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Short Communication

Role of Bisphosphonates in the Development of the Osteonecrosis of the Jaws

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The jaw bone tissue is affected by many factors, including various medicaments, e.g., bisphosphonates (BPs). These medicaments are taken by certain group of the patients, where it is necessary to stop the ongoing pathological processes in the course of treatment. This is the drug of choice for the treatment of osteoporosis, as well as metastatic bone cancer, multiple myeloma, Legg-Calve-Perthes and Paget diseases, for children in the cases of osteogenesis imperfecta, idiopathic juvenile osteoporosis, and osteopenia due to rheumatoid arthritis. The BP group, reducing loss of the skeletal bone mass, are synthetic analogues of non-organic pyrophosphate and were introduced in 1969 [2,3]. Their mode of action was explained more precisely only in 1990, when *Fosamax (alendronate)* was introduced [4]. BP biocompatibility with bone tissue is high; therefore they are effectively used in clinical practice. In the organism part of BPs connects to the bone tissue, contacts with osteoclasts directly and inhibits resorption of bone, another part is transported to liver, kidneys and spleen [1,3,5]. However, their effect may be not only beneficial. Like many other medicaments they exhibit side effects – gastric irritation, atypical femoral fractures, esophageal cancer, heart rhythm disorders and eye inflammation may develop due to their consumption [6]. In some cases BPs may cause local osteonecrosis – bisphosphonate related osteonecrosis (BON) of the jaws. This is recently identified phenomenon, which may result in surgical complications – impaired healing of the wounds, requiring surgical or periodontal, endodontic treatment of oral cavity [7]. BON is diagnosed in such cases, when osteonecrosis, lasting more than 8 weeks, develops in patients without previous radiation treatment but who were taking BPs. Osteonecrosis develops and bone tissue of the jaws becomes uncovered [8-11]. The first case of osteonecrosis related to use of BPs was described in 2003 [9]. About 25% of BON are treated as spontaneous and not related to any trauma. Researchers hypothesize that potential predisposing factor, responsible for the development of BON, may remain undetected [1]. Fleisher., *et al*. state that such factors may be untreated dental caries, purulent processes or widened periodontal ligament [12]. It is established, that BON develops more often in jaws than other parts of the skeleton and mandibular angle and body being affected more often than maxilla. Compared to maxilla, mandibular cortical bone layer is larger and less vascularized and has only one source of blood supply – a. alveolaris inferior, what can be important factors in the development of pathological process [13-15]. BON is common complication in cancer patients taking BPs, especially following radiation or chemotherapy [16]. Assael., *et al*. indicate, that the ratio of BON may be from 1:100 000 to 1:10 000 and may reach up to 1:300 following tooth extraction [16]. Tooth extraction, as procedure, inducing development of BON, was noted by Torres., *et al*. [10]. Kobayashi., *et al*. examined the effect of *Zoledronic acid* on the healing of the wounds following tooth extraction and proved that the amount of bone and blood vessels in healing alveolus was significantly lesser than in control group. *Zoledronic acid in vivo* significantly inhibits angiogenesis, cellular proliferation and migration of epithelial cells (important factors in wound healing) as well as increases adhesion of *Streptococcus mutans* to hydroxyapatite and proliferation of other bacteria that form normal microflora of the oral cavity [17]. The mode of BP action on jaw pathogenesis is not sufficiently clear, few hypotheses were proposed, authors of which agree on one – one common feature is leading in the development of osteonecrosis – bacterial infection [1,18]. Some authors state, that bone, cohering with BPs, especially with ones having amino group, promotes bacterial adhesion, leading to the development of bony necrosis and osteomyelitis [17]. Others point, that initially necrosis develops due to inhibition of bone remodeling and only afterwards is followed by infection [19]. Pautke., *et al*. conducted a study and

proved that BON may also spread to other areas of the bone or even to bone transplant, e.g., microvascular transplant of the iliac bone, used for reconstruction following partial mandibulectomy [20]. Solomon., *et al*. described that oral BPs cause erosions of mucous membrane as well as healing retardation and anomalies of the mucous membrane. Therefore it is easier for oral microflora to adhere and proliferate in such lesions [19]. American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed several hypotheses, explaining the development of BON: 1. Inhibition of osteoclast regulated bony resorption and remodeling, which is highly enhanced by BPs, resulting in cellular apoptosis; 2. Development of inflammation and (or) infection – following tooth extraction bone becomes exposed to pathogens (bacteria, fungi or viruses); 3. Inhibition of angiogenesis – formation of new blood vessels from endothelial cells ceases and newly formatting bone is not sufficiently supplied with blood; 4. Toxicity of soft tissues, which cells undergo BP induced apoptosis as well; 5. Congenital or acquired immune deficiency – therefore processes, determining necrosis, may develop faster [18].

According to mode of administration, BPs are divided into oral or intravenous ones. Clinical, histological and radiographic investigations show, that BON is more linked to intravenous administration of BPs (6,7 – 9,1% of the patients), compared to oral administration (0,09 – 0,35% of the patients) [9,10,21,22]. Osteonecrosis usually develops up to the II grade in patients, taking oral BPs and in most cases healing improves after discontinuation of BPs [16]. Collagen type I levels and concentration of carboxy-terminal telopeptide of type I collagen (CTX) drop in blood serum after initiation of treatment with BPs. Patients with CTX concentration of 200 pg/ ml and less are exposed to the greatest risk of BON development [23]. CTX is the most commonly used serum biochemical marker for evaluation of BON risk [12,23,24,25]. With the acceleration of remodeling of bone tissue, osteoclasts break down type I collagen, thus releasing CTX molecules. As it is already known, organic matrix of bone tissue is mainly, 90-98% approximately, composed of type I collagen [24]. CTX levels depend on age and gender, smoking, ovulation, administration of drugs potentiating each other's action, physical activity, circadian rhythms, renal function and fasting [12,21].

Clinical symptoms of BON in patients with long history of BP administration were clearly named in 2010. In the mildest cases BON is characterized by local pain, inflammation and swelling of gums, pathological tooth mobility is detected in previously immobile teeth without exposion of bone tissue. In this stage one of the main radiological findings is significant osteosclerosis in the area of aforementioned symptoms [26]. BON mainly manifests as inflammation of bony tissue without inflammatory symptoms of mucous membrane. Radiological picture shows no changes or osteosclerosis of cortical layer and trabecular bone. Patients complain on pain and paresthesias; while erythema, purulent secretion, sequestration, jaw deformation of significant degree and trismus may develop in later stages [15]. Fleisher., *et al*. detected widening of periodontal ligament space in corresponding area prior to manifestation of clinical signs of BON in 83% of the patients from their study [12].

In most cases it is necessary to differentiate between BP induced osteonecrosis and osteomyelitis, post-radiation osteonecrosis, malignant processes, AIDS related osteonecrosis [15]. Histopathological analysis helps in differentiation from malignant processes. BON differs from gingivitis by the injury of the bone in toothless area [27].

Careful evaluation of the patient and awareness about possible use of BPs prior to surgical intervention is necessary in clinical dental practice. Because of potential complications and side effects, BPs should be prescribed only based on the indications and dentist should be informed accordingly.

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