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## Osteonecrosis of the jaw and atypical femoral fractures as complications of antiresorptive therapy

### Martwica żuchwy i atypowe złamania kości udowej jako powikłania terapii antyresorpcyjnej

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#### INTRODUCTION

Osteoporosis-related fractures result in increased mortality, morbidity, and huge social costs worldwide. After the age of 50, one in three older women and one in five older men will experience a fragility fracture, mainly of the spine, hip, and forearm (1-3).

The landscape of anti-osteoporotic therapies, for the last two decades, have been dominated by bisphosphonates (BPs). The results of randomized placebo-controlled trials of at least 3-4 years duration supported the efficacy of nitrogen-containing BPs in decreasing the risk of vertebral fractures (by 40-70%), hip fractures (by

#### Summary

Bisphosphonates (BPs) and denosumab (DSB) significantly reduce the risk of vertebral and nonvertebral fractures in patients with osteoporosis and decrease the risk of skeletal-related events in patients with cancer and metastatic bone disease. Osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFFs) are rare but potentially serious side effects of antiresorptive treatment with high potency bisphosphonates and denosumab. Higher doses of antiresorptive drugs given to patients with neoplastic diseases expose them to higher risk of both complications than patients with osteoporosis or Paget's disease of bone. The causes and pathophysiology of ONJ and AFFs remain not well understood.

Atypical femoral fractures located in the subtrochanteric region and diaphysis of the femur have been reported in patients taking BPs and in patients on DSB, but they also occur in persons not exposed to these drugs.

#### Streszczenie

Bisfosfoniary (BPs) i denosumab (DSB) istotnie ograniczają ryzyko złamań kręgosłupa i złamań pozakręgowych u pacjentów z osteoporozą oraz zmniejszają ryzyko wystąpienia powikłań kostnych u pacjentów z chorobą nowotworową i przerzutami do układu kostnego. Martwica kości szczęki/żuchwy (ONJ) oraz atypowe złamania kości udowej (AFFs) są rzadkimi, ale potencjalnie poważnymi, niepożądanymi objawami terapii antyresorpcyjnej z wykorzystaniem silnych bisfosfoniów i denosumabu. Wyższe dawki leków antyresorpcyjnych stosowane u pacjentów z chorobami nowotworowymi narażają ich na większe ryzyko obu powikłań niż pacjentów z osteoporozą lub chorobą Pageta. Przyczyny i patofizjologia ONJ i AFFs pozostają wciąż niedostatecznie poznane.

Atypowe złamania kości udowej zlokalizowane w regionie podkrętarzowym i trzonie kości udowej były rejestrowane zarówno u pacjentów przyjmujących BPs, jak i DSB, ale występują one także u osób nienarażonych na działanie tych leków.

20-50%) and non-vertebral fractures (by 15-39%), depending on the drug used, skeletal site, and individual risk profile. BPs have been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of postmenopausal, glucocorticoid-induced, and male osteoporosis (1).

Within the last several years, however, reports on serious complications, potentially related to the long-term therapy with BPs, have been published. The most alarming of them are osteonecrosis of the jaw (ONJ), first reported by dentists and oral surgeons in 2003, and atypical femoral fractures (AFFs), first described in 2007.

Many subsequent publications, including 3 major reports of American Society for Bone and Mineral Research (ASBMR) Task Forces paid attention to the possible correlations between long-term BP therapy and morbidities mediated by decreased bone turnover due to reduced osteoclast function (1, 4-6). It has been noticed, however, that AFFs could occur in patients not receiving any antiresorptive therapy (1, 7-9). Growing number of incidents of AFFs in patients on long-term treatment with BPs induced FDA in 2010 to review available data and release "Warnings and Precautions", suggesting that information on the risk of AFFs should be added to the labels of all BP products approved for the prevention and/or treatment of osteoporosis (6, 10). In 2011 FDA re-reviewed long-term safety and efficacy of BPs and recommended physicians to verify indications for continuation of long-term therapy with BPs beyond the period of 3-5 years (1, 11).

### DRUG HOLIDAY CONCEPT

The concept of "drug holiday" has been suggested to minimize side effects and maximize benefits of long-term treatments of chronic diseases (1, 12). Two clinical trials provided data on benefits and risks of long-term use of BPs in patients with osteoporosis. Fracture Intervention Trial Long-Term Extension (FLEX) revealed that postmenopausal women treated with alendronate for as long as 10 years experienced fewer clinical vertebral fractures than patients switched to placebo after 5 years of active therapy. In the HORIZON extension trial, women given 6 annual infusions of zoledronic acid had less morphometric vertebral fractures compared with those switched to placebo after 3<sup>rd</sup> dose of the drug. Beneficial response to continued therapy was observed, however, only in women with low bone mineral density (BMD): T-score at femoral neck between -2 and -2.5 in FLEX trial and below -2.5 in HORIZON extension study. Considering these results the ASBMR Task Force have suggested to reassess risk-benefit ratio after 5 years of oral or 3 years of intravenous therapy with BPs. Continuation of oral treatment for up to 10 years or intravenous therapy up to 6 years, with its periodic evaluation, should be considered in patients at high risk for fracture, with low BMD, previous major osteoporotic fracture, or in women who experienced fracture on therapy. In other patients 3-5 years of treatment with BPs should be followed by a period of "drug holiday" lasting 2-3 years. Suggested approach could be applicable, with some adaptations, to men and patients with glucocorticoid-induced osteoporosis (1).

The American Association of Clinical Endocrinologists (AACE) guidelines have suggested a "drug holiday" after 4-5 years of BP treatment in patients at moderate risk of fractures, and after 10 years of active therapy for high-risk patients, but terms "high" and "moderate" risks have not been defined (1, 13).

### OSTEONECROSIS OF THE JAW

Osteonecrosis of the jaw (ONJ) as a possible complication of bisphosphonate therapy was first reported

in 2003, in patients with metastatic cancer treated with high doses of intravenous BPs. The incidence of ONJ in patients with osteoporosis was estimated to be between 1/10,000 and 1/100,000, only slightly higher than the incidence of the disease in general population (1, 14).

### Definition

Osteonecrosis of the jaw is characterized by:

- an exposed necrotic bone in the maxillofacial region persisting for at least 8 weeks in spite of appropriate therapy,
- exposure to potent anti-resorptive or anti-angiogenic agents,
- no history of radiation therapy on the jaw (15).

The clinical course of the disease was originally grouped into three stages: the presence of exposed bone without pain or signs of infection (stage 1), with pain and signs of infection (stage 2) and with the appearance of fistulas, fractures and osteolysis (stage 3). Recently stage 0 characterized by certain symptoms and radiological changes in the absence of exposed bone has been additionally proposed. The majority of cases of ONJ in patients with osteoporosis are at stages 0-1, whilst in cancer patients at stages 2-3.

### The pathogenesis and risk factors

The pathogenesis of ONJ remains unclear, but several potential mechanisms have been proposed. These include long-term suppression of bone remodeling, reduced blood supply due to inhibition of angiogenesis, recurrent microtraumas, infection/inflammation and immune dysfunction. Higher incidence of ONJ in Asian populations suggests genetic predisposition to the disease (16). The cases of ONJ in cancer patients treated with high doses of potent BPs or denosumab (DSB) strongly suggest that profound and prolonged inhibition of bone remodeling may be the primary cause. Significant suppression of the bone turnover with BPs in the jaw bones, observed in animal studies, may explain predisposition of this region to ONJ compared with other parts of the skeleton (16-18).

Inhibition of angiogenesis can be another important mechanism as ONJ is a form of avascular necrosis. It was found that zoledronic acid *in vitro* inhibited angiogenesis and in cancer patients decreased serum vascular endothelial growth factor (VEGF) concentration. The results of clinical studies has combined ONJ and treatment with antiangiogenic drugs, such as bevacizumab and tyrosine kinase inhibitors. On the other hand it was found that treatment with DSB did not result in inhibition of angiogenesis (19-21).

The main localization of ONJ is mandible and only one-third of cases occur in the maxillary bone. It suggests that frequent, recurrent microdamages inflicted upon the lower jaw bones with mastication might play role in pathogenesis of the disease (18, 21). Other potential risk factors of ONJ in patients treated with antiresorptive drugs include poor oral hygiene, ciga-

rette smoking, diabetes mellitus, concomitant glucocorticoid- and/or chemotherapy, and invasive dental procedures, such as dental extractions or implants, especially in patients with preexisting periodontal or periapical disease. Complex biofilms have been found on the bone/tooth and mucosal surfaces around BP-related ONJ, composed of *Actinomyces* and other organisms including fungi and viruses. It is still unknown whether BP-related ONJ is the result of direct drug toxicity to the bone and/or soft tissues that become secondarily infected or a primary infection is subsequently exacerbated by the treatment with anti-resorptive agents (17-24).

### Treatment and prevention of ONJ

Over the last years treatment of ONJ has generally shifted away from aggressive surgical interventions to conservative therapy with limited debridement, antibiotics and oral rinses with chlorhexidine or hydrogen peroxide. In the majority of patients with osteoporosis treated with BPs the clinical course of ONJ is mild and self-limited (18, 25). In most such cases conservative management may be sufficient, resulting in healing 30-60% of patients, although some cases become chronic and develop complications (26-28). Microbial cultures from areas of exposed bones usually isolate normal oral microbes although sometimes they can help to define comorbid oral infections and to select appropriate antibiotic regimen, especially when there is extensive soft tissue involvement (18, 29). The areas of necrotic bone, being a source of chronic soft tissue irritation, and loose bony sequestra need to be removed or recontoured to optimize soft tissue healing (18, 30). The extraction of symptomatic teeth within exposed, necrotic bone should be considered as it appears unlikely that extraction will worsen the established necrotic process. Surgical resection of necrotic bone should be reserved for refractory or advanced cases and performed by experienced oral and maxillofacial surgeons as it may occasionally result in larger areas of exposed and painful, infected bone (30-34).

There are no prospective data to stop antiresorptive or antiangiogenic therapy in patients with ONJ. Discontinuation of antiresorptive therapy might stabilize ONJ, reduce the risk of developing new sites, and help to control clinical symptoms but, especially in cancer patients, it could result in recurrence of bone pain and increase skeletal-related events. The decision must be made individually, on a case-by-case basis, taking into account the estimated risks and benefits. Some authors reported better outcomes of ONJ with discontinuation of treatment with BPs for a period of 1-6 months, but it could result in recurrence of bone pain and progression of bone metastases in oncological patients (18, 35). As bisphosphonates accumulate in bone tissue for months or years, the rationale for discontinuation of therapy in patients with ONJ is the interruption of their effects on oral soft tissues, especially epithelial cells and fibroblasts surrounding ONJ.

Few reports describe healing or complete resolution of ONJ in patients given iv therapy with BPs within several months of cessation of these agents. On the other hand there are publications on spontaneous resolution of ONJ with continued therapy. The American Dental Association as well as the American Association of Oral and Maxillofacial Surgeons do not recommend routine discontinuation of BP treatment in osteoporotic patients prior invasive dental procedures (18, 36, 37).

Denosumab, a RANK ligand inhibitor, that significantly decreases bone resorption does not accumulate in bone tissue, and its skeletal effects are reversible over several months. There are no reliable prospective data, as yet, to advise the patient to discontinue therapy with the drug once ONJ developed. During clinical trials, however, all patients with ONJ had therapy with DSB discontinued and in some of them the treatment was reinitiated after resolution of ONJ symptoms (18, 37).

Prior to initiation of antiresorptive therapy preventive procedures to decrease the risk of ONJ are strongly recommended. According to guidelines of the American Society of Clinical Oncology and EMA all patients qualified to antiangiogenic or antiresorptive therapy at oncological doses need to have detailed dental examination and preventive dentistry before starting treatment (38-40). Non-restorable and not likely to be salvageable teeth should be extracted but minor procedures with preservation of dental roots should be preferred over total extraction. Active oral infections should be treated and sites at high risk for infection need to be eliminated. The initiation of antiresorptive therapy should be delayed until the extraction site is mucosalized (usually 14-21 days) or until adequate osseous healing is achieved. Patients with full or partial dentures need to be examined for areas of mucosal trauma, educated in proper oral hygiene as well as instructed to take care of regular dental evaluations and prompt contact with a doctor in case of any pain, swelling, or exposed bone in oral cavity. It was found that proper dental treatment before initiating therapy with zoledronic acid in patients with multiple myeloma was able to reduce the risk of ONJ almost 3 times (41, 42).

Once antiresorptive and/or antiangiogenic therapy has been started, patients should maintain excellent oral hygiene with daily flossing, brushing and antibacterial rinses, and should be encouraged to stop smoking. All planned, necessary dental procedures should be performed prior to administration of next dose of the antiresorptive agent and all invasive dental procedures, such as dental extractions or implants should be avoided, if possible. On the other hand patients should be assured that relatively noninvasive dental procedures such as dental cleaning, repair of cavities, placement of crowns or filling of root canals do not increase the risk of ONJ. Such strict procedures are not obligatory in osteoporotic patients as even after four years of low-dose antiresorptive treatment teeth extractions and other invasive procedures within the oral cavity were found to be safe with appropriate antibiotic therapy (18).

## ATYPICAL FEMORAL FRACTURES

Atypical femur fractures (AFFs) are rare complications of antiresorptive therapy. In a large retrospective analysis of over 1.8 million adults, including approximately 10% who had been treated with BPs, 142 AFFs were identified, of which 128 were found in subjects exposed to BPs. AFFs usually occur with little or no antecedent trauma, are often preceded by pain of thigh or groin, and may occur bilaterally (1, 7).

### Definition

According to updated diagnostic criteria published in 2014, AFF can be recognized if the fracture is located at femoral diaphysis between distal part of the lesser trochanter and proximal part of the supracondylar flare, and complies with at least four of five major features:

- the fracture is associated with minimal or no trauma, e.g. a fall from a standing height or less,
- fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur,
- incomplete fractures involve only lateral cortex while complete fracture extends through both cortices and may be associated with a medial spike,
- the fracture is noncomminuted or only minimally comminuted,
- fracture site is accompanied by localized periosteal or endosteal thickening of the lateral cortex.

Fractures of femoral neck, intertrochanteric fractures with spiral subtrochanteric extension as well as periprosthetic and pathological fractures associated with primary or metastatic bone tumors and metabolic bone diseases (e.g. Paget's disease, fibrous dysplasia) are excluded.

Minor features, such as:

- generalized increase in cortical thickness of the femoral diaphysis,
- unilateral or bilateral pain in the groin or thigh previous to femoral fracture,
- bilateral fractures of femoral diaphyses (incomplete or complete),
- delayed fracture healing

are not required for the diagnosis of AFF but they sometimes occur with the fracture.

Some of the studies suggest a strong dose response relationship between incidence rates of AFF and exposure to BPs. It was found that age-adjusted incidence rate increased from 1.8/100,000 persons/year to 113/100,000 persons/year in patients treated with BPs for 2 and 8-9.9 years, respectively (1, 7).

### Pathogenesis

The mechanisms of development of AFFs are still not fully understood. In normal bone a concentration of mechanical stresses leads to the formation of microcracks, which heal by bone remodeling processes consisted of osteoclastic bone resorption, followed by

osteoblastic new bone formation. It was found that prolonged therapy with BPs resulted in significant inhibition of bone remodeling and reduction in the ability of bones to repair microdamages especially at the sites of maximum mechanical forces (42). Radiological features of AFFs, such as focal hypertrophy of the lateral cortex, periosteal and endosteal callus formation and the transverse fracture line at the lateral cortex, suggest long-term accumulation of small fatigue damages within the compact bone.

Ettinger et al. and Saita et al. suggested that suppression of bone turnover led to deterioration of bone tissue quality. They revealed that long-term decrease in bone turnover resulted in tissue brittleness, increased homogeneity of osteonal and interstitial structures as well as advanced glycation of extracellular bone matrix that deteriorate mechanical properties of bone tissue, allow unimpeded crack progression and development of AFF (42, 43).

Histomorphometric examinations of transiliac bone biopsy samples obtained from patients with BP-associated AFFs showed significantly reduced number of both osteoclasts and osteoblasts (6). Some of the few published reports on femoral bone biopsies of patients with AFF revealed normal lamellar bone texture without any evidence of adynamic bone disease or impaired mineralization. Other studies found microcracks mostly perpendicular to the long axis of bone within the fracture gap, without any signs of remodeling or callus formation, and with significant part of empty osteocyte lacunae (43-45).

### Risk Factors for AFF

The analysis of 152 femoral fractures that occurred in 152 patients in Australia showed that 20 of them (13%) could be classified as AFFs. As much as 85% of these patients were current users of oral BPs, while only 2.3% of patients with typical femoral fractures were taking BPs (43, 46). Schilcher et al., after reviewing of 1234 radiographs of female patients who had had femoral fracture, identified 59 AFFs. They found that 78% of patients with AFF and 10% of individuals with typical femoral fractures had received BPs, corresponding to a multivariable-adjusted odds ratio (OR) of 33.3 (44). A small case-control study that included 10 patients with AFFs and 30 patients with low-energy typical subtrochanteric/femoral shaft fractures revealed that treatment with BPs was a significant risk factor for developing AFFs with OR = 36.0 (43). It was found that the risk of AFF increased with duration of BP treatment by 30% per 100 daily doses, and diminished by 70% per year after drug withdrawal with most dramatic risk reduction within first year of discontinuation (7, 8, 43).

Documented AFFs have been described in individuals treated with DSB given subcutaneously every 6 months. The incidence of the events was found to be similar to those observed in patients treated with BPs. There are no confirmed data on the risk of AFF in individuals treated with BPs who have been switched

to therapy with DSB but careful scrutiny of the relevant risk factors for AFF should be performed in such patients (43, 47-51).

Several additional risk factors were found to be significantly associated with the risk of AFFs. These included history of low-energy fracture (OR = 3.2), glucocorticoid (GC) therapy for more than 6 months (OR = 5.2), active rheumatoid arthritis (OR = 16.5), collagen disease (OR = 9.0), and low serum 25-OH vitamin D concentration < 16 ng/mL (< 40 nmol/L) (OR = 3.5). Female gender and younger age were also considered as significant risk factors, while diabetes and use of proton pump inhibitors (PPI) have been postulated (43, 52, 53). Contrary to these observations Feldstein et al., after reviewing of 122 typical fractures of femoral shaft and 75 AFFs, did not find any correlation between AFFs and exposure to GCs or PPI (46).

## CONCLUSIONS

Both, ONJ and AFF, are serious but rare complications of antiresorptive therapy. It is important to note that for the vast majority of patients treated for osteoporosis with BPs or DSB, the benefits of reduced fracture risk are greater than the risks of developing either ONJ or AFF. The informed and judicious use of BPs/DSB confers a clear clinical benefit in most carefully selected patients that outweighs potential risks associated with antiresorptive therapy. The risk of bone fractures is substantially decreased by BPs and DSB, and remains much higher than the risk of developing ONJ (185 fold) or AFF (4835 fold) (fig. 1) (1).

If ONJ or AFF occur in a patient on chronic antiresorptive treatment for osteoporosis discontinuation of the drugs is suggested. In patients with ONJ the American Association of Oral and Maxillofacial Surgeons recommends conservative therapy including proper dental hygiene, anti-bacterial mouth rinse, oral antibiotics and surgical debridement if

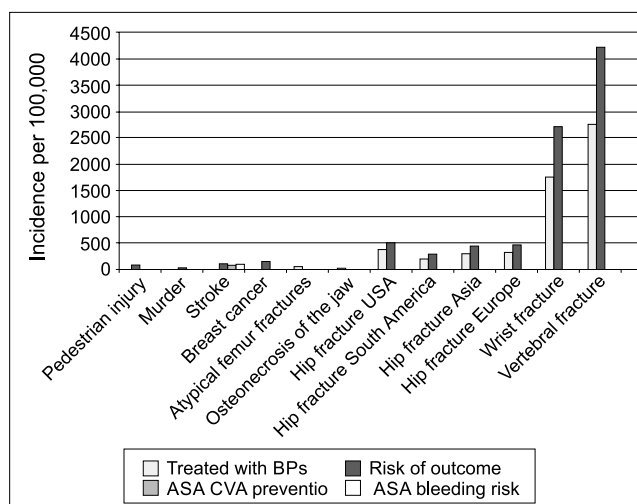


Fig. 1. Risks associated with bisphosphonate use and other health outcomes

necessary, based on the stage of ONJ. It needs to be remembered, however, that in high risk patients discontinuation of antiresorptive therapy may not be advisable.

In the past few years case reports and small prospective studies have reported healing of ONJ or AFF within a few months of therapy with teriparatide or strontium ranelate. Based on available reports as well as recommendations of the ASBMR Task Force and the International Consensus report on ONJ a limited treatment with teriparatide may be considered to accelerate healing of BP-related AFF or ONJ (1).

Clinicians need to determine the most appropriate pharmacological therapy after a careful assessment of the risk: benefit profiles of the drugs in each patient. Patients should receive a detailed explanation of treatment goals, so that the therapeutic benefit could be maximized by good compliance and persistence.

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