Chronic Periodontal Disease

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Periodontitis (PD) is an infection-driven inflammatory disease of periodontal tissues caused by pathogenic microorganisms, which have been characterized by disruption of the tooth-supporting structures. In periodontal disease treatment, the conventional route of drug administration has many drawbacks such as poor biodistribution, low selectivity of the therapeutic effect, burst release of the drug, and damage to healthy cells. To overcome these difficulties, controlled drug delivery systems have been evolved as an alternative method to address oral infectious disease ailments. The use of drug delivery devices proves to be an excellent auxiliary method in enhancing the quality and effectiveness in periodontitis treatment, which includes inaccessible periodontal pockets. In the literature, there have been described as many various polymer-based delivery systems such as hydrogels, liposomes, micro-, and nanoparticles, which can be used in the treatment of chronic periodontal disease. The review shows the current state of knowledge regarding the applications of various polymer-based delivery systems such as hydrogels, liposomes, micro-, and nanoparticles in the treatment of chronic periodontal disease.

1. Definition

Periodontitis (PD) is an infection-driven inflammatory disease of periodontal tissues caused by pathogenic microorganisms, which have been characterized by disruption of the tooth-supporting structures.

2. Introduction

Periodontitis (PD) is a localized chronic inflammatory disease of periodontal tissues caused by pathogenic microorganisms and characterized by disruption of the tooth-supporting structures [1]. The inflammation is primarily localized to the gum but penetrates deeper if left untreated, creating pockets that host anaerobic bacteria which can then lead to further erosion of the tooth attachment and eventually to tooth loss. Periodontitis includes various degenerative and inflammatory states of the tissue surrounding the tooth, e.g., gingival, periodontal ligaments, cementum, and alveolar bone.

According to the World Health Organization report, it is one of the world's most widespread chronic ailments occurring after the age of 35 [2][3]. Figure 1 shows a schematic depiction of periodontal disease.
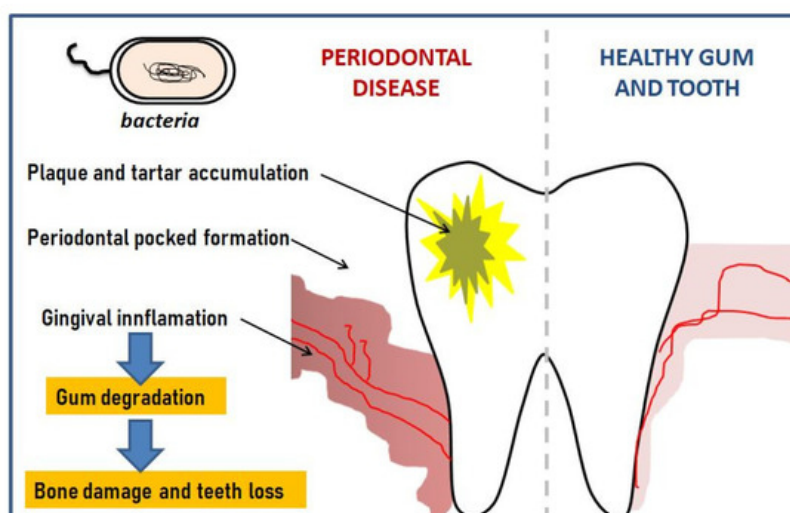
Figure 1. Schematic development of periodontal disease.

The current treatment of periodontal disease involves oral hygiene such as mechanical cleaning (brushing and flossing), together with the use of dentifrices and antibacterial mouthwashes. Non-surgical treatment methods for periodontitis include mechanical scaling and root planning [4]. Additionally, antibiotics, especially tetracyclines, β-lactam, and nitroimidazole antibiotics are mostly used for the treatment of periodontal disease [5].

Conventional drug administration routes are the most popular methods of drug treatment due to certain advantages, such as ease of use and a very high degree of dosage flexibility. This method is used to eliminate or inhibit gingival bacteria flora, decrease inflammation, and help to discontinue bone desorption. However, conventional drug administration pathways also have many drawbacks such as serious side effects, poor biodistribution, low selectivity of the therapeutic effect, burst release of the drug, and damage to healthy cells [6],[7]. The efficacy of conventional antimicrobial therapy has often been hampered by the difficulties of achieving and maintaining an appropriate concentration of curative agents at the periodontal site when a low dose of the drug is given. To overcome these limitations, a more effective approach to administering drugs into the periodontal pocket needs to be developed.

Recently, there has been growing interest in controlled drug delivery systems as a whole and as a potential method to address oral infectious disease ailments in particular [8]. Drug delivery systems (DDS) are used vehicles to transport therapeutic agents including antibodies, peptides, vaccines, drugs, and enzymes to a target location and safely achieve the desired therapeutic effect. Thus, the administration and efficacy of these pharmaceutical compounds are improved [9],[10]. The effectiveness of medicine has increased with the development of the fabrication of drug delivery carriers, which can administer accurate doses of drugs, minimize side-effects, and improve healthcare treatment of patients [5][11].

Polymers continue to play an important role in the development of drug delivery technology due to their favorable physicochemical properties and offering the possibility of further modifications. Advanced polymer delivery systems have been developed, in recent years thanks to the innovations in chemical engineering technology. Modern advances in drug delivery systems are now based on the design of polymers adapted to specific drugs and designed to perform distinct biological functions. To control the release of drugs and other active substances, a wide range of natural and synthetic origin polymer-carriers have been used. Polymers are potential drug carrier candidates but they must present some characteristics such as efficacy, hydrophilicity, lack of immunogenicity, lack of biological activity, and the presence of functional groups for covalent coupling of drugs or target moieties [12][13][14].

In recent years the field of controlled release drug delivery have been utilizing biodegradable polymers that can biodegrade within the body, such as polylactides (PLA), polyglycolide (PGA), poly(lactide-co-glycolides) (PLGA), polyanhydrides, polyorthoesters, all of which were previously known for other medical applications. The greatest advantage of these biodegradable polymers is that they are broken down into biologically tolerable molecules that are metabolized and removed from the body via normal metabolic pathways [15]. Apart from all these advantages, the use of polymeric carriers also has some limitations. For instance, naturally occurring polymers although highly abundant and biodegradable are difficult to reproduce and purify whereas, empty non-biodegradable polymers delivery devices needed to be removed by surgery after releasing the drug at the targeted site. Moreover, biodegradable materials do produce degradation byproducts that must be tolerated within the biological environment and therefore, both the desired and unwanted by-products must be carefully tested.

Polymer therapeutics include linear or branched polymer chains which act either as the bioactive molecule, e.g., polymeric drug or as the inert carrier to which a drug can be covalently linked, e.g., polymer-drug conjugates, dendrimers, polymeric micelles, nanocapsules, nanospheres, hydrogels, liposomes, etc. However, in order to successfully be used in controlled drug delivery formulations, a polymeric carrier must be chemically inert and free of leachable impurities. In other words, it must have an appropriate physical structure, with minimal undesired aging, and be readily processable [16].

The elaborated periodontal pocket drug delivery devices based on polymers improve the antimicrobial efficacy and demonstrate many consequent clinical benefits. It is worth mentioning that local sustained administration of drugs into the periodontal pockets in the mouth is challenging due to the continuous secretion of saliva. This facilitates for the implant to leave the periodontal pocket easily and it could then be swallowed by the patient [17]. Usage of a local drug delivery system in the treatment of periodontitis allows to achieve and maintain a greater concentration of drug at the diseased area than possible with conventional therapy, preventing the side effects of free-drugs.

3. The Pathogenesis of Periodontitis Diseases

In healthy individuals, the periodontium is mostly colonized by harmless, commensal bacterial communities [18]. A proper balance in their composition prevents the immune system from a potentially detrimental reaction. A dental plaque is defined as a polymicrobial biofilm on the surface of the tooth and tooth root. Presumably, due to poor hygiene or risk factors, excessive dental plaque may accumulate leading to the destruction of periodontal connective tissue and alveolar bone, the disease known as periodontitis [19]. One more important process is connected with this pathological state: a shift in microbial composition from mostly Gram-positive to mostly Gram-negative bacterial species [20][21]. Nevertheless, the mechanism causing the bacterial transition from one state to the other remains to be elucidated and a model implicating Gram-negative bacteria as the sole etiologic factor is rather oversimplistic [21].

The gingival epithelium constitutes an interface between the human organism and complex microbial community inhabiting the oral cavity. Hence, it is constantly challenged by numerous bacterial species. Any perturbations must be immediately faced by the immune system. The adaptive immune response requires several days before it may start to combat microbes, therefore innate immunity plays a critical role in the early stages of infection [22]. Pathogen associated molecular patterns (PAMPs) are defined as conserved microbial moieties that trigger the innate arm of the immune system which, in turn, directs adaptive immunity. Usually, they are crucial for microbial survival, thus their evolution rate is strongly inhibited. As PAMPs may serve diverse pathogen structures like lipopolysaccharide (LPS), flagellin, or fimbriae [23][24][25][26]. Pattern recognition receptors (PRRs), located on/in immunologically-relevant cells, are host receptors involved in PAMP recognition and initiation of the inflammatory response. Usually, such a response is beneficial, because it restricts infection and allows for pathogen removal from the host organism, but when the reaction is exaggerated or lasts too long, the inflammation may lead to detrimental effects on the host tissues, including tissue injury, perfusion defects, chronic inflammation state, and sepsis [27].

A healthy junctional epithelium is rich in many innate mediators [19], and an appropriate expression of interleukin 8 (IL-8), intracellular adhesion molecules (ICAMs) and E-selectin enables neutrophils' presence within the tissue. Their role is to keep bacteria forming dental plaque under control [28][29]. Since periodontitis is related to a shift from Gram-positive to predominately Gram-negative flora, one of the essential steps for host defense is to correctly detect such a transition. The best characterized PAMP of Gram-negative bacteria is LPS, a major component of the outer membrane. When a pathogen invades the tissues, LPS might be released from the cell surface. Subsequently, it binds to LPS binding protein (LBP), complexes with a soluble or membrane-anchored CD14, and as the LPS-LBP-CD14 complex is transferred to another complex, namely TLR4-MD-2 (Figure 2) [30].
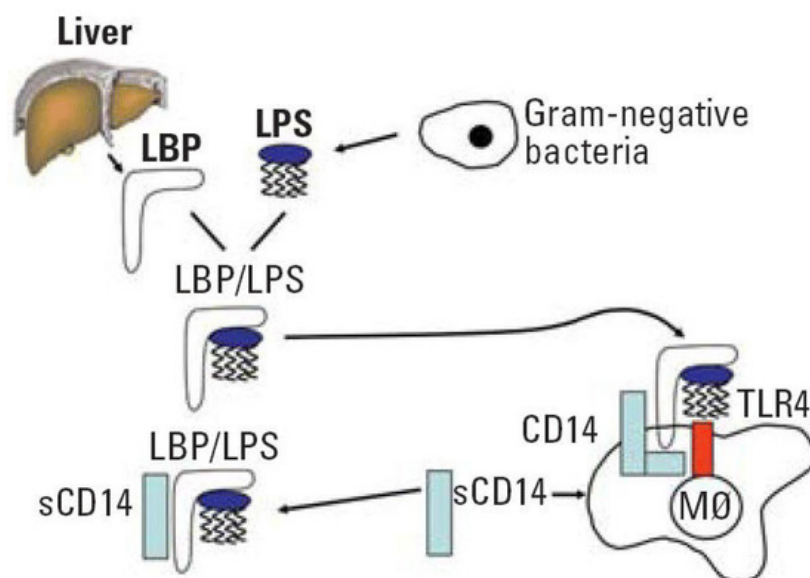

Figure 2. LPS recognition system. Abbreviation: LPS, lipopolysaccharide; LBP, lipopolysaccharide binding protein; CD, cluster of differentiation; sCD14, soluble CD14; TLR4, toll-like receptor 4; M∅ macrophage. Reprinted with permission from [30]. Copyright Environ. Health Perspect., 2006.

After activation, TLR-4 undergoes oligomerization and triggers downstream molecular cascade which ends with the synthesis of the proinflammatory cytokines and type-1 interferon. The effect of this pathway is then intensification of the immune response and, under standard conditions, infection eradication [25]. An interesting finding made by Ren and

colleagues [31] is that LBP levels in healthy gingival tissues were significantly higher when compared to tissue with already developed periodontitis. Nonetheless, whether this is a cause or effect of the growing infection is not established. It is worth noting that other PRRs like TLR2 may induce a destructive inflammatory response [32].

One of the major symptoms of periodontitis is bone loss. Once the immune system fails to limit a local gingival infection, the inflammatory state expands finally reaching alveolar bone and causing severe tissue destruction [33]. In healthy individuals, bone remodeling understood as bone resorption and bone formation is equable [34]. The receptor–activator of nuclear factor-κB ligand (RANKL) /osteoprotegerin (OPG) ratio maintains this equilibrium. OPG functions as a soluble receptor for RANKL, the ligand for the receptor–activator of nuclear factor-κB (RANK) receptor, which is produced by osteoblasts and exists either as a soluble or membrane-anchored protein The interaction between OPG and RANKL prevents RANKL from binding RANK, the receptor RANK present on the osteoclasts and their precursors. RANK binds RANKL and directs precursor cells to differentiate into ones producing enzymes breaking down a bone (Figure 3) [35]. Proinflammatory cytokines such as IL-1β, -6, -11, and -17 and TNF-α lead to greater RANKL expression and drop in the OPG levels [36]. It was proved that in periodontitis the RANKL/OPG balance is disturbed in favor of higher RANKL/OPG ratios [37][38].
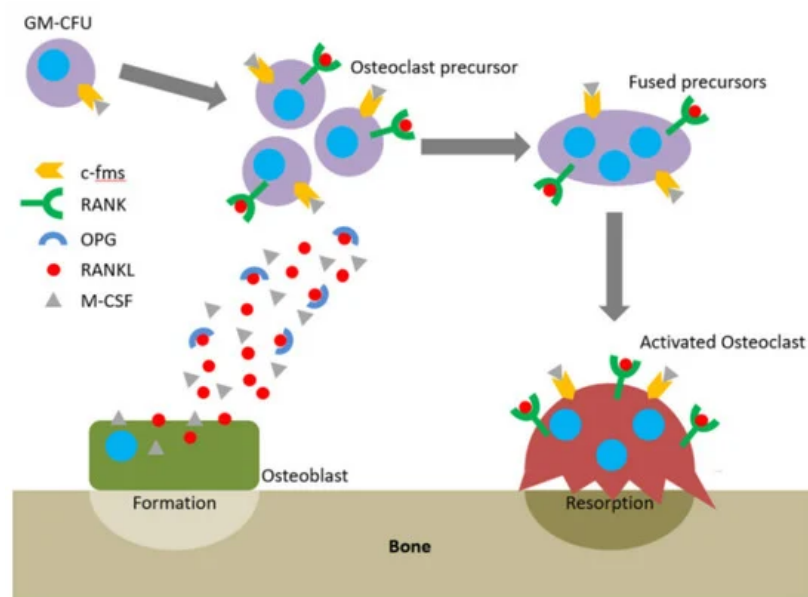

Figure 3. The RANKL/RANK/OPG axis and M-CSF direct osteoclastogenesis and activation. Reprinted with permission from [35]. Copyright Owen and Reilly (2018).

However, the bone loss process in periodontitis is more intricate than simple shifts in the RANKL/OPG ratio and involves more signaling molecules like IL-1, IL-6, TNF, or metalloproteinases [39][40][41]. The latter ones are a very important group from the periodontitis pathogenesis point of view. They are protein-degrading enzymes playing a variety of roles, including proteolysis of chemokines, receptors, inhibitors, and collagen, hence significantly influencing inflammation regulatory processes.

Collagen is a basic extracellular matrix component of connective tissue and its destruction results in remarkable tissue impairment [41] In periodontitis-affected tissues elevated levels of MMP-8 were reported [42] and increased activity of MMP-9 and MMP-13 were observed [43]. It seems that MMP-13 is particularly implicated in the periodontal soft tissue and alveolar bone destruction. MMPs and their detailed role in periodontal tissue breakdown are covered by numerous articles and reviews [41][43].

Although the current model of periodontitis attributes the most severe consequences like tissue defects and teeth loss to be the effects of the oral homeostasis disturbance and overly active immune response [19][41] rather than direct action of periopathogens, some interesting findings have been made in establishing its bacterial aetiology. Two bacterial complexes so-called "orange" and "red" are comprised of species believed to be the major aetiological factors of periodontitis. The orange complex appears first and includes anaerobic or microaerophilic Gram-negative species mainly from *Prevotella*, *Fusobacterium*, and *Campylobacter* genera. As the pathological state progresses, red-complex bacteria—*Tannerella denticola, Tannerella forsythia*, and *Porphyromonas gingivalis* start to multiply and colonize gingival tissue [44]. Among them, *P. gingivalis* is the best studied. It uses numerous strategies to circumvent the immune response that allows for a further thriving of surrounding bacterial community ultimately leading to chronic inflammation of periodontal tissues [45]. Examples of its virulence factors are lipid A 1- and 4′-phosphatases that alter LPS into a non-immunogenic form [46],

fimbriae promoting colonization of epithelial cells and inducing CXCR4/TLR2 cross-talk which leads to immune response evasion [47] or Hgp44 [48] functioning as bacterial adhesion, to name a few. Although many sides of *P. gingivalis* biology has been unveiled, a lot of aspects remain to be investigated, and it is only the tip of the iceberg. Periodontitis affected tissues are inhabited by plenty of interrelated bacterial species that interact with the host immune mechanisms thus creating extremely complicated signaling and dependencies network.

Altogether, periodontitis begins with oral homeostasis changes, proceeds with bacterial communities' expansion to a chronic inflammatory state. Finally, prolonged inflammation severely damages the gingival and alveolar bone tissue integrity.

4. Conclusions and Future Perspectives

Conventional treatment of periodontal disease is long-term, and the currently available therapeutic substances are insufficiently effective and highly toxic to humans. Likewise, there are frequent side effects of drug use like poor biodistribution, low selectivity of the therapeutic effect, burst release of the drug, and damage to healthy cells. The above side effects are generally caused by incorrect drug dosing. From the medical point of view, an interesting approach is the use of controlled drug release systems, in which dynamic development has been observed in recent years in treating periodontal disease. The solution is modern drug formulations that allow increased bioavailability (solubility, stability *in vivo*, membrane permeability), and improve the overall therapeutic effectiveness Polymeric drug carriers compared with other carriers have shown attractive properties such as biodegradability, tissue biocompatibility, and effectiveness for encapsulation of different antibiotics. In the literature, a large number of scientific articles on the formation of controlled release systems of antibacterial substances with the use of synthetic and natural polymers such as poly(d,l-lactide-co-glycolide), polylactide or chitosan has been observed. Various types of DDS have been developed as potential drug vehicles such as nanoparticles, hydrogels, liposomes, etc., which showed effective antibacterial action against various bacterial strains. Local drug delivery systems have been developed to provide controlled and sustained release of antibacterial agents in the vicinity environment of the inflammation site.

With the continuous development in the pharmaceutical fields, there is no doubt that drug delivery systems based on biopolymers can vastly improve the treatment of various infections and diseases. Targeted pharmacological therapy for periodontitis is an active area of ongoing research that needs to be further developed to evolve better therapeutic strategies and improve the patient experience. There is still a high demand for new, effective drug delivery systems for the treatment of periodontal disease, and further studies on this area are therefore highly anticipated.

The present review has demonstrated many different polymer-based drug delivery systems that can be potentially used to fight against periodontitis diseases. However, there are some challenges in using polymers as carriers in DDS for the treatment of periodontal disease, which should be resolved in the future. The first of them is related to a portfolio of appropriate polymers for application in DDS for periodontal treatment. To meet these requirements of effective drug delivery systems, the tailor-made polymers with relatively complex structures are increasingly used, which is associated with the complexity of their synthesis. That is why it is important to develop procedures that allow the synthesis of such polymeric carriers with high homogeneity (low dispersity) in a repeatable manner. The second direction, which can improve the comfort of patients can be the optimization of the size of devices used for local treatment. In this case, a promising effect can give the development of nanoscale intrapocket devices which through delivery even of a low dose of the drug, enable efficient treatment. This idea, however, requires the use of both suitable polymer materials, a method of processing them as well as the method of the preparation of the respective medical devices.

Currently, different antibiotics such as tetracyclines including doxycycline and minocycline, metronidazole, and chlorhexidine are used for local delivery, however, these are known to cause undesirable side effects, such as stomatitis, onycholysis, skin discoloration and decreased blood platelets, just to name a few. Therefore, it is important to implement a new trend utilizing natural products (i.e., drugs possessing antibiotic properties) in such systems. It is also expected that cooperation among polymer chemists, biologists, and dental specialists in the forthcoming future as well as results of their studies significantly broaden the knowledge of the possibility of using polymeric carriers of herbal active substances in the field of medical science, particularly in the field of periodontal disease treatment.

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