Review Article

Caries Research

Caries Res 2019;53:491–501
DOI: 10.1159/000499194

Received: August 31, 2018
Accepted after revision: February 26, 2019
Published online: May 6, 2019

Oral and Systemic Effects of Xylitol Consumption

Sok-Ja Janket[a] Jaspreet Benwait[b] Paul Isaac[c] Leland K. Ackerson[d]
Jukka H. Meurman[e]

[a]Translational Oral Medicine, Forsyth Institute, Cambridge, MA, USA; [b]Boston University School of Public Health, Boston, MA, USA; [c]Research Externship, Edwin O. Smith High School, Storrs, CT, USA; [d]Department of Public Health, University of Massachusetts, Lowell, MA, USA; [e]Department of Oral and Maxillofacial Diseases, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Keywords
Anticariogenicity · Antiacidogenicity · Glucosyltransferase · Gut dysbiosis · Low-glycemic effects · Gut microbiome

Abstract
Recent results of randomized trials testing the efficacy of xylitol in caries prevention have been conflicting. This narrative review reveals the sources of discrepancy. The following databases were searched for the terms "xylitol" or "artificial sweeteners" restricted to the English language: PubMed, Web of Science, Evidenced-Based Medicine, Scopus, and the Cochrane database. In a separate search, the terms "dental caries" or "cariogenicity" or "glucosyltransferase" or "low glycemic" or "low insulinemic" or "dysbiosis" or "gut microbiome" were used and then combined. In section I, findings regarding the role of xylitol in dental caries prevention, the appropriateness of research methods, and the causes for potential biases are summarized. In section II, the systemic effects of xylitol on gut microbiota as well as low-glycemic/insulinogenic systemic effects are evaluated and summarized. The substitution of a carbonyl group with an alcohol radical in xylitol hinders its absorption and slowly releases sugar into the bloodstream. This quality of xylitol is beneficial for diabetic patients to maintain a constant glucose level. Although this quality of xylitol has been proven in in vitro and animal studies, it has yet to be proven in humans. Paradoxically, recent animal studies reported hyperglycemia and intestinal dysbiosis with artificial sweetener consumption. Upon careful inspection of evidence, it was revealed that these reports may be due to misinterpretation of original references or flaws in study methodology. Any systemic benefits of xylitol intake must be weighed in consideration with the well-established adverse gastrointestinal consequences. The contribution of xylitol to gut dysbiosis that may affect systemic immunity warrants further research.

Role of Xylitol in Dental Caries Prevention

Obstacles in the Quantification of Caries Activities

Although xylitol is widely believed to have anticariogenic properties [Mäkinen et al., 1996b], the scientific evidence quantifying the reduction in caries incidence is sparse. This impediment is due to the time lapse in the emergence of dental caries after cariogenic exposure [de

E-Mail karger@karger.com
www.karger.com/cre

Jaspreet Benwait, BDS, MPH
Boston University School of Public Health
715 Albany Street
Boston, MA 02118 (USA)
E-Mail jaskaur4@bu.edu

Paola and Alman, 1972] and the reversible nature of de- and remineralization of dental enamel. Although some studies had a long enough duration to observe cariogenicity [Sintes et al., 1995; Mäkinen et al., 1996a; Sintes et al., 2002; Mäkinen et al., 2005], various methodological deficiencies make it difficult to conclusively determine the efficacy of xylitol in caries prevention. Furthermore, many factors affect cariogenicity, including the acidogenic potential of fermentable carbohydrates, alterations in salivary flow, frequency, and type of carbohydrate exposure, stickiness of carbohydrates, and oral hygiene self-care [DePaola et al., 1989]. Unfortunately, confounding factors such as oral self-care practice, diet characteristics, and fermentable carbohydrate exposure frequency have not been controlled for in any of the studies evaluating the anticariogenic effect of xylitol.

To offer as evidence for causality, only original research in longitudinal or intervention studies should be considered as scientific proof. Thus, reviews or expert opinions were not included. To date, many studies have substantial shortcomings such as poor evidence of causal direction and absence of an appropriate control group. Nevertheless, others listed studies that used no or inappropriate controls as strong evidence for the anticariogenicity of xylitol [Maguire and Rugg-Gunn, 2003]. Most well-conducted reviews reported the evidence of "poor quality" without critical assessment of the methodology or the deficiencies thereof. Clear delineation of deficiencies in each study will expand our scientific understanding and knowledge.

Low- or anticariogenicity of xylitol can be attributable to its passive substitution of fermentable carbohydrates [Van Loveren, 2004] and subsequent reduction of acidogenic potential [Bradshaw and Marsh, 1994], increased salivary flow [Dowd, 1999], and inhibition of cariogenic *Streptococcus mutans* [Vadeboncoeur et al., 1983; Trahan et al., 1985]. However, a recent research trend testing xylitol as an active caries suppressor resulted in many null results.

Methodologic Issues in Caries Research

Several randomized trials in children reported reduced caries activities after intervention with xylitol, but the study designs and executions were fraught with deficiencies and biases. In multigroup comparison analyses such as in ANOVA, one group (for example, no chewing gum group) can result in a highly significant *p* value. To avoid biases such as this, if the intervention is chewing xylitol gum, increased salivary flow due to the mechanical action of chewing has to be controlled by employing chewing gum base without the active ingredient as a reference. Not using any gum as a comparator group will bias the results as shown in one study [Mäkinen et al., 1995]. Nevertheless, this study has been quoted as the largest study with a positive impact of xylitol chewing gum on dental caries.

If xylitol wipes were used as an intervention, the control group should employ wipes without xylitol, to eliminate bias from the mechanical removal of biofilm by wiping [Zhan et al., 2012]. Wiping action with different forces will also generate another bias. Additionally, if the outcome was measured by dmfs or dmft in the mixed dentition, missing teeth due to natural exfoliation might have a different rate of caries, and this will bias the results.

A recent elaborate trial in adults resulted in a null result due to using a control that has similar anticaries action [Bader et al., 2013]. This study employed as a reference group sucralose, which also inhibits glucosyltransferase in *S. mutans* [Bowen and Pearson, 1992; Bowen, 2013]. Thus, both experimental and control groups used low-cariogenic sweeteners which decreased the contrast between the groups [Smith et al., 1979; Devulapalle and Mooser, 2001]. For the same reason, comparing xylitol-containing toothpaste to sorbitol-containing toothpaste did not generate a significant reduction in dental caries in children [Chi et al., 2014]. As expected, the contrast between xylitol and other low-cariogenic sweeteners such as sucralose or sorbitol was not significantly different. We recognize the ethical dilemma of not employing sucrose as a control group because it has been proven to be cariogenic in humans. Nevertheless, using other low-cariogenic controls will diminish the difference between the groups and result in a nonsignificant anticaries action of xylitol. This will generate the impression that xylitol has no anticariogenic action, which may not be correct.

To determine statistically significant differences in this kind of trial, the changes from baseline to the study end in the experimental group must be compared to the changes in the control group. Unfortunately, many trials compared only the values after the test. As shown in Figure 1 (simulated data), if only posttreatment values are compared, it appears the xylitol group has lower caries activities. However, if using the correct method of comparing the changes from baseline in the two groups, the results will not be significant, because the two groups are exactly parallel, which means the intervention did not bring any changes. In a recent trial, xylitol-containing chewing gum plus oral health education was compared to oral health education alone among hearing- and vision-impaired children. The results showed the significant anticaries and antiplague effects of xylitol-containing chew-

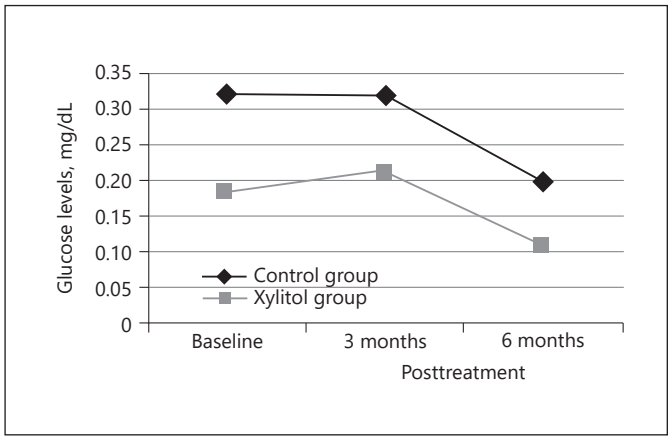

Fig. 1. Salivary glucose levels in the xylitol chewing gum and control groups (simulated data). Simulated diagram showing the statistical knowledge requirement in intervention trials.

ing gum use. However, this study may also be biased because the study ignored the chewing-related salivary flow increase and its cleansing action [Watthanasaen et al., 2017]. Notably, chewing gum may not be an appropriate intervention for the elderly population who commonly have temporomandibular dysfunction [Nguyen et al., 2018].

Superiority of Xylitol over Other Sugar Alcohols

To demonstrate the superiority of xylitol over other low-cariogenic sweeteners, the results must show a significant decrease in caries incidence in the xylitol group. However, xylitol was superior in one study [Splieth et al., 2009], and sorbitol was superior in another [Wennerholm and Emilson, 1989]. Comparing erythritol/maltitol versus xylitol/maltitol (which is basically comparing erythritol to xylitol because maltitol is constant in both groups) did not result in caries reduction [Lenkkeri et al., 2012]. All these conflicting results brought skepticism regarding the anticariogenicity of xylitol in the public's view. However, the meta-analysis by Deshpande and Jadad [2008], which we did not include in our review because it is not an original research, reported that that chewing gums containing xylitol decreased caries rate by 58.7% and those containing sorbitol by 20%. However, their results did not account for caries reduction due to salivary flow or mechanical stimulation of chewing-related anticariogenicity and, thus, may be biased [Deshpande and Jadad, 2008].

Perhaps, it is useful to define "anticariogenicity" here as "any process that decreases caries experience." Anticariogenicity in this context includes fluoride application, Listerine mouth rinse, chlorhexidine rinse, and increased salivary flow. Xylitol decreases caries by inhibiting glucosyltransferase which blocks glucose utilization by *S. mutans* and their adhesion to the tooth surface. The anticariogenicity of xylitol chewing gum, however, is the combined effect of glucosyltransferase-related anticariogenicity plus chewing-related anticariogenicity. Thus, to prove the pure anticaries action of xylitol, the control group must chew similar gum base without xylitol.

Cariogenic Bacteria Quantification

Several studies quantified *S. mutans* or *Streptococcus mitis* when xylitol was consumed. Significantly decreased *S. mutans* in the saliva was observed with xylitol consumption [Wennerholm et al., 1994]. However, sugar restriction also decreased the level of *S. mutans* indicating that the inhibition of *S. mutans* is a passive suppression via sugar depletion [Wennerholm et al., 1995]. Meanwhile, consumption of xylitol-containing snacks and candy did not reduce *S. mutans* levels [Roberts et al., 2002]. The *S. mutans* quantification may assume that *S. mutans* is the leading cariogenic microbe. In reality, *Lactobacillus* spp. and *Actinomyces* could also contribute to caries development [Brailsford et al., 1999; Beighton, 2005; Caufield et al., 2007; Thabuis et al., 2013]. However, all these microbes could be innocent bystanders that tolerate low pH generated by fermentation of carbohydrates and may not be causative agents for caries [Beighton, 2005]. This bystander theory can be corroborated by the fact that their numbers and pH-lowering potential were not statistically different between caries-prone groups and groups that are not caries prone [Sansone et al., 1993].

Maternal Transmission of Cariogenic Bacteria to Children

Several groups examined mother and child pairs assessing the maternal xylitol consumption and transmission of bacteria to their child in randomized trials. When the child is newly born, the mother's immunity may affect the neonate's immunity. But after 6 months, when the child starts eating solid foods, the mother's xylitol gum chewing may have a very little impact on the child's oral microbiome. It is well known that the microbial community evolves with the available substrates and the diet, as shown in the gut microbiome [David et al., 2014; Vieira et al., 2014] as well as in the oral cavity [Ribeiro et al., 2017]. Interestingly, the time frame of solid food introduction coincided with the reported colonization of *S. mutans* in 20% of infants aged 6–9 months [Mohan et al., 1998]. Nevertheless, several studies reported a potentially

spurious correlation of maternal xylitol consumption with offspring dental caries incidence [Isokangas et al., 2000; Söderling et al., 2001]. Meanwhile, others did not find any such protective action of maternal xylitol consumption on children's caries activities [Thorild et al., 2004; Hanno et al., 2011]. Also, 50% of children in the low-*S. mutans* group were cared for by persons other than the mother suggesting that the *S. mutans* level might have been linked to the diet shared by mother and child [Caufield et al., 1993]. The child's inoculation of oral *S. mutans* is multifactorial. It has been proven that age, number of teeth, and bottle with sugared beverage usage were all related to the emergence of *S. mutans* in the child's oral cavity [Mohan et al., 1998].

Comparison of Xylitol to Fluoride Products

It has been reported that the low acidogenicity of xylitol may aid subsequent low-cariogenic action as a "passive process of substituting sugar or other fermentable carbohydrates" [Imfeld, 1993]. A clear reduction of fermentation of xylitol compared with natural glucose, sucrose, and fructose has been shown in vitro, and xylitol did not lower the pH below the critical value of 5.5 [Splieth et al., 2009; Almståhl et al., 2013]. Some early studies, however, did not observe any changes in the acidogenic potential with xylitol mouth rinse in comparison to fluoride rinse [Giertsen et al., 1999]. This study has proven that anticariogenicity of xylitol mouth rinse is not superior to fluoride rinse.

Several recent randomized trials exhibited better methodologic quality, and yet results were conflicting [Zhan et al., 2012; Lee et al., 2015]. Lee et al. [2015] reported that "Xylitol consumption did not have an additional benefit over fluoride treatment." In 2012, Zhan et al. enrolled 6- to 35-month-old children ($n = 44$) and randomly assigned them to xylitol wipes or wipes without active ingredients. At the end of the study (12 months), they observed "significant reduction in new caries in xylitol wipes group" but "no significant differences were observed in levels of mutans streptococci and lactobacilli at all time-points between the two groups" [Zhan et al., 2012]. However, the imbalance in maternal snacking patterns and the force of wiping biofilm could have biased the results of this trial. Randomization may not balance all risk factors when the sample size is small [Rothman, 1977].

Another recent trial among adults reported a significant decrease in incipient dental caries and progression of the same in the xylitol chewing gum group compared with the group that chewed gum sweetened with a combination of isomalt, sorbitol, mannitol, and maltitol for 1 year [Cocco et al., 2017]. Unlike in the previous study [Bader et al., 2013], Cocco et al. [2017] prohibited other dental caries-limiting activities such as fluoride treatment during the experiment, except for personal oral hygiene practices, but we question the ethical basis for this prohibition. They reported a significantly lower caries increment with xylitol chewing gum use for 1 year compared with polyol gum use. Their overall results should read "The comparison between the two follow-up evaluations (12 and 24 months from baseline) showed no statistically significant differences between the two groups" but xylitol gum chewing showed slightly lower dental caries experience in the severe-caries group. However, gum chewing may be contraindicated in older adults to avoid temporomandibular dysfunction [Tabrizi et al., 2014; Nguyen et al., 2018].

Concluding Remarks

The relationship of xylitol with dental caries can be summarized as follows:

The evidence that chewing gum containing xylitol is superior to chewing sugared gum is reasonably strong with relatively little bias [Scheinin et al., 1975].

The evidence for the mechanism that xylitol suppresses dental caries via inhibition of glucosyltransferases in cariogenic bacteria is reasonably strong [Devulapalle and Mooser, 2001; Bowen and Koo, 2011]. However, sorbitol and sucralose also demonstrated similar anticariogenic effects in animal models [Bowen and Pearson, 1992].

The evidence regarding low acidogenicity of xylitol is sufficiently strong [Marsh et al., 1992; Almståhl et al., 2013].

The evidence for superior noncariogenicity of xylitol over other sugar alcohols is not sufficient. Several studies reported that erythritol may be comparable [Thabuis et al., 2013] or superior to xylitol in caries inhibition [Falony et al., 2016]. However, many of these studies were conducted in children with mixed dentition where missing teeth might have different rates of caries, and this information was not considered. Thus, the missing teeth would have biased the results.

The evidence is insufficient to support the thesis that the anticariogenic effect of xylitol is comparable to fluoride or chlorhexidine [Giertsen et al., 1999]. However, some large-scale trials in school children reported improved anticaries action of toothpaste with added xylitol in addition to fluoride [Sintes et al., 1995, 2002]. However, the outcome which ignored caries activities in missing teeth could have biased the results.

The evidence regarding whether xylitol promotes remineralization is equivocal. In 2 in vitro studies, one study result supports the remineralization capability of xylitol [Cardoso et al., 2014] while the other does not [Shen et al., 2017]. In the former study, the remineralization was observed in conjunction with fluoride plus xylitol. Thus, the independent action of xylitol on remineralization cannot be determined.

The evidence regarding maternal xylitol consumption preventing children's dental caries is highly spurious. Other prenatal nutrients (for example, vitamin D) could influence the enamel strength and subsequent dental caries susceptibility [Schroth et al., 2014]. Thus, attributing lower dental caries incidence in children solely to maternal xylitol consumption is overly simplistic.

In summary, xylitol may be useful as a low-cariogenic sweetener [Fontana and González-Cabezas, 2012], and this benefit is from passively replacing fermentable sugar [Imfeld, 1993]. Additionally, some systemic adverse effects must be considered before recommending wider xylitol use. These systemic effects of xylitol consumption will be discussed in the next section.

Xylitol in Systemic Health

Xylitol and Low-Glycemic Effects

In 1986, the United States Food and Drug Administration declared xylitol as safe for human use. Since then, it has been registered as "generally safe" for utilization in foods, pharmaceuticals, and oral health care products in many countries. Generally, safe amounts of xylitol consumption are 50 g/day for adults and 20 g/day in children, respectively [Ur-Rehman et al., 2015]; 50 g of xylitol are also safe in infusion solutions for parenteral nutrition [Schneider et al., 2014].

Xylitol belongs to the group of sugar alcohols, polyols, in which the carbonyl moiety (- – - C = O) of carbohydrates is replaced by an alcohol radical (- – - CH-OH). For this reason, most names of sugar alcohols end with "ol" [Nadimi et al., 2011]. Substitution of the carbonyl group with an alcohol group hinders digestion and metabolism, which contributes to the low-glycemic and insulinemic properties [Livesey, 2003]. The increased carbon number of the backbone structure is inversely related to the absorption rate in the intestine. Absorbed xylitol is converted to glycogen or glucose, which is slowly released to the bloodstream. Thus, xylitol demonstrated low-glycemic as well as low-insulinemic indices [Livesey, 2003]. These qualities of xylitol are highly desirable for maintaining stable glucose levels in diabetic subjects [Livesey, 2003].

Also, gastric emptying was significantly slower with xylitol intake as shown in a recent double-blind, crossover, randomized trial among 5 lean and 5 obese humans [Wölnerhanssen et al., 2016]. This can prevent hunger sensation and food intake. However, low-insulinemic effects were only slightly affected [Wölnerhanssen et al., 2016]. Interestingly, in lean subjects, xylitol intake did not affect glucose excursion, but in obese individuals, it significantly increased plasma glucose response ($AUC_{0–180\ min}$) suggesting that obesity is the effect modifier [Wölnerhanssen et al., 2016].

The hallmark of low-glycemic foods is low postprandial glucose excursion, which prevents the subsequent severe hypoglycemic trough [Zhang et al., 2012]. Some more important factors in determining postprandial glycemic response include the fiber contents, ripeness of fruits, fat contents, and the degree of pulverization (in whole grains) [Janket et al., 2008]. In general, low-glycemic foods require extensive mastication due to high fiber content. Thus, dental health directly affects healthy glycemic control aside from a standpoint of inflammation of oral infections [Janket et al., 2008]. With low-glycemic response and slow gastric emptying [Livesey, 2001], xylitol helps in both preventing obesity and maintaining a steady glucose level, an ideal condition for diabetic patients [Nguyen et al., 1993; Natah et al., 1997].

However, recent animal studies conflict with these human studies [Natah et al., 1997; Reyna et al., 2003]. In mice, artificial sweeteners reportedly caused impaired glucose responses [Swithers et al., 2013; Suez et al., 2014]. High-sugar/high-fat diets given to the mice simultaneously in these studies might have biased the results. Weight gain alters the microbiome as previously reported [Janket et al., 2015, 2018]. Although a prominent medical website also has warned readers of the hyperglycemic effects of sugar alcohol consumption [Mayo, 2016], this claim was proven to be a misinterpretation of the original reference [American Diabetes, 2016]. Furthermore, the results from human randomized trials did not support the thesis that artificial sweeteners produce hyperglycemic responses [Grotz et al., 2003; Barriocanal et al., 2008; Maki et al., 2008]. Only when a low-calorie experimental diet was given with sucralose, were significant low-glycemic effects observed [Reyna et al., 2003]. Thus, diet and body weight are strong confounders in the glycemic responses from artificial sweeteners [Reyna et al., 2003; Janket et al., 2015]. The glycemic benefits of artificial sweeteners are likely via the replacement of fermentable car-

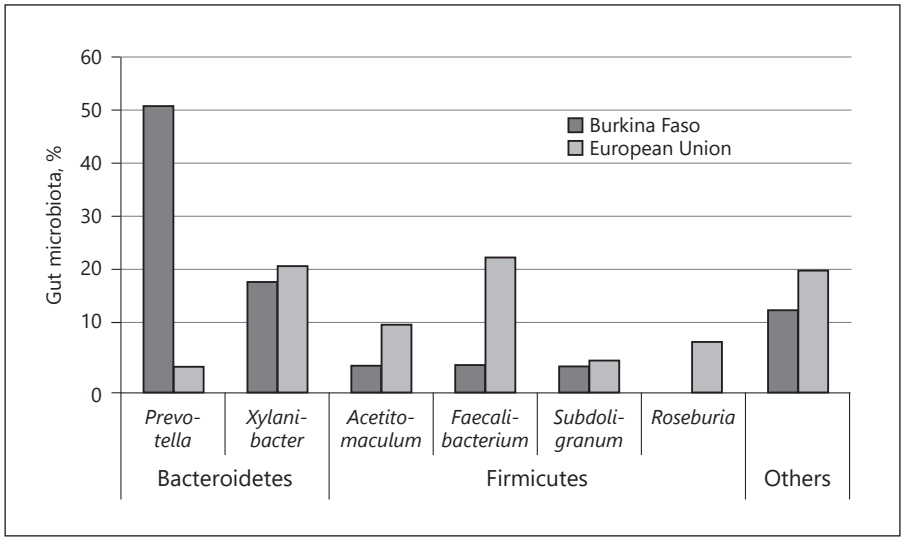

Fig. 2. Different gut microbiota proportions (%) according to dietary patterns.

bohydrates rather than any direct effects [Gardner et al., 2012]. The controversies regarding the role of artificial sweeteners on weight and glycemic control will not subside until large-scale randomized trials in humans with controlled physical activities and diets can be conducted.

The potential untoward consequences associated with the xylitol consumption must also be mentioned. Unabsorbed xylitol can be fermented in the colon by bacteria, resulting in the production of a considerable amount of hydrogen. Some researchers speculate that hydrogen from fermented carbohydrates may alleviate autoimmune colitis by neutralizing oxidative stress [Zhang et al., 2012]. Also, unabsorbed and subsequently fermented xylitol may contribute to the generation of butyric acid that helps in maintaining healthy colonic mucosa [Mäkeläinen et al., 2007]. However, the hydrogen gas can also cause flatulence [Sels et al., 1998; Mäkeläinen et al., 2007], and unabsorbed xylitol in the gut can also increase osmotic pressure and cause laxation and diarrhea [Mäkinen, 1984; Storey et al., 2007; Mäkinen, 2016;]. Additionally, the fecal microbiome was reported to shift from gram-negative to gram-positive bacteria with xylitol consumption [Salminen et al., 1985]. Therefore, utilization of xylitol for its low-glycemic/insulinemic benefits requires careful consideration [Livesey, 2001]. Intestinal dysbiosis associated with xylitol consumption will be discussed further in the next section.

Xylitol Intake and Gut Dysbiosis

The human gut has approximately 100 trillion microbes encompassing 35,000 bacterial species called "gut microbiome" [Frank et al., 2007]. Specific anatomical niches have unique microbiomes [Lloyd-Price et al., 2016], and they are cohabiting and co-evolving with humans. The 4 predominant groups of the gut microbiome are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria followed by archaea, viruses, and fungi. A healthy gut contains Firmicutes (32.4–36.5%) and Bacteroidetes (42.0–46.3%). These proportions change in obesity to Firmicutes 48.1% and Bacteroidetes 31.3% [Koliada et al., 2017].

Unlike the gut, the oral cavity is dominated by Firmicutes (41%) and Proteobacteria (20.1%) followed by Bacteroidetes (13%) and Actinobacteria (11.3%) [Dewhirst et al., 2010]. Well-known oral Firmicutes include staphylococci and streptococci, while oral proteobacteria are comprised of gram-negative phyla that include Pseudomonadaceae, *Neisseria, Campylobacter,* and *Helicobacter* genera [Dewhirst et al., 2010]. Meanwhile, predominant gut proteobacteria include *Brucella, Rickettsia* as well as *Escherichia, Shigella, Salmonella,* and *Helicobacter*. Lastly, oral Bacteroidetes are comprised of the genera *Prevotella, Bacteroides, Porphyromonas, Tannerella, Bergeyella, Capnocytophaga,* and Actinobacteria [Dewhirst et al., 2010]. Some oral Bacteroidetes are implicated in periodontitis [Mombelli et al., 2000].

What one eats has profound impacts on the oral and gut microbiome and general health [Cani et al., 2008]. Another example of diet influencing the microbiome can be found in the study by De Filippo et al. [2010] where *Prevotella* and *Xylanibacter* are enriched in children eating high-fiber diets in Burkina Faso (Fig. 2). These bacte-

ria are minimally present in European children consuming a high-sugar/high-fat Western diet. These facts suggest that a high-fiber African diet may encourage Bacteroidetes growth while the Western diets enrich the growth of Firmicutes [De Filippo et al., 2010]. The microbial composition changes due to different diets are shown in Figure 2.

It is plausible for the microbiome to change with artificial sweeteners like xylitol which inhibits the growth of predominantly glucose fermenting microbiotas via glucosyltransferase. Indeed, the fecal microbiome shifted from gram-negative to gram-positive bacteria in humans and mice after xylitol consumption [Salminen et al., 1985]. It can be postulated that Firmicutes including streptococci die off in the gut and be excreted in feces.

Also, several animal studies reported dysbiosis with artificial sweetener consumption resulting in subsequent impaired glucose metabolism and weight gain [Suez et al., 2014; Burke and Small, 2015]. More specifically, moderate doses of xylitol consumption added to high-fat diets in mice resulted in decreased Bacteroidetes proportion, notably the genus *Barnesiella* in the family of Porphyromonadaceae while increasing the Firmicutes proportion [Uebanso et al., 2017]. These changes are consistent with the observation in obesity, where the Firmicutes/Bacteroidetes ratio was increased. However, upon examining this study carefully, xylitol in the control diet did not change the weight of the mice. Thus, these dysbiotic changes may be attributable to the high-fat diet [Uebanso et al., 2017].

Gut dysbiosis has been widely believed to cause the metabolic syndrome and other obesity-related comorbidities, but studies that put forth this hypothesis have failed to apply all the causality establishment criteria [Janket et al., 2018]. In a murine model, mice fed Splenda (sucralose and maltodextrin) increased proteobacteria, dysbiosis, and myeloperoxidase reactivity [Rodriguez-Palacios et al., 2018]. However, the increase in proteobacteria could be filling the voids generated by decreased Firmicutes (i.e., streptococci). Indeed, one expert stated that erroneous conclusions can be drawn in identifying one specific microbiota from the microbiome [Cani, 2018]. In vitro human fecal culture with xylitol has increased *Anaerostipes hadrus or A. caccae*, butyrate producers [Sato et al., 2017]. However, fecal culture is totally different from human trials where many foods and microbiotas are present simultaneously. It is nearly impossible to find one or several microbes causative to the human condition [Foster et al., 2017; Geva-Zatorsky et al., 2017]. Clearly, diet alters the gut microbiome. Therefore, unless the diet is identical in these studies, artificial sweeteners cannot be held culpable for gut dysbiosis. Further research is needed to elucidate how the microbiome changes with the intake of xylitol while holding the diet strictly the same between the compared groups.

Despite the low-glycemic and insulinemic effects of xylitol intake [Natah et al., 1997], several studies reported increased oxaluria, calciuria, and phosphaturia, which are risk factors for urolithiasis [Nguyen et al., 1993; Rodgers et al., 2009]. Researchers speculated that ketohexokinase and aldolase might be involved in oxalic acid formation [Rodgers et al., 2009]. The cause for the oxaluria, calciuria, and phosphaturia from xylitol consumption could be attributable to osmotic diarrhea which may cause metabolic acidosis [Narchi, 1998]. In acidosis, calcium reabsorption decreases leading to calciuria [Lemann et al., 1967]. However, any reference that shows xylitol consumption actually leads to urolithiasis in humans cannot be found.

On a positive note, an in vitro study has proven that xylitol suppressed the growth of α-hemolytic, β-hemolytic streptococci, and *S. pneumoniae* [Kontiokari et al., 1995]. Assuming the same is true in vivo, xylitol use in cold medications would be beneficial in this regard [Janket, 2012]. Unfortunately, more detrimental results of consumption of xylitol or other artificial sweeteners are mounting. In murine models, Streptococcaceae *Streptococcus, Dehalobacterium, Anaerostipes, and Ruminococcus* were reduced in sucralose-treated mice as expected from glucosyltransferase inhibition [Bian et al., 2017]. These bacteria were inversely associated with colonic inflammation [Willing et al., 2010; Munyaka et al., 2016]. However, upon careful inspection of the reference, it became evident that the gut inflammation caused dysbiosis [Willing et al., 2010; Munyaka et al., 2016], not the artificial sweetener. The sequence of biologic phenomena is important in establishing causality. In the study by Munyaka et al. [2016], gut inflammation was developed by colitis which was induced by dextran sulfate sodium, and colitis resulted in dysbiosis [Janket et al., 2018].

Lastly, some caveats must be stated regarding blind trust in microbiome sequencing data. Due to the variety of factors, this hugely popular concept of gut microbiome research has several flaws. Some studies revealed that microbiome alteration due to diet is largely dependent on genetics [O'Connor et al., 2014] and the analysis technique [Hugon et al., 2013]. Thus, the true diversity of the human gut microbiome remains unknown, and using fecal analyses to estimate the gut microbiome can be a major source of bias in understanding the causal role of the microbiome in human health [Janket et al., 2018].

Table 1. Systemic effects of xylitol intake

Relationships	Conclusions
Xylitol and low-glycemic effects	
Positive effects	
Absorbed xylitol converted to glycogen or glucose, slowly released to the bloodstream	• Results in low-glycemic as well as low-insulinemic indices [Livesey, 2003] • Desirable for maintaining stable glucose levels in diabetic subjects [Livesey, 2003]
Xylitol intake and slow gastric emptying	• Prevent hunger sensation and food intake; low-insulinemic effects were only slightly affected [Wölnerhanssen et al., 2016] • Lean subjects: xylitol intake did not affect glucose excursion • Obese individuals: glucose excursion significantly increased plasma glucose response ($AUC_{0–180\ min}$) suggesting that obesity is the effect modifier [Wölnerhanssen et al., 2016]
Xylitol + low-glycemic response + slow gastric emptying	• Helps in preventing obesity and maintaining a steady glucose level, an ideal condition for diabetic patients [Nguyen et al., 1993; Natah et al., 1997] • Only a low-calorie experimental diet given with sucralose resulted in significant low-glycemic effects [Reyna et al., 2003]; thus, diet and body weight are strong confounders in the glycemic responses from artificial sweeteners [Reyna et al., 2003; Janket et al., 2015]
Xylitol and butyric acid	• Helps in maintaining healthy colonic mucosa [Mäkeläinen et al., 2007]
Negative effects	
Xylitol in the gut	• Increase osmotic pressure and cause laxation and diarrhea [Mäkinen, 1984; Storey et al., 2007; Mäkinen, 2016]
Xylitol and fecal microbiome	• Reported to shift from gram-negative to gram-positive bacteria with xylitol consumption [Salminen et al., 1985] • Hence, utilization of xylitol for its low-glycemic/insulinemic benefits requires careful consideration [Livesey, 2001]
Xylitol intake and gut dysbiosis	
Positive effects	
Role of xylitol in suppressing the growth of α- and β-hemolytic streptococci, as well as *S. pneumoniae* in vitro [Kontiokari et al., 1995]	• Assuming the same is true in vivo, xylitol use in cold medications would be beneficial in this regard [Janket, 2012]
Negative effects	
Xylitol and microbiome	• Suppression of glucosyltransferase by xylitol inhibits the growth of predominantly glucose-fermenting microbiotas • Fecal microbiome shifted from gram-negative to gram-positive bacteria in humans and mice after xylitol consumption [Salminen et al., 1985]
Xylitol and dysbiosis (animal studies)	• Resulted in subsequently impaired glucose metabolism and weight gain [Suez et al., 2014; Burke and Small, 2015] • Moderate doses of xylitol consumption added to high-fat diets in mice resulted in decreased Bacteroidetes proportion, notably the genus *Barnesiella* in the family of Porphyromonadaceae while increasing the Firmicutes proportion [Uebanso et al., 2017] • These changes are consistent with obesity, where the Firmicutes/Bacteroidetes ratio was increased • Upon examining this study carefully, xylitol in the control diet did not change the weight of the mice; thus, these dysbiotic changes may be attributable to the high-fat diet [Uebanso et al., 2017] • These facts suggest that a high-fiber African diet may encourage Bacteroidetes growth while the Western diets enrich the growth of Firmicutes [De Filippo et al., 2010]
Xylitol and metabolic acidosis Xylitol consumption could be attributable to osmotic diarrhea which may cause metabolic acidosis [Narchi, 1998]	• This relationship results in increased oxaluria, calciuria, and phosphaturia, which are risk factors for urolithiasis [Nguyen et al., 1993; Rodgers et al., 2009] • In acidosis, calcium reabsorption decreases leading to calciuria [Lemann et al., 1967] • However, any reference that shows xylitol consumption actually leads to urolithiasis in humans cannot be found

In conclusion, xylitol has anticaries action when it replaces sugar. Also, low-glycemic and insulinemic effects of xylitol may be beneficial in maintaining a steady glucose level in both diabetic and nondiabetic populations. Whether our attempt to reduce dental caries by suppressing *S. mutans* will inadvertently cause dysbiosis must be elucidated in future research. Additionally, adverse systemic effects of xylitol require careful further scrutiny. Systemic effects of xylitol intake are summarized in Table 1.

Disclosure Statement

The authors declare no conflicts of interest.

Author Contributions

Dr. Janket and Dr. Meurman are the principal investigators; they designed the investigation, participated in the analyses, drafted and finalized the manuscript.

Dr. Ackerson, Dr. Benwait, and Paul Isaac participated in drafting the article and revising it critically for the content.

All authors gave approval for the final submitted version.

References

Almståhl A, Lingström P, Eliasson L, Carlén A. Fermentation of sugars and sugar alcohols by plaque Lactobacillus strains. Clin Oral Investig. 2013 Jul;17(6):1465–70.

American Diabetes A. Sugar alcohols. http://www.diabetes.org/food-and-fitness/food/what-can-i-eat/understanding-carbohydrates/sugar-alcohols.html, 2016.

Bader JD, Vollmer WM, Shugars DA, Gilbert GH, Amaechi BT, Brown JP, et al. Results from the Xylitol for Adult Caries Trial (X-ACT). J Am Dent Assoc. 2013 Jan;144(1):21–30.

Barriocanal LA, Palacios M, Benitez G, Benitez S, Jimenez JT, Jimenez N, et al. Apparent lack of pharmacological effect of steviol glycosides used as sweeteners in humans. A pilot study of repeated exposures in some normotensive and hypotensive individuals and in Type 1 and Type 2 diabetics. Regul Toxicol Pharmacol. 2008 Jun;51(1):37–41.

Beighton D. The complex oral microflora of high-risk individuals and groups and its role in the caries process. Community Dent Oral Epidemiol. 2005 Aug;33(4):248–55.

Bian X, Chi L, Gao B, Tu P, Ru H, Lu K. Gut Microbiome Response to Sucralose and Its Potential Role in Inducing Liver Inflammation in Mice. Front Physiol. 2017 Jul;8:487.

Bowen WH: Xylitol for adult caries. J Am Dent Assoc. 2013;144(5):470.

Bowen WH, Koo H. Biology of Streptococcus mutans-derived glucosyltransferases: role in extracellular matrix formation of cariogenic biofilms. Caries Res. 2011;45(1):69–86.

Bowen WH, Pearson SK. The effects of sucralose, xylitol, and sorbitol on remineralization of caries lesions in rats. J Dent Res. 1992 May;71(5):1166–8.

Bradshaw DJ, Marsh PD. Effect of sugar alcohols on the composition and metabolism of a mixed culture of oral bacteria grown in a chemostat. Caries Res. 1994;28(4):251–6.

Brailsford SR, Tregaskis RB, Leftwich HS, Beighton D. The predominant Actinomyces spp. isolated from infected dentin of active root caries lesions. J Dent Res. 1999 Sep;78(9):1525–34.

Burke MV, Small DM. Physiological mechanisms by which non-nutritive sweeteners may impact body weight and metabolism. Physiol Behav. 2015 Dec;152 Pt B:381–8.

Cani PD. Human gut microbiome: hopes, threats and promises. Gut. 2018 Sep;67(9):1716–25.

Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008 Jun;57(6):1470–81.

Cardoso CA, de Castilho AR, Salomão PM, Costa EN, Magalhães AC, Buzalaf MA. Effect of xylitol varnishes on remineralization of artificial enamel caries lesions in vitro. J Dent. 2014 Nov;42(11):1495–501.

Caufield PW, Cutter GR, Dasanayake AP. Initial acquisition of mutans streptococci by infants: evidence for a discrete window of infectivity. J Dent Res. 1993 Jan;72(1):37–45.

Caufield PW, Li Y, Dasanayake A, Saxena D. Diversity of lactobacilli in the oral cavities of young women with dental caries. Caries Res. 2007;41(1):2–8.

Chi DL, Tut O, Milgrom P. Cluster-randomized xylitol toothpaste trial for early childhood caries prevention. J Dent Child (Chic). 2014 Jan-Apr;81(1):27–32.

Cocco F, Carta G, Cagetti MG, Strohmenger L, Lingström P, Campus G. The caries preventive effect of 1-year use of low-dose xylitol chewing gum. A randomized placebo-controlled clinical trial in high-caries-risk adults. Clin Oral Investig. 2017 Dec;21(9):2733–40.

David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014 Jan;505(7484):559–63.

De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci USA. 2010 Aug;107(33):14691–6.

de Paola PF, Alman J. Assessment of the reliability of radiographic diagnosis in a clinical caries trial. J Dent Res. 1972 Sep-Oct;51(5):1431–7.

DePaola PF, Soparkar PM, Tavares M, Kent RL Jr. Clinical profiles of individuals with and without root surface caries. Gerodontology. 1989;8(1):9–15.

Deshpande A, Jadad AR. The impact of polyol-containing chewing gums on dental caries: a systematic review of original randomized controlled trials and observational studies. J Am Dent Assoc. 2008 Dec;139(12):1602–14.

Devulapalle KS, Mooser G. Glucosyltransferase inactivation reduces dental caries. J Dent Res. 2001 Feb;80(2):466–9.

Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, et al. The human oral microbiome. J Bacteriol. 2010 Oct;192(19):5002–17.

Dowd FJ. Saliva and dental caries. Dent Clin North Am. 1999 Oct;43(4):579–97.

Falony G, Honkala S, Runnel R, Olak J, Nõmmela R, Russak S, et al. Long-Term Effect of Erythritol on Dental Caries Development during Childhood: A Posttreatment Survival Analysis. Caries Res. 2016;50(6):579–88.

Fontana M, González-Cabezas C. Are we ready for definitive clinical guidelines on xylitol/polyol use? Adv Dent Res. 2012 Sep;24(2):123–8.

Foster KR, Schluter J, Coyte KZ, Rakoff-Nahoum S. The evolution of the host microbiome as an ecosystem on a leash. Nature. 2017 Aug;548(7665):43–51.

Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA. 2007 Aug;104(34):13780–5.

Gardner C, Wylie-Rosett J, Gidding SS, Steffen LM, Johnson RK, Reader D, et al.; American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Disease in the Young; American Diabetes Association. Nonnutritive sweeteners: current use and health perspectives: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care. 2012 Aug;35(8):1798–808.

Geva-Zatorsky N, Sefik E, Kua L, Pasman L, Tan TG, Ortiz-Lopez A, et al. Mining the Human Gut Microbiota for Immunomodulatory Organisms. Cell. 2017 Feb;168(5):928–943.e11.

Giertsen E, Emberland H, Scheie AA. Effects of mouth rinses with xylitol and fluoride on dental plaque and saliva. Caries Res. 1999;33(1):23–31.

Grotz VL, Henry RR, McGill JB, Prince MJ, Shamoon H, Trout JR, et al. Lack of effect of sucralose on glucose homeostasis in subjects with type 2 diabetes. J Am Diet Assoc. 2003 Dec;103(12):1607–12.

Hanno AG, Alamoudi NM, Almushayt AS, Masoud MI, Sabbagh HJ, Farsi NM. Effect of xylitol on dental caries and salivary Streptococcus mutans levels among a group of mother-child pairs. J Clin Pediatr Dent. 2011;36(1):25–30.

Hugon P, Lagier JC, Robert C, Lepolard C, Papazian L, Musso D, et al. Molecular studies neglect apparently gram-negative populations in the human gut microbiota. J Clin Microbiol. 2013 Oct;51(10):3286–93.

Imfeld T. Efficacy of sweeteners and sugar substitutes in caries prevention. Caries Res. 1993;27 Suppl 1:50–5.

Isokangas P, Söderling E, Pienihäkkinen K, Alanen P. Occurrence of dental decay in children after maternal consumption of xylitol chewing gum, a follow-up from 0 to 5 years of age. J Dent Res. 2000 Nov;79(11):1885–9.

Janket S, Nunn ME, Salih E, Baird AE. Evidence-based approach in transaltional dental research. In: Meurman JH, editor. Translational Oral Health Research. Berlin, Germany: Springer; 2018. https://doi.org/10.1007/978-3-319-78205-8_8.

Janket SJ. Sugar-free sweeteners. Pediatrics for Parents. 2012;28.

Janket SJ, Javaheri H, Ackerson LK, Ayilavarapu S, Meurman JH. Oral Infections, Metabolic Inflammation, Genetics, and Cardiometabolic Diseases. J Dent Res. 2015 Sep;94(9 Suppl):119S–27S.

Janket SJ, Jones JA, Meurman JH, Baird AE, Van Dyke TE. Oral infection, hyperglycemia, and endothelial dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 Feb;105(2):173–9.

Koliada A, Syzenko G, Moseiko V, Budovska L, Puchkov K, Perederiy V, et al. Association between body mass index and Firmicutes/Bacteroidetes ratio in an adult Ukrainian population. BMC Microbiol. 2017 May;17(1):120.

Kontiokari T, Uhari M, Koskela M. Effect of xylitol on growth of nasopharyngeal bacteria in vitro. Antimicrob Agents Chemother. 1995 Aug;39(8):1820–3.

Lee W, Spiekerman C, Heima M, Eggertsson H, Ferretti G, Milgrom P, et al. The effectiveness of xylitol in a school-based cluster-randomized clinical trial. Caries Res. 2015;49(1):41–9.

Lemann J Jr, Litzow JR, Lennon EJ. Studies of the mechanism by which chronic metabolic acidosis augments urinary calcium excretion in man. J Clin Invest. 1967 Aug;46(8):1318–28.

Lenkkeri AM, Pienihäkkinen K, Hurme S, Alanen P. The caries-preventive effect of xylitol/maltitol and erythritol/maltitol lozenges: results of a double-blinded, cluster-randomized clinical trial in an area of natural fluoridation. Int J Paediatr Dent. 2012 May;22(3):180–90.

Livesey G. Tolerance of low-digestible carbohydrates: a general view. Br J Nutr. 2001 Mar;85(S1 Suppl 1):S7–16.

Livesey G. Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. Nutr Res Rev. 2003 Dec;16(2):163–91.

Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. Genome Med. 2016 Apr;8(1):51.

Maguire A, Rugg-Gunn AJ. Xylitol and caries prevention—is it a magic bullet? Br Dent J. 2003 Apr;194(8):429–36.

Mäkeläinen HS, Mäkivuokko HA, Salminen SJ, Rautonen NE, Ouwehand AC. The effects of polydextrose and xylitol on microbial community and activity in a 4-stage colon simulator. J Food Sci. 2007 Jun;72(5):M153–9.

Maki KC, Curry LL, Reeves MS, Toth PD, McKenney JM, Farmer MV, et al. Chronic consumption of rebaudioside A, a steviol glycoside, in men and women with type 2 diabetes mellitus. Food Chem Toxicol. 2008;46 Suppl 7:S47–53.

Mäkinen KK. Effect of long-term, peroral administration of sugar alcohols on man. Swed Dent J. 1984;8(3):113–24.

Mäkinen KK. Gastrointestinal Disturbances Associated with the Consumption of Sugar Alcohols with Special Consideration of Xylitol: Scientific Review and Instructions for Dentists and Other Health-Care Professionals. Int J Dent. 2016;2016:5967907.

Mäkinen KK, Bennett CA, Hujoel PP, Isokangas PJ, Isotupa KP, Pape HR Jr, et al. Xylitol chewing gums and caries rates: a 40-month cohort study. J Dent Res. 1995 Dec;74(12):1904–13.

Mäkinen KK, Hujoel PP, Bennett CA, Isotupa KP, Mäkinen PL, Allen P. Polyol chewing gums and caries rates in primary dentition: a 24-month cohort study. Caries Res. 1996a;30(6):408–17.

Mäkinen KK, Isotupa KP, Mäkinen PL, Söderling E, Song KB, Nam SH, et al. Six-month polyol chewing-gum programme in kindergarten-age children: a feasibility study focusing on mutans streptococci and dental plaque. Int Dent J. 2005 Apr;55(2):81–8.

Mäkinen KK, Mäkinen PL, Pape HR Jr, Peldyak J, Hujoel P, Isotupa KP, et al. Conclusion and review of the Michigan Xylitol Programme (1986-1995) for the prevention of dental caries. Int Dent J. 1996b Feb;46(1):22–34.

Marsh PD, Percival RS, Challacombe SJ. The influence of denture-wearing and age on the oral microflora. J Dent Res. 1992 Jul;71(7):1374–81.

Mayo C. Artificial sweeteners: Any effect on blood sugar? - Mayo Clinic; 2016. https://www.mayoclinic.org/diseases-conditions/diabetes/expert-answers/artificial-sweeteners/faq-20058038.

Mohan A, Morse DE, O'Sullivan DM, Tinanoff N. The relationship between bottle usage/content, age, and number of teeth with mutans streptococci colonization in 6-24-month-old children. Community Dent Oral Epidemiol. 1998 Feb;26(1):12–20.

Mombelli A, Schmid B, Rutar A, Lang NP. Persistence patterns of Porphyromonas gingivalis, Prevotella intermedia/nigrescens, and Actinobacillus actinomyetemcomitans after mechanical therapy of periodontal disease. J Periodontol. 2000 Jan;71(1):14–21.

Munyaka PM, Rabbi MF, Khafipour E, Ghia JE. Acute dextran sulfate sodium (DSS)-induced colitis promotes gut microbial dysbiosis in mice. J Basic Microbiol. 2016 Sep;56(9):986–98.

Nadimi H, Wesamaa H, Janket SJ, Bollu P, Meurman JH. Are sugar-free confections really beneficial for dental health? Br Dent J. 2011 Oct;211(7):E15.

Narchi H. Serum bicarbonate and dehydration severity in gastroenteritis. Arch Dis Child. 1998 Jan;78(1):70–1.

Natah SS, Hussien KR, Tuominen JA, Koivisto VA. Metabolic response to lactitol and xylitol in healthy men. Am J Clin Nutr. 1997 Apr;65(4):947–50.

Nguyen MS, Saag M, Voog-Oras Ü, Nguyen T, Jagomägi T. Temporomandibular Disorder Signs, Occlusal Support, and Craniofacial Structure Changes Among the Elderly Vietnamese. J Maxillofac Oral Surg. 2018 Sep;17(3):362–71.

Nguyen NU, Dumoulin G, Henriet MT, Berthelay S, Regnard J. Carbohydrate metabolism and urinary excretion of calcium and oxalate after ingestion of polyol sweeteners. J Clin Endocrinol Metab. 1993 Aug;77(2):388–92.

O'Connor A, Quizon PM, Albright JE, Lin FT, Bennett BJ: Responsiveness of cardiometabolic-related microbiota to diet is influenced by host genetics. Mamm Genome. 2014 Dec;25(11–12):583–99.

Reyna NY, Cano C, Bermúdez VJ, Medina MT, Souki AJ, Ambard M, et al. Sweeteners and beta-glucans improve metabolic and anthropometrics variables in well controlled type 2 diabetic patients. Am J Ther. 2003 Nov-Dec;10(6):438–43.
Ribeiro AA, Azcarate-Peril MA, Cadenas MB, Butz N, Paster BJ, Chen T, et al. The oral bacterial microbiome of occlusal surfaces in children and its association with diet and caries. PLoS One. 2017 Jul;12(7):e0180621.
Roberts MC, Riedy CA, Coldwell SE, Nagahama S, Judge K, Lam M, et al. How xylitol-containing products affect cariogenic bacteria. J Am Dent Assoc. 2002 Apr;133(4):435–41.
Rodgers A, Bungane N, Allie-Hamdulay S, Lewandowski S, Webber D. Calciuria, oxaluria and phosphaturia after ingestion of glucose, xylitol and sorbitol in two population groups with different stone-risk profiles. Urol Res. 2009 Jun;37(3):121–5.
Rodriguez-Palacios A, Harding A, Menghini P, Himmelman C, Retuerto M, Nickerson KP, et al. The Artificial Sweetener Splenda Promotes Gut Proteobacteria, Dysbiosis, and Myeloperoxidase Reactivity in Crohn's Disease-Like Ileitis. Inflamm Bowel Dis. 2018 Apr;24(5):1005–20.
Rothman KJ. Epidemiologic methods in clinical trials. Cancer. 1977 Apr;39(4 Suppl):1771–5.
Salminen S, Salminen E, Koivistoinen P, Bridges J, Marks V: Gut microflora interactions with xylitol in the mouse, rat and man. Food Chem Toxicol. 1985 Nov;23(11):985-90.
Sansone C, Van Houte J, Joshipura K, Kent R, Margolis HC. The association of mutans streptococci and non-mutans streptococci capable of acidogenesis at a low pH with dental caries on enamel and root surfaces. J Dent Res. 1993 Feb;72(2):508–16.
Sato T, Kusuhara S, Yokoi W, Ito M, Miyazaki K. Prebiotic potential of L-sorbose and xylitol in promoting the growth and metabolic activity of specific butyrate-producing bacteria in human fecal culture. FEMS Microbiol Ecol. 2017 Jan;93(1):93.
Scheinin A, Mäkinen KK, Tammisalo E, Rekola M. Turku sugar studies XVIII. Incidence of dental caries in relation to 1-year consumption of xylitol chewing gum. Acta Odontol Scand. 1975;33(5):269–78.
Schneider AS, Schettler A, Markowski A, Luettig B, Momma M, Seipt C, et al. Assessment of xylitol serum levels during the course of parenteral nutrition including xylitol in intensive care patients: a case control study. Clin Nutr. 2014 Jun;33(3):483–8.
Schroth RJ, Lavelle C, Tate R, Bruce S, Billings RJ, Moffatt ME. Prenatal vitamin D and dental caries in infants. Pediatrics. 2014 May;133(5):e1277–84.
Sels JP, Verdonk HE, Wolffenbuttel BH. Effects of acarbose (Glucobay) in persons with type 1 diabetes: a multicentre study. Diabetes Res Clin Pract. 1998 Aug;41(2):139–45.
Shen P, Walker GD, Yuan Y, Reynolds C, Reynolds EC. Polyols and remineralisation of enamel subsurface lesions. J Dent. 2017 Nov;66:71–5.
Sintes JL, Elías-Boneta A, Stewart B, Volpe AR, Lovett J. Anticaries efficacy of a sodium monofluorophosphate dentifrice containing xylitol in a dicalcium phosphate dihydrate base. A 30-month caries clinical study in Costa Rica. Am J Dent. 2002 Aug;15(4):215–9.
Sintes JL, Escalante C, Stewart B, McCool JJ, Garcia L, Volpe AR, et al. Enhanced anticaries efficacy of a 0.243% sodium fluoride/10% xylitol/silica dentifrice: 3-year clinical results. Am J Dent. 1995 Oct;8(5):231–5.
Smith DJ, Taubman MA, Ebersole JL. Effect of oral administration of glucosyltransferase antigens on experimental dental caries. Infect Immun. 1979 Oct;26(1):82–9.
Söderling E, Isokangas P, Pienihäkkinen K, Tenovuo J, Alanen P. Influence of maternal xylitol consumption on mother-child transmission of mutans streptococci: 6-year follow-up. Caries Res. 2001 May-Jun;35(3):173–7.
Splieth CH, Alkilzy M, Schmitt J, Berndt C, Welk A: Effect of xylitol and sorbitol on plaque acidogenesis. Quintessence Int. 2009;40(4):279–85.
Storey D, Lee A, Bornet F, Brouns F. Gastrointestinal tolerance of erythritol and xylitol ingested in a liquid. Eur J Clin Nutr. 2007 Mar;61(3):349–54.
Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014 Oct;514(7521):181–6.
Swithers SE, Sample CH, Davidson TL. Adverse effects of high-intensity sweeteners on energy intake and weight control in male and obesity-prone female rats. Behav Neurosci. 2013 Apr;127(2):262–74.
Tabrizi R, Karagah T, Aliabadi E, Hoseini SA. Does gum chewing increase the prevalence of temporomandibular disorders in individuals with gum chewing habits? J Craniofac Surg. 2014 Sep;25(5):1818–21.
Thabuis C, Cheng CY, Wang X, Pochat M, Han A, Miller L, Wils D, Guerin-Deremaux L: Effects of maltitol and xylitol chewing-gums on parameters involved in dental caries development. Eur J Paediatr Dent. 2013;14(4):303–8.
Thorild I, Lindau B, Twetman S. Salivary mutans streptococci and dental caries in three-year-old children after maternal exposure to chewing gums containing combinations of xylitol, sorbitol, chlorhexidine, and fluoride. Acta Odontol Scand. 2004 Oct;62(5):245–50.
Trahan L, Bareil M, Gauthier L, Vadeboncoeur C. Transport and phosphorylation of xylitol by a fructose phosphotransferase system in Streptococcus mutans. Caries Res. 1985;19(1):53–63.
Uebanso T, Kano S, Yoshimoto A, Naito C, Shimohata T, Mawatari K, et al. Effects of Consuming Xylitol on Gut Microbiota and Lipid Metabolism in Mice. Nutrients. 2017 Jul;9(7):9.
Ur-Rehman S, Mushtaq Z, Zahoor T, Jamil A, Murtaza MA. Xylitol: a review on bioproduction, application, health benefits, and related safety issues. Crit Rev Food Sci Nutr. 2015;55(11):1514–28.
Vadeboncoeur C, Trahan L, Mouton C, Mayrand D. Effect of xylitol on the growth and glycolysis of acidogenic oral bacteria. J Dent Res. 1983 Aug;62(8):882–4.
Van Loveren C. Sugar alcohols: what is the evidence for caries-preventive and caries-therapeutic effects? Caries Res. 2004 May-Jun;38(3):286–93.
Vieira SM, Pagovich OE, Kriegel MA. Diet, microbiota and autoimmune diseases. Lupus. 2014 May;23(6):518–26.
Watthanasaen S, Merchant AT, Luengpailin S, Chansamak N, Pisek A, Pitiphat W. Xylitol-containing Chewing Gum for Caries Prevention in Students with Disabilities: A Randomised Trial. Oral Health Prev Dent. 2017;15(6):519–27.
Wennerholm K, Arends J, Birkhed D, Ruben J, Emilson CG, Dijkman AG. Effect of xylitol and sorbitol in chewing-gums on mutans streptococci, plaque pH and mineral loss of enamel. Caries Res. 1994;28(1):48–54.
Wennerholm K, Birkhed D, Emilson CG. Effects of sugar restriction on Streptococcus mutans and Streptococcus sobrinus in saliva and dental plaque. Caries Res. 1995;29(1):54–61.
Wennerholm K, Emilson CG. Effect of sorbitol- and xylitol-containing chewing gum on salivary microflora, saliva, and oral sugar clearance. Scand J Dent Res. 1989 Jun;97(3):257–62.
Willing BP, Dicksved J, Halfvarson J, Andersson AF, Lucio M, Zheng Z, Jarnerot G, Tysk C, Jansson JK, Engstrand L: A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. Gastroenterology 2010 Dec;139(6):1844–54.
Wölnerhanssen BK, Cajacob L, Keller N, Doody A, Rehfeld JF, Drewe J, et al. Gut hormone secretion, gastric emptying, and glycemic responses to erythritol and xylitol in lean and obese subjects. Am J Physiol Endocrinol Metab. 2016 Jun;310(11):E1053–61.
Zhan L, Cheng J, Chang P, Ngo M, Denbesten PK, Hoover CI, et al. Effects of xylitol wipes on cariogenic bacteria and caries in young children. J Dent Res. 2012 Jul;91(7 Suppl):85S–90S.
Zhang DQ, Zhu JH, Chen WC. Acarbose: a new option in the treatment of ulcerative colitis by increasing hydrogen production. Afr J Tradit Complement Altern Med. 2012 Oct;10(1):166–9.