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Osteonecrosis of the jaw

Osteonekroza żuchwy

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Abstract

This review looks at osteonecrosis in the stomatognathic system (mainly the jaws). Osteonecrosis of the jaw (ONJ) is a rare but serious clinical condition. It affects patients treated with bisphosphonates, and also with denosumab, mainly in oncological doses. In osteoporosis, it is a problem of relatively small significance. Article presents a thorough review of this phenomenon, including its definition, pathogenesis, risk factors, prevention and treatment methods, and its incidence rate. **(Pol J Endocrinol 2011; 62 (1): 88–92)**

Key words: *osteonecrosis of the jaw, bisphosphonates, denosumab*

Streszczenie

Praca poglądowa dotyczy osteonekrozy w układzie stomatognatycznym (głównie żuchwy). Osteonekroza żuchwy jest zjawiskiem rzadkim, ale poważnym. Dotyczy pacjentów leczonych bisfosfonianami, ale także denosumabem, głównie w dawkach onkologicznych. W osteoporozie jest to problem o bardzo małym znaczeniu. W pracy przedstawiono: definicję, patogenezę, czynniki ryzyka, sposoby zapobiegania i leczenia oraz częstość występowania tego zjawiska. **(Endokrynol Pol 2011; 62 (1): 88–92)**

Słowa kluczowe: *osteonekroza żuchwy, bisfosfoniany, denosumab*

Necrosis

From the pathological point of view, necrosis is a retrograde change, meaning death of cells or tissues in a live organism. It is induced by the activities of injuring factors, which (either directly or indirectly) inhibit blood supply to the tissues [1].

Osteonecrosis

Necrosis affects different tissues. When it affects osseous tissue, it is referred to as osteonecrosis. It is always an effect of acute ischemia, frequently resulting from: corticosteroid therapy (affecting mainly the femoral and the humeral bone), mechanical injuries of vessels, e.g. bone fractures, the presence of thrombi and embolisms developing by various causes, and medical conditions such as vasculitis or osteomyelitis [1].

There is also aseptic bone necrosis (avascular necrosis), which occurs in children and adolescents as a result of circulation disorders. This particular type of necrosis is localised in the femoral head (Perthes disease), the humeral head (Panner's disease), vertebral bodies (Scheuermann's disease) or in the sternal end of the clavicle (Friedrich's disease) [1].

Osteonecrosis in the stomatognathic system

Osteonecrosis may also affect bones in the stomatognathic system, mainly the lower and upper jaw. The most frequently observed medical conditions include:

— osteoradionecrosis (after X-ray therapeutic irradiation of head and neck regions);
— osteonecrosis in the course of corticosteroid therapy;
— osteonecrosis in the course of osteomyelitis [2].

Recently, a new type of osteonecrosis of the jaws (ONJ) has been described:

— **osteonecrosis associated with the use of bisphosphonates** (BP) (BP-induced osteonecrosis of the jaw, BONJ). The first case of BONJ was described by Marx in 2003 [3]. BONJ is a rare but serious medical condition, which may occur in patients treated with bisphosphonates, mainly in oncological doses.

BONJ definition

Understanding the proper BONJ definition is important, as it allows for its proper diagnosis.

BONJ is clinically characterised by exposed bones in the mandibular, maxillary or palatal regions, the lesions either not healing at all or healing poorly over 6–8

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Table I. *BONJ staging and treatment strategies*
Tabela I. *Stopnie zaawansowania osteonekrozy żuchwy i metody ich leczenia*

BONJ intensity stage	Definition	Treatment
Stage 1	— oral mucosa defect with bone exposure — lack of symptoms — no infection features	— prophylactic (mouth washing with 0.12% chlorhexidine solution)
Stage 2	— oral mucosa defect with bone exposure — painfulness — clinical features of infection	— prophylactic (mouth washing with 0.12% chlorhexidine solution and antibiotic therapy)
Stage 3	— oral mucosa defect with bone exposure — painfulness — clinical features of infection — additionally one or more of these symptoms: pathological fracture, fistula, osteolysis involving e,g. the lower edge of the mandible	— surgical (resection of necrotically changed tissues) — antibiotic therapy

weeks. This condition concerns subjects treated with bisphosponates, mainly in oncological doses, after exclusion of roentgenotherapy applied in this particular region, or a local neoplasmatic process [4–6].

Clinical features of BONJ

BONJ is characterised by defects of oral mucosa with bone exposure (this lesion is usually painful). Usually, the lesion occurs in the mandible (two thirds of cases) or the maxilla (one third of cases) [5, 7, 8]. Very rarely, it may affect the palate. A case report has been published describing internal auditory meatus involvement [9] and its course may be chronic and complicated.

BONJ has three intensity stages, which differ by treatment mode (Table I) [10]. Stage 1 is characterised by oral mucosa defect with bone exposure. However, this lesion does not give any symptoms and no infection features are observed. In Stage 2, the lesion is painful with clinical features of infection. Stages 1 and 2 of the disease are prophylactically treated. In Stage 3, the lesions are as described for Stage 2, but additionally accompanied by: pathological bone fraction or fistula or by extensive osteolysis. In Stage 3, surgical intervention is applied to resect necrotically damaged tissues [10].

Subjects at risk of developing BONJ

Those at some risk of BONJ development include patients treated with bisphosphonates in oncological doses, significantly exceeding the doses used in osteoporotic therapy. These are patients with malignant neoplasms, mainly carcinomas (mostly breast carcinoma, prostate carcinoma or multiple myeloma), treated for disorders of skeletal bone metabolism in the course of neoplasmatic diseases: cancer-induced bone disease and metastatic bone disease. Bisphosphonates (mainly zoledronate and pamidronate) are administered intravenously. BONJ develops, on average, after 1.5–3 years of therapy [2, 5–8, 11–13].

Risk factors for BONJ development

A number of risk factors for BONJ development have been reported in the literature [4, 5, 8, 10–13]. The higher the number of such risks in a given patient, the higher the risk of BONJ occurrence. Risk factors for BONJ development include:

— malignant neoplasmatic disease (mainly in the course of multiple myeloma and breast carcinoma, where the prevalence of BONJ cases amounts to 1–10% of BP-treated patients);
— antineoplasmatic therapy (BPs, chemotherapy);
— changes within the oral cavity of different character: surgical procedures, mainly tooth extractions (38–80% of patients), dental diseases such as caries(29% of patients), periodontitis (84% of patients), poor oral hygiene, poorly fixed dentures, traumas in the oral cavity;
— the presence of a toothless section in the mandible or the maxilla;
— intravenous BP administration (with i.v. administration, BP bioavailability is markedly higher: 50% of the drug becomes incorporated as opposed to 1% with oral BP);
— corticosteroid therapy (mainly dexamethasone);
— alcohol;
— smoking;
— concomitant diseases: anaemia, diabetes, obesity, renal insufficiency, rheumatoid arthritis, immunosuppression;
— female gender (in women, the incidence of BONJ is eight times that of men);
— old age (the risk of BONJ development increases by 1% with each life decade).

Table II. *Influence of bisphosphonates (BPs) on different cell types*
Tabela II. *Wpływ bisfosfonianów (BP) na różne linie komórkowe*

BP type	Osteoclasts	Fibroblasts	Squamous epithelial cells	BONJ
Clodronate N(–)	+	weakly +	–	none
Ibandronate N(+)	++	++	++	reported
Pamidronate N(+)	+++	+++	+++	reported
Zoledronate N(+)	++++	++++	++++	reported

N(–) nitrogen-free BP; N(+) nitrogen-containing BP; suppressive effect + ; – no suppressive effect

BONJ's pathogenesis

In the pathogenesis of BONJ, a multifactorial model is taken into consideration, in which the following factors are specified:
— a different sensitivity of the stomatognathic system *vs.* other areas of the skeleton;
— bone metabolism disorders;
— infectious factor;
— a toxic effect of BPs on soft tissues in the oral cavity;
— genetic factors;
— disorders in angiogenesis [2, 4, 8, 11, 12, 14–17].
BONJ's pathogenesis remains unexplained.

Sensitivity of the stomatognathic system [2, 4, 8, 14, 16]

Because of the continuous impact of chewing forces, the jaws are characterised by higher bone metabolism than other areas of the skeleton (e.g. 10–20% higher than in the femoral bone). This higher bone metabolism is necessary to repair chewing-related microfractures. On the other hand, a higher bone metabolism requires better vascularisation, which, in the therapy with bisphosphonates, is responsible for their higher concentrations in bone tissue. Additionally, oral mucosa is thin and susceptible to injuries and damage, which facilitates bacterial access to bones. These circumstances may support BONJ development.

Bone metabolism disorders exerted by BP effects [2, 4, 8, 11, 14, 16]

It is known that bisphosphonates inhibit bone resorption by suppressing osteoclasts via apoptosis. It slows the rate of bone metabolism and reduces bone tissue vascularisation, which in turn inhibits the replacement of the old osseous tissue by new bone structures, leading to an accumulation of microfractures. Further damage to oral mucosa gives way to bacterial penetration, facilitating BONJ development.

Infection factor [4, 16]

Infection is a constant component of BONJ (*Actinomyces* is typically identified). Periodontitis is also observed in most patients with BONJ, while BONJ-associated delayed wound healing, as mentioned in the definition of this medical condition, encourages bacterial penetration into bone.

Toxic effects of BPs on soft tissues in the oral cavity [15]

A new hypothesis regarding BONJ development was presented in Davos in March 2010. This hypothesis assumes toxic BP effects on oral soft tissues. An *in vitro* model was used to evaluate BP effects on various cell lines, demonstrating a suppressive effect of BPs on squamous epithelial cells, an effect which is responsible for the delayed healing process of oral mucosa defects, bacterial penetration and, finally, for BONJ development. Of the available bisphosphonates, clodronate, a nitrogen-free BP, has not yet shown any inhibitory effect for squamous epithelial cells; neither have any BONJ cases been recorded in the world following clodronate administration. Regarding nitrogen-containing BPs, three drugs have been evaluated, for which cases of BONJ development have been noted in the world. The strongest cell-suppressing effect has been demonstrated by zoledronate (Table II).

Genetic factors [12, 17]

In 2009, a report was published discussing a probable role for genetic factors in BONJ development. In patients with multiple myeloma, receiving BPs by intravenous administration, polymorphism of the CYP2C8 gene was observed. This gene is associated with metabolism of medicinal agents in the liver. However, it is known that BPs are not metabolised in the liver, so another location should be considered when searching for the causes of BONJ development. The CYP2C8 gene is also connected with the arachidonic acid cycle and plays some role in vascularisation control. Perhaps then it is responsible in the mandible for its worse vascularisation and, in consequence, for an increased risk of BONJ development (by as much as 12.5 times).

Angiogenesis disturbances [2, 11]

Disturbances in angiogenesis are the least probable BONJ development related factors. In the oncological

aspect, BPs inhibit tumour angiogenesis, induce apoptosis of neoplasmatic cells and suppress their adhesion to the osseous tissue, thus inhibiting metastases. In this respect, BPs would then negatively affect the bone tissue, reducing its vascularisation, which would consequently lead to lower bone metabolism and BONJ development. However, this effect does not cause osteonecrosis in any other part of the skeleton, while drugs other than BPs with antiangiogenic activity do not cause mandibular osteonecrosis at all. Moreover, it has been demonstrated on an animal model that angiogenesis in the osseous tissue remains normal during BP therapy.

BONJ prevention

In 2009, German recommendations were published regarding BONJ prevention [5]. Prior to BP therapy onset in oncological doses, the patient should be referred to a dentist for oral cavity control and, if necessary, dental procedures. Patients should be informed of the need for oral hygiene compliance and asked to regularly attend the dentist (every six months), avoid surgical procedures within the oral cavity, stop smoking and reduce alcohol consumption. If any surgery is required in the course of BP therapy, BP withdrawal should be considered for 6-8 weeks before and after surgery, while antibiotic therapy should be implemented on the day before the procedure.

Similar recommendations can be found in other literature reports regarding BONJ prophylactics and therapy [2, 4, 6–8, 11, 12, 16].

The incidence of BONJ

At the Congress in Davos in March 2010, Prof. D. Felsenberg presented German data concerning the cases of BONJ, based on the German Register of this condition [18]. This Register contains data of BP-treated patients including: 84.4% for oncological reasons,(mainly patients with breast carcinoma, prostate carcinoma or with multiple myeloma), 4.3% for osteoporosis, 4% simultaneously for oncological reasons and osteoporosis, and 7.3% for other reasons. The most frequently used bisphosphonate is zoledronate (63.9% of treated patients), followed by pamidronate (15.3%), ibandronate (9.5%), and alendronate (3.8%), with other BPs below 1%.

The incidence of BONJ in patients with malignant neoplasms, i.e. treated with BP in oncological doses, amounts in Germany to 1–2% (BONJ affects one or two in every 100 treated patients). The occurrence of BONJ was in those patients preceded by tooth extraction (33%), poorly matched dentures (10%), periodontitis (8%) or root canal treatment (4%).

The incidence rate of BONJ in BP-treated patients for osteoporosis is very low, 0.0028%, i.e. it affects one patient in every 36,000.

American data shows the incidence of BONJ to be also low [2]. In 2005, alendronate belonged to the group of 50 drugs most frequently prescribed in the United States (20 million times), while only 170 cases of BONJ were noted in the course of its use. During that same year, 12 cases of BONJ were recorded for risedronate, which is among the 100 most frequently prescribed drugs (almost 10 million times).

The European position regarding BONJ in the course of osteoporosis treatment

In 2008, the working group of researchers at the World Health Organisation (WHO), chaired by Prof. R. Rizzoli, published their statement regarding BONJ in BP-treated patients for osteoporosis [4]. This was formulated on the basis of a thorough review of the medical literature in English published 1995–2006. This paper presents the definition, pathogenesis, risk factors and methods of BONJ prophylactics and treatment, as discussed above.

Based on epidemiological data, it was determined that the risk for BONJ development in BP-treated patients with osteoporosis is very low, amounting to one case per 20,000–110,000 patient-years. Nevertheless, a patient's attention should be drawn to prophylactic activities (oral hygiene and regular visits to the dentist). If BONJ is diagnosed, it is usually at the first or second stage of disease progression, and prophylactic management is then most often effective.

BONJ summary

1. BONJ is a rare or very rare but serious condition concerning mostly patients who receive BPs in oncological, intravenous doses for at least, 1.5–3 years.
2. BONJ is a multi-factorial condition of still undetermined pathogenesis.
3. The risk of BONJ depends on a number of issues, of which the significant factors include: BP dose and the route of administration, therapy duration, concomitant diseases, hygiene status and surgical procedures in the oral cavity.
4. In osteoporosis, it is a minor problem of very little significance.

The most recent data on ONJ

Very recently, new data on ONJ has been published, slightly modifying the views presented in the paper above.

Table III. *The incidence of ONJ in patients on denosumab or zoledronate therapy*

Tabela III. *Częstość występowania osteonekrozy żuchwy (ONJ) u pacjentów leczonych denosumabem lub zoledronianem*

	Denosumab (Prolia, AMGEN) 120 mg subcutaneously	Zoledronate (Zometa, NOVARTIS) 4 mg i.v.
2,046 women with breast cancer and bone metastases ONJ cases	n = 20 (0.98%)	n = 14 (0.7%)
1,776 subjects with malignant neoplasms (except breast cancer, prostate cancer and multiple myeloma) ONJ cases	n = 10 (0.6%)	n = 11 (0.6%)

There is no significant difference between the number of ONJ cases with the use of the above-mentioned drugs

This new information is related to a new medical agent, used in the therapy of osteoporosis and malignant neoplasmatic diseases. This new drug is denosumab (Prolia, AMGEN). It is a monoclonal antibody against the ligand for the RANK receptor of osteoclasts, the effect of which is bone resorption inhibition [1]. This newer therapeutic option has a different mechanism of action to BPs.

Denosumab in oncological doses and ONJ

In 2009, data was published of the almost three-year use of denosumab or zoledronate in oncological doses, administered to 2,046 women with breast cancer and bone metastases [19]. In a performed evaluation of results, the incidence of ONJ was also considered. It was found that ONJ could occur during therapy with denosumab. This was an equally rare phenomenon, affecting less than 1% of treated women, while the incidence of ONJ did not significantly differ for either drug (p = 0.39) (Table III). Similar data, presented by the AMGEN company [20], has indicated that the incidence of ONJ in patients treated with oncological doses is identical for both drugs, amounting to 0.6% (Table III).

Denosumab in the therapy of osteoporosis and ONJ

In 2009, results were published of the FREEDOM prospective study of denosumab application [21]. The study comprised 7,868 women aged 60–90 with indications for osteoporosis therapy. The patients were treated with denosumab (60 mg subcutaneously every six months for three years) and compared to a placebo group. Not a single case of ONJ was noted during the three-year observation period.

Summary

It has become clear that ONJ may occur not only when BPs are used, but in therapy with denosumab as well, i.e. drugs of different mechanisms of action. Both groups of medical agents are applied in the therapy of bone metabolic diseases. ONJ, associated with the use of the above-mentioned drugs, is a rare condition and affects patients treated with oncological doses. The problem is of little significance in subjects treated for osteoporosis, while the pathogenesis of ONJ still remains unexplained and multifactorial.

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