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*Perspective*

# Underestimated Roles of Osteocytes in Medication-Related Osteonecrosis of the Jaw

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**Abstract:** Medication-related osteonecrosis of the jaw (MRONJ) is a grievous complication after the long-duration administration of some bone-modifying agents, mainly containing bisphosphonates (BPs), denosumab, angiogenesis inhibitors, immunosuppressors, glucocorticoids, and chemotherapeutics. Its prevalence is rare but mounting due to the widespread application of MRONJ-associated drugs in the aging population and cancer patients. Although MRONJ is excruciating, there has been no specific and efficient remedy for it. To date, the understanding of MRONJ is not thorough, and various theories on MRONJ have been proposed, among which impaired bone remodeling as a result of inhibited osteoclast generation and activity is the predominant one. However, the role of osteocytes in MRONJ has been omitted, given their crucial roles in governing bone metabolism: they not only communicate with osteoblasts for bone formation but also promote osteoclastogenesis.

**Keywords**: osteocytes; medication-related osteonecrosis of the jaw; microdamage; apoptosis; inflammation

## 1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but mounting complication after the extensive consumption of some bone-modifying agents (BMAs), mainly including bisphosphonates (BPs) and denosumab. Due to their widespread prescription for osteonecrosis and cancer treatment, MRONJ prevalence is increasing, severely exacerbating the quality of life of patients. Diagnostic criteria for MRONJ have been stated clearly in the position paper of the American Association of Oral and Maxillarfcail Surgeons (AAOMS) in 2022 [1]. However, its etiology and pathogenesis remain unclear, leading to compromised clinical treatment outcomes. In current MRONJ treatment, symptomatic treatment contains mouth rinse, antibiotics, anti-inflection, and pain relief is the mainstream. However, most treatments are long-duration, and in some cases, these non-invasive strategies are inefficient. Thus, unfortunately, these patients have to undergo partial or even total mandible resection.

Various clinical findings contribute to diverse theories on MRONJ, among which impaired bone turnover and bone remodeling are the mainly acknowledged ones. In these theories, the aberrant bone metabolism process characterized by abnormal bone resorption leads to eventual necrosis of the jawbone. Since osteoclasts exert bone resorption, and they and their precursors are the direct targets of BPs and denosumab, it behooves osteoclasts to receive the most attention in MRONJ studies. However, the vital role of another category of bone cells, i.e., osteocytes, in MRONJ is underestimated on account of comprehensively orchestrating bone metabolism and remodeling.

## 2. Osteocytes

Osteocytes, descendants of osteoblasts, are the most common cells in mature bone tissue, accounting for 90–95% of all bone cells [2], whereas they receive less focus than well-studied bone marrow mesenchymal stem cells, osteoblasts, and osteoclasts because they are embedded in a dense mineralized bone matrix. Osteocytes can be identified by their morphology with protruded dendritic processes (Figure 1A) and their location in the lacunae. As mechanosensors, osteocytes communicate with the external environment via these processes and the lacuno-canalicular network (LCN) (Figure 1B,C) embedded in the mature bone matrix. Intact canaliculi and LCN are essential for the viability of osteocytes. It has been well-investigated that impaired processes and LCN structures will induce apoptotic osteocytes [3].

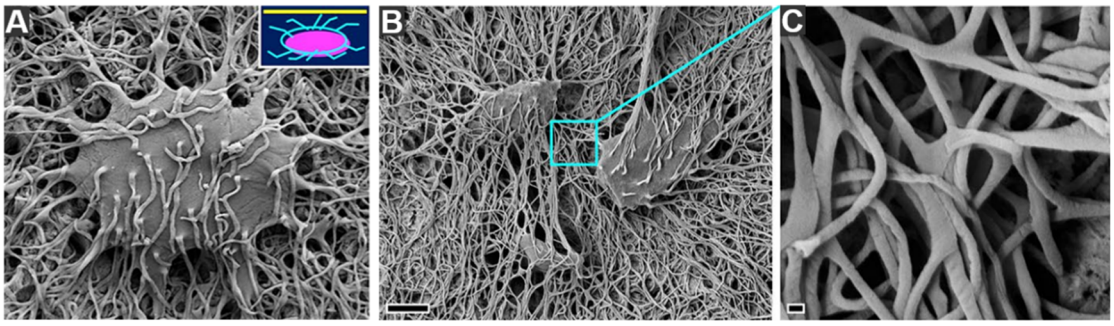


**Figure 1.** Morphology of osteocytes and lacuno-canalicular network. (**A**), an osteocyte embedded in lacuna; (**B**,**C**), the osteocyte lacuno-canalicular network in rat bone. Adapted from Moriishi et al. [4].

## 3. Osteocytes in Bone Remodeling

Thanks to advanced understandings of osteocytes, their more sophisticated roles, especially in orchestrating osteoblasts and osteoclasts in bone remodeling, have been illustrated. Osteocytes are the main source of the receptor activator of nuclear factor kappa beta ligand (RANKL) [5] which is essential for the maturity of osteoclasts. In addition, they can secrete sclerostin to inhibit osteoblast differentiation [6]. In turn, to avoid extensive osteoclastogenesis and following bone resorption, osteocytes also promote bone formation directly or indirectly [7] (Figure 2). Meanwhile, apoptotic osteocytes are responsible for osteoclastogenesis, to some extent, initiating bone remodeling for bone microdamage repair, as described in our previous review [8]. Therefore, the role of osteocytes in MRONJ that has not been showcased is worth being investigated.

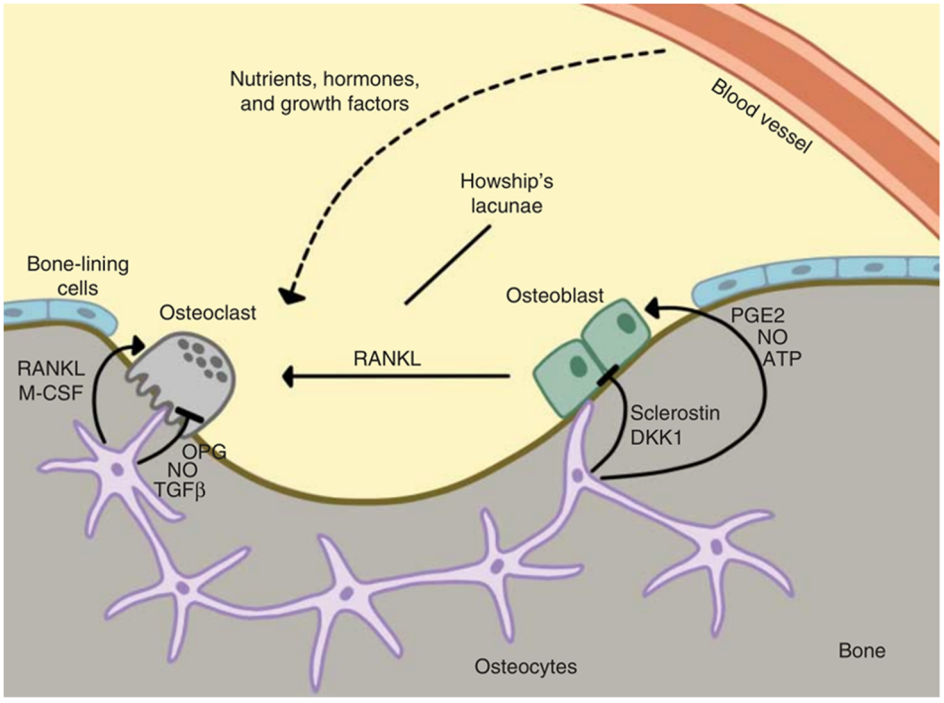


**Figure 2.** Ostocytes orchestrate bone remodeling by regulating osteoblasts and osteoclasts through various cytokines. Reproduction from Niedźwiedzki et al. [9].

## 4. Osteocyte Apoptosis in MRONJ

Physiologically, apoptotic osteocytes and their apoptotic bodies can be eliminated via phagocytosis during bone remodeling facilitated by osteoclasts and osteoblasts [10]. After taking MRONJ-associated drugs, bone remodeling is disturbed. In addition, the functions of osteoclasts and immune cells, including dendric cells, macrophages, T cells, and neutrophil granulocytes, are suppressed [11], leading to a delayed clearance of these apoptotic bodies. This causes the inflammation characteristic of MRONJ and stimulates pro-inflammation cytokines accumulation in the local microenvironment [12], which in turn, induces the apoptosis of surrounding health osteocytes, described as a “vicious circle”.

MRONJ most occurs in individuals with MRONJ-associated drug history and subsequent invasive dental treatments, particularly tooth extraction. It is reasonable to suspect that during these dental treatments, LCN and processes of osteocytes are damaged, causing apoptotic osteocyte accumulation in treated areas, leading to abundant empty lacunae in MRONJ specimens, which have been confirmed by using histological evaluations (Figure 3). Unfortunately, these dead osteocytes cannot be eliminated due to the suppression effects of BMAs or other MRONJ-associated drugs on osteoclasts and immune cells, deteriorating inflammation conditions. Eventually, inflammation triggers necrosis of bone tissues. Intriguingly, similar histological features are also reported in osteomyelitis, including empty osteocytic lacunae and inflammation cell infiltration [13], suggesting the crucial role of inflammation in bone diseases.

Various factors can induce osteocyte apoptosis, such as disturbed LCN structure, reactive oxygen species (ROS), and hypoxia. Alike to most cells, osteocyte apoptosis relies on the cascade of caspase proteins, which has been well-reviewed by Ru et al. [3]. The osteocyte apoptosis may explain glucocorticoid-induced MRONJ in the animal model and clinical cases. High-dose glucocorticoids accumulate destroyed proteins, damaged nucleic acids, and accumulated oxygen radicals in cells, leading to cell apoptosis. On the other hand, glucocorticoids similar to other immunosuppressors can weaken immune cell functions, thereby also abating the clearance of apoptotic osteocytes and mitigating the local inflammation environment. Hence, compared to these existing theories on MRONJ, the osteocyte-targeted hypothesis can comprehensively explain the distinguishing clinical features as a result of consumption of different MRONJ-associated drugs and pro-MRONJ conditions.

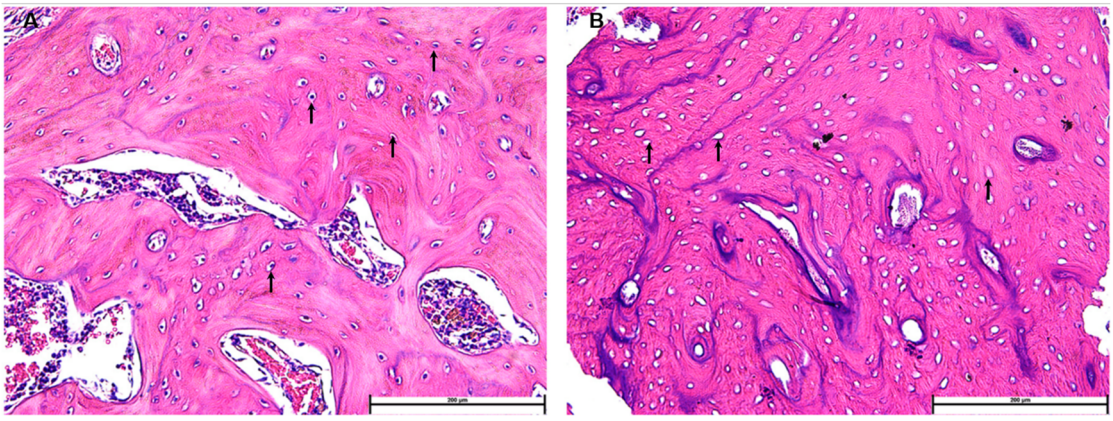


**Figure 3.** Histology images of normal alveolar bone tissue (**A**) and MRONJ specimens (**B**). Normal lacunae with osteocytes and empty lacunae have been identified by black arrows, respectively. Adaption from Kuehn et al. [14].

## 5. Prospect

Although, to date, there are various theories on MRONJ, most current attention has been paid to osteoclasts for advanced understanding of MRONJ and effective remedies for this disease, as osteoclasts are the direct or indirect targets of MRONJ-associated medications. However, none of these current theories and hypotheses can thoroughly reveal the etiology and pathogenesis of MRONJ. Based on adequate previous studies, osteocytes play a pivotal role in MRONJ that has not been well-illustrated. They comprehensively modulate the performances of osteoblasts, osteoclasts, and the microenvironment in bone tissue. On the other hand, the viability and functions of osteocytes can be disturbed by diverse factors, such as angiogenesis inhibitors, bisphosphonates, and inflammation, implying irregular physiological events of osteocytes may integrate these established theories.

To evaluate the roles of osteocytes in MRONJ development, an appropriate animal model should be proposed. Since 2009, BP alone or with additional dexamethasone has been predominantly applied for the establishment of the MRONJ model in rats [15]. However, this model needs to extract mandibular molars, involving various MRONJ risk factors (alveolar bone microfracture, bacteria infection, inflammation, disturbed blood supplement,

etc.). Therefore, it is hard to focus on the effects of osteocytes on MRONJ in such a model. A few modified MRONJ models have been reported, including immunocompromised models, periodontitis models, hyper-occlusion models, and ovariectomized (OVX) rat models [16–19], whereas osteocyte-targetting MRONJ models have not been developed. It is well-investigated that extensive mechanical loading can induce the apoptosis of osteocytes [20], and some devices have been employed to load mechanical stress on the limbs of rats, i.e., axial loading, to evaluate the altered physiological or pathological events in osteocytes [21]. Thus, it is likely to transfer this research strategy and instruments to MRONJ studies, thereby concentrating on osteocytes and eliminating other influence factors.

The clinical experience also suggests the "initiator role" of osteocyte apoptosis in MRONJ. MRONJ is usually diagnosed after dental practice, particularly tooth extraction. During tooth extraction, cortical bone microdamage is common, which can destruct the LCN and contribute to the apoptosis of osteocytes. In a physiological condition, apoptotic osteocytes will provoke bone remodeling, diminishing the damage and refraining from osteonecrosis, which has been summarized in a previous review [8]. However, in patients on MRONJ-associated drugs, due to phagocytosis suppression, these osteocyte-derived apoptotic bodies cannot be eliminated from the microenvironment, resulting in aggressive inflammation and ultimate bone tissue necrosis.

The role of osteocytes in rare bone diseases has been reviewed by Pathak et al. [22], and his colleagues Yan et al. also summarized osteocyte-mediated cellular signaling via mechanical stimuli [23]. According to their work, some cytokines and signalings have the potential for MRONJ diagnosis and treatment. For instance, sclerostin only expressed by mature osteocytes can inhibit bone formation by blocking the Wnt signal pathway [24]. Its monoclonal antibody, Romosozumab, has been used to treat osteoporosis [25], while it is also associated with MRONJ [25,26], implying the importance of vital osteocytes for bone homeostasis. Other osteocyte-specific cytokines, such as fibroblast growth factor-23 (FGF-23), are also associated with bone diseases. Hence, their roles in MRONJ should be investigated as well in the future, and they may be the targets for MRONJ treatment.

As osteocytes are embedded in dense bone matrix, it is hard to observe and evaluate them directly. Currently, observations on osteocytes mainly rely on confocal laser scanning electron microscopy (CLSM), scanning electron microscopy (SEM), and ultra-high voltage electron microscopy [22]. Nonetheless, these methods are not feasible for clinical practice due to the invasion. Alternatively, collecting extracellular vesicles and exosomes excreted by osteocytes is available in clinical settings. Analyzing the miRNAs, circular RNAs, mRNAs, and various proteins in them may reflect the function of osteocytes.

Taking together, currently, the role of osteocytes in MRONJ should have received more attention, which is not parallel with its pivotal role in bone metabolism and remodeling. New insight into osteocytes in MRONJ may revolutionize the appreciation of and the clinical treatment strategy for MRONJ and mitigate the controversy among current MRONJ theories.

## Author Contributions

C.X.: conceptualization, writing—original draft preparation; Y.W.: supervision; writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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## Conflicts of Interest

The authors declare no conflict of interest.

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