RESEARCH REPORTS
Clinical

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J Dent Res 92(6):512-517, 2013

Tooth-surface-specific Effects of Xylitol: Randomized Trial Results

ABSTRACT

The Xylitol for Adult Caries Trial was a three-year, double-blind, multi-center, randomized clinical trial that evaluated the effectiveness of xylitol *vs*. placebo lozenges in the prevention of dental caries in caries-active adults. The purpose of this secondary analysis was to investigate whether xylitol lozenges had a differential effect on cumulative caries increments on different tooth surfaces. Participants (ages 21-80 yrs) with at least one follow-up visit (n = 620) were examined at baseline, 12, 24, and 33 months. Negative binomial and zero-inflated negative binomial regression models were used to estimate incidence rate ratios (IRR) for xylitol's differential effect on cumulative caries increments on root and coronal surfaces and, among coronal surfaces, on smooth (buccal and lingual), occlusal, and proximal surfaces. Participants in the xylitol arm developed 40% fewer root caries lesions (0.23 D_2FS/year) than those in the placebo arm (0.38 D_2FS/year; IRR = 0.60; 95% CI [0.44, 0.81]; $p < .001$). There was no statistically significant difference between xylitol and control participants in the incidence of smooth-surface caries ($p = .100$), occlusal-surface caries ($p = .408$), or proximal-surface caries ($p = .159$). Among these caries-active adults, xylitol appears to have a caries-preventive effect on root surfaces (ClinicalTrials.gov NCT00393055).

KEY WORDS: dental caries prevention, clinical trials, root caries, caries data analysis, sugar substitutes.

DOI: 10.1177/0022034513487211

Received February 22, 2013; Last revision March 28, 2013; Accepted March 28, 2013

INTRODUCTION

Dental caries results from an imbalance of demineralization and remineralization processes at the tooth-biofilm interface over time (Featherstone, 2004). These processes are modulated by modifying factors such as biofilm composition and pH, Ca and PO_4 saturation in and buffer capacity of saliva, use (frequency and type) of fluoride and other caries-preventive agents, oral hygiene, diet, and tooth anatomy (Dawes, 2003; Khoo *et al*., 2005; Featherstone, 2008). Relative to the latter, conditions for demineralization-remineralization dynamics can be affected by specific ecological factors that characterize different tooth surfaces. For example, occlusal surfaces in posterior teeth have a different susceptibility to biofilm attachment (and possibly different biofilm composition and virulence) than do buccal surfaces in anterior teeth (Huang *et al*., 2011; Seneviratne *et al*., 2011). Smooth (buccal and lingual) coronal and root surfaces are more readily exposed to saliva's remineralizing potential than are proximal surfaces and occlusal fissures. Additionally, because the critical pH for demineralization is higher for dentin than it is for enamel (Fejerskov and Kidd, 2008), root surfaces are considered to be at a higher caries risk than coronal surfaces (McIntyre *et al*., 2000). Therefore, when one is studying the effectiveness of interventions on caries prevention, it is important to examine their effects on these different tooth surfaces as a whole as well as separately (McDonald and Sheiham, 1992).

The Xylitol for Adult Caries Trial (X-ACT) was a three-year, placebo-controlled, double-blind, multi-center, randomized clinical trial that evaluated the effectiveness of xylitol lozenges in the prevention of dental caries in caries-active adults (Bader *et al*., 2010). The principal results of the X-ACT trial showed that daily use of 3 to 5 grams of xylitol did not result in a statistically significant reduction in overall caries increment when compared with use of a placebo (Bader *et al*., 2013). However, for the reasons discussed above, it is conceivable that xylitol may have different caries-preventive effects on various tooth surfaces.

The purpose of this study was to compare the caries-preventive effects of xylitol (1) on root and coronal surfaces and (2) among coronal surfaces, on smooth (buccal and lingual), occlusal, and proximal surfaces.

MATERIALS & METHODS

Study Design

The X-ACT study design has been described in detail elsewhere (Bader *et al*., 2010) and is summarized here. In total, 681 participants were randomized at 3 study clinical sites: The University of Alabama at Birmingham (UAB), The

University of North Carolina at Chapel Hill (UNC), and The University of Texas Health Sciences Center at San Antonio (UTHSCSA). The Kaiser Permanente Center for Health Research (Portland, OR) served as the Data Coordinating Center. Institutional Review Boards at each clinical site approved the study, and all participants provided informed consent.

Recruitment, Inclusion and Exclusion Criteria

We recruited participants from dental school clinics, community dental clinics, and the general community. To be eligible, participants had to be aged 21 to 80 yrs, have at least 12 teeth with exposed dental surfaces, and have one or more coronal or root caries lesions either at the time of the baseline examination or documented within the preceding 12 mos. Exclusion criteria included the presence of more than 10 teeth with caries lesions, history of head and neck radiation, history of receiving long-term antibiotic therapy, and allergy to xylitol or other mint components. Following a 4-week run-in period (with placebo lozenges), eligible participants were randomized to receive xylitol or placebo lozenges. For the secondary analysis reported here, only participants with at least one follow-up visit and complete data on all covariates (n = 620, 91% of the 681 randomized participants) were included. This strategy avoided the inclusion of participants with questionable adherence data from one study site, as reported in the main outcomes paper (Bader *et al*., 2013). Data for all randomized participants are available at http://www.xactstudy.org.

Study Procedures

Participants received a caries examination at baseline and were scheduled to return yearly for three follow-up caries examinations. Before the 24-month visits began, the final examination schedule was shifted to 33 mos to adjust for slower-than-expected enrollment.

Study Treatments

The intervention consisted of 5 lozenges spaced across the day and dissolved in the mouth. The active lozenge contained 1.0 g of xylitol as a sweetening agent (other ingredients: polydextrose, magnesium stearate, and natural flavors). The placebo lozenge was identical to the active lozenge but was sweetened with sucralose. Both lozenges were supplied by Fennobon Oy (Karkkila, Finland).

Oral Examination

Caries examinations were completed at baseline, 12, 24, and 33 mos. To the extent possible, the follow-up examinations were performed by the same examiner who conducted the baseline examination. Examiners were trained and certified at the outset of recruitment and roughly annually thereafter (Banting *et al*., 2011). They also completed second examinations of approximately 5% of participants annually to determine intra-examiner reliability. Examiners used a dental mirror and a Community Periodontal Index of Treatment Needs (CPITN) dental probe. Magnifying loupes were used at the discretion of the examiner, but consistently throughout the trial. Radiographs were not used. With the help of a trained study recorder, examiners recorded coronal and root surfaces as either missing, sound, carious, restored (filled or crowned), or sealed, as well as surfaces that were unable to be scored. Root surfaces were anatomically defined as those surfaces apical to the cemento-enamel junction (CEJ).

Tooth surfaces were dried for 5 sec with an air/water syringe. Examiners used a modification of the International Caries Detection and Assessment System (ICDAS II) (Ismail *et al*., 2007) with 4 disease levels possible for each coronal surface [sound (S), non-cavitated enamel lesion (D_1), cavitated lesion penetrating the enamel (D_2), and cavitated lesion penetrating the dentin, or "shadowing" (D_3)] and 3 disease levels possible for each root surface [sound (S), non-cavitated root lesion (D_1), or cavitated root lesion (D_2)]. Restored surfaces were noted as filled (F) or crowned (C), and pit-and-fissure sealants (P) were noted as sound. In addition, D_3 lesions were grouped with D_2 lesions (and are hereafter described as D_2FS), and lesions adjacent to coronal or root restorations, crowns, and pit-and-fissure sealants were noted as such.

The mean intra-examiner reliability values (unweighted kappa, D_2D_3 *vs*. all else) for primary examiners combined were 0.58, 0.88, 0.67, and 0.71 for the baseline and 12-, 24-, and 33-month examinations, respectively (Bader *et al*., 2013).

Questionnaire Data

Participants completed a series of baseline and annual questionnaires that included information on demographics (including, age, gender, and race), medical history, and dental and oral health. Relevant questionnaire items considered for this secondary analysis included participants' age, dental visit history, brushing/flossing frequency, and over-the-counter fluoride exposure (use of fluoridated toothpaste and fluoridated mouthwash after brushing). Complete questionnaire items are available at http://www.xactstudy.org.

Statistical Analyses

The primary outcome variable for the main X-ACT trial was the annualized D_{23}FS (cavitated caries lesions) caries increment for combined root and coronal surfaces, computed as the weighted sum of changes (transitions) in tooth-surface status (Bader *et al*., 2010). Reversals were considered invalid transitions and scored 0. Null transitions (*e.g*., F to F), transitions from D_2 to treated status (F or C), or to or from an unscorable status (*e.g*., missing surfaces) were also scored 0. In the secondary analysis reported here, we conducted separate analyses for root and coronal surfaces and, among the latter, for smooth (buccal and lingual), occlusal, and proximal surfaces.

Consistent with the trial's primary outcome analysis, we used negative binomial (NB) regression to model the coronal increment scores. However, given the large number of zero increments for root surfaces, we used zero-inflated negative binomial (ZINB) regression to model the root increment scores (Preisser *et al*., 2012). Treatment was included in the log rate part of the

Table 1. Baseline Characteristics of X-ACT Trial Participants with at Least One Follow-up Visit and Complete Data on All Covariates

All Clinical Sites	Xylitol n = 308	Placebo n = 312	Total n = 620
Mean age in yrs (SD)	46.4 (13.5)	48.1 (13.7)	47.3 (13.6)
Race/Ethnicity			
Non-Hispanic white	44.5%	50.6%	47.6%
Non-Hispanic black	28.9%	25.0%	26.9%
Hispanic	23.4%	21.2%	22.3%
Other	2.9%	3.2%	3.1%
Female	62.3%	66.7%	64.5%
Brushes 2+ times/day[1]	63.0%	69.9%	66.5%
Flosses 1+ times/day[2]	47.7%	47.4%	47.6%
Dental visit in past year[3]	31.8%	31.7%	31.8%
Self-reported dry mouth[4]	5.2%	8.0%	6.6%
Extent of fluoride exposure[5]			
Toothpaste *or* mouthwash fluoride	52.6%	61.5 %	57.1%
Both toothpaste and mouthwash fluoride	38.6%	31.1%	34.8%

[1]Percentage of participants who self-reported brushing at least twice *per* day.
[2]Percentage of participants who self-reported flossing at least once *per* day.
[3]Percentage of participants who self-reported having had a routine dental visit for a dental examination or a dental cleaning in the year before the baseline study visit.
[4]Percentage of participants who self-reported dry mouth when eating or constantly.
[5]Percentages of participants who self-reported regularly using over-the-counter fluoridated toothpaste or mouthwash, or both, after brushing.

ZINB model, but not in the logistic part (because it was believed that treatment would not affect zero-inflation). As a result, both the NB and ZINB models give rise to incidence rate ratios (IRR), representing overall effects for comparing the effect of xylitol *vs*. placebo lozenges on annualized mean caries increments. For both the NB and ZINB models, we included dental visit history, over-the-counter (OTC) fluoride exposure from toothpaste, mouthwash, or both, brushing/flossing habits, clinical site, and age as covariates and duration of follow-up as a model offset. For the coronal surfaces, we also assessed treatment by surface type interaction in a multivariate model, to test whether the effect of treatment varied across the different types of coronal surfaces. These analyses adjusted the standard errors to account for the intraclass correlation of the D_2FS indices within participants using the clustered empirical sandwich estimator.

Finally, we also examined whether any 'treatment by surface type' effects differed by clinical site by examining whether the 'clinical site by treatment' (for root and coronal surface analyses) or the 'clinical site by treatment by surface type' (proximal, occlusal, and smooth coronal surface analysis) interactions were significant.

We used a two-tailed alpha of 0.05 to define statistical significance and conducted analyses using a combination of both SAS 9.2 (Cary, NC, USA) and Stata 11.2 (College Station, TX, USA).

RESULTS

Among the 620 participants included in this secondary analysis, 308 were randomized to the xylitol arm and 312 to the placebo arm. Mean duration of follow-up was 2.61 yrs, and loss to follow-up was balanced between study arms. Mean age was 47.3 yrs (range, 21-80 yrs), and 65% were women (Table 1). The majority brushed at least twice/day and were exposed to fluoride through office visits or toothpaste, or both (communities in all 3 clinical sites have fluoridated municipal water). Very few reported having dry mouth. We observed similar participant characteristics across the clinical sites.

Xylitol's effects on root and coronal caries increments, as well as for each coronal surface type, are presented in Table 2. Participants in the xylitol arm developed 40% fewer root caries lesions than those in the placebo arm (0.23 *vs*. 0.38 D_2FS/yr; IRR = 0.60; 95% CI for IRR = [0.44, 0.81], $p < .001$). The magnitude of risk reduction was not significantly different across clinical sites. Coronal caries incidence rates did not differ significantly between participants in the xylitol and placebo arms (2.51 *vs*. 2.70 D_2FS/yr; IRR = 0.93; 95% CI [0.83, 1.05], $p = .242$). Finally, the 'treatment by surface type' interaction in the unified coronal surfaces model was not significant ($\chi^2 = 3.96$, $p = .138$). We also compared the treatment effects across clinical sites and found no clinical site-specific effects.

DISCUSSION

Xylitol is a naturally occurring non-fermentable polyol used as a sugar substitute and is therefore considered a non-cariogenic sweetener (Maguire and Rugg-Gunn, 2003). Xylitol promotes remineralization by increasing salivary flow and inhibits bacterial growth and metabolism in the plaque biofilm (Ly *et al*., 2006; Milgrom *et al*., 2006; Söderling, 2009). Despite these favorable anti-cariogenic properties, the evidence for the clinical effectiveness of xylitol as a caries-preventive agent is controversial (Mäkinen, 1998; Scheie and Fejerskov, 1998). In addition, one recently published systematic review reported that the current evidence of the effect of xylitol for caries prevention contains high risk of bias and may be limited by confounder effects, suggesting that high-quality randomized trials are needed to evaluate xylitol's effectiveness (Mickenautsch and Yengopal, 2012). Another recently published systematic review

Table 2. Mean Annual D_2FS Increments for Root and Coronal Surfaces[1]

	Xylitol n = 308	Placebo n = 312	IRR[2]	95% CI[3]	*p*
Type of surface					
Root	0.23[4]	0.38	0.60	[0.44, 0.81]	< .001
Coronal	2.51	2.70	0.93	[0.83, 1.05]	.242
Type of coronal surface					
Smooth	1.06	1.19	0.89	[0.77, 1.02]	.100
Occlusal	0.38	0.35	1.09	[0.89, 1.34]	.408
Proximal	0.94	1.05	0.90	[0.77, 1.04]	.159

[1]Zero-inflated negative binomial regression was used for modeling root caries increment; the logistic part of the model did not include treatment, or brushing/flossing habits, the latter omitted due to convergence issues.
[2]Incidence Rate Ratio.
[3]Confidence Interval.
[4]Model-based annualized means adjusted for clinical site, age, age-squared, dental visit history, over-the-counter fluoride use, oral hygiene practices, and severity of baseline caries (D_2FS).

suggests that xylitol could have tooth-surface-specific caries-preventive effects (Antonio *et al*., 2011) but did not examine coronal *vs*. root surfaces. Furthermore, most evidence of xylitol for caries prevention is derived from studies on children and adolescents with no root surfaces at risk.

X-ACT was designed and conducted as a highly controlled randomized clinical trial to test the effectiveness of xylitol in preventing caries in adults. The placebo lozenge used in the trial was sweetened with sucralose, which lacks any plausible biologic cariostatic or cariogenic properties (Mandel and Grotz, 2002). Bader *et al.* (2013) found that daily consumption of 3 to 5 grams of xylitol in lozenges reduced the overall (coronal and root) caries increment by 11%, which was not statistically significant when compared with placebo use. However, when tooth surfaces were analyzed separately as in the current analysis, xylitol lozenges had a statistically significant caries-preventive effect on root surfaces, though not on coronal surfaces.

These results have important implications for root caries prevention and management and are consistent with previous reports of xylitol preventive effects on root surfaces (Mäkinen *et al*., 1995, 1996; Deshpande and Jadad, 2008). Although coronal caries is more prevalent than root caries, root caries is an increasingly important clinical problem in dentistry, with an annual incidence of 27% among older adults (Griffin *et al*., 2004; Ritter *et al*., 2010). Nonetheless, little research emphasis is given to preventing caries in adults and, specifically, to preventing root caries. A recent randomized clinical trial on root caries prevention in elders showed that oral hygiene instruction alone is less effective in preventing root caries than when preventive agents such as chlorhexidine varnish, sodium fluoride varnish, and silver diamine fluoride solution were used (Tan *et al*., 2010). While fluoride agents have been shown to be moderately effective in the prevention of root caries (Jensen and Kohout, 1988; Ekstrand *et al*., 2008), there is continuing interest in the study of alternative low-risk and low-cost anticaries agents (ten Cate, 2012; Walls and Meurman, 2012).

The results of this secondary analysis indicate that xylitol appears to be effective for root surface caries, but less so for coronal surface caries. There are several plausible explanations for this root-surface-specific effect. First, it is possible that there might be differences in composition/virulence between root and coronal biofilms (Sansone *et al*., 1993; Aamdal-Scheie *et al*., 1996; Huang *et al*., 2011), hence modifying the susceptibility of these substrates to xylitol effects and caries development. Supporting this hypothesis, it has been shown that some strains of oral bacteria are more sensitive to xylitol's inhibitory effect than others (Söderling, 2009). Second, anatomic factors render root surfaces more prone to biofilm stagnation and plaque build-up, and xylitol may have a more pronounced effect in areas with stagnant biofilm such as root surfaces. This hypothesis is supported to some extent by the results of this analysis on the various coronal surfaces, *i.e*., xylitol appears to be more effective (although non-significantly) on smooth than on occlusal coronal surfaces. Third, it is known that the critical pH for dentin demineralization is higher than that for enamel demineralization (Featherstone, 2004). Because root surface caries is mostly a dentin caries phenomenon (as opposed to coronal enamel caries), it is plausible that xylitol exerts a higher caries-preventive effect at the pH range of dentin demineralization than that of enamel. However, it should be noted that the critical pH is not a constant, since the levels of calcium and phosphate in the biofilm fluid vary among individuals (Dawes, 2003).

Although we observed a significant preventive effect on root surfaces, these results are limited by the relatively small number of participants with root caries, given that approximately 70% of the root surfaces either were not at risk or had no disease. However, the observed root caries incidence is consistent with previously reported data (Griffin *et al*., 2004), considering that this was a high-risk population. The overall root caries (D_2FS) 33-month incidence in the sample was 29.52% (24.03% in the xylitol arm, 34.94% in the placebo arm). As noted above, the mean age for participants in this study was 47 yrs. An older population would likely yield more representative results relative to root caries prevention. Another consideration is that, as reported above, all participants lived in communities with fluoridated water, and many used home care fluoride products (Table 1). Therefore, xylitol was an add-on intervention, and any interpretation of the observed results should take that into account. Finally, while the xylitol dosage used in X-CT was considered adequate when the trial was designed, more recent

information suggests that the 5 gm/day dose may fall below a therapeutic threshold (Milgrom *et al*., 2009).

While the root-caries-preventive effect observed in this study was *statistically* significant (40% less root surface caries/yr), the magnitude of the risk reduction effect (0.15 surface/yr) was *clinically* modest. In light of the fact that this was a secondary analysis of the data, and the study's primary outcome analysis was not statistically significant (Bader *et al*., 2013), these results should be viewed with caution. Nonetheless, we believe that these results, combined with those of previous studies, support the clinical recommendation that patients use xylitol lozenges – given their low cost, low risk, and ease of use – to help prevent root caries.

ACKNOWLEDGMENTS

This work was supported by the following National Institute of Dental and Craniofacial Research grants: U01DE018038, U01DE018047, U01DE018048, U01DE018049, and U01DE018050. These are, respectively, the "Xylitol Adult Caries Trial (X-ACT) Study Chair," "Xylitol Adult Caries Trial (X-ACT) Data Coordinating Center," "Xylitol Adult Caries Trial (X-ACT) UNC Clinical Center," "Xylitol Adult Caries Trial (X-ACT) UAB Clinical Center," and the "Xylitol Adult Caries Trial (X-ACT) UTHSC San Antonio Clinical Center."

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

The authors thank the X-ACT Data Safety and Monitoring Board and the X-ACT participants who made this study possible.

The X-ACT collaborative research group is comprised of the following people: (from the University of North Carolina – Chapel Hill) Daniel A. Shugars, DDS, PhD, MPH, Jan C. Holland, RDH, MS, André V. Ritter, DDS, MS, MBA, Debbie S. Robinson, CDA, MS, and J. D. Bader, DDS, MPH; (from the University of Alabama – Birmingham) Gregg H. Gilbert, DDS, MBA, Sonia K. Makhija, DDS, MPH, and Mona Z. Anabtawi, DDS, MS; (from the University of Texas Health Sciences Center –San Antonio) Bennett T. Amaechi, BDS, MS, PhD, Anna Theresa Vega, RDA, Bithiah Radcliffe, John P. Brown, BDS, MS, PhD, and Belinda Vitolas, RDA; (from the Coordinating Center at the Kaiser Permanente Center for Health Research, OR) William M. Vollmer, PhD, Reesa L. Laws, BS, Michael C. Leo, PhD, Kimberly A. Funkhouser, BS, Donna J. Eubanks, BSCS, Kelly Kirk, C. Chen, PhD, Deborah Reck, Jeanette Bardsley, BA, Arthur R. Dixon, MSTM, and Elizabeth J. Esterberg, MS; and (from the NIDCR Project Office) Jane C. Atkinson, DDS.

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