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Xylitol-associated remineralization of caries lesions*

The repair (remineralization) of minor enamel defects (calcium-deficient tooth sites) is a normal physiological process, the teaching of which is part of propedeutic dentistry and oral biology classes at universities worldwide. This process can be accelerated or facilitated by various dietary and oral hygiene procedures. It has become evident that the remineralization (rehardening) process may also concern dentin caries lesions. The disease is reversible, if detected and treated sufficiently early. The wealth of scientific and clinical information available today indicates that habitual use of xylitol, a sugar alcohol of the pentitol type, is associated with remineralization of both enamel and dentin caries lesions. Suitable xylitol-containing "vehicles" include chewing gum and various hard candies and gum arabic-based saliva stimulants. The present review provides an account of xylitol-associated tooth remineralization and presents authentic quotations from leading dental authorities who have endorsed the occurrence of xylitol-associated remineralization of carious lesions.

Keywords: Remineralization, xylitol, dental caries

Xylit-assoziierte Remineralisation von Kariesläsionen

Die Reparatur (Remineralisation) von geringfügigen Schmelzdefekten (Calciumdefiziten an den Zähnen) ist ein normaler physiologischer Prozess, welcher weltweit an den Universitäten als Teil der Propädeutischen Zahnheilkunde und oralen Biologie gelehrt wird. Durch verschiedene Diäten und Mundhygienetechniken kann dieser Prozess beschleunigt oder begünstigt werden. Die Evidenz hat gezeigt, dass der Remineralisationsprozess ebenso die Läsionen am Dentin betrifft. Die Defekte sind reversibel, wenn sie frühzeitig entdeckt und behandelt werden. Es hat sich gezeigt, dass die heutige Wissenschaft und die verfügbaren klinischen Informationen, den gewohnheitsmäßigen Gebrauch von Xylit, einem fünfwertigen Zuckeralkohol (Pentosealkohol) mit der Remineralisation von Schmelz- und Dentinläsionen assoziiert. Entsprechendes Xylithaltiges „Trägermaterial" umfasst Kaugummis und andere verschiedene Süßwaren und Speichelstimulierendes Gummi Arabicum. Diese Übersicht ermöglicht eine Darstellung von Xylit-assoziierter Remineralisation an Zähnen und gibt authentische Belege renommierter Wissenschaftler aus der Zahnmedizin wieder, die die Häufigkeit von Xylit-assoziierter Remineralisation von Kariesläsionen bekräftigen.

Schlüsselwörter: Remineralisation, Xylit, Zahnkaries

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* Paper presented at the symposium "Xylit von 0 bis 100" at the "Tag der Zahngesundheit" in connection with the 15th Annual conference of the German Association for Paediatric Dentristry (DGK) in Dresden, September 25, 2008.

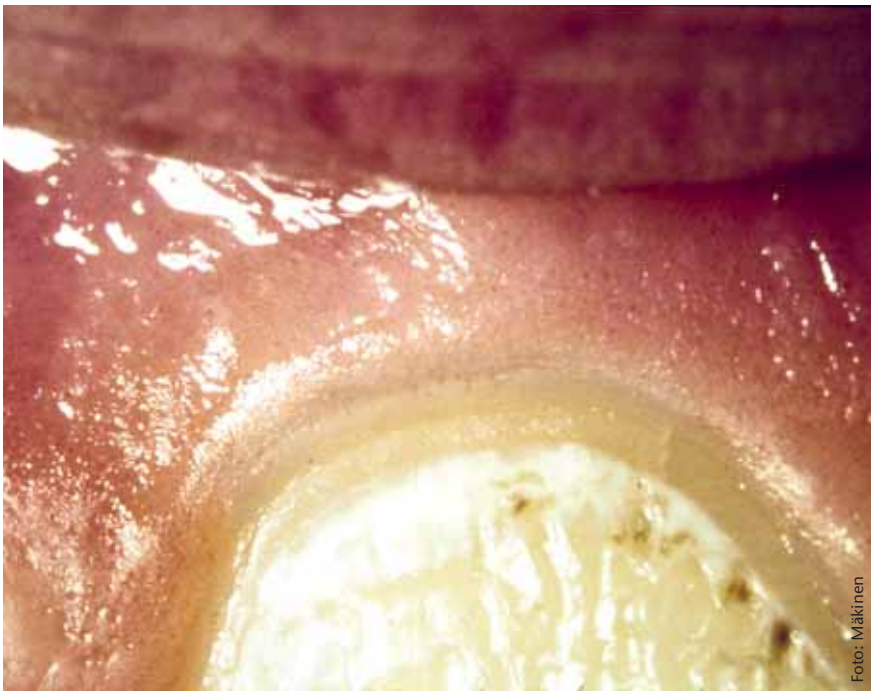


Figure 1 "Chalk caries" near the gum line in a subject of the Turku study at baseline [36].

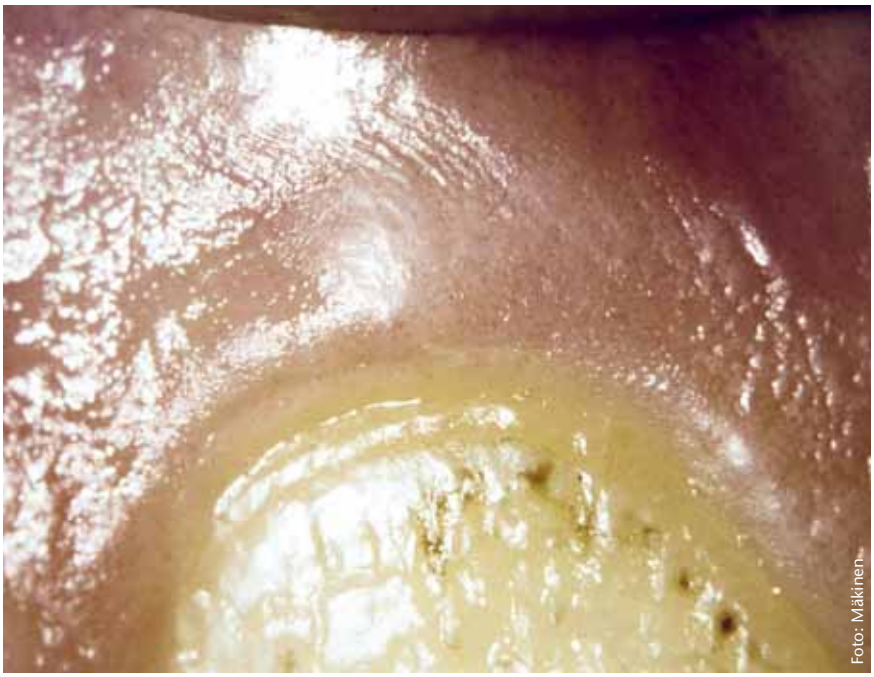


Figure 2 The same tooth site after 12-month consumption of xylitol diet. Planimetric measurement showed the reduction in lesion size exceeding 50 %. Other information and data from similar cases were shown in [24, 33, 34].

1 Introduction

The objective of this review article is to focus on the following two points:

(i) The natural, physiologic repair of early enamel caries lesions is a normal host defence process involving the precipitation of natural hydroxyapatite-like structures in calcium-deficient tooth sites. Consequently, the objective is to recall the well-known partial reversal of the enamel caries process and to emphasize the naturalness of this reaction as part of normal oral biology affecting all consumers.

(ii) Facilitation of the above natural repair process by means of habitual consumption of xylitol, a dietary sugar alcohol of the pentitol type. Consequently, the objective is to provide scientific evidence for the contention that programmed, habitual usage of certain chewable and suckable xylitol products (such as chewing-gums and chewable hard candies) occasions natural repair of early enamel defects and re-hardening of dentin caries lesions.

Scientific literature is replete with studies that deal with the above two topics, i. e. the natural repair process of early enamel lesions and the xylitol-associated facilitation of this process. The authors of scientific and clinical papers investigating the natural repair of early caries lesions have used a wide variety of terms to describe this phenomenon (*vide infra*). In essence, from a pathological and chemical point of view, the question is about a normal, physiologic repair process of early enamel defects involving the precipitation of hydroxyapatite-like structures at the site of mineral loss. This process presumes the participation of innate salivary factors that are normally operative in the saliva of all individuals.

Both physical and chemical evaluation of this reverse process indicates that the incipient caries lesion can undergo a type of rehardening (remineralization) reaction. Remineralization of enamel (and dentin) has not always been recognized by the dental research community. The concept developed in the 1960s and 1970s. It was recognized that tooth mineral, if left in an environment where acid and physical attack are minimized, will heal itself [7, 43]. Early

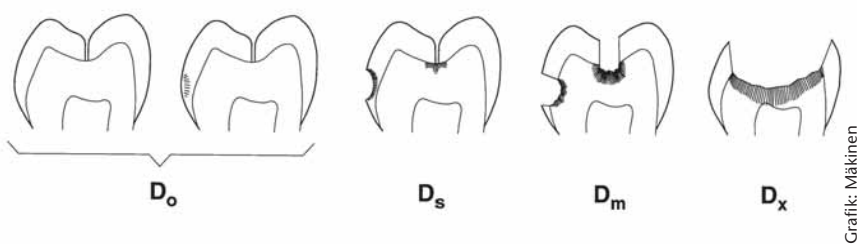


Figure 3 Caries coding used in the Belize studies [26–29] that showed remineralization of enamel and dentin caries lesions. Do stands for sound surface and white spots and enamel and caries lesions unpenetrable to a sharp explorer. Enamel caries with detectable loss of substance was labelled Ds (in line with the Radike sticky fissure). Caries lesions with fractured surrounding enamel (owing to undermining carious lesion) were labelled Dm, while Dx represented severe caries lesions, normally with pulp involvement [26]. The deep lesion shown in figure 4 and figure 5 was labelled Dx. The lesion shown in figure 1 was labelled Do.

researchers spoke about "arrest of caries", "negative caries reversals", or, even more cautiously, "caries stabilization". In the 1980s remineralization became an equal partner to demineralization. A review of the terminology used by past and present authors shows that at least the following descriptions have been employed for this reverse process:

- Remineralization
- Rehardening
- Caries arrest
- Caries stabilization
- Negative caries reversals
- Repair of enamel defects
- Deposition of mineral(s)
- Formation of new (hydroxy)apatite crystals
- Precipitation of calcium phosphate(s)
- The turning of an active lesion into a chronic state
- Induration
- Eburnation

Regardless of the term used to describe this phenomenon, a prerequisite in all cases is the deposition of mineral in the mineral-deficient tooth sites. The outer surface of the tooth is not an inactive structure in the mouth. The enamel surface is in a constant process of dissolution (demineralization) and formation (remineralization). Enamel and dentine caries occurs as a result of a shift in equilibrium between the demineralization and remineralization processes, with demineralization predominating. When demineralization predominates, the initial caries lesion can progress to cavitation. Remineralization, if applied sufficiently early, can arrest the caries process, thus avoiding the need for restoration. The repair process can be stimulated or facilitated by means of the administration of various dental health adjuvants (such as cariostatic minerals containing fluorides, and calcium and phosphate salts) and by dietary means.

2 Standard course book and textbook quotations

Previous researchers and clinicians paid attention to the remineralization process already in the 1940s, perhaps even earlier. For example *Herbert* and *Vale* stated in 1962 that "In fortunate cases the exposed [tooth] surface of the dentine seems to indurate, and it may darken in colour. In time the tooth erupts further and comes into occlusion with those of the opposing jaw and may do service for many years" [13]. Accordingly, early scholars noted that also dentine lesions can indurate (remineralize). *Herbert* and *Vale* continued as follows: "The placing of a badly devised filling in such a place may actually reproduce the conditions that constitute a danger area and caries will commence again" [13].

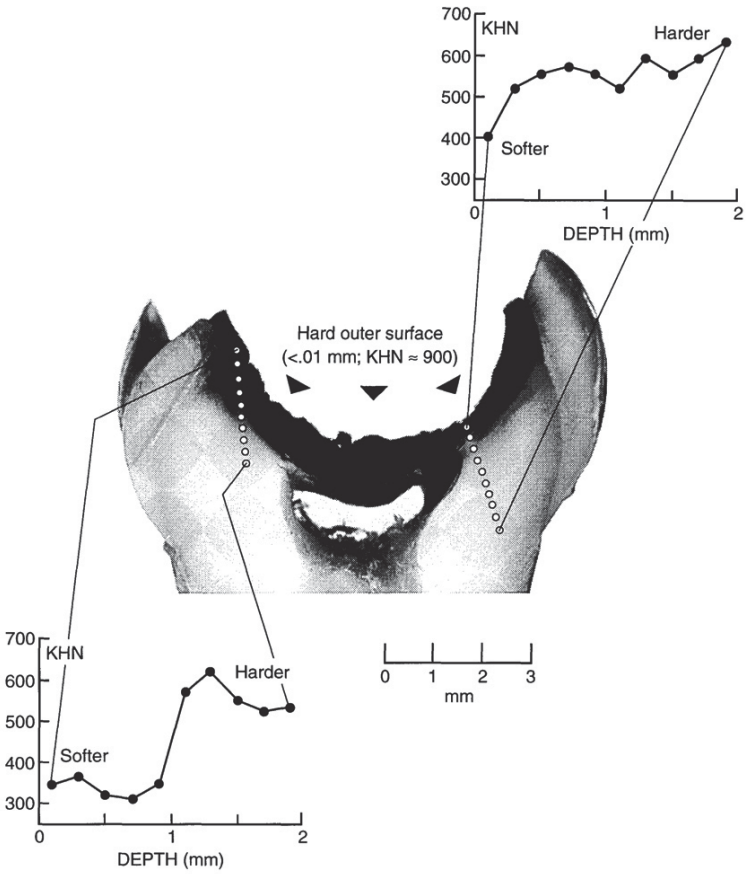
The Operative Dental Surgery textbook by *C. M. Sturdevant* stated in 1995 that "...inactive, arrested lesions show eburnated dentin (sclerotic dentin) that is firm to the touch of an explorer, may be rough but is cleanable, and is seen in patients whose oral hygiene and diet in recent years are good. Generally, these lesions should not be restored except when elected by the patient" [43]. Consequently, the clinician may let the natural repair process continue for the benefit of an individual tooth.

In a 1986 cariology textbook *Fejerskov* and *Thylstrup* [7] stated as follows: "Erupting teeth are consequently exposed to microbial plaque from one to several months before functional occlusion is obtained. During that period of time, innumerable de- and re-mineralizing processes occur at the enamel/plaque interface..". The textbook further states: "Inactive lesions with a long history are often discoloured due to the uptake of dyes. Classically, such inactive lesions are designated as chronic lesions, arrested lesions or brown spot lesions. Gentle probing will typically reveal that they have the same hardness as normal enamel in contrast to the more soft surface of the active lesion". Concerning carious dentin, the textbook states that "Similar to the observations in the enamel, these large [and more irregular] crystals in the dentine tubules are considered to represent the result of remineralization".

As a logical consequence of the above, *Fejerskov* and *Thylstrup* [7] finally concluded: "It is, however, important to understand that if the cariogenicity of the environment is fully controlled and the cavity is open and readily kept free of bacterial plaque and food remnants, even larger dentin carious areas may undergo remineralization. Clinically, the area will become dark brown in colour and the consistency will appear almost leathery. It is noticeable that painful responses in such teeth are generally absent..". (*Vide infra* for similar experience obtained in Belize study subjects who used xylitol chewing-gum; fig. 5). Consequently, standard cariology textbooks recognize the remineralization of even carious dentin.

3 Remineralization – a popular and competition-driven research topic

There has been a steady and significant increase in the number of published articles that address tooth mineralization. This is an indication that the scientific community has accepted the clinical value of this process and that its



Grafik: Mäkinen

Figure 4 Measurement of the Knoop Hardness Numbers (KHN) on the surface of a diamond-cut half of a seriously cariotic (Dx; cf fig. 2) primary molar exfoliated from an eight-year old subject at the termination of a two-year trial (the Dangriga/Belize study) involving continuous use of a xylitol chewing gum [27, 28]. The outer surface layer of the lesion (normally < 0.01 mm) exhibited the highest KHN scores of about 900 which approached the hardness value obtained with sound enamel. Clinical, physical, histologic, and chemical studies of remineralized exfoliated primary teeth were published separately [30].

basic physical-chemical mechanisms have become known. As an indication of the growth of research activity in this area, a PubMed literature search for "mineralization" or "mineralisation" showed the following number of published articles since 1940:

Years	References	References per year
1940–1975	1	0.1
1976–1984	10	1.1
1985–1990	180	30.0
1991–1995	156	31.2
1996–1999	154	38.5
2000–2004	215	43.0
2005–2008	242	60.5

The absolute number of published papers per year may change over time in the PubMed and other literature searches, since new articles can retroactively be included in the data base. The 2008 figure represents papers listed by December 17. Expressions such as "rehardening of enamel" or "enamel rehardening" yielded a little more than one hundred references through the ages, the oldest from 1960.

4 Chemical conditions of physiologic remineralization

The chemical conditions for tooth remineralization include the following:

- Sufficiently high pH value of saliva and plaque fluid
- Sufficiently high calcium concentration in saliva and plaque
- Sufficiently high inorganic phosphate concentration in saliva and plaque
- Presence in saliva of specific nucleating factors
- Participation of crystal growth-governing salivary factors (such as statherins) and other innate salivary peptides
- Presence of the correct inorganic and organic matrix for crystal growth (i.e. a mineral-deficient tooth site or an early caries lesion)

The availability of the fluoride ion within the normal, physiologic, salivary concentration range will facilitate remineralization. The phosphate component may also be partly derived from a dietary organic source, such as casein and other protein phosphates. Typical dietary phosphate sources include milk, other dairy products (cheese), and various nuts. The nucleating and crystal growth-governing salivary factors are normally present in the saliva of all normal individuals. The concentration of calcium and inorganic phosphate in mixed saliva, i. e. 1 to 2 mmole/l and 2 to 10 mmole/l, respectively, are normally sufficient to create the required supersaturated state (of calcium phosphate precipitation) in human saliva. The overall effect of the salivary buffers gives a range of 6.2 to 7.4 in the saliva of most adults. These chemical conditions can be regarded as normal for remineralization.

The overall chemical reaction involved in the demineralization and remineralization processes, presented in a simplified way, is as follows:

Demineralization →

$Ca_{10}(PO_4)_6(OH)_2 + 8H^+ =$

$10Ca^{2+} + 6(HPO_4)^{2-} + 2HOH$

← Remineralization

In the cariogenic challenge, the addition of acid, i. e. H^+, will shift the equilibrium toward demineralization. Addition of calcium and/or phosphate will favour remineralization (which can be facilitated by physiologic fluoride levels). From this it is apparent that stimulation of saliva (that is normally supersaturated with regard to calcium and phosphate) by means of dietary measures that will not cause an acid attack (decrease of pH) will provide a physical-chemical opportunity for remineralization. For

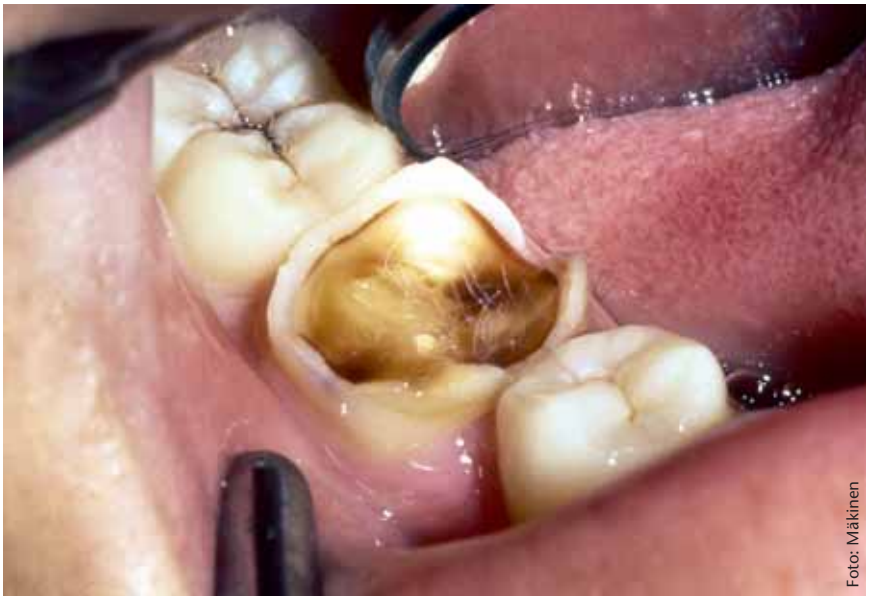


Figure 5 Remineralization of a deep cavity of a 12-year-old subject in the Belize study after 28-month use of a xylitol-sorbitol (3:2) chewing gum [27]. Tooth 46 with full coronal remineralization and exhibiting scratch marks on the hardened dentinal surface from repeated examination with heavy pressure from a sharpened dental explorer. The lesion was soft and sore to the touch at baseline and did not provide painful response at the re-examination. Reproduced by permission [27].

example, habitual use of chewing-gums containing essentially non-fermentable bulk sweeteners can be expected to shift the equilibrium toward remineralization. In the remineralization of an enamel defect, the tooth site in question can be visualized as being surrounded by an extra salivary (or plaque interface) level of calcium and phosphate ions (supersatured calcium and phosphate level), the predominating process at a sufficiently high pH value being a flux of those ions into the mineral-deficient zone of enamel or dentine.

5 Xylitol-associated remineralization – background

The background of xylitol-associated remineralization can be found in the following chemical and biochemical properties of xylitol:

- Owing to its pentitol nature, the xylitol molecule does not generally support the growth of the cells of mutans streptococci and lactobacilli.
- Because of this, xylitol cannot be regarded as an important source of acids present in dental plaque.
- Research has shown that the use of xylitol reduces the growth of mutans streptococci in dental plaque and in saliva, and that reductions can also be observed in salivary Lactobacillus levels.
- Research has shown that the use of xylitol reduces the quantity (mass) of dental plaque, making it less sticky and less acidic than plaque grown in the presence of sugar.
- Chemical analyses have shown that dental plaque grown in the presence of xylitol contains more calcium than plaque grown in the presence of sucrose. This calcium is partly present in soluble form and can be available for remineralization of calcium-deficient tooth sites.
- Bio-inorganic literature has shown that xylitol can stabilize calcium phosphate solutions by forming natural and physiologic complexes with calcium. Xylitol can thus act as a calcium carrier, prolonging the time during which remineralization progresses. The sucrose molecule, for example, does not behave in this way. Also other polyols can form complexes with calcium, but some polyols (such as sorbitol) tend to support the growth of mutans streptococci and dental plaque.
- As a sweet substance, xylitol stimulates salivation, thereby maintaining the required, elevated levels of salivary calcium and phosphate, and the required higher pH value. Under these conditions the extra "mineral bath" renders physiologic remineralization possible.

Most of the above claims can be found in a large number of publicly available reviews [5, 11, 17, 19, 21, 22, 24, 31, 32, 44, 46].

6 Evidence based on scientific literature – basic science and laboratory observations

Dietary sugar alcohols differ decisively from one another in terms of several physical-chemical and structural properties. Such differences inevitably manifest themselves in a number of biological processes. For example, sorbitol is regarded as a "glucose polyol", owing to the close structural and metabolic relationship between glucose and sorbitol. Xylitol, on the other hand, can be regarded as "non-glucose polyol" [8, 31]. Dietary hexitols (such as sorbitol and mannitol) and pentitols (such as xylitol) thus differ substantially from each other in spite of the fact that these molecules also exhibit a number of common polyol properties. These substances do exert selective, specific biochemical and clinical effects on biologic systems. The following list deals with some properties of xylitol that can be considered important in evaluating the participation of xylitol in the remineralization-associated dental processes.

6.1 The xylitol molecule penetrates fast into the aqueous phase of human enamel [1] and may inhibit acid dissolution (demineralization) by interfering with the transport of dissolved enamel. More than twice as many xylitol as sucrose molecules diffuse through dental enamel [45]. The calcium ions can be favourably solvated by a xylitol-water mixture (because of differences between the radii of the molecules and the viscosity involved). Human enamel showed a significant reduction in demineraliz-

ation after xylitol treatment [41; *vide infra*].

6.2 The solubility of various calcium salts in saliva depends on the presence of simple dietary carbohydrates. In the presence of polyols (such as xylitol and sorbitol), the stability constants calculated for polyol-Ca complexes indicate that such complexes can contribute to the transport of Ca-ions to Ca-deficient environments [20]. Polyols can thus favourably govern the remineralization of carious lesions. Sorbitol, however, normally promotes the growth of dental plaque and mutans streptococci, in line with the "glucose polyol" nature of sorbitol.

6.3 Addition of common dietary carbohydrates to human saliva either enhances or inhibits the formation of salivary precipitates, while some carbohydrates show no effect [23]. The precipitates contain a substantial portion of a crystalline phase that has the crystal structure of apatite with a Ca:P ratio of 1.46. Xylitol and sorbitol penetrate enamel and carious lesions and may exert stabilizing effects on these structures. The carbohydrates tested exerted a clear selective effect on the rate of the precipitation of apatite [23]. This selectivity indicates that these polyols, when consumed habitually, may exert different effects on the precipitation of Ca-salts at mineral-deficient enamel and dentine sites. Sorbitol, however, normally supports the growth of dental plaque and mutans streptococci.

6.4 The remineralizing properties of mucin- and carboxymethylcellulose-containing saliva substitutes are enhanced by xylitol, indicating a favourable complex formation with Ca- ions. Sorbitol was significantly less effective [47].

6.5 Human enamel shows a significant reduction in demineralization after xylitol treatment [41]. Mineral loss after the sucrose and water (control) treatments was about three times higher than after the xylitol treatment. The presence of xylitol in the chemical environment thus protected enamel against dissolution.

6.6 The use of xylitol-containing toothpastes is associated with a slightly elevated fluoride content in the enamel compared with glycerol-containing toothpastes [40]. (In line with this, the complexes formed by glycerol with calcium ions are not as strong as those formed by xylitol.) Related to these observations, it is important to emphasize the new finding on the synergistic inhibition of the glycolysis of mutans streptococci by a combination of xylitol and fluoride [18].

6.7 Xylitol displayed remineralization when it was used in a self-administered mouth-rinse [6] and a mucin-containing artificial saliva preparation for xerostomic patients [4]. Consequently, xylitol has contributed to remineralization of enamel defects regardless of the physical form (gum, tablet, pastille, rinse, paste, saliva substitute) in which xylitol has been administered. This evidence speaks to the involvement of direct, chemical and active mechanisms of xylitol in facilitating the natural remineralization process. Such effects cannot be solely explained in terms of the salivation-stimulating effect of xylitol, nor in terms of the removal of the cariogenic sugar challenge.

7 Evidence based on human clinical trials

7.1 *Turku Sugar Studies*. Historically, the first scientific report on the remineralizing potential of xylitol in enamel caries was published as part of the Turku Sugar Studies I-XXI papers [36]. There were two separate reports, the first one focusing on the two-year feeding study while the second one described the simultaneously conducted one-year chewing-gum study. In the former, the au-thors stated that "The results showed a massive reduction of the caries increment in relation to xylitol consumption". The study also showed xylitol to have "non- and anticariogenic properties" based on the "lack of suitability of xylitol for microbial metabolism and physico-chemical effects in plaque and saliva". The results of the one-year gum study also indicated "a therapeutic, caries inhibitory effect of xylitol". In both studies, the remineralization of incipient enamel caries lesions was one of the major clinical outcomes. The overall caries reductions brought about by xylitol consumption in these two studies were estimated to be "close to 90 %" and "exceeding 82 %", respectively, compared with the consumption of a regular sucrose diet. Figure 1 shows a typical xylitol-associated remineralization of initial caries in a xylitol-consuming subject in the Turku study.

7.2 *Planimetric verification*. Separate planimetric measurements of the sizes of the carious lesions ("white spots"; an example is depicted in figures 1 and 2) showed that, in the Turku Sugar Studies, the consumption of sucrose enhanced the further progress of caries lesions, whereas xylitol consumption favoured an opposite development in terms of arrest and decrease of the lesion size. The remineralizing effect in this evaluation was higher on buccal surfaces than on proximal surfaces [33, 34]. The outcomes of these re-examinations strongly indicated the involvement of a xylitol-associated repair process of partially demineralized enamel sites.

7.3 *Ylivieska Studies*. A field study in the town of Ylivieska in Central Finland suggested "the existence of a cariostatic mechanism induced by peroral xylitol". The same subjects were examined after three and five years following the termination of programmed use of xylitol gum [15]. The results of these re-examinations showed that the same preventive effect that was observed upon the termination of the trial proper (in 1984) was still present several years later, i. e. in 1987 and 1989, although the use of xylitol chewing-gum had been terminated several years earlier. This suggests that a strong remineralizing potential was directed to the dentition of those subjects who had received xylitol during the original two-year trial. The teeth that were protected by xylitol during the trial continued to remain sound (indicating a predominating remineralizing process) also during the post-trial years. The authors of the study stated that the use of xylitol gum had "permanently prevented caries" [15].

7.4 *Belize Studies*. The Belize study series provided further evidence of the operation of an enamel-repairing chemical mechanism associated with the use of xylitol-containing chewing-gum [26] (figures 3-6). The young subjects of these trials generally exhibited strong caries activity, and a large number of subjects had untreated, open dentin caries lesions, even ones involving pulp [27]. The clinical experience obtained

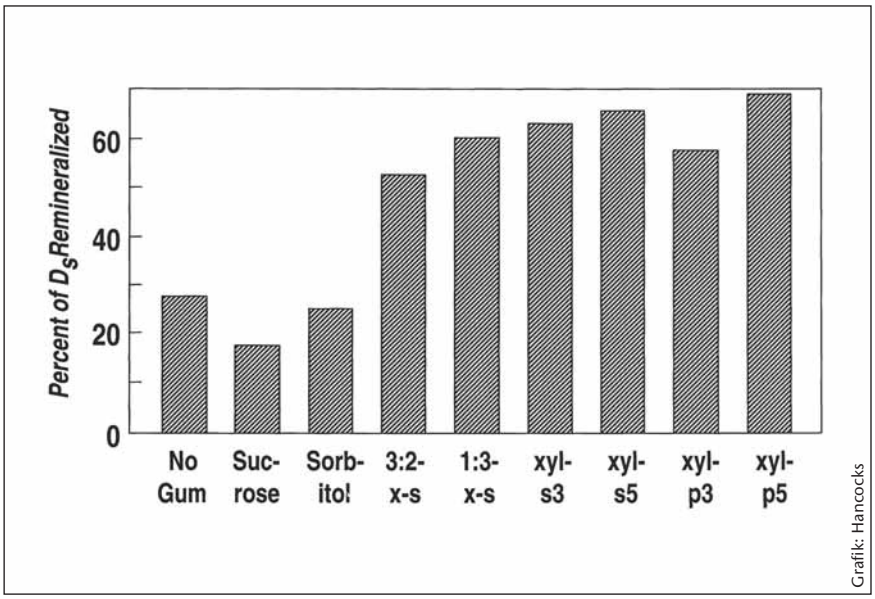


Figure 6 Remineralization of Ds lesions (cf. fig. 2) in the Belize 40-month chewing gum trial [26, 27] involving nine study cohorts. Abbreviations: 3:2 x-s = 30 % xylitol/20 % sorbitol gum; 1:3 x-s = 10% xylitol/30 % sorbitol gum; xyl-s3 = 100 % xylitol stick gum 3 x/day; xyl-s5 = 100 % xylitol stick gum 5x/day; xyl-p3 = 100 % xylitol pellet gum 3 x/day; xyl-p5 = 100 % xylitol pellet gum 5x/day. Sucrose (stick), sorbitol (pellet), and the xylitol-sorbitol combination gums were used five times a day. The number of subjects at baseline with active Ds lesions normally ranged from 40 to 60 per group. Statistics: No-gum, sucrose, and sorbitol vs. all other groups: $p < 0.05$. The six xylitol gum groups did not differ (however, xyl-p5 vs. xyl-p3 and 3:2-x-s approached significance). Based on original caries data from the Belize studies [26, 27]. Reproduced by permission [28].

from these trials suggested the presence of, among other things, the following remineralization-related processes:

– The number of early enamel caries lesions detected at baseline reduced and remineralized most significantly in xylitol-using subjects during the 40-month follow-up (fig. 6).
– A large number of untreated dentin caries lesions of deciduous teeth displayed rehardening as evidenced by means of clinical, histologic, chemical and physical measurements of naturally exfoliated deciduous teeth [30] (fig 4).
– Clinical diagnoses of arrested dentin caries lesions involving pulp showed that habitual use of xylitol chewing-gum had reduced the soreness of those lesions (cf. above, the comment of *Fejerskov* and *Thylstrup* on the absence of painful responses after remineralization). At the same time, the lesion surface had become hard, as shown, for example, by probing with sharp caries explorers (fig. 5) [27]. (A large number of close-up colour photographs of caries lesions that had undergone a rehardening process are available [27].)

7.5 *Costa Rica Studies*. The ability of xylitol to induce anticaries effects was accentuated in studies where xylitol-containing oral health adjuvants were used only twice a day. Two subsequent clinical studies in Costa Rica showed that dentifrices that contained 10 % xylitol were statistically significantly more effective in preventing caries than the control dentifrice without xylitol [38,39]. The xylitol-containing dentifrices reduced both of the caries indexes measured, i. e. the DFS and the DFT scores. Consequently, this low-frequency use of xylitol was an effective anticaries procedure, also affecting the early enamel caries lesions of the subjects using xylitol. The dentifrices tested contained either NaF or Na_2FPO_3, indicating that combinations of xylitol and fluoride can have a concerted caries-preventive effect.

7.6 *Kuwait Study*. Another clinical trial, carried out in Kuwait among disabled school children, showed a relatively low daily frequency (three) and low daily quantity (3.6 g) of xylitol use to occasion "a clear remineralizing effect on caries" [14]. This effect was measurable already after 18 months' intervention and included a large number of initial (early) enamel caries lesions that were favourably influenced by xylitol.

A combination report on the caries diagnoses carried out in Belize separately analyzed the stabilization of rampant caries in the Belize programme. Based on clinical observations and statistical evaluations of data, the article concluded that "These results and previous studies suggest that high-xylitol chewing-gum usage can retard or arrest even rampant dentine caries in conditions where effective restoration and prevention programmes have not been instituted, and can also provide additional protection against further caries development during full implementation of restorative procedures by holding the lesion in a non-progressive condition" [27, 28]. This type of caries arrest presumes the participation of a (salivary) repair mechanism facilitated by the use of a non-acidogenic sugar substitute (xylitol).

Also other successfully completed human xylitol trials on dental caries have separately reported the effects of xylitol administration on the D component of the DMFS or DFT scores. Analysis of the overall caries reduction figures and those that separately reported enamel caries findings indicate that a substantial portion of the overall caries reduction can in each case be attributed to xylitol's effect on enamel caries [reviews: 2, 31, 32].

8 Authentic statements from leading clinical researchers

(Citations not referenced below are from [25].)

Human studies:

– "The results indicated a therapeutic and remineralizing effect [of xylitol] on dental caries" [36].

- "Partial substitution of sugar with xylitol clearly prevented the cavitation [i. e. demineralization] of the teeth". (Especially enamel caries lesions did not develop during the xylitol regimen, i.e. the enamel repair process was active. *A.N. Galiullin* 1981)
- "Partial substitution of sugar by xylitol is a useful tool in preventing caries..." (*D. Kandelman* 1988).
- "Chewing xylitol gum had a beneficial effect on the caries process for all types of tooth surfaces..." "...Regular use of chewing-gum containing xylitol could lead to remineralization" (*D. Kandelman* and *G. Gagnon* 1990).
- "We conclude that the use of xylitol... resulted in permanent prevention of caries". (Long-term preventive effects were observed; [15] and references therein).
- "...Systematic use of polyol-based chewing gums reduces caries rates in young subjects, with xylitol gums being more effective than sorbitol gums" [26].
- "These results suggest that high-xylitol chewing gum usage can retard or arrest even rampant dentine caries..." [27].
- "Xylitol seemed to have a strong preventive and a clear remineralizing effect on caries" [14].
- "The xylitol/NaF combination provided significantly more remineralisation of dentine than fluoride by itself".
- "The reduction in DMFS score resulted mostly from the changes in the D component of the index and possibly reflected a stabilization of the carious process and rehardening of some caries lesions to a non-progressive carious state" [27, 29].
- "...Xylitol consumption caused remineralization of incipient white-spot lesions of buccal surfaces" [33].
- "The results indicate the existence of cariostatic mechanisms induced by peroral xylitol" ([36], p. 269). In the English language, the term cariostatic can be interpreted to mean "inhibition of the growth of caries".

In vivo/in vitro experiments:

- "...Significant reduction in enamel demineralization was found after xylitol treatment" [41].
- "The best rehardening properties were observed for low viscous mucin- or CMC-containing saliva substitutes with xylitol" [47].
- "Dentine lesions in the control slabs (sucrose solution only) were 21.9 µm deep ... while lesions formed under additionally supplied xylitol turned out to be just 9.4 µm deep..." [37].
- "It was found that xylitol gum enhanced the remineralization of initial caries-like enamel lesions..." [35]. (The effect was strengthened by the addition of funoran and calcium hydrogenphosphate.)
- "The differences between the groups were highly significant, the predemineralized halves [of bovine enamel slabs] showing pronounced rehardening at exposure to xylitol" [35].
- "...Regular use of polyol chewing gums may induce changes in dentin caries lesions, which ...show typical characteristics of rehardening and mineralization" [30]. (More arrested dentin caries lesions were detected in subjects who had used xylitol over a period of two years).
- "Xylitol gum showed a superior effect with respect to remineralization potential and plaque reduction" [42]. (Compared to sorbitol gum.)

Animal studies:

- "...Xylitol is not merely a bland, non-cariogenic agent but is genuinely exerting a therapeutic action against caries" [16].
- "This study confirms the suggested therapeutic effect of xylitol even when mixed with sucrose..." [9, 10].
- "Therefore, it can be concluded with some certainty that ... xylitol possesses anticariogenic properties" [10]. (In the English language, the term anticariogenic can be considered to describe the therapeutic action of a food ingredient.)

9 Notes on animal studies

A large number of animal studies on xylitol and dental caries were carried out between the 1960s and 1980s. All animal studies carried out before 1988 (after which only a few animal tests have been published) have been reviewed [22]. A total of 33 studies were reported, out of which only two did not indicate a positive caries-reducing effect of xylitol. In one of these studies the caries scoring system has been criticized; in practice, all "spots" on the teeth were diagnosed as caries. In the other, the authors used a diet consisting of a mixture of 46 % sucrose, 17.75 % wheat flour, and only 2 % xylitol. Consequently, the available scientific data seem to demonstrate the value of xylitol as an exceptionally effective caries-reducing instrument in experimental animals. In all of the animal studies referred to above, the expressions "therapeutic" and "anticariogenic" were found to include a significant impact of the intervention on the progress of enamel caries.

10 Authoritative independent reviews

Several authoritative and independent reviews have thrown light on the caries-inhibitory action of xylitol. Professor *W. M. Edgar* (School of Dentistry, University of Liverpool) stated in 1998, among other things, that "Clinical trials indicate that xylitol gum has a useful anticaries role, superior to the effects of sorbitol gum. In conclusion, both sorbitol and xylitol chewing gums are non-cariogenic in contrast to sugared gum, and exhibit beneficial anticaries properties through salivary stimulation. In addition, xylitol's antibacterial properties seem likely to lead to caries reductions superior to the more modest reductions with sorbitol gum" [5].

Professor *R. S. Levine* (Scientific Adviser to the Health Education Authority, London) stated in 1998: "Xylitol has therefore a clear advantage over sorbitol and all other bulk and intense sweeteners. It is the only one to show both passive and active anti-caries-effects" [17]. (Researchers have determined that "active anti-caries-effects" include those rendering remineralization of incipient enamel caries lesions possible, i. e. "repair" of early enamel defects.)

Dr. *Catherine Hayes* (Assistant Professor, Harvard School of Dental Medicine, Boston; commissioned by the U.S. National Institutes of Health to review the evidence on the effect of non-cario-

genic sweeteners on the prevention of dental caries) wrote in 2001: "The highest caries reductions were observed using xylitol" [11]. Finally, Dr. *Hayes* states that "...since the evidence suggests a strong caries protective effect of xylitol, it would be unethical to deprive subjects of its potential benefits". After rectifying misinterpreted clinical findings of a xylitol study (a community intervention trial) carried out in Lithuania, Dr. *Hayes* stated: "To still observe a significant caries lowering effect of xylitol with such a small dosage is quite remarkable". In this study, a full-xylitol gum was the only gum that had a significantly lower DMFS increment than the no-gum control at three years" [12]. (The other gums contained sorbitol and carbamide, sorbitol, or a mixture of acesulfame K and saccharine.)

Professor *Rugg-Gunn* and Dr. *Maguire* (School of Dental Sciences, Newcastle University) wrote in 2003 that "...we may conclude that xylitol exhibits dental health benefits which are superior to other polyols in all areas where polyols have been shown to have an effect" [19].

Professor *B. A. Burt* (School of Public Health, University of Michigan; Editor-in-Chief of *Community Dentistry and Oral Epidemiology*) concluded in 2006: "The evidence is strong enough to support the regular use of xylitol-sweetened gum as a way to prevent caries, and it can be promoted as a public-health preventive measure" [3].

Related to the conclusions of the above reviews is the ongoing development within the American Academy of Pediatric Dentistry (AAPD). The AAPD currently recognizes the benefits of caries preventive strategies involving sugar substitutes, particularly xylitol, on the oral health of infants, children, adolescents, and persons with special health-care needs. The AAPD's new "Policy on the Use of Xylitol in Caries Prevention" is intended to assist oral health-care professionals make informed decisions about the use of xylitol-based products in caries-prevention" (quote from a recent AAPD working paper).

11 Conclusions

The wealth of scientific and clinical information contained in publicly available research papers and authoritative reviews, of which a part has been referred to above, clearly indicates that habitual usage of especially high-xylitol chewable or suckable saliva stimulants is associated with impressive caries reduction figures. A significant portion of the caries lesions present at baseline in xylitol-consuming study subjects has been active enamel or dentin caries lesions. After exposure to xylitol, a large number of such lesions have displayed clinical, histologic, chemical, and physical changes that can be interpreted as rehardening, remineralization, or partial repair of the enamel defect. Such effects have been detected significantly more consistently only in subjects who have habitually used high-xylitol oral health adjuvants, such as chewable gums and hard and chewable candies (tablets and pastilles). The remineralization of early enamel defects, associated with long-term, habitual use of xylitol, cannot be regarded as unusual, but as a natural consequence of the operation of biologic and chemical laws.

Physiologic repair of minor and early caries-related tooth defects can be regarded as a normal, innate defence mechanism of the human host, mediated by normal salivary flow. This process can be facilitated by various dietary and oral hygiene-related means. The accumulated basic science observations combined with the clinical evidence obtained in long-term clinical trials and laboratory experiments strongly support the contention that programmed and habitual use of xylitol facilitates the action of the salivary host-defence mechanisms, and that such use of xylitol can be associated with clinically significant remineralization ("repair") of early enamel caries lesions. Regarding the anticariogenic efficacy of other polyols, the present author's prediction is that once a sufficient number of controlled clinical trials have been completed, the efficacy of simple dietary alditols in caries reduction will follow the homologous series; i. e. the number of hydroxyl groups present in the alditol molecule will determine the efficacy as follows: erythritol > xylitol > sorbitol.

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