IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 13, Issue 3 Ver. IV. (Mar. 2014), PP 36-39
www.iosrjournals.org

Probiotics in Periodontal Diseases

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I. Introduction

The oral cavity has been shown to be the home to almost 700 different species of bacteria[1]. This includes both potential pathogenic microorganisms and beneficial microorganisms, and a balance between the host friendly and host hostile microorganisms decide the state of the health or disease of the host. In the past, the line of management of an infection was through administration of antibiotics. Antibiotics are chemotherapeutic substances that destroy harmful microorganisms that cause infection, while inadvertently destroying the beneficial microbes as well. Overuse and misuse of antibiotics over time has led to the development of drug resistant microbes and destruction of the indigenous flora of the host. Over time, the strategy of managing infection has shifted from destruction of bacteria with the use of antibiotics, to the recreation of the healthy microbial environment through the use of microorganisms that are non-pathogenic, associated with health, capable of inhibiting the growth of pathogenic microorganisms and stimulating the host immunity. Probiotics are live microorganisms that are administered in sufficient amounts to produce a beneficial effect on the host animal[2].

The concept of probiotics was first introduced by Elie Metchnikoff, a Russian scientist, following his observation that Bulgarian people had a longer life span due to the consumption of fermented milk containing viable bacteria. The term "Probiotic" was initially proposed by Lilley and Stillwell in 1965. Etymologically, the term appears to be a composite of the Latin preposition *pro* ("for") and the Greek noun bios, ("life"). First probiotic species to be introduced in research was *Lactobacillus acidophilus* by Hull et al in 1984; followed by *Bifidobacterium bifidum* by Holcombh et al in 1991[3].

In medicine, the use of probiotics is well established in the prevention and reduction of virus induced or antibiotic associated diarrhoea, prevention of allergies and atopic diseases in infants, reduction of cancer-promoting enzymes, treatment of gastrointestinal diseases, and prevention of respiratory tract infections – common cold and influenza. In dentistry, probiotics have shown to be effective in reducing halitosis, candidiasis, tooth decay and periodontitis. When a comparison of the microbiota of the oral cavity was done in health, gingivitis and periodontitis, certain changes in the general characteristics of the microbes were identified. There was a shift from gram positive to gram negative organisms, from cocci to rods, from nonmotile to motile, from fermenting to proteolytic species and from facultative anaerobes to obligate anaerobes[4]. By preventing the shift of microbes that are associated with health to microbes that are associated with disease, the onset and progress of periodontal disease can be prevented or delayed. The management of periodontal disease has evolved significantly over the years– initially, the treatment was directed towards mechanical reduction in the bacterial load in the oral cavity through scaling and root planing. Later, antibiotics were used as adjuvant either through systemic or local delivery along with scaling and root planing. Recently the probiotics are also used along with mechanical reduction of bacterial load to treat periodontal disease. The probotics for periodontal diseases are delivered in various forms like food products (curd/ youghurt) tablets, lozenges, mouthrinses, toothpaste and chewing gum.

Characteristics of an ideal microorganism to be used as probiotic[5].

- Should be non pathogenic
- Should be of human origin
- Should be able to send signals and interact with immune cells
- Have High cell viability and resistance to low pH
- Adhesion to cancel the flushing effect
- Have capacity to influence local metabolic activity

The mechanisms by which beneficial bacteria act are[6,7]

- By passively occupying a niche that may be otherwise colonised by pathogens
- Actively limiting the pathogens ability to adhere to appropriate surfaces
- By adversely affecting the vitality or growth of the pathogen
- By affecting the ability of the pathogen to produce virulence factors
- By degrading the virulence factors produced by the pathogen

- By modulating the immunological parameters, epithelial permeability and translocation
- By providing bioactive or regulatory peptides

The most common microbes among the probiotic strains are lactobacillus and bifidibacterium. The probiotic potential of the lactobacilli are due to its ability to produce different antimicrobial components like organic acids, hydrogen peroxide, low molecular weight antimicrobial substances, bacteriocins and adhesion inhibitors[2]. Koll in 2008 isolated 22 strains of lactobacilli from the oral cavity that exhibited antimicrobial potential against oral pathogens including periodontal pathogens[8]. Majority of the strains of *Lactobacillus salivarius* suppressed the growth of *Aggregatibacter actinomycetemcomitens, Porphyromonas gingivalis* and *Prevotella intermedia.*

Probiotics and halitosis

Halitosis occurs either due to intraoral causes or from extra oral causes of which intraoral causes are the most common. Halitosis is produced by the liberation of volatile sulphur compounds that are produced by intraoral bacteria during degradation of salivary and food proteins. *Fusobacterium nucleatum* showed reduced potential to form VSC following ingestion of *Weissella cibaria* (bacteria commonly present in fermented milk) due to the inhibition of the proliferation of *Fusobacterium nucleatum* by the hydrogen peroxide produced by *Weissella cibaria*. *Weissella cibaria* also competed with secondary colonizers for adhesion sites thereby slowing down the transmission to more pathogenic plaque[9]. When *Lactobacillus salivarius* WB12 and xylitol in tablet form were given daily to patients with genuine halitosis for a period of 4 weeks, a statistically significant reduction in the organoleptic scores of halitosis and bleeding on probing were observed[10].

Streptococcus salivarius is another microorganism that has the potential to reduce halitosis by virtue of its ability to produce bacteriocins and salivaricins that reduces the number of bacteria that produce volatile sulphur compounds. The level of volatile sulphur compounds showed a reduction following use of lozenges containing *Streptococcus salivarius* K12. *Streptococcus salivarius* K12 also suppressed the growth of black pigmented bacteria[11].

Evidence for effectiveness of probiotics in periodontal disease

Probiotics can reduce the formation of plaque and calculus by lowering the pH. They also form antioxidants that prevent plaque formation. When patients with moderate to severe gingivitis were given *Lactobacillus reuteri* formulations, the plaque and gingivitis scores were considerably reduced. Three mechanisms for the change have been suggested.

Lactobacillus *Lactobacillus reuteri* secretes bacteriocins like reuterin and reutericyclin that inhibits growth of pathogenic bacteria

2. Have a strong affinity to host tissues, competing with the pathogenic bacteria for adhesion siteStreptococcus

3. anti-inflammatory effects of *Lactobacillus reuteri*[12]. *Lactobacillus brevis* showed significant anti-inflammatory effects when used in patients with chronic periodontitis. This effect has been attributed to its antagonistic effect on the other microbes, and its capacity to prevent the production of nitric oxide, release of PGE2 and activation of MMPs induced by nitric oxide[13]. When mice treated with topical application of *Lactobacillus brevis* CD2 were examined 5 days later, there was a lower expression of TNF-α, IL-1β and IL-6 and a reduction in the number of anaerobic bacteria and an increase in the number of aerobic bacteria. The anti-inflammatory effects were dependent on the presence of functional arginine deiminase, an enzyme that can inhibit nitric oxide synthesis[14]. *Lactobacillus salivarius* and *Lactobacillus fermentum* exhibit an antagonistic effect on the growth of *Streptococcus mutans, Streptococcus sangius* and *Porphyromonas gingivalis.* The inhibitory effect was different for each periodontopathogen and it was dose dependent. *Lactobacillu fermentum* exhibited a stronger inhibitory effect than *Lactobacillus salivarius*[15]. *Lactobacillus acidophilus* is capable of decreasing the production of *Porphyromonas gingivalis* induced IL-1β, IL-6, and IL-8 by gingival cells when *Lactobacillus acidophilus* was co cultured with *Porphyromonas gingivalis* and gingival epithelial cells[16].

Oral lactobacilli like *Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus casei* and *Lactobacillus salivarius* exhibited a strong inhibitory effect against *Streptococcus mutans, Streptococcus sobrinus, Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans.* The inhibitory effect was enhanced in the presence of 5% glucose and lower pH[17]. In a study that evaluated the efficacy of Inersan (contained 10^8 colony forming units per gram of *Lactobacillus brevis)* alone, in combination with 100mg doxycycline and doxycycline alone in treating aggressive periodontitis, plaque index, gingival index, probing depth and clinical attachment levels were reduced in all the three groups, but they were not statistically significant[18]. Use of mouthrinses containing *Bacillus subtilis*[19] and oral administration of tablets containing *Lactobacillus salivarius*[20] has shown a reduction in the number of periodontal pathogens.

When the relationship between periodontal health and consumption of dairy products such as cheese, milk and yoghurt was assessed, it was observed that probing depth and clinical attachment loss was lesser in patients who consumed yoghurt regularly. However, similar effect was not observed with regular consumption of milk or cheese. The lactic acid bacteria present in yoghurt is responsible for the beneficial effect by

controlling the growth of the pathogenic bacteria[21]. During the fermentation process in milk, Lactobacillus *helveticus* produces short peptides that act on osetoblasts and increase osteogenesis thereby reducing bone resorption associated with periodontitis. The plaque and gingivitis scores showed a significant reduction when curd was added on a daily basis to the diet in 104 healthy school children after scaling and root planing[22]. When milk enriched with probiotic *Lactobacillus casei* was ingested for a period of 8 weeks, a reduction in MMP-3 and elastase activity was observed in individuals with plaque induced gingivitis[23].

Guided periodontal pocket recolonization

The concept of replacing the pathogenic bacteria in the gingival sulcus with beneficial bacteria is called guided periodontal pocket recolonization. Studies in this aspect was pioneered by Teughels who observed that when a bacterial mixture that contained *Streptococcus sangius*, *Streptococcus mitis* and *Streptococcus salivarius* were applied subgingivally after scaling and root planing in beagle dogs, the recolonisation of canine *Porphyromonas gingivalis* and *Prevotella intermedia* were suppressed[24]. Delay in recolonisation by periodontal pathogens, reduction in inflammation and improvement in bone level and bone density was observed by Nackaerts when *Streptococcus sangius*, *Streptococcus salivarius* and *Streptococcus mitis* were applied subgingivally in dog models[25].

Commercially available Probiotics with periodontal effects

Gum – perio balance, the first probiotic specifically designed to fight periodontal disease is a lozenge containing at least 2x 10^8 *Lactobacillus reuteri* belonging to two strains having synergistic properties in fighting cariogenic and periodontopathogenic bacteria. It has to be used daily to allow the bacteria to spread and attach to the oral surfaces[3]. Acilact a biopreperation of live lympholised acidophilic lactobacillus has shown to reduce gingivitis and periodontitis[26]. Prodentis a *Lactobacillus reuteri* preparation showed to inhibit plaque formation, exert anti-inflammatory activity and antimicrobial activity. The preparation could be recommended during nonsurgical treatment and during maintenance phase of periodontal treatment[27]. Periobiotic is a fluoride free tooth paste containing *Lactobacillus paracasei* ADP-1 strain. ProBiora3 is a mouthwash containing 3 specific strains of naturally occurring oral bacteria - *Streptococcus oralis strain KJ3sm*, *Streptococcus uberis strain KJ2sm*, and the spontaneous lactic acid-deficient variant of *Streptococcus rattus, strain JH145*[28].

Risks and side effects associated with probiotics

All the strains of a species do not exhibit similar properties. Hence it is essential that the various strains be carefully studied and selected before their use as a probiotic. This, though difficult and complex, is of utmost importance in minimising the drawbacks and enhancing the benefits associated with the use of probiotics. Side effects caused by probiotics are usually mild and digestive. More serious effects have been reported rarely. Bacteraemia and fungaemia has been reported following use of probiotics in immunocompromised individuals, infants, patients with chronic disease, short gut syndrome and individuals with prior history of prolonged hospitalization and surgical intervention[3]. Lactobacillus endocaritis was reported following dental treatment in a patient with mitral regurgitation who was taking a probiotic preparation containing *Lactobacillus rhamnosus*[5]. Following use of probiotic containing *Lactobacillus rhamnosus* GG (LGG) liver abscess was reported in a 74 year old diabetic female[29]. Land et al reported the case of a 4 month old infant who developed LGG endocarditis 3 weeks after being on a probiotic therapy of LGG 10^{10} CFU/day for antibiotic related diarrhoea after cardiac surgery[30]. Richard et al reported four cases of bacteremia that developed following use of an oral preparation containing *Bacillus subtilis* spores which was used for treatment of tube feeding related diarrhea[31]. Lactobacillus and other lactic acid bacteria are capable of preventing pathogenic colonisation in the oral cavity because of its ability to produce acids. However, this can create an environment conducive to the development of caries. None of the cases with serious side effects were reported in healthy individuals.

Limitations regarding probiotics

The probiotic potential of a microbial species is strain specific. It is necessary to identify the strain that exhibits the highest probiotic potential without exhibiting any pathogenic potential. Though many microbes are being studied to assess their probiotic potential, clarity is still lacking in terms of the concentration of the microbes that is needed to elicit a beneficial or inhibitory effect, the duration for which the probiotic has to be administered, and the possibility for the development of resistant strains of bacteria. Another area of concern is the lack of long term studies that assessed whether the administered microbes have the potential to permanently colonise the oral cavity. The time duration for which these probiotics are available (sustainability of the probiotic) in the oral cavity is an important parameter that decides the long term effect of this treatment modality. Studies comparing the effect of probiotics and antibiotics as adjuncts to scaling and root planing were few. Studies comparing the bioavailability of the probiotic administered in the various formulations were also lacking.

II. Conclusion

The use of probiotics to deliver periodontal health benefits is widely studied and positive results have been observed. However long term studies are essential to have a better understanding of the duration for which the effect of an administered probiotic is sustained in the oral cavity, and the long term consequences that occur following such induced changes in the oral ecosystem. Methods to extent the availability of the probiotics in the oral cavity has to be developed. A probiotic that has a beneficial role on one aspect of oral health should not have a detrimental effect on another aspect. The willingness of patients to consume or use microorganisms as a treatment modality can come only through proper education of the patients regarding its merits.

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