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Mini Review

The Modes of Dental Caries Prevention with Xylitol

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Introduction

The importance of dietary factors in the etiology of dental caries has been acknowledged, and the role of proper nutrition in improving the health of the population cannot be disputed [1]. The American Academy of Pediatric Dentistry (AAPD) acknowledges the benefits of sugar substitutes, particularly xylitol as caries preventive strategies on the oral health of infants, children, adolescents, and persons with special health care needs. Thus, the AAPD has intended a policy about the use of xylitol-based products in caries prevention [2].

The discovery of xylitol is credited to two groups of researchers in 1890, the German chemistry professor Fischer, and the French chemist Bertrand [3]. Xylitol is a natural carbohydrate sweetener that belongs to the pentitols (five-carbon sugar alcohol) [4]. The first trials for xylitol were done in the late 1960s and early 1970s in Turku, Finland [5]. A two-year study showed that subjects who had xylitol in their diets as a substitute for sucrose developed almost no new carious lesions compared to the other groups [6]. Based on Turku study results, several other trials and a large number of laboratory studies ensued. The first significant dental recommendations for the use of xylitol began to appear in the United States' dental literature in the early 1990s. Anderson et al. presented the medical model approach to dental caries incorporating sealants, antimicrobials, fluorides, and xylitol [7].

Use of Xylitol in Dental Practice

The use of xylitol in caries prevention does not require professionals, clinical visits and treatment, equipment, or repeated individual check-ups. Therefore, one can easily start a preventive program with xylitol, while professionals can use their clinical hours to treat subjects with more acute needs [8]. The use of xylitol in dietary foods has been approved by the United States (U.S.) Food and Drug Administration since 1963. It has been introduced for children in different forms, such as candies, gum, syrups, gelatin, in addition to other products like multivitamins, toothpaste, and oral rinses [9]. Chewing gum has been established as the most effective vehicle for the delivery of xylitol to the oral cavity. However, though this may be an effective means of consuming xylitol for most adult populations, it is a limiting factor for its use in small children and as a public health method of intervention in organized preschool programs [10]. Additionally, dentists should emphasize that xylitol chewing gum is an added measure, not a replacement for other preventive programs like fluoride, consciously applied oral hygiene practices and regular dental visits [11,12].

Xylitol-sweetened gum is not as available in the U.S. as are sucrose- and sorbitol-sweetened gums. Evidence showed that xylitol-sweetened gum offers more caries reduction benefits than did sorbitol-sweetened gum. Still, chewing sorbitol-sweetened gum several times per day is better than chewing sugared gum in reducing caries [11,13,14]. Sorbitol is another sugar alcohol that is frequently used in several sugar-free chewing gums and over-the-counter medicines [13,15]. Due to the relatively high cost of xylitol, sorbitol and xylitol are often combined with a better clinical effect than with pure sorbitol [16,17]. Sorbitol should be considered a low cariogenic sweetener rather than a non-cariogenic one because the

consumption of larger amounts increases both the acid production in plaque and the number of sorbitol-fermenting micro-organisms [18].

The long-term effects of xylitol chewing gum have been demonstrated in several studies [19-21]. Teeth erupting after the end of the gum-chewing program showed the most significant long-term caries reductions. For the utmost outcome, chewing xylitol gum should be started at least one year before permanent teeth erupt, i.e., during preschool and early elementary school years [22]. Moreover, several clinical studies provide evidence of the effectiveness of xylitol-sweetened gum in reducing maternal transmission of cariogenic bacteria [23-27]. A range of 6 to10 grams divided into three times per day is necessary for xylitol chewing gum to be useful [19,20,28-30]. The main side effect associated with xylitol consumption is osmotic diarrhea. It usually occurs when consumed in large quantities, four to five times those needed for the prevention of dental caries [31].

Mechanism of Caries Inhibition

Most oral micro-organisms do not ferment xylitol, and its caries-reducing effects have been attributed mainly to this lack of fermentation. However, specific effects on microbial growth and metabolism, on certain salivary factors, and the physicochemical processes of de- and remineralization have also been claimed [32-34].

Effect on bacteria

Dental plaque formation: Several studies have shown xylitol to reduce the amount of dental plaque formation, adhesiveness, and acidogenic potential of dental plaque when compared with the chewing of sucrose-containing gums or not chewing gum [14,35-37].

Bacterial metabolism & growth inhibition: Sugar transport into bacterial cells plays a role in the expression of the virulence (cariogenicity) of *Streptococcus* mutans. The high-affinity phosphoenolpyruvate-dependent sugar: phosphotransferase system (PTS) is the principal route for transporting most sugars in oral *streptococci*. The other two transport systems are: fructose-specific and sucrose phosphorylase [38]. Some carbohydrate sweeteners are neither taken up nor metabolized to acids by *Streptococcus* mutans. Since xylitol possesses a 5-carbon sugar alcohol structure, it is taken up via PTS by *Streptococcus* mutans. Still, it cannot be metabolized to acid and is accumulated as non-metabolizable, toxic xylitol phosphate [most likely xylitol 5-phosphate], resulting in inhibition of both bacterial growth and acid production. Xylitol phosphate is further dephosphorylated to xylitol with the waste of phosphoenolpyruvate potential. This futile cycle can also retard the growth of *Streptococcus* mutans [34,39,40]. Furthermore, xylitol phosphate inhibits several enzymes of the glycolytic pathway (e.g., phosphoglucoisomerase, 6-phosphofructokinase, and pyruvate kinase) [40].

Most of the mutans *streptococci* strains tested (e.g., S. mutans, S. rattus, and S. sobrinus strains) are sensitive to xylitol when grown in the presence of glucose plus xylitol [38,41-46]. Sensitivity to xylitol was defined as an inhibition of the growth of wild-type strains in the presence of xylitol and is thus called "xylitol-sensitive" (X.S.) strains [41]. On the other hand, an earlier in vitro study in 1972 showed that when *Streptococcus* cells were transferred from normal media into xylitol media and the overall bacterial cell metabolism seemed to be retarded. Consequently, the induction of aminopeptidase-like enzymes occurred. It may suggest that the cells were forced to use proteins and peptides to a greater extent for synthetic purposes. After several months of storage in polyol-containing broth, the cells grew almost normally, and the induction of aminopeptidases by xylitol was reduced almost to the level exerted by cells grown in a normal medium. This suggests that xylitol, in long-term use, could be used by oral micro-organisms [47]. Therefore, it is necessary to further investigate mechanisms of effects of xylitol on *Streptococcus* mutans metabolism, especially at the molecular level [48]. Moreover, other in vitro study showed that xylitol is not phosphorylated by the fructose PTS in the presence of fructose.43 Since fructose competes with xylitol for the fructose PTS and prevents phosphorylation of xylitol by *Streptococcus* mutans strains. Therefore, no significant growth inhibition is observed when mutans strains are cultured on fructose or sucrose in the presence of xylitol [41,46]. Such competition between xylitol and fructose for the fructose PTS, could result in selective pressure of variable efficiency. This selective pressure indicates that fructose and sucrose may not prevent the uptake and the phosphorylation of xylitol by growing cells, as was thought previously, and enough growth inhibition could occur. Evidence for a selective pressure by xylitol includes:

1) A variation in the inhibition of the growth of a given strain, depending on the nature of the growth sugar, whether a PTS sugar (glucose, fructose, or sucrose) or a non-PTS sugar (lactose).

2) The emergence, or lack of emergence, of xylitol-resistant populations during growth on any given sugar depending on the mutans species or strains.

3) A variation in the time it takes for xylitol-resistant populations to emerge [46].

Some in vitro studies have studied the inhibitory effect of xylitol on acid production at several pH levels under the strictly anaerobic condition found in the deep layer of dental plaque. At pH 5.5-7.0, xylitol inhibited the rate of acid production from glucose. Also, the activity of phosphoenolpyruvate PTS for xylitol was greater at higher pH resulting in the accumulation of intracellular xylitol phosphate. Though these results were not evident at pH 5.0, and it is suggested that xylitol could be incorporated more efficiently at higher or neutral pH [40,49]. Besides, certain strains of salivary lactobacilli, which are involved in the progression of carious lesions, can metabolize polyols resulting in pH drop to values sufficiently low to demineralize the hard tissues of the teeth. Therefore, the limited information available concerning fermentation rate of these polyols and the formation of various metabolic end products by lactobacilli fermenting these polyols necessitates further studies [50].

The emergence of xylitol-resistant mutants: Long-term consumption of xylitol leads to the emergence of xylitol-resistant mutans populations in humans [41,44,46,51,52]. These "xylitol-resistant" (X.R.) mutants are unable to accumulate the toxic xylitol phosphate due to lack of fructose PTS activity responsible for xylitol uptake and phosphorylation [41,43-45]. Two operons encoded the fructose PTS activity. The fru I gene encodes for a protein that transports fructose and xylitol. Its deletion renders the mutant cell's metabolism and growth resistant to xylitol. By contrast, fru CD gene encodes for a protein that transports fructose but does not transport xylitol. Fru CD deletion does not render the mutant cell's metabolism and growth resistant to xylitol. In xylitol-resistant strains, the fru I gene was deleted.38 A shift from xylitol-sensitive to xylitol-resistant mutans *streptococci* populations in the plaque of xylitol consumers does not necessarily indicate a loss of the anti-cariogenic properties of xylitol. Various preliminary results supported the hypothesis that xylitol-resistant mutants are less virulent and less cariogenic than their wild-type parent strains. A study by Tanzer et al. showed that X.R. strains of *Streptococcus* mutans are of diminished virulence by compromised colonization of the teeth and compromised ability to induce lesions that penetrate dentin [53]. Such characteristics might be beneficial and maybe one of the numerous modes of action of this caries-preventive carbohydrate sweetener. Xylitol-resistant mutants are also persisting many years after the xylitol is removed from the diet [51].

Expression of HSP: Some environmental conditions make living organisms express different adaptive responses that allow survival under the physiological stress created by a new environment. The emergence of mutans populations is not the only way to survive in the new environment. Thermal shock studies led to the discovery of heat shock proteins (HSP), also called stress proteins.54 Stress proteins are generally divided into families: HSP-60 and HSP-70. They are needed for essential cellular functions and adaptation to the environment [55-58]. A study investigating the effect of a xylitol exposure on the expression of HSP-60 and HSP-70 proteins in *Streptococcus* mutans was carried out. The results suggest that xylitol creates a stressful environment that disturbs protein synthesis and reduces the expression of HSP-70 and HSP-60 proteins in the xylitol-sensitive *Streptococcus* mutans but not in the xylitol-resistant natural mutant strain [59]. Since the stressing action of a chemical agent is mediated through its incorporation into the cell; then it could be easy to explain the lack of xylitol effect on xylitol-resistant cells by the absence of xylitol uptake by these natural mutants [60].

Glucan-binding protein C induction: Another adaptive response that allows survival under the physiological stress created by a new environment due to the accumulation of non-metabolizable xylitol phosphates was described by the experiments of Sato et al. [48,61] It was noticed that xylitol has other target sites, i.e., induction of a glucan-binding protein C (GbpC) gene expression. The GbpC protein mediates dextran-dependent aggregation (ddag), which mediates adhesion on surfaces such as dental plaque under normal circumstances. Therefore, for *Streptococcus* mutans, elevated GbpC expression may be disadvantageous to tooth adhesion (i.e., less ability to adhere) depending on how saliva is moving in the oral environment. The results of Sato et al. studies could explain earlier findings by Trahan et al., who observed that the proportion of xylitol-resistant mutans *streptococci* did not increase in dental plaque but did so in saliva as a result of more easily shedding of xylitol-resistant strains from the tooth surface than xylitol-sensitive strains [51]. Moreover, this explanation is often used to explain reduced plaque formation and reduced colonization of mutans *streptococci* after frequent use of xylitol [62].

Effect on demineralization and remineralization process

Data analysis from clinical and laboratory studies support the hypothesis that xylitol promotes remineralization and can arrest established dental caries in children [63-65]. Another study showed that histologic and physiochemical changes in dentin caries lesions, which are typical of arrested (rehardened) lesions were more seen in subjects with regular long-term use of xylitol chewing gum than other subjects. The hard, although thin surface layer could be attributable to the precipitation of calcium phosphate salts in the lesion's outer zone, enclosing the advancing caries process. The propagation of the process requires that the micro-organisms that have invaded the tissue continue to receive nutrients. The availability of nutrients is impaired by the formation of a hard barrier and by the washing action of saliva [66]. This suggests that xylitol, in addition to its non-cariogenic effect, may have therapeutic effects. More studies are needed to support the caries inhibitory benefits of xylitol.

Effect on saliva

Peroxidase activity: Lactoperoxidase belongs to the natural defense mechanisms of the oral cavity; it is attributed to the possible inhibition of lactobacillus and *Streptococcus* growth. It was found that the overall salivary peroxidase activity was increased fourfold to tenfold in persons receiving a strict xylitol diet for two years. It is suggested that the xylitol-induced elevation of the salivary lactoperoxidase activity and the anticarcinogenic properties of xylitol are partly interrelated phenomena [67].

Salivary flow stimulation: Undoubtedly, increased saliva secretion results in a higher salivary pH, buffer capacity, and glucose clearance. Since saliva stimulation is typical for all chewing gums, it was practically impossible to measure the role of salivary stimulation by xylitol chewing gum in all studies in this field [68]. Aguirro-Zero et al. studied the effect of chewing xylitol gum on the salivary flow rate by comparing four groups: no gum, sucrose, sorbitol, and xylitol gum. The findings did not show any significant effect on the salivary flow [69].

Clearance of oral cavity: Chewing of any gum could have a mechanical cleaning effect, but do not affect *Streptococcus* mutans

counts. In a study by Soderling et al., there was no effect on either the amount of plaque or the numbers of *Streptococcus* mutans in plaque and saliva in the placebo base group. They concluded that polyols are active ingredients of chewing gums that can modulate the amount of plaque and its microbial composition [35]. However, the importance of chewing would also explain why gum pellets with a harder texture were more effective in caries prevention than were softer gum sticks, as demonstrated in the Belize study [28,70]. Moreover, the frequency of chewing may be more important than the actual daily dose of xylitol. In the study by Isokangas, the chewing of xylitol gums containing 3.5g xylitol three times daily (total daily dose, 10.5g) reduced caries incidence significantly, whereas 7 to 9g of xylitol, chewed fewer than three times, gave no significant reduction in caries increment [71].

Conclusion

Xylitol is a natural sugar substitute with anti-cariogenic properties. Data from earlier studies indicate that xylitol can reduce the occurrence of dental caries in schoolchildren and young children via their mothers. Several mechanisms have demonstrated the anti-cariogenic effect of xylitol: reducing mutans *streptococci* counts, inhibiting plaque accumulation and enamel demineralization, and enhancing remineralization of early lesions. The effective daily dose of xylitol is 6 to 10g, divided into 3 to 5 times chewed for a minimum of five minutes after meals. There is a demand for providing less expensive xylitol-containing products that should make it more accessible to public health programs directed to high-risk preschool populations.

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Conflict of Interest

No conflict of interest.

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