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Extracorporeal Shockwave Treatment for Managing Biofilm-mediated Infections in Dentistry: Current Knowledge and Future Perspectives

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Abstract

At present, chronic non-communicable diseases are becoming more prevalent across the world. Among these pathologies, oral diseases such as dental caries and periodontitis are some of the most frequently observed in populations worldwide. These biofilm-mediated infections are produced as a consequence of a series of factors that modify the oral microenvironment and lead to dysbiosis among residing biofilms, which are particularly difficult to treat with pharmacological approaches due to their structural and anatomical characteristics. Furthermore, the recent sharp increase in antimicrobial resistance has potentiated the need for the development of novel techniques to effectively treat biofilm-mediated diseases in the mouth. One option that has recently shown promising results in vitro is the use of focused high-energy extracorporeal shockwave therapy (fhESWT) for the control of microbial growth and biofilm formation. Several studies have shown the effect of fhESWT on the treatment of biofilm-mediated infections associated with bone fractures and orthopedic implant infection, although the mechanisms behind this effect are still unknown. Regarding the oral cavity, there remains a lack of clinical studies but there are some limited in vitro and in vivo investigations that shed light on the potential of fhESWT for biofilm control. Therefore, the objective of this review is to discuss the most relevant available literature regarding the in vitro and in vivo effects of fhESWT over biofilm control, as well as the potential use of fhESWT for the treatment of oral biofilm-mediated diseases in the future.

Keywords: Bacteria, Biofilms, Extracorporeal shockwave therapy, Focused high-energy extracorporeal shockwave therapy, Fungi, Microorganisms

Introduction

Oral biofilms and their association to health and disease

The human microbiome encompasses all the communities of microorganisms that reside within humans. Among these microorganisms, the oral microbiome is believed to contain over 700 different species of bacteria and is important for the maintenance of oral homeostasis and colonization prevention by non-resident microbes [1]. Most of these bacteria can be found attached to surfaces as part of complex microbial communities known as biofilms [2]. In this context, the oral cavity presents favorable conditions for the development of biofilms such as a temperature of 37°C and pH 6.5–7 under physiological conditions, as well as wide availability of nutrients and environmental niches [1]. On teeth, biofilms can develop either above (supragingival) or below (subgingival) the gingival margin, and this anatomical distinction plays an important role in the type of microbial species that will dominate the biofilm at further stages [3].

In all cases, the process of biofilm formation in the mouth is initiated by the attachment of early colonizers and bacterial clusters to the surface of teeth, soft tissues, or biomaterials [4, 5, 6, 7]. This adhesion of bacteria to a surface occurs initially by non-specific long-range interactions, where the predominance of attractive forces will allow the bacteria to physically approach the surface. Subsequently, at closer ranges (>50 nm), the formation of specific short-range interactions between the bacteria and the surface occurs, stabilizing the interaction and initiating the secondary "locking" phase. Once secondary interactions have occurred, adhesion is considered irreversible, and bacteria can only be removed by means of mechanical or chemical methods [8]. In the oral cavity, the most relevant initial colonizers are Streptococcus spp. as they express a wide range of adhesion-specific proteins – adhesins – on their surface that allows binding to a wide range of matrix molecules, salivary constituents, and abiotic surfaces [9, 10]. Streptococcus mitis, Streptococcus mutans, Streptococcus sanguinis, and Streptococcus oralis are some of the most relevant oral streptococci involved in early colonization of substrates [1].

After adhesion between initial colonizers and a surface is achieved, the process of biofilm

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formation is initiated by several biological mechanisms that include bacterial mechanosensing, biofilm-promoting gene expression, and secretion of extracellular polymeric substance (EPS) [11]. Once initial biomass is acquired, the early biofilm acts like an anchoring point for the attachment of secondary oral bacterial colonizers through specific adhesin interactions and bacterial coaggregation. This bacterial progression leads to the establishment of a complex multispecies biofilm that can generate different niches for specific bacteria to flourish. The incorporation of fungal species such as Candida albicans into the oral biofilm is also relevant, especially in the context of dental caries, implant-related infection, and candidiasis [12, 13].

With time, the maturation of the biofilm provides certain benefits to all individual cells within the community. For example, the presence of EPS delivers protection to the biofilm against pH changes, toxins, antibiotics, and external microorganisms [14]. Furthermore, members of a biofilm can communicate through quorum sensing, a system based on the release of extracellular signals which can be detected by nearby microorganisms. These signals increase exponentially over time until a determined maximum concentration of population is reached. This allows the biofilm to survive within parameters that allow it to function optimally to avoid nutrient depletion or toxin buildup [15]. Despite biofilms being present on oral surfaces in health, the balance of community members can be lost due to the effect of certain environmental factors including frequent sugar consumption, reduction of salivary flow, or immune changes, among others [16]. This loss of homeostasis – also known as dysbiosis – is the crucial ecological change that drives the development of dental caries and periodontal disease. Furthermore, the overgrowth of certain keystone pathogens – such as Porphyromonas gingivalis – over other members of the community can further promote dysbiosis by immune modulation and biofilm overgrowth promotion [17, 18, 19].

The current burden of oral biofilm-mediated diseases

The biomedical field has experienced great development and progress in recent decades. Important goals have been achieved regarding the control of communicable diseases – such as HIV and tuberculosis – that have contributed to their prevention and reduced mortality [20]. Despite these advances, there has been an exponential increase in the prevalence of chronic non-communicable diseases in populations worldwide.

In this context, diseases of the oral cavity are some of the most prevalent in both men and women, affecting approximately 3.47 billion people in 2017 [20]. Among these oral pathologies, dental caries and periodontal disease are among the most common [21]. Dental caries is a chronic disease that affects the mineralized tissues of the tooth and occurs as a consequence of chronic demineralization of the dental surface. This demineralization occurs mostly due to the increased proliferation and activity of sugar-fermenting Gram-positive bacteria such as S. mutans and lactobacilli [16]. Regarding the prevalence of dental caries, Kazeminia et al. evaluated 164 studies in a systematic review with meta-analysis that observed children between 1995 and 2019. The results show that the prevalence of dental caries in primary teeth corresponds to 46.2%, while for permanent teeth, it is equivalent to 53.8% [22], and overall, it is the major cause of tooth loss in children worldwide [21].

On the other hand, periodontal disease affects the supporting tissues of the tooth, causing irreversible tissue loss and bone resorption in the affected area. This disease is driven by a crucial microbiological component, associated with certain anaerobic bacteria that thrive within the specific environmental niche created between the tooth and periodontal tissues [23]. Among these relevant bacteria, P. gingivalis plays an important role in periodontitis as a keystone pathogen that favors an optimum environment of dysbiosis that promotes the overgrowth of periodontal biofilm while altering the local host immune response toward a chronic and destructive inflammatory state [24].

Furthermore, peri-implantitis is an irreversible condition affecting the tissues surrounding dental implants that also involve polymicrobial anaerobic infection. Some of the most common clinical observations in peri-implantitis are bone resorption, osseointegration loss, and local suppuration of peri-implant tissues [25]. It is important to note that peri-implant tissues are more susceptible to inflammation processes due to the reduced vascularization in the area. Until recently, it was believed that the periodontal and peri-implant biofilms were remarkably similar; however, recent research has demonstrated important differences between the two. Most importantly, the peri-implant biofilm contains bacteria such as Staphylococcus aureus, which is not found as part of the tooth microbiome and has shown a high affinity with titanium that can explain its presence in peri-implantitis-associated infections [25].

Besides bacterial biofilms, fungal species such as C. albicans can also play an important role in biofilm-mediated diseases. Although these fungi are part of the resident oral microbiome, under certain conditions such as immunosuppression, they can overgrow and initiate oral candidiasis [26]. Furthermore, the formation of multispecies biofilms including C. albicans on the surface of acrylic dentures can lead to chronic inflammation of the palate, especially in elderly individuals [27]. In addition, Wan et al. studied the binding forces between C. albicans and S. mutans or Streptococcus gordonii, and found that extracellular glucans favor the union of C. albicans with S. mutans over other bacterial species during biofilm formation [13]. This discovery contributes to the understanding of caries-associated biofilm formation on dental tissues and the role that C. albicans plays in this process. Furthermore, it has been shown that C. albicans can adhere to titanium, similar to S. aureus. Souza et al. observed that in sites with peri-implantitis, there is a greater amount of C. albicans compared to healthy sites [12]. These results are relevant as they further illustrate the diverse microbiological factors that play a role in the development of oral diseases; however, more studies are necessary to better understand the specific role each microorganism plays during these processes.

Overall, oral biofilm-mediated diseases are highly prevalent and can affect both the tooth and its surrounding supporting tissues. In many cases, the damage is irreversible, and invasive treatments are required to restore form and functionality. In the case of dental caries, infected tissues must be mechanically removed, and the tooth must be later rebuilt with the use of biomaterials [28, 29]. For

periodontal disease and peri-implantitis, tissue destruction is irreversible and both non-surgical and surgical treatments may be necessary to preserve functionality [25, 30]. Therefore, clinical approaches are centered on prevention and early intervention to reduce long-term complications.

Current techniques to prevent and treat oral biofilm-mediated diseases

As discussed above, oral biofilms are present in health and disease, and their formation occurs on both, natural tissue and biomaterial surfaces. Even though their presence does not necessarily lead to the onset of disease, the control of biofilm buildup by mechanical removal is the gold standard for maintaining health in the oral cavity. Among these, the treatment of excellence is tooth brushing, which can be performed with a wide range of techniques that are adapted to the specific needs of each patient. Nevertheless, tooth brushing depends primarily on the individual's ability to achieve an effective movement that assures an accurate disruption of biofilm for its correct removal [14]. In certain situations, such as a reduction in motor skills, the accomplishment of efficient techniques of manual tooth brushing is not possible. In these cases, the development of electric toothbrushes can facilitate proper oral hygiene and nowadays, further alternatives such as ultrasound toothbrushes are also available. Regarding the latter, they operate at frequencies above 20 kHz permitting higher hydrodynamic forces, and studies have concluded that ultrasound toothbrushes are better in removing dental plaque than manual toothbrushes when a combination of mechanical movements and acoustic action is used [14].

Besides the use of mechanical techniques, some chemical treatments are also used to control oral biofilm buildup and disease progression. For example, chlorhexidine (CHX) as an antiseptic agent has been in use since the late 20th century, as it has an important antibacterial effect over a wide range of oral microorganisms. In a recent study, Bescos et al. investigated the effect of CHX mouthwash on the oral microbiome. The experiment was carried out for 2 weeks, where 36 healthy human individuals were asked to rinse for 1 min with a placebo mouthwash twice a day (week 1) followed by the use of a CHX mouthwash (week 2). At the end of each week, samples of blood and saliva were taken to analyze a variety of parameters including pH and microbial diversity. Among the results, authors reported that the long-term use of CHX induced an acidic environment within the oral cavity, which could be a risk to oral health as it creates a favorable environment for the onset of certain diseases such as dental caries [31]. However, more studies should be carried out in the following years to further clarify the potential association between long-term CHX use and dental caries.

Furthermore, recent investigations have been looking for new ways to modulate oral biofilms to prevent and treat the onset of disease.]. Some of these components include nanoparticles, quaternary ammonium salts, small molecules, arginine, and natural products [32]. Furthermore, recent in vitro research has also shed light on the potential use of naturally derived exosomes for the modulation of oral streptococci [33]. Although there are several promising new approaches stemming from this research, more studies should be carried out to verify their therapeutic effect in the clinical setting. Furthermore, there remains a need to explore other ways to potentially prevent and control bacterial attachment biofilm formation onto relevant oral substrates.

Extracorporeal Shockwave Therapy and its Potential in the Control of Oral Diseases

Extracorporeal shockwave therapy

Extracorporeal shockwaves are sound waves characterized by a fast initial increase that reaches a positive peak of up to 100 MPa within 10 ns, followed by a slower decrease into a negative amplitude of up to −10 MPa. The total life cycle of a shockwave is around 10 μs [34]. Extracorporeal shockwave therapy (ESWT) is a treatment based on the use of shockwaves at a determined frequency and intensity, where the pressure waves applied to tissues generate regeneration and reparation of damaged surfaces [35]. Historically, ESWT was first developed for the physical destruction of kidney stones, following a series of in vitro and in vivo experiments. After favorable results were achieved and the device was deemed safe for clinical use, trials were performed and in 1982, its use in medicine began with the opening of the first lithotripsy center worldwide [36]. Although shockwave therapy was introduced for the treatment of kidney stones, it was subsequently found to have pro-regenerative effects in a growing number of conditions, including long-bone non-union [37, 38] and chronic wound healing [39, 40], as well as for the treatment of many other chronic inflammatory conditions.

What is known regarding the antimicrobial and antibiofilm effect of focused high-energy ESWT (fhESWT)?

Despite its widespread use in regenerative medicine, recent investigations have begun exploring the use of fhESWT for the treatment of infections and infection-related complications in different tissues. Puetzler et al. assessed the effect of fhESWT in combination with conventional treatment on fracture-related infection in rabbits [41]. The experiment was carried out for 4 weeks. At the start of week 1, osteotomies with subsequent fixation of a compression plate were performed followed by S. aureus inoculation into the surgical site. At the end of week 2, revision surgery was carried out followed by implant placement and a 2-week regeneration period. Four different groups were evaluated: Control, fhESWT, antibiotics, or a combination of both fhESWT and antibiotics. It was found that all individuals became infected with S. aureus and that both the antibiotics group (nafcillin and rifampin) and the fhESWT + antibiotics group showed a significant diminution of infection rate and total bacterial load when compared to the control group, but no significant difference was observed [41]. These results suggest that fhESWT combined with antibiotics can be an effective approach in reducing S. aureus infection in bone-related lesions.

Qi et al. also evaluated the effect of fhESWT on the disruption of S. aureus biofilms, in the presence or absence of gentamicin, in both in vitro and in vivo models. In vitro biofilms were adhered to stainless steel surfaces and divided into four groups: A control group (no treatment), fhESWT alone, gentamicin alone, and a combination of fhESWT and gentamicin. Their findings demonstrated that the combination of fhESWT with gentamicin had the highest inhibition of S. aureus biofilm compared to all other

conditions. Subsequently, the in vivo experiment was carried out by inoculating living S. aureus into the medullary cavity to induce implant-related osteomyelitis over time. The same four treatment groups were evaluated, and significant antibacterial results were observed for the fhESWT + gentamicin combination group compared to the control group [42].

Other groups have explored biofilm formation on titanium surfaces, a clinically relevant material in both orthopedic surgery and implant dentistry, and the role of fhESWT in preventing biofilm formation on these substrates. Milstrey et al. evaluated the effect of fhESWT alone or in combination with antibiotics in the control of S. aureus biofilms on titanium surfaces. Briefly, biofilms were established in vitro on titanium discs and incubated with either PBS, rifampin, or rifampin + nafcillin. In an initial stage, investigators applied fhESWT on both sides of the titanium discs in PBS bags with 250, 500, and 1000 impulses, and compared the results with a control group (zero impulses). Results showed that the use of fhESWT decreased the biofilm population independent of the number of impulses. In a second stage, a fhESWT dose of 500 impulses was applied to all groups and compared against the control. The authors concluded that antibiotics without application of fhESWT decreased the bacterial population; furthermore, the combination of fhESWT with rifampin and nafcillin showed even lower numbers of bacteria compared to titanium discs exposed only to antibiotics [43]. The importance of this study lies in the fact that fhESWT is apparently effective in reducing the bacterial population in biofilms, as well as providing important support to conventional antibiotic treatment.

Regarding the use of fhESWT for the direct prevention and treatment of oral biofilm-mediated diseases, studies remain uncommon in the literature. However, an article by Datey et al. investigated the effect of fhESWT on chronic periodontitis biofilms, in combination with different antimicrobials such as amoxicillin + metronidazole, tetracycline, 0.25% sodium hypochlorite, and 0.12% CHX [44]. Oral biofilm samples were taken from 25 patients with chronic periodontitis and the experimental study was carried out in two different stages. The first stage aimed to determine the effect of fhESWT and antimicrobials on periodontal biofilms in vitro. Authors found that the use of fhESWT before the application of the antimicrobial results in the best antibacterial effect. This is believed to be due to fhESWT achieving a mechanical disruption of the biofilm and allowing antimicrobials to penetrate and reach the bacteria more effectively. In a second stage, the subgingival region of 8-week-old Sprague-Dawley rats was inoculated with bacteria obtained from chronic periodontitis samples followed by treatment with either fhESWT or antimicrobials. Among all treatment groups, the use of fhESWT in combination with antimicrobials evidenced a decrease in symptoms associated with chronic periodontitis [44]; however, future work is necessary to determine if this could potentially be a viable treatment option for periodontal conditions.

Conclusion

As discussed throughout this review, there remains a need to develop new approaches to control oral biofilm formation to prevent and treat dental caries and periodontal disease. Within this context, the use of fhESWT has shown promising antibacterial effects on clinically relevant bacteria and biofilms, both as a standalone treatment and in combination with antimicrobials. However, research on microbial strains associated with dental caries and periodontal disease is still undeveloped, and therefore, further investigations are crucial to elucidate if fhESWT may have a potential clinical benefit for the control of oral biofilm-mediated diseases.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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