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Review

Impaired Osteoclastogenesis in Medication-Related Osteonecrosis and Potential Clinical Management with BMP-2

Chunfeng Xu [1], Yin Xiao [2], Yiqun Wu [1], Astrid Bakker [3] and Yuelian Liu [3,*]

[1] Department of Second Dental Center, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, College of Stomatology, Shanghai Jiao Tong University, National Centre for Stomatology, National Clinical Research Center for Oral Diseases, Shanghai Key Laboratory of Stomatology, Shanghai Research Institute of Stomatology, Shanghai 201900, China
[2] School of Medicine and Dentistry & Institute for Biomedicine and Glycomics, Griffith University, Gold Coast Campus, QC 4222, Australia
[3] Department of Oral Cell Biology, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and Vrije Universiteit Amsterdam, 1081 LA Amsterdam, The Netherlands
* Correspondence: y.liu@acta.nl; Tel.: +31-205980626

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Abstract: Medication-related osteonecrosis of the jaw (MRONJ) is a rare, but severe, complication of applying inhibitors of osteoclasts, specifically bisphosphonates and the monoclonal antibody of receptor activator of nuclear factor kappa-B ligand (RANKL), inhibitors of angiogenesis, and some chemotherapeutics. MRONJ is painful for the patients, while current treatments are unsatisfactory. Thus, it is imperative to understand the etiology and pathogenesis of MRONJ to improve treatment options and enable prevention. Various hypotheses have been proposed over the years to elucidate the pathogenesis of MRONJ. Noticeably, impaired osteoclastogenesis shines some light on novel preventive and treatment strategies. In this review, we summarized the current understanding of the role of osteoclastogenesis in the development of MRONJ and have put forward a hypothesis concerning the application of BMP2 in the clinical management strategy for MRONJ.

Keywords: medication-related osteonecrosis; bisphosphonates; anti-RANKL mAb; osteoclastogenesis; bone remodeling; BMP-2

1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is severely pathological bone deconstruction in the jaw. It is tightly associated with the administration of high doses of inhibitors of osteoclasts and angiogenesis or chemotherapeutics, most frequently prescribed against various types of cancer, followed by dental care. Drugs that cause MRONJ include bisphosphonates (BPs) [1,2], denosumab (an anti-receptor activator of nuclear factor kappa-B ligand monoclonal antibody [anti-RANKL mAbs]) [3,4], bevacizumab (an inhibitor of angiogenesis) [5,6], and methotrexate [7,8].

While MRONJ is still rare, there has been a notable increase in case reports within the dental practice, particularly following tooth extractions [9–11] and dental implant placement [12–15]. This rise is largely attributed to the increased number of patients who are prescribed BPs or denosumab for osteoporosis and preventing bone metastases of cancer following dental surgery. MRONJ occurs only very rarely in patients receiving bisphosphonate or denosumab therapy for osteoporosis, since the treatment dose is much lower compared to that for bone metastases, yet the number of people receiving these drugs as anti-osteoporosis therapy is relatively high.

The appreciation of MRONJ is still ongoing, and the definition of MRONJ has also been updated. The latest version was released in a position paper published by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2022. The first case of osteonecrosis of the jaw (ONJ) caused by high-dose BPs was reported in 2003 [16], and this ONJ was termed bisphosphonate-related osteonecrosis of the jaw (BRONJ). Figure 1 shows a clear example of BP-related osteonecrosis of the jaw. Afterwards, apart from BPs, other drugs, e.g., denosumab and anti-angiogenesis agents, were also reportedly associated with ONJ in the clinic. Therefore, the term, BRONJ, was superseded by MRONJ in 2014 [17]. According to the latest diagnostic criteria released in 2022, MRONJ will be diagnosed based on three characteristics: (1) history of antiresorptive therapy alone or cooperation with immunomodulation or inhibitors of angiogenesis; (2) exposed bone or bone probed through an intraoral or extraoral fistula(e) in the jaw that has existed for more than eight weeks; (3) without radiotherapy or metastatic disease to the jaw [18]. Of note, the exclusion of radiation therapy in the definition distinguishes MRONJ from osteoradionecrosis of the jaw which has different etiology and management strategies compared to MRONJ, even though they share necrotic bone as a symptom. The etiology of MRONJ remains controversial, and diverse hypotheses on MRONJ have been proposed over the years, but none explain all aspects of MRONJ. Because of the increase in clinical cases, it is crucial to enhance understanding of MRONJ, thereby advancing the clinical treatment of MRONJ.

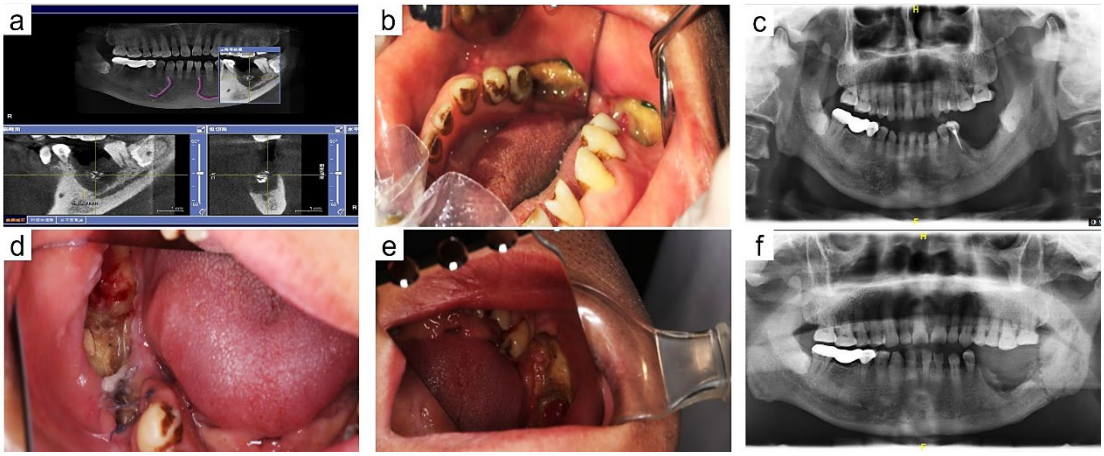

Figure 1. A prostate cancer patient prescribed BPs suffered MRONJ after dental implant placement. (**a**) CBCT scan after dental implant removal due to failed osteointegration; (**b**) exposed sequestrum was identified after bone substitute filling and followed partial mandibulectomy; (**c**) panoramic radiography of (**b**); (**d**,**e**), curettage of exposed sequestrum one and two months later, respectively; (**f**) fracture of the mandible one year after the treatment when biting peanuts.

2. Specific Occurrence in the Jaw

Compared to other regions in the body, craniofacial areas have a higher MRONJ incidence, with 65–73% in the maxilla and 22.5–28.4% in the mandible, while only 0.1% was identified in other areas [19]. This difference in the occurrence of exposed bone, or of bone probed through a fistula(e), between the oral cavity and elsewhere in the body, may be attributed to the unique biological properties of craniomaxillofacial bone, invasive dental clinical practice, as well as the microbial-rich environment in the oral cavity, as outlined in the following paragraphs [20].

2.1. Unique Osteoblasts and Osteoclasts

Considerable discrepancies exist between osteoblasts and osteoclasts in the jaw versus long bones. Osteoblasts collected from the mandible of rats showed different gene expression profiles from their counterparts in the tibia, with 54 upregulated genes and 18 downregulated ones [21]. These disparities may be explained by their distinct embryonic origins: neural crest versus mesoderm [22]. Concerning osteoclasts, in 2021, Azari et al. reported that osteoclasts derived from the marrow of long bones prefer to adhere to bone matrix in vitro, while those from craniofacial bone marrow prefer dentin [23]. Murine mandibular-derived osteoclasts also are 2-fold bigger compared to femur–derived osteoclasts. In this study, specific osteoclast populations, $Ly6C^{High+}$ and $Ly6C^{int}$ that were not discovered in long bones, were sorted from mandibular-osteoclasts, and these cells may stimulate osteoclast differentiation [24]. Moreover, it has been verified that osteoclasts in different anatomical areas resorb bone via different proteinases. Metallomatrix proteinase-2 (MMP-2) is essential for the degradation of bone in

craniofacial bone, but not in long bones [25]. These differences in origin and protein expression suggest that the osteoblasts and osteoclasts in the jaw may also respond differently to drugs compared to those in long bones, leading to a higher MRONJ occurrence in the jaw.

2.2. Invasive Maxillofacial Surgery

Invasive procedures in dental practice may also contribute to the increased occurrence of osteonecrosis in the jaw compared to other anatomical locations. Tooth extraction is the primary reported risk factor for developing MRONJ [26], although dental disease, without extraction, in animals receiving antiresorptive treatment has been reported to be sufficient for developing MRONJ [27,28]. MRONJ in the mandible accounts for 65% of all tooth extraction-associated MRONJ cases (28.4% in the maxilla and 6.5% in both) [29]. Although the underlying mechanism for this difference in occurrence is still unknown, the lower blood circulation in the mandible may explain this difference. Dental implant treatment, such as dental implant insertion and removal, bone grafting, and peri-implantitis treatments, may also induce MRONJ [19,30,31]. However, a nationwide cohort study in Japan suggested that dental implant treatments did not increase MRONJ [32]. Furthermore, periodontal disease and periodontal surgery are also associated with MRONJ [33–35]. These studies imply that bone damage during invasive dental treatment and failed bone repair can lead to the preference for MRONJ in the jaw.

2.3. Oral Infection

The oral cavity is a microorganism-rich environment, and bacteria-induced infection likely plays a role in the occurrence of MRONJ [36]. Multiple bacteria have been isolated in cases of MRONJ, and among them, Actinomyces are the most common microflora. Although it indicated that the accumulation of Actinomyces may represent an infection [35], Actinomyces mainly indirectly impose a risk of oral infection. They promote the adherence of other microorganisms, promoting the development of infection [37]. In turn, improving oral hygiene may drastically decrease the risk of developing MRONJ [38]. Infection-induced bone resorption via bacteria and associated fibroblast-like cells resorbing bone may be one of the mechanisms of MRONJ [39–41]. As micro-organisms rarely infect bones at other anatomical locations, this could explain the preferential occurrence of osteonecrosis in the jaw.

3. Prevailing Theories on MRONJ

3.1. Bone Remodeling and the Role of Osteoclasts in Bone Remodeling

An abnormal bone remodeling process is recognized as the main causative factor for MRONJ. Bone tissue is a dynamic hard connective tissue in the body that constantly undergoes bone remodeling throughout life. This regulation process, i.e., bone remodeling, constitutes new bone formation closely tied to bone resorption, brought about by osteoblasts and osteoclasts. Bone remodeling accounts for the maintenance of bone strength and integrity and prevents the accumulation of microdamage to the bone. In turn, impaired bone remodeling, an imbalance of bone formation and bone resorption, leads to bone diseases, such as osteoporosis when there is excess bone loss compared to bone formation and osteopetrosis as a result of loss of bone resorption, or, in some cases, excessive bone formation. The jaw has a higher bone remodeling rate than other parts of the skeleton. For example, the bone formation rate in the alveolar process of the mandible is sixfold higher than in the femur in dogs [42]. Considering the importance of bone remolding, it is not surprising that impaired bone remodeling associated with some drugs contributes to MRONJ. These related drugs are discussed below.

3.2. Osteoclast in Bone Homeostasis

Hematopoietic stem cells are deemed the origin of osteoclasts, and monocytes are the major precursors of osteoclasts. Owing to the advancements in transcriptomics, a growing body of evidence suggests some osteoclasts also derive from dendritic cells [43,44], implying a tight communication between the bone environment and the immune system. Mature osteoclasts are multinucleated cells and can be identified via the expression of markers, e.g., tartrate-resistant acid phosphatase (TRAP), cathepsin K, calcitonin receptor, and MMP-9 [45].

As the only effector cells that execute phagocytosis of bone matrix, active osteoclasts dissolve the mineralized bone matrix using protons. To adapt to bone resorption, osteoclast differentiation is initiated by RANKL and the macrophage colony-stimulating factor secreted by bone marrow mesenchymal stem cells, osteoblasts, and particularly osteocytes [46–49]. To implement bone matrix degradation, osteoclasts bind to the surface of the bone via integrin $\alpha_v\beta_3$, encouraging the realignment of their actin rings to form a sealing zone. In the area, the released

H^+ and effector cytokines will damage the inorganic and organic components of the bone (Figure 2) [50]. After completing bone resorption, most osteoclasts undergo apoptosis and the bone resorption phase is terminated, ensuring that excess resorption does not occur.

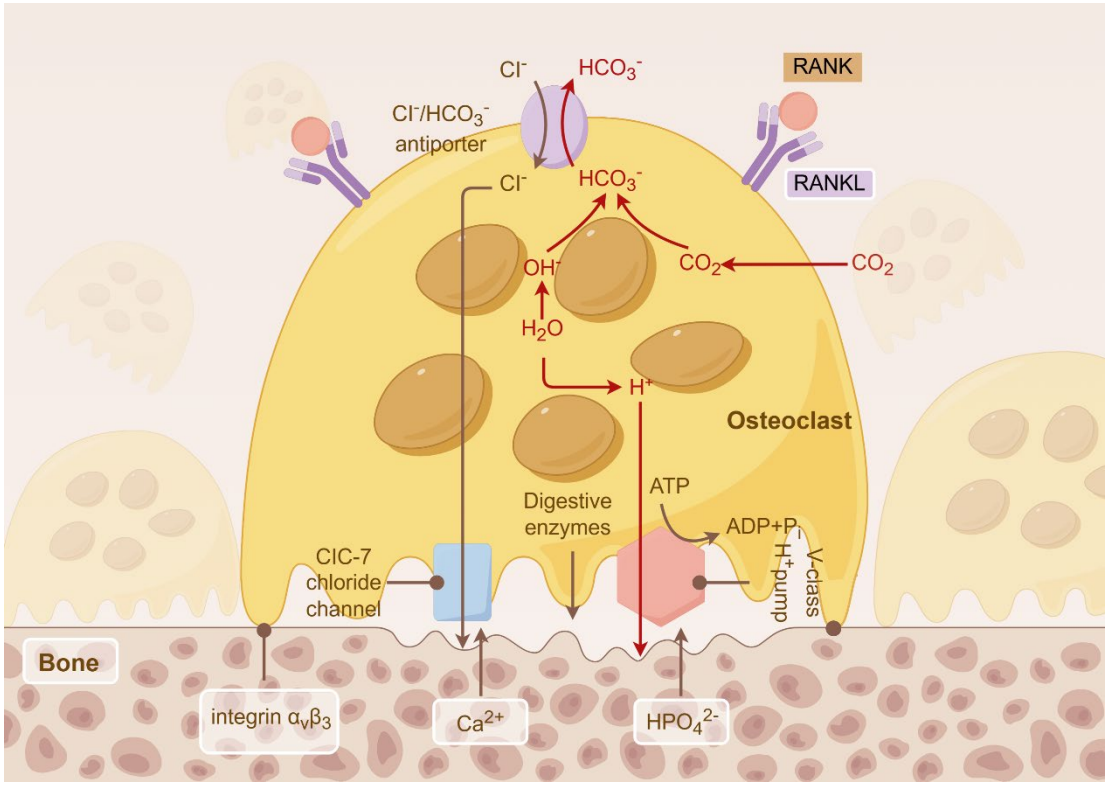

Figure 2. Osteoclasts resorb bone. Mature osteoclasts with ruffled borders and sealing zones bond to the bone matrix via integrin and initiate the resorption. Vacuolar H+-ATPase localized to the ruffled border transports protons into the resorption lacuna, while the chloride channel balances the ionic charge by transporting chloride simultaneously. Enzymes are secreted into the resorption lacuna to degrade bone matrix. Matrix degradation products are endocytosed from the ruffled border and released from the functional secretory domain.

Osteoclasts are notorious for their capability of resorbing bone, especially their overactivity in osteoporosis. However, the activity of osteoclasts is also vital for bone homeostasis and structural integrity. Osteoclasts prevent microdamage accumulation in the bone tissue that may lead to bone fracture [51]. It has been well-documented that osteocyte apoptosis plays a pivotal role in removing the microdamage in the bone. Microdamage severs osteocyte processes, leading to the production of RANKL by adjacent osteocytes and the release of apoptotic bodies. This way, apoptosis of osteocytes stimulates osteoclast precursors to adhere to the damaged area, promotes osteoclastogenesis, and stimulates osteoclasts to absorb the damaged matrix. Afterwards, osteoblasts take over, resulting in the repair of bone, thereby avoiding the accumulation of damage in the bone tissue [52–54].

Interestingly, osteoclasts may also directly orchestrate bone formation via the release of cytokines. In 2008, Karsdal et al. reported that conditioned medium collected from osteoclasts facilitated bone formation [55]. Some cytokines in the conditioned medium responsible for bone formation have been identified, including sphingosine-1-phosphate, Wingless-type MMTV integration site family, member 10B, slit guidance ligand 3, etc. [56–59]. Besides, as shown in Figure 3, after bone resorption by osteoclasts, some pro-osteogenesis growth factors, comprising transforming growth factor-β1 and insulin-like growth factor 1, are also released from the bone matrix, promoting osteoblast differentiation. This evidence explains the molecular basis for coupling of osteoclast and osteoblast activity in bone remodeling, and why over-suppressed osteoclasts also lead to dysregulated bone remodeling. Osteoblasts can also work without the presence of osteoclasts, in a process called modeling. In modeling, osteoclast and osteoblast activity are not coupled as in remodeling. In the adult skeleton, however, remodeling is by far the predominant biological process. The phenomenon of coupling also explains why osteoblast activity is affected in osteoporosis treatments targeting osteoclasts. A clear example of the coupling phenomenon is seen during denosumab treatment for osteoporosis, where osteoblast activity dramatically drops, albeit not to zero when osteoclast formation and activity are reduced upon the start of the treatment. Upon

discontinuation of denosumab treatment, a rebound effect occurs, in which osteoclast number and bone resorption quickly rise, followed by osteoblast number and activity. This phenomenon is further outlined below.

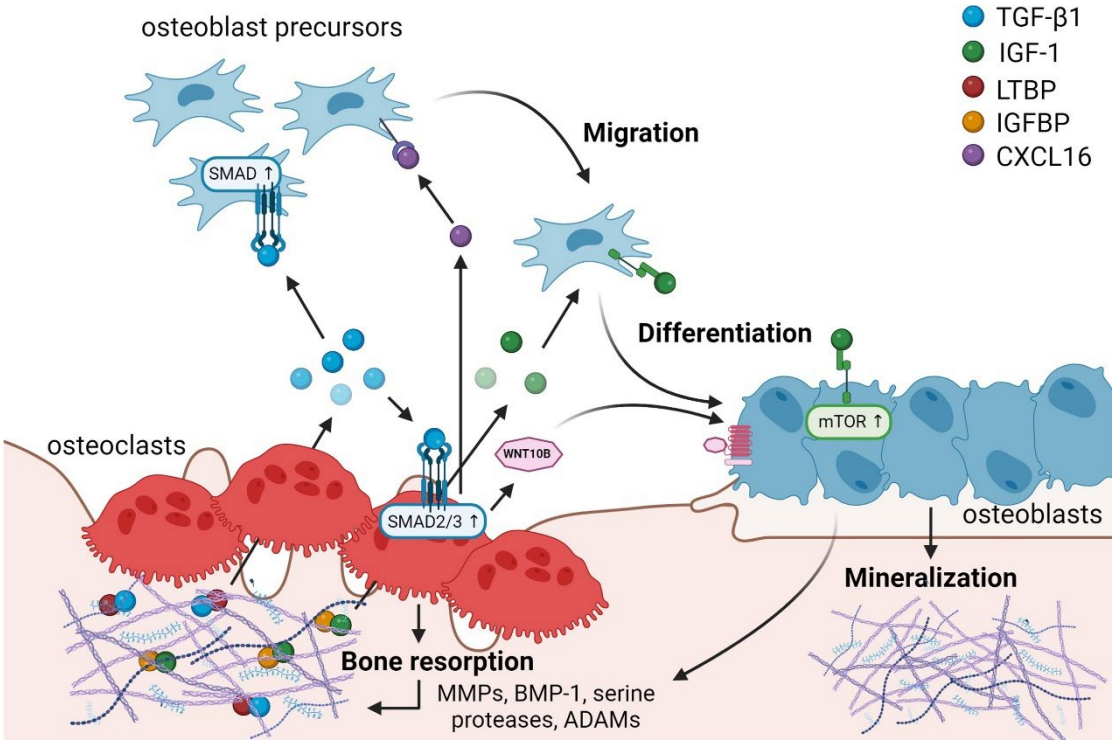

Figure 3. To carry out bone resorptive activity, mature osteoclasts secrete serine proteases, MMPs, ADAMs, and BMPs to cleave latency-associated proteins and liberate coupling factors from the extracellular matrix (ECM). TGF-β1 and IGF-1 are the two major factors that are released from the ECM following osteoclast bone resorption. TGF-β1, released after cleavage of LTBP by osteoclast-secreted proteases, acts on osteoblast precursors by activating SMAD signaling to promote cell migration, and on osteoclasts to stimulate the production of WNT10B and CXCL16. WNT10B stimulates osteoblast differentiation and mineralization, while CXCL16 collaborates with TGF-β to enhance osteoblast precursor migration to the resorptive sites. IGF-1 is activated after cleavage of its regulatory protein IGFBP by proteases secreted by osteoblasts upon bone resorption. Active IGF-1 induces differentiation of osteoblast precursors recruited by TGF-β1 by activating the mammalian target of rapamycin(mTOR) signaling pathway. BMP-1: bone morphogenetic protein 1; CXCL16: C-X-C motif chemokine ligand 16; IGF-1: insulin-like growth factor 1; IGFBP: insulin-like growth factor-binding protein; LTBP: latent TGF-β-binding protein; MMPs: metalloproteinases; TGF-β1: transforming growth factor-β1. Reproduction from Daponte et al. [56].

3.3. Disturbed Bone Remodeling in MRONJ

Disturbed bone remodeling or bone turnover is the main characteristic of MRONJ, being caused by some reported drugs, and this characteristic cannot always be reversed in a short period after discontinuation of the drugs. BPs are used in low to moderate doses to prevent bone fractures in osteoporosis patients, and in high doses to treat bone metastases. BPs can increase atypical bone fracture [60,61] during their application. To avoid this, and other rare, but serious side effects as a result of BP's long-term administration, introducing a "Drug holiday" is a practicable strategy applied in the clinic [62]. In stark contrast, stopping denosumab is associated with increased fracture risk [63]. After discontinuing denosumab injection, some bone turnover markers, such as P1NP (osteoblast activity) and CTX (osteoclast activity), both increased for 2 years; however, the bone mineral density decreased 1 year after the drug stopped, because osteoclast activity increased more than osteoblast activity does [64]. Similar to these findings, denosumab discontinuation prolongs osteoclast lifetime, contributing to the increase in bone resorption and subsequent loss in bone mass, inducing bone fracture [65].

4. Drugs Associated with MRONJ

4.1. Bisphosphonates

BPs are synthetic stable derivatives of inorganic pyrophosphate that were first synthesized in Germany in 1865 [66], and based on their chemical structures (Figure 4), they are divided into two groups: nitrogen-containing BPs (N-BPs) and non-nitrogen BPs (N-N-BPs). In general, BPs can firmly bind to the bone and remain there for decades, due to their unique chemical structures [67]. After the uptake in osteoclasts, these two subtypes of BPs present distinct pharmacological effects to curb osteoclast-induced bone resorption. N-BPs mainly affect the mevalonate pathway that modulates the trafficking of pivotal regulatory proteins to the cell membrane by the prenylation of proteins [68], leading to the apoptosis of osteoclasts. In contrast, N-N-BPs interrupt the mitochondrial adenosine diphosphate (ADP)/ATP translocase, which also causes osteoclast apoptosis [69]. It has been reported that N-BPs overwhelm N-N-BPs with 100–10,000-fold antiresorptive potencies (Table 1) [70].

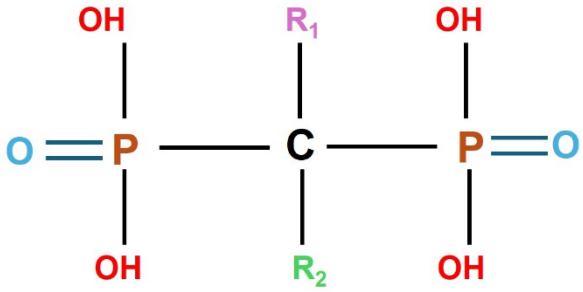

Figure 4. The chemical structure of BPs. The N-BPS and non-N-BPs are distinguished according to the appearance or disappearance of nitrogen in the R_1 or R_2 group.

Table 1. Information on bisphosphonates.

Bisphosphonates	Nitrogen-Containing	Oral	IV	Relative Effectiveness
Etidronate		+	+	1
Clodronate		+	+	10
Tiludronate		+		10
Pamidronate	+	+	+	100
Neridronate	+		+ [71]	100
Olpadronate	+	+		100–1000
Alendronate	+	+		100–1000
Ibandronate	+		+	1000–10,000
Risedronate	+	+		1000–10,000
Zolendronate	+	+ [72,73]	+	>10,000

+: available. Adapted from Attina et al. [74].

Interestingly, it has been reported that BPs can prevent osteocyte apoptosis and promote the expression of RANKL in osteocytes [75,76]. Regarding the important effect of osteocytes on osteoclastogenesis, it is necessary to evaluate the effect of BPs on osteocytes in the development of MRONJ [75,76].

BP use is the most common cause of MRONJ, resulting from its widespread prescription for various abnormal bone metabolism conditions, such as osteoporosis, Paget diseases, osteogenesis imperfecta, and the bone metastasis of malignancy. Two BPs, pamidronate and zoledronate, were initially linked to MRONJ in the early 2000s reported by Max [16]. In his study, Max also claimed the intravenous application of these two BPs induced a higher incidence of MRONJ than oral uptake. This vital information helps physicians estimate patients who receive IV administrations of BPs before setting a treatment strategy, thereby diminishing the potential MRONJ. Albeit it has reached the consensus that BPs are potent risks for MRONJ, the relative mechanism is still unclear.

4.2. Anti-RANKL Monoclonal Antibody

Anti-RANKL mAbs are also employed in the clinic to treat osteoporosis [77,78] and bone metastasis of cancer, and among these drugs, the most well-known one is denosumab. Anti-RANKL mAbs competitively bind to RNAKL, which impedes osteoclast differentiation and causes the apoptosis of these cells [79,80].

Anti-RANKL mAbs can be cleared rapidly from circulation. It has been reported that tiny concentrations of denosumab have been identified at the end of the 6-month dosing interval [81]. By contrast, BPs, as mentioned above, bind to the bone matrix firmly, enforcing a continuous antiresorptive effect. Hence, anti-RANKL mAbs are considered safer than BPs and an ideal alternative to BPs in treating bone metabolism diseases. However, the first denosumab-associated MRONJ was reported in 2010 [82], and a growing body of evidence suggests anti-RANKL mAbs are also involved in MRONJ [83,84], even with a higher MRONJ occurrence than BPs in cancer patients [85].

4.3. Angiogenesis Inhibitors

Angiogenesis means the formation of new vessels, orchestrating abundant physiological and pathological processes in the body due to the promoted transportation of oxygen, blood, nutrition, immune cells, and waste products. The crucial role of angiogenesis in bone remodeling has been well established [86–88]. Thus, disrupted angiogenesis can potentially affect the homeostasis of bone remodeling, deteriorating into MRONJ.

Vascular endothelial growth factor (VEGF) is a potent molecular factor that induces angiogenesis and is usually overexpressed in cancer. Bevacizumab, an inhibitor of VEGF, has achieved tremendous success in cancer treatments. However, some studies have proven this VEGF inhibitor can cause the occurrence of MRONJ in cancer patients. The first case report associating bevacizumab with the incidence of MRONJ was published in 2008 [89]. In this case report, a female with metastatic breast cancer treated with a chemotherapeutic agent (capecitabine) along with bevacizumab was reported bone protrusion that was discovered in the mandible 6 weeks after this treatment strategy. During her treatment, she did not receive any bisphosphonate therapy or tooth removal. Cessation of both bevacizumab and capecitabine for a few weeks resulted in complete resolution of the exposed bone. But in this case report, a chemotherapeutic was also involved, which may also count for MRONJ. Thus, to ensure the link between bevacizumab and an increased risk for MRONJ, Guarneri et al. [90] analyzed the data from a single open-label safety study (ATHENA) and two randomized controlled clinical studies (AVADO and RIBBON-1). According to their findings, it suggested that patients received a drug combination of BPs and bevacizumab had a 30-fold increase in the incidence of MRONJ (1.8%, 12/658 vs. 0.06%, 2/2902 with bevacizumab alone). Consistent with this study, Christodoulou et al. [91] showed that the incidence of MRONJ among bevacizumab recipients was lower compared with those who received zoledronate or ibandronate.

4.4. Chemotherapeutics

Since BPs are used to prevent bone metastasis of some cancers, the cancer patient is a high-risk group of MRONJ. Additional chemotherapeutics may deteriorate this situation. Thus, the concern about chemotherapy-induced MRONJ is growing [92]. To date, most of the reported chemotherapy-induced MRONJ is attributed to methotrexate, which may be explained by disrupted bone remodeling [93–96]. Chemotherapeutic agents have been reported to be toxic to the origin of osteoblasts, i.e., mesenchymal stem cells [97,98], and affect the biological performance of mononuclear cells, where osteoclasts may derive from [99,100]. On the other hand, chemotherapeutics also damage angiogenesis [101,102]. This may be parallel to the role of angiogenesis inhibitors in MRONJ.

4.5. Other Drugs

On top of these well-reported drugs, some new drugs are also linked to MRONJ, such as mTOR inhibitors (everolimus) [103,104] and IL-23 inhibitors (guselkumab) [105], which may be explained by the ability of mTOR and IL-23 to promote osteoclastogenesis [106–111].

5. Impaired Osteoclastogenesis in MRONJ

Various theories (impaired bone remodeling, inhibited angiogenesis, infections, etc.) on the cause of MRONJ have been proposed. However, none of these theories can fully explain the occurrence and clinical characteristics of MRONJ. For instance, although BPs are the leading cause of MRONJ, cancer patients who do not consume BPs also suffer from MRONJ [8,112].

Contemporary theories on MRONJ are not perfect and distinguishing, but impaired osteoclastogenesis is the shared factor in most theories on the cause of MRONJ. It has been proven that disordered bone remodeling is one of the characteristics of MRONJ, and all the previously mentioned medications can interrupt bone remodeling via impairing osteoclastogenesis. BPs and anti-RANKL mAbs inhibit osteoclasts directly; suppressed angiogenesis hinders the transportation of oxygen, nutrition, and cytokines, thereby downregulating the activation of osteoclasts;

chemotherapeutic agents are toxic to osteoclast precursors, osteoclasts, and osteocytes that are vital for osteoclastogenesis.

In addition, the overlap of these drugs' pharmacological functions in osteoclastogenesis inhibition reflects that impaired osteoclastogenesis may be the rationale of MRONJ. For example, BPs have been identified as having the capacity to decrease angiogenesis, working as angiogenesis inhibitors that negatively affect osteoclastogenesis [113–115]. Moreover, the altered tissue repair function of macrophages, one of the precursor cells of osteoclasts, caused by chemotherapeutics, was also reported [116]. Given these, impaired osteoclastogenesis has the vast potential to unify some existing theories and decipher the prime pathology of MRONJ, which may revolutionize the clinical treatment of MRONJ.

6. Retrospective Treatments and the Application of BMP-2 in the Management of MRONJ

6.1. Current MRONJ Treatments

To date, there has been no specific treatment for MRONJ, and the prevailing treatment protocol usually follows the guide from AAOMS based on the staging of MRONJ [17]. Generally, it has reached a consensus that conservative therapy is the mainstream treatment for MRONJ [77,78], which is in line with no significant difference in the cure rate between surgical and nonsurgical treatments [117]. Meanwhile, various strategies have been presented for the non-surgical treatment of MRONJ, some of which have achieved clinical success, as described below.

Although oral infection is common in MRONJ, antibiotics should be prudently prescribed to patients at any stage [118] because it has been believed infection is not directly responsible for the development of MRONJ. It is worth noting that antibiotics are not excluded from MRONJ treatment. For patients with infection-related symptoms and substantial necrosis, antibacterial therapy is beneficial for the healing of MRONJ [118].

Due to the multifaceted effects of hyperbaric oxygen therapy, including pro-angiogenesis and suppression of inflammation and microbes [119,120], hyperbaric oxygen therapy is employed for MRONJ [121,122], but hyperbaric oxygen alone is insufficient for complete cure of MRONJ [123]. Thus, it suggested hyperbaric oxygen should be combined with other remedies in a comprehensive treatment strategy for MRONJ. In addition, the actual clinical efficacy of hyperbaric oxygen therapy in MRONJ treatment still needs more investigation.

Teriparatide (TPTD), a parathyroid hormone, is primarily used for osteoporotic patients in the clinic as it can increase osteoclastogenesis in high doses and osteoblast generation in lower doses. It has been experimentally introduced to clinical MRONJ treatments [124] after its validation in animal studies [125–127]. Cheung et al. also reported the successful treatment with TPTD for Alendronate-induced MRONJ [128]. Frustratingly, TPTD seems powerless for denosumab-related MRONJ [129].

Since there are dives cytokines and growth factors, various blood-derived products, such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factors (CGF), have been widely used in regeneration medicine and dental practice. It is not surprising these products are also involved in MRONJ treatments. PRF, the second-generation product, has been used to fill in bone defects after surgical debridement and marginal osteotomy [130]. Due to the higher concentration of contained growth factors, CGF is more popular than the other two products. Based on some studies, CGF did not dramatically increase the completed healing rate, but it promoted bone regeneration in MRONJ [131,132].

6.2. Potential BMP-2 Administration in MRONJ

According to the new insight presented in this review, an osteoclastogenesis-targeted strategy may be effective for treating MRONJ. However, such a drug for the osteoclastogenesis-target strategy has not been reported. The dual effects of BMP-2 on the regulation of osteoblasts and osteoclasts, which are induced by its low and high doses, respectively, make BMP-2 a potential candidate for advancing MRONJ treatment.

BMP-2, one of the members of the transforming growth factor-beta (TGF-β) superfamily, plays a critical role in bone and cartilage development, which has been extensively documented [133,134]. BMP-2 or BMP-2-associated medical devices have been widely investigated in bone formation [135,136]. On the other hand, it has been reported that BMP-2 can upregulate osteoclast activity [137–139], and BMP receptors are also detected on the membrane of osteoclast precursors that play crucial roles in osteoclast formation [138,140]. The BMP receptors are reported to initiate osteoclast differentiation by activating the BMP receptor-Smad signal [141,142]. Intriguingly, except for the direct modulation, BMP-2 also promotes osteoclastogenesis indirectly by affecting the osteoprotegerin/RANKL ratio in osteoblasts [143]. These findings indicate that BMP-2 has the potential to be used for the osteoclastogenesis-target strategy for MRONJ. Of course, trying to enhance osteoclast formation and

activity in an environment containing BPs might prove challenging. In the past, BMP-2 delivered by various carriers was used to treat or prevent MRONJ in animal models [144–148]. In these studies, the remission of MRONJ was primarily ascribed to improved new bone formation. However, some of these studies also suggested that promoted osteoclastogenesis [144,148], an intact osteocyte network, and decreased microdamage induced by BMP-2 [146,148] relieved MRONJ. However, it is not clear whether the new bone, de facto, is the cause or post hoc fallacy in these cases. Meanwhile, a clinical study was conducted to investigate the effect of BMP-2 with leukocyte-rich and platelet-rich fibrin (L-PRF) on MRONJ [149]. The result indicated that BMP-2 strengthened the early effects of MRONJ. Moreover, a BMP-2 absorbable collagen sponge was also applied after sequestrectomy for MRONJ patients. Similar to the animal studies, more new bone formation was found after BMP-2 administration [150]. These studies support the potential of BMP-2 in addressing MRONJ by promoting or recovering bone remodeling. Integrating BMP-2 into MRONJ treatments may help counteract inhibited osteoclastogenesis and improve clinical outcomes. However, the underlying mechanism remains unclear, and the appropriate dose and delivery of BMP-2 in MRONJ management have not been well investigated. Hence, further basic and clinical research should be conducted.

7. Summary and Conclusion

MRONJ is rare, but in terms of the aging population and the increased application of BPs or denosumab in cancer treatment, more MRONJ cases have been reported. The rationale of MRONJ has not been completely unraveled. The prevailing theories on MRONJ put impaired osteoclastogenesis and disturbed bone remodeling at the forefront. In accordance, all MRONJ-associated drugs suppress osteoclastogenesis either directly or indirectly, which severely disturbs the normal bone remodeling process. Frustratingly, there is currently no specific medicine or treatment for MRONJ in clinical practice. To treat MRONJ, apart from antibiotics, mouth rinse and surgery, various experimental treatments, such as growth factors and hyperbaric therapy, have been conducted; however, their results are controversial and not highly convincing. The solution might be found in compounds capable of simultaneously enhancing osteoclast formation and activity and osteoblast formation and activity. Since BMP-2 can comprehensively modulate bone remodeling by influencing osteoblasts and osteoclasts alike, it might be a promising factor to be investigated.

Author Contributions

C.X. drafted the manuscript and was responsible for the visualization; Y.X. and Y.L. conceived this work; Y.W. offered the clinical photographs; Y.X., Y.W., A.B. and Y.L. did crucial reviews and modifications of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

Conflicts of Interest

The authors declared that they have no conflicts of interest in this work.

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