

# The use of xylitol as a strategy for prevention of dental caries

## Utilização do xilitol como uma estratégia para prevenção da cárie dentária

### Abstract

Dental caries is a multifactorial disease, which depends on the fermentation of carbohydrates by microorganisms of the dental biofilm. Xylitol is a sugar-alcohol, which cannot be fermented by oral cariogenic bacteria. This article aimed to review the literature on the use of xylitol for prevention of dental caries. There is little conclusive scientific evidence about this subject, although several studies have been performed. The development of products and clinical protocols should be based on studies with sound experimental design, which will permit the understanding of clinical and laboratorial parameters, such as mechanisms of action, vehicles of delivery, dose-response effects, and frequency of use of the polyol. Clarification of the potential and limitations of the use of xylitol for prevention of dental caries would help clinicians to select preventive protocols more efficient and cost-effective for specific groups.

**Key words:** Dental caries; prevention & control; xylitol

### Resumo

A cárie dentária é uma doença multifatorial, dependente da fermentação de carboidratos por microrganismos formadores do biofilme dentário. O xilitol é um açúcar-álcool que não pode ser fermentado por bactérias orais cariogênicas. Esta revisão da literatura teve por objetivo propiciar o maior entendimento sobre o uso do xilitol na prevenção da cárie dentária. Apesar de inúmeros trabalhos realizados na área, poucas são as evidências científicas sobre o tema. O desenvolvimento de produtos e protocolos capazes de tornar o xilitol mais eficiente e eficaz contra a cárie dentária só será possível através da realização de estudos mais bem delineados, pautados no entendimento de parâmetros clínicos e laboratoriais, como mecanismos de ação, veículo de administração, efeito dose-resposta e frequência de uso. O esclarecimento do potencial e das limitações de uso do xilitol para prevenção de cárie dentária auxiliaria o cirurgião dentista na seleção de protocolos preventivos mais eficientes e com melhor custo-benefício para grupos específicos.

**Palavras-chave:** Cárie dentária; prevenção e controle; xilitol

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## Introduction

Dental caries is a multifactorial disease, which depends on the use of fermentable carbohydrates by acidogenic and aciduric microorganisms forming the dental biofilm. Acids are mainly produced by mutans streptococci (MS) during the metabolism of sugars, especially of sucrose. The spreading of these acids at the interface between dental biofilm and enamel promotes a fast decrease of pH and a resultant stimulus to the demineralization process. The risk for developing clinical signals of dental caries increases when the teeth are exposed to critical conditions of low pH (1). Although the process of demineralization-remineralization can be controlled, it inevitably happens during lifetime (2).

The research focusing the anticariogenic effects of xylitol started in the 1970's in Turku, Finland. Some studies showed the capacity of this sugar to decrease the growth of *S. mutans* (MS) and production of acids by cariogenic bacteria (3,4), but the ideal parameters of use of xylitol to prevent dental caries remain unclear. The consumption of large amounts of this sugar can produce side effects, such as osmotic diarrhea, flatulence, and gastrointestinal pain. The usual recommended daily doses of xylitol are 60-70 g for adults (10-30 g per intake), and 50 g for children (10 g per intake). The side effects may decrease in response to organic adaptation after the successive consumption of large amounts of xylitol (5). However, safety and effectiveness of dose-response of xylitol intake still lack a consensus.

The aim of this article is to review the literature about the use of xylitol for prevention of dental caries, analyzing clinical and laboratory parameters, such as mechanisms of action, vehicles, dose-response effects, and frequency of use of xylitol.

## Mechanisms of action of xylitol

Several studies aimed to understand the effects of xylitol on the metabolism (6-11) and the acidogenic capacity of MS (11-13), as well as the influence of this sugar on salivary stimulus (14-16) and the process of enamel remineralization (17-21).

### "Futile Cycle"

Xylitol can be incorporated by mutans streptococci and, then, it can inhibit the process of glycolysis of these microorganisms by the use of fructose phosphotransferase system, interfering on their growth and metabolism (6). Inside the bacteria cell, the molecule of this sugar is phosphorylated, resulting in the production of xylitol-5-phosphate, which cannot be metabolized (7). The accumulation of this metabolite results in the inhibition of the glycolytic enzyme production. After administration of xylitol to *Streptococcus mutans* NCTC 10449, Maehara et al. (8) observed the inhibition of many intermediate products of the glycolytic via, such as glucose-6-phosphate, fructose-6-phosphate, glyceraldehyde-3-phosphate, fructose-1,6-biphosphate, 3-phosphoglycerate, 2-phosphoglycerate, and

phosphoenolpyruvate. These substances are essential for enzymatic activation and, therefore, their inhibition prevents the metabolism of this sugar and, consequently, leads to a low production of energy (9). Subsequently, the xylitol-5-phosphate is dephosphorylated and excreted from the bacteria cell (10). This process is responsible for a "futile cycle" (7), which consumes energy but not produces the necessary energy for bacteria maintenance and development.

Kakuta et al. (11) found that the increase of accumulation of xylitol-5-phosphate inside MS decreased the growth of microorganisms and acid production, after administration of xylitol associated or not with other types of sugar. However, a low amount of xylitol-5-phosphate inside the bacteria cells was observed when the administration of xylitol was associated with fructose. Moreover, the production of acids by MS was decreased. These results showed that the administration of xylitol with fructose prevented the efficient formation of xylitol-5-phosphate, because fructose was preferably transported by the fructose phosphotransferase system instead of xylitol.

### Acidogenic capacity of microorganisms

Long-chain acids produced by the metabolism of cariogenic bacteria are considered the main responsible for the demineralization process during the progression of dental caries. The molecular structure of five carbons of xylitol is stoichiometrically unfavorable to be fermented by MS (11,12).

Low pH levels determine competitive advantages for acidogenic and aciduric bacteria. MS and lactobacilli tolerate an acid environment for long periods of time, which is not observed in other oral bacteria. Besides, ability to pump protons in acid conditions, presence of enzymes that work in low pH levels, and the production of proteins because of acid stress are specific characteristics that allow bacteria growth and development in pH lower than 7.0. Xylitol cannot be fermented by the majority of oral bacteria and, therefore, it is not able to promote competitive advantages for acidogenic and aciduric microorganisms (12). For example, Haukioja et al. (13) showed no relevant drop in pH after 30 min of the administration of xylitol (100 mM) to bifidobacteria and probiotic lactobacilli *in vitro*. Otherwise, glucose, sucrose, lactose, and sorbitol were responsible for critical drops in pH, which would start the process of enamel demineralization.

### Salivary flow rates

Salivary flow rates can be stimulated by chewing and by the sweet flavor of xylitol chewing gums, which increase the buffer capacity of saliva and, consequently, may help to prevent dental caries (14). According to Machiulskiene et al. (15), subjects who used chewing gums daily had lower incidence of dental caries lesions in comparison with non-consumers; however, significant statistical differences were not found between the groups that used or not xylitol chewing gum. Therefore, these findings suggest that the mechanical

salivary stimulus of chewing *per se* may be more important to prevent dental caries than the type of chewing gum.

#### Influence of xylitol on the demineralization-remineralization process

The hydrophilic molecule of xylitol is able to form complexes with calcium in solution by ionic mechanism of bond formation (17). This process can stabilize the systems of calcium phosphate found in saliva (18). The saturation of calcium ions in saliva promotes a trend of remineralization of dental tissues by deposition of calcium ions. This saturation is able to control or prevent the dissolution of solid calcium salts (17).

Previous studies evaluated the administration of xylitol in combination or not with other substances to optimize the effects on the dental demineralization-remineralization process. Amaechi et al. (19) observed that 20% xylitol plus 0.5 ppm fluoride solution was more efficient to control the mineral loss of bovine enamel than 20% xylitol solution, 0.5 ppm fluoride solution, or acid buffer solution. However, xylitol solutions were not able to promote more remineralization of bovine enamel than artificial saliva or 0.5 ppm fluoride solution. Chunmuang et al. (20) verified that the addition of 25% xylitol associated or not with 1 ppm fluoride in orange juice was efficient to decrease the enamel erosion. The same result was noticed when the demineralized surfaces were previously treated with 40% xylitol solution associated or not with 227 ppm fluoride solution. Fluoride contributed to decrease the enamel erosion in both cases.

The effect of xylitol on dental remineralization may be different depending on the depth of the demineralized area. Miake et al. (21) proved that higher levels of *in vitro* remineralization were obtained in the deeper and middle layers of enamel than in the outer layers, when artificial lesions were exposed to 20% xylitol solution. Moreover, xylitol was not efficient to promote remineralization in the outer layers of enamel. These findings suggested an improvement of movement and access of calcium ions up to deeper layers of enamel when xylitol was present.

### Xylitol in the prevention of dental caries: Clinical studies

There are not many randomized clinical trials that assessed the efficacy of xylitol on the control of risks factors for dental caries. Controlled clinical studies are needed to develop protocols based on sound scientific evidence to define some clinical parameters, such as ideal vehicles for delivery of xylitol, the doses and frequencies of use, and the target population who would be more benefitted with the use of this polyol. Some relevant studies published on this subject are discussed in this section and summarized in Figure 1.

#### Ideal doses and dose-response effects

There is no consensus in the literature about the minimal effective dose and dose-response effects of xylitol in the

prevention of dental caries. According to Peldyak and Mäkinen (22), daily administration of 4-12 g of xylitol by use of chewing gums at least four times per day is the best mode to administer this sugar to prevent dental caries. However, some studies have already obtained satisfactory results with lower doses (23-25). Kandelman e Gagnon (23) observed a reduction of the DMFS index among children who consumed 0.8 g or 3.4 g of xylitol per day in comparison with those who did not use it. However, statistical significant differences were not found among the groups of subjects who used xylitol in different concentrations. Conversely, the results of the study by Mäkinen et al. (26) permitted to establish a positive linear correlation between the increase of ingested xylitol doses (4.3 g until 9.0 g/day) and the reduction of dental caries lesions increment.

The findings of positive preventive effects of xylitol on dental caries development, in combination or not with other substances, are controversial in the literature. Some studies showed that the combination of xylitol and other substances may help to decrease caries occurrence. For example, after 30 months, Sintes et al. (24) showed that the use of dentifrice containing 10% xylitol plus 1100 ppm fluoride, twice per day, was more efficient to decrease the DFS index in children than the use of dentifrice containing 1100 ppm fluoride alone. Likewise, the use of xylitol associated with others polyols may interfere on the dose-response relation. Peng et al. (25) verified a significant reduction of the DMFS index in children who consumed daily a mixture of 0.14 g of xylitol, 1.78 g of sorbitol, and 0.01 g of carbamide.

On the other hand, other studies found no advantage with the combined administration of xylitol and other substances. Machiulskiene et al. (15) reported that the DMFS index was not significantly different between children who used 2.95 g of xylitol or sorbitol per day or those who used chewing gums without addition of polyols. Stecksén-Blicks et al. (27) also did not observe significant differences in the DMFS index increment among people who consumed or not chewing gums containing 2.5 g of xylitol associated or not with 1.5 mg of fluoride. Differently, Kovari et al. (28) obtained favorable results to prevent dental caries after the application of the same protocol used by Stecksén-Blicks et al. (27). These findings highlight the complex interaction of multiple variables to assess prevention of dental caries.

Some studies used surrogate outcomes (pH, MS counts) of dental caries endpoints to evaluate the potential preventive effect of xylitol and its combinations. Lif Holgersson et al. (29) showed a significant increase of pH of interdental biofilm in absence or presence of sucrose until 5 min after use of chewing gums containing 6.0 g of xylitol. When a dose of 2.0 g of xylitol was ingested before the consumption of sucrose, the acidogenicity levels of dental biofilm were higher than those verified in the control group, which used paraffin gum. The same researchers observed in other study (30) that the lactic acid production decreased after the use of chewing gums containing 6.18 g of xylitol or an association of 4.14 g of sorbitol with 0.3 g of carbamide.

AUTHOR/YEAR	VEHICLE OF ADMINISTRATION	MAIN OBJECTIVES	MAIN CHARACTERISTICS OF THE SAMPLES	GROUPS (N; DOSES)/ FREQUENCY/TIME OF STUDY	MAIN RESULTS
Aaltonen et al./ 2000 (43)	Mechanism of slow release (pacifier)	Effects on MS counts and prevention of dental caries	122 children; 1 year-old; high risk for dental caries	T (n=34; 0.25 mg NaF + 159 mg xylitol + 153 mg sorbitol, into pacifier); C (n=88; same dose mixed into meals)/1x/day (night)/ 1 year	% children MS(+): C (25%) > T (9%) (P<0.05); T developed lower number of dentin caries lesions than C (P<0.001)
Haresaku et al./ 2007 (37)	Chewing gum	Effects on MS counts in dental biofilm and saliva	127 adults, 28 year-old (18-53); healthy	XYL (n=33; 7.9 g/day); MAL (n=34; 7.1 g/day); C (n=27; no gum)/ after meals/ 6 months	MS levels: XYL<C<MAL (P<0.05 in saliva; P<0.001 in dental biofilm)
Hildebrandt; Sparks/2000 (38)	Chewing gum	Effects on maintenance of MS; suppression in saliva	151 adults, 36 year-old (21-71), high MS levels	Previous rinsing with 0.12% chlorhexidine, 2x/day, 14 days; After: XIL (n=51; 2 pellets); SOR (n=50; 2 pellets); C (n=50; no gum)/ 3x/day/ 3 months	MS levels after 3 months: XIL (3.6) < C (4.4) < SOR (4.7) (P<0.05)
Honkala et al./ 2006 (44)	Candies	Effects on the prevention of dental caries	145 patients, 10-27 year-old; physically disabled	T (n=105; 49% xylitol candies); C (n=40; no candies)/ 3x/day, in scholar days/ 18 months	Baseline: CS = 3.4 (T) and 3.9 (C); CPOS = 8.2 (T) and 9.8 (C); After 18 months: CS = 1.9 (T) and 3.9 (C); CPOS = 7.1 (T) and 13.2 (C); CS and CPOS: T<C (P<0.001)
Hujoel et al./ 1999 (41)	Chewing gum	Benefits after the use of xylitol, sorbitol and sorbitol + xylitol for a long period of time	288 children, 6.1 year-old (3.4-8.8); 5 years after a program of use of polyols for 2 years	NG (n=70); SOR pellet (n=35; 10.67 g/day); SOR stick (n=33; 10.42 g/day); 4:1 XS (n=43; 9.68 g xylitol + 2.69 g sorbitol/day); 3:2 XS (n=43; 7.11 g xylitol+2.70 g sorbitol/day); XIL pellet (n=22; 10.67 g/day); XIL stick (n=42; 10.42 g/day)/ 5x/day/ 2 years	After 5 years: 59% (100% XIL chewing gums) and 44% (XIL+SOR chewing gums) lower dental caries risk than CG; irrupted teeth after 1 or 2 years from the beginning of use of chewing gum were more benefitted than other teeth
Isokangas et al./ 2000 (49)	Chewing gum	Relation between maternal xylitol consumption and dental caries lesions in children	195 mother-child pairs; mothers with high salivary MS levels	XIL (n=120; 6-7 g/day)/ 4x/day (from the 3 <sup>rd</sup> month of child life); CHX (n=32); F (n=36)/ 3x (one session of varnish application at 6, 12 and 18 months after birth)/ 2 years	Children (5 year-old): dentin caries lesions = a reduction of 70% in XIL in comparison with CHX and F
Isotupa et al./ 1995 (32)	Chewing gum	Effects on weight of plaque and MS counts in dental biofilm and saliva	60 children, 11-15 year-old; orthodontic patients	SOR (n=15; 11.3 g/day); XS4:1 (n=16; 9.72 g xylitol + 2.46 g sorbitol/day); XS3:2 (n=14; 7.29 g xylitol + 4.76 g sorbitol/day); XIL (n=15; 10.5 g/day)/6x/day/ 4 weeks	The weight of dental biofilm decreased in all groups, being higher in XIL (P<0.05); MS counts in dental biofilm and saliva decreased significantly in XIL and 80% XIL + 20% SOR (P<0.05)
Kandelman; Gagnon/1990 (23)	Chewing gum	Effects on incidence and progression of dental caries lesions	274 children, 8-9 year-old; high incidence of dental caries lesion	XYL65 (n=87; 3.4 g/day); XYL15 (n=90; 0.8 g/day); C (n=97; no chewing gum)/ 3x/day/ 2 years	DMFS index increment: XYL65=XYL15=2.24<C=6.06 (P<0.05)
Lif Holgerson et al./2005 (29)	Chewing gum	Effects on pH of interdental biofilm	11 children, 10-15 year-old; habitual consumers of xylitol	Previous consumption of 4.0 g xylitol/14 days; After: CTR (paraffin gum, control); LX (2.0 g xylitol); HX (6.0 g xylitol)/1x each, with and without the use of sucrose rinsing after the use of gum (crossover study)/4 weeks	pH (no sucrose rinsing): 5 min after chewing = HX > LX > CTR, being HX > CTR (P<0.05); pH (with sucrose rinsing): 5 min after chewing = HX > CTR > LX, being HX > LX (P<0.05); After 10, 15, 20, 25 and 30 min, significant statistical differences were not observed in other situations
Lif Holgerson et al./2006 (35)	Chewing gum (G); Tablets (T); Candies (C); Dentifrice (D); Solution (S)	Xylitol concentration in saliva and dental biofilm after use of different products containing the polyol	12 children, 11.5 year-old (6-13); healthy	Xylitol in dental biofilm: CTR (distilled water); LX (2.0 g solution); HX (6.0 g solution)/ 1x each (cross-over study)/ 14 days; Xylitol in saliva: G (1.32g); T (0.84 g); C (1.12g); D (1.0g); S (1.0g); P (paraffin)/1x each (crossover study)	Xylitol (dental biofilm): HX > baseline (until 30 min after rinsing); LX > baseline (until 15 min after rinsing); After 15 min: HX > LX (P<0.05); Xylitol (saliva): G and S > baseline (until 16 min after the use); T, G and D > baseline (until 8 min after the use); After 1 min: G > T > S > C > D, being G > T (P<0.05)
Lif Holgerson et al./2007 (30)	Chewing gum	Effects on MS counts and lactic acid production in saliva	128 children, 10.2 year-old (7-12); children with and without caries experience	C (4.14 g sorbitol + 0.3 g maltitol/day); XIL (6.18 g/day)/ 3x/day/ 4 weeks	Lactic acid produced in saliva decreased in both groups (P<0.05); %MS in relation to total viable bacteria: only XIL< baseline (P<0.05); MS counts in saliva was reduced only among caries-free children
Ly et al./2006 (39)	Chewing gum	Relation between frequency and MS levels in dental biofilm and saliva	132 adults, 34 year-old (18-73); healthy	XIL1 (n=33; 10.32 g/day/2x/day), XIL2 (n=33; 10.32 g/day/3x/day) or XIL3 (n=33; 10.32 g/day/4x/day); C (n=33; 9.828g sorbitol+0.7g maltitol/day)/4x/day/5 weeks	MS levels in saliva and dental biofilm: linear reduction with increase of frequency of use of xylitol; XIL1 was not different from C; XIL2 and XIL3 < C (P<0.05)
Ly et al./ 2008 (33)	Gummy bear snacks	Relation among xylitol doses and <i>S. mutans</i> , <i>S. sobrinus</i> and <i>Lactobacillus</i> ssp levels in dental biofilm	154 children, 8.4 year-old; students in rural schools	XIL16 (n=53; 15.6g/day); XIL12 (n=49; 11.7g/day); MAL45 (n= 52; 44.7g/day)/3x/day in scholar days/6 weeks	<i>S. mutans</i> and <i>S. sobrinus</i> levels decreased in all groups (P=0.0001), however without significant differences between groups. <i>Lactobacillus</i> ssp. levels: all groups were not different from baseline

Abbreviations used: MS - mutans streptococci; T - test group; C - control group; XYL - xylitol group; MAL - maltitol group; SOR - sorbitol group; NG - group no consumption of chewing gums; CHX - chlorhexidine; F - fluoride; ERI - erythritol; CG - control gum group; CAR - carbamide.

Fig. 1. Summary of the methods and main results of clinical studies on the influence of xylitol on dental caries (cont.)

AUTHOR/YEAR	VEHICLE OF ADMINISTRATION	MAIN OBJECTIVES	MAIN CHARACTERISTICS OF THE SAMPLES	GROUPS (N; DOSES)/ FREQUENCY/TIME OF STUDY	MAIN RESULTS
Machiulskiene et al./ 2001 (15)	Chewing gum	Effects on the prevention of dental caries	602 children, 11.7 year-old (9-14); healthy	SOR/CAR (n=118; at least 2.85 g sorbitol and 0.1 g carbamide/day); SOR (n=118; at least 2.95 g/day); XIL (n=126; at least 2.95 g/day); CG (n=120; control gum); C (n=120; no gum)/after meals/ 3 years	DMFS index increment (after 3 years): 11.8 (SOR/CAR); 9.0 (SOR); 8.1 (XIL); 8.3 (CG); 12.4 (C); XIL, SOR and GC < C (P<0.05); Significant statistical differences were not observed between SOR/CAR and C or among SOR, XIL and GC
Mäkinen et al./ 1995 (26)	Chewing gum	Effects on the prevention of dental caries	1277 children, 10.2 year-old; healthy	Frequency 5x/day: C (n=121; no gum); CG (n=119; 9.0g saccharose+1.3g corn sugar/day); SOR (n=129; 9.0 g/day); 3:2XS (n=120; 5.9g xylitol + 3.8 g sorbitol/day); 1:3XS (n=121; 2.0 g xylitol+6.0 g sorbitol/day); XIL2 (n=126; 9.0g xylitol + 1.3g Lycasin®/day); XIL4 (n=125; 8.5209g xylitol/day); Frequency 3x/day: XIL1 (n=141; 5.4 g xylitol+0.7g Lycasin®/day); XIL3 (n=133; 4.3 g xylitol/day)/ 40 months	The number of new dental caries lesions in each group was: 579 (C); 739 (CG); 527 (SOR); 325 (3:2XS); 288 (1:3XS); 323 (XIL1); 297 (XIL2); 233 (XIL3); 172 (XIL4). The risk for development of dental caries lesions was lower among groups that used xylitol (XIL1, XIL2, XIL3 e XIL4) than for groups that did not use it. Risk for development of dental caries lesions in CG was higher than in other groups
Mäkinen et al./ 2002 (42)	Chewing gum	Effects on <i>S. mutans</i> counts in dental biofilm and saliva	98 patients; mentally handicapped	XIL (5.4g/day); SOR (5.4 g/day); 1:1XIL/ERI (2.7g xylitol+2.7g erythritol); 1:1SOR/ERI (2.7g sorbitol+2.7g erythritol)/5x/day/ 64 days	<i>S. mutans</i> levels in dental biofilm and saliva: lower than baseline in XIL and 1:1XIL/ERI (P<0.05); % <i>S. mutans</i> in relation to total streptococci increased in SOR (P<0.05) and decreased in all other groups
Mäkinen et al./ 2005 (45)	Chewing tablets; dentifrices	Effects on MS counts in saliva and dental biofilm, growth of biofilm	136 teenager students, 17 year-old	All groups with n=30-40: XIL (7.0g/day); ERI (7.0 g/day); SOR (7.0g/day); C (no tablets or dentifrices)/ 6x/day/ 6 months+ dentifrice containing 34.5% of one of those studied polyols/2x/day/ same time of the use of tablets (6 months)	MS levels in dental biofilm and saliva: lower than baseline in XIL and ERI (P<0.001). The weight of dental biofilm decreased only in XIL and ERI (P<0.05)
Mäkinen et al./ 2005 (40)	Chewing gum	Effects on growth of MS and dental biofilm	126 children, 5 year-old; kindergarten-age	XIL (4.5-5.0 g/day); SOR (4.5-5.0 g/day); C (no gum)/ 5x/day, being 4x at kindergarten and 1x at home/ 6 months	MS levels in interdental biofilm: XIL<SOR (P<0.05); Plaque index (Quigley & Hein) tended to a reduction only in group XIL
Milgrom et al./ 2006 (31)	Chewing gum	Relation between dose of xylitol and effects on MS counts	132 adults, 35 year-old (18-73); healthy	G1 (n=33; 9.83g sorbitol+0.702g maltitol/day); G2 (n=33; 3.44g xylitol/day); G3 (n=33; 6.88g xylitol/day); G4 (n=33; 10.32g xylitol/day)/4x/day/ 6 months	After 5 weeks: MS levels in dental biofilm were 10x lower than baseline in G3 (p=0.007) and G4 (p=0.003); There were not significant differences in saliva. After 6 months: MS levels were 10x lower than baseline in dental biofilm (P<0.05) and 8-9x lower than baseline in saliva (P<0.05) in G3 e G4
Peng et al./ 2004 (25)	Chewing gum	Effects on the increment of new dental caries lesions and gingival bleeding	1143 children, 6-7 year-old; healthy	C (n=370; control group, no intervention); E (n=410; oral health education); G (n=363; oral health education + chewing gum, 0.14 g xylitol + 1.78 g sorbitol+0.01 g carbamide/day)/4x/day/2 years	DMFS index increment: group G was 42% lower than groups E and C (P<0.05); Gingival bleeding: G<C (71%, P<0.01); E<C (42%, P<0.05)
Scheie et al./ 1998 (34)	Chewing gum	Effects on the formation of dental biofilm and its acidogenic potential	30 young adults, 19-28 year-old; healthy, without dental caries lesions	XIL (n=10; 4.0g/day); XIL/SOR (n=10; 1.3g xylitol+3.1g sorbitol); C (n=10; sucrose gum)/5x/day/ 30 days	Formation of dental biofilm, acidogenic potential and glycolytic profile were similar at baseline and after the experiments in all groups. Glycolytic metabolites did not accumulate inside of bacteria that formed the dental biofilm
Sintes et al./ 2002 (24)	Dentifrice	Effects on the increment of new dental caries lesions	2539 children, 7-12 year-old; healthy	T (n=1280; 1100 ppm F+10% xylitol); C (n=1259; 1100 ppm F)/ 2x/day/30 months	DFS index increment: 1.30 (T) and 1.51 (C) (P<0.05); DFT index increment: 0.69 (T) and 0.81 (C) (P<0.05)
Söderling et al./ 2000 (51)	Chewing gum	Effects on the consumption of xylitol on the prevention of transmissibility of cariogenic bacteria	169 mother-child pairs; mothers with high MS levels in saliva	XYL (n=106; 65% xylitol in each gum)/at least 2-3x/day/2 years; CHX (n=30; chlorhexidine varnish EC40); F (n=33; fluoride varnish Duraphat®)/3x (6, 12 and 18 months after birth of baby)	Salivary MS levels (mothers): they remained high and were not different in all groups; Children (2 year-old): 9.7% (XYL), 28.6% (CHX) and 48.5% (F) showed detectable MS levels
Stecksén-Blicks/ 2008 (27)	Lozenges	Effects on the development of proximal dental caries lesions	160 children, 10-12 year-old; healthy, with high risk for dental caries	XYL (n=80; 2.5g/day); XF (n=80; 2.5 g xylitol+1.5 mg fluoride/day)/ 3x/day/ 2 years; CG (n=70; no intervention)	DMFS index increment: it was not significantly different between groups; DFS index increment (only children with good compliance): XF (1.0) < XYL (3.3) (P<0.05)

Abbreviations used: MS - mutans streptococci; T - test group; C - control group; XYL - xylitol group; MAL - maltitol group; SOR - sorbitol group; NG - group no consumption of chewing gums; CHX - chlorhexidine; F - fluoride; ERI - erythritol; CG - control gum group; CAR - carbamide.

Fig. 1. Summary of the methods and main results of clinical studies on the influence of xylitol on dental caries (concl.)

Milgrom et al. (31) reported that a dose of 3.44 g of xylitol per day was not able to decrease the MS counts, but a dose of 6.88 g/day was efficient. The consumption of 10.32 g of xylitol per day did not increase the inhibition of bacterial growth in comparison with consumption of 6.88 g of the sugar, which suggested a plateau effect. In another study, Isotupa et al. (32) found a significant reduction of the MS counts in dental biofilm and saliva of children who used 10.5 g of xylitol or an association of 9.72 g of xylitol with 2.46 g of sorbitol per day, during 4 weeks. A daily dose of 7.29 g of xylitol associated with 4.76 g of sorbitol was not able to decrease MS counts in relation to the baseline. The findings of Milgrom et al. (31) were different probably because of the presence of more types of bacteria able to use sorbitol to obtain energy (13).

Ly et al. (33) showed that the consumption of xylitol (11.7 g or 15.6 g/day) or maltitol (44.7 g/day) was able to decrease *S. mutans* and *S. sobrinus* counts. However, significant statistical differences were not observed among different groups. However, Scheie et al. (34) did not find any differences on dental biofilm formation, acidogenicity levels, and bacterial glycolytic profile among young adults who consumed or not 4.0 g of xylitol per day in chewing gums.

#### Ideal vehicles and frequencies

The vehicle of administration is an essential factor for the success of techniques involving the use of drugs and/or any chemical substance to treat or prevent diseases. These vehicles must be able to permit the delivery of therapeutic agents in adequate *loci*, allow maximal bioavailability with comfort and ease of use. Thus, the patient may be more compliant with the treatment and, consequently, better results can be achieved.

Xylitol must be detected above of a threshold of salivary concentrations to have some effect in the prevention of dental caries. Lif Holgerson et al. (35) observed that the use of chewing gums containing 1.32 g of xylitol or the use of 10 mL of xylitol solution containing 1.0 g of the polyol were able to increase significantly the salivary xylitol levels for up to 16 min. Tablets, candies, and dentifrices were able to spread the sugar in detectable amounts, but for up to 8 min after their consumption. Tapiainen et al. (36) showed salivary concentrations of xylitol equal or higher than 1% until 15 min after the use of xylitol chewing gums (1.68 g) and until 10 min after the use of xylitol solution (2.0 g/5 mL).

Many studies about the influence of xylitol on the acidogenicity of dental biofilm, reduction of MS counts, and prevention of new dental caries lesions used chewing gum as the vehicle of administration (15,23,25,26,29-32,34,37-42). One explanation is that the use of xylitol chewing gums would provide higher levels of salivary concentrations of the polyol than the use of other vehicles. In addition, chewing gums stimulate the salivary flow, which is a very important factor to increase the buffer capacity of saliva and contribute to the remineralization process of dental tissues. For instance, Mickenaustch et al. (16) showed that sugar-free

chewing gums were able to produce non-cariogenic effects without addition of xylitol or sorbitol.

Most studies using chewing gum as the vehicle of administration of xylitol showed positive results to control some risks factors for the development of dental caries and to prevent this disease (23,25,26,29,31,32,37-42). However, these studies did not have a control group who used chewing gums without addition of any sugar. Other studies with inclusion of a control group using paraffin chewing gums did not show any significant effect of chewing gum with xylitol (15,34). Therefore, based on the available literature, it is still not possible to separate the influence of salivary stimulus produced by the use of chewing gums and the addition of xylitol to prevent dental caries. Moreover, preventive results were only seen when patients used the chewing gums for 3-6 times/day (15,23,25,26,29,31,32,34,37-42), which may be cumbersome (31).

As infants and young children cannot use chewing gums, other vehicles of administration of xylitol have been tested, such as pacifiers, candies, tablets, dentifrices, lozenges, and solutions (24,27,33,40,43,44). Most vehicles stimulate salivary flow rates by chewing, suction and/or mouth rinsing. The efficiency of these vehicles on MS control and for prevention of dental caries should be further investigated because the available evidences are still not conclusive.

Favorable results of prevention of early acquisition of mutans streptococci and development of new dental caries lesions were obtained after the administration of 0.25 mg of fluoride associated with 159 mg of xylitol and 153 mg of sorbitol per day, by using lozenges introduced into pacifiers (43). This device can be used by young children during sleep, when the salivary flow is very low. Also, it can allow a gradual and slow delivery of the polyol.

There is no consensus on the effectiveness of dentifrices, candies and/or lozenges containing xylitol for prevention of dental caries. While the consumption of 2.5 g of xylitol lozenges per day failed to show any effect of this sugar on the reduction of DMFS index in children (27), the consumption of 10% xylitol associated with 1100 ppm fluoride dentifrice was able to decrease the number of new decayed and filled dental surfaces in comparison with a control group, which used 1100 ppm fluoride dentifrice (24). Honkala et al. (44) noticed the reduction of DMFT and DMFS indexes among physically disabled subjects, who consumed 49% xylitol in candies. The progression of 212 dental caries lesions was arrested because of the ingestion of this sugar.

Daily consumption of gummy bears snack containing more than 10 g xylitol was not efficient to decrease the *S. mutans* e *S. sobrinus* counts in comparison with daily use of 44.7 g maltitol (33). The use of 7.0 g erythritol was as efficient as the use of 7.0 g xylitol to decrease the MS counts in saliva and dental biofilm after the use of dentifrice containing specific polyols (45).

Isokangas (46) reported that chewing gums should be consumed for at least 3 times/day to have a preventive effect on dental caries development. A reduction of DMFS index was found by Rekola (47) when the frequency of

administration of xylitol chewing gums was increased. Ly et al. (39) found a linear reduction of MS levels in dental biofilm and saliva after increasing the frequency of use of xylitol. Furthermore, when the same dose (10.32 g) was divided into two intakes per day, the bacteria counts were not modified in comparison with the control group. Although the results on this clinical parameter seem to be homogeneous, few controlled studies could provide a high level of scientific evidence.

#### Other important considerations

The early acquisition of cariogenic bacteria in children increases the risk for developing dental caries lesions (48). Söderling et al. (49) observed lower levels of intraoral MS counts in children whose mothers consumed chewing gum with xylitol, which was more efficient than the use of chlorhexidine or fluoride varnish. Another study found a reduction rate of 70% of dental caries in dentin among 5 year-old children whose mothers used xylitol during the first two years of the child life (49).

Subjects featuring some limitation to perform a correct mechanical control of the dental biofilm are under high risk for the development of dental caries, and would be candidates for biofilm chemical control. Xylitol has already been successfully used in patients with high MS levels (38) and many caries lesions (23), as well as physically disabled or mental handicapped subjects (42,44), orthodontic patients (32), and teenagers (45).

Positive (30,32,37,38,44) and negative (15) results were obtained with the use of xylitol between or after meals. According to Lif Holgerson et al. (29), the use of xylitol chewing gums before meals promoted lower reduction of pH after sucrose rinsing than in control groups. However, this effect was only observed up to 5 min after sucrose rinsing.

The pH changes in the dental biofilm are observed immediately after the use of different vehicles of administration of the polyol (29). MS counts can be modified after 4 weeks of consumption of xylitol (32), firstly in the dental biofilm and then in saliva (31). This information would be relevant to determine the most appropriate research design for a given protocol. Direct clinical effects of xylitol for prevention of

dental caries are shown after 12 months of uninterrupted consumption of the polyol (43). The use of xylitol for a long period of time can select resistant *S. mutans* as the amount of dental biofilm is temporarily decreased for 4-14 days (37). However, dental biofilm composed of xylitol-resistant bacteria may be more easily removed from the dental surfaces than those composed of xylitol-sensitive bacteria, and this issue needs further investigation (50).

The quality of preventive methods should be assessed by their immediate and late effects. Immediate effects can be measured after the suspension of the therapy. Hujoel et al. (41) observed that the risk for developing dental caries among consumers of xylitol for the previous five years was 59% lower than that of patients who did not use the polyol. Furthermore, teeth erupted until 1-2 years after the beginning of the systematic use of xylitol would have stronger positive response.

## Conclusions

The real benefits and advantages of the use of xylitol for prevention of dental caries have not been clarified yet. Further studies following sound research design are necessary to refine the concepts of dose-response, frequency of use, vehicles of delivery, mechanisms of action, immediate and late effects, and groups at caries risk who would be target of the systematic use of xylitol. Thus, the development of products and adoption of clinical protocols should be based on scientific evidence to use xylitol as a more efficient and effective substance against dental caries. However, xylitol must not represent a single preventive strategy but should be considered as an auxiliary agent mainly used when the mechanical control of dental biofilm is unsatisfactory and insufficient to avoid the development of dental caries lesions.

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