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Use of Antibiotics Versus Probiotics in Periodontitis Therapy

***Corresponding Author(s): Nada Tawfig Hashim**

Department of Oral Rehabilitation (Periodontology Division) Faculty of Dentistry, University of Khartoum, Sudan

Tel: +24 991 234 7374;

Email: nadatawfig@yahoo.com

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Abstract

Periodontal disease is an inflammatory disease, provoked in response to periodontopathogens in the biofilm of the subgingival plaque, affecting tissues supporting the teeth. Members of the red complex, such as *Porphyromonas gingivalis* and *Tannerella forsythia* are considered as the most pathogenic microbial components at present. Likewise, *Aggregatibacter actinomycetemcomitans* is associated with periodontal disease, but it does not belong to the red complex. The gold standard in periodontal treatment is formed by scaling and root planing.

Systemic antibiotic therapy is indicated to control deep periodontal pockets with microbial invasion at epithelial level that are difficult to access with disease progressing overtime. Resistance of bacterial species to antibacterial treatment has been considered as a global problem following the excessive use of these drugs. The use of probiotics which display a strong inhibitory effect against the Gram-negative periodontal pathogens has become more common in recent years. Thus, this review deliberates the adjunctive use of antibiotics versus probiotics in periodontitis therapy.

Introduction

Periodontal diseases are plaque-induced inflammatory conditions affecting the periodontium, characterized by mononuclear cell infiltration into gingival tissues, leading to connective tissue destruction and alveolar bone resorption and if left untreated, they may lead to destruction of the tooth-supporting apparatus and ultimately tooth loss that potentially damages the dentition [1,2].

The primary etiological factor for periodontal diseases is dental plaque biofilm which defined as organized and complex aggregations of bacteria and their products on the tooth surface. Approximately 700 different bacterial species have been identified in the oral microbiota, among which only a small group of 10 to 15 species has been identified as being significantly associated with the initiation and progression of periodontitis [3].

It is generally approved that microorganisms residing in periodontal pockets are responsible for periodontitis, however uncertainty exists concerning the exact mechanisms by which periodontal tissues are destroyed [4].

The main organisms associated with periodontitis are *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythus*, and *Aggregatibacter actinomycetemcomitans* [1].

Other gram negative anaerobic rods, some gram positive bacteria and even enteric rods/ pseudomonas may also play roles in the etio-pathogenesis of periodontitis [5].

Nonsurgical periodontal therapy (NSPT) is the cornerstone of periodontal therapy through which a mechanical debridement of the root surface is accomplished. Non-surgical periodontal therapy (NSPT) is the first recommended approach to the control of periodontal infections [6].

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In spite of the microbial specificity of periodontal infection, however, mechanical debridement of the root surface for treatment of periodontitis remains highly unspecific. This nonspecific treatment approach has proven successful on a longterm basis for many patients, although a small, but significant proportion of sites and patients may not respond satisfactorily [6,7].

A successful treatment of periodontitis thus requires decrease of the bacterial load to enhance the ability of the periodontal tissue to repair itself [8].

Mechanical debridement is a highly challenging therapeutic procedure, however, it doesn't remove all periodontopathic bacteria from the subgingival environment, especially those in inaccessible areas such as furcations, grooves, concavities, and tortuous pockets [9].

Given the infectious nature of periodontal diseases and the limited results with conventional mechanical therapies for the treatment of certain forms of periodontal diseases, the use of antibiotics is warranted in certain cases to improve the clinical outcomes and periodontal conditions [3,10].

Rationale for the use of antibiotics in periodontal therapy

The complex structure of the periodontal biofilm, embracing multiple bacterial communities residing in a glycocalyx matrix, reduced susceptibility to antimicrobials compared to planktonic or free floating bacteria. Hereafter mechanical debridement is crucial to disrupt the biofilm when using systemic antibiotics to treat periodontitis. The rationale for use of adjunctive systemic antimicrobials is to promote reduction of the bacterial load facilitating resolution of the inflammation in the periodontal pocket.

The recommendation for using antibiotics is restrictive to limit the development of microbial antibiotic resistance in general [11].

Non-surgical scaling and root planing may eliminate subgingival Campylobacter rectus however it is often ineffectual against *Porphyromonas gingivalis*, *Prevotella intermedia, Tannerella forsythus* and enteric rods and may not considerably decrease the amount of *Aggregatibacter actinomycetemcomitans* or *peptostreptococcus* [12].

Systemic antibiotics enter the periodontal tissues and periodontal pocket via serum and can affect microorganisms outside the reach of cleaning by periodontal instruments. Additionally systemic antibiotic therapy has the potential to suppress periodontal pathogens residing on the tongue or other oral surfaces, and by this means delaying subgingival recolonization of pathogens [13].

The use of systemic antibiotics as a part of the periodontal therapy has been recommended as an adjunctive therapy in specific situations such as with patients showing progressive periodontal breakdown even after conventional mechanical treatment, aggressive periodontitis, necrotizing periodontal diseases and periodontal abscess [14].

The main methods to systemic antibiotic therapy for periodontal treatment are based on mono-therapy, even though combinations of antibiotics are becoming more common. The most frequently used antibiotics are metronidazole, the tetracyclines, clindamycin, ciprofloxacin and amoxicillin [10].

It has been reported that the most of patients diagnosed with chronic periodontitis can be effectively treated following mechanical debridement, adequate oral hygiene and regular maintenance care.

Hererra et al. in their review concluded that systemic antibiotics used in conjunction with scaling and root planing can give further benefit over scaling and root planing alone in terms of reduction of probing depth and clinical attachment level [15].

Another review by Haffajee et al. reported additional clinical outcomes in attachment level gain after prescribing systemic antibiotics as an adjunct to surgical mechanical debridement in deep pockets. However this finding has been disputed by Hererra et al. who concluded that there was insufficient data so as to decide whether adjunctive antibiotics were beneficial when combined with periodontal surgery or not [16,17].

Furthermore, aggressive periodontitis is frequently associated with the presence of high levels of A. actinomycetemcomitans, and/or Porphyromonas gingivalis, bacteria that have the potential to invade the periodontal tissues. The adjunctive use of antibiotic in such case is required to eradicate or suppress these pathogens [13].

A number of studies have appraised the use of antibiotics to control or reduce the progression of periodontitis. Systemically administered antibiotics demonstrated a statistically significantly more gain in attachment and reduction in depth of periodontal pockets, irrespective of initial probing methods or therapeutic modalities (antibiotic therapy alone, in conjunction with scaling and root planing, or in conjunction with scaling and root planing plus surgical therapy).

However, the therapeutic benefits observed are clinically significant in only a limited number of situations. For instance, attachment gain is greater among patients with aggressive periodontitis than among those with chronic periodontitis [4,16,18].

Disadvantages of antibiotics

The use of systemic antibiotics in treatment of periodontitis is only useful when used in conjunction with adequate mechanical debridement for disruption of the subgingival biofilm. However it remains controversial for the reasons that the wider context of the over-prescription of antibiotics and the rise of antimicrobial resistance (AMR) [13,19].

Nowadays AMR forms a great threat to humanity and it is evenly balanced to that from terrorism and climate change. The consensus recommendation of the Sixth European Workshop on Periodontology in 2008 was that, antibiotics should be limited for use with particular patient groups and conditions, for example in aggressive and severe cases of periodontitis. In addition, the use of the broad-spectrum antibiotics, such as amoxicillin and metronidazole, have no specific microbiological target and only a small part of the intake dose reaches the target organ. The remaining dose reaches all the other organs and systems in the body, with no beneficial effect and only side-effects. The "price" that is paid to the community for the extensive use of antibiotics is the increase in antibiotic resistance which considered as a life-threatening.

It is therefore noteworthy to control such a price by ensuring that all antibiotics are properly prescribed and by applying selected beneficial bacteria as an adjunct to scaling and root planning (SRP) to develop novel non-antibiotic treatments, which would also inhibit periodontal pathogen recolonization of periodontal pockets and thus achieve and sustain periodon-

tal health [20,21].

What are probiotics?

Probiotics are defined as bacteria with physiological benefits for humans, they influence both the development and stability of microbiota, thus preventing the colonization of pathogens, enhancing the mucosal barrier via tropic effects on the epithelium, and stimulating both the innate and the adaptive immune systems [22].

When probiotics administered in adequate amounts, they repopulate the beneficial bacteria, which can help in killing pathogenic bacteria and fight against infection. Probiotics administered orally, may benefit oral health by preventing the growth of harmful microbiota or by modulating mucosal immunity in the oral cavity [23].

History of probiotics

The term probiotic is derived from Latin (pro) and Greek (bios) meaning literally for life. It was first used by Kollath in 1953 to generically define various organic and inorganic supplements that were thought to have the ability to restore the health of malnourished patients [1].

In 1965 the term probiotics was used by Lilly and Stillwell to represent 'substances' secreted by one organism which stimulates the growth of another" [24,25].

In 2001, the World Health Organization defined probiotics as "Live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [26].

Criteria for probiotics

The following criteria should be fulfilled by the bacteria to be classified as oral probiotics [27]:

1. Scientifically demonstrated beneficial physiologic effects.
2. Human origin, safety for human use, and stability in acid and Bile.
3. Should adhere to and colonize on dental tissue, and should be a part of the biofilm.
4. Should not ferment sugars, which subsequently lowers the pH and is detrimental to dental health.

The most frequently used and studied genera satisfying the above criteria are *Lactobacillus* and *Bifidobacterium* [23].

Lactobacilli constitute about 1% of the cultivable oral microflora in humans. The species most often found in saliva are *Lactobacillus acidophilus*, *L. scasei*, *L. fermentum, L. plantarum, L. rhamnosus* and *L. salivarius*. The species found in dairy products are *L. acidophilus, L. casei, L. fermentum* and *L. rhamnosus*. It has also been reported that people who consumed yoghurt containing *L. rhamnosus* on a daily basis host this microorganism in the saliva for up to 3 weeks after discontinuing yoghurt consumption [28,29].

Potential mechanisms of probiotics effects in the oral cavity

The mechanisms of probiotic action in the oral cavity can be categorized into three main categories: normalization of the oral microbiota, modulation of the immune response, and metabolic effects [30] (Figure 1).

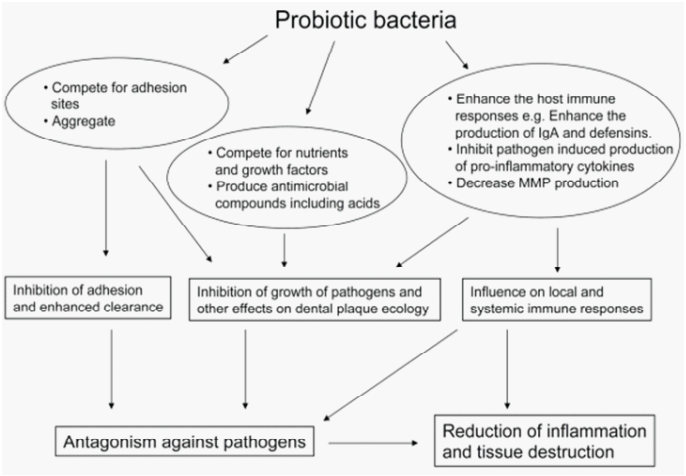

Figure 1: Potential mechanisms by which probiotic bacteria could affect oral health [29].

Probiotic and periodontal disease

The most common oral diseases including periodontal diseases are caused by a shift in the balance of the resident microbiota [31-33].

In periodontal diseases, there is an increase in plaque mass and a shift toward increasingly obligatory anaerobic and proteolytic bacteria. The damage caused to the host is due to the synergestic effect of subgingival biofilm, and the host response to the diverse bacterial populations [34-36].

In respect to commensal oral microbes, several aspects support the idea that it may be possible to find bacteria that could be useful in prevention or treatment of periodontal disease. The ecological plaque hypothesis proposes that selective pressure in environmental conditions can change the balance between oral health and disease. As bacteria can also influence their environment, and both synergistic and antagonistic interactions are suggested for bacteria in dental plaque, the environmental pressure described in the ecological plaque hypothesis could be introduced partly by bacteria [29].

Probiotics conventionally used in medicine field are now used to control and treat periodontal disease by the introduction of bacterial replacement therapy. Nowadays, probiotics are widely used in the oral health perspective due to the emergence of antibiotic resistance and frequent recolonization of treated sites with pathogenic bacteria [37].

Oral probiotic bacteria adhere and colonize periodontal tissue including hard non-shedding surfaces and become part of the biofilm. They should not ferment sugars, which subsequently lower the pH, thereby resulting in caries [38].

Probiotics have demonstrated inhibition of plaque formation by lowering of the salivary PH, therefore, bacteria associated with plaque formation unable to form plaque. Probiotics are also known to produce antioxidants, which in turn prevent plaque formation by neutralizing the free electrons which are needed for the mineralization of plaque. Moreover, probiotics are capable of breaking down putrescent odor by fixing on volatile sulfur compounds and changing them to gases needed for metabolism.

A few studies shown that probiotic Lactobacillus strains were beneficial in reducing gingival inflammation and the number of black-pigmented rods including Porphyromonas gingivalis in the saliva and subgingival plaque. Additionally Lactobacilli were found reduce the levels of periodontal pathogens on the tongue which constitutes a major reservoir for their transmission and thereby indirectly reduce the colonization of subgingival plaque by periodontal pathogens [39,40].

The inhibitory activity exhibited by homofermentative lactobacilli against periodontal pathogens was mainly correlated to their production of acid, and not to H2O2 or bacteriocin production [41].

The concept of replacing the pathogenic bacteria in the gingival sulcus with beneficial bacteria is called guided periodontal pocket recolonization. Subgingival application of beneficial bacteria S. sanguis, S. salivarius, and S. mitis , has been shown to delay re-colonization by periodontal pathogens, reduce inflammation and improve bone density and bone levels in beagle dogs [26,42].

Products containing probiotics for periodontal disease management

Few product containing probiotics are available in the form of lozenges, toothpaste, chewing gums, or mouthwashes.

Gum PerioBalance is the first probiotic marketed by Sunstar (Etoy, Switzerland), specifically formulated to fight periodontal disease. Gum PerioBalance contains a patented combination of 2 strains of *L. reuteri* specially selected for their synergistic properties in fighting both cariogenic bacteria as well as periodontopathogens.

PeriBiotic this toothpaste is an all-natural, fluoride-free oral hygiene supplement containing Dental-Lac, a functional *Lactobacillus paracasei* probiotics not found in any other toothpaste.

Bifidumbacterin, Acilact, Vitanar this probiotics preparation of a complex of five live lyophilized lactic acid bacteria is claimed to improve both clinical and microbiologic parameters in gingivitis and mild periodontitis patients [43].

Conclusion

The current understanding of periodontal diseases clearly establishes them as infections caused by specific microbiota, residing in subgingival biofilms on the non-shedding surfaces of the oral cavity. The main etiological factors of periodontal disease seem to be the absence of beneficial bacteria, the presence of pathogenic bacteria, and a susceptible host. Present treatment options propose the modification of ecological niches, from pathogenic organisms to a biofilm of commensals [44].

The use of probiotics has re-emerged as a mean to restore and boost the beneficial microbes in oral cavity. The timing of growing interest in this field coincides with the need to augment or replace antibiotics whose side effects are undesirable and whose efficacy is diminishing due to drug resistance. Evidence that probiotic strains can substitute antibiotic therapy by reducing adverse effects, and enhancing mucosal immunity is mounting [45]. Therefore in order to avoid the deleterious side-effects of antibiotics, the administration of beneficial bacteria in the form of probiotics can be a valuable alternative in the treatment of periodontitis [46].

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