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Six Months of Daily High-Dose Xylitol in High-Risk Schoolchildren: A Randomized Clinical Trial on Plaque pH and Salivary Mutans Streptococci

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Key Words
Chewing gum · Mutans streptococci · Plaque pH · Xylitol

Abstract
A randomized clinical trial was designed to evaluate the effect of daily high-dose xylitol chewing gum on plaque pH and salivary mutans streptococci (MS) in a sample of schoolchildren at high risk of caries. The study was performed on 204 subjects (acceptance rate 88.3%). Inclusion criteria were: >1 and <4 carious lesions, and a salivary MS concentration $>10^5$ CFU/ml. Subjects were randomly assigned to the xylitol or control group. Study design included one examination at baseline (t_0), one after 3 months of chewing (t_1), one after 6 months of chewing (t_2) and the last 3 months after the end of chewing period (t_3). Plaque pH was assessed using the MicroTouch technique, following a sucrose challenge. The area under the curve ($AUC_{5.7}$ and $AUC_{6.2}$) was recorded. Whole saliva was collected in sterile vials and MS CFU/ml were counted. Data were analysed using repeated-measures ANOVA. The main result was that plaque acidogenicity was reduced in both groups. The differences between treatments were statistically significant both for plaque pH and MS concentration; the interaction term for treatment and time was statistically significant ($p < 0.01$). At t_2, the xylitol group children with a salivary MS concentration $>10^5$ and those with $\leq 10^5$ showed significantly lower $AUC_{5.7}$ and $AUC_{6.2}$ values than the control group. These results suggest that the long-term use of high-dose non-sucrose chewing gums had beneficial effects on plaque pH, and that this effect was statistically greater when using xylitol chewing gums, both on plaque pH and MS salivary concentration.

Dental caries is one of the most common diseases among children, despite the fact that today it is known to be almost totally preventable. During the last decades, a decrease in dental caries has been observed in most industrialized countries [Marthaler, 2003], and the widespread use of fluoride in toothpaste is considered the main reason for this decline [Beltran-Aguilar et al., 2005]. Nevertheless, a proportion of children (albeit reduced) still experience severe caries [Marthaler, 2003; Campus et al., 2007, 2009; Marja-Leena et al., 2008].

Development of dental caries is the result of the interaction between cariogenic microflora, a diet rich in fermentable carbohydrates and host factors (including saliva secretion rate and buffering capacity) over time [Selwitz et al., 2007]. High caries risk status is characterized by increasing numbers of highly-acid-tolerant and acidogenic bacteria in dental plaque, with the potential to low-

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er plaque pH [Lingström et al., 2000]. Several preventive programs to control caries risk factors – focusing on dietary modification and enhancing host resistance through the use of fluoride and sealants – have been recommended [Petersen and Lennon, 2004]. However, measures directed towards eliminating caries-associated microorganisms have proven difficult [Zero, 2006].

A useful way to reduce caries risk is the use of sugar substitutes. Today, non-fermentable sweeteners are incorporated into many products, such as chewing gums. The main sugar substitutes used in chewing gum are polyols, such as sorbitol, a hexanol derived from glucose, and xylitol, a naturally occurring pentanol [Burt, 2006]. It has been hypothesized that pentanols have higher efficacy than hexanols in caries prevention [Ly et al., 2008]. Sorbitol should be considered a low-cariogenic sweetener rather than a non-cariogenic one, as it may be fermented by mutans streptococci (MS) [Edgar, 1998]; thus, increasing the plaque acidogenicity [Burt, 2006].

Although the mechanisms of xylitol are not fully known, several studies have demonstrated its benefits, and clinical trials have shown that xylitol possesses both non-cariogenic and cariostatic properties [Deshpande and Jadad, 2008; Splieth et al., 2009]. Some studies have demonstrated the efficacy of low doses of xylitol in caries prevention [Alanen et al., 2000; Thorild et al., 2004]. However, many studies have indicated that a relatively high daily dose of xylitol is needed to obtain positive effects [Oscarson et al., 2006; Milgrom et al., 2009; Twetman, 2009].

The aim of the present investigation was to evaluate the effect of high-dose xylitol (11.6 g, administered daily through a chewing gum) on salivary plaque pH and MS in a sample of Italian schoolchildren at high risk of caries.

Materials and Methods

Preliminary Screening

This randomized clinical trial was designed and approved by the Ethical Committee of the University of Sassari (registration No. 2006/24). The survey was carried out in Sassari (Italy), where the total number of resident children aged 7–9 years in 2007 was 3,195: 1,684 (52.71%) boys and 1,511 (47.29%) girls.

Preliminary screening was carried out from October to December 2007 to select children who presented 2–3 manifest caries lesions and a salivary MS concentration $>10^5$ CFU/ml. Caries lesions were diagnosed when there was a cavity at dentinal level D_3. Subjects with a history of systemic antibiotic, topical fluoride or chlorhexidine treatment within 30 days of the baseline were excluded.

Sample size was calculated on the basis of previous studies regarding Sardinian caries prevalence [Campus et al., 2007, 2009]. It was increased by 15% to safeguard the estimates at an optimal level of precision (5%) against the possible effect of disease reduction compared to previous studies and number of non-responders. Thus, the theoretical sample size was set at 846.

Schoolchildren were recruited using systematic cluster sampling; each class was identified as a cluster, and compiled into a list. The first cluster was randomly chosen, while the others were selected at the systematic interval of 3 classes. The number of subjects in each class was approximately the same. Altogether 1,120 children were recruited for the preliminary screening.

An information leaflet, explaining the aim of the study and requesting their child's participation with a signed consent form, was given to parents or guardians. Only children with their parent's signed consent were called for examination (1,073 subjects). The clinical examination and the saliva sampling were performed during the school day without any adults present. MS counts were assessed using the dip-slide technique (CTR Bacteria, Ivoclar-Vivadent, Liechtenstein, Europe). Of the 957 children who showed up for the examination at the correct time, 231 met the inclusion criteria and were enrolled in the study. The flow chart of the study design is shown in figure 1.

A second leaflet explaining the aim of the clinical trial and requesting child participation was mailed to all parents/guardians of the 231 children. The investigation had a randomized placebo-controlled study design with 2 parallel arms (plaque acidogenicity and microbiological evaluation) and an experimental period of 9 months.

Follow-up was carried out from January to September 2008. The study design included an examination (saliva sample and plaque pH evaluation) at baseline (t_0), after 3 months (t_1) and 6 months (t_2) of gum use, and 3 months after gum use (t_3) (fig. 1).

Two groups of children were formed: a xylitol group, using non-sucrose chewing gum containing xylitol, and a control group, using non-sucrose chewing gum without xylitol. Considering a significant difference of 25% between the test and the control group and a 95% probability to obtain a significant difference between groups at 5% level, the number of subjects per group was set to 66. The acceptance rate was 88.3% (n = 204). Using a computer program (Excel 2003 for Mac OsX), the randomization was carried out on an individual basis by G.C. and M.G.C. Twenty-eight subjects were absent at the start of the experiment, so the final study sample was 176. At the t_1 interim evaluation, 11 children were excluded, (8 from the xylitol group and 3 from the control group); at t_2, 2 more children were excluded from the xylitol group (10 had received systemic antibiotic therapy and 3 did not return the empty chewing gum blister packs); at t_3, 6 children refused to complete the experiment (4 in the xylitol group and 2 in control group). Thus, only 157 children completed the 9-month experimental period: 74 in the xylitol group and 83 in the control group.

Treatment and Sample Collection

The xylitol chewing gum contained: xylitol (36.6%), sorbitol (17.7%), maltitol (9.7%), mannitol (7.1%), gum base, flavours, humectants, food colouring, acidity regulator and glazing agents. The ingredients of the non-xylitol chewing gum were: isomalt (30.0%), sorbitol (17.7%), maltitol (16.3%), mannitol (7.1%), gum base, flavours, humectants, food colouring, acidity regulator and

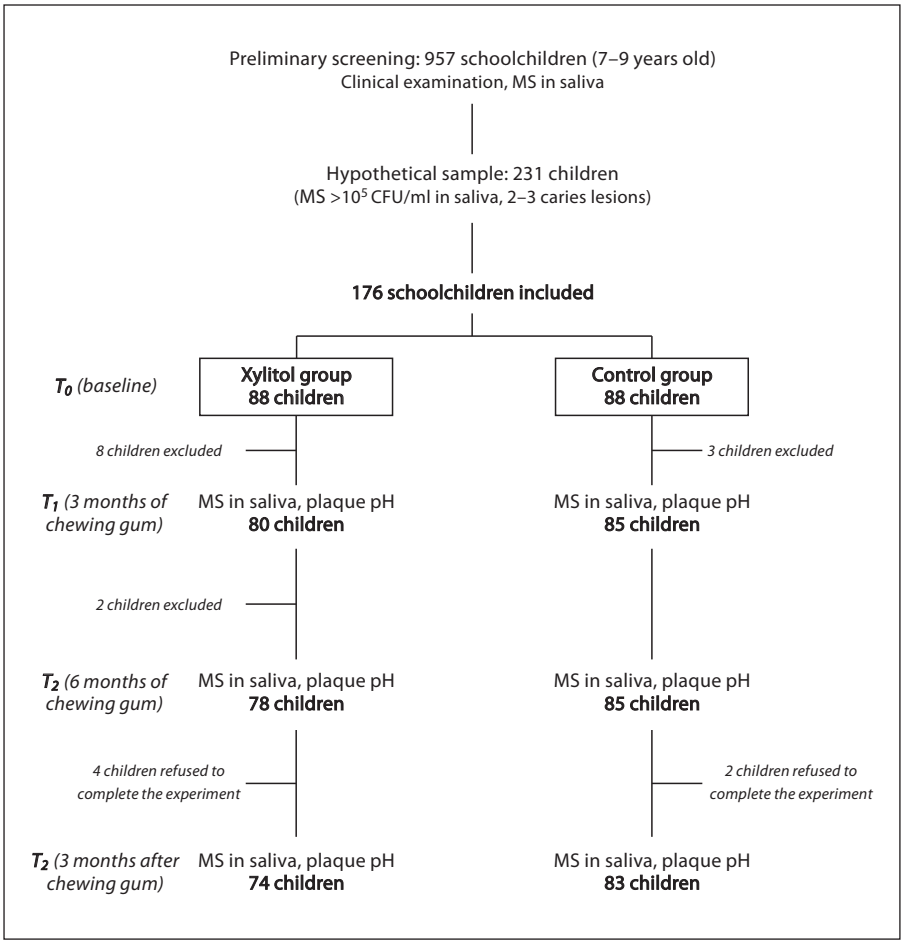

Fig. 1. Flowchart of the study design.

glazing agents. Apart from sweeteners, the 2 chewing gums were identical in composition as well as in weight (3.17 g) form, colour and packaging. They were produced and supplied by Perfetti Van Melle (Lainate, Italy) and coded as either 'green' or 'red'. The code was sealed by an independent monitor, and not broken until the statistical analysis was finalized. The children were instructed to chew 2 pellets for 5 min, 5 times a day [Mäkinen et al., 1995]. Thus, the total daily intake of xylitol was 11.6 g. The chewing times were 8.30 a.m. and 1.00, 3.00, 6.00 and 9.00 p.m. Subjects were instructed to use the chewing gum immediately after main meals and snacks.

The last chewing gum of the day was used after oral hygiene procedures. The parents/guardians were asked to make no changes in dietary and oral hygiene habits of their children. Tooth brushing was not allowed for at least 1 h after the chewing gum. All subjects received a fluoridated toothpaste containing 1,450 μg/g NaF (Mentadent P, Unilever Italia, Milano, Italy) to be used during the experimental period. They were asked to avoid any other oral hygiene adjuvant and any commercial xylitol or sorbitol products during the study.

In order to evaluate the success of the administration of chewing gum at school and home, teachers and parents were given chewing gums necessary for a single month at a time, and asked to return the empty blister packs when receiving those for the following month. This procedure was repeated for all 6 months of the experimental (chewing) period.

Plaque pH Evaluation

The children refrained from eating, drinking and using chewing gum 1 h before plaque pH evaluation. No tooth brushing or other tooth cleaning methods were allowed in the morning of the measuring day. Plaque acidogenicity was assessed using the MicroTouch technique after a previous sucrose challenge. Evaluations of pH were carried out at 2 proximal sites (between deciduous molars) in the left and right sides of the upper jaw. The pH of each site was measured in quintuplicate at 6 different time points: at baseline (before sucrose rinse) and 2, 5, 10, 15 and 20 min after a 1-min rinse with 10 ml 10% sucrose, using active movements. An iridium touch microelectrode (diameter 0.1 mm; Beetrode NMPH-1, World Precision Instruments, Sarasota, Fla., USA, [Lingström et al., 1993]) with a porous glass reference electrode (MERE 1, World Precision Instruments) was used. A salt bridge was created in a KCl (3 M) solution between the reference electrode and a finger of the subject. Before each session of pH evaluation, the electrode was calibrated using buffer solution at pH 7.00 and 4.00 [Scheie et al., 1992].

Table 1. Plaque pH values: $AUC_{5.7}$ and $AUC_{6.2}$ (means ± SE)

	$AUC_{5.7}$ (pH min.)			$AUC_{6.2}$ (pH min.)		
	xylitol	control	p value[1]	xylitol	control	p value[1]
t_0 (baseline)	12.7 ± 0.7	11.5 ± 0.6	0.20	21.5 ± 0.8	20.0 ± 0.8	0.19
t_1 (after 3 months)	10.2 ± 0.5	11.7 ± 0.6	0.05	10.2 ± 0.5	17.6 ± 0.6	0.05
t_2 (after 6 months)	5.5 ± 0.5	8.0 ± 0.4	<0.01	8.0 ± 0.4	13.5 ± 0.7	<0.01
t_3 (3 months after the end)	11.0 ± 0.6	12.8 ± 0.6	0.03	19.3 ± 0.7	21.2 ± 0.8	0.07
p value (one-way ANOVA)	<0.01	0.02		0.04	0.03	

[1] One-way ANOVA.

Microbiological Analyses

Non-stimulated whole saliva was collected over 150 s in sterile vials (Nunc, Kamstrup, Denmark). The samples were processed within 45 min after collection. The samples were serially diluted in sterile PBS (Sigma Chemicals, St. Louis, Mo., USA). Aliquots of 5 μl were inoculated on mitis-salivarius bacitracin agar [Gold et al., 1973] for evaluation of MS. The plates were incubated in a 5% CO_2 environment at 37°C for 72 h and the colony forming units (CFU) were identified by morphology, size and colour, and were counted in a stereomicroscope; MS concentration in saliva was expressed as $\log_{10}$ CFU/ml.

Statistical Methods

The mean pH of the five pH readings, registered in the 2 sites at 6 different time points, was calculated. After this, the mean of the 2 sites at the different time points was calculated, as well as minimum pH and maximum pH fall. Area under the curve, as the area between reference pH (6.2 or 5.7) and the pH curve, was calculated using the computer program PlaquepH [Larsen and Pearce, 1997]. Salivary concentrations of MS were transformed to $\log_{10}$ values to normalize the data, and the mean and SE were calculated for each group and time point. Data were analysed for statistically significant differences using repeated one- and two-way ANOVA. At t_2, the subjects were divided according to salivary MS concentration ($\leq 10^5$ and $>10^5$) and the areas under the plaque pH curve ($AUC_{5.7}$ and $AUC_{6.2}$) for the 2 groups were compared to evaluate the possible linking between salivary concentration of MS and plaque pH. The difference between t_0 and t_2 in the AUC and in the salivary concentration of MS was also calculated for each subject, and linear regression analysis was computed. All the analyses were carried out using Stata SE software 10.0. A value of $p < 0.05$ was considered statistically significant.

Results

No adverse effects were reported in children of either group. A total of 157 children completed the experimental period (fig. 1); data on plaque pH and cariogenic bacteria refer to 74 subjects in the xylitol group and 83 in the control group. At t_0, plaque pH and salivary MS concentration values in both groups were quite similar, and no statistically significant differences for the 2 variables were observed between the 2 groups ($p = 0.23$ and $p = 0.36$ respectively).

Changes in Plaque pH

Regarding the plaque pH values, statistically significant differences between the 2 groups were observed. Table 1 presents the means ± SE for $AUC_{5.7}$ and $AUC_{6.2}$ during the experimental period for the 2 groups of children. No significant differences between the 2 groups were found at t_0. $AUC_{5.7}$ differed significantly at all 3 following time points (t_1, t_2 and t_3), reaching the largest difference at t_2. Significant differences were found in each group regarding time intervals ($p < 0.01$ in xylitol group and $p = 0.02$ in the $AUC_{5.7}$ control). Regarding $AUC_{6.2}$, the same trend was reported, except for the evaluation at t_3. The AUC were statistically significant at the different time points and between the 2 experimental groups, and the interaction term for treatment and time was statistically significant ($p < 0.01$ for $AUC_{5.7}$ and $p < 0.01$ for $AUC_{6.2}$). Minimum pH was quite constant between t_0 and t_2 for the xylitol group (mean value 4.6), while a decrease was found for the control group, from 4.7 (t_0) to 4.2 (t_2). A statistically significant difference between xylitol and control groups was found at t_1 and t_2 ($p < 0.05$), numerical differences only in the maximum pH fall between the 2 groups were found ($p > 0.05$) at t_1, t_2 and t_3 (table 2). The interaction term for treatment and time was statistically significant ($p < 0.01$ for minimum pH and maximum pH fall).

Changes in MS Concentration

Between t_1 and t_2 as well as between at t_1 and t_3, children in the xylitol group showed a reduction in MS compared to baseline, revealing a significantly lower MS con-

Table 2. Minimum pH and maximum pH fall (mean ± SE)

	Minimum pH			Maximum pH fall		
	xylitol	control	p value	xylitol	control	p value
t_0 (baseline)	4.6 ± 0.04	4.7 ± 0.04	0.08	1.9 ± 0.06	1.7 ± 0.05	0.44
t_1 (after 3 months)	4.6 ± 0.04	4.5 ± 0.05	0.03	2.2 ± 0.05	2.2 ± 0.05	0.57
t_2 (after 6 months)	4.6 ± 0.4	4.2 ± 0.05	<0.01	2.3 ± 0.04	2.4 ± 0.05	0.08
t_3 (3 months after the end)	4.4 ± 0.05	4.3 ± 0.05	0.07	2.2 ± 0.05	2.3 ± 0.05	0.20
p value (one-way ANOVA)	0.25	0.04		0.04	0.03	

Table 3. Concentration of MS (log_{10}[CFU/ml saliva] presented as means ± SE)

	Xylitol	Control	p value[1]
t_0 (baseline)	5.37 ± 0.3	5.36 ± 0.2	0.36
t_1 (after 3 months)	5.28 ± 0.6	5.36 ± 0.2	0.04
t_2 (after 6 months)	5.25 ± 0.5	5.36 ± 0.3	0.02
t_3 (3 months after the end)	5.35 ± 0.6	5.36 ± 0.4	0.08
p value (one-way ANOVA)	0.02	0.21	

[1] One-way ANOVA.

centration than children from the control group at t_1 and t_2 (table 3). However, a comparison of p values between t_0 and t_3 did not evidence further change between the 2 groups (p = 0.36 vs. p = 0.08). Two-way ANOVA showed a statistically significant difference in the different times and treatments regarding salivary MS concentration ($p < 0.01$).

MS and Plaque pH

Comparisons of AUC ($AUC_{5.7}$ and $AUC_{6.2}$) and salivary MS concentrations in the 2 groups at t_2 are shown in table 4. At t_2, $AUC_{5.7}$ and $AUC_{6.2}$ values were significantly lower in all subjects from the xylitol group when compared to children from control group, both for children with MS concentrations $>10^5$ and $\leq 10^5$. Nevertheless, the children from the xylitol and the control groups with lower levels of the cariogenic bacteria showed statistically significant smaller AUC than others from the same groups with higher MS levels in saliva. In the xylitol group, linear regression analysis (table 5) showed a statistically significant relationship between the difference (Δ) in log_{10}[MS salivary concentration] over the interval t_0–t_2 and the difference over the same time interval in $\Delta AUC_{5.7}$ (p = 0.01) and $\Delta AUC_{6.2}$ (p = 0.01). In the control group, a statistically significant relationship was only observed for $\Delta AUC_{6.2}$ (p = 0.01).

Discussion

The effect of 11.6 g xylitol (daily, 5 times/day) on plaque pH and salivary MS concentration in a group of children at high risk of caries was evaluated. The main result of this double-blind randomized clinical trial is that non-sucrose chewing gum was effective in reducing plaque acidogenicity, whereas a statistically significant reduction in salivary MS concentration was only found in the xylitol group.

Previous studies have demonstrated the capacity of xylitol to affect the oral ecology by decreasing plaque acidogenicity and by suppressing the proportion of oral MS in plaque as well as unstimulated saliva [Splieth et al., 2009]. However, the caries-preventive effect of xylitol has been reported to be dose- and frequency-dependent [Mäkinen et al., 1995; Milgrom et al., 2006]. Nevertheless, it was demonstrated that when high therapeutic doses are administered, similar reductions in cariogenic bacteria are obtained, indicating a plateau effect. Approximately 10 g xylitol per day seems to be able to induce a caries-preventive effect when administered at a frequency of 3 times/day or more [Ly et al., 2008]. In the present study, a high dose of the sugar alcohol with a high exposure frequency was used to maximize its preventive effect.

A statistically significant reduction in the plaque acidogenicity, as demonstrated by the $AUC_{5.7}$ and $AUC_{6.2}$ values, was found after 3 months' use of xylitol chewing gum. Similar findings were reported in a recent study [Splieth et al., 2009], where the authors reported a change in plaque acidogenicity after 4 weeks' consumption of a similarly high dose of xylitol (10 g/day). The interdental plaque pH was recorded in a group of children submitted

Table 4. $AUC_{5.7}$ and $AUC_{6.2}$ in relation to salivary MS concentration ($\leq 10^5$ and $>10^5$) at t_2

	$AUC_{5.7}$			$AUC_{6.2}$		
	MS $\leq 10^5$	MS $>10^5$	p value[1]	MS $\leq 10^5$	MS $>10^5$	p value[1]
Xylitol	4.7 ± 0.5 (34)	6.3 ± 0.5 (40)	0.03	7.6 ± 0.6 (34)	8.4 ± 0.2 (40)	0.04
Control	7.4 ± 0.1 (18)	8.6 ± 0.3 (65)	0.05	12.9 ± 0.6 (18)	14.1 ± 0.8 (65)	0.04
p value (one-way ANOVA)	<0.01	0.01		<0.01	<0.01	

Data presented as means ± SE (n). [1] One-way ANOVA.

Table 5. Linear regression analysis of the relationship between the difference (Δ) in MS salivary concentration (log_{10}[CFU/ml]) and in $AUC_{5.7}$ and $AUC_{6.2}$ over the period t_0–t_2

Y variate			95% CI	t	p value	r^2
Xylitol group						
$\Delta AUC_{5.7}$	slope (SE)	0.03 (0.01)	0.001 to 0.05	2.47	0.01	0.72
	intercept (SE)	0.07 (0.07)	–0.08 to 0.21	0.94	0.35	
$\Delta AUC_{6.2}$	slope (SE)	0.04 (0.01)	0.01 to 0.06	3.05	0.01	0.61
	intercept (SE)	–0.04 (0.10)	–0.23 to 0.15	–0.41	0.68	
Control group						
$\Delta AUC_{5.7}$	slope (SE)	0.02 (0.01)	0.01 to 0.07	1.58	0.11	0.14
	intercept (SE)	0.20 (0.10)	0.001 to 0.40	1.98	0.05	
$\Delta AUC_{6.2}$	slope (SE)	0.06 (0.02)	0.03 to 0.10	3.37	0.01	0.07
	intercept (SE)	–0.16 (0.15)	–0.32 to 0.28	–0.11	0.91	

to different xylitol chewing gum exposures. Previously, 6 g in a single dose was demonstrated to produce significantly less reduction in pH, after a sucrose 5% rinse, in comparison to a lower dosage [Holgerson et al., 2007].

The data from the present study show that xylitol chewing gum appears to be capable of producing a reduction in oral MS in children at high risk of caries. A statistically significant difference between time and treatment was observed after 6 months for children in the xylitol group. Three months after the end of the chewing period, no significant difference was found between the 2 groups. These results were expected, and reinforce previous findings [Mäkinen et al., 1989; Holgerson et al., 2007].

Interesting findings were revealed for the relationship between MS and plaque pH. Subjects that used xylitol chewing gum, but for whom no MS reduction in saliva was recorded (MS $>10^5$), showed a significantly lower plaque acidogenicity after a sucrose rinse than children from the control group with the same amount of cariogenic bacteria in saliva. This effect could be due to the capacity of xylitol-containing chewing gum to interfere with the microbial metabolism. In addition, in vitro studies have reported that regular xylitol consumption could select MS strains that are not sensitive to the inhibitory effect of the polyol, called MS 'xylitol-resistant', but are less cariogenic than MS 'xylitol sensitive' [Söderling et al., 1998; Assev et al., 2002]. In vivo studies have also correlated frequent xylitol consumption with the presence in plaque and saliva of 'xylitol-resistant' MS strains [Söderling et al., 1998; Meurman et al., 2005]. The present study did not evaluate the effect of xylitol on different MS strains; nevertheless, the finding that children using a high dose of xylitol for 6 months, but in whom salivary MS concentration remained at high level, had a smaller AUC of plaque pH could be explained by the selection of less virulent MS strains. This hypothesis seems to be supported by the evidence that strong correlations of the changes in $AUC_{5.7}$ and $AUC_{6.2}$ with the MS reduction were found in both groups during the chewing period, but were significantly higher for children in the xylitol group.

The exact reason for the reduction in plaque acidogenicity was not evaluated in the present study, but can be attributed to several factors, such as change in number and virulence of cariogenic microorganisms, change in plaque composition or reduced plaque amount. In a sample of Sweden schoolchildren using a xylitol-containing chewing gum for 4 weeks, the amount of visible plaque and acid production were significantly reduced for children using xylitol as well as sorbitol and maltitol chewing gums, yet only the xylitol-containing gum produced a modification in microbial composition [Holgerson et al., 2007]. Therefore, the significantly lower plaque acidogenicity recorded in the xylitol group of the present study might be related to other factors. It would be of interest in further studies, using the same high xylitol dosage, to follow changes in MS concentration in plaque as well as in saliva.

This randomized clinical trial suggests that the use of high-dose xylitol chewing gum has beneficial effects on plaque pH and MS in children at high risk of caries.

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