Xylitol, Mutans Streptococci, and Dental Plaque

E.M. Söderling

Institute of Dentistry, University of Turku, FI-20520 Turku, Finland; eva.soderling@utu.fi

Adv Dent Res 21:74-78, August, 2009

The caries-controlling or preventing effect of xylitol is more than just excluding fermentable sugars from the diet. This review aims to discuss the specific effects of xylitol which could have contributed to the results of the caries trials. Xylitol promotes mineralization by increasing the flow of saliva, an effect it has in common with all sweeteners. What is unique for xylitol is that it is practically non-fermentable by oral bacteria. Xylitol is known to inhibit growth, metabolism, as well as polysaccharide production of mutans streptococci. During habitual xylitol consumption, the counts of mutans streptococci decrease and remain on a lower level as long as the consumption lasts. Habitual xylitol consumption also prevents mother-child transmission of mutans streptococci. In addition to growth inhibition, the reduction of insoluble extracellular polysaccharides is probably of importance for the xylitol-induced decrease in both counts and transmission of mutans streptococci.

INTRODUCTION

A landmark study of dental caries research is the Turku Sugar Studies, conducted in the early 1970s, involving total substitution of almost all dietary sugars with xylitol. Since then, the xylitol caries studies carried out have been partial substitution or chewing gum/pastille supplementation studies (for reviews, see Maguire and Rugg-Gunn, 2003; Ly *et al.*, 2006). A new approach has been the use of xylitol to decrease mother-child transmission of mutans streptococci, resulting in primary prevention of caries in young children (Isokangas *et al.*, 2000; Söderling *et al.*, 2000). Xylitol, as a sweet substance, promotes mineralization by increasing the flow of saliva, especially in association with the use of chewing gums or large xylitol pastilles, but this effect is common for all other sweeteners. What is unique for xylitol is that it is practically non-fermentable by oral bacteria (Havenaar *et al.*, 1978). In addition, habitual xylitol consumption decreases counts of mutans streptococci (MS) as well as the amount of plaque (Maguire and Rugg-Gunn, 2003; Ly *et al.*, 2006). The aim of the present review is to evaluate specific effects of xylitol on MS and plaque.

XYLITOL AND GROWTH OF MUTANS STREPTOCOCCI

Xylitol inhibits the growth and metabolism of several bacterial species, but among the oral bacteria, the MS appear to be the target organisms of xylitol (Vadeboncoeur *et al.*, 1983; Loesche *et al.*, 1984; Bradshaw and Marsh, 1994).

Some MS strains are inhibited by xylitol (xylitol-sensitive MS), whereas others are not (xylitol-resistant MS; for review, see Trahan, 1995), and the degree of inhibition varies among strains (Vadeboncoeur *et al.*, 1983). Significant growth inhibition can be obtained with xylitol concentrations as low as 0.01% (0.66 mM; Fig. 1) when xylitol is present in the medium during growth (Söderling *et al.*, 2008). These results may be useful in prediction of the effects of xylitol dissolving from slow-release vehicles, which have been suggested to have a future as delivery methods for xylitol (Featherstone, 2006). MS cells are thought to incorporate xylitol as xylitol-5-phosphate through the major route of sugar transport: the phosphoenolpyruvate phosphotransferase (PEP-PTS) system. The xylitol-5-phosphate inhibits glycolytic enzymes, resulting in the inhibition of both growth and acid production. Moreover, the so-called 'futile xylitol-5-phosphate cycle' can slow the growth of MS (Trahan, 1995; Miyasawa-Hori *et al.*, 2006). Recently, it was shown that the xylitol:PEP-PTS activity was related to the degree of growth inhibition found for xylitol (Miyasawa-Hori *et al.*, 2006).

Several studies have shown that long-term, habitual xylitol consumption selects for MS not inhibited by xylitol (Trahan, 1995). Habitual xylitol consumption, resulting in typical "xylitol effects" on MS and plaque, can be defined as daily consumption of 5-7 g xylitol/day, with a consumption frequency of at least 3 times a day (Milgrom *et al.*, 2009). In habitual xylitol consumers, the percentage of the so-called xylitol-resistant MS constitutes more than 80% of total MS counts (Trahan *et al.*, 1992; Trahan, 1995). MS not inhibited by xylitol have been suggested to be less virulent compared with strains inhibited by xylitol (Trahan, 1995; Tanzer *et al.*, 2006), but contradictory results have also been published (Assev *et al.*, 2002).

Key Words

Xylitol, mutans streptococci, plaque, transmission, dental.

Presented at the International Conference on Novel Anti-caries and Remineralizing Agents, held in Vina del Mar, Chile, January 10-12, 2008

The authors declare no conflict of interest.

DOI: 10.1177/0895937409335642

XYLITOL AND COUNTS OF MUTANS STREPTOCOCCI

The finding that xylitol consumption selects for MS not inhibited by xylitol is convincing (Trahan, 1995), but in practice it means that after the xylitol consumption has lasted for some time, xylitol should lose its ability to inhibit the majority of MS. However, decreased MS counts of plaque/saliva have been demonstrated for habitual xylitol consumption in short-term studies lasting from 2 weeks to a few months (Loesche *et al.*, 1984; Söderling *et al.*, 1997; Holgerson *et al.*, 2007). The MS counts seem to remain on a lower level as long as the xylitol consumption lasts (Loesche *et al.*, 1984; Holgerson *et al.*, 2007). No such effects have been reported for other polyol sweeteners. Long-term habitual xylitol consumption has been reported either to decrease or to cause no change in the MS counts. Three recent six-month studies have demonstrated a xylitol-associated decrease of MS counts in plaque (Mäkinen *et al.*, 2005; Milgrom *et al.*, 2006; Haresaku *et al.*, 2007), and in resting (Milgrom *et al.*, 2006) and stimulated saliva (Haresaku *et al.*, 2007). In a two-year study, the plaque MS of 11- to 12-year-old children decreased and remained low throughout the study (Mäkinen *et al.*, 1989). In another two-year study, however, no significant decreases could be observed in the salivary MS counts of 10-year-old children (Mäkinen *et al.*, 1996). In our mother-child study, discussed in detail later, mothers consumed xylitol habitually for 21 months, but no decrease was found in the high MS counts (Söderling *et al.*, 2000). We think that the total MS counts of the mothers habitually consuming xylitol decreased in line with results from most other long-term studies discussed above. However, in our study, MS were assessed only from the stimulated saliva of the mothers. A xylitol-induced change in the plaque-saliva distribution of the MS (Söderling *et al.*, 1991; Trahan *et al.*, 1992) may have hidden the fact that the total MS counts of the mothers had actually decreased (Fig. 2). Thus, the mothers' unstimulated saliva, involved in mother-child contacts, may have contained MS levels below those needed for MS transmission to take place. Our current concept is that xylitol consumption changes the plaque-saliva distribution of MS, but this phenomenon may depend on oral hygiene, dietary habits, and the MS strains involved.

Xylitol was demonstrated to decrease the synthesis of insoluble polysaccharides by *Streptococcus mutans in vitro* (Söderling *et al.*, 1987). The plaque of habitual xylitol users also appears to contain fewer insoluble polysaccharides compared with the plaque of non-users (Mäkinen *et al.*, 1985). Thus, MS exposed to habitual xylitol consumption *in vivo* may in fact be less adhesive compared with those of non-consumers of xylitol (Fig. 2). In addition to growth inhibition, the reduction of insoluble extracellular polysaccharides is probably of importance for the xylitol-induced decrease in both counts and transmission of MS.

XYLITOL AND TRANSMISSION OF MUTANS STREPTOCOCCI

S. mutans has been implicated as a major etiological agent of dental caries, even though other bacterial species may also play important roles in caries progression (Aas *et al.*, 2008). Since *S. mutans* can be detected by chairside methods, it is a useful tool in caries prediction, especially in young children (Thenisch *et al.*, 2006). Early MS colonization is always a risk for a child's future dental health.

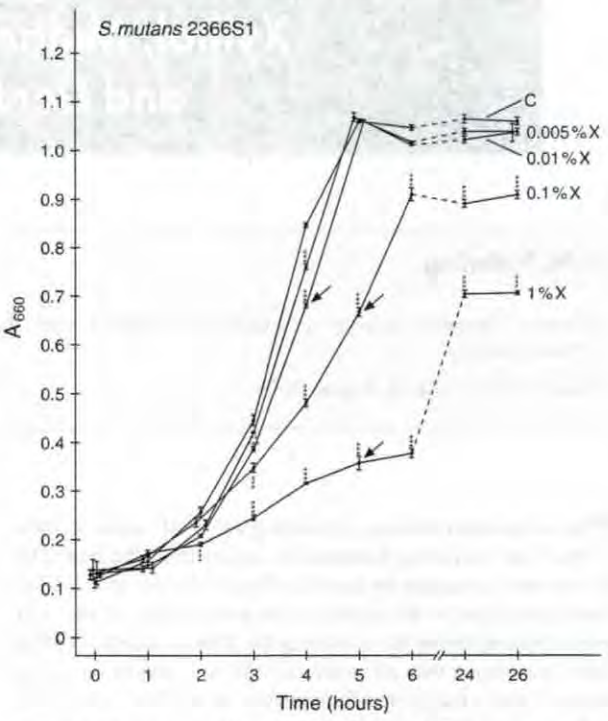

Figure 1. Growth curves of a clinical isolate of *S. mutans* in the presence of various concentrations of xylitol (X). Significant differences compared to the control curve (C): $***p < 0.001$; $**p < 0.01$; $*p < 0.05$. The arrows indicate maximal growth inhibition during log-phase compared with the control. Mean ± SD, n = 4 (Söderling *et al.*, 2008).

In the early 1990s, we initiated a randomized, controlled field study in the Finnish Health Care Centres of Ylivieska, Sievi, and Alavieska. In the study, xylitol chewing gum consumption was compared with fluoride (Duraphat®) and chlorhexidine (CHX; EC 40®) varnish treatments. F varnish has no effect on MS, and CHX treatment was supposed to reduce MS counts significantly. Pregnant women (n = 195; approximately half of all women screened) with high salivary MS counts ($\geq 10^5$ CFU/mL) participated in the study. The interventions lasted up to the child's age of two years; the children received no preventive treatment apart from the routine prevention of the Health Care Centres. In the Xylitol group, the mothers consumed 6-7 g xylitol *per* day (100% xylitol gum), the mean daily usage frequency being four times a day. The F and CHX varnish applications were performed bi-annually. Microbiological follow-up was continued until the child's age of six years, and caries follow-up of the primary dentition until the child's age of 10 years. In children at two years of age, the colonization percentages were 10% in the Xylitol, 29% in the CHX, and 49% in the F groups (Söderling *et al.*, 2000). Thus, the child's risk of having MS colonization was five-fold in

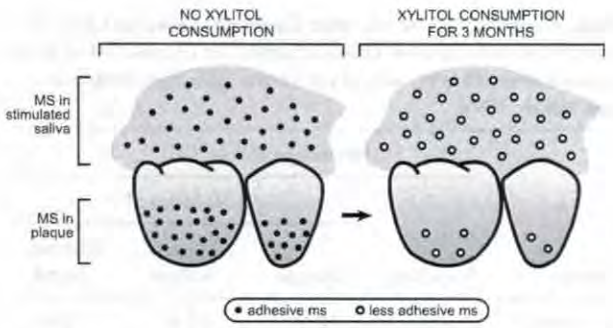

Figure 2. The effect of habitual xylitol consumption on MS may be explained both by a decrease in total counts and by the adhesivity of MS. Xylitol may reduce the synthesis of extracellular polysaccharides *in vivo*, leading to a change in the plaque-saliva distribution of MS. The MS loosely bound to plaque are suggested to be easily shed to the saliva during mechanical saliva stimulation.

the F-varnish group compared with the Xylitol group. The early MS colonization and the early manifestation of caries were in agreement in all groups (Isokangas *et al.*, 2000). In children at the age of five years, the caries occurrence (mean dmf index) was 71% lower in the Xylitol group as compared with the F-varnish group (Fig. 3). Thus, the xylitol intervention had resulted in true primary prevention of caries. The number needed to treat (NNT) of the xylitol intervention group has been calculated from the original data of the study to be 4: Four mothers should chew xylitol gum to keep one child caries-free (Pienihäkkinen, personal communication). The caries occurrence in the F-varnish and CHX-varnish groups did not differ, indicating that the given CHX treatment was not effective. In the microbiological follow-up of children at six years of age, the Xylitol group still showed significantly lower MS counts as compared with the other two groups (Söderling *et al.*, 2001). The 10-year caries follow-up of the primary dentition showed results which were in line with the five-year findings. The need for restorative dentistry was the lowest in the Xylitol group. Cost-benefit/-effectiveness analyses concerning the prevention obtained with xylitol in the mother-child study will be published in the near future (Laitala, personal communication).

In a later study carried out in Sweden with mutans-positive mothers, all groups used chewing gum. The study used basically the same approach as our mother-child study, but the intervention lasted only one year, starting from the child's age of 6 months. The study compared a 100% xylitol gum with gums containing CHX and F. The daily dose of xylitol was low, approximately 2 g *per* day. However, the results of the study were in line with those of the Finnish mother-child study (Thorild *et al.*, 2006). Also, results from a recently completed Japanese study agree with those of both the Finnish and Swedish studies (Nakai, personal communication). However, a study in which mothers chewed xylitol gum for 9 months with a daily xylitol dose of 4.2 g failed to show any effects on the mother-child transmission of MS (Fontana *et al.*, 2009). This finding emphasizes that the duration of the xylitol intervention as well as the xylitol dose (Milgrom *et al.*, 2009) are of importance.

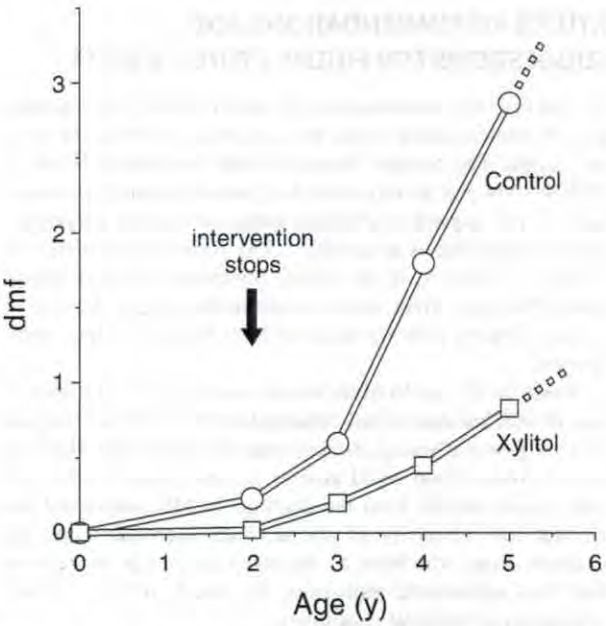

Figure 3. Annual mean dmf indices of children whose mothers had used xylitol chewing gum when the child was 3-24 months old. In children at the age of five years, the caries occurrence was 71% lower in the Xylitol group as compared with the Control group. The arrow indicates the discontinuation of the intervention (data from Isokangas *et al.*, 2000).

XYLITOL AND DENTAL PLAQUE

Intermittent treatment of a mixed culture of oral bacteria with xylitol prevented enrichment of *S. mutans*, while sorbitol had the opposite effect (Table). In the recent study by Badet *et al.* (2008), a biofilm containing 6 bacterial species was exposed to 1% and 3% xylitol. The xylitol exposure significantly inhibited the biofilm formation.

Several clinical studies in healthy individuals have demonstrated a decrease in the amount of plaque in association with habitual xylitol consumption (for review, see Maguire and Rugg-Gunn, 2003). Chewing *per se* does not explain the decrease in plaque, since chewing gum base does not decrease the amount of plaque (Söderling *et al.*, 1997). In clinical trials, xylitol gum has been found to be superior to sorbitol gum in retarding regrowth of supragingival plaque (Cronin *et al.*, 1994; Maguire and Rugg-Gunn, 2003). Xylitol doses decreasing MS counts also reduce the amount of plaque (Söderling *et al.*, 1997; Maguire and Rugg-Gunn, 2003). However, in the case of poor oral hygiene, the otherwise "effective" xylitol dose does not seem to affect the amount of plaque (Merikallio and Söderling, 1995). The lack of effect can be explained by emphasizing that xylitol is a rather inert molecule which is not retained in the oral cavity, and which penetrates plaque only by means of diffusion. Thus, "effective" doses of xylitol may not reduce plaque in individuals with very poor oral hygiene. The mechanism by which xylitol reduces plaque is probably a decrease in the adhesivity of plaque, as discussed above.

XYLITOL RECOMMENDATIONS AND SUGGESTIONS FOR FUTURE XYLITOL STUDIES

Xylitol has been recommended by several dental associations, but recommendations based on systematic literature reviews are scarce. The Scottish Intercollegiate Guidelines Network (SIGN; www.sign.ac.uk) states that "patients should be encouraged to use sugar-free chewing gum, particularly containing xylitol, when this is acceptable". The American Academy of Pediatric Dentistry, in its Policy Statement (www.aapd.org/media/Policies), gives some recommendations on the use of xylitol chewing gum for children from the age of four years onward.

Based on the results of the studies on mother-child transmission of MS, habitual xylitol consumption may be recommended for care-givers of young children under the age of two. Habitual xylitol consumption could also be recommended for persons who should benefit from the decrease in MS counts and the amount and adhesivity of plaque. Such individuals are, for example, those who have an increased caries risk for reasons like fixed orthodontic appliances, dry mouth, old age, mental retardation, or physical disabilities.

In spite of the abundant literature on xylitol, still more research is needed on the mechanisms of action of xylitol. For example, more information is needed on the clinical significance of xylitol resistance, and on the effect of xylitol on the plaque-saliva distribution of MS. Biofilm models could be very useful in xylitol research. Only a few publications exist on the synergistic effects of xylitol and other oral-health-promoting product components. A recent approach combines xylitol with probiotics beneficially influencing the gut microflora (Taipale *et al.*, 2007). Such probiotics, like *Lactobacillus reuteri* and *L. rhamnosus* GG, effective in reducing counts of oral pathogens (for review, see Twetman and Stecksén-Blicks, 2008), could benefit from the presence of xylitol in the product. There is also a clear need for properly designed, randomized, controlled, clinical trials, to demonstrate: (1) the feasiblity of xylitol prevention in different populations with different dietary and oral hygiene habits; (2) suitable delivery vehicles for xylitol; (3) the extent to which xylitol can be "diluted" with other polyols without losing the caries-preventive effects; and (4) the minimum daily dose and frequency required to obtain "xylitol effects" on MS, plaque, and, most importantly, on caries occurrence.

CONCLUSION

Several studies have shown that xylitol, when used in effective doses/frequencies, reduces dental plaque as well as the number of mutans streptococci. Xylitol-based caries prevention has been claimed to be expensive, but if true primary prevention of caries in young children is to be attained, as demonstrated in the mother-child study, it may be worth it.

ACKNOWLEDGMENT

Dr. Sára Karjalainen's valuable comments are gratefully acknowledged.

Table. Comparison of the Microbial Community Before and After 10 Daily Pulses with Glucose, Glucose/Sorbitol, or Glucose/Xylitol (final concentration, 28 mM), without pH Control (data from Bradshaw and Marsh, 1994)

	Percentage of Total CFU*			
		10 Pulses of		
Species	Pre-pulsing	Glucose	Glucose/ Sorbitol	Glucose/ Xylitol
S. mutans	0.2	18.9	40.9	2.6
S. oralis	14.7	1.3	6.2	12.7
S. gordonii	31.5	0.2	0.04	26.5
L. casei	0.1	36.1	6.9	23.0
A. viscosus	0.8	2.3	0.01	0.5
N. subflava	0.2	n.d.	1×10^{-4}	8×10^{-5}
V. dispar	6.6	41.4	45.9	31.1
P. nigrescens	34.5	6×10^{-4}	4×10^{-5}	0.5
F. nucleatum	11.4	2×10^{-4}	0.01	3.1

* CFU = colony-forming unit.

REFERENCES

Aas JA, Griffen AL, Dardis SR, Lee AM, Olsen I, Dewhirst FE, *et al.* (2008). Bacteria of dental caries in primary and permanent teeth in children and young adults. *J Clin Microbiol* 46:1407-1417.

Assev S, Stig S, Scheie AA (2002). Cariogenic traits in xylitol-resistant and xylitol-sensitive mutans streptococci. *Oral Microbiol Immunol* 17:95-99.

Badet C, Furiga A, Thebaud N (2008). Effect of xylitol on an *in vitro* model of oral biofilm. *Oral Health Prev Dent* 6:337-341.

Bradshaw DJ, Marsh PD (1994). Effect of sugar alcohols on the composition and metabolism of a mixed culture of oral bacteria grown in a chemostat. *Caries Res* 28:251-256.

Cronin M, Gordon J, Reardon R, Balbo B (1994). Three clinical trials comparing xylitol- and sorbitol-containing chewing gums for their effect on supragingival plaque accumulation. *J Clin Dent* 5:106-109.

Featherstone JD (2006). Delivery challenges for fluoride, chlorhexidine and xylitol. *BMC Oral Health* 6(Suppl 1):8.

Fontana M, Catt D, Eckert GJ, Ofner S, Toro M, Gregory RL, *et al.* (2009). Xylitol: acquisition of cariogenic species in infants. *Pediatr Dent* 31:257-266.

Haresaku S, Hanioka T, Tsutsui A, Yamamoto M, Chou T, Gunjishima Y (2007). Long-term effect of xylitol gum use on mutans streptococci in adults. *Caries Res* 41:198-203.

Havenaar R, Huis in 't Veld JHJ, Backer Dirks O, de Stoppelaar JD (1978). Some bacteriological aspects of sugar substitutes. Health and sugar substitutes. In: Proc. ERGOB Conf., Geneva, 1978. Basel: Karger, pp. 192-198.

Holgerson PL, Sjöström I, Twetman S (2007). Decreased salivary uptake of (^{14}C)-xylitol after a four-week xylitol chewing gum regimen. *Oral Health Prev Dent* 5: 313-319; *erratum* in *Oral Health Prev Dent* 6:81, 2008.

Isokangas P, Söderling E, Pienihäkkinen K, Alanen P (2000). Occurrence of dental decay in children after maternal consumption of xylitol chewing gum, a follow-up from 0 to 5 years of age. *J Dent Res* 79:1885-1889.

Loesche WJ, Grossman NS, Earnest R, Corpron R (1984). The effect of chewing xylitol gum on the plaque and saliva levels of *Streptococcus mutans*. *J Am Dent Assoc* 108:587-592.

Ly KA, Milgrom P, Rothen M (2006). Xylitol, sweeteners, and dental caries. *Pediatr Dent* 28:154-163.

Maguire A, Rugg-Gunn AJ (2003). Xylitol and caries prevention—is it a magic bullet? *Br Dent J* 194:429-436.

Mäkinen KK, Söderling E, Hurttia H, Lehtonen OP, Luukkala E (1985). Biochemical, microbiologic, and clinical comparisons between two dentifrices that contain different mixtures of sugar alcohols. *J Am Dent Assoc* 111:745-751.

Mäkinen KK, Söderling E, Isokangas P, Tenovuo J, Tiekso J (1989). Oral biochemical status and depression of *Streptococcus mutans* in children during 24- to 36-month use of xylitol chewing gum. *Caries Res* 23:261-267.

Mäkinen KK, Mäkinen P-L, Pape HR Jr, Peldyak J, Hujoel P, Isotupa KP, *et al.* (1996). Conclusion and review of the Michigan Xylitol Programme (1986-1995) for the prevention of dental caries. *Int Dent J* 46:22-34.

Mäkinen KK, Isotupa KP, Mäkinen P-L, Söderling E, Song KB, Nam SH, *et al.* (2005). Six-month polyol chewing-gum programme in kindergarten-age children: a feasibility study focusing on mutans streptococci and dental plaque. *Int Dent J* 55:81-88.

Merikallio MC, Söderling E (1995). Xylitol as a plaque-control agent in military conditions. *Mil Med* 160:256-258.

Milgrom P, Ly KA, Roberts MC, Rothen M, Mueller G, Yamaguchi DK (2006). Mutans streptococci dose response to xylitol chewing gum. *J Dent Res* 85:177-181.

Milgrom P, Ly KA, Rothen M (2009). Xylitol and its vehicles for public health needs. *Adv Dent Res* 21:44-47.

Miyasawa-Hori H, Aizawa S, Takahashi N (2006). Difference in the xylitol sensitivity of acid production among *Streptococcus mutans* strains and the biochemical mechanism. *Oral Microbiol Immunol* 21:201-205.

Söderling E, Alaräisänen L, Scheinin A, Mäkinen KK (1987). Effect of xylitol and sorbitol on polysaccharide production by and adhesive properties of *Streptococcus mutans*. *Caries Res* 21:109-116.

Söderling E, Isokangas P, Tenovuo J, Mustakallio S, Mäkinen KK (1991). Long-term xylitol consumption and mutans streptococci in plaque and saliva. *Caries Res* 25:153-157.

Söderling E, Trahan L, Tammiala-Salonen T, Häkkinen L (1997). Effects of xylitol, xylitol-sorbitol, and placebo chewing gums on the plaque of habitual xylitol consumers. *Eur J Oral Sci* 105:170-177.

Söderling E, Isokangas P, Pienihäkkinen K, Tenovuo J (2000). Influence of maternal xylitol consumption on acquisition of mutans streptococci by infants. *J Dent Res* 79:882-887.

Söderling E, Isokangas P, Pienihäkkinen K, Tenovuo J, Alanen P (2001). Influence of maternal xylitol consumption on mother-child transmission of mutans streptococci: 6-year follow-up. *Caries Res* 35:173-177.

Söderling EM, Ekman TC, Taipale TJ (2008). Growth inhibition of *Streptococcus mutans* with low xylitol concentrations. *Curr Microbiol* 56:382-385.

Taipale T, Pienihäkkinen K, Alanen P, Jokela J, Söderling E (2007). Dissolution of xylitol from a food supplement administered with a novel slow-release pacifier: preliminary results. *Eur Arch Paediatr Dent* 8:123-125.

Tanzer JM, Thompson A, Wen ZT, Burne RA (2006). *Streptococcus mutans*: fructose transport, xylitol resistance, and virulence. *J Dent Res* 85: 369-373.

Thenisch NL, Bachman LM, Imfeld T, Leisebach Minder T, Steurer NL (2006). Are mutans streptococci detected in preschool children a reliable predictive factor for dental caries risk? A systematic review. *Caries Res* 40:366-374.

Thorild I, Lindau B, Twetman S (2006). Caries in 4-year-old children after maternal chewing of gums containing combinations of xylitol, sorbitol, chlorhexidine and fluoride. *Eur Arch Paediatr Dent* 7:241-245.

Trahan L (1995). Xylitol: a review of its action on mutans streptococci and dental plaque—its clinical significance. *Int Dent J* 45(1 Suppl 1):77-92.

Trahan L, Söderling E, Dréan MF, Chevrier MC, Isokangas P (1992). Effect of xylitol consumption on the plaque-saliva distribution of mutans streptococci and the occurrence and long-term survival of xylitol-resistant strains. *J Dent Res* 71:1785-1791; *erratum* in *J Dent Res* 72:87-88, 1993.

Twetman S, Stecksén-Blicks C (2008). Probiotics and oral health effects in children. *Int J Ped Dent* 18:3-10.

Vadeboncoeur C, Trahan L, Mouton C, Mayrand D (1983). Effect of xylitol on the growth and glycolysis of acidogenic oral bacteria. *J Dent Res* 62:882-884.