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Chapter 10: Probiotic Bacteria and Dental Caries

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Abstract

The World Health Organization has defined probiotics as "Live microorganisms which, when administered in adequate amounts, confer a health benefit to the host." Traditionally, probiotic microorganisms (mainly *Lactobacillus* ssp. and *Bifidobacterium* ssp.) have been used to prevent or treat diseases in the gastrointestinal tract. In the past 20 years, there has been an increased interest in possible oral health effects of probiotics. In vitro studies have shown promising results with growth inhibition of mutans streptococci (MS) and *Candida albicans*. There are only a few clinical studies with caries development as the primary outcome while more studies have been focusing on control of caries risk factors or so-called surrogate outcomes. Several studies have evaluated the effects of probiotic bacteria on MS in saliva and/or plaque, and a number of probiotic strains show ability to reduce the number of MS. Probiotic bacteria have not been shown to permanently colonize the oral cavity; in early-in-life interventions or in subjects with a mature microbiota. To date investigated strains are transiently present in saliva during and shortly after an intervention. There are eight randomized controlled clinical trials with dental caries as outcome and probiotic strains, administration, duration of the intervention, and target group varied. In a majority of the studies (75%), the interventions resulted in caries reduction in the treatment groups. Although a majority of these studies suggest a caries-preventive effect of probiotic bacteria, more long-term clinical studies are needed in this field before probiotics could be recommended for preventing or treating dental caries.

Introduction

Because of an increasing resistance to antibiotics, research on complementary ways of manipulating the microflora has arisen. Proposed alternatives to antibiotic treatment include the use of plant-derived compounds, antimicrobial peptides from various sources and probiotics [1]. Our understanding with regard to the effect of microbes on human health has evolved from knowledge of pathogens inducing infections to a mutually beneficial interaction with indigenous microorganisms that contribute to normal human physiology [2]. High diversity in the microbiome in the intestinal tract is associated with health, whereas reduced diversity is associated with diarrhoea, Crohn's disease and ulcerative colitis, allergy/atopy, and obesity [3, 4]. The importance of the composition of intestinal microbiota in the development of the immune system and the links between intestinal microbiota and diseases such as allergies, atopic eczema and obesity are of great interest [5, 6]. The understanding of the importance of the resident microflora in protecting the body from pathogens has led to an increased interest in probiotic therapy. The term "probiotic" was introduced by Lilli and Stillwell in 1965, as opposed to antibiotic [7]. Today, the World Health Organization define probiotics as "Live microorganisms which, when administered in adequate amounts, confer a health benefit to the host" [8].

Lactic acid bacteria are found naturally in human and cow's milk [9, 10]. These bacteria have been used for hundreds of years to ferment cow's milk into yoghurt and thereby extend the durability of the milk. Fermentation of milk into yoghurt improves its digestibility [3]. The Nobel Prize laureate Èlie Metchnikoff earlier ascribed the beneficial effects of fermented dairy products to changes in the microbial balance in the gut; he believed that harmful effects of toxins produced by intestinal bacteria could be replaced by beneficial effects of lactic acid bacteria [11].

Many beneficial effects on health have been attributed to probiotics. Traditionally, probiotic microorganisms have been used for the prevention and treatment of gastrointestinal infections or diseases [12, 13]. The strongest evidence available on the beneficial effects of probiotic lactobacilli and bifidobacteria is related to the prevention or treatment of infections in the lower part of the gastrointestinal tract [14–16]. In addition, probiotics are better than placebo for preventing acute infections of the upper respiratory tract and reducing the use of antibiotics in both children and adults [17]. The use of probiotics to combat biofilm-mediated oral diseases, dental caries and gingivitis/periodontitis has been studied during the last 20 years. The oral cavity is densely colonized with bacteria and the composition of the microbiome may be altered by oral environmental changes, and dysbios can increase the risk for oral diseases [18]. An example of a dysbiotic effect in oral disease is the overgrowth of cariogenic microorganisms in dental caries. The current understanding is that this process is driven by a shift in the biofilm homeostasis towards less diversity [19, 20]. The switch from homeostasis to dysbiosis is driven by acid production from sugars which create environmental conditions that favour acid-tolerant bacterial species such as mutans streptococci (MS) [18]. The impact of dietary free sugars on caries risk has been reviewed and sugar intake has been graded as the most important risk factor for dental caries [21; see also this monograph – chapter 7].

Proposed Mechanism of Action for Probiotic Bacteria

The approach with probiotic therapy in the oral cavity relies on the hypothesis that harmless bacteria could occupy a space in a biofilm that otherwise would be colonized by a pathogen [22]. It is important to stress that the effect is strain specific. The effects of one probiotic strain should not be generalized because different strains exert different effects [23, 24]. Since the microbiome for each individual is unique, the probiotic effect in individuals is difficult to predict. Probiotic bacteria interact with the commensal microbiota in different ways; however, the mechanisms of action are still poorly understood and most studies on them are in vitro and on animals [25]. It is hypothesized that both systemic and local mechanisms occur. The mechanisms include: (1) interference with other microorganisms; the ability to exclude or inhibit pathogens, (2) modulation of host immune responses resulting in both local and systemic effects, and (3) influencing the function of the intestinal epithelial barrier [26]. The local effect is the effect that probiotic bacteria have when they interact with other bacteria in the biofilm and hamper growth by pathogens through production of hydrogen peroxide, bacteriocins and organic acids. While organic acids lower the pH and promote the growth of acid-tolerating bacteria, the production of bacteriocins may inhibit the growth of other pathogenic species. Systematic effects are thought to be mediated through immunological pathways. Each probiotic strain is associated with a unique profile of cytokines secreted by lymphocytes, enterocytes, or dendritic cells interacting with the particular bacterium [24]. Immunological effects are seen in the mucosa, that is, increased IgA production, stimulated macrophage activity, and increased phagocytosis.

Probiotic Strains and Vehicle

Most studies targeting oral bacteria and oral health, both in vitro and in vivo, have used probiotic strains originally developed for gastrointestinal health. Common probiotic bacteria used in clinical studies targeting oral health are *Lactobacillus* spp. and *Bifidobacterium* spp., in vehicles such as milk, yogurt, cheese, drops, gum, ice cream, lozenges and tablets (Table 1).

Effects of Probiotic Bacteria Shown in In vitro Studies

Probiotic lactobacilli and bifidobacteria are considered both acidogenic and aciduric. Acid production from probiotic bacteria is thought to be critical for their ability to affect other bacteria, but this is also the direct causative factor for the demineralization of teeth [19, 26]. Therefore, one side effect could be that the acidogenicity in the dental plaque increases with the use of probiotics. In vitro studies on monocultures of different probiotic lactobacilli strains have shown a varying acid production [27, 28], while clinical trials have not revealed an impact on plaque acidogenicity [29, 30]. Two simple tests to study bacterial interactions are growth inhibition and co-aggregation. These tests have demonstrated the ability of a number of probiotic strains to inhibit growth and to co-aggregate with oral pathogens, which is a desired feature since it may interfere with biofilm formation. The effects have been shown to be strain- and dose-dependent and depended on the pH in the medium [31–33].

It has been hypothesized that bacteria associated with healthy oral conditions will be more effective than traditional, gut-associated probiotic strains in key aspects such as colonization of the oral site where disease takes place and oral health promoting functions. An example of these active colonizers is *Streptococcus dentisani*, isolated from dental plaque of caries-free individuals. *S. dentisani* inhibits the growth of major oral pathogens such as *Streptococcus mutans* and *Streptococcus sobrinus* through the production of bacteriocins. It also buffers extracellular acidic pH through an arginolytic pathway [34]. There are in vitro studies demonstrating the inhibition of *S. mutans* by naturally occurring lactobacilli isolated from the resident microbiota. Isolates of naturally occurring *Lactobacilli* from breastfed 4-month-old babies showed growth inhibition of *S. mutans* and *Candida albicans* [35]. Additionally, naturally occurring lactobacilli isolated from caries-free subjects had a greater inhibitory potential on MS compared to lactobacilli isolated from subjects with caries [36].

Colonization of Probiotic Bacteria

Clinical studies on the possible incorporation and survival of probiotic lactobacilli in the target biofilm, performed in subjects with a mature microbiota, show that probiotic lactobacilli can be recovered in the oral cavity during an intervention; however, they act as transient colonizers [37–41]. One philosophy for the selection of certain strains is whether they are naturally occurring in the

Table 1. Clinical studies with mutans streptococci (MS) as outcome

Reference	Strain	Vehicle	Target group		Outcome
			age*	*n*	
Nase et al. [49], 2001	*Lactobacillus rhamnosus* GG	Milk	1–6	594	MS↓
Ahola et al. [50], 2002	Lactobacilli mix	Cheese	18–35	74	MS↓
Nikawa et al. [51], 2004	*Lactobacillus reuteri* ATCC 55730	Yoghurt	20	40	MS↓
Montalto et al. [52], 2004	Lactobacilli mix	Capsule/drops	23–37	35	MS↔
Caglar et al. [53], 2005	*Bifidobacterium animalis* DN-173010	Yoghurt	21–24	21	MS↓
Caglar et al. [54], 2006	*Lactobacillus reuteri* ATCC 55730	Straw/tablet	21–25	120	MS↓
Caglar et al. [55], 2007	*Lactobacillus reuteri* ATCC 55730	Chewing gum	20–24	80	MS↓
Caglar et al. [56], 2008	*Lactobacillus reuteri* ATCC 55730, *Lactobacillus reuteri* PTA 5289	Lozenge	20	20	MS↓
Caglar et al. [57], 2008	*Bifidobacterium lactics* Bb-12	Ice cream	20	24	MS↓
Cildir et al. [58], 2009	*Bifidobacterium animalis* DN-173010	Yoghurt	12–16	24	MS↓
Stecksen-Blicks et al. [59], 2009	*Lactobacillus rhamnosus* LB21	Milk	1–5	174	MS↔
Lexner et al. [60], 2010	*Lactobacillus rhamnosus* LB21	Milk	13–17	18	MS↔
Singh et al. [61], 2011	*Lactobacillus acidophilus* La5, *Bifidobacterium lactis* Bb-12	Ice cream	12–14	40	MS↓
Jindal et al. [62], 2011	*Lactobacillus rhamnosus, Bifido-bacterium longum, Saccharomyces cereviasae*	Powder with freeze dried bacteria	7–14	150	MS↓
Chuang et al. [63], 2011	*Lactobacillus paracasei* GMNL-33	Tablet	20–26	70	MS↓
Marttinen et al. [29], 2012	Probiotic mix	Tablet	20–30	13	MS↔
Petersson et al. [64], 2011	*Lactobacillus rhamnosus* LB21	Milk	58–84	160	MS↔
Cildir et al. [65], 2012	*Lactobacillus reuteri* ATCC PTA 5289, *Lactobacillus reuteri* DSM 17938	Tablet	4–12	19	MS↔
Taipale et al. [46], 2012	*Bifidobacterium animalis* BB-12	Tablet	2–24 months	160	MS↔
Juneja et al. [66], 2012	*Lactobacillus rhamnosus hct* 70	Milk	12–15	40	MS↓
Sudhir et al. [67], 2012	*Lactobacillus acidophilus*	Curd	10–12	40	MS↓
Mortazavi et al. [68], 2012	*Lactobacillus casei*	Cheese	18–37	60	MS↓
Keller et al. [30], 2012	*Lactobacillus reuteri* ATCC PTA 5289, *Lactobacillus reuteri* DSM 17938	Tablet	26 mean	18	MS↔
Stensson et al. [73], 2014	*Lactobacillus reuteri* DSM 55730	Drops	1–12 months	113	MS↔
Nishihara et al. [69], 2014	*Lactobacillus salivarius* WB21, *Lactobacillus salivarius* TI 2711	Tablet	22–26	64	MS↓
Teanpaisan et al. [70], 2014	*Lactobacillus paracasei* SD1	Milk	18–25, 40		MS↓

* Years, unless otherwise stated.

target site [42]. An example of this is *Lactobacillus reuteri* ATCC PTA 5289, which is an oral isolate from a Japanese [43]. In a Swedish study, it was tested whether the persistence of *L. reuteri* DSM 17938 and ATCC PTA 5289 in saliva could delay the regrowth of MS after a full-mouth disinfection with chlorhexidine in 62 healthy adults. *L. reuteri* ATCC PTA 5289 was frequently detected during the 6 weeks intervention period but in only 3 test group subjects at follow-ups after 3 and 6 months [41]. It has been suggested that exposure early in life may facilitate a permanent incorporation into the oral microbiota [44] and that it could be easier to alter a caries-associated microbiota at the time of colonization compared to later in life when the microbiota has been firmly established [45]. Infants were exposed to *Bifidobacterium animalis* subsp. *lactis* BB-12 from 2 to 24 months but no permanent colonization was detected [46]. Hasslof et al. [47] studied whether an intervention with probiotic *Lactobacillus paracasei* subsp. *paracasei* strain F19 during weaning resulted in an incorporation into the oral microbiota. When the participants were followed up 8 years after the intervention terminated, the probiotic bacteria were not detected in either saliva or in faeces [47, 48].

Effect of Probiotic Bacteria on Caries Risk Factors

There are only a few studies with caries development as outcome while more studies have been focusing on control of caries-related risk factors or so-called surrogate outcomes. These studies have mainly been short-term and the majority of them, listed in Table 1, have demonstrated the capacity to reduce MS counts in saliva and/or plaque [29, 30, 46, 49–70]. It was concluded in a systematic review that probiotics have demonstrated the ability to reduce MS counts in saliva and/or plaque in the short-term [71]. Short-term administration of *Lactobacillus salivarius* TI 2711 had an effect not only on MS but also on salivary buffering capacity [69]. Ninety days oral treatment with *S. salivarius* M18 resulted in a 30% reduction in the Cariogram outcome and all parameters except "caries experience", "related diseases" and "clinical judgment" improved [72].

Effect of Probiotic Bacteria on Dental Caries

To date only 8 well-designed randomized controlled trials with dental caries as primary outcome have been published (Table 2). Probiotic strains, administration, duration of intervention, and target group have varied. In a majority of the studies (75%), the interventions resulted in caries reduction in the treatment groups. Three studies investigated the long-term effect of an intervention during infancy. Hasslof et al. [47] showed that feeding probiotic *L. paracasei* subsp. *paracasei* strain F19 during weaning (4–13 months of age) had no effect on either counts of MS or on dental caries at follow-up at 9 years of age. In contrast, Stensson et al. [73] showed that an intervention with *L. reuteri* ATCC 55730 during the first year of life reduced the prevalence of approximal caries lesions in the primary dentition at 9 years of age. Eighty-two percent of the children in the probiotic group and 58% in the placebo group were caries-free. There was no effect on MS counts. Taipale et al. [74] investigated in a low caries population, if an intervention with *Bifidobacterium animalis* subsp. *lactis* BB-12 during infancy (2 months to 2 years of age) affected caries at 4 years of age but no effect on dental caries of the intervention could be shown. However, fewer episodes of respiratory infections were observed in the treatment group [75].

In pre-school children attending daycare centres, three studies evaluated the caries-preventive effect of daily consumption of milk with added probiotic bacteria. A Finnish report suggested that *Lactobacillus rhamnosus* GG could reduce the incidence of caries [49] and a Swedish

Table 2. Clinical studies with dental caries as outcome

Reference	Strain	Vehicle	Target group		Duration, months	Outcome
			age	*n*		
Nase et al. [49], 2001	*Lactobacillus rhamnosus* GG	Milk	1–6 years	594	7	Dental caries ↓
Stecksén-Blicks et al. [59], 2009	*Lactobacillus rhamnosus* LB21	Milk	1–6 years	248	21	Dental caries ↓
Petersson et al. [64], 2011	*Lactobacillus rhamnosus* LB21	Milk	58–84 years	160	15	Dental caries ↓
Hasslof et al. [47], 2013	*Lactobacillus paracasei* F19	Cereals	4 months	179	9	Dental caries ↔
Stensson et al. [73], 2014	*Lactobacillus reuteri* DSM 55730	Drops	at birth	113	12	Dental caries ↓
Hedayati-Hajikand et al. [78], 2015	*Streptococcus uberis* KJ, *Streptococcus oralis* KJ, *Streptococcus rattus* JH14	Tablet	2–3 years	138	12	Dental caries ↓
Taipale et al. [74], 2013	*Bifidobacterium animalis subsp. lactis* BB-12	Tablet	2 months	106	15	Dental caries ↔
Rodriguez et al. [77], 2016	*Lactobacillus rhamnosus* SP1	Milk	2–3 years	205	10	Dental caries ↓

study with *L. rhamnosus* LB21 suggested similar effects, although a confounding effect from the fluoride, which had been added to the test milk, could not be excluded [59]. Both these studies also displayed reduced frequencies of otitis media (middle ear infection) and less use of antibiotics in the treatment groups [59, 76]. Evidence for an effect of probiotics on otitis media has been systematically reviewed in 12 trials with 3,720 participants including children, adults, and older people [17]. Later, a study from Chile showed that regular intake of milk supplemented with *L. rhamnosus* SP1 reduced the caries development in children aged 2–3 years [77]. Additionally, in a high caries population in Sweden, administration of a probiotic chewing tablet with *Streptococcus uberis* KJ2, *Streptococcus oralis* KJ3 and *Streptococcus rattus* JH145 was effective in preventing caries in 2- to 3-year-old children [78]. In elderly, the effect on primary root caries lesions of interventions with milk supplemented with 5 ppm fluoride and/or probiotic *L. rhamnosus* LB21 were studied [64]. Results indicated an effect on reversal of the soft and leathery texture of primary root caries lesions. The beneficial effect was strongest when both fluoride and lactobacilli were added to the milk.

Conclusions

It seems possible to alter the levels of MS in the short-term with the daily use of probiotic bacteria. Permanent colonization has not been shown, in early-in-life interventions or in subjects with a mature microbiota. Few randomized controlled trials have been conducted on the long-term effect of probiotic bacteria on caries development. These few studies have targeted different age groups and used different probiotic strains and different vehicles for administration. Further studies are needed to support the present weak evidence for the caries reducing potential of probiotics. In addition, further studies are needed to clarify the mechanisms of action.

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