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REVIEW ARTICLE

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Effects of xylitol and erythritol consumption on mutans streptococci and the oral microbiota: a systematic review

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ABSTRACT

Objective: A systematic review of published data was conducted with the aim of assessing effects of xylitol and erythritol consumption on levels of mutans streptococci (MS) and the oral microbiota.

Materials and methods: Electronic and hand searches were performed to find clinical microbiological studies concerning the consumption of xylitol and erythritol chewing gum or candies, and published between 2000 and 2019. Prospective randomized controlled clinical trials conducted in healthy subjects were included in the review.

Results: The initial search identified 561 xylitol and 83 erythritol studies. After applying inclusion and exclusion criteria, 21 xylitol studies and one erythritol study were reviewed. The review identified nine xylitol studies with a fair or high quality, four conducted in children and five in adults, all demonstrating a decrease in MS levels in association with habitual consumption of xylitol. The three microbiota studies employing multispecies probe approaches revealed no effects for xylitol on the microbiota. The only erythritol study fulfilling the inclusion criteria showed no consistent effects on MS levels.

Conclusions: Xylitol consumption is likely to decrease MS counts but it may not change the overall microbiota. Xylitol shows thus properties of an oral prebiotic. More studies are needed to demonstrate the effects of erythritol on MS.

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Xylitol; erythritol; mutans streptococci; microbiota; prebiotic

Introduction

Dental caries results from microbiome dysbiosis involving multiple cariogenic species, including among others *Streptococcus mutans* and *Streptococcus sobrinus* (mutans streptococci, MS), other acid-tolerant *Streptococcus*, *Actinomyces*, *Lactobacillus*, *Veillonella* species and *Scardovia wiggsiae* [1,2]. The relevancy of MS in the aetiology of dental caries has been questioned [3]. However, MS have key pathogenic properties as extracellular polysaccharide matrix producers, and as acidogenic and aciduric organisms [1–4]. Timing and colonization of MS affect microbiome dysbiosis. Young children acquire the MS from their primary caregivers increasing the future caries risk of the children [2,5,6]. High counts of MS in the dentition appear also to be one of the strongest risk indicators associated with early childhood caries [7,8]. Caries can occur in the absence of MS but it may still be important to consider the role of MS in the multifactorial caries process in order to bring about effective preventive and clinical treatments [2,3,9]. The MS in supragingival plaque are important for the microbiome of plaque-related diseases, such as caries and periodontal disease.

Xylitol is a five-carbon polyol sweetener that appears to have specific, beneficial effects on oral health [10–12]. It is also a prebiotic, increasing the numbers of bifidobacteria in the large intestine of humans [13]. Habitual consumption of xylitol is suggested to reduce caries occurrence, plaque and MS numbers [10–12]. In addition to xylitol chewing gums, also pastilles and wipes have been shown to decrease MS counts [14,15]. Oral rinses have not shown this effect, most probably due to short exposure times [16]. Interestingly, maternal consumption of xylitol was associated with a significant reduction in mother–child transmission of MS [17]. Also, prenatal and perinatal xylitol chewing by mothers delayed *S. mutans* carriage in children [18]. Systematic reviews on the caries-preventive effect of xylitol have resulted in varying outcomes [19,20]. In the literature, however, the MS-reducing effect of xylitol is often acknowledged even though not all existing studies confirm this effect [21]. This is reflected for example in the Policy on the Use of Xylitol by the American Academy of Pediatric Dentistry (2015) which concludes that there is a lack of consistent evidence showing significant reductions in MS in children associated with the use of xylitol [22]. The studies on the effects of xylitol on MS counts, published before 2000, have been reviewed by Maguire and Rugg-Gunn [10]. The majority of these studies were published by Finnish researchers. Most of the studies published before the year 2000 probably suffer from a high risk of bias, at least in terms of reporting the methods used, when taking into consideration the present demands for RCTs.

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Erythritol is a four-carbon polyol sweetener that has recently become a subject of wide interest [23]. It has been suggested that erythritol outshines xylitol with regard to oral health benefits [23]. Erythritol is not laxative which enables its use in a variety of products, not only small products such as chewing gums or pastilles. There are, however, only a few clinical studies evaluating the effects of erythritol on oral health-related variables [23]. These studies were all published after the year 2000.

With this systematic review, we wanted to answer the defined research question: does xylitol/erythritol consumption influence occurrence of MS in the oral cavity and the overall microbiota? To answer this question, we reviewed the literature published during the last 20 years (2000–2019) in relation to the effect of xylitol and erythritol chewing gums and candies on MS and the microbiota in healthy children and adults.

Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, www.prisma-statement.org) was used as a guideline in the present systematic review. The review was not registered before data collection.

Information sources for data extraction

A systematic review to identify all the relevant studies published between 1 January 2000 and 31 December 2019 was conducted from three databases: PubMed, EMBASE and The Cochrane Library. Grey literature was searched on www.clinicaltrials.gov. The searches were conducted on 26 March 2019 and updated on 31 December 2019.

Search strategies

The following terms were used in the search for xylitol studies:

PubMed: (xylitol* OR 'Xylitol'[Mesh]) AND (mutans streptococci* OR 'Streptococcus mutans'[Mesh] OR streptococcus mutans* OR s mutans* OR streptococci mutans* OR microbiome* OR microbiota* OR microflora*).

EMBASE: ('xylitol'/exp OR xylitol*) AND ('Streptococcus mutans'/exp OR mutans NEXT/1 streptococci* OR streptococcus NEXT/1 mutans* OR 's mutans' OR streptococci NEXT/1 mutans* OR 'microbiome'/exp OR microbiome* OR microbiota* OR microflora*).

Cochrane: (xylitol*) AND (mutans NEXT streptococci* OR streptococcus NEXT mutans* OR 's mutans' OR streptococci NEXT mutans* OR microbiome* OR microbiota* OR microflora*).

In the search for erythritol studies, the term 'xylitol' was changed for 'erythritol'.

Study inclusion and exclusion criteria

Prospective randomized controlled clinical trials (RCTs) conducted in healthy subjects were included in the review. The literature review includes literature from 20 years and started from the year 2000 since studies published before that are unlikely to meet the present standards of RCTs. The aims of the included trials were to study effects of xylitol or erythritol consumption on oral counts of MS and/or the composition of the oral microbiota. MS/the microbiota were either the primary or secondary outcome measures in the included studies. Ten oral microbial species was considered the minimum number of microbes to represent oral microbiota. Only studies in which chewing gums or candies (including pastilles/tablets/gummy bears) were the xylitol/erythritol vehicles were included in the review. The comparison was a polyol gum or candy or no product. Xylitol/erythritol should be the polyol with the highest concentration in the tested product to meet with the inclusion criteria.

Xylitol studies

Exclusion criteria used when evaluating abstracts: *in vitro* studies; studies done in subjects having problems with their general health; studies not related to oral health; reviews, abstracts, comments or study protocols; the polyol vehicles are oral rinses, toothpastes, oral sprays, pacifiers, milk or wipes; mother–child transmission studies; the study is not available in English.

Exclusion criteria used when evaluating full text articles: the control did not fulfil the inclusion criteria (12); MS assessment not specific for MS (5); study not prospective or randomized (4); subjects were patients (3); Materials and Methods lacks vital information (2); MS were not an outcome of the study (1); the test product contained more sorbitol than xylitol (1); no information on the daily dose of xylitol (1).

Erythritol studies

Exclusion criteria when evaluating abstracts: *in vitro* studies; studies not related to oral health; reviews, abstracts, comments or study protocols; outcome not MS or oral microbiome; study not in English.

Exclusion criteria when evaluating full text articles: study done in patients (2); study not prospective (1); study not RCT (1).

Data extraction and assessment of methodological quality and risk of bias

The articles that fulfilled the inclusion criteria were selected for full-text review and data extraction. The following data were collected: author and year of publication, study site, number and age of participants, study design, intervention and controls, assessment method, main results.

The risk of bias of the selected articles was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [24]. Two authors (ES, KP) independently evaluated the included abstracts and full-length articles and, based on mutual agreement, eliminated discrepancies between each individual assessment. The first author was an

author in four of the evaluated papers. For these papers, a third evaluator (VL) was consulted.

The studies were appraised according to the following aspects: random sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting, funding bias and other biases. Each aspect was classified as having either low, high or unclear risk of bias. The overall level of risk for each study was classified as low (all quality items were met: high quality), unclear (unclear risk of bias for one or more domain: fair quality) or high (high risk of bias for one or more domain: low quality) [24,25].

Results

Study selection

In the search for xylitol studies, total of 561 titles were screened for relevance: (198 PubMed, 258 Embase, 105 Cochrane). Removing the duplicates left 310 titles are to be evaluated. Based on the information of the abstract, 260 studies were removed. When full-text articles were assessed for eligibility, 29 articles were removed. After applying inclusion and exclusion criteria altogether 289 studies not meeting the inclusion criteria were excluded, leaving 21 articles to be reviewed (Figure 1).

In the search for erythritol studies, a total of 83 titles (PubMed 31, Embase 47, Cochrane 5) were screened for relevance. After removal of duplicates, 45 papers were evaluated for abstracts. Based on the information in the abstracts, 40 studies were removed. Five studies were assessed as full-text articles. Four of them did not meet the inclusion criteria and were excluded. The one article left was also one of the above 21 xylitol studies to be reviewed.

Study characteristics

All studies included in the review were prospective, randomized, controlled studies published between 1 January 2000 and 31 December 2019 [26–46]. In the 21 articles included in the review (Table 1), all participants were classified as healthy by the authors. All studies reported the age of the participants (age range 2–73 years), sample size (ranging from 10 to 485) and study duration (from 2 days to 3 years). The delivery modalities included chewing gums or candies (pastilles/tablets/gummy bears). In 11 studies, the subjects were children (<18 years), and in 10 studies the participants were adults (Table 1).

Twenty of the 21 studies that fulfilled the inclusion criteria targeted the effects of xylitol on MS counts, and only one focussed on the microbiota in general. In three of these 20 papers, the effects of xylitol on both MS and the microbiota were studied. Only one paper on the effects of erythritol on MS counts fulfilled the inclusion criteria.

In the majority of the studies, the primary outcome measures were MS of plaque and/or saliva (Table 1). In four studies, the primary outcome measure was the amount or acidogenicity of plaque [27,36], and in two caries occurrence [42,44]. Two of the studies used plaque or saliva microbiota as the primary outcome measure [45,46] and two studies used the microbiota as the secondary outcome measure [38,43].

Assessment of risk of bias

Figure 2 summarizes the risks of bias in the evaluated studies. The risk bias assessment revealed that four studies had a low risk of bias [30,34–36], five studies had an unclear risk of bias [32,33,38,43,44] and the rest of the studies (11 studies) were scored as having a high risk of bias.

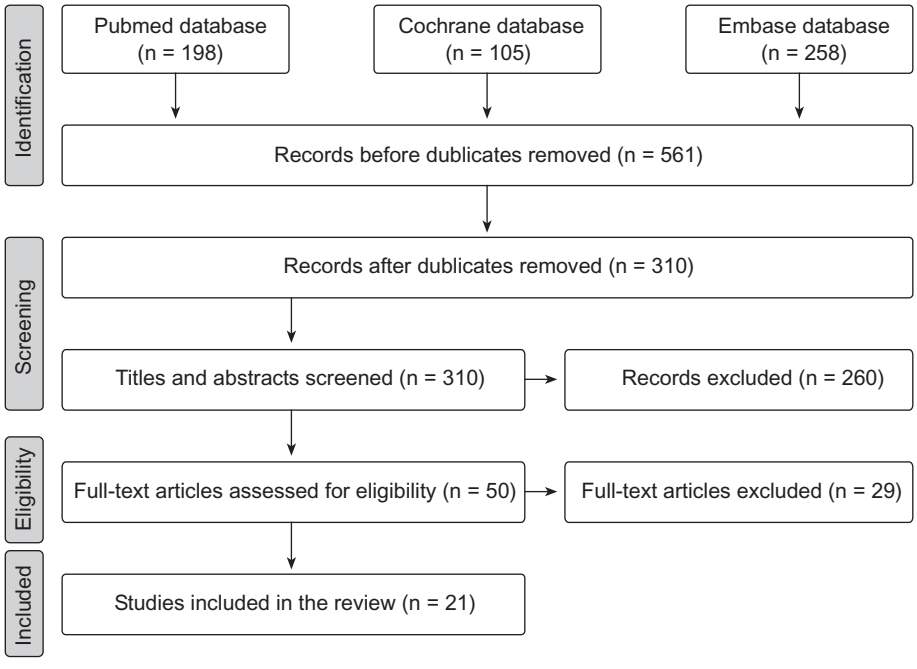

Figure 1. Flowchart.

Table 1. Summary of the included studies on effects of xylitol/erythritol on MS counts and the microbiota.

Study, study site	Subjects, *n*	Study design; outcome measure	Duration	Intervention	Comparative	Assessment method	Results
Xylitol studies							
Autio (2002); Starke, FL, USA	3–5-yr-old children, $n = 61$	Single-blind, randomized, controlled study; saliva MS	3 wk	Xylitol chewing gum (65%, 4.1 g/d, 3xd)	No gum	Dentocult SM Strip mutans	A shift to lower SM scores was observed in the XYL group ($p<.05$). No changes in the control group.
Twetman and Stecksén-Blicks (2003); Halmstad, Sweden	3–4-yr-old children, $n = 10$ (ds > 2)	Single-blind, randomized, controlled cross-over study; saliva MS (som)	2 wk	Xylitol chewing gum (65%, 5 g/d, 3xd)	Sorbitol chewing gum	Dentocult SM Strip mutans	No change in the distribution of SM scores in either group.
Mäkinen et al. (2005); Daegu, South Korea	Appr. 5-yr-old children, $n = 149$	Double-blind, randomized, controlled study; MS from plaque and saliva	6 mo	Xylitol chewing gum (80%, 4.5 g/d, 5xd)	Sorbitol chewing gum, no gum	Plate culturing of MS (plaque), Dentocult SM Strip mutans (saliva)	A decrease in MS of plaque ($p<.001$) and saliva ($p<.001$) in the XYL group. No changes in the control groups.
Ly et al. (2006); Seattle, USA	18–73-yr-old adults, $n = 132$ (MS log CFU ≥ 4)	Double-blind, randomized, controlled trial; plaque and saliva MS	5 wk	Xylitol chewing gum (65%, 10.3 g/day, 2/3/4 times a day)	Sorbitol chewing gum	Plate culturing of MS	At 5 wk groups that chewed XYL gum 3x or 4xd showed lower MS counts compared to control ($p<.1$).
Milgrom et al. (2006); Seattle, USA	18–73-yr-old adults, $n = 132$ (MS log CFU ≥ 4)	Double-blind, randomized, controlled trial; plaque and saliva MS	6 mo	Xylitol chewing gum (65%, daily dose 3.4, 6.9 or 10.3 g, 4xd)	Sorbitol chewing gum	Plate culturing of MS	In the XYL group a dose-dependent decrease in plaque MS/5 wk ($p<.01$) and plaque and saliva MS/6 mo ($p<.05$). No changes in the control.
Oscarson et al. (2006); Lycksele, Sweden	2-yr-old children, $n = 132$	Single-blind, randomized, controlled trial; plaque MS	1.5 yr	Xylitol sucking tablets (appr. 50%, 0.5–1 g/day, 1–2xd)	No tablets	Dentocult SM Strip mutans	The low-dose XYL programme did not influence MS-colonization.
Caglar et al. (2007); Istanbul, Turkey	21–24-yr-old adults, $n = 80$	Double-blind, randomized, controlled study; saliva MS	3 wk	Xylitol gum (77%, 4 or 6 g/d, 2 or 3xd)	Sorbitol chewing gum	Dentocult SM Strip mutans	Saliva MS decreased in the XYL group consuming 6 g XYL 3xd ($p<.05$). No changes in the control group.
Haresaku et al. (2007); Japan	18–53-yr-old adults, $n = 127$	Double-blind, randomized, controlled study; saliva and plaque MS.	6 mo	Xylitol chewing gum (78%, 7.9 g/d, two gums after every meal)	Maltitol chewing gum, no gum	Plate culturing of MS	MS decreased in plaque ($p<.001$) and saliva ($p<.05$) in the XYL group. No changes in the control groups.
Lif Holgerson et al. (2007); Sävar, Sweden	7–12-yr-old children, $n = 128$	Double-blind, randomized, controlled study; saliva MS	4 wk	Xylitol chewing gum (77%, 6.2 g/d, 3xd)	Sorbitol chewing gum	Plate culturing of MS	MS decreased in caries-free children ($p<.05$) and the MS% in all children ($p<.01$) in the XYL group. No changes in the control group.
Ly et al. (2008); Washington State, USA	First-fifth grade children (mean age 8.4 yr), $n = 154$	Double-blind, randomized, controlled trial; plaque MS	6 wk	Xylitol gummy bears (26%, 11.7 or 15.4 g/d, 3xd)	Maltitol gummy bears	Plate culturing of MS	MS decreased in all groups ($p<.001$) when children with non-measurable MS were excluded.
Campus et al. (2009); Sassari, Italy	7–9-yr-old children, $n = 176$ (high caries risk, MS log CFU > 5)	Double-blind, randomized, controlled study; saliva MS (som)	6 mo	Xylitol chewing gum (36.6%, 11.6 g/d, 5xd, gum contained other polyols 31.1%)	Polyol gum (30% isomalt, 41.1% other polyols)	Plate culturing of MS	Salivary MS decreased at 3 and 6 mo ($p<.005$) in the XYL group. No changes in the control group.
Seki et al. (2011); Tokyo, Japan	3–4-yr-old children, $n = 248$	Blinded, randomized, controlled study; plaque and saliva MS	3 mo	Xylitol gum (high conc., 5.3 g/d, 4x/d)	No gum	Dentocult SM Strip mutans	No change in MS counts in the XYL group, an increase in MS in the control group.
Söderling et al. (2011); Oulu, Finland	28–38-yr-old adults, $n = 12$	Double-blind, randomized, controlled cross-over study; plaque and saliva MS, microbiome (som)	4 wk	Xylitol chewing gum (65% Xyl, 6 g/d, 3xd)	Sorbitol gum	MS: plate culturing; microbiome: DNA–DNA hybridization	Plaque MS decreased in the XYL group ($p<.001$). No changes in the control group. No changes in the saliva MS and microbiota.
Bahador et al. (2012); Tehran, Iran	20–28-yr-old dental students, $n = 24$	Double-blind, randomized, controlled, cross-over study; salivary MS	3 wk	Xylitol chewing gum (70%, 6.6 g/d, 3xd)	Sorbitol gum	Plate culturing of MS	*S. mutans* ($p<.01$) and *S. sobrinus* ($p<.05$) decreased in the XYL group, but not the control group.
Shinga-Ishihara et al. (2012); Okayama, Japan	19–40-yr-old pregnant women, $n = 107$ (MS log ≥ 5)	Single-blind, randomized, controlled study; saliva MS	13 mo	Xylitol chewing gum (high conc., 5.3 g/day, 4xd)	No gum	Dentocult SM Strip mutans	The proportion of high SM counts decreased in the XYL group ($p<.001$), no change in the control.
Thabuis et al. (2013); Yixing, China	13–15-year-old children, $n = 288$	Randomized, controlled study; plaque MS (som)	30 d	Xylitol chewing gum (59%, 10 g/d, 5xd)	Gum base and no gum	Plate culturing of MS	*S. mutans* and *S. sobrinus* decreased in the XYL group compared to no gum, gum base groups ($p<.05$).
Runnel et al. (2013); Tartu, Estonia	7–8-yr-old children, $n = 485$	Double-blind, randomized, controlled trial; plaque and saliva MS (som)	3 yr	Xylitol candies (90%, daily dose appr. 7.5 g, 3xd)	Sorbitol candies	Dentocult SM Strip mutans	No differences in the MS levels within or between the two groups during the trial.
Söderling et al. (2015); Kuwait	11–12-year-old boys, $n = 73$ (MS $>$ log 5)	Double-blind, randomized, controlled study; saliva MS, microbiome	5 wk	Xylitol chewing gum (65%, 6 g/d, 3xd)	Sorbitol gum (63% sor)	Plate culturing of MS, microbiome: HOMIM	A decrease in saliva MS in both groups ($p<.05$). No XYL- or SOR-induced changes in the salivary microbiota.

(*continued*)

Table 1. Continued.

Study, study site	Subjects, *n*	Study design; outcome measure	Duration	Intervention	Comparative	Assessment method	Results
Xylitol studies							
Cocco et al. (2017); Sassari, Italy	30–45-yr-old adults, $n = 179$ (high caries risk, MS log CFU > 5)	Double-blind, randomized, controlled trial (1 yr); saliva MS (som)	1 yr	Xylitol chewing gum (30%, 2.5 g/d, 3xd)	Polyol mixture chewing gum	Plate culturing of MS	Salivary MS decreased at 12 mo ($p<.01$), but not at 6 mo. No change in the control group.
Rafeek et al. (2019); St. Augustine, Trinidad	20–30-yr-old adults, $n = 30$	Double-blind, randomized, cross-over study; saliva MS, microbiome	3 wk	Xylitol chewing gum (70%, 6 g/d, 3xd)	Sorbitol chewing gum	16S rRNA high throughput gene sequencing analysis	*S. mutans* sequence reads were very low but appeared unaffected by XYL gum. No effect on the microbiota.
Takeuchi et al. (2018); Yamaguchi, Japan	19–52-year-old men, $n = 76$	Single-blind, randomized, controlled study; saliva microbiome	2 d	Xylitol chewing gum (33% xylitol, 7 g/d, 7xd) (29% maltitol, calcium, funoran)	No gum	16S rRNA next-generation gene sequencing analysis	The 2-d use of XYL gum had no effects on the microbiota.
Erythritol studies							
Runnel et al. (2013); Tartu, Estonia	7–8-yr-old children, $n = 485$	Double-blind, randomized, controlled trial; plaque and saliva MS (som)	3 yr	Xylitol candies (90%, daily dose appr. 7.5 g, 3xd)	Sorbitol candies	Dentocult SM Strip mutans	At the 3rd study year a decrease in MS in 2/4 plaques ($p<.05$) and saliva ($p<.01$). No changes at 1st and 2nd years, or control.

XYL: xylitol; SOR: sorbitol; MS: mutans streptococci; ds: decayed surfaces; CFU: colony-forming units; d: days; wk: weeks; mo: months; yr: years; som: secondary outcome measure.

Figure 2. Risk of bias summary.

The randomization procedure was the most common bias found in the studies under review: in 13 studies, the randomization of the subjects was done in clusters, the randomization was not based on computer generated randomization or the authors failed to describe the randomization process in detail. In the study by Mäkinen et al. [28] the randomization was made according to kindergarten, which is a practical way to perform chewing gum studies, but may result in some bias.

The MS counts or the composition of the microbiota were the primary outcomes in the present review, thus it was important that the MS/microbiota analyses were performed blinded. In this regard, only in two studies was proper blinding not carried out [31,41]. However, problems with

allocation concealment and blinding are inevitable when the control group does not chew gum or consume candies [26,27,31,37,40,41,46].

An unclear or high risk of bias in the incomplete outcome data was mainly based on not taking dropouts into consideration [31,37,41,42,44,46].

A high risk of bias was found in selective reporting consisting both of reporting results in the abstract or conclusions not supported by the findings [28,42,45] or leaving some findings out, such as study-induced changes within groups [29] or in the control group [29,40]. In the studies by Seki et al. [37] and Thabuis et al. [41], results were presented in a way that made them very difficult to interpret, leading to a high risk of bias. In the paper by Takeuchi et al. [46], the conclusions were not necessarily supported by the results, leading to an unclear risk of bias.

Most of the evaluated studies reported that they obtained the tested xylitol and control products as gifts from various companies without other apparent funding. However, four studies appeared to be partly [28,33] or fully industry-funded [42,46] resulting in an unclear risk of funding bias.

In the studies by Ly et al. [29] and Shinga-Ishihara et al. [40], the failure to report the results of the control group caused a high risk of bias. Haresaku et al. [33] did not give the gender of their subjects possibly leading to an unclear risk of bias. In the study by Seki et al. [37], the groups were not comparable at baseline leading to a high risk of bias. Also a high risk of bias was found in the study by Bahador et al. [39] in which subjects with caries history were excluded, and their MS counts were very low. In the paper by Thabuis et al. [41], the authors report that subjects with low MS counts were selected for the study, even though the results suggest otherwise. In the study by Takeuchi et al. [46], the test gum contained two active agents in addition to xylitol: funoran and Ca-phosphate, leading to a high risk of bias.

Influence of xylitol on MS counts

Sixteen of the 19 studies using culture-based methods in the MS determination found decreases in MS counts in association with habitual xylitol consumption. Four of these studies were found to have a low risk of bias and five an unclear risk of bias indicating fair quality. The finding was similar in children [34–36,43] and adults [30,32,33,38,44]. In eight of the nine studies with good or fair quality, a polyol product was the control. In seven of these studies, no change was detected in the polyol control group, while a decrease in MS counts was found in the xylitol group [30,32–34,36,38,44]. The MS decreases varied from small but significant changes in MS counts [33,36,44] to more than 10-fold decreases in the MS numbers [30]. Also the studies with a high risk of bias showed MS decreases in association with xylitol consumption [26,28,29,39–41].

Fifteen of the 19 studies lasted from 2 weeks to 6 months and four were long-term studies. Xylitol-associated MS decreases were reported in 14/15 studies lasting up to 6 months [26,28–30,32–39,41,43] and in 2/4 long-term studies [40,44], respectively. No effects were thus reported in three studies that used culture-based methods [27,31,42] or in one recent study that used a multispecies probe approach [45].

Studies lasting from 2 weeks to 6 months

In 14 of the 15 evaluated studies, reductions in MS counts were found in comparison with the control group. Eleven studies compared a high-concentration chewing gum (59% xylitol or more) with a polyol control chewing gum or gum base and found a decrease in either plaque or saliva MS or both [28–30,32–34,36,38,39,41,43]. In 10 of these studies, xylitol consumption resulted in decrease in MS values also compared to baseline [28,30,32–34,36,38,39,41,43]. In three studies, the xylitol and control product was a gummy bear or the control was a no-gum group. In the study by Ly et al. [35], children consumed for 6 weeks gummy bears sweetened with xylitol (11.7 or 15.4 g xylitol/day) or maltitol (44.7 g maltitol/day). MS decreased in all groups when children with non-measurable MS were excluded [35]. The 3-week long study by Autio [26] showed a decrease in saliva MS counts, which was not seen in the no gum control group. In the 3-month study by Seki et al. [37], the authors concluded that a beneficial change in MS counts in the xylitol group was found compared to the no-gum control, but the results were presented in a confusing way. In all of these studies, daily xylitol consumption exceeded 4 g/day. No xylitol-associated effects on saliva MS were reported in the study by Twetman and Stecksén-Blicks [27] where 10 children used a xylitol chewing gum (65%) for 2 weeks. In one recent study, a multispecies probe approach was used to assess both MS and the composition of the microbiome [45]. In the study, the number of *S. mutans* and *S. sobrinus* sequence reads were very low; however, the authors still concluded that neither xylitol nor the sorbitol control had any effects on the MS counts [45] (Table 1).

Studies lasting more than 6 months

Two of the studies lasting more than 6 months reported xylitol-associated decreases in MS counts, and two found no effects on MS. Shinga-Ishihara et al. [40] found a xylitol consumption-associated decrease in MS counts of mothers, with no change in the no gum control group. Cocco et al. [44] studied high-caries-risk adults who consumed for 1 year a xylitol chewing gum with 30% xylitol (2.5 g xylitol/day) and monitored MS at 6 and 12 months. The MS counts showed small but significant decreases at 12 months, but not at 6 months, compared to the polyol gum control and baseline. In a low-dose xylitol tablet trial (0.5–1 g xylitol/day), lasting 1.5 years MS-colonization of 2-year-old children was not affected [31]. In the trial by Runnel et al. [42] saliva and plaque MS counts were monitored on a yearly basis for 3 years. The study found no changes in MS numbers in the xylitol candy or sorbitol control candy groups (Table 1).

Post-intervention follow-ups

Three of the above-mentioned studies monitored the MS levels after xylitol consumption was discontinued [36,40,44]. Campus et al. [36] reported a decrease in saliva MS at 3 and 6 months during xylitol use, but 3 months after the consumption had stopped, the levels returned to baseline. Shinga-Ishihara et al. [40] found a carry-over effect of 13 months on MS levels of mothers following of xylitol consumption. Cocco et al. [44] who found a decrease in the high MS levels of the subjects after 12 months of xylitol consumption, reported reduced MS levels still at the 24-month follow-up. These results were statistically significant but the changes in the MS levels were small.

Influence of xylitol on the microbiota

Four short-term trials studied the influence of xylitol consumption on the microbiota [38,43,45,46]. In two of these studies also MS counts were assessed [38,43]. Four weeks of xylitol gum use (6 g xylitol/day) resulted in no changes in the numbers of 14 microbial plaque species (not including *S. mutans* or *S. sobrinus*) assessed with DNA–DNA hybridizations [38]. Also no changes were observed in the sorbitol control group [38]. In this study, MS were assessed by plate culturing. Xylitol gum use (6 g xylitol/day) for 5 weeks decreased MS determined by plate culturing but had no effect on the overall saliva microbiota, assessed with a multispecies probe approach, HOMIM [43]. In the sorbitol control group, *Veillonella atypica* decreased [43]. In this study, the HOMIM signals of MS were too low to be analysed even though the subjects were screened before the study for high counts of MS with the Dentocult® SM Strip mutans test [43]. Two studies used 16S rRNA gene sequencing analysis, a multispecies probe approach, in the microbiota analysis. In the three-week study, use of xylitol chewing gum (6 g xylitol/day) did not result in changes in the saliva or plaque microbiota, but in the sorbitol control group numbers of several salivary species were affected [45]. In the Japanese study, two-day exposure to xylitol (7 g xylitol/day) resulted in no change in the salivary microbiota including the genus *Streptococcus* [46]. Also the control, a no-gum group, showed no study-induced changes (Table 1).

Effects of erythritol on MS levels

Only one erythritol study qualified the inclusion criteria: Runnel et al. [42]. In the trial, erythritol candy use was associated with lower MS counts compared to baseline only at the three-year examination, but not at the one-year or two-year examinations [42]. No changes were detected in the control, the sorbitol candy group or the xylitol reference group [42] (Table 1).

No prospective RCTs on the effects of erythritol consumption on the oral microbiota were identified.

Adverse effects

Possible adverse effects connected with the use of the test and control products were recorded and reported in nine of the 21 studies. In eight studies, no adverse effects were found either in the test or control groups [26,28,32,36,40,41,43,44]. In the study by Seki et al. [37], 11% of the children in the xylitol chewing gum group experienced diarrhoea; however, in the no-gum control group, the percentage of children with diarrhoea was higher, 24%.

Discussion

The main finding of the present review was that xylitol consumption decreased MS counts in plaque and/or saliva. The main finding is consistent with results from clinical studies published before the year 2000 [10,11,21].

The first study on the effects of xylitol consumption on MS counts consisted of the reports of the Turku sugar studies [47]. After that several trials with different study designs have evaluated the effects of xylitol consumption on MS numbers. The majority of them have suggested that xylitol could have a MS-reducing effect; however, not all of them have confirmed this effect [21]. In recent years, with the development of multispecies microbiota analysis techniques effects of xylitol on the microbiota have been studied [43,45,46] and fewer papers have been published with saliva or plaque MS as the primary outcome measure. However, especially Indian research groups have recently published several papers on the effects of xylitol chewing gums and other xylitol vehicles on MS counts in children and adults [48–50]. Unfortunately, these papers did not meet the inclusion criteria for the present review.

The xylitol studies have suggested that there is a dose dependency in the effects of xylitol on both MS counts and caries occurrence [30,51]. Xylitol is not an antimicrobial substance and shows no retention to the oral cavity, thus the oral health effects may presuppose several daily exposures to xylitol. The published xylitol studies have indicated that daily doses of 4–5 g or more are needed for the MS-decreasing effect of xylitol [11]. All four xylitol papers with a low risk of bias were conducted with daily xylitol doses of 6 g or more [30,34–36]. In four of the five studies with a fair quality, the daily xylitol dose was also 6 g or more [32,33,38,43]. In the xylitol study with a rather low xylitol dose (2.5 g/day), caries occurrence decreased significantly in the xylitol group while the MS decreases were small though statistically significant [44]. In three studies, the test products contained 26–37% xylitol w/w but still performed well in reducing MS [35,36,44]. Actually, of all 21 studies included in the review only the study by Oscarson et al. [31] was conducted with a very low xylitol dose (0.5–1 g/day). The xylitol dose should always be taken into consideration when planning xylitol studies or writing xylitol reviews. For example, the technically skilful Cochrane review on xylitol-containing products for preventing dental caries included only 10 papers for evaluation [52]. Five of these studies were conducted with very low daily xylitol doses and one in subjects with a very low

caries occurrence. Thus, the conclusions of the review are questionable since they are based on the results of only four papers [52].

Few recent studies have set out to evaluate the effects of habitual xylitol consumption on the microbiota. The studies included in this review had either an unclear [38,43] or high risk of bias [45,46]. Based on the results of the three studies that employed multispecies probe approaches no effects on the overall microbiota were detected by xylitol consumption [43,45,46]. Also the results of the pilot study involving 14 microbial plaque species supports this idea [38]. The study by Takeuchi et al. [46] lasted only two days, which may be too short a test period to even expect any changes in the microbiota. In one of the above studies that included pre-screening of the subjects for high MS counts, not only microbiota analysis with HOMIM but also plate culturing of MS was used [43]. The HOMIM signals for MS were reported to be very low, and thus the results of the plate culturing were used to interpret changes in MS counts [43]. Such a finding is logical since MS form only a small percentage of the oral flora of healthy subjects even in 'mutans-millionaires' [53]. Consequently, the microbiota analyses based multispecies probe approaches used in the papers included in this review may not be appropriate if conclusions also on MS counts are to be drawn. The study by Rafeek et al. [45], employing high throughput sequencing of the 16S rRNA gene, appears to be a good example of the problem. It is highly unlikely that 29 adult subjects of whom at least some had a history of caries would show hardly detectable numbers of both *S. mutans* and *S. sanguinis*, and no lactobacilli in their microbiota? It has been suggested that targeted assays by PCR would be better in detection of MS than multispecies approaches [2]. As Banas and Drake [3] discuss in their method-oriented review, 16S rRNA gene-based approaches for cataloguing microbial diversity may suffer from potential experimental errors especially in detection of oral streptococci. On the other hand, for example, the multispecies approach Illumina MISeq sequencing method has detected MS in numbers comparable to culturing [54]. The multispecies approaches are useful in obtaining a 'big picture' of the oral microbiota in health and disease, but some of them may still need more method development.

The study by Runnel et al. [42] included in this review showed MS decreases in association with erythritol consumption only in the third study year, but not at the one- or two-year examinations. This was not reported in the abstract and thus the trial was deemed to suffer from selective reporting. The authors postulated that treatment during the span of the study was relatively mild: test products were only consumed three times a day with the last consumption around 2 pm, the test products were consumed only during weekdays, and not consumed at all during 2 months of school vacation [42]. These drawbacks apply to the results obtained in the study for xylitol effects as well [42]. In *in vitro* studies erythritol has inhibited growth of MS [55] and polysaccharide-mediated adherence of MS [56]. The few published clinical studies with erythritol chewing gums or candies have shown contradictory results for erythritol effects on MS counts [14,55]. In these studies, the daily erythritol doses were 5 g per day or more. In one study [55], MS decreased both in the erythritol and xylitol group, while in the other [14] only in the xylitol group. These studies did not meet with the inclusion criteria of the present review since the study subjects were not healthy.

An important factor when conducting MS studies especially with MS as the primary outcome measure should be pre-screening of the subjects at least for presence of MS. If a high number of the subjects have no MS in their plaque or saliva samples the results will be biased. Of the 20 studies that set out to analyse effects of xylitol on MS counts, only four that were deemed high or fair quality included pre-screening of the subjects for MS [30,36,43,44]. In two of these studies, the subjects showed in addition a high caries risk [36,44]. Also the study by Shinga-Ishihara et al. [40] used pre-screening of the subjects for MS. The study by Ly et al. [35] took this point into consideration by analysing all subjects and those with non-measurable MS separately. Also the study by Lif Holgerson et al. [34] reported the number of children with no MS at baseline. The low mean values of MS in the studies of Seki et al. [37] and Bahador et al. [39] may be a reflection of a high number of subjects with non-measurable counts of MS. This may be a problem also in the Runnel et al. trial [42], but most probably the low salivary MS counts reflect omitting stimulating saliva by chewing before the MS test was performed. Also washout periods are of importance especially in countries, where xylitol or erythritol products are available. A washout period before the study may eliminate one confounding factor and also reduce the effects of mouthwashes and toothpastes on the oral microbiome before the study starts. Only four of the studies included in this review had a washout period [38,39,43,45].

Digestive disorders are often connected in the literature with polyol consumption, the only exception being erythritol. Xylitol belongs to FODMAP (fermentable oligo-, di-, monosaccharides and polyols) substances which may not suit persons with a tendency for digestive disorders. For dental health benefits, however, relatively small daily doses of xylitol are needed [10,11]. In fact, complaints about digestive discomfort in xylitol studies are rare [57]. The results of our review support the idea of xylitol being well tolerated in doses benefiting dental health. Eight of nine studies in which adverse effects were enquired and reported [26,28,32,36,40,41,43,44], three of them being of high or fair quality [32,43,44], found no adverse effects in connection with xylitol consumption. The results of the low-quality study by Seki et al. [37] are confusing since diarrhoea was experienced twice as much in the no-gum control group compared to the xylitol gum group.

The MS decreases associated with xylitol consumption have been attributed to growth inhibition, elevated pH in the mouth, and a decrease in adhesive polysaccharides produced by MS [11]. In some reviews, the caries-preventive effect of xylitol was attributed to the chewing process [58] even though xylitol administered with pastilles [59], syrup [60] and wipes [15] has also reduced caries. The decreases in the MS counts in the xylitol studies appeared not to be

affected by the 'chewing effect'. In eight of the nine xylitol studies with a high or fair quality, a polyol product was the control. In seven of these studies, no change was detected in the polyol control group, while a decrease in MS was found in the xylitol group [30,32–34,36,38,44]. In the study by Ly et al. [35], the control group showed decreases in MS counts, but the controls consumed 44.7 g maltitol per day, which may have been a confounding factor. Only one study with fair quality used both a polyol chewing gum and no gum as the controls, in both control groups, no changes in MS counts were detected [33]. These results are in line with earlier ones, supporting the idea that xylitol has a specific MS- decreasing effect [11,12].

Whatever the mechanisms behind the xylitol-associated MS decreases, xylitol consumption appears to result in a favourable shift in the composition of the oral microbiota since only MS appear to be targets of xylitol. Prebiotics are traditionally defined as promoters of the growth of beneficial intestinal microorganisms. However, the term prebiotic has recently been applied to the oral microbiota to describe substances that drive beneficial changes in the oral microbiota increasing resistance to dysbiosis and recovery of health [61]. Arginine may beneficially change the composition of the caries microbiota and has been classified as a prebiotic in the literature [61]. Accordingly, xylitol could be called an oral prebiotic, since by decreasing MS without affecting the overall microbiome it is associated with a beneficial change in the caries microbiota.

We found 21 studies that met the inclusion criteria of the review. Surprisingly, many studies showed a high or fair quality, altogether nine. The studies evaluated were very heterogeneous with respect to subjects, methods and study designs. A weakness of the review is that no meta-analysis was used. Also a more detailed scoring of the papers might have improved the review [62]. One strength of the review, however, is that it takes into consideration methodological issues, which are often overlooked.

The present review identified nine studies on xylitol and MS with either a high or fair quality. Based on their results, it is likely that habitual consumption of xylitol chewing gum or candies decreases MS counts in children and adults both in short-term and long-term consumption. Xylitol consumption appears not to influence the overall microbiota, but this topic clearly needs further study. As for erythritol, in the only study that met the inclusion criteria, erythritol consumption did not show consistent effects on MS counts. The topic, too, needs further, well-controlled studies.

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