of the jaw, which may affect the success of dental implantation. In patients using oral bisphosphonates, this risk is lower, but cannot be completely ruled out. The decision to implant should be made on an individual basis, taking into account the duration of therapy, the dose of the drug, and local and general factors. Patient education, careful treatment planning, and close monitoring of the condition of the tissues surrounding the implant are also crucial. Current evidence confirms the need for

interdisciplinary cooperation between dentists, implantologists, and physicians treating osteoporosis.

Disclosure

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