Bisphosphonates induced osteonecrosis of the jaws pdf

Osteonecrosis of the jaw in patients treated with bisphosphonates is a relatively rare but well-known complication on maxillofacial units around the world. It has been speculated that the drug, especially long-term i.v. bisphosphonate treatment, could cause sterile necrosis of the jaw. The aim of this narrative review of the literature was to develop the pathological mechanisms behind the disease and also to collect an update of the incidence, risk factors and treatment of bisphosphonate-associated osteonecrosis of the jaw. A total of ninety-one articles were reviewed. All have been published in internationally recognised journals with refereeing systems. We can conclude that necrotic lesions in the jaw appear to follow when the bone is exposed, for example after tooth extractions, while other procedures such as implant placement do not increase the risk of osteonecrosis. Since exposure to the bacterial environment in the oral cavity appears essential for the development of necrotic lesions, we believe that the condition is indeed chronic osteomyelitis, which should be treated appropriately.1. IntroductionThe first report on osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates came in 2003 [1]. Since then, this condition, sometimes called BRONJ (bisphosphonate-related osteonecrosis of the jaw), has shown a growing interest from dentists and oral maxillofacial surgeons. It is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks in a patient who is currently receiving bisphosphonate medication and has not had radiation in the head and neck area. The diagnosis is usually made clinically. It is believed to be mainly associated with high-dose intravenous bisphosphonate therapy, but sometimes the condition occurs even in patients with low-dose osteoporotic treatment. The current perception among dentists and oral maxillofacial surgeons seems to be that low-dose bisphosphonate treatment for osteoporosis is associated with an increased incidence of ONJ, while endocrine scientists, on the other hand, may suggest an increased prescription to reduce the incidence of osteoporosis fractures. This review aims to develop the pathogenic mechanisms behind bisphosphate-associated necrosis of the jaw and incidence, prevention and treatment of the disease.2. MethodsThis paper is written as a contribution to the narrative review. Data synthesis and analysis: The items were selected and sorted according to their respective focus.3. ResultsNine studies were included, consisting of 9 reviews, 79 original papers, 2 letters and 1 thesis.4. Discussion4.1. Structure and bioactivity of (BPs) are anti-resorptive drugs that have a specific effect on osteoclasts and thus maintain bone density and strength [2]. The drug is used for many indications, including prevention and treatment of primary and secondary osteoporosis, hypercalcemia, multiple myeloma and osteolysis due to Metastases and Paget disease [3, 4]BPs act on both osteoblasts and osteoclasts. BPs have been shown to promote the proliferation and differentiation of human osteoblast-like cells [5] and inhibit osteoclasts. The BPs are synthetic analogues with a P-C-P bond instead of the P-O-P bond of inorganic pyrophosphates used as bone-specific radionuclides in technetium 99 m methylene diphosphonate (Tc 99 m MDP) bone scans. Unlike pyrophosphates, bisphosphonates are degraded by enzymatic hydrolysis, which explains their accumulation in the bone matrix and their extremely long half-life [6]. The P-C-P structure (Figure 1) allows for a variety of possible variations, in particular by changing the two lateral chains (R1 and R2) in the carbon atom. The two phosphate groups are essential for binding to the bone mineral such as hydroxyapatite and act together with the R1 side chain as bone hooks. A hydroxyl or amino group at the R1 position increases the affinity to calcium and thus to bone mineral [7, 8] Figure 1.The structure and three-dimensional conformation of the R2 side chain determine the antiresorptive potency and the improved binding to hydroxyapatite [7, 9]. It is known that bisphosphonates, which contain a primary primary nitrogen atom in an alkyl chain such as alendronate, are 10-100 times stronger in inhibiting bone resorption than BPs of the previous generation such as clodronate, which lack this feature. Compounds containing tertiary nitrogen, such as ibandronate and olpadronate, are even stronger in inhibiting bone resorption. Risedronate and zoledronate are among the strongest BPs containing a nitrogen atom in a heterocyclic ring [10]. Gastrointestinal uptake of orally administered BPs is low with a bioavailability of 0.3-0.7% [11, 12]. Poor absorption of BPs can probably be attributed to their very poor lipophilicity, which prevents transcellular transport via epithelial barriers. Consequently, BPs must be absorbed by the paracellular pathway, which means that the pores of the narrow nodes pass between the epithelial cells. Bisphosphonates are completely ionized to the physiological pH (7.4) in the blood. Therefore, plasma protein binding is high, probably as an ion bond. Lin and colleagues [13] showed that alendronate binds to serum albumin in rats and this bond appears to be dependent on serum calcium levels and pH. Plasma protein binding was found to be lower in humans, with alendronate showing an unbound fraction of 22% compared to 4% in rats [13]. On the other hand, the intravenous administration of a single dose of alendronate leads to a rapid accumulation of this drug in bone tissue, about 30% in 5 min and 60% in 1 hour [14]. The half-life in plasma 1-2 hours and this rapid elimination is due to bone absorption and renal clearance. Once incorporated into the bone, bisphosphonates are only released when the bone in which it was deposited is resorebed. Therefore, the rate of Sales affect the half-life of this drug [15]. The distribution of BPs in the bone is determined by blood flow and promotes deposition at the sites of the skeleton that undergo active absorption [14]. Neither oral nor intravenously managed BPs are metabolized in humans [16].4.2. Mechanism of actionDuring bone resorption, bisphosphonates impair the ability of osteoclasts to form the ruffle boundary, adhere to the bony surface and produce the protons necessary for further bone resorption [17-19]. After cellular uptake, a characteristic morphological feature of bisphosphonate-treated osteoclasts is the absence of a ruffle boundary, which leads to a reduced adhesion to the bony surface. Bisphosphonates also promote osteoclast apoptosis by reducing osteoclast precursor development and recruitment [20]. Nevertheless, after exposure to certain bisphosphonates, inhibition of the osteoclast proton pump H-ATPase phosphatases and lysosomal enzymes could also contribute to the loss of the absorption capacity of osteoclasts [21, 22]. Clodronates are the first-generation non-nitrogen bisphosphonates that have entered osteoclasts, incorporated into non-hydrolysable analogues of adenosine triphosphate (ATP) and converted into methylene (AppCp type) analogues of ATP. The accumulation of these toxic by-products impairs mitochondrial function and ultimately leads to apoptosis of osteoclasts [23, 24]. Nitrogen-containing bisphosphonates (such as zoledronate and pamidronate) act by inhibiting farnesyl pyrophosphate (FPP) synthase and geranylgeranyl pyrophosphate (GGPP), two key enzymes in the mevalonate pathway. As a result, the disturbance of the mevalonate pathway by nitrogen-containing bisphosphonates leads to impaired protein prenylation and activation of small GTPases such as Ras, Rho, Rac and Cdc42. The small GTPases are important signaling proteins that regulate osteoclast morphology, cytoskeleton arrangement, membrane ruffling and human trafficking and cell survival [10, 25]. It has been suggested that another target of BPs could be osteoblast, which in turn affects the osteoklasts. It has been experimentally shown that BPs inhibit the expression of the receptor activator of NF-kappa B liganligan (RANK-L) in rat osteoblast cells and increase the expression of osteoprotegerin (OPG) in human osteoblastic cells, which suggests that the anti-resorptive effect of BPs is mediated by denim effects of osteoblasts on RANK-L signaling [26, 27].4.3. Systemic and local delivery of bisphosphonatesSeveral experimental studies showed that systemic bisphosphonates reduced bone loss of alveolar [28–30]. In animal models, several researchers have shown that surface immobilized bisphosphonates metal screws in the form of increased bone-implant contact and increased pull-out force [31-35]. The unique systemic infusion of zoledronate has shown promising results in the initial fixation of cementless orthopaedic implants [36, [36, The use of BPs throughout joint surgery has shown that the migration of metal prostheses, measured by radiostereometry,[38]. In a recent series of randomized controlled trials, local treatment of periodontitis with a gel containing a very high concentration of alendronate was successful in the regeneration of a large part of the lost bone, while placebo had little effect [39-41]. In the randomized study of 16 patients, a thin bisphosphonate-eluting fibrinogen coating improved the fixation of dental implants in the human bone Abtahi et al. [42]. The efficacy of topical administration of bisphosphonates in implant therapy has been investigated by Zuffetti et al. [43]. Until the 5-year follow-up, no implant defect had been detected in the test group.4.4. Osteonecrosis of the jaw (ONJ)Historically, osteonecrosis of the jaw (ONJ) was first reported by occupational exposure to white phosphorus, which was referred to as phossy pine [44, 45]. ONJ has also seen osteopetrosis, a rare hereditary disease with impairment of bone resorption and remodelling [46]. More recently, ONJ is defined as a complication of head and neck radiation therapy [47]. The definition of ONJ is not healingexposed jawbone for more than 8 weeks in patients taking BPs and without local radiotherapy. Clinically, the disease presents itself as an exposed alveolar bone that becomes apparent after surgery such as tooth removal or periodontitis therapy [48, 49] Figure 2.Signs and symptoms that may occur before the development of clinically detectable osteonecrosis are pain, dental mobility, mucosal swelling, erythema and ulceration. The incidence of ONJ in bone malignancy cases, which are mainly treated with high-dose intravenous bisphosphonates, is approximately 1-12% [48, 49]. Wang and colleagues [50] found that the incidence of ONJ was at least 3.8% in patients with multiple myeloma, 2.5% in breast cancer patients and 2.9% in prostate cancer patients. In osteoporosis, bisphosphonate-associated osteonecrosis of the jaw is rare and the incidence must not be greater than the natural background incidence. Epidemiological studies have shown an estimated incidence of less than 1 case per 100 000 person-years of exposure to oral bisphosphonates.4.5. PathogenesisThe etiology of the ONJ remains uncertain. Initially, when the condition was called bisphosphonate-related osteonecrosis of the jaw (BRONJ) [48], its similarities with radiation-induced osteonecrosis led to the assumption that the condition began with sterile necrosis of the jawbone. Therefore, the term osteonecrosis was otherwise reserved for sterile bone death usually due to limited blood supply. At this time, that BPs could cause osteonecrosis by effects on the blood vessels in the bone, possibly by inhibiting vascular endothelial growth [51]. Later it was suggested that the condition does not begin as a form of classical osteonecrosis, but actually osteomyelitis from the beginning [52, 53]. Bacterial contamination contamination Actinomyces and Staphylococcus can play a role in maintaining osteomylite wounds, and since the bPs bone tissue in the jaw-face bone is slowly absorbed, it is conceivable that contaminated bones cannot be removed quickly enough to prevent the development of chronic osteomyelitis. This view is supported by the fact that similar lesions occur after treatment with anti-RANK-L antibodies that reduce osteoclast recruitment [54]. Thus, it seems that reduced resorptive activity is a key factor in the impaired healing ability of these lesions [55]. We suggest that the term BRONJ should be avoided and replaced by the term bisphosphonate-associated osteomyelitis of the jaw, BAOJ, which better reflects the conditions of etiology. Antibiotics can prevent the development of ONJ-like lesions in a rat model [56]. One hundred and twenty animals underwent tooth extraction and received a combination of dexamethasone and pamidronate at different times. Animals receiving the same treatment with the exception of the addition of penicillin had four times fewer ONJ-like lesions than the other group. There is no clinical study on the use of antibiotics associated with ONJ. However, in the clinical situation antibiotics has its use, since the condition is considered as osteomyelitis of the jaw. The antiangiogenic role of bisphosphonate is still unclear and ONJ is proceeding despite the use of antibiotics in some cases. One explanation could be the fact that bacterial contamination maintains chronic osteomyelitis of the jaw. Another explanation may be the reduced microcirculation of the gingiva, which causes the soft tissue not to heal. Corticosteroids and chemotherapy drugs have been suggested as factors that can predispose ONJ or increase the risk of onJ development; the duration of BP therapy also appears to be related to the likelihood of developing necrosis with longer treatment regimens associated with a higher risk [55]. The average time for the development of osteonecrosis after I.v. zoledronate treatment was 1.8 years, after i.v pamidronate 2.8 years and after oral BP therapy, such as alendronate, the mean time was 4.6 years [57]. Numerous studies have investigated the toxic effects of BPs on a variety of epithelial cells [58-62]. There is a clear documentation of bisphosphonattoxicity for gastrointestinal epithelia [63]. It has been suggested that high levels of bisphosphonate in the oral cavity (bone tissue) interfere with the oral mucosa [64]. Failure to heal the soft tissue can lead to a secondary infection of the underlying bone. However, this theory has not yet been accepted by investigators. in a rat model of ONJ after tooth extraction, a high dose of alendronate (200 g/kg) did not cause ONJ-like lesions [65]. When calculated as a dose per body weight per day, the rat dose was 100 times higher than the human dose.4.6. Clinical propertiesThe supply of the cortical

bone is derived from the periost and the exposed bone surface indicates necrosis in the Bone layers. The condition can then progress to a heavier bony lesion with nerve disorders, movable teeth, fistulas and, at the end, fracture [66]. Pain is common and these signs and symptoms are often evident in patients with jawbone osteomyelitis who are not on BP treatment. X-rays can be sclerotic bones, sclerotic lamina dura to show individual teeth and widened periodontal bands, but there is no report indicating specific characteristics for BP-associated osteomyelitis [67].4.7. IncidenceThe incidence of BP-associated osteomyelitis can be divided into 2 groups: the high dose i.v treated e.v treated e-band cancer patients and osteoporotic patients. In a systematic review, Kahn et al. found that the cumulative incidence in the first group varied between 1% and 12% after 36 months of treatment [66]. However, most of the reported cases are related to the intravenous use of bisphosphonates (zoledron and pamidronic acid) to combat metastatic bone disease or multiple myelomemite. The incidence of ONJ in these studies ranges from 4 to 10% [1, 68, 69] and the mean time of onset varies from 1 to 3 years [55, 70, 71]. Osteoporosis is a common and costly disease that affects quality of life [71]. It is estimated that 10 million people (aged >50 years) in the United States suffer from osteoporosis, by 2010 [72]. Few studies have reported the prevalence of ONJ in individuals receiving exclusive oral bisphosphonate therapy. No cases of ONJ have been reported in clinical trials involving nearly 17,000 patients [73]. The authors estimated the global reporting rate of ONJ at <3/100,000 years of exposure [72]. In osteoporosis patients, Kahn et al. estimated the incidence of ONJ at <1 case per 100,000 person-year exposure [66] through systemic testing. Similar results were reported by German investigators, as shown by cases recorded by a German central register [73, 74]. Using the postmarketing monitoring method, Abtahi et al. identified a case of ONJ in 952 patients receiving chronic oral bisphosphonate therapy [75]. In addition, these findings contrast with those of an Australian study that identified ONJ cases by nationwide survey of maxillofacial surgeons [70]. The trigger for the development of necrotic bones in BP-treated patients appears to be dental extractions. A review of 114 cases of BP-associated ONJ in Australia showed that 73% of cases occurred after dental extractions. The incidence of ONJ in BP-treated osteoporic patients was 0.01%–0.04%, and when dental extraction was 0.09% –0.34%. In patients with BPs for bone malignancies the incidence of 0.33%–1.15% and after dental extractions 6.7%–9.1% [70].4.8. Risk factorsThere are general and local risk factors for the development of ONJ. General risk factors include malignancies, chemotherapy, glucocorticium treatment and high-dose or long-term bisphosphonate treatment [48, 66]. Local risk factors are anatomical characteristics in which protruding cortical bones are associated with such as Tori and exostoses, a greater risk of necrosis and periodontitis, any surgical intervention that breaks the mucous membrane, especially tooth extractions [48, 67]. An experimental study by Abtahi and colleagues [75] showed that immediate soft tissue coverage after tooth extraction completely prevented ONJ, while all uncovered sites developed ONJ in osteoporotic rats treated with alendronate, Figure 3. a) b) c) c) b) b) c) The use of bisphosphonates is associated with the development of ONJ in some patients. The duration of exposure appears to be the main risk factor for this complication, with an estimated range between 1.6 and 4.7 years, depending on the bout type [55]. Following the ONJ development, the minimum useful life of 6 months was reported [76, 77]. Barasch and colleagues showed that the risk of onJ development begins within 2 years of treatment, for both cancer and non-cancer patients, showing that even the less potent bisphosphonates are associated with ONJ after a relatively short treatment period [76]. In addition, this risk appears to increase significantly in non-cancer patients after 5 years. This underlines the importance of drug leave after 5 years of treatment. A prospective study by Bamias et al. investigated the incidence of ONJ in patients treated with bisphosphonates for bone metastases. The incidence of ONJ increased with the exposure time of 1.5% in patients who which were treated for 4 to 12 months, to 7.7% for treatment for 37 to 48 months [77].4.9. Bisphosphonates and oral implant therapyIn a systematic review from 2009, Madrid and Sanz [78] included studies in which patients were in BP treatment for 1-4 years prior to implant placement. None of the patients developed osteonecrosis for up to 36 months postoperatively and the survival rate of the implant was between 95 and 100%. This may indicate that exposed/uncovered bone is necessary for a bacterial invasion and an osteomyelitic process. In addition, in a 2010 study, Coca and colleagues found high implant survival rates for both bisphosphonate users and non-users in postmenopausal women [79].4.10. TreatmentThe optimal treatment strategy for ONJ is still pending. The discontinuation of THE BP treatment will not suffice. A multidisciplinary team approach to assessing and managing conditions is recommended, including a dentist, a oral maxillofacial surgeon and an oncologist. In early stages, surgical debridement and coverage was successful [80]. Hyperbaric Oxygen (HBO) is an effective adjunct therapy in situations where normal wound healing is impaired and the effects of HBO therapy are affected by multiple discussed [81, 82]. The authors showed that patients with ONJ, adjunctive HBO2 therapy had remission or improvement in over 62.5% of patients. Low-intensity laser therapy has been reported for the treatment of ONJ by improving the reparative process, increasing the osteoblastic index and stimulating lymphandic and blood capillaries. Be. [83–85]. Segmental osteotomies are recommended only for severe cases [86-89], as morbidity is relatively high and the quality of life of patients is impaired [90]. In a study by Holzinger et al. [91], 108 patients underwent bisphosphonate therapy and 88 patients were followed over an average period of 337 days. Surgical treatment improved the stage distribution from 19% stage I, 56% stage II and 25% stage III to 59% intact mucosa, 19% stage I and 13% stage II and 8% stage III. The improvement in the stage of the disease achieved by surgery was statistically significant. However, the choice between surgery and conservative therapy is a difficult topic and must be made individually. Recently, there have been discussions about the applicability of drug holidays to minimize long-term bisphosphonate exposure and avoid potential adverse events such as ONJ. However, given the long half-life of bisphosphonates in the bone (measured in years), it is not known whether a temporary cessation of treatment with these active substances would reduce the associated risks. These questions require further investigation. Antibiotics: Samples should be taken for culture and sensitivity tests before starting treatment. Traditionally, the antibiotics of choice for the treatment of osteomyelitis include flucloxacillin or clindamycin.Prevention is a cornerstone to reduce the incidence of ONJ and before starting BP therapy, the patient should be referred for a thorough dental assessment to identify and treat any possible source of infection. The start of BP therapy should be delayed by 4-6 weeks to allow adequate bone healing [90]. Treatment of bisphosphonate-related osteonecrosis of the jaw is generally difficult. For this reason, prevention plays a predominant role in the treatment of this disease.5. ConclusionThis narrative review, based on experimental and clinical original papers as well as previous reviews, shows that osteonecrosis of the jaw appears to be triggered by exposed bones and subsequent bacterial contamination in BP-treated patients, typically after dental extraction, and that sterile necrosis of the jaw is unlikely. We therefore suggest that the condition could be characterized by bisphosphonate associated osteomyelitis of the jaw. Conflict of interestBoth authors stated that they have no conflict of interest.