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Review Article

Clodronate: Underexplored Therapeutic Approach in Periodontal Diseases

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Abstract

Periodontitis is a chronic, multifactorial inflammatory disease characterized by dysbiosis of the subgingival biofilm, immune system activation, and progressive destruction of the periodontal tissues. Bacterial components (PAMPs) trigger recruitment and activation of macrophages, neutrophils, and lymphocytes, leading to the release of pro-inflammatory cytokines, reactive oxygen species, and matrix metalloproteinases (MMPs). These mediators drive osteoclastogenesis, alveolar bone resorption, and periodontal tissue breakdown. External systemic and local risk factors further exacerbate inflammation and disease progression. This review examines a therapeutic approach that remains underexplored: the preservation of bone structure and the periodontal ligament through modulation of immune-inflammatory pathways. Particular attention is given to clodronate, an atypical non-aminobisphosphonate with distinct pharmacological properties, including low affinity for hydroxyapatite, high biocompatibility with gingival tissues, and the ability to inhibit vesicular ATP storage and release in activated immune cells. Through these mechanisms, clodronate reduces cytokine expression, MMP activity, osteoclast activation, and the formation of neutrophil extracellular traps (NETs). Unlike other bisphosphonates, clodronate does not accumulate excessively in bone and presents minimal risk of jaw osteonecrosis, while also exhibiting unique analgesic effects. Its combined anti-inflammatory, anti-resorptive, and MMP-inhibitory actions suggest that clodronate may serve as a valuable adjunct to conventional periodontal therapies aimed at limiting inflammation, preserving alveolar bone, and improving long-term clinical outcomes.

Keywords: *Periodontitis; Alveolar Resorption; Inflammation; Bisphosphonates*

Introduction

Periodontitis represents a highly disabling dental pathology. In its chronic form, it is characterised by bacterial invasion and an inflammatory reaction involving the recruitment of immune cells and the release of mediators that promote bone resorption and destruction of the periodontal tissues.

The bacteria associated with periodontitis are predominantly Gram-negative species, including *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*. Some strains, such as *P. gingivalis*, have evolved sophisticated strategies to evade the host immune system, whereas other bacteria act directly as pro-inflammatory agents [1].

The disease is associated with a multifaceted and dynamic interaction between specific infectious agents, the host immune response, exposure to a harmful environment, and genetic susceptibility. For many years, it has been recognised that periodontitis can manifest in several clinical forms, and clinicians have attempted to define various classifications [2,3]. However, despite these efforts, it has become evident that each classification must be periodically revised in light of new clinical, microbiological, and pathological evidence, including the effects on the bone structure. Ultimately, any classification system should remain adaptable to the evolution of scientific knowledge.

During the course of periodontitis, a range of local and systemic conditions may develop, potentially exerting a negative impact on the periodontal attachment apparatus. Common manifestations include gingival recession, dental mobility, hypersensitivity, and lesions on exposed root surfaces. Among systemic conditions, diabetes mellitus, cardiomyopathy, neoplastic diseases, tobacco use, and hormonal disorders play a particularly important role. Nevertheless, it is not always clear whether the detrimental effects observed in periodontitis are primarily due to the bacterial biofilm of dental plaque, to mechanical trauma, to the toxicity of dental materials, or to a combination of these factors [4].

It is, however, widely accepted that the subgingival dental biofilm elicits an inflammatory and immune response, which in turn leads to irreversible destruction of the periosteum - namely, the alveolar bone and periodontal ligaments - in susceptible individuals.

Periodontitis can therefore be considered a multifactorial condition resulting from the combined effects of pathogenic microbial agents, local and systemic risk factors, and individual susceptibility. Consequently, therapeutic outcomes are often uncertain due to the multiplicity and variability of the factors involved.

Numerous guidelines have been published in the scientific literature to indicate the most appropriate treatment strategies for periodontitis, aiming to improve overall systemic health and quality of life [5].

Aim of the Review

Periodontitis is characterised by the progressive destruction of the tooth-supporting apparatus, clinically manifesting as the loss of clinical attachment level (CAL) and alveolar bone resorption. If left untreated, these processes can ultimately result in tooth loss [6].

The aim of this review is to evaluate one of the therapeutic aspects least addressed in the literature: the optimal approach to preserving bone structure and the periodontal ligament in the context of pathogenetic events induced by inflammation and alveolar bone resorption [7].

Inflammation and bone resorption

Periodontitis is associated with a chronic inflammatory condition sustained by extensive bacterial dysbiosis. This dysbiosis triggers the release of substances that activate immune cells, leading to the expression of enzymes and mediators of bone resorption, which culminate in the destruction of tooth-supporting tissues and eventual tooth loss. These processes are further influenced by external factors that amplify both the inflammatory stimulus and the host immune response [8].

Although several contributing factors are recognised, inadequate oral hygiene inevitably promotes dysbiosis and the release of bacterial components. Various bacterial antigens derived from the pathogenic flora - referred to as pathogen-associated molecular patterns (PAMPs) - present in the subgingival biofilm activate resident dendritic cells and macrophages, stimulate the recruitment of

natural killer (NK) cells, and attract T lymphocytes and polymorphonuclear neutrophils (PMNs) [9,10]. Once activated, these immune cells respond by producing mitochondrial ATP, which is incorporated into transport vesicles and released extracellularly, where it interacts with purinergic receptors. Activation of the purinergic system by ATP and its degradation products (ADP and adenosine) induces nuclear signalling responsible for the expression of a broad spectrum of pro-inflammatory cytokines, including TNF-α, IL-1, IL-6, and IL-14 [6,11].

Several studies have demonstrated the pivotal role of activated neutrophil accumulation at the periodontal site and the pathogenetic importance of neutrophil extracellular traps (NETs). Together with the cytokine IL-17, NETs contribute to the amplification of the inflammatory process and to increased local bone resorption [12].

Particularly noteworthy is the dual role of IL-17, which exerts essential host-defence functions such as neutrophil recruitment, phagocytosis, and mucosal immunity, but whose excessive expression leads to persistent chronic inflammation and bone loss [13].

In addition, cytokines such as TNF-α, IL-6, and IL-1β - typically released by M1 macrophages activated by bacterial antigens (PAMPs) - exert a strong osteoclastogenic stimulus. In this context, macrophage activation induces ATP production, its packaging into vesicular nucleotide transporter (VNUT)-containing vesicles, and subsequent exocytosis, allowing ATP to interact with purinergic receptors. This cascade promotes nuclear cytokine expression, polarisation towards the pro-inflammatory M1 phenotype, and the release of collagenases and elastases (MMP-8 and MMP-13), similarly to neutrophil-mediated mechanisms [14-16].

Although macrophages and neutrophils play a crucial role in host defence against pathogenic periodontal infections, their excessive activation and accumulation can lead to tissue damage and osteoclast activation, resulting in alveolar bone resorption [17].

In summary, periodontitis can be viewed as a chronic inflammatory disease characterised by sustained activation of immune cells, resulting in the release of multiple cytokines that modulate monocyte/macrophage phenotype and stimulate osteoclast recruitment and activation at the local level. The enhanced alveolar bone resorption and release of matrix metalloproteinases (MMPs) ultimately cause destruction of the periodontal tissues and loss of attachment to the alveolar bone.

Thus, even disregarding the various predisposing factors, it is clear that bacterial dysbiosis - through excessive microbial load - initiates immune system activation and the production of mediators that drive the loss of tooth attachment to alveolar bone.

Bisphosphonates - Clodronate

Leaving to other studies the various strategies aimed at reducing or normalising the oral bacterial flora, we sought to highlight a potential therapeutic approach capable of acting upon the fundamental stages of the pathogenetic process - namely, immune system activation, cytokine and MMPs expression, and bone resorption.

This approach involves the use of bisphosphonates (BPs), and in particular Clodronate, which represents a unique and atypical BP with pharmacological characteristics that distinguish it from all other bisphosphonates and make it suitable for dental applications.

The pharmacological and clinical properties of bisphosphonates have been extensively described in a substantial body of literature dating back to the mid-1970s [18-20], where these compounds were introduced for the treatment of bone and joint diseases.

In more recent years, however, the clinical safety of some bisphosphonates has been questioned due to reports of osteonecrosis of the jaw in patients undergoing dental surgery. One major factor contributing to this risk lies in the high affinity of certain BPs for hydroxyapatite, leading to prolonged binding and local accumulation, which can predispose to osteonecrosis.

As previously mentioned, Clodronate (CLD) differs from other bisphosphonates not only by the absence of an amino group in its chemical structure - responsible for the enhanced pharmacological activity of amino-BPs - but also by the absence of a hydroxyl group bound to the central carbon atom. The lack of this hydroxyl group allows CLD to form only a bidentate bond with hydroxyapatite, resulting in a lower affinity and therefore easier removal from remodelling bone, preventing potentially harmful accumulation [21,22] (Figure 1).

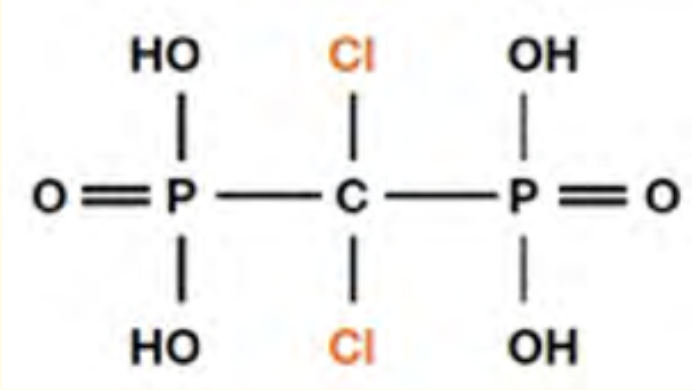

Figure 1: *Clodronate: non nitrogen bisphosphonate chemical structure.*

Another property distinguishing CLD from other BPs is its excellent biocompatibility with gingival epithelial cells. In contrast, amino-BPs exhibit cytotoxic effects on human keratinocytes. The high concentrations of amino-BPs released from bone undergoing rapid remodelling may delay gingival wound healing and predispose to bacterial infections [23,24].

However, the most distinctive characteristic of Clodronate lies in its specific inhibitory activity on macrophages, neutrophils, and lymphocytes activated by bacterial antigens. Cells of the immune system - like all other body cells, including neurons and keratinocytes - respond to injury by producing ATP, which serves both as an energy source and as a signalling molecule to amplify cellular responses. Intracellular ATP is accumulated within transport vesicles via the vesicular nucleotide transporter (VNUT) and subsequently released into the extracellular space, where it contributes to chronic inflammatory signalling and neurotransmission [25,26].

Clodronate can enter macrophages and neutrophils through phagocytosis or endocytosis, and also via SLC20-34 phosphate channels, thereby modulating the immune response against pathogen-associated molecular patterns (PAMPs) and influencing the adaptive immune system - including the activation of B and T lymphocytes, clonal expansion of T cells, and antibody production. ATP itself has also been identified as a damage-associated molecular pattern (DAMP), capable of activating the innate immune system [27]. Activated macrophages and neutrophils release extracellular ATP, a potent activator of the inflammasome complex [28,29].

Recent studies have demonstrated that once inside immune cells, Clodronate can inhibit the vesicular uptake of ATP through the SLC17A9 channel, with an IC_{50} of 15.6 nM [25,26]. This inhibition prevents ATP accumulation and storage within vesicles, as well as its extracellular release and subsequent activation of membrane-bound purinergic receptors. Through this mechanism, Clodronate inhibits immune cell activation and exerts its anti-inflammatory effects by reducing the release of cytokines, chemokines, reactive oxygen species (ROS), and prostaglandins.

Clodronate also exhibits a direct inhibitory effect on several matrix metalloproteinases (MMPs), as it can penetrate their active site and chelate the zinc ion (Zn^{2+}) essential for enzymatic activity, thus preventing the proteolytic degradation of periodontal connective tissue [15].

In addition to its local and systemic anti-inflammatory activity [30,31], Clodronate possesses unique analgesic properties among bisphosphonates. It can inhibit the release of key pain mediators such as ATP and glutamate at the intramedullary synapses between peripheral nociceptive fibres and ascending central pathways. This reduction in neurotransmitter release contributes to an analgesic effect not shared by other agents of the same class [32].

Finally, the anti-osteoclastic and anti-resorptive actions of Clodronate are expressed - as with other bisphosphonates - in bone areas characterised by high turnover, such as those affected by periodontal disease. However, Clodronate achieves these effects without forming harmful local accumulations or interfering with gingival wound healing. Bisphosphonates, including CLD, have already been employed in dental pathologies, demonstrating good tolerability and clinical efficacy [33-35].

The clinical application of Clodronate is thus supported by its biological activity at both the cellular and molecular levels, encompassing not only inhibition of osteoclast recruitment and activity, but also suppression of macrophage function, prostaglandin synthesis, and several MMPs.

Conclusion

Although the management of periodontitis (PD) requires lifelong periodontal maintenance, including reassessment of local dysbiosis and various risk factors, it is also essential to provide effective interventions to reduce chronic inflammation, alveolar bone resorption, and destruction of the periodontal ligaments.

Clodronate is a bisphosphonate with pharmacological properties that make it a drug of choice for the treatment of dental and maxillofacial bone conditions. In addition to its typical anti-osteoclastic activity, it exhibits inhibitory effects on matrix metalloproteinases (MMPs) and exerts anti-inflammatory action. The anti-inflammatory effects, also confirmed in clinical studies on systemic diseases, are mediated through inhibition of immune cell activation, preventing the transformation of local macrophages into the pro-inflammatory M1 phenotype and thereby reducing the production of cytokines that activate osteoclasts. Neutrophils are similarly inhibited, with reduced phagocytosis and extracellular trap (NET) formation, while lymphocyte activity is modulated to complement the overall anti-inflammatory effect on periodontal tissues.

Importantly, clodronate-whether administered orally or locally-does not present a significant risk of inducing jaw osteonecrosis due to its low bone affinity, minimal toxicity, and excellent tolerability in soft tissues. These properties suggest that clodronate could provide valuable support as an adjunct to conventional therapies or surgical interventions in the management of periodontitis.

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