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Use of Polyols in Oral Biology Research

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1. Introduction

The use of polyol (sugar alcohol) sweeteners in oral biologic research has predominantly stemmed from their anticipated non-cariogenicity in human nutrition and their inclusion in certain oral hygiene products (such as dentifrices) as humectants. The wide-spread use of polyols in food manufacturing, and in pharmacologic and cosmetic products, presumes that the oral effects of polyols must be well researched. The metabolism and safety of most of the common dietary polyols is indeed well known. Occasional reports on polyols applied in biomaterials research have also been published. Most alditol-based information published in the field of dentistry has generated from caries-associated research. Most studies have unfortunately dealt with xylitol and D-glucitol (sorbitol) only, leaving researchers unaware of the potential of other alditols. From the dental and nutritional point of view, however, naturally only alditols with sufficient sweetness have raised interest, since they have been originally used as sweeteners, i.e. to replace sugar in confectioneries and other food items. Several medical applications, however, rely on the osmotic effects of alditols, such as D-glucitol and D-mannitol.

What makes polyols chemically such interesting research objects in biomedicine? The chemical and physiologic rationales behind the interest in polyols generate from their ubiquitous presence in nature, their promising applications in various fields of medicine and technology, and their well-known molecular structure and metabolism. The latter aspects have been reviewed in numerous articles and can be summarized as follows:

i. The common dietary polyols, such as erythritol, xylitol, D-glucitol, D-mannitol, and related alditols (the term used in the subsequent text to include the above and similar molecules) are normal constituents of virtually all living tissues in the plant and animal kingdoms, although significant differences exist between species, and, regarding plants, also between seasons. Since simple straight-chain polyols can be regarded as reduced forms of corresponding aldoses and ketoses, it is possible that the corresponding alditol molecules preceded aldoses and ketoses in the chemical evolution in the early oxygen-poor environment of the Earth. Synthetic dietary disaccharide polyols include maltitol and lactitol. Hydrogenated glucose or maltose syrups may contain higher polyols consisting of more than two monosaccharide units. Industrial-scale polyol syrups often derive their sweetness from D-glucitol and maltitol, with traces of reducing sugars also contributing to sweetness.
ii. The above alditol molecules are characterized by the absence of a reducing carbonyl group, by the chemical reducing power they can exert in biologic environments (owing to the "extra" hydrogen atoms present in the alditol molecules), by their complexation

ability (alditols can complex, for example, calcium atoms, designated as Ca(II) below), by their free-radical-scavenging ability, by their ability to strengthen hydrophobic interactions of proteins (increasing protein stability), by their hydrophilicity, and other properties.

Regardless of the above, general polyol properties, all polyols naturally also exert their own specific effects on metabolic processes and, therefore, on health and disease. Therefore, from a physiologic point of view, alditols cannot be regarded as identical substances; their metabolism and detailed physicochemical properties differ. Each member of the homologous series also affects the nutrition and metabolism of cariogenic and periodontopathic organisms differently. In the present article, this homologous series consists of tetritols, pentitols, and hexitols, containing 4, 5, or 6 hydroxyl groups, respectively. The diverse effects of these substances on mammalian and microbial metabolism result from the detailed molecular configuration and ability to interact with water molecules. The simple ladder structure formulas of several alditols are shown in Fig. 1. The structures shown include some alditols whose oral biologic effects have not been studied but which, based on their detailed chemical configuration, warrant future investigation as potential chemical effectors of dental plaque.

Several text books and research papers have elucidated the chemistry and physiology of alditols in detail (Carr & Krantz, 1945; Lohmar, 1962; Touster & Shaw, 1962; Mills, 1974; Angyal et al., 1974; Gekko & Satake, 1981; Georgieff et al., 1985; Mäkinen, 2000, 2010, 2011). There is an ever-growing body of research describing the medical, pharmaceutical, nutritional, technical, cosmetic, and other applications of alditols. The volume of such investigations is simply too overwhelming for any review article to cover them all. Therefore, this review will predominantly focus on the following oral biologic processes or conditions where alditols have been shown to exert specific oral biologic effects: 1) complexation of Ca(II) and stabilization of the salivary Ca(II) phosphate system; 2) nitrogen and protein metabolism of whole-mouth saliva and dental plaque, and their carbohydrase activities; 3) oral counts of mutans streptococci (MS), and growth of dental plaque. A substantial number of "forgotten", significant oral biologic studies were conducted during the 1970s and 1980s. The importance of some of the results obtained then presumes their re-evaluation. Consequently, this review will first recall some important earlier observations made in this field of oral biology, and will subsequently discuss reports on new applications of alditols in oral biologic research where specific alditol effects, listed under (*ii*) above, are assumed to play a role. Specifically, these earlier observations will focus on MS, on the microbial and chemical composition of dental plaque and whole-mouth saliva, and on certain aspects of periodontal disease and gingival inflammation. The alditols will be examined together, which should render their comparison convenient. A few studies outside oral biology will finally be mentioned owing to their possible relevance to future dental research.

2. The significance of the "extra" hydrogen atoms

Important polyol properties include— the chemically reduced state of the alditol molecules, as compared to the corresponding ketoses and aldoses. This chemical feature plays a role in all oral biologic effects of alditols. The multifaceted nature of the biomedical effects of alditols thus receives a chemical explanation when one examines the chemical profile of the alditol molecules. Alditols are substances that can produce abundant NADH and NADPH.

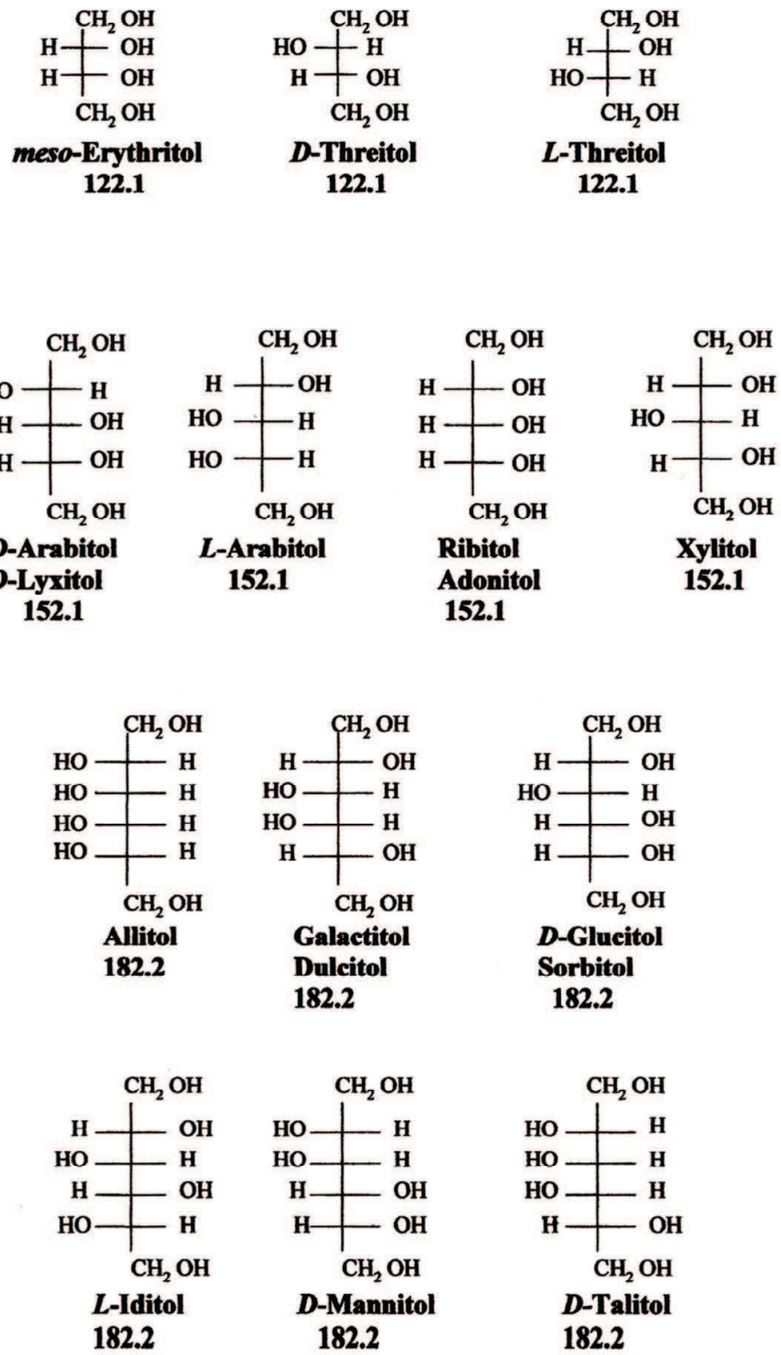

Fig. 1. Simple "ladder" structure formulas of several alditol molecules. The molar mass of each alditol is shown with one-decimal accuracy (in g/mol). It is important to recall that the differences between the molar masses play a significant role in the metabolic fate of these molecules in dental plaque and in the human body after ingestion. Although no oral biologic research has been carried out on some of the rare alditols shown, they are included here since their molecular configuration and conformation may bring about interesting oral biologic effects

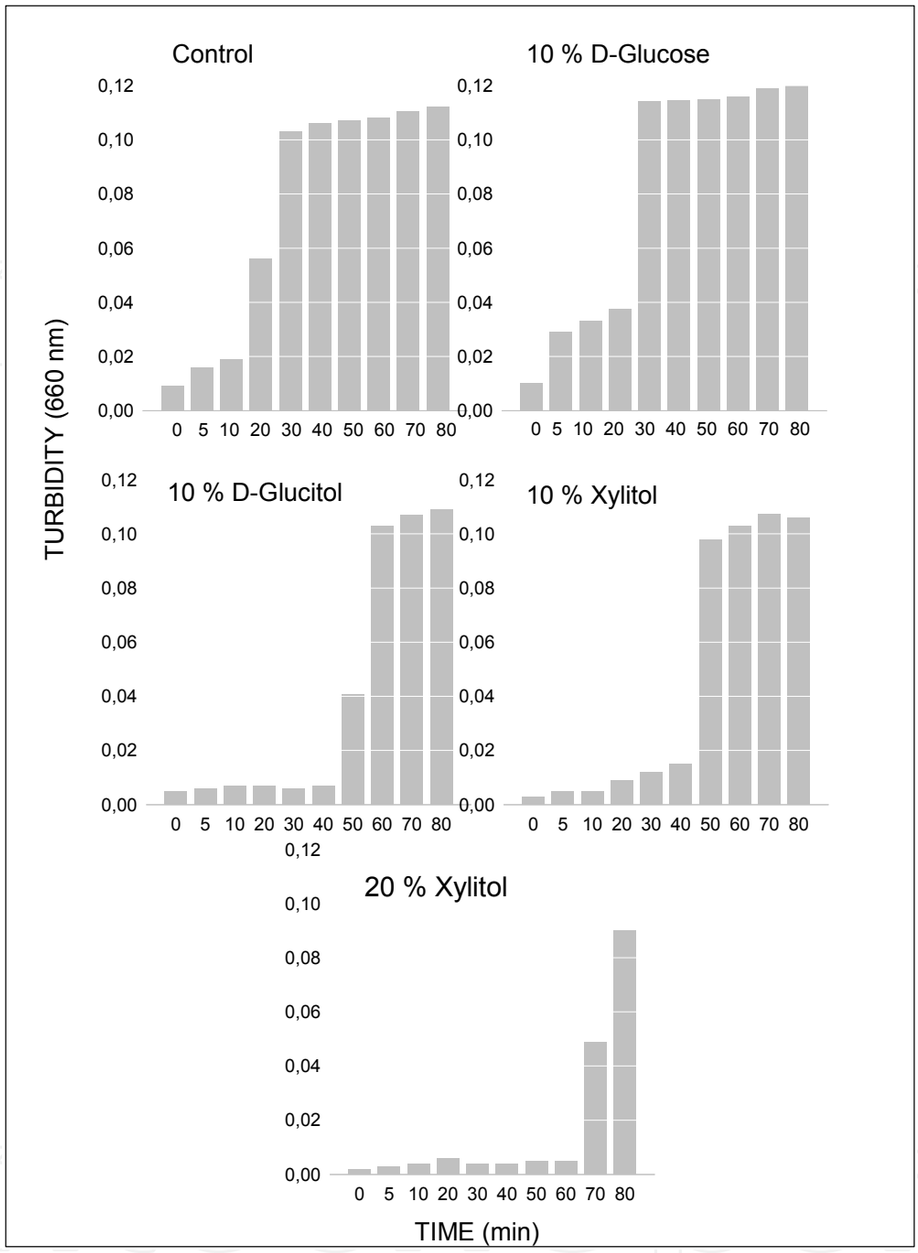

Fig. 2. An example of the stabilizing effect of alditols on the calcium phosphate system in an aqueous solution at pH 7.4. Inhibition by D-glucose, D-glucitol, and xylitol of Ca(II) phosphate precipitation at 37°C. The reactions were carried out using $CaCl_2$ as the source of Ca(II) and NaH_2PO_4 as the source of phosphate (starting Ca(II) and phosphate concentrations were 2.40 mM and 1.44 mM, respectively). The formation of Ca(II) precipitates was monitored over a period of 80 min by measuring the turbidity of the mixtures at 660 nm. The procedures have in principle been described in Mäkinen & Söderling, 1984

These reduced forms of coenzymes can in turn affect the cellular redox potential, which in turn can regulate the levels of other coenzymes and hormones. The alditol molecules can thus be regarded as reservoirs of "extra" hydrogen atoms which can be enzymatically

deposited onto other molecules, eventually generating reduced forms of coenzymes (such as NADH and NADPH). Alditols are of the type $(CH_2O)_n2H$, whereas aldoses and ketoses are of the type $(CH_2O)_n$.

Dental plaque contains microbial enzymes that can convert aldoses and ketoses to their corresponding alditols. Using aldoses as precursors, the formation and naming of some alditols can be shown as follows:

Precursor	Alditol
D- or L-erythrose + 2H	erythritol (*meso*-erythritol)
D-arabinose + 2H	D-arabitol (D-arabinitol)
D- or L-ribose + 2H	ribitol (adonitol)
D- or L-xylose + 2H	xylitol
D-glucose + 2H	D-glucitol (sorbitol)
L-glucose + 2H	L-glucitol
D- or L-galactose + 2H	galactitol (dulcitol)
D-mannose + 2H	D-mannitol

In the same way maltose + 2H results in the formation of maltitol and lactose + 2H in the formation of lactitol, respectively. The term *meso* (used above with erythritol) stands for optical inactivity owing to internal compensation in the molecule. Some sources use the *i*-prefix. These erythritol prefixes have been omitted in the present text.

3. Biochemical consequences in dental plaque after ingestion of alditols

3.1 Stabilization of the Ca(II) phosphate system by alditols; effect on protein stability

Complex formation between carbohydrates and metal cations is a well-studied bioinorganic research area. Complexation of Ca(II) with alditols, such as erythritol and xylitol, may play a role in the remineralization of caries lesions—an interesting possibility that has been discussed elsewhere (Mäkinen, 2010, 2011). In the present review, another oral biologic effect of alditols will be recalled: stabilization of the Ca(II) phosphate system of the oral cavity. This effect is predominantly directed at the solubility of salivary (or plaque fluid) Ca(II) and phosphate, rendering their prolonged, dissolved, supersaturated state possible, compared with the effects of, say, sucrose, D-glucose, or D-xylose, or similar non-polyol carbohydrates. The latter substances tend to initiate instantaneous precipitation of Ca(II) and phosphate from saliva, thus eliminating a part of those substances from remineralization. Consequently, the alditols' role in whole-mouth saliva and plaque fluid is one of stabilization: Ca(II) and phosphate are stabilized in the presence of alditols and will remain in solution even at supersaturated concentrations. Although the stability constants of the Ca(II)-alditol complexes in simple and well-characterized chemical mixtures are known, no such information is available on the possible differences between alditols in complex biological systems, such as saliva and plaque fluid. In principle, this alditol-associated stabilization of the Ca(II) and phosphate system resembles the one caused by innate salivary polypeptides, such as statherin. One particular biological role of those peptides is to govern the precipitation/crystallization kinetics of Ca(II) and phosphate in the oral cavity.

The above stabilizing effect will be illustrated here first in a simple aqueous solution consisting of Ca(II) and phosphate (Fig. 2). Depending on conditions, calcium phosphate salts will eventually start to precipitate in the mixture. The formation of precipitates can be graphically followed by measuring the turbidity of the mixtures at 660 nm. Fig. 2 shows the

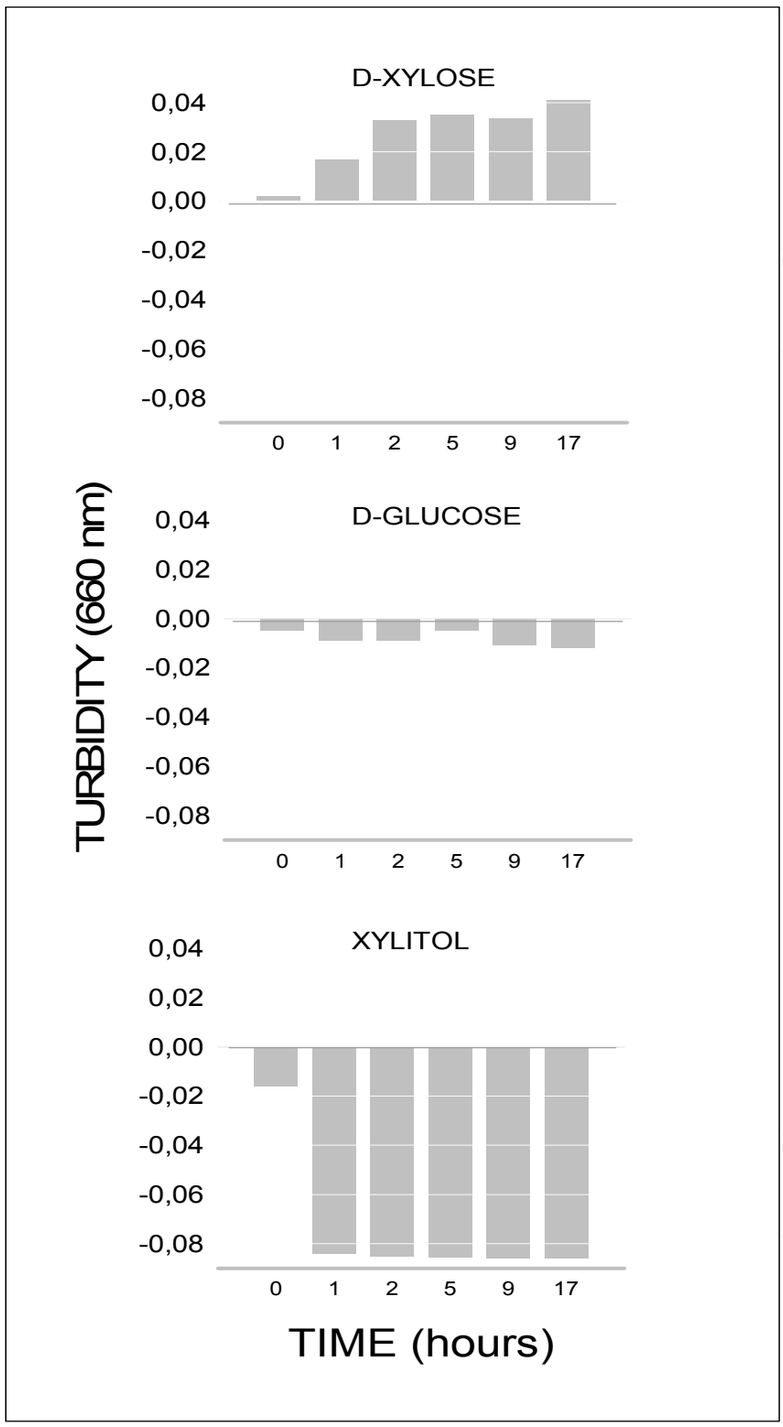

Fig. 3. Stabilizing of the Ca(II) phosphate system by 10% xylitol in human whole-mouth saliva (following centrifugation and Millipore-treatment of saliva) at 37°C in long-term incubations (17 h). The stabilizing effect of xylitol (shown by negative turbidity development) was compared with that of two aldoses (10% D-xylose and 10% D-glucose). Adapted from Mäkinen et al., 1989

pronounced stabilizing effect, observed during a period of 80 min, of 10% and 20% xylitol, and of 10% D-glucitol, on the Ca(II)-phosphate system, compared with 10% D-glucose. The stabilizing effect of the alditols and D-glucose differ significantly. Fig.3 illustrates a similar stabilizing effect observed over a period of 17 h, measured in Millipore-treated human whole-mouth saliva. Again, in the presence of 10% xylitol, a clear stabilizing effect was observed as compared to D-xylose and D-glucose. Fig. 4 in turn depicts a similar experiment with a commercial dextran preparation, D-xylose, and xylitol, this time monitored over a period of 120 min. Clearly, the polyol nature of the alditols played an important role in the system's stabilization. The stabilizing effect prevailed under the conditions described over at least a period of 17 h (Fig. 3). The exact biological role of this stabilizing effect on oral health is not known. However, these effects are real and based on well-researched basic physicochemical properties of alditols. Although several alditol effects on oral bacteria can be predominantly explained in terms of bacterial biochemistry, the above complexation and stabilizing aspects cannot be ignored.

Another specific property of alditols (or polyhydroxy alcohols in general), is their ability to protect protein molecules against denaturation (such as unfolding) caused by heat and other physical and chemical factors. The physical chemistry of these effects has been actively researched (Gekko & Satake, 1981; reviewed in Mäkinen, 1985). A recent paper (Liu et al., 2010) elucidated the molecular mechanism of structural stability of a protein (chymotrypsin inhibitor 2) in polyol solutions (glycerol, xylitol, D-glucitol: also trehalose and sucrose were included). The protein protection by polyols was positively correlated with the molecular volume and the fractional polar surface area. There was preferential hydration on the protein surface, and polyol molecules clustered around the protein at a distance of about 4 Å (Liu et al., 2010). Such preferential exclusion of polyols leads to indirect interactions, preventing the protein molecule from unfolding. The water structure also becomes more ordered with the increase of the molecular weight of the polyol. The bearing of these effects on oral health is not known. However, the point here is to elucidate the versatile effects alditols can exert on biological systems in general. Therefore, even when an investigating team focuses on one particular feature (such as the growth of MS) in an alditol-based clinical program, all of the above-described physicochemical, bioinorganic, and physiologic effects of alditols act simultaneously with full force.

3.2 Nitrogen and protein metabolism; carbohydrase activities

Remarkable differences between sucrose- and xylitol-consuming subjects were found in the activity levels of combined invertase-sucrase enzymes obtained from whole-mouth saliva and dental plaque (Fig. 5). The consumption of xylitol significantly reduced the activity levels of these enzymes. These studies did not reveal which enzyme group, invertases or sucrases, was involved, but an important point here is that both enzymes can be regarded as sucrose-splitting, and thus as sucrose-exploiting. Reduced sucrose-hydrolyzing capacity in whole-mouth saliva (which normally contains large quantities of plaque bacteria) and in dental plaque itself is most likely associated with reduced acidity in dental plaque. Xylitol loading tests have shown that also the activity levels of salivary amylase are affected: consumption of sucrose increased these activities, whereas xylitol consumption reduced them significantly (Fig. 5). Such results can be regarded as normal and expected: habitual consumption of larger quantities of a carbohydrate substrate normally elicits the formation of enzymes that hydrolyze those substrates or which are otherwise involved in the latter's metabolism.

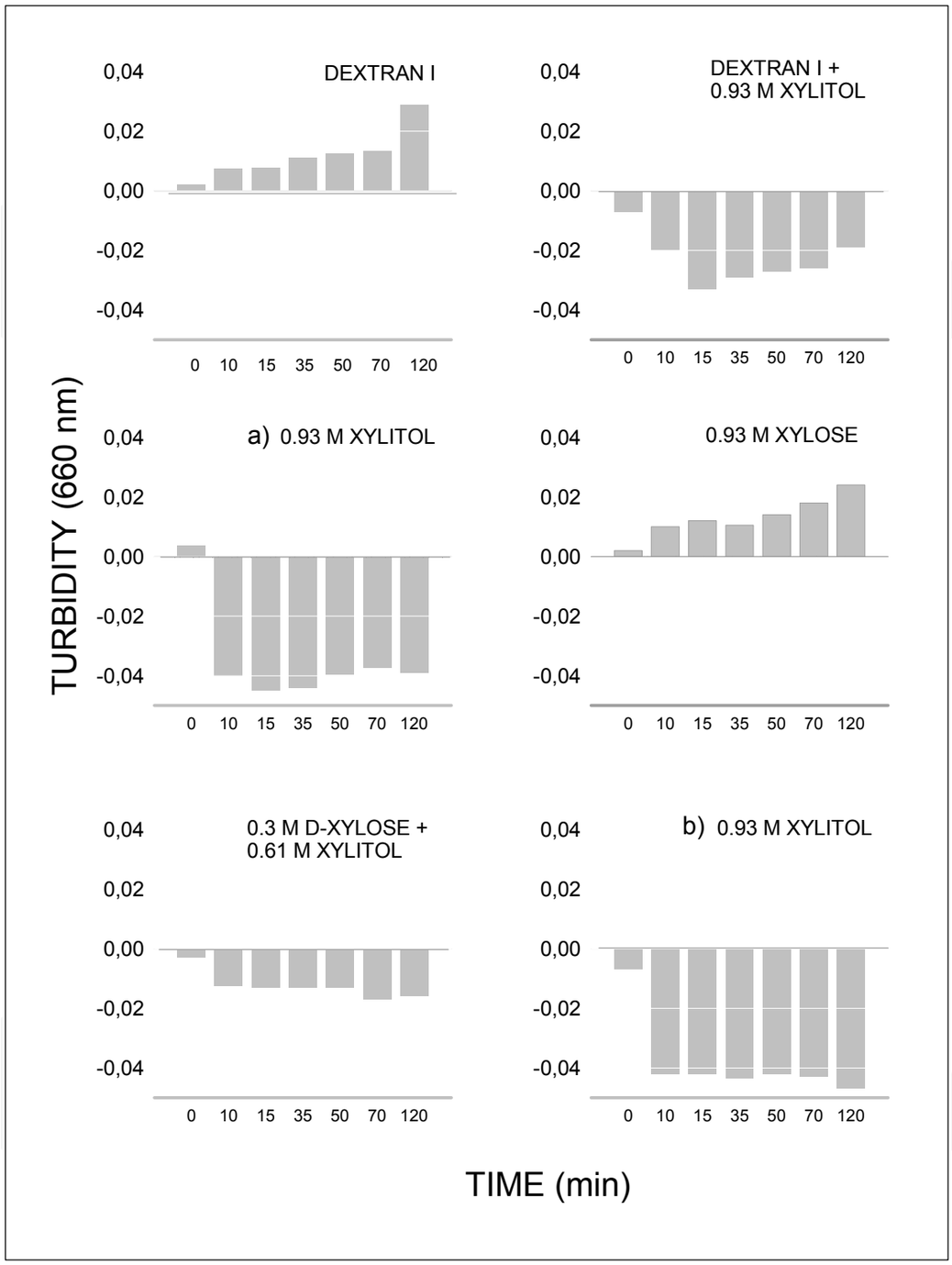

Fig. 4. Stabilizing of the Ca(II) phosphate system by xylitol in human whole-mouth saliva (following centrifugation and Millipore-treatment of saliva) at 37°C in short-term incubations. The stabilizing effect was monitored by measuring the turbidity of the mixtures at 660 nm and was compared to the effect occasioned by "dextran I" (1×10^6 – 2×10^6 daltons) and 0.93 M D-xylose. 0.93 M xylitol prevented turbidity formation over at least 120 min (negative values). a) and b) represent two separate tests with 0.93 M xylitol. Adapted from Mäkinen et al., 1989

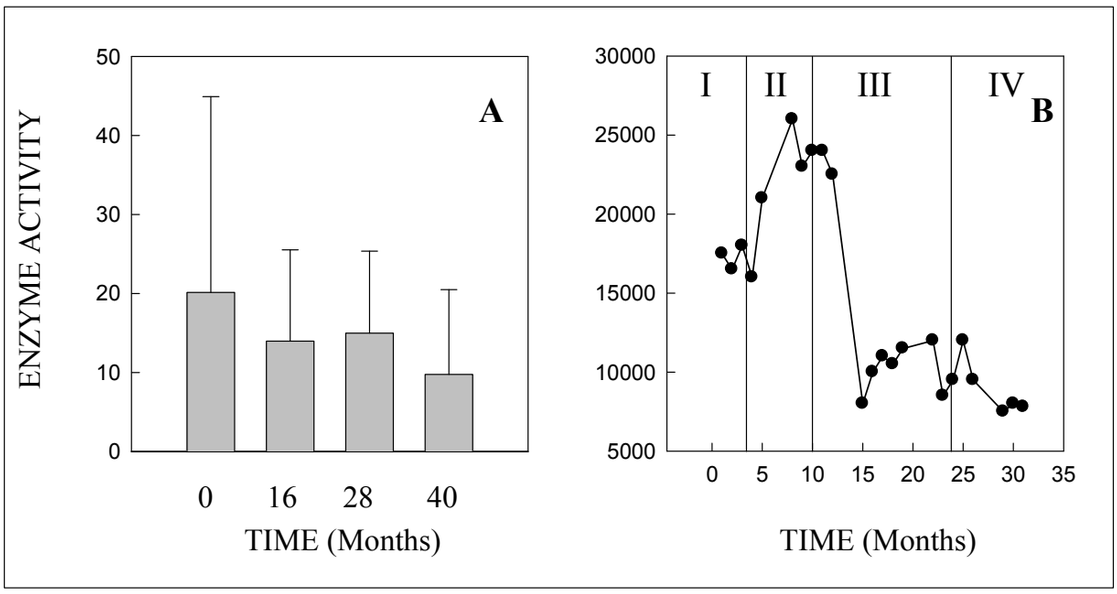

Fig. 5. Examples of the effect of habitual xylitol consumption on carbohydrate-splitting enzymes present in human whole-mouth saliva. Panel A: Activity levels of the combined invertase-sucrase system in initially 8-year-old subjects during 40-month use of xylitol chewing gum (maximum daily intake of xylitol: 9 g per subject). The difference between baseline and 40 months was significant ($p<0.05$) and indicative (p value approach significance) between baseline and 16- and 28-month measurements, respectively. The enzyme activity was determined by means of the neocuproine assay which measures the amount of reducing sugars formed (in nmol/min/mg). The data were adapted from Mäkinen et al. (1966) which also described the general methodology used. Panel B: Activity levels of whole-mouth saliva amylase in a 30-day xylitol loading test consisting of period I (normal diet), period II (formula diet + 70–100 g of sucrose daily), period III (formula diet + 70–100g of xylitol daily), and period IV (normal diet). The study was carried out on nine adult subjects who had habitually used xylitol during a period of 4.3 to 5.3 years. The enzyme activity is shown in amylase units per ml. Note the strong dependency of enzyme activities on the presence of xylitol in daily diet. Low activity levels persisted during period IV (no measurements after day 31 were made). The general methodology was described by Mäkinen et al. (1982). The data are from the present author's files

The partial metabolic inertness of xylitol in human dental plaque leads to various biochemical phenomena that clearly differ from those associated with the consumption of sucrose or hexitols. Provided that the consumption levels of xylitol are large enough, such as those consumed by the Turku Sugar Study subjects (i.e. 10-100 g/day) (Mäkinen & Scheinin, 1975), the plaque microorganisms may become deprived of their preferred substrates (such as C_6-based carbohydrates) and start to synthesize extracellular proteolytic enzymes for the hydrolysis of proteins and peptides present in the medium. For example, when cells of *S. mutans* (strain Ingbritt) were maintained in a medium containing xylitol instead of D-glucose, the cells showed no measurable uptake of ^{14}[C(U)]-xylitol, but exhibited strong increase in the extracellular proteinase activity (Fig. 6) (Knuuttila & Mäkinen, 1981). Xylitol thus behaved as an inert carbohydrate with respect to increases in the extracellular proteolytic activities. This observation is most likely associated with a general increase in

protein and nitrogen metabolism upon starvation of a fermentable carbohydrate (D-glucose). Similar increases in proteinase activities, although not as pronounced, occurred in whole-mouth saliva and dental plaque when high quantities of xylitol were consumed. Owing to the obvious non-specificity of the proteinases discovered, they may attack salivary proteins and peptides *in vivo*. Increased proteinase activity against denatured haemoglobin was found in whole-mouth saliva of subjects habitually receiving high amounts of xylitol. Because saliva contains glycoproteins, it may be considered understandable that the activity levels of plaque glycosidases also increased during xylitol consumption (Mäkinen & Scheinin, 1975). These metabolic events may be related to decreased use of gluconeogenetic enzymes in dental plaque. The nitrogen and protein metabolism are simultaneously increased. Thus, when sucrose is replaced with xylitol, there is an increased search for metabolizable proteinaceous substrates of the medium (i.e. saliva and plaque extracellular phase), with a concomitant increase in the general nitrogen metabolism. Consumption of larger quantities of xylitol thus also leads to an increase in the size of the free amino acid pool of saliva and to a decrease in the production of lactic acid in plaque. The increase of the pool of free amino acids also renders higher deamination rates possible. This can in turn boost the production of ammonia in dental plaque, a phenomenon that has been observed to take place in long-term and short-term xylitol feeding studies (Mäkinen & Scheinin, 1975; Pakkala et al., 1981). The presence of D-glucose in the growth medium of *S. mutans* reduces the pool of free amino acids while the presence of xylitol increases the size of the pool.

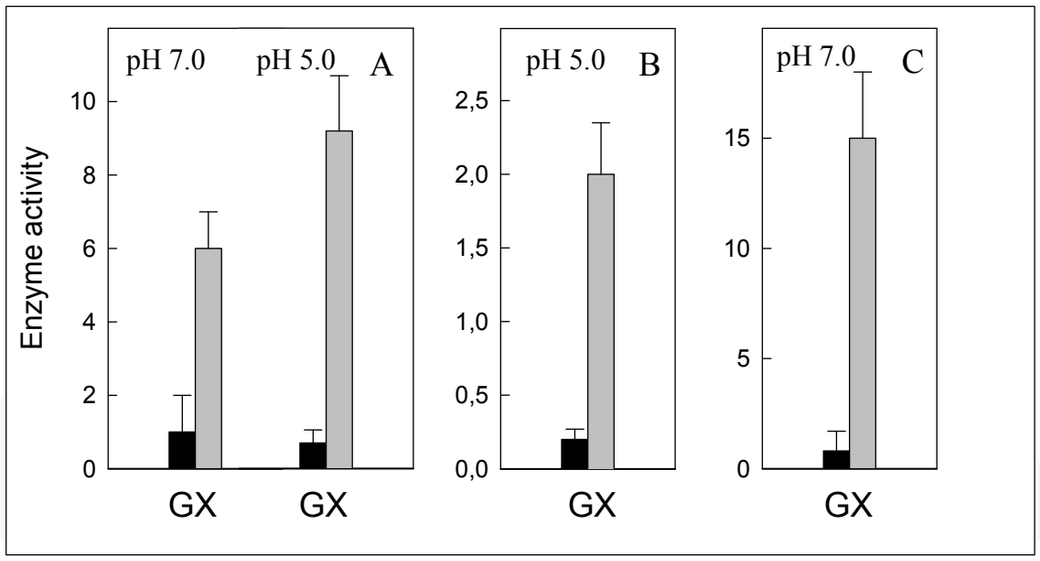

Fig. 6. Extracellular hydrolase (proteinase) activity of the cells of the oral bacterium *Streptococcus mutans* (strain Ingbritt) grown on D-glucose (G) or xylitol (X). The illustration demonstrates the appearance of new or enhanced proteinase activity when the bacterial cells were stored in the presence of 0.25% xylitol or 0.25% D-glucose (for 18 months) at 5°C. The induced proteinase activity supported the growth of the cells and was associated with generally increased protein and nitrogen metabolism of the xylitol-grown cells. Panel A: Hydrolysis of casein at pH 7.0 and 5.0. Panel B: Hydrolysis of a chromophore-collagenase substrate (4-phenylazobenzyloxycarbonyl-L-prolyl-L-leucylglycyl-L-prolyl-D-arginine dihydrate) at pH 5.0. Panel C: Hydrolysis of native collagen at pH 7.0. General methodology is described in Knuuttila & Mäkinen, 1981. The data are from the present author's personal files

The above findings suggest that quantification of dental plaque by means of its protein and nitrogen content cannot be correct. Plaque grown in the presence of xylitol may contain increased protein and nitrogen levels although its volume, mass, adhesiveness, and other caries-associated properties may have decreased. Thus, studies exploiting nitrogen assay of plaque, and claiming that xylitol therefore increases plaque growth (Scheie et al., 1998), do not necessarily reflect the true clinical situation.

3.3 Effect of alditols on oral bacterial counts and dental plaque

Oral biologic literature is replete with studies on the effects of alditols on the growth and metabolism of MS, lactobacilli, and occasionally other oral bacteria and yeasts. A large number of long-term and short-term studies have attempted to evaluate the effects of alditols on the mass and adhesiveness of dental plaque. Typical examples of such studies will be discussed below.

The World Health Organization-associated field trials in Hungary included various oral biologic studies which unfortunately have received little attention. One of those studies investigated 3-year habitual use of fluorides or xylitol on the visible plaque index (VPI) in 688 institutionalized children initially aged 7 to 10 years (Szöke et al., 1985). Although the determination of the VPI may be regarded as a relatively rough clinical procedure, the consistent pattern of the results increases confidence in the results (Fig.7). Regardless of the age group investigated, the VPI values remarkably and consistently declined during the last intervention year in children who had received xylitol. These results are in agreement with those obtained in other long-term xylitol intervention studies, such as the Turku Sugar Studies, which demonstrated a 50% reduction in plaque growth in xylitol-consuming subjects (Mäkinen & Scheinin, 1975). The total number of experiments showing xylitol to reduce the growth and adhesiveness of dental plaque currently amounts to over fifty, with fewer than ten showing a nugatory plaque-reducing effect.

Most studies have shown that D-glucitol and D-mannitol, owing to their hexitol nature, support the growth of MS and dental plaque. Erythritol in turn has been shown to reduce the growth of MS almost to the same extent as xylitol (Mäkinen et al., 2005), although published information is still scant (reviewed in Mäkinen, 2010). Recently, Yao et al. (2009) reported in a Chinese study that the growth and acid production of *S. mutans* were higher in low (2% and less) concentrations of erythritol than in similar concentrations of xylitol, while they were lower at higher (<8%) erythritol levels than at corresponding xylitol levels. This finding may support an earlier (Mäkinen et al., 2005) contention that the mechanism of the inhibitory effect of erythritol and xylitol on the growth of MS differ, and that perhaps combinations of these alditols may turn out to be effective in caries limitation. Another Chinese study reported that maltitol chewing gum may lead to similar reduction of dental plaque as xylitol chewing gum (Li, 2010).

Several recent studies have confirmed the generally accepted idea that xylitol exerts a special growth-retarding effect on MS (Ribelles et al., 2010; Paula et al., 2010; Fraga et al., 2010; Duane, 2010; Söderling et al., 2011; Campus et al., 2011). The study by Duane (2010) demonstrated that children receiving 4.24 g xylitol daily (in five chewing episodes) in the form of chewing gum showed reduced bacterial counts even when the gum contained hexose-based polyols. This study also emphasizes a point that has received serious attention owing to occasional implementation of clinical trials whose very design has nullified the anticipated xylitol effects already in advance (Mäkinen, 2010, 2011). Some points of concern

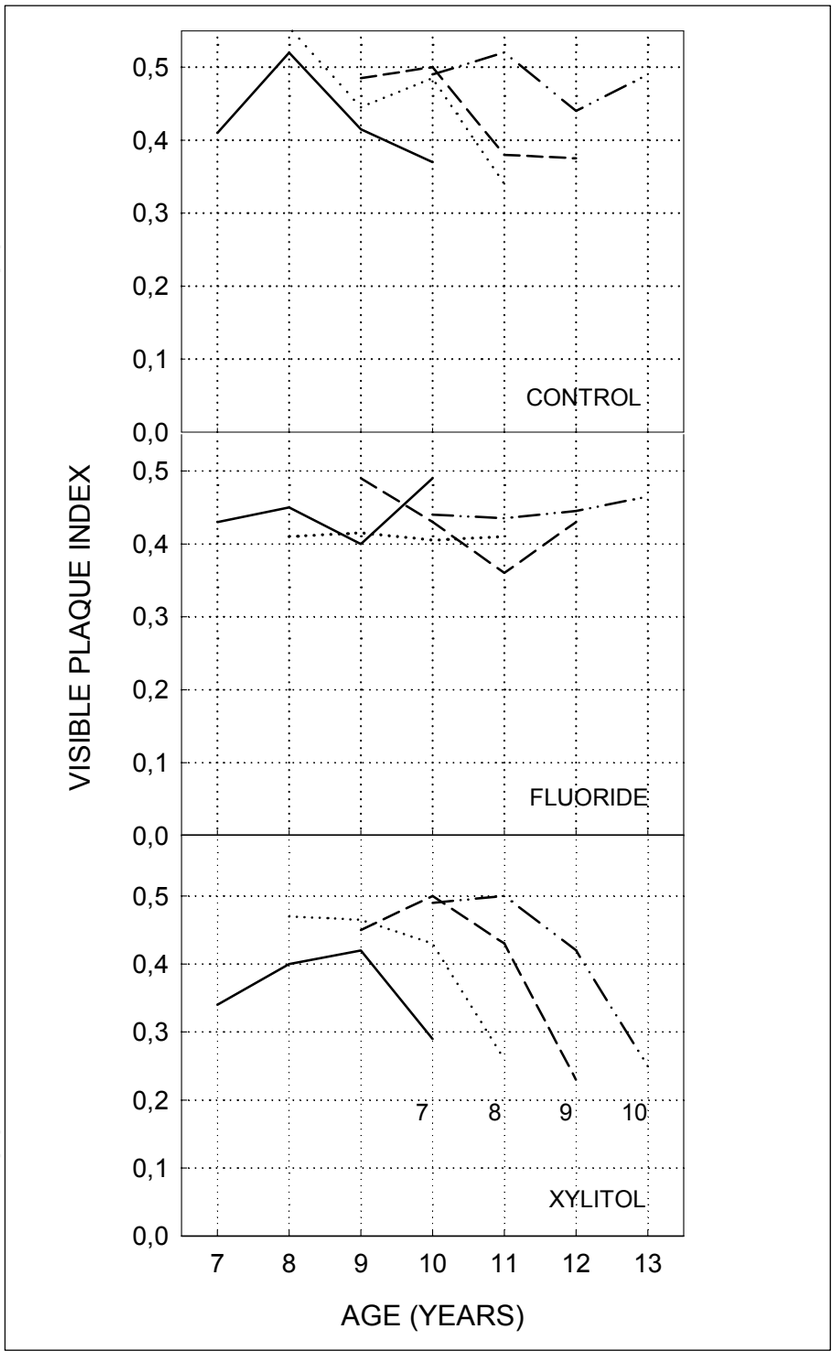

Fig. 7. Effect of three-year xylitol and systemic fluoride treatments on oral hygiene in institutionalized children aged 7 to 10 years at baseline. Oral hygiene was assessed by means of the visible plaque index (VPI). The baseline ages are shown in the lower panel. Fluoride was administered in milk or drinking water and xylitol (maximum daily intake 20 g per subject) was consumed in the form of confectioneries. Note the change in the xylitol group VPI values during the last year of the study, and the consistent pattern of VPI decrease in all age groups. Adapted from Szöke et al., 1985

are that in the recruitment of subjects, it has not always been considered whether the subjects harbour sufficiently high oral MS counts and whether sufficiently frequent daily exposure to xylitol has been observed. Several studies have impoverished the xylitol program by using too-small daily xylitol doses that have been administered only three times per day in subjects with relatively pronounced caries resistance. In most successfully completed studies the daily xylitol dose has been at least 5–10 g per subject.

The study by Söderling et al. (2011) in turn re-emphasizes the close biochemical relationship between plaque MS and xylitol. Xylitol reduced the counts of these bacteria in dental plaque while the effect of salivary MS levels was nil and the microbial composition of the dental plaque (and whole-mouth saliva) in general was not affected. Since the enamel hydroxyapatite surface constitutes the natural growth site of MS in humans, the presence of those organisms in whole-mouth saliva normally results from shedding of the bacteria from plaque. Therefore, determination of oral counts of MS should normally be carried out on dental plaque, although several reports do exist on successful effects also in whole-mouth saliva provided that the growth of dental plaque has been abundant and the plaque MS levels high. The report by Campus et al. (2011) suggested that a combination of xylitol and magnolia bark extract reduces the salivary MS levels, plaque acidogenicity, and bleeding on probing.

The above findings and earlier clinical observations on the caries-limiting role of xylitol receive interesting support from the Raman spectroscopy studies of Palchaudhuri et al. (2011), who suggested that uptake of xylitol by Gram-positive and Gram-negative pathogens occurs even in the presence of other high-calorie sugars. Stable integration of xylitol within the bacterial cell wall may discontinue bacterial multiplication. Much earlier animal experiments by Havenaar et al. (1984) showed that xylitol can limit dental caries even when mixed with a highly cariogenic diet.

4. Alditols in periodontal research

Laboratory experiments and clinical studies have not reported periodontally detrimental effects upon the use of xylitol and D-glucitol in the diet. There is no information on the effect of other alditols on periodontal and gingival health. Differentiation between xylitol and D-glucitol has been difficult, although xylitol, owing to its pentitol nature, has been more effective than D-glucitol in reducing the growth and adhesiveness of dental plaque. More specifically, researchers have come to the following conclusions concerning the relationship between xylitol and periodontal disease: 1) No known periodontopathic organism seems to use xylitol as an important energy source; 2) Xylitol inhibits the growth of several periodontopathogens; 3) Xylitol consumption reduced the adhesiveness of dental plaque (Rekola, 1981); 4) *In vivo* experiments using a hamster cheek pouch microcirculation system suggested that gingival exudate obtained from xylitol-consuming subjects was less inflammatory than that obtained from subjects who received regular sucrose diet or fructose diet (Luostarinen et al., 1975); 5) A bone culture experiment indicated that xylitol plaque was less inflammatory than plaque obtained from sucrose-using substrates (Tenovuo et al., 1981); 6) A study in which 5-day old dental plaque was tested suggested that xylitol plaque was less irritating to macrophages and bone tissue than sucrose plaque (Mielityinen et al., 1983); 7) A study involving experimental gingivitis showed that xylitol mouth rinses were periodontally less harmful than sucrose rinses (and equal to non-sugar Na-cyclamate rinses) (Paunio et al., 1984); 8) A later hamster cheek pouch microcirculation study suggested that

sucrose plaque (obtained after sucrose rinses) caused inflammation to a much greater extent than plaque obtained from subjects who used xylitol or Na-cyclamate rinses (Luostarinen et al., 1984); 9) Two consecutive experiments on young subjects indicated that the use of chewable tablets and candies containing xylitol was associated with reduced plaque mass and lowered gingival bleeding (Harjola et al., 1978; Pakkala et al., 1981). More recently, xylitol was shown to inhibit cytokine expression by a lipopolysaccharide from *Porphyromonas gingivalis*, which is one of the suspected periodontopathic organisms (Han et al., 2005).

One of the laboratory studies that has dramatically illustrated the differences that may occur between dietary sugars is number 4) above (Luostarinen et al., 1975). Fig. 8 shows results from hamster cheek pouch microcirculation measurements involved in the study in question. Gingival crevicular exudate that was obtained from subjects who habitually consumed a xylitol-containing diet was significantly less inflammatory to microcirculation than plaque received from sucrose- or fructose-consuming subjects. The difference shown between the three dietary carbohydrates can be considered remarkable and may in part explain why long-term xylitol administration has in general turned out to be periodontally harmless.

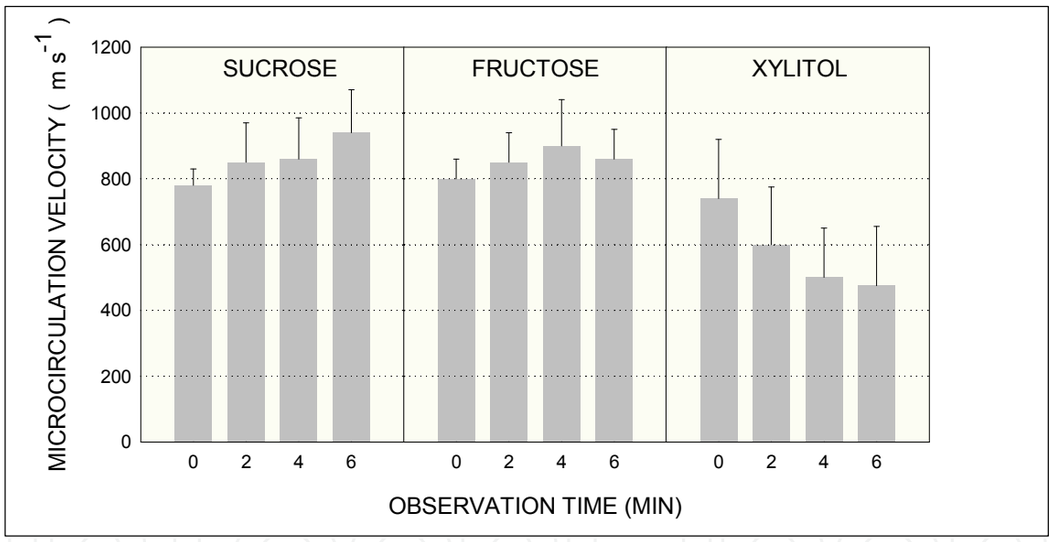

Fig. 8. Effect of gingival exudate on the microcirculation of hamster cheek pouch. Gingival exudate samples were obtained by means of a filter paper method from subjects who had habitually used sucrose, fructose, or xylitol diets over a period of 12 to 13 months. The exudate samples (normally 10 µl) were investigated by means of an intravital microvasculature study using hamster cheek pouches (adapted from Luostarinen et al., 1975). The velocity of circulation was determined at 110x magnification using the "flying spot technique". Measurements of corpuscular velocity were performed every 30-60 sec during the first 6 min. The values shown are means±SD. The number of subjects was 8 in the sucrose and fructose groups, and 14 in the xylitol group

A similar intravital technique was used to assess the response to microcirculation of plaque extracellular fluid (Fig. 9) (Luostarinen at al., 1984). The samples of dental plaque were obtained from subjects who had refrained from oral hygiene for a period of 12 days. During

this period, the subjects rinsed their mouth six times a day either with 0.4 M xylitol, 0.4 M sucrose, or 0.01 M sodium cyclamate solutions. Plaque fluid obtained from the sodium cyclamate and xylitol groups produced a slight increase in the blood velocity in the microcirculation, whereas plaque fluid obtained from the sucrose group displayed a strong decrease in velocities. Consequently, plaque fluid and gingival exudate caused opposite effects on microcirculation, exemplifying the complex nature of the pathophysiological responses involved. However, the occurrence of leucocytes and their attachment to capillary walls diminished after the application of plaque fluid from the xylitol and sodium cyclamate groups. The levels of histamine at the site of irritation in the cheek pouch were highest after treatment with plaque from the sucrose group. However, these results generally suggested that long-term neglect of oral hygiene with simultaneous use of sucrose mouthrinses increases the capacity of dental plaque to cause inflammation and that rinsing the mouth with a xylitol solution is much less inflammatory. These tests essentially compared sucrose with xylitol and leave the question of the effects of other alditols unanswered. However, an important point here is to recall earlier results that have received less attention but provide impressive evidence on the oral biologic differences that can exist between dietary sweeteners.

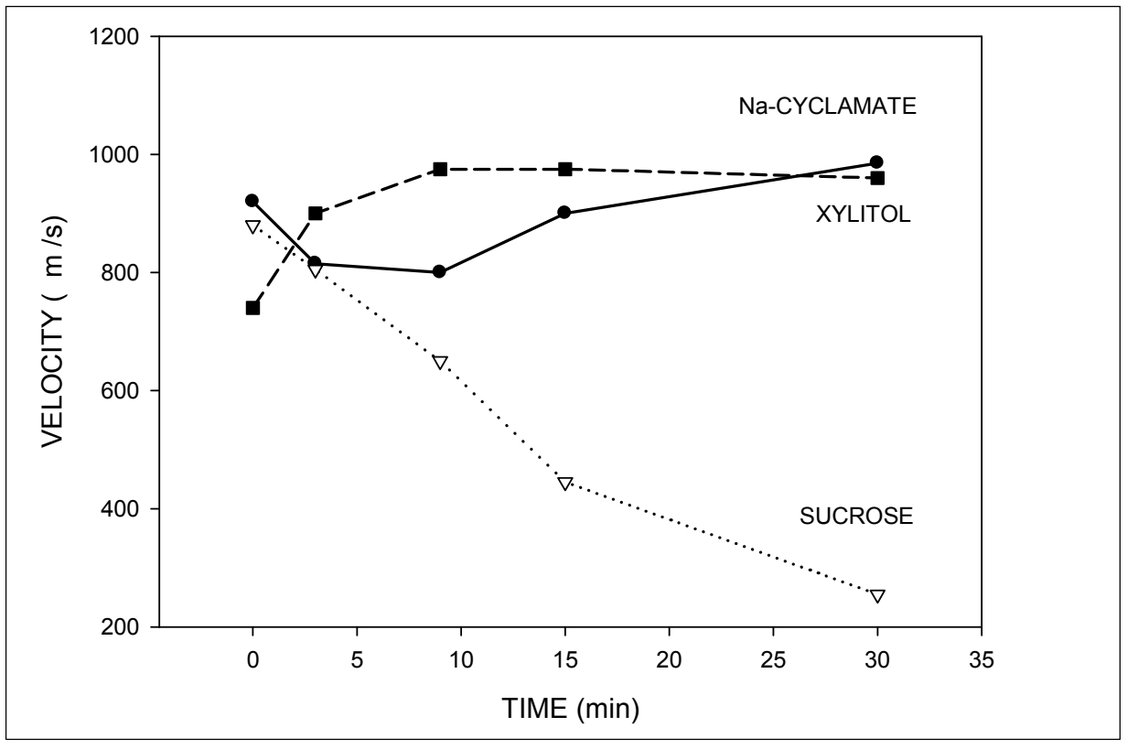

Fig. 9. Effect of the extracellular fluid of dental plaque on hamster cheek pouch microcirculation. Plaque fluid was obtained from young adult subjects who refrained from oral hygiene over a period 12 days and who rinsed their mouth during this period with aqueous solutions containing either sucrose (0.4 M), xylitol (0.4 M), or Na-cyclamate (0.01 M) (n = 11 in each group). The curves show the effect on microcirculation by pooled plaque fluid. The effect on microcirculation by 10 µl samples was measured as in Fig. 8. Measurement with individual plaque samples followed the general pattern shown. Adapted from Luostarinen et al. (1984)

5. Comments on the use of alditols in nutrition

Although several sugar alcohols may generate interest owing to their chemical effects on dental plaque and dental caries, a number of practical reasons limit their application. Firstly, the sweetness of some alditols and higher polyols may be insufficient from the point view of consumer acceptance. The sweetest sugar alcohols seem to be xylitol and erythritol, whose sweetness, as assessed by most test panels, is comparable to that of sucrose. The sweetness of D-glucitol and D-mannitol is about 0.5 compared to the value (1.0) given for sucrose. Another feature of dietary sugar alcohols is their normally slow rate of absorption. This may cause osmotic diarrhoea in unadapted subjects, particularly if the consumption levels are high. This property is common to all slowly absorbed substances, such as D-fructose. In the case of sugar alcohols, the cathartic effect naturally depends on the molecular weight of the substance, D-glucitol (a hexitol), for example, being more effective than xylitol and erythritol (a pentitol and a tetritol, respectively). Erythritol, owing to its small molecular weight, normally causes no harmful gastrointestinal effects. De Cock and Bechert (2002) ranked some common dietary polyols based on the maximum bolus dose not causing laxation. D-glucitol had the lowest value, i.e. 0.17 (in g/kg body weight), while xylitol, maltitol, and isomalt gave a value of 0.3, which can be compared to that of 0.66, assessed for erythritol. Habitual use of dietary sugar alcohols often leads to increased tolerability.

6. Recent advances made in biomaterials and other biomedical research

Some alditols, such as erythritol, xylitol, and D-glucitol (along with ethylene glycol and glycerol) have been tested as dentine primers (Ohhashi et al., 1997). Contraction gap formation was completely prevented in an aqueous solution of 62.5% ethylene glycol (wt/wt), although 37.5% erythritol was also effective. The other alditols were less effective. Since the required polyol levels were very high, the mechanism of action of the polyols tested must be related to their pronounced hydrophilicity and replacement of water molecules. Earlier studies had shown that esterification of methacrylate with glycerol and erythritol also prevented the formation of a contraction gap by a commercial light-activated resin composite (Manabe et al., 1991). Both esters thus contain hydrophobic and hydrophilic groups. The above tests with mere polyols suggest that hydrophobic interactions may not be necessary in the process.

In a study investigating the biocompatibility of dental restorative materials, ascorbic acid increased in a dose-dependent manner the toxic effect of most of those restorative materials tested (Soheili Majd et al., 2003). However, D-mannitol was found to neutralize the toxicity of ascorbic acid. Another application of xylitol resulted from its polycondensation reactions with sebacic acid (1,8-octanedicarboxylic acid). The substances synthesized can be used as biodegradable elastomers. These elastomers exhibited increased biocompatibility compared with, for example, poly(L-lactic-co-glycolic acid) (Bruggeman et al., 2010).

Using a particular wound biofilm model, Dowd et al. (2009) showed that biofilm formation was completely inhibited by 20% xylitol and 10% erythritol. More specifically, xylitol displayed an increasing inhibitory effect on *Pseudomonas aeruginosa* at all concentrations tested, while erythritol had an inhibitory effect on *P. aeruginosa* and *Staphylococcus aureus* at over 5% concentrations. Also these findings support the contention that the biochemical

mechanism of action of erythritol and xylitol on common pathogenic microorganisms can differ remarkably. Biofilm production was also effectively controlled using a combination of xylitol and chlorhexidine (Paula et al., 2010). Xylitol also interfered with the biofilm formation by *Streptococcus pneumoniae* and lowered the autolysin-encoding gene lytA expression levels (Kurola et al., 2011). However, the presence of D-glucose and D-fructose abolished the xylitol effect. This is an important observation that should be considered when planning clinical trials on xylitol in otitis media patients.

Although xylitol cannot be said to prevent dental erosion, it may be possible to alleviate this problem by first eliminating the erosion-inducing conditions and adding a suitable xylitol program to the treatment strategy. Using bovine enamel as a model, 20% xylitol treatment appeared to partially reduce enamel erosion (Souza et al., 2010; Rochel et al., 2011). Indirectly related to these findings is the potential of xylitol as a component in saliva stimulants designed for Sjögren-syndrome patients (de Silva Margues, et al., 2011). Since xylitol may act effectively in preventing irritative dermatitis, suppressing the sodium lauryl sulphate-induced transepidermal water loss (Korponyai et al., 2011), it is possible that xylitol (along with glycerol) could indeed be tested as a potential constituent in saliva substitutes designed for Sjögren-syndrome patients.

Results with possibly remarkable practical value were reported by Uittamo et al. (2010) who showed that 0.11 M xylitol can inhibit the formation of carcinogenic acetaldehyde (produced from ethanol) by *Candida* species. Xylitol reduced acetaldehyde production from ethanol below the mutagenic level of 40-100 μM.

The team of Knuuttila et al. have shown during the past 20 years that dietary alditol administration can elicit beneficial effects on the bone and connective tissue metabolism of rats (earlier studies reviewed in Mäkinen, 2000). Recently, these contentions received support in a study by Sato et al. (2011): bone density increased in the femurs of rats receiving 10% and 20% xylitol in their diet. These results should be contemplated against the ability of xylitol to complex with Ca(II), as discussed in several connections (Angyal et al., 1974; Mäkinen, 2000, 2010).

Finally the potential of erythritol as a safe and efficacious sugar substitute in oral biologic applications must be emphasized. Regarded as a "sweet antioxidant" (de Cock & Bechert, 2002; den Hartog et al., 2010), this alditol has been shown to yield promising results in preliminary caries and laboratory tests (dentally related literature reviewed in Mäkinen, 2010). Potential future alditol applications may include the study of combinations of erythritol and xylitol. Such studies are indeed warranted because it is possible that the mechanism of action of these alditols on MS differ (Mäkinen et al., 2005), making their combined effects additive and possibly clinically more effective than when using either one of these alditols separately.

7. Conclusions

Most of the polyols discussed in this review are simple dietary alditols or disaccharide sugar alcohols. These molecules are characterized by several common "polyol properties" such as the absence of reducing chemical groups in the molecular structure, pronounced hydrophilicity, ability to strengthen hydrophobic interactions of protein molecules, tendency to form complexes with divalent cations, and other properties. Each alditol or disaccharide polyol also constitutes a unique molecular species of its own; these polyols are

by no means exactly identical regarding their physiologic and pharmacologic effects and their detailed chemical behaviour in biological environments. Therefore, oral biologic research can benefit from the diversity of these specific polyol effects. Although regular medical and physicochemical researchers have been familiar with the existence of specific polyol effects, some oral biologic and dental researchers have experienced difficulties in adopting this inevitability. Numerous ordinary physicochemical papers have routinely reported important differences between alditols. Such differences often result from differences in water activities in alditol solutions which in turn lead to different networks of hydrogen bonds that differ from alditol to alditol. Physicochemical research has shown that the mobility of water molecules around each individual oxygen atom of the alditol molecule differs remarkably, resulting in differences in the chemical behaviour of the alditol. Such differences are eventually likely to manifest themselves also in biological systems.

Regarding oral pathological processes such as dental caries and periodontal disease, decisive factors that can lead to different polyol effects in disease prevention include the length of intervention, the daily amount of alditol used, and the frequency of use per day (Mäkinen, 2011). Therefore, new attempts to design alditol-based caries trials (Bader et al., 2010) are welcome but will not provide final answers if the consumption level of the alditol, the frequency of alditol use, or the overall duration of intervention, are defective. Regarding xylitol, for example, customary instructions call for preferably 5x/daily use, the required daily dose being at least 5 to 7 g xylitol (in some trials 10 g has been administered daily) during a period extending beyond three years. Deliberate impoverishment of a clinical program and failure to pay attention to the above requirements may not provide valid evidence-based research findings. Serious errors have been made in polyol-based caries trials by investigating inherently caries-resistant patient cohorts. A trial aimed at studying a preventive instrument must be implemented on patients who represent normal predisposition to the disease involved. Other errors made in clinical trials include saliva stimulation (for example, by gum chewing) that extends beyond 10 min. In some studies 20-30-min chewing episodes have been used. Prolonged chewing will lead to so-called salivary effects only, masking possible pharmacologic, alditol-based effects. The present author has mostly used 5-min stimulation.

Future oral biologic alditol research should elucidate the biochemical mechanism of action of erythritol in caries prevention. Future clinical trials on sugar alcohols should also investigate possible caries-limiting potential of their mixtures. Preliminary experiments suggest that mixtures of xylitol and erythritol may be more effective in affecting the growth of MS than those of D-glucitol and xylitol (Mäkinen et al., 2005). It has been suggested that the caries-limiting potential of common dietary alditols will increase as the number of hydroxyl groups decreases (Mäkinen, 2010). This assertion would concern hexitols, pentitols, and tetritols, which would be represented by D-glucitol or D-mannitol, xylitol, and erythritol, respectively. This suggestion is right now largely based on theoretical considerations and on cultivation of MS in the presence of xylitol and erythritol (Mäkinen et al., 2005). Clearly, future studies should elucidate the caries-reducing potential of the above alditols so that the alditols will be compared in the same, truly long-term trial. Likewise, it is possible that combinations of xylitol with maltitol and combinations of xylitol, erythritol, and maltitol, would turn out to be clinically promising. Such clinical trials should be accompanied by concerted oral biologic analyses of the chemistry and microbiology of dental plaque and whole-mouth saliva.

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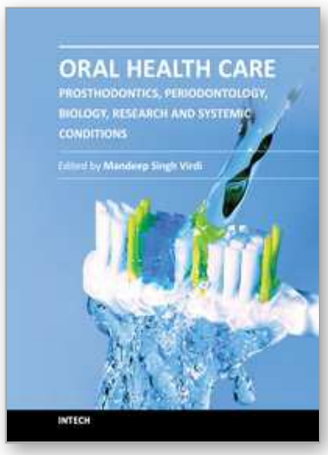

Oral Health Care - Prosthodontics, Periodontology, Biology, Research and Systemic Conditions

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Geriatric dentistry, or gerodontics, is the branch of dental care dealing with older adults involving the diagnosis, prevention, and treatment of problems associated with normal aging and age-related diseases as part of an interdisciplinary team with other healthcare professionals. Prosthodontics is the dental specialty pertaining to the diagnosis, treatment planning, rehabilitation, and maintenance of the oral function, comfort, appearance, and health of patients with clinical conditions associated with missing or deficient teeth and/or oral and maxillofacial tissues using biocompatible materials. Periodontology, or Periodontics, is the specialty of oral healthcare that concerns supporting structures of teeth, diseases, and conditions that affect them. The supporting tissues are known as the periodontium, which includes the gingiva (gums), alveolar bone, cementum, and the periodontal ligament. Oral biology deals with the microbiota and their interaction within the oral region. Research in oral health and systemic conditions concerns the effect of various systemic conditions on the oral cavity and conversely helps to diagnose various systemic conditions.

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