Cariologic aspects of xylitol and its use in chewing gum: A review

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Several studies indicate that xylitol is not metabolized to acids either in pure cultures of oral microorganisms in vitro or in dental plaque in vivo. Chronic consumption of xylitol-sweetened chewing gum resulted in reduction of dental plaque, suppression of mutans streptococci, and reduced adhesiveness of plaque. So far, four field studies with regimens including chewing gum and other xylitol-containing products and four clinical trials have been carried out. All of the latter studies showed that a daily intake of two to three pieces of xylitol gum resulted in a defined reduction of caries. There are indications that regular and prolonged use of xylitol chewing gum may have a caries-preventive effect. □ *Clinical trials; field studies; mutans streptococci*

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Sugar consumption and dental caries

It is well established that dietary sugars play a crucial role in the development of dental caries (1–4). However, owing to several intervening factors, such as tooth resistance, use of fluorides, salivary properties, and composition of plaque, there is no direct relationship between sugar consumption and caries. Analysis of the relationship between sugar consumption and caries incidence shows that frequent consumption of sugars is clearly associated with caries (5–7). On the other hand, recent reports on a decrease in caries have documented the efficacy of preventive measures, particularly the application of fluorides in toothpaste in combination with maintenance of oral hygiene. These observations have, to some extent, reduced the concern about the adverse oral effects of sugars (8).

One would be misled to conclude from a reported 30% to 80% caries reduction in children that caries is no longer a health problem. A substantial fraction of children still have a high incidence of tooth decay (9–12). Moreover, nearly all epidemiologic studies of caries have been carried out in children. Comparatively little is thus known about the trends in adults. A few recent studies suggest that the caries incidence is still considerable (13, 14) and that in the future, root caries may occur more frequently in the elderly as an increasing number of teeth are retained (15). Therefore, dietary counseling remains important for caries prevention in addition to instruction in oral hygiene and the use of fluorides.

Advice on changing dietary patterns has traditionally concentrated on the frequency of intake of sugar-containing foods (16). Although such measures have been stressed by dentists for decades, their practical effect has remained limited. Recent investigations on dietary habits and snacking suggest that the consumption of sweets is still increasing (17–19). Consequently, it appears logical to emphasize the importance of replacing sugars with noncariogenic sweeteners, especially in foods consumed frequently and known to have high cariogenic potential.

Use of sugar substitutes for caries prevention

One of the main conclusions from the classi-

cal Vipeholm study, published in 1954 (20), was that sugar in sticky, between-meal products was associated with high caries activity. These findings stimulated research on hypo- and non-acidogenic sugar substitutes that do not cause pH falls in dental plaque (21). It was not until around 1970, however, that systematic studies on alternative sweeteners for caries prevention were available (22–24).

The sugar substitutes can be separated into two major groups: noncaloric and caloric. Saccharin, cyclamate, aspartame, and acesulfame-K are examples of the former group. These substitutes are used in low-caloric beverages and as sweeteners in coffee and tea. The caloric group includes sugar alcohols (such as sorbitol, xylitol, and maltitol) and sugars (such as fructose and invert sugar).

Many bacteriologic, animal, and experimental studies in man have been carried out on several sugar substitutes (25). Studies evaluating the cariogenic potential of sweeteners have yielded substantial evidence that xylitol is the most promising sweetener. Several review articles supporting this statement have been published (26–29). In the field of dentistry more than 100 articles containing the word "xylitol" in the title or as a keyword (Medline Computer Basic) were published during the 12-year period 1981–93. The present review aims to focus on the scientific data on xylitol and its use in chewing gum for prevention of dental caries. Most of these studies were published during the past 10 years; however, when relevant, some earlier publications are also included.

Xylitol is a pentitol—that is, a polyalcohol with five hydroxy groups. It occurs naturally in fruits and plants and is manufactured on a large scale by hydrogenation of xylose, mostly extracted from birch. Xylitol, which is isosweet to sucrose, is an intermediate metabolite and has been approved for dietary use in many countries worldwide.

Cariologic aspects of xylitol

Several aspects should be considered when evaluating a sugar substitute from a cariologic point of view (25). The most important issues are 1) metabolism by oral microorganisms, 2) metabolism by dental plaque, 3) influence on plaque quantity and adhesion, 4) effects on counts of mutans streptococci, 5) microbial adaptation, 6) role in de- and re-mineralization, and 7) influence on pH of plaque and on saliva.

Metabolism by oral microorganisms

Several studies have shown that xylitol is not fermented by most oral streptococci or by other microorganisms (30). However, some few strains of *Streptococcus mutans* are able to utilize xylitol as a carbon and energy source in the absence of other carbohydrates (31).

It is well established that xylitol exerts a bacteriostatic effect on mutans streptococci (32–34). The inhibitory effect is apparently due to the entry of xylitol into the bacterial cell via the fructose phosphotransferase system (35, 36). The xylitol 5-phosphate thus formed inhibits bacterial growth, partly by establishing an energy-consuming futile cycle and partly by inhibiting glucose uptake and metabolism (34). Recent studies indicate the existence of an additive effect of fluoride and xylitol on the intracellular accumulation of xylitol 5-phosphate in *S. mutans*, which in turn increases the inhibitory effect on acid (lactate) production in the cells (37).

Ultrastructural studies of *S. mutans* and *S. sobrinus* have shown that the presence of xylitol in the incubation medium results in cell degradation and autolysis, intracellular vacuoles, lamellated formations in the cytoplasmic membrane (38) and in other ultrastructral alterations (39). This presumably constitutes further evidence of a bacteriostatic effect of xylitol on mutans streptococci.

An interesting observation is that the presence of sorbitol in the growth medium enhances the inhibitory effect of xylitol on *S. mutans* (40). The inhibition seems to be dose-related; that is, increasing concentration of xylitol causes lower growth of bacteria (41). Thus, these in vitro studies indicate that mixtures of xylitol and sorbitol with a high xylitol content may have greater inhibitory effect on mutans streptococci than both xylitol and mixtures with low xylitol content. Addition of xylitol to suspensions

of *S. mutans* also inhibits the acid production from sorbitol (42, 43).

Extracellular polysaccharide production from sucrose is considered to be a caries-inducing factor, since these substances, especially of the water-insoluble type, increase the adhesiveness of dental plaque. When sorbitol and xylitol were compared by batch culture techniques, xylitol, in contrast to sorbitol, led to an increase in the production of soluble polysaccharides, paralleled by a decrease of insoluble polysaccharides (44). The increase in the ratio between soluble and insoluble polysaccharides reduced the adhesion of the cells to glass surfaces. This phenomenon might explain the reduced formation of sticky plaque formed in vivo after consumption of xylitol (45).

Metabolism by dental plaque

It is well established that xylitol does not lower the pH of dental plaque in vivo (46) or in vitro (47, 48). This is in contrast to sorbitol, which results in a decrease of the pH of plaque, although much less than sucrose (Fig. 1). It has been speculated that xylitol may have an inhibitory effect on the acid production from sucrose and glucose in dental plaque. The data are conflicting, as some studies have shown such an effect (49), whereas others have failed to demonstrate a direct inhibitory action of xylitol on the acid production from easily fermentable carbohydrates (46). Nevertheless, the nonacidogenicity of xylitol in dental plaque is well documented and probably one of the most important factors related to its noncariogenicity.

When xylitol is consumed frequently and for a long period of time, the metabolism of dental plaque has been found to be altered, resulting in less acid formation from sucrose (50–52). This may be caused by ecologic changes of the microflora or by less dental plaque. Another possible mechanism may be the accumulation of xylitol 5-phosphate in plaque after exposure to xylitol (53–55). It was found that the capacity of plaque to form xylitol 5-phosphate was not reduced during 12 weeks' exposure to xylitol (55). This metabolite is known to inhibit growth and acid formation of mutans streptococci. Further studies are, however, required, before definite conclusions can be drawn about the inhibitory effect of xylitol on the acid production in plaque in vivo.

Influence on plaque quantity and adhesion

Short- and long-term studies have shown that a low dose of xylitol in chewing gum and lozenges reduces the quantity of dental plaque (50, 51, 56). Some studies, however, failed to demonstrate any plaque-inhibitory effect of xylitol compared with sorbitol when using a plaque index (57, 58). In one of these studies (57), however, a mixture of xylitol and sucrose was used, which makes comparison difficult. The explanation of these conflicting observations may be that scoring the plaque by means of an index is a cruder method than a gravimetric method. The effect of xylitol on plaque accumulation is, as expected, more pronounced than that of sucrose. A series of short-term studies showed that xylitol gum in place of sucrose gum resulted in a decrease of plaque (59–63).

Although the plaque-reducing effect of xylitol should not be overemphasized from a cariologic point of view, it may be useful in controlling oral hygiene in extremely difficult conditions. As an example, mentally handicapped children were given an average of 20 g xylitol daily in tablets, consumed after meals for a 2-month period (64). Use of the xylitol tablets improved the state of oral hygiene. A positive effect of xylitol on dental plaque was also found in a population of schoolchildren from poor socioeconomic areas with a high caries rate (65). Thus, use of xylitol gum, distributed three times daily over a 2-year period at school, significantly reduced the plaque index by about 10–20% in comparison with a control group using no gum.

A long-term study, the Ylivieska study, demonstrated that not only the amount but also the adhesiveness of plaque decreased after regular xylitol consumption (66). A follow-up study of habitual xylitol consumers, who continued to use xylitol gums at

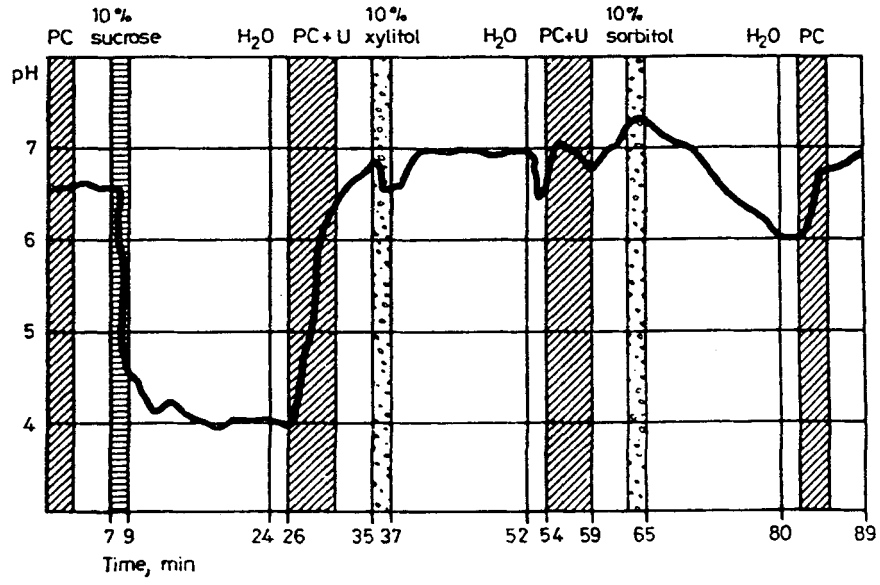

Fig. 1. Telemetrically recorded interproximal plaque pH in a subject with 7-day-old plaque. Paraffin chewing (PC), 10% sucrose rinse, water rinse (H_2O), paraffin chewing and carbamide rinse (PC + U), 10% xylitol rinse, and 10% sorbitol rinse. After Mühlemann et al. (46).

least twice daily for 4–6 years, showed that they had less sticky plaque than the controls not using gums (45).

Effects on counts of mutans streptococci

One of the most interesting effects of xylitol, besides being nonacidogenic, is its ability to reduce the population of mutans streptococci. This has been found in several short- and long-term studies. The mutans streptococci are considered to be closely associated with dental caries activity (67, 68). The reason is that these microorganisms possess a unique combination of properties rendering them more "cariogenic" than other plaque bacteria. Thus, mutans streptococci have a high acid production rate even at low pH and the ability to synthesize extracellular polysaccharides from sucrose.

The effect of sorbitol, xylitol, and a mixture of xylitol and sorbitol in chewing gums was recently compared in adults (51). The plaque and salivary levels of *S. mutans* generally increased in the sorbitol group but decreased in the two groups using xylitol. A clear dose-response effect in this respect (Fig. 2) was recently found in a 3-week cross-over study by Wennerholm et al. (58). Four types of gums, containing 70% xylitol, 35% xylitol and 35% sorbitol, 17.5% xylitol and 52.5% sorbitol, or 70% sorbitol, were compared.

Plaque and saliva samples were analyzed for *S. mutans* from initially 11- to 12-year-old children who participated in a field study designed to test the efficacy of xylitol chewing gum in caries prevention (66). At the end of the 2-year period, the level of these microorganisms was lower in children using xylitol gum than in control children. In a follow-up study among the children who were considered to be at high risk with regard to dental caries, the xylitol-consuming subjects showed significantly lower salivary *S. mutans* counts than the controls (66). An interesting observation was that there was a dose-dependent effect with regard to the decrease of mutans streptococci in plaque and the number of pieces of xylitol gum used per day.

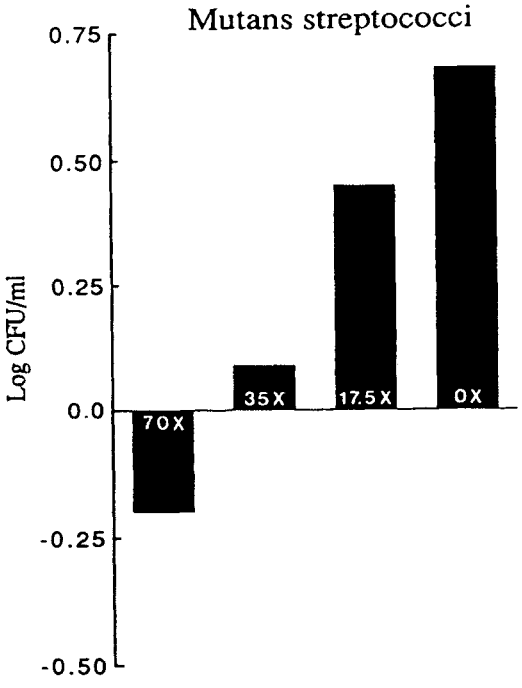

Fig. 2. Mutans streptococci counts in saliva ($n = 17$), expressed as log colony-forming units (CFU), for four different chewing gums, containing: 1) 70% xylitol (70X), 2) 35% xylitol and 35% sorbitol (35X), 3) 17.5% xylitol and 52.5% sorbitol (17.5X), and 4) 70% sorbitol (OX). A bar under the line indicates a decrease and a bar above the line an increase during the 3-week period. After Wennerholm et al. (58).

When 10–20% xylitol was added to a fluoride dentifrice, the level of mutans streptococci in saliva was reduced (69, 70). On the other hand, a recent report on a dentifrice containing only 3% xylitol indicated that the salivary dip-slide scores of mutans streptococci were not affected (71). The absence of an effect may be due to the low content of xylitol in the toothpaste or to the lack of sensitivity of the microbial test.

Microbial adaptation

According to Trahan et al. (72), consecutive periods of growth of *S. mutans* and *S. sobrinus* on glucose in the presence of xylitol in vitro result in a progressive loss of sensitivity to xylitol by the bacterial population. This is a consequence of a selective enrichment of a naturally occurring xylitol-insensitive or xylitol-tolerant mutant lacking the constitutive fructose phosphotransferase system, responsible for xylitol uptake (73, 74). These xylitol-tolerant mutants have been named "xylitol-resistant" (X^R). They are maintained in the oral cavity several years after xylitol consumption (72). X^R strains have also been found in higher numbers in chronic xylitol consumers than in control subjects (75).

The above "adaptation" to xylitol should not be misinterpreted in the sense that there would be an increased risk of acid formation or of ecologic changes as for sorbitol (76), resulting in increased counts of mutans streptococci. Thus, there are no indications that the X^R strains could grow at the expense of xylitol or that they produce acid from xylitol. In this respect, xylitol has an advantage over sorbitol. Long-term use of the latter results in an increase of mutans streptococci paralleled by an increased acid formation from sorbitol in dental plaque (77, 78). Although the clinical consequences of the adaptation to sorbitol have been questioned (79, 80), xylitol has an advantage in this respect as no such adaptation has been observed for xylitol.

Another interesting observation is that the presence of xylitol in a sorbitol-sweetened product seems to inhibit the adaptation of the plaque flora to sorbitol (79). Thus, several short-term chewing gum studies have shown that mixtures of xylitol and sorbitol decrease the number of mutans streptococci and acid production from sorbitol in comparison with pure sorbitol gum (50, 51, 58).

Role in de- and re-mineralization

In the Turku sugar studies (24) there were indications that some of the caries lesions at base line remineralized after 2 years' use of xylitol. This has later been confirmed in a long-term study by Rekola (81), who concluded that xylitol consumption caused remineralization of incipient white spot lesions on buccal tooth surfaces. It might be argued that these changes may be caused by the absence of fermentable carbohydrates in com-

bination with salivary stimulation instead of the effects mediated by xylitol.

Animal experiments have often been used to study the cariogenic potential of carbohydrates. Leach & Green (82, 83) observed that remineralization of caries lesions was facilitated by xylitol and sorbitol. The data further support the concept that xylitol is noncariogenic. Ingestion of high doses of sugar alcohols in the diet has, however, been associated with severe catharsis in rodents. By administering the polyols in solution, this problem may be eliminated, according to observations by Bowen & Pearson (84). These authors concluded that xylitol and other sweeteners added to drinking water resulted in a caries reduction in comparison with negative controls.

Salivary stimulation, with its concominant effect on buffer capacity, pH, and calcium and phosphate concentrations, exerts a remineralizing effect especially on incipient carious lesions. Daily use of sugar-free chewing gum, used for 20 min after each meal or snack over a period of 3 weeks, in combination with daily use of a fluoride dentifrice, enhanced the remineralization potential (85). However, the effect appears not to be specific for xylitol, as recently confirmed in a crossover study with xylitol- or sorbitol-sweetened chewing gum (58). Thus, xylitol and sorbitol remineralized enamel to the same extent. It must be remembered, however, that these short-term experiments do not necessarily predict the difference between sorbitol and xylitol in long-term use.

A possible direct xylitol-mediated influence on enamel de- and re-mineralization has been studied in a series of in vitro experiments (86–89). These studies give some indication of an additive effect of fluoride ions and high xylitol content. Xylitol may "interact with the calcium in enamel mineral and penetrate into demineralized enamel" (86–89). It should be recognized, however, that no comparisons with other polyols were carried out. Thus, further studies are required before any conclusions can be drawn about xylitol and its direct effect on de- and remineralization.

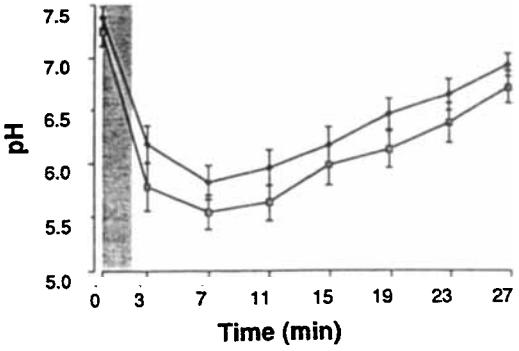

Fig. 3. Stephan curves after a 2-min mouthrinse with 10% sucrose before (open symbols) and after (filled symbols) a 2-week period of frequent use of sorbitol chewing gum. Error of bars indicate the SEM, and hatched bars the period of rinse ($n = 11$). After Dodds et al. (92).

Influence on pH of plaque and on saliva

Chewing of a sugar-free gum has several potentially beneficial effects on dental health (90, 91). During the past 10 years, interest has been focused on using such gums after meals and snacks. Chewing thus resulted in neutralization of low pH of plaque by increasing the buffer capacity of saliva and also in enhanced clearance of fermentable carbohydrates from the oral cavity. It may be expected that sorbitol and xylitol have similar effects in this respect. The reason is that both sweeteners, in combination with chewing and sucking, have an almost identical salivary-stimulating effect. It should be considered, however, that the phenomenon is caused by a single intake and, accordingly, does not reflect the long-term microbiologic changes after repeated dosage.

An interesting observation with regard to daily gum-chewing is the long-term effect of increased mastication on the salivary gland output. Jenkins & Edgar (90) and Dodds et al. (92) found that 2 weeks of daily chewing of sugar-free gum increased the salivary flow, pH, and buffer capacity of unstimulated and stimulated saliva; however, not all of the changes were significant. Moreover, the pH response in plaque to a 10% sucrose rinse was less after the test period than before (Fig. 3). Regrettably, only sorbitol-sweet-

ened gums were tested. In a similar study, however, Söderling et al. (51) found that xylitol-sweetened chewing gum, used for 2 weeks, resulted in a lower acid production from sucrose in plaque than sorbitol gum. The data are thus somewhat conflicting in this respect, which can further be exemplified by the study by Wennerholm et al. (58). They observed that the plaque pH response to a sorbitol rinse, but not to a sucrose rinse, was inhibited by use of xylitol gum over a 3-week period.

Clinical trials of xylitol

The final conclusion about the cariogenicity or noncariogenicity of a sweetener must be based on long-term clinical trials in man. Up to now, the Turku sugar studies (24) and four "field studies" have been published—that is, the WHO field trials in Thailand and French Polynesia (93) and the collaborative WHO xylitol field studies in Hungary (94) and French Polynesia (95).

In the Turku sugar studies, sucrose was more or less totally replaced by xylitol, whereas the field studies were based on partial substitution. They all ran for 2 or 3 years. Although xylitol-sweetened chewing gums were included as an important vehicle in the field studies, several other products containing xylitol, like sweets (Hungary), fluoride dentifrices (Hungary), and fluoride chewing gums (Thailand), were given to the subjects. The conclusion from the almost complete replacement of dietary sucrose by xylitol in the Turku sugar studies was that "xylitol is non or even anti-cariogenic" (24). The main conclusion from the WHO field studies was that "partial sugar substitution by xylitol is a useful tool in preventive caries and should be considered in addition to fluoridation and oral hygiene measures in public oral health programmes" (95).

Clinical trials with xylitol in chewing gum

So far, four long-term trials of xylitol in chewing gums have been conducted: the Turku chewing gum study (96), the Ylivieska study (97), the Montreal study (65), and, recently, the Belize study (98).

The Turku chewing gum study

The subjects (young adults) were assigned to the xylitol or sucrose gum groups on a random basis, in contrast to the trial with total substitution (96). The caries incidence after 1 year, assessed independently by clinical and radiographic means, expressed as the mean increment of decayed (including white spot lesions), missing, and filled tooth surfaces, was 2.9 in the sucrose and −1.0 in the xylitol group. The corresponding values when also considering secondary caries were 3.8 and 0.3, respectively. The authors concluded that "the findings clearly indicate a therapeutic, caries inhibitory effect of xylitol".

The Ylivieska study

The schoolchildren in this study were all participating in organized dental health programs on an annual basis (97). The children were randomly divided into two groups, a xylitol and a control group. On the basis of interviews after 1 and 2 years, the subjects were placed into three subgroups in accordance with the number of xylitol gum pieces used daily. There was a clear dose-response effect; that is, children who used an average of three pieces per day had a more pronounced caries reduction than those with lower frequency of intake. In a follow-up the preventive benefit of xylitol-chewing was more notable during the 3rd year in the high caries groups (97). The authors concluded that "xylitol gum, used 2–3 times per day in combination with basic fluoride prevention, constitutes a strong instrument in caries prevention in caries-active age groups and caries-active individuals. The results also indicate the existence of a cariostatic mechanism induced by peroral xylitol".

Two to 3 years later, the children were re-examined for a possible long-term preventive effect (99). A significant caries reduction was found, especially among the girls. The authors speculated that "the prob-

able explanation for the difference between the xylitol and control groups is the occurrence of microbiological changes in the mouth and/or the maturation of the erupting teeth under favorable physico-chemical conditions". The latter hypothesis was partly confirmed in a microbiologic study of proximal tooth surfaces in a group of former habitual xylitol gum users (100).

The Montreal study

The subjects in this study (101), like those in the Ylivieska study (97), participated in an ongoing preventive dental school program. The participants were at base line assigned to one of three groups, two xylitol groups and one control group. The gums were distributed three times a day by the teacher supervising the 5-min chewing period. Of the original 574 children, two-thirds were examined after 1 year, and half of the subjects after 2 years. After 12 months (101) there was a significantly lower DMFS increment in the two xylitol groups than in the control group. Children who used chewing gum with 65% xylitol had less caries than those who used a gum with 15% xylitol. After 24 months (65) the caries incidence was still lower in the two test groups than in the control group, but the difference between the 65% and the 15% xylitol groups became smaller. The lack of a dose-dependent relationship during year 2 may, according to the authors, be explained by the many dropouts. Nevertheless, "the study demonstrated an impressive reduction in caries incidence with the additional use of xylitol-containing chewing gum in a school preventive programme" (65).

The Belize study

This study was carried out in Belize, Central America, in initially 10-year-old children whose caries rate was moderate or high (98). Altogether 1277 children were divided into 9 groups, one of which received sugar gum. In seven other groups either xylitol or sorbitol gums or gums that contained mixtures of these polyols were consumed. The children in the ninth group received no gum as part of the program. The use of gum was supervised by teachers on about 200 school-days per year and unsupervised or partly supervised by parents and guardians on about 165 days per year. The chewing time at school was 5 min. In gum-using groups the average individual consumption of polyols or sucrose in gum was about 8 to 10 g, normally in the form of five chewing episodes. After 28 months of intervention, the highest mean DMFS scores were found in the two groups using either sugar gum or no gum. The lowest DMFS scores were observed in groups using 100% xylitol gum. The sorbitol gum and the gums containing mixtures of xylitol and sorbitol resulted in somewhat higher DMFS scores than the gum containing only xylitol. However, the data should be interpreted with caution until a full report has been published.

Dental therapeutic claims

Xylitol has been used for many years to replace sugar, mostly in chewing gum. On the basis of several experimental and clinical studies, xylitol is universally accepted to be a "noncariogenic" sweetener. This statement is based on observations that it is not metabolized into acids either in dental plaque or in pure cultures of oral microorganisms. Xylitol may also be classified as "cariostatic", since several short- and long-term studies in man and experiments in animals have shown that xylitol reduces the caries incidence. The claim "anticariogenic" for xylitol has also been suggested, since clinical and experimental studies in man indicate that xylitol promotes the reversal (remineralization) of early caries lesions.

"Cariostatic" and "anticariogenic" are therapeutic claims, whereas "noncariogenic" (or "safe for teeth") could be classified as a health claim (102). Advertisements in dental journals and other magazines have made various claims for xylitol-sweetened products. Although these should be based on strictly scientific data, it is difficult to separate the claims for xylitol as a sweetener and for a xylitol-sweetened product. It is also important to consider the proportion of

xylitol and other components of the product. In Finland, Sweden, and Iceland a manufacturer is allowed to use the special logo approved by the national dental associations when the xylitol content equals or exceeds 50% of the total amount of non- or low-cariogenic sweeteners. Although expressions like "cariostatic" and "anticariogenic" may be relevant to xylitol-sweetened chewing gums, the final decision as to whether such claims are acceptable must be based on national laws and customs.

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