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XYLITOL CHEWING GUM**  
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# MAINTAINING MUTANS STREPTOCOCCI SUPPRESSION WITH XYLITOL CHEWING GUM

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## ABSTRACT

**Background.** One strategy for treating dental caries is to suppress oral mutans streptococci, or MS, with chlorhexidine, or CHX, mouthrinse. Oral MS levels, however, tend to quickly return to baseline values without further intervention. In this clinical study, the authors evaluated the effect of xylitol chewing gum on MS regrowth.

**Methods.** The authors selected 151 subjects with elevated oral MS levels ( $\geq 105$  colony-forming units per milliliter, or CFU/mL, of paraffin-stimulated saliva). Subjects rinsed with 0.12 percent CHX gluconate mouthrinse twice daily for 14 days. The authors then randomly assigned the subjects to one of three groups. Those in the test group ( $n = 51$ ) chewed a commercial xylitol gum three times daily for a minimum of five minutes each time for three months. The placebo group subjects ( $n = 50$ ) used a commercial sorbitol gum, and the control group subjects ( $n = 50$ ) did not chew gum. The authors estimated MS load on the dentition using paraffin-stimulated saliva samples.

The authors serially diluted the samples, plated them on selective media and incubated them anaerobically; they then enumerated the colonies under a stereomicroscope.

**Results.** MS levels were not significantly different between the three groups at baseline (mean log CFU/mL  $\pm$  standard deviation:  $5.4 \pm 0.7$ ,  $5.4 \pm 0.8$ ,  $5.2 \pm 0.7$ , respectively) nor after CHX therapy ( $2.7 \pm 0.8$ ,  $3.1 \pm 1.1$ ,  $3.0 \pm 1.1$ , respectively). After three months of gum chewing, the test group subjects had significantly lower salivary MS levels ( $3.6 \pm 1.2$ ) than did the placebo ( $4.7 \pm 1.2$ ) or control ( $4.4 \pm 1.3$ ) group subjects.

**Conclusions.** Xylitol chewing gum appears to have the ability to prolong the effect of CHX therapy on oral MS.

**Clinical Implications.** Maintaining long-term caries-pathogen suppression is feasible with currently available commercial products and can be expected to result in significant caries inhibition.

Dental caries is a significant public health problem for a large segment of society.<sup>1,2</sup> For people with caries, the dental health care team needs to apply care strategies beyond restoration placement. Unless the underlying pathology is addressed, the excision and restoration of carious tooth structure alone will not prevent continued dental morbidity.

Several strategies are proposed for controlling dental caries. In clinical practice, control efforts tend to focus on dietary modification and enhancing host resistance through the use of various forms of fluoride and occlusal pit-and-fissure sealants.

Another strategy is to suppress mutans streptococci, or MS, levels on the dentition. There now is a preponderance of evidence to suggest that

MS represent the chief pathogen responsible for human coronal and root surface caries.<sup>3,4</sup> A means of predictably eradicating MS from the oral cavities of subjects harboring high levels of this organism would represent a significant advance in the treatment of dental caries. Combating the microflora, at least in the United States, is largely neglected because there is no method available to predictably and reliably eliminate, or suppress for prolonged periods, MS on the dentition.

The antimicrobial agent chlorhexidine, or CHX, is well-suited to the task of oral MS suppression. It exhibits significant substantivity (retarded oral clearance), MS are more sensitive to it than are other types of oral flora, and it has a long history of safety with few side effects.

CHX mouthrinses have the potential to suppress MS to very low or undetectable levels. In clinical trials, however, there is considerable variability in the response of MS to CHX treatment. In the subjects most favorably affected by treatment, MS can remain suppressed for many months after treatment ceases.<sup>5-7</sup>

Not all people harboring high MS levels, however, respond optimally to CHX treatment. Also, once CHX treatment ceases, how quickly people return to pretreatment MS levels varies considerably from subject to subject<sup>8,9</sup> and appears to be related primarily to incomplete eradication of, rather than reinoculation with, the pathogen.<sup>10-12</sup> Variability in MS response to CHX treatment probably is related to the presence of retentive areas in the dentition—incipient lesions, pit and fissures, restoration margins—where MS evade antimicrobial therapy. On average, without further treatment, pathogen levels tend to return to baseline levels within three months.<sup>6, 8, 13-17</sup>

Suppression of oral MS to low levels by topical CHX, if maintained, has been shown to significantly reduce caries activity.<sup>18-21</sup> To maintain MS suppression for several months or years requires either repeated CHX treatment<sup>17</sup> or some other form of intervention. Repeated use of CHX at tight intervals for an indefinite period is not a viable therapeutic option, as staining of the teeth and restorations and taste alteration can be expected to interfere with long-term compliance.

Sugar restriction in a hamster model demonstrated its ability to prevent MS from returning after CHX suppression<sup>5</sup>; however, lack

of compliance with dietary recommendations involving sucrose restriction limits the application of this same strategy in humans.

Topical fluoride treatments are capable of prolonging MS suppression for up to 12 weeks after CHX treatment; fluoride may have interfered with the metabolic activity of surviving MS and, thus, postponed its return to pretreatment levels. The relatively modest results, however, required a vigorous fluoride regimen.<sup>22</sup>

Topical application of MS-specific monoclonal antibodies after CHX suppression also has been shown to prevent the return of MS to pretreatment levels.<sup>23</sup> This technique, however, has undergone only preliminary clinical testing. Further safety and efficacy studies are necessary before it becomes broadly available.

Use of sugar-free chewing gum has been proposed as another strategic tool in combating caries. Xylitol chewing gum—a caloric sugar substitute that is not readily fermented by oral microorganisms—has a well-documented inhibitory effect against dental caries.<sup>24-28</sup> Its inhibitory effect has several different mechanisms, including antimicrobial effects against MS; salivary stimulation that leads to an increase in salivary buffering capacity, increase in clearance of fermentable carbohydrates from the teeth and enhancement of remineralization capabilities; replacement of cariogenic carbohydrates in the diet; and direct biochemical effects against demineralization.<sup>29</sup> Xylitol chewing gum, through its effects on microflora, diet and salivary flow should retard proliferation of MS after the patient has

stopped using a chemotherapeutic agent to suppress MS.

We conducted this study to assess the ability of xylitol chewing gum to maintain MS suppression after the patient ceased topical CHX treatment.

#### SUBJECTS, MATERIALS AND METHODS

**Subjects.** The following study protocol was reviewed and approved by the University of Minnesota's Institutional Review Board Human Subjects Committee. We screened and enrolled subjects to obtain a final sample size equivalent to that determined by power analysis—a statistical method for calculating minimum sample size based on projected data variability and expected magnitude of results. From adult dentate patients, students, faculty and staff members of the University of Minnesota, we screened 227 potential subjects who had evidence of previous caries in the form of multiple proximal restorations demonstrating the typical pattern of tissue morbidity encountered in excavating carious dentin.

Using a paraffin chewing method, we screened potential subjects for salivary MS levels of at least 105 colony-forming units per milliliter, or CFU/mL.

Of the 181 subjects who qualified, 164 enrolled. Accepted subjects were not using antibiotics, wearing removable dental prostheses or prone to temporomandibular joint complaints. Subjects were not enrolled unless all frank carious lesions were closed. All enrolled subjects furnished written informed consent before participation.

During the course of the study, 14 subjects withdrew—nine because of difficulty with

scheduling or travel and five due to objection to the taste or staining of the CHX rinse. Of the 151 subjects who successfully completed the study, 85 (56 percent) were women, 138 (91 percent) were Caucasian, and the mean age was 36 years  $\pm$  15 years standard deviation, or SD; range 21-71 years. The mean decayed, missing and filled surfaces, or DMFS, score was  $48 \pm 28$  SD, and the mean decayed, missing and filled teeth, or DMFT, score was  $15 \pm 7$  SD.

**Treatment protocol and sample collection.** A timeline for the study is shown in Figure 1. We randomly assigned subjects to one of three groups (Figure 1): a test group, a placebo group or a control group. Each subject rinsed with 15 mL of 0.12 percent CHX gluconate oral rinse for 30 seconds twice daily—morning and bedtime—for two weeks. We provided each subject with a new toothbrush to limit the chances of reintroducing MS onto the dentition.<sup>30</sup>

After the two-week CHX protocol, the 51 subjects in the test group chewed two pellets of xylitol-sweetened chewing gum for at least five minutes three times daily after meals for three months. The 50 subjects in the placebo group chewed one stick each of a sorbitol-, aspartame- and saccharin-sweetened chewing gum for at least five minutes, three times daily, after meals for three months. The 50 subjects in the control group did not chew gum. Demographic variables (race, sex, age, DMFS, DMFT) were uniformly distributed across the three study groups.

We obtained saliva samples from the test group subjects before and after the CHX rinse

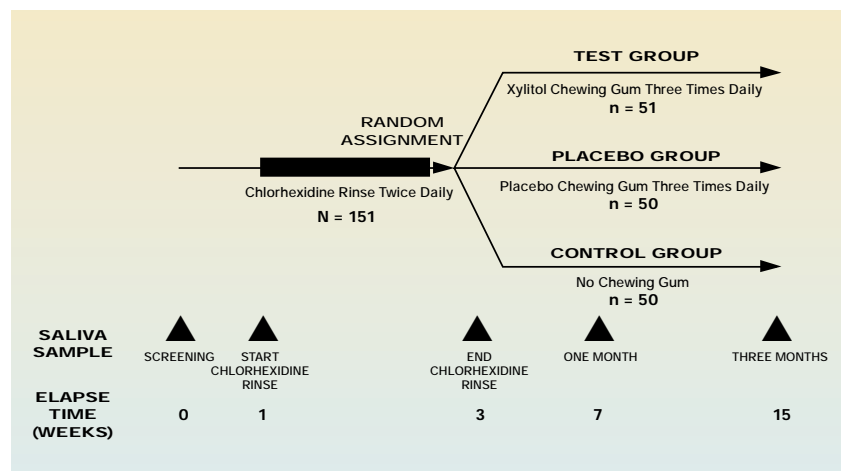


Figure 1. Study timeline.

regimen, as well as after one and three months of gum chewing. We also obtained saliva samples from the control group subjects one and three months after cessation of the CHX rinse (Figure 1). We collected samples from each subject at the same time of day at each visit. We asked them to avoid having their teeth professionally cleaned during the study period. No attempt was made to analyze or modify the diet or oral hygiene practices of the enrolled subjects. The majority of the subjects kept use-diaries to estimate compliance both with the CHX rinse regimen (141/151) and chewing gum protocols (42/51 test, 43/50 placebo).

**Sample culturing.** To estimate MS load on the subjects' dentition, we had subjects chew paraffin for five minutes to stimulate the production of saliva, which we collected and immediately diluted 1:10 in reduced transport fluid, or RTF.<sup>31</sup> We handled saliva samples from each appointment in an identical fashion and processed them the same day as they were collected. Processing involved vortex mix-

ing and dispersion of cell aggregates for 10 seconds with an ultrasonic cell disrupter. We serially diluted the samples in RTF and plated them on HLR-S, a selective agar medium for MS.<sup>32</sup> The plates were incubated in an anaerobic chamber with an atmosphere of 85 percent nitrogen, 10 percent hydrogen and 5 percent carbon dioxide at 35 C for five days, and the CFUs were enumerated under a stereomicroscope. Enumeration was blind to subject group assignment.

#### Statistical analysis.

Counts of MS were logarithm to base 10, or  $\log_{10}$ , transformed to control variance. Samples with undetectable MS were set to the threshold of detectability—2.0 log CFU/mL. Statistical analysis was by analysis of covariance, comparing MS levels among groups three months after cessation of CHX rinsing. Adjustment was made for the slight difference between groups in MS levels immediately after CHX rinsing. Post hoc group comparison was by Tukey-Kramer test.

#### RESULTS

The completed questionnaires and use-diaries implied that

TABLE 1

## ESTIMATES OF CHLORHEXIDINE RINSING TIME, GUM-CHEWING BEHAVIOR AND SALIVA SAMPLE VOLUME BY STUDY GROUP.\*

VARIABLES	TEST GROUP			PLACEBO GROUP			CONTROL GROUP		
	n	Mean	SD <sup>†</sup>	n	Mean	SD	n	Mean	SD
<b>Self-Reported Chlorhexidine Rinse Time (Seconds per Rinse)<sup>‡</sup></b>	48	29.2	2.9	46	28.7	3.2	47	27.9	1.9
<b>Self-Reported Chewing Frequency (Sessions per Week)<sup>§</sup></b>	42	18.4	4.5	43	20.0	3.9	NA**	NA	NA
<b>Self-Reported Chewing Duration (Minutes per Session)<sup>§</sup></b>	42	22.1	21.3	43	19.9	21.9	NA	NA	NA
<b>Paraffin-Stimulated Saliva Volume (Milliliters per Five Minutes)</b>	199	6.7	3.5	196	6.7	3.8	197	6.8	3.8

\* Chlorhexidine rinsing time and gum-chewing frequency and duration are estimates from use-diaries kept by a subset of the subjects.

† SD: Standard deviation.

‡ Subjects were instructed to rinse for 30 seconds twice daily for 14 days.

§ Subjects were instructed to chew gum for a minimum of five minutes three times daily for three months.

\*\* NA: Not applicable.

subjects' compliance with CHX rinse instructions was good. There was no statistical difference in reported use of CHX rinse among the study groups (Table 1).

The questionnaires and use-diaries implied that compliance with chewing gum instruction was good. Subjects were instructed to chew three times per day, or 21 times per week. Mean self-reported chewing frequency reported in the questionnaires was 19.1 times per week  $\pm$  4.3 SD, and in the use-diaries it was 18.7 times per week  $\pm$  2.8 SD. There was no difference in reported gum-chewing frequency between placebo and test groups (Table 1).

Although we asked subjects to chew the appropriate chewing gum for their group for at least five minutes after each meal, we told them that they could chew as long as they liked. Actual chewing time was recorded for a

sampling of the subjects by use-diary. Of the 85 gum-chewing subjects who completed use-diaries, mean gum-chewing time was 21.0 minutes (median 13.9 minutes  $\pm$  21.5 SD, range 2.9-119.7 minutes). There was little difference in chewing time between the test and the placebo group subjects by use-diary (Table 1); perceived average chewing time as measured by the questionnaire agreed with the use-diary sample (mean 21.2 minutes  $\pm$  21.0 SD,  $n = 97$ ).

Of the gum chewers who completed use-diaries, 50 were women and 35 were men; chewing time between sexes was similar ( $P = .89$ ), 21.2 minutes  $\pm$  20.8 SD vs. 20.6 minutes  $\pm$  22.7 SD, respectively. The portion of the study cohort older than the mean age of 28.6 years reported chewing gum for a slightly shorter period (mean 15.5 minutes  $\pm$  18.7 SD) than did those younger than the

mean age (mean 26.3 minutes  $\pm$  22.9 SD), according to use-diaries ( $P = .019$ ). According to the questionnaire, we observed a similar difference for those older than the mean age compared with those at or younger than the mean age, 16.8 minutes  $\pm$  14.9 SD vs. 25.6 minutes  $\pm$  25 SD,  $P = .038$ , respectively. There was no significant difference in chewing time between the test and placebo groups by use-diary ( $P = .64$ ) or by questionnaire ( $P = .73$ ).

The mean saliva volume procured during the five minutes each subject chewed paraffin was 6.7 mL  $\pm$  3.7 SD. We found no significant differences in saliva volume among groups (Table 1) or between appointments.

MS levels were not significantly different among the test, placebo and control groups before CHX treatment (baseline) nor after CHX therapy (Table 2). Mean MS levels for

TABLE 2

MUTANS STREPTOCOCCI LEVELS IN SALIVA SAMPLES AFTER FIVE MINUTES OF PARAFFIN STIMULATION BY STUDY GROUP OVER TIME.						
SAMPLING APPOINTMENT	MUTANS STREPTOCOCCI LEVELS (LOG COLONY-FORMING UNITS PER MILLILITER)					
	Test Group*		Placebo Group*		Control Group	
	Mean	SD†	Mean	SD	Mean	SD
<b>Baseline</b>	5.4	0.7	5.4	0.8	5.2	0.7
<b>End of CHX‡ Treatment</b>	2.7	0.8	3.1	1.1	3.0	1.1
<b>One Month After CHX Use</b>	3.3	1.2	4.3	1.1	4.0	1.0
<b>Three Months After CHX Use</b>	3.6	1.2	4.7	1.2	4.4	1.3

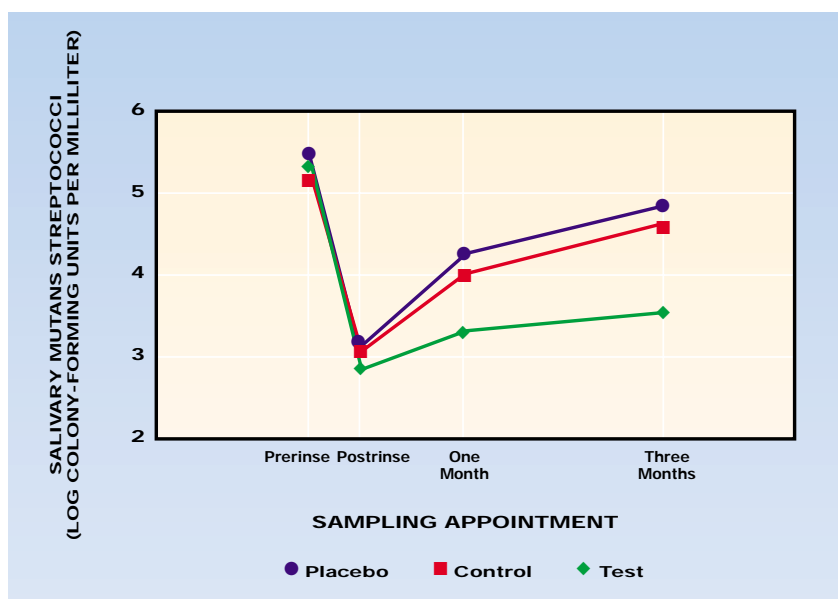
\* Test and placebo group subjects chewed gum three times daily during the three months after chlorhexidine use.  
† SD: Standard deviation.  
‡ CHX: Chlorhexidine.

all subjects at baseline was 5.3 log CFU/mL. After CHX treatment, mean MS levels for all subjects was 2.9 log CFU/mL. This is a decline in mean MS levels of 2.4 log units, approximately a 250-fold reduction.

After CHX rinsing, MS levels in each study group began to return to baseline but at differing rates (Table 2, Figure 2). At one month, mean MS levels in the three groups had diverged from one another. Mean MS levels between the placebo and control groups had increased at least 10-fold.

Three months after CHX rinsing, mean MS levels increased from the immediate postrinse levels equivalent to a 40-fold increase for the placebo group, a 25-fold increase for the control group and an eightfold increase for the test group (Table 2).

After CHX treatment, 39.7 percent of subjects (60/151) had undetectable levels of salivary MS (Table 3). These subjects were fairly evenly distributed over the three study groups.



**Figure 2.** The effect of chewing gum on salivary mutans streptococci levels after chlorhexidine suppression. The test group subjects received xylitol chewing gum; the placebo group subjects received chewing gum containing a sweetening mixture of sorbitol, aspartame and saccharin; and the control group subjects did not receive chewing gum.

One month after CHX treatment, the number of subjects with undetectable MS levels decreased to 13.9 percent (21/151), 66.6 percent of these being in the test group. Three months after CHX treatment, the number of samples with

undetectable MS levels decreased slightly to 10.6 percent (16/151)—56.2 percent of these being in the test group. Thus, freedom from detectable MS persisted in more subjects in the test group than in the other two groups.

TABLE 3

NUMBER OF SUBJECTS WITHOUT DETECTABLE LEVELS OF MUTANS STREPTOCOCCI.*			
STUDY GROUP	END OF CHLORHEXIDINE TREATMENT	ONE MONTH AFTER CHLORHEXIDINE TREATMENT	THREE MONTHS AFTER CHLORHEXIDINE TREATMENT
<b>Test Group† (n = 51)</b>	22	14	9
<b>Placebo Group† (n = 50)</b>	17	5	3
<b>Control Group (n = 50)</b>	21	2	4
<b>TOTAL (N = 151)</b>	<b>60</b>	<b>21</b>	<b>16</b>

\* Threshold of detectability is 2.0 log colony-forming units per milliliter.  
† Test and placebo group subjects chewed gum three times daily during the three months after chlorhexidine use.

When we compared the three study groups' MS levels three months after CHX rinsing, we found significant differences ( $P = .0002$ ). Pairwise comparison showed that there were significant differences between the control and test groups ( $P = .019$ ) and very significant differences between the placebo and test groups ( $P < .0001$ ). Differences between the control and placebo group were not statistically significant ( $P = .27$ ).

Further analysis showed that MS levels immediately after CHX rinsing were positively related to three-month MS levels (slope = + 0.39,  $P = .0002$ ), substantiating the need to adjust for postrinse MS levels in the statistical model. DMFT scores were positively related to MS levels three months after CHX rinsing (slope = + 0.03,  $P = .07$ ). Those with higher DMFT scores tended to rebound more rapidly toward baseline MS levels. Men tended to have higher MS levels three months after CHX rinsing (4.44 log CFU/mL) than did women (4.14 log CFU/mL), although this tendency was only marginally significant ( $P = .07$ ).

Collected mouthrinse ques-

tionnaires (n = 150) demonstrated a bimodal distribution of responses to statements about taste of the mouthrinse, indicating there is considerable variation in sensitivity to the taste influences of CHX. Unpleasant side effects, such as oral burning sensation or perception of dental staining, were not common. Twenty-two subjects (14.6 percent) reported that the mouthrinse was so unpleasant it was difficult to use. It should be noted, however, that these people did complete the mouthrinse regimen.

We administered chewing-gum questionnaires twice during the gum-chewing period: once after the first month of chewing and once at the end of the three-month chewing period. We found no significant difference between the responses at one and three months. Differences in subjective experience between chewing the xylitol pellet gum and the placebo stick gum were not significant. Surprisingly, 30.6 percent of the test group subjects (15/49) and 16.6 percent of the placebo group subjects (8/48) complained that chewing gum

caused jaw or joint pain. It is noteworthy, however, that only 4.1 percent of the test group subjects (2/49) and 4.2 percent of the placebo group subjects (2/48) reported that these complaints were enough to make the gum difficult to use as prescribed.

#### DISCUSSION

Although CHX is a powerful antimicrobial agent for suppressing oral MS, variability from patient to patient in the suppression level and rapidity of return to pretreatment MS levels has limited its use in practice. In an attempt to improve the reliability of results, repeated treatments with CHX have demonstrated only limited success.<sup>15,17,33,34</sup> For antimicrobial treatment of dental caries to become a popular treatment strategy among U.S. dentists, a more predictable treatment must be found.

Variability in suppression level and rapidity of return suggests some microorganisms are not reached by the CHX. Restoration margins may provide an environment in which microorganisms can evade

chemotherapeutic treatment and, thus, survive and spread to surrounding tooth structure. This may explain why DMFT scores were positively related to MS levels three months after CHX rinsing in this study. This corroborates the findings of others that chemotherapeutic suppression of MS is more effective on people with fewer restored surfaces.<sup>8,35</sup>

Chewing gums sweetened solely with xylitol have demonstrated the ability to decrease oral MS levels.<sup>36,37</sup> Diet modification—although capable of prolonging CHX-induced MS suppression in laboratory animals—historically has not produced the same results of caries control in humans, presumably because of lack of adherence to dietary restrictions. On the other hand, chewing gum use in this country is widespread and compliance with chewing gum recommendations is expected to be less problematic.<sup>38</sup> Commercially available chewing gums advertised as “sugar-free” generally have sorbitol as the sole or major sweetener. Although sometimes promoted as “cavity fighting,” these chewing gums do not predictably reduce, and may in fact promote, proliferation of oral MS.<sup>24,36,39</sup>

This study demonstrated that xylitol chewing gum can be used to extend the MS suppression period after the cessation of rinsing with CHX mouth-rinse. The inadequate performance of the placebo gum likely is due to the different sweeteners used—but some difference may be attributable to the difference in form. Pellet gum has the majority of its sweeteners in the candy coating, which are released rapidly at onset of use. Stick gums have sweeteners

mixed throughout that may be more gradually released. The clinical significance of this difference in sweetening agent placement probably is negligible, however, as after a few dozen chewing strokes, the two forms become indistinguishable.

One mechanism purported for the cariostatic effects of xylitol chewing gum is the stimulation of saliva. This study showed that there was considerable difference in regrowth of MS on the dentition depending on whether subjects were chewing xylitol chewing gum or chewing gum containing a sorbitol-aspartame-saccharin mixture. Since saliva stimulation is common to both chewing gums, it is unlikely that saliva stimulation is the dominant mechanism by which xylitol chewing gum exerted its effects in this study.

Another mechanism by which xylitol chewing gum may be cariostatic is through the replacement of fermentable carbohydrates in the diet—that is, “satisfying the sweet tooth.” It is possible that MS were suppressed in this study because dietary intake of fermentable carbohydrates was altered by the introduction of regular xylitol chewing gum use. Xylitol is not metabolized by MS and, in fact, is inhibitory to them. It also is conceivable that MS were allowed to regrow on the teeth even though dietary intake of fermentable carbohydrates may have been altered by the introduction of sorbitol-based chewing gum use. MS are capable of fermenting sorbitol, and replacement of fermentable carbohydrates in the diet with sorbitol-based chewing gum is likely not to exert a strong effect on MS levels or caries



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incidence.<sup>24</sup>

The treatment protocol tested in this study appears to be capable of

producing a three-month period of suppression of oral MS levels in subjects initially harboring high levels of this organism. Long-term suppression of MS levels, in and of itself, can be expected to result in a significant reduction in dental caries—even without other interventions such as topical fluorides, home-use fluoride prescriptions and diet modification.<sup>24,25,40</sup> Because these products are commercially available, this protocol has immediate applicability to the clinical practice of dentistry. Further study is needed to assess the effect of this protocol on caries increment for caries-active patients.

#### CONCLUSION

Use of xylitol chewing gum can retard return of oral MS after chemotherapeutic suppression of this cariogenic organism. Using chewing gum that contains a sorbitol-aspartame-saccharin sweetening mixture, as well as not using chewing gum at all are similarly ineffective protocols for maintaining MS suppression.

Maintaining long-term caries-pathogen suppression is

feasible with available commercial products. Used in conjunction with other caries control strategies, such as diet modification, fluoride and occlusal sealants, a xylitol-sweetened gum-chewing protocol appears to be a helpful caries control treatment. ■

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