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### Influence of *Treponema denticola* on apical periodontitis due to infection of endodontal origin

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#### Abstract

**Introduction:** The ultimate goal of endodontic therapy is to eliminate all pathogenic bacteria from the root canal system in order to prevent apical periodontitis.

**Aim:** Review of literature on the influence of *Treponema denticola* on apical periodontitis due to infection of endodontal origin.

**Methodology:** Search was carried out in the database PubMed and EBSCO.

**Results:** *T. denticola* is one of the most frequently identified microorganisms within the root canals and these spirochetes are partly responsible for the pathogenesis of periapical bone lesions such as apical periodontitis. They are found within the biofilm and their aggressiveness is due to a diversity of virulence factors, highlighting their dentilysin, mobility and their ability to modulate the host's defensive response.

**Conclusion:** *T. denticola* has a series of molecular determinants that could allow it to cause tissue damage and evade the host immune response. In addition, it has several virulence determinants that allow it to promote disease progression.

**Keywords:** *Treponema denticola*, periodontitis apical, biofilm, virulence factors

#### 1. Introduction

Once the pulp tissues are necrotic and collapsed, the entire root canal system becomes a reservoir for microorganisms and their specific metabolic products [1]. Due to the lack of circulation within the necrotic pulp tissues, the entire root canal system becomes a kind of sanctuary for bacteria that can survive there safe from the systemic and local immune response [2]. The microbiota is found in highly organized and complex entities, known as biofilms, whose characteristics are fundamentally different from those of microbes in planktonic suspensions. Root canal infections are mediated by biofilms. The complexity and variability of the root canal system, together with the multi-specific nature of biofilms, make disinfection of this system extremely difficult [3]. The ultimate goal of endodontic therapy is to eliminate all pathogenic bacteria from the root canal system. Unfortunately, most endodontic pathogenic bacteria are able to pass through the apical foramen of the tooth and invade the periapical bone tissue [4]. Consequently, they cause localized damage that contribute greatly to the occurrence of symptomatic chronic periapical lesions associated with infections of the root canal system [5]. Infections of the root canal system with facultative and mandatory anaerobic bacteria have been associated with different clinical signs and symptoms [6]. Recent studies using molecular biology techniques suggest that *T. denticola* is likely to be one of the microorganisms frequently identified within the root canals and that these spirochetes may be responsible for the pathogenesis of periapical bone lesions [7]. These studies suggest that the clinical signs and symptoms of periapical lesions may somehow correlate with the bacterial load and the species of microorganisms identified within the root canal system. In other words, the different bacterial species that originate at the endodontic site of the infection are capable of causing different clinical signs and symptoms by evading through the apical foramen of the tooth and invading the periapical bone [8].

## 2. Materials and methods

Data collection for this narrative review was carried out using the online database PubMed and EBSCO. All results were obtained by entering the following keywords or a combination of words: *Treponema denticola*, apical periodontitis, biofilm, virulence factors. The types of articles selected include reviews, clinical trials and *in vitro* studies; In addition, all its summaries have been analyzed to exclude those that are irrelevant.

## 3. Results & Discussion

### 3.1 Biofilm

Many microorganisms are capable of forming microbial communities attached to the surface known as biofilms. In fact, biofilms are communities of microorganisms attached to a surface and embedded in a matrix of polysaccharides and proteins, forming a viscous layer<sup>[9]</sup>. As in the oral cavity, more than 500 different bacterial species or phytopes have already been detected in root canals infected by culture or by molecular methods such as 16S rRNA gene sequencing or metagenomic sequencing<sup>[10]</sup>. Bacteria are the microorganisms that are most frequently found in root canals, belonging to 20 filaments according to current knowledge. These microorganisms can be suspended in the luminous flux of the root canal (Planktonic form) or attached to the walls of the root canal, forming a biofilm (Sessile form)<sup>[7]</sup>. Periapical biofilms are isolated biofilms found in the periapical region of endodontically affected teeth. They may or may not depend on root canal infection<sup>[11]</sup>. The microbiota in most of the teeth associated with apical periodontitis is restricted to the root canal, since most of the microbial species that infect the root canal are opportunistic pathogens that do not have the ability to survive host defense in tissues periapical Rarely, microbial species or even strains within a species may possess strategies to survive and, therefore, infect periapical tissues<sup>[12]</sup>. This condition consists in the establishment of microorganisms in the periapical tissues, either due to their adhesion to the apical root surface in the form of biofilm-shaped structures or inside the body of the inflammatory lesion, usually in the form of cohesive colonies.<sup>[13]</sup> Root canal infections are mediated by biofilms and endodontic infections are polymicrobial. They are predominantly *Bacteroides*, *Prophyromonas*, *Prevotella*, *Fusobacterium*, *Treponema*, *Peptostreptococci*, *Eubacteriu* and *Camphylobacter*<sup>[3]</sup>. The survival and virulence of oral treponemas depend on their ability to form biofilms, grow in this medium, interact with the other species in the biofilm, and, presumably, escape from the biofilm, depending on environmental conditions<sup>[14]</sup>. Microbial biofilms play an essential role in several infectious diseases such as pulp and periradicular pathology. These can be found inside the root canals or outside these in the root wall. It is important to eliminate it to avoid diseases in the host.

### 3.2 Apical periodontitis

Apical periodontitis is primarily a consequence of root canal infection, characterized by inflammation and destruction of periradicular tissues as a result of the interaction between microbial factors and the host's immune response<sup>[15]</sup>. Therefore, tissue and immunological responses are essential to protect against the spread of infectious agents to other places. Due to the status of the infection in the root canal, an acute or chronic inflammatory reaction may develop. In apical periodontitis, bone destruction is caused by both a microbial infection and the immune response as part of the defense reaction<sup>[16]</sup>. There is clear evidence that microbial interaction

plays an important role in the pathogenesis of apical periodontitis. Microorganisms can cause direct tissue damage and modulate the immune response by secreting products, including enzymes, exotoxins and final metabolic products<sup>[17]</sup>. There is convincing evidence that treponemas are involved in the etiology of several chronic diseases, including chronic periodontitis, as well as other forms of periodontal disease. There are interesting parallels with other chronic diseases caused by treponemes that may indicate similar virulence characteristics<sup>[15]</sup>. Chronic apical periodontitis is a polymicrobial disease, and recent animal studies indicate that coinfection of *Treponema denticola* with other periodontal pathogens may accentuate alveolar bone resorption<sup>[18]</sup>. When the bacteria that colonize the root canal damage the periradicular tissues; and this periradicular inflammation can be observed even before the entire root canal becomes necrotic<sup>[19]</sup>. As the infection progresses, cell infiltration intensifies and tissue destruction continues with the formation of small abscesses and necrotic foci in the pulp, which ultimately leads to total pulp necrosis<sup>[4]</sup>. After pulp necrosis, usually as a consequence of tooth decay, the root canal environment provides a selective habitat for the establishment of a mixed microbiota with a predominance of anaerobic bacteria<sup>[11]</sup>. To exert its pathogenic effects, the root duct microbiota must invade periradicular tissues or evoke (due to its products and / or structural components) a defensive response in the host for the establishment of apical periodontitis<sup>[20]</sup>. Apical periodontitis is a common infectious disease worldwide and is caused by a microbial infection in the dental pulp. One of the main microorganisms involved in this disease is *Treponema denticola* due to its pathogenic effects.

### 3.3 *Treponema denticola*

Oral treponemas, along with more than 600 other bacterial species, exist as part of a polymicrobial biofilm attached to the surface of the tooth in the gingival groove<sup>(21)</sup>. Treponemas are members of the Spirochetes family, a group that is now believed to be distinct from Gram-positive and Gram-negative bacteria, which are believed to have undergone a broad horizontal transfer of genes with the Archaea and, possibly with eukaryotic organisms<sup>[22]</sup>. Treponemas play a role in the etiology of several chronic diseases of humans, including syphilis (*Treponema pallidum*), periodontal diseases, including chronic periodontitis and acute necrotizing ulcerative gingivitis (*Treponema denticola*, *Treponema lecithinolyticum*, *Treponema socranskii* and others), and endodontic infections, as well as some acute dental abscesses<sup>[23]</sup>. All oral spirochetes are classified in the genus *Treponema*. Recently, a layer of extracellular polysaccharide has been visualized on the *Treponema denticola* oral spirochete. Other unifying characteristics of spirochetes are the resistance to the antibiotic rifampin and, with the exception of leptospire, the presence of ornithine in the cell wall of the peptidoglycan<sup>[24]</sup>. Pulp infection, usually comes from a deep carious process, in which microorganisms from the environment reach the area, with saliva and food<sup>(2)</sup>. This is how *T. denticola* arrives and is conditioned in deep places such as root canals, where the oxide reduction conditions are negative, proliferate, activating all its bacteria from enzymes and toxins, generating necrotic root canals and apical periodontitis where usually they are predominant<sup>[15]</sup>. *T. denticola*, is a small to medium spirochete of 6-16 um, with flagellar arrangement 2-4-2, which is presenting a very fast jerky movement. It is a negative gram, presenting variations

at the level of the outer membrane of its wall, they do not have lipopolysaccharides (LPS), since they lack hydroxy-deoxy-hand-octulosonic acid, heptase and hydroxy fatty acid. Presenting a glycerol-based lipid content, replacing LPS have lipooligosaccharides, which has a similar functional activity as LPS [25]. Among its most important biochemical characteristics, it is being a fermenting amino acid, using pyruvate, excellent sulphurous hydrogen (H<sub>2</sub>S) producers, as well as the presence of the phosphated enzyme [26]. Oral spirochetes are microorganisms that cause many chronic diseases that should be treated appropriately since they have important characteristics that make them resistant in the host and that could generate antibiotic resistance.

### 3.4 Virulence factors

Recent studies using molecular biology techniques suggest that *T. denticola* is likely to be one of the microorganisms frequently identified within the root canals and that these spirochetes may be responsible for the pathogenesis of periapical bone lesions [6]. It has been proposed that dentilysin is an important virulence factor of *T. denticola*, since it is an active protease located on the cell surface that is divided into phenylalanyl / alenyl and prolyl / alenilic bonds [27]. It contributes to the progression of the disease by interrupting or modulating the signaling pathways of the intercellular host and by degrading the proteins of the host cell matrix. Dentilysin potentially allows the penetration of epithelial cell layers by *T. denticola* by degradation of intercellular adhesion proteins and modulates the immune responses of the host cell by degradation of interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, tumor necrosis factor alpha (TNF- $\alpha$ ) and monocyte chemotactic protein 1 [28]. It has been shown that most strains of *T. denticola* adhere well to extracellular proteins such as fibronectin, which are synthesized by human gingival fibroblasts and bind to the plasma membrane of the fibroblast. In the presence of anti-human fibronectin antibodies, adherence to human gingival fibroblasts was reduced, but not completely inhibited [29]. It has also been shown that *T. denticola* adheres to the basement membrane proteins laminin, fibronectin and type IV collagen, as well as to type I collagen, gelatin and fibrinogen [18]. Adhesion of oral spirochetes in the gingival groove is not in itself a pathogenic process. Only when the cytopathic effects of bacterial adhesion and colonization occur can the initial colonization be considered a virulence factor. Therefore, if bacteria adhere benevolently to a site that does not damage host cells, colonization is not a virulence factor [30]. The locomotor capacity of pathogenic spirochetes is one of the factors associated with their virulence. This ability allows pathogenic spirochetes to negotiate viscous fluids on the surface of the mucosa and in the intercellular and intracellular spaces of the host body [31]. Basic studies have been conducted on the inherent ability of oral spirochetes such as *T. denticola* to orally locomote in viscous fluids. The results indicate that oral spirochetes are capable of locomoting through viscous environments. However, it was demonstrated that the optimal locomotion correlated with well-defined viscosity values of the medium [21]. *Treponema denticola* is a relevant pathogen in periodontal and pulp processes, its aggressiveness is due to a variety of virulence factors, highlighting its dentilysin, mobility and its ability to modulate the defensive response of the host.

### 4. Conclusions

There is convincing evidence that treponemas are involved in the etiology of several chronic diseases, including chronic

periodontitis, as well as other forms of periodontal disease. Chronic periodontitis is a polymicrobial disease, and recent studies indicate that co-infection of *Treponema denticola* with other periodontal pathogens may improve alveolar bone resorption. The bacterium has a number of molecular determinants that could allow it to cause tissue damage and evade the host's immune response. In addition, it has several virulence determinants that allow it to interact with other pathogenic bacteria and with the host in ways that are likely to promote disease progression.

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