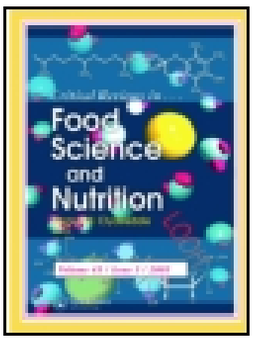

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REVIEW

Metabolic effects of the natural sweeteners xylitol and erythritol: A comprehensive review

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ABSTRACT

Xylitol and erythritol are widely used in a variety of food and oral care products as sugar substitutes. Although a number of studies have been conducted on the health benefits of xylitol since the 1960s, erythritol only attracted the attention of researchers during the early 1990s. Historically, researchers mainly focused on the effects of xylitol and other sugar alcohols on oral and dental healthcare while the anti-diabetic or antihyperglycemic effects have only been revealed recently. Though a few reviews have been published on the health benefits of sugar alcohols in the last few decades, none of them closely evaluated the antihyperglycemic potential and underlying mechanisms, particularly with a focus on xylitol and erythritol. The current review thoroughly analyzes the anti-diabetic and antihyperglycemic effects as well as other metabolic effects of xylitol and erythritol using articles published in PubMed since the 1960s, containing research done on experimental animals and humans. This review will help researchers ascertain the controversies surrounding sugar alcohols, investigate further beneficial effects of them as well as aid food industries in exploring the possibilities of using sugar alcohols as anti-diabetic supplements in diabetic foods and food products.

KEYWORDS

Xylitol; erythritol; sweetener; diabetes; tolerance

Introduction

The human species seems to have an innate preference for sweet taste, and, in our diets, table sugar or sucrose is normally used as a universal sweetening agent. A number of previous studies reported that routine or excessive consumption of refined sugar might cause being overweight, obesity, diabetes and metabolic syndrome (Chan et al. 2014; Bray and Popkin 2014). Alternative natural sweetening agents such as honey, fructose, high fructose corn sirup and maple sirup have similar undesired metabolic effects (Johnson et al. 2013; Feinman and Fine 2013; Ha et al. 2013). Hence, low or non-caloric artificial sweeteners and some other alternative sweeteners are gaining popularity among normal- and overweight people, as well as diabetic patients. Sugar alcohols are gaining more popularity amongst the above-mentioned individuals. This is not only due to their potential as a sugar substitute and their well-studied beneficial effects on oral health (de Cock et al. 2016; Mäkinen 2011) but also due to their number of health benefits, including hypoglycemic, anti-hyperglycemic, anti-diabetic and anti-obesogenic effects. The usefulness of xylitol and erythritol as sugar alternatives on diabetics has been studied since the 1960s (Mellinghoff 1961; Baessler et al. 1962) and the 1990s (Noda, Nakayama, and Modderman 1996), respectively; however, their anti-hyperglycemic potentials have only been extensively studied in recent years. Almost all of the studies on xylitol published during the 1960s–1980s are in Japanese or in Russian, and the abstracts are unavailable in English. Therefore, not many people have reaped the benefits of those studies (Domareva 1967; Rogala and Sieradzki 1971; Lang 1971; Nesterin 1980).

There is no recent review on the anti-diabetic potential of sugar alcohols. The only publications written include a short review published decades ago on the use of fructose, sorbitol or xylitol as sweeteners in diabetes mellitus (Brunzell 1978). An extensive review on the health potentials of polyols as a sugar replacer taking into consideration their low glycemic properties has been published more than decay ago (Livesey 2003). Moreover, although a number of reviews of erythritol have been written since 1990s (Mäkinen 2016; Fowler 2016; Moon et al. 2010), none of them focus on diabetes or obesity. Mäkinen (2016) primarily discussed the gastrointestinal side effects associated with the consumption of sugar alcohols. He paid particular attention to xylitol in patients, who consume it for its oral care and dental caries preventive effects (Mäkinen 2016). Fowler (2016) reviewed the effects of low calorie sweeteners (not only sugar alcohols) on energy balance after assessing the results of some animal trials and particularly large-scale clinical trials

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(Fowler 2016). Finally, some reviews on the biological, biochemical, metabolic and toxicological effects of erythritol have been published about 20 years ago (Bornet et al. 1996b; Munro et al. 1998).

A number of studies have been conducted on experimental animals and humans thereafter prompting the need to review the results from more recent studies. The current article carefully reviewed the articles published since 1960s until March 2018. Specific focus was paid on the anti-diabetic and metabolic effects of xylitol and erythritol with or without associated mechanism of actions. The results of animal and clinical studies are presented separately to help researchers to understand the similarities and discrepancies of the anti-diabetic effects of these sugar alcohols between animals and humans.

Methods

The manuscripts have been thoroughly searched in PubMed via Medline, using keywords such as 'xylitol', 'erythritol', 'diabetes', 'metabolic', 'animals', 'humans', 'tolerance' as a single word or in their various combinations. Any works conducted with xylitol or erythritol or both in terms of their anti-diabetic or hypoglycemic effects, tolerance, side effects or toxicities in vitro, ex vivo, in vivo and in clinical levels were included in this review. Some studies with xylitol and erythritol were initiated in the early 1960s and abstracts of these trials are not available in PubMed. The articles that were published in either Japanese or Russian were not included in this study. Hence, the articles published in English since 1960s until March 2018 were included in this study as per the above-mentioned criteria. Additionally, three tables have been created in order to summarize the metabolic effects of xylitol (Table 1) and erythritol (Table 2) and to show the possible mechanisms of action (Table 3) of the two polyols in terms of their anti-diabetic or antihyperglycemic potential.

Xylitol

Animal studies

Anti-oxidative properties. Chukwuma and Islam (2017) demonstrated the anti-oxidative properties of xylitol by measuring various anti-oxidative enzymes in non-diabetic and type 2 diabetic rats. Some other parameters such as catalase, super oxide dismutase, glutathione reductase, glutathione peroxidase, reduced glutathione and level of lipid peroxidation in serum and various organs, including liver, heart, kidney and pancreas after supplied with a 10%-xylitol solution over five weeks compared to drinking water only (Chukwuma and Islam 2017). From the results of this study, authors conclude that xylitol is an antioxidant and cannot only serve as a sugar substitute for diabetic patients, but might also be able to ameliorate diabetes-associated oxidative stress.

Body weight and food intake. Islam (2011) could show that when non-diabetic rats were given a 10%-xylitol solution ($n = 6$) vs. 10%-sucrose ($n = 6$) or water ($n = 5$) ad libitum for 5 weeks, both xylitol and sucrose lead to reduced food intake and subsequently less body weight gain (Islam 2011). The overall body weight gain was lower in the xylitol-group compared to the sucrose-group, but significant differences were only seen for week one and two. The same research group showed that after a five-week ad libitum supplementation of 10%-xylitol solution to an experimentally induced rat model of type 2 diabetes, food intake was also significantly reduced (Islam 2012). In their subsequent dose-response study with three different dosages (2.5, 5 and 10%) of xylitol over four weeks in a type 2 diabetic model of rats, food intake decreased dose-dependently, while body weight gain followed a different pattern: with 2.5% xylitol, body weight gain was significantly reduced compared to diabetic controls, but 5% and 10% xylitol lead to a dose-dependent increase in body weight gain (Rahman and Islam 2014). The authors conclude that the reduced food intake might be related to the longer gastric emptying time, which has been described in humans (Salminen et al. 1989; Shafer et al. 1987; Wölnerhanssen et al. 2016).

Glycemic control. Kishore et al. (2012) examined the ability of xylitol to prevent non-esterified fatty acid (NEFA)-induced insulin resistance in 24 non-diabetic Sprague-Dawley rats and reported that co-infusion of xylitol and NEFA for five hours significantly reduced NEFA-induced insulin resistance. The authors conclude that xylitol has beneficial insulin-sensitizing effects (Kishore et al. 2012).

Islam (2011) investigated the effects of an ad libitum oral 10%-xylitol vs. sucrose solution over three weeks on glycemic control in non-diabetic Sprague-Dawley rats (Islam 2011). The rats were randomly divided into three groups (control $n = 5$, sucrose $n = 6$ and xylitol $n = 6$) and had free access to the following solutions: water, 10% sucrose or 10% xylitol. Glucose tolerance was significantly better in the xylitol-consuming group compared to the sucrose-consuming and control group. The same research group showed that after a 5-week ad libitum supplementation of 10%-xylitol solution to an experimentally induced rat model of type 2 diabetes, blood glucose and serum fructosamine (albumin glycation; representing average glucose levels over approximately 2–4 weeks) were significantly decreased, whereas serum insulin levels and glucose tolerance were significantly increased in the xylitol-consuming group compared to the control group (Islam 2012; Islam and Indrajit 2012).

Rahman and Islam (2014) also conducted a dose-response study with three different dosages (2.5, 5 and 10%) of xylitol solution given ad libitum in a type 2 diabetic rat model over four weeks (Rahman and Islam 2014). Overall diabetes related parameters were again significantly improved, including reduction in blood glucose and serum fructosamine levels, improved glucose tolerance and increased serum insulin concentration. Additionally, pancreatic islet morphology was studied: feeding a 10%-xylitol solution significantly improved pancreatic islet morphology in that an increase in islet size and a higher number of β-cells were observed. The authors conclude that a 10% xylitol solution has beneficial effects on glycemic control in non-diabetic

Table 1. Effects of xylitol on glycemic and metabolic parameters.

Dose and frequency	Duration	Subjects	Positive or neutral effects	References
10% xylitol solution vs. 10% sucrose solution or water (control)	3 weeks	Non-diabetic rats	• Improved glucose tolerance compared to control and sucrose group • Serum lipids lower in the xylitol group compared to sucrose group, except triglycerides (increased in xylitol group)	(Islam 2011)
1 or 2 g xylitol per 100 kcal of diet	8 weeks	High-fat diet-fed rats	• Reduced visceral fat mass and plasma lipid concentration • Dose-dependent increased lipogenic enzymes, ChREBP and fatty acid oxidation related gene expression	(Amo et al. 2011)
10% xylitol solution instead of water	5 weeks	Type 2 diabetic rats	• Improved glucose tolerance and increased serum insulin • Reduced food and fluid intake, body weight, blood glucose, serum fructosamine and most serum lipids except triglycerides: no change	(Islam 2012) (Islam and Indrajit 2012)
2.5%, 5% and 10% xylitol solution instead of water	4 weeks	Type 2 diabetic rats	• Diabetes related parameters including pancreatic morphology improved • Serum lipids improved except triglycerides: no change	(Rahman and Islam 2014)
Various concentrations and dosages of xylitol	Various	Non-diabetic and type 2 diabetic rats	• Inhibited alpha-amylase and alpha-glucosidase activities and jejunal glucose absorption • Increased muscle glucose uptake and digesta transit • Delayed gastric emptying • Decreased blood glucose level	(Chukwuma and Islam 2015)
30 g xylitol vs. glucose in 200 mL water	Single oral dose	Non-diabetic human subjects	• Motilin secretion stimulated, no effect on GIP • Delayed gastric emptying, accelerated intestinal transit • Small rise in plasma glucose and insulin	(Salminen et al. 1989)
50 g xylitol in 200 mL water via nasogastric tube over 2 min	Single oral dose	Lean, non-diabetic and obese, glucose- intolerant humans	• Increased cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1) • Delayed gastric emptying • Small rise in plasma glucose and insulin	(Wölnerhanssen et al. 2016)
35 g xylitol in 200 mL water via nasogastric tube over 2 min	Single oral dose	Non-diabetic human subjects	• Increase in uric acid • No effect on serum lipids	Wölnerhanssen and Meyer-Gerspach (unpublished)
80–100 g of xylitol/d	for 18 days	Non-diabetic human subjects	• Trend to decreased plasma cholesterol levels while triglyceride levels remained unchanged	(Förster, Quadbeck, and Gottstein 1982)
30 g of xylitol/d	4 weeks	Insulin-dependent diabetic children	• Increase in uric acid	(Förster, Boecker, and Walther 1977)
20–430 g of xylitol/d	1–2 years	Non-diabetic human subjects	• No changes in plasma glucose and insulin • No changes in uric acid, blood lipids	'Turku studies' (Huttunen, Mäkinen, and Scheinin 1976)
a. 25 g of either xylitol or glucose b. Preload of 25 g xylitol, glucose, fructose, sucrose or water	Single oral dose	Non-diabetic human subjects	• Gastric emptying prolonged after xylitol ingestion compared to glucose • Xylitol preload vs. water resulted in a significantly lower subsequent calorie intake	(Shafer et al. 1987)

and diabetic rats with amelioration of some common and some organ-specific abnormalities seen in T2DM.

Mushtaq et al. (2014) found that supplementation of a 10%- or 20%-xylitol (extracted from mung bean hulls) containing diet for three weeks, dose-dependently reduced serum glucose in normal and streptozotocin-induced diabetic rats and reduced food intake and weight gain (Mushtaq et al. 2014). The authors conclude that the mung bean hulls have a high potential as a new feedstock for xylitol production and the extracted xylitol should be considered in diet-based therapies for weight loss programs. However, there was no difference between the pure and xylitol extracted from mung bean hulls in terms of chemical structure.

Carbohydrate digestion, intestinal glucose absorption and muscle glucose uptake. Chukwuma and Islam (2015) investigated the mechanisms behind the anti-diabetic effects of

Table 2. Effects of erythritol on glycemic and metabolic parameters.

Dose and frequency	Duration	Subjects	Positive or neutral effects	References
0.5 g erythritol per kg body weight	Single oral dose	Alloxan-induced diabetes mellitus mice model vs. healthy controls	• Reduces postprandial blood glucose level via inhibiting α-glucosidase enzyme activity	(Wen et al. 2018)
Various concentrations and dosages of erythritol	Various	Non-diabetic and type 2 diabetic rats	• Increased muscle glucose uptake • Reduced glucose intestinal absorption • Delayed gastric emptying • Decreased blood glucose level • Improved diabetes-induced reduction of muscle hexokinase and liver glucokinase activities and diabetes-induced elevation of glucose-6 phosphates activity in the liver • Enhanced Glut-4 and IRS-1 mRNA expression in diabetic animals	(Chukwuma et al. 2018)
0.12, 0.2 or 0.4 g erythritol per kg body weight per day	10 days	Streptozotocin-induced diabetic rats	• Decreased blood glucose	(Yokozawa, Kim, and Cho 2002)
0.3 g erythritol per kg body weight	Single oral dose	Non-diabetic human subjects	• No effect on serum glucose, insulin, lipids	(Noda, Nakayama, and Oku 1994)
50 g erythritol in 200 mL water via nasogastric tube over 2 min	Single oral dose	Non-diabetic human subjects	• No effect on serum glucose, insulin, lipids and uric acid	Wölnerhanssen and Meyer-Gerspach (unpublished)
75 g erythritol (ca. 0.9 g/kg body weight) in 200 mL water via nasogastric tube over 2 min	Single oral dose	Lean, non-diabetic and obese, glucose-intolerant humans	• Release of cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1) • Delayed gastric emptying • No change in plasma glucose and insulin	(Wölnerhanssen et al. 2016)
75 g erythritol	Single oral dose	Non-diabetic human subjects	• No effect on uric acid	(Oku and Okazaki 1996)
8 g erythritol as part of a breakfast test meal	Single oral dose	Lean and obese non-diabetic human subjects	• Release of glucagon-like peptide 1 (GLP-1) and PYY	(Overduin et al. 2016)
20 g erythritol	Single oral dose	Diabetic human subjects	• No change in blood glucose and serum insulin • Increased non-esterified fatty acids	(Ishikawa et al. 1996)
20 g erythritol/day	2 weeks	Diabetic human subjects	• Reduced serum glucose and glycated hemoglobin	(Ishikawa et al. 1996)
24 g erythritol (as a single bolus) or 36 g erythritol per day (over 4 weeks)	Single dose resp. 4 weeks	Diabetic human subjects	• Improved endothelial function, decreased central pulse pressure and carotid-femoral pulse wave velocity	(Flint et al. 2014)

xylitol by using various experimental approaches, including in vitro, ex vivo and in vivo rat models (Chukwuma and Islam 2015). Firstly, the effects of increasing concentrations of xylitol on α-amylase and α-glucosidase enzyme were examined in vitro and xylitol dose-dependently inhibited the activities of these two enzymes. Secondly, small intestinal glucose absorption and muscle glucose uptake was examined under ex vivo conditions from isolated rat psoas muscle and jejunum. Xylitol dose-dependently decreased intestinal glucose absorption and increased muscle glucose uptake with or without insulin. Thirdly, under in vivo conditions, diabetic and non-diabetic rats received an oral single bolus dose of glucose including phenol red (as a recovery marker). Rats were given the bolus with or without xylitol and were sacrificed thereafter. Gastric emptying, glucose absorption and digesta transit was examined. The authors found a significantly delayed gastric emptying, but increased intestinal transit time in non-diabetic and diabetic rats, who had received the xylitol bolus compared to their respective controls (Chukwuma and Islam 2015). Feeding of xylitol reduced glucose absorption significantly in non-diabetic and diabetic rats. The authors conclude that xylitol exhibits potential hypoglycemic and anti-diabetic effects by decreasing carbohydrate digesting enzymes, reducing intestinal glucose absorption, delaying gastric emptying, while increasing intestinal digesta transit and muscle glucose uptake.

Blood lipids. Islam (2011) could show that when non-diabetic rats were given a 10%-xylitol solution ($n = 6$) vs. 10%-sucrose ($n = 6$) or water ($n = 5$) ad libitum for five weeks, total high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were not significantly different in the xylitol-group compared to the sucrose-group. However, the level of serum triglycerides increased in the xylitol-consuming group compared to the other two groups (Islam 2011). In contrast, Islam and Indrajit (2012) observed in their subsequent trial that if 10%-xylitol was given in a type 2 diabetic model of rats ($n = 7$) vs. diabetic controls ($n = 7$) over four weeks, total cholesterol and LDL were significantly lower in the xylitol-group, while triglycerides and HDL-cholesterol were not affected (Islam and Indrajit 2012). Rahman and Islam (2014) also conducted a dose-response study with three different dosages (2.5, 5 and 10%) of xylitol given ad libitum in a type 2 diabetic rat model over four weeks and confirmed that total cholesterol and LDL decreased significantly in a dose-dependent manner, while

Table 3. Possible underlying modes of action of xylitol and erythritol on glycemic control and metabolic parameters.

In vitro	• Bacterial production of short-chain fatty acids (SCFA), especially butyrate ↑ (X) • Muscle glucose uptake ↑ (X, E) • Antioxidant activity (E)
In vivo	Acute ingestion: • Gastric emptying ↓ (X, E) • Gut transit ↑ (X, E) • Intestinal glucose absorption ↓ (X, E) • Inhibition of carbohydrate digesting enzyme activity: ○ α-Glucosidase activity ↓ (X), α-Amylase activity ↓ (X, E) • Blood glucose ↓/↔ (X, E) • Release of gut hormones after acute ingestion: • CCK ↑, GLP-1 ↑, PYY ↑ (X, E); GIP ↔ (X) • Endothelial function ↑ (E) • Hyperuricemia ↑ (X), ↔ (E) • Serum lipids in non-diabetic condition ↔ (X, E) Chronic exposition: • Food intake/body weight gain ↓/↔ (X, E) • Fasting glucose ↓/↔ (X, E) • Fasting insulin ↓/↔ (X, E) • C-peptide ↓ (X, E) • HbA1c ↓ (X, E) • Glucose tolerance ↑ (X, E) • Fructosamine ↓ (E) • Trophic effect on pancreatic islets: ↑ islet size and ↑ number of β-cells (X) • Endothelial function ↑ (E) • Visceral fat accumulation ↓ (X) • Antioxidant activity (X) ○ Hyperuricemia ↔ (X) Serum lipids in non-diabetic condition (X): • Cholesterol ↓/↔ • LDL ↓ • HDL ↑ • TG ↑/↔ /↓ Serum lipids in a diabetic condition (X, E): • Cholesterol ↓ • LDL ↓ • HDL ↔ /↑ • TG ↑/↔ /↓

X, xylitol; E, erythritol; SCFA, short chain fatty acid; CCK, cholecystokinin; GLP-1, glucagon like peptide 1; GIP, gastric inhibitory peptide; HbA1c, glycated hemoglobin; LDL, low density lipo-protein; HDL, high density lipo-protein; TG, triglyceride.

HDL and triglycerides increased (Rahman and Islam 2014). The authors conclude that the effect of xylitol on triglyceride levels may not be the same between diabetic and non-diabetic conditions. Additionally, the dose of xylitol and duration of intake may affect the results.

Amo et al. (2011) examined Sprague-Dawley rats receiving a high-fat diet supplemented with either 0 g ($n = 6$), 1 g ($n = 6$) or 2 g ($n = 6$) of xylitol per 100 kcal diet over eight weeks. They found that the xylitol-fed rats had a significantly reduced visceral fat mass and plasma lipid concentrations, while a significant increase was found in lipogenic enzymes, ChREBP and fatty acid oxidation related gene-expression compared to only high fat diet fed rats (Amo et al. 2011). These results were more pronounced in the higher xylitol-consuming group. The authors concluded that intake of xylitol may be beneficial in preventing the development of obesity and metabolic abnormalities. Also, fears of up-regulation of gene transcription of lipogenic enzymes observed in in vitro experiments are not justified: lipogenesis does not occur in vivo as the high-fat induced visceral fat accumulation is suppressed.

Uebanso et al. (2017) showed that 16–18 weeks feeding of lower doses of xylitol ($n = 5$ with 40 mg/kg bw/day and $n = 5$ with 194 mg/kg bw/day) has no effect on hepatic and serum lipid parameters in normal vs. high fat diet-fed mice (Uebanso et al. 2017). The authors conclude that dietary xylitol in mice did not ameliorate high-fat induced dyslipidemia.

Mushtaq et al. (2014) found that supplementation of a 10%- or 20%-xylitol containing diet for three weeks, dose-dependently reduced cholesterol and triglycerides in normal and streptozotocin-induced diabetic rats (Mushtaq et al. 2014). The authors conclude that glucose and insulin regulate the synthesis of triglycerides and fatty acids, which might explain the positive effect of xylitol on blood lipid parameters. Although Islam (2011) reported that five-week xylitol feeding significantly increased serum triglycerides in normoglycemic rats (but not in type 2 diabetic rats) (Islam 2012), the results from Amo et al. (2011), Kishore et al. (2012), and Mushtaq et al. (2014) showed that xylitol has lipid-lowering activity, which may be largely associated with the duration of feeding and the applied dose. The amount of dietary xylitol supplied in the study by Mushtaq et al. (2014) was higher than in any of the above-mentioned studies so the dose of xylitol seems to be an important factor in reducing serum lipids in normal or diabetic rats. Further studies are needed to ascertain the lipid lowering effects of xylitol.

In summary, studies in diabetic and non-diabetic rats indicate that xylitol exerts anti-oxidative properties, has beneficial insulin-sensitizing effects, improves glycemic control and has trophic effects on pancreatic β-cells, while food intake and weight gain is reduced. Carbohydrate digestion and intestinal glucose absorption is decreased, and muscle glucose uptake is increased, which might explain the glucose-lowering effect. The effect of chronic xylitol intake on blood lipids remains controversial at this point: some groups found an increase in serum triglycerides in normoglycemic rats (but not in type 2 diabetic rats), others showed that xylitol has lipid-lowering activity.

Human studies

Acute effects on blood glucose and insulin. In humans, ingestion of xylitol leads to an acute small increase in blood glucose and insulin. An effect which has been known for many years and has been confirmed in several studies in which xylitol was compared to a variety of other polyols and carbohydrates (Muller-Hess et al. 1975; Livesey 2003).

In 1981, Hassinger et al. exchanged starch iso-calorically in a breakfast meal with either 30 g xylitol or 30 g sucrose in 14 insulin-dependent diabetic subjects (Hassinger et al. 1981). Insulin requirement and blood glucose were measured using a glucose-controlled insulin infusion system. Sucrose induced a greater post-prandial rise in blood glucose levels despite counter-regulation by the glucose-controlled insulin infusion system. The results for starch and xylitol were similar. The insulin requirement of sucrose consuming subjects was significantly higher than the xylitol and starch consuming subjects after the first 60 min or 2 h, respectively (Hassinger et al. 1981). The authors conclude that xylitol behaves like starch in regards to the effects on blood glucose and insulin requirement.

In 1993, Otto et al. examined different enteral formulas containing xylitol or fructose and fibers as well as a fiber-free product in order to study their effects on glucose and lipid metabolism in eight lean non-diabetic subjects (Otto et al. 1993). Although no significant difference was observed in terms of blood glucose levels among the formulas, the area under the curve of postprandial insulin was significantly smaller for the fructose- and the xylitol-containing formulas than the other formulas. The authors conclude that in nutrition of non-insulin dependent diabetic patients, enteral formulas containing xylitol should be preferred to those containing large amounts of glucose-equivalent carbohydrates because of lower insulin levels. Salminen et al. (1989) observed a small rise in plasma insulin after a single oral bolus of 30 g of xylitol in five non-diabetic volunteers (Salminen et al. 1989). Additionally, Wölnerhanssen et al. (2016) found that 50 g xylitol ingestion lead to a small but significant rise in plasma insulin and glucose compared to tap water in 10 lean and 10 obese non-diabetic volunteers, but an equisweet load of glucose (75 g) compared to xylitol (50 g) lead to a significantly higher rise in blood glucose and insulin secretion (Wölnerhanssen et al. 2016).

Of note, an intravenous administration of xylitol also results in a rise in blood insulin. In 1976, Dubach et al. studied the effects of intravenous sorbitol or xylitol on insulin secretion given at a faster and a slower rate (0.5 g/kg bw within 10 min or 0.5 g/kg bw/hour for 2 hours) in overnight fasted subjects with non-insulin requiring maturity onset diabetes (Dubach 1976). Although insulin secretion was higher with the speedy infusion of sorbitol compared to xylitol, more pronounced insulin secretion was observed with xylitol when infused at a slower rate and a longer period. Mäkinen et al. (1976, 1982, 2016) extensively examined chronic exposition of xylitol in the context of the Turku studies (Mäkinen 1976; Mäkinen et al. 1982; Mäkinen 2016). In healthy, non-diabetic subjects, chronic intake of xylitol of up to 430 g had no effect on fasting insulin or glucose (Huttunen, Mäkinen, and Scheinin 1976).

Gastric emptying, intestinal transit and gut hormones. In 1987, Shafer et al. studied gastric emptying by means of scintigraphy: 25 g of either xylitol or glucose in 50 mL of water was given together with a 99mtechnetium sulfur colloid labeled scrambled egg meal to 10 healthy volunteers (Shafer et al. 1987). Gastric emptying of the solid phase of the meal was markedly prolonged after xylitol ingestion compared to glucose. In addition, food intake was measured in nine volunteers after an oral preload of either 25 g glucose, fructose, sucrose, xylitol or placebo (water) with a subsequent buffet meal. Only the xylitol preload resulted in a significantly lower subsequent calorie intake compared to placebo (water). When the preload test was repeated with lower doses (25 g, 15 g, 5 g), a reduction in food intake was only found for 25 g of xylitol. The authors conclude that ingestion of 25 g xylitol prolongs gastric emptying, reduces food intake and may be a potentially useful agent in the control of energy intake.

In 1989, Salminen et al. scintigraphically studied the effect of an oral bolus dose of 30 g of either xylitol or glucose in 200 mL water mixed with a 99mtechnetium-tin (99mTc-Sn) colloid on the rate of gastric emptying, intestinal transit and motilin and Gastric Inhibitory Peptide (GIP) secretion in five non-diabetic volunteers. They found that xylitol caused a marked prolongation in gastric emptying, but concomitantly, accelerated intestinal transit compared to glucose. While glucose suppressed motilin and stimulated GIP secretion, xylitol stimulated motilin secretion but had no effect on GIP (Salminen et al. 1989). The authors conclude that the accelerated intestinal transit and increase in plasma motilin observed after xylitol ingestion might be causally related to the diarrhea and gastrointestinal discomfort produced by it and might explain the decreased energy intake (Shafer et al. 1987). Wölnerhanssen et al. (2016) investigated the effects of 50 g intragastric xylitol (supplied via nasogastric tube) on gut hormone secretion, gastric emptying and glycemic responses in lean and obese non-diabetic subjects (Wölnerhanssen et al. 2016). Gastric emptying was measured by the noninvasive 13 C-sodium acetate breath test. The results demonstrate that xylitol markedly increased cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1) release while delaying gastric emptying in both lean and obese subjects. These gut hormones have various favorable metabolic effects: they promote satiation directly through stimulation of central nervous receptors in the hypothalamic region and indirectly through deceleration of gastric emptying (Holst 2013). Moreover, GLP-1 exerts trophic effects on pancreatic β-cells and increases insulin secretion as well as insulin-sensitivity in both α-cells and β-cells, promoting insulin sensitivity and decrease in glucagon secretion (Holst 2007). In contrast, the gut hormone GIP shows metabolically unfavorable effects regarding insulin sensitivity, fatty liver disease, subclinical inflammation and promotion of diabetes and cardiovascular disease (Pfeiffer and Keyhani-Nejad 2018). Therefore, xylitol offers the ideal profile for low glycemic food with no release of GIP, while stimulating GLP-1.

Gut microbiota. In an experiment using a colon simulator (an anaerobic culture system mimicking the conditions in the human large intestine with bacterial inocula obtained from different human donors), xylitol was reported to increase the bacterial production of short-chain fatty acids (SCFA), especially butyrate (Makelainen et al. 2007). Short chain fatty acids have been shown to exert multiple beneficial effects such as improvement of blood lipids and glycemic control (den Besten et al. 2013). In vivo studies with chronic intake of xylitol are lacking so far. Hence, further studies are needed to examine the beneficial effects of the chronic consumption of xylitol in humans.

Blood lipids and uric acid. Otto et al. (1993) examined acute effects of different enteral formulas containing maltodextrine, fructose, sucrose and xylitol on blood lipid concentrations in eight healthy volunteers (Otto et al. 1993). While postprandial total cholesterol, high-density lipoprotein

(HDL) and low-density lipoprotein (LDL) cholesterol levels revealed no significant differences among the five formulas, triglyceride (TG) and very low-density lipoprotein (VLDL) triglycerides differed remarkably. The xylitol-containing formula lead to a significant increase in TG and VLDL compared to all other formulas. The authors conclude that xylitol should be preferred over glucose-equivalent carbohydrates because of lower postprandial insulin levels, but noted that triglycerides rose significantly after the ingestion of xylitol-containing formula.

Wölnerhanssen and Meyer-Gerspach recently carried out a trial with 12 healthy volunteers. Acute ingestion of 35 g of xylitol had no effect on total cholesterol, LDL, HDL and triglycerides (unpublished data). Förster, Quadbeck, and Gottstein (1982) examined subchronic consumption of xylitol in 12 healthy human volunteers who received oral supplementation of 80–100 g of xylitol/day for 18 days. They observed a trend where plasma cholesterol levels decreased, while triglyceride levels remained unchanged (Förster, Quadbeck, and Gottstein 1982). The authors conclude that subchronic consumption of a considerable amount of xylitol led to no relevant changes in clinical parameters. Chronic intake such as in the Turku sugar studies demonstrated that inclusion of xylitol into a normal diet does not increase blood lipid concentration (Huttunen, Mäkinen, and Scheinin 1976).

The effects of xylitol intake on plasma uric acid are not well studied. Wölnerhanssen and Meyer-Gerspach recently carried out a trial with 12 healthy volunteers where acute ingestion of 35 g of xylitol lead to a rise in plasma uric acid by 100 µmol/L within 30 min (unpublished data). Yamamoto et al. (1999) administered a 10% xylitol solution intravenously in six healthy volunteers. Results showed an enhanced purine and pyrimidine degradation, resulting in an increase in plasma uric acid (Yamamoto et al. 1999). Förster, Boecker, and Walther (1977) studied the effect of 30 g xylitol per day as a sugar substitute over four weeks in 18 insulin-dependent diabetic children. A significant increase in serum uric acid concentration was the main side effect of xylitol (Förster, Boecker, and Walther 1977). In a subsequent study carried out by the same study group, oral supplementation of 80–100 g of xylitol/day for 18 days to 12 healthy human volunteers did not make any difference in plasma uric acid (Förster, Quadbeck, and Gottstein 1982). Chronic intake – such as in the Turku sugar studies – demonstrated that inclusion of xylitol into a normal diet does not increase urine or serum urate concentration (Huttunen, Mäkinen, and Scheinin 1976). From the results of the above-mentioned studies, the effects of xylitol on blood lipids and uric acid levels are still controversial and further studies are needed to ascertain the effects.

Tolerance. Xylitol is not completely absorbed. Absorption rates of xylitol ranging from around 50 to 95% (depending on the dose level) have been described by Asano, Levitt, and Goetz (1973). Bacteria in the large intestine might also ferment some of the ingested xylitol passing through the small intestine. Variable individual tolerance levels in humans make it difficult to define a tolerable dose. Studies vary in the type of administration (single bolus, several doses spread out over the day, dose dissolved in water or part of a solid meal, acute or chronic effects with an adaption period), and there is no clearly defined threshold for xylitol tolerance applicable to any situation. A number of tolerance and toxicity related studies have been conducted during the 1970s and early 1980s (Mäkinen et al. 1982; Akerblom et al. 1982), and an extensive review on this topic was presented in 2016 by Mäkinen (2016). Mäkinen suggests that for xylitol, the largest safe doses range is from 20 to 70 g per day or around 0.3 g/kg bw for a single bolus dose. Wölnerhanssen et al. (2016) investigated the effects of a 50 g xylitol bolus in 200 mL tap water (corresponding to 0.6 g/kg) supplied via nasogastric tube over 2 minutes on gut hormone secretion, gastric emptying and glycemic responses. The volunteers had not consumed xylitol on a regular basis before, and 70% experienced mild forms of bloating and diarrhea, which is in line with Mäkinen (Wölnerhanssen et al. 2016).

Long-term tolerance of healthy human subjects to high amounts of xylitol were also studied in detail by Mäkinen (1976). Fifty-two volunteers consumed around 1.5 kg of xylitol a month following a strict diet and were observed over two years. They consumed doses up to a maximum of 430 g per day, and no adverse effects were observed (Mäkinen 1976). However, significant individual variation is seen and adaptation to tolerate increasing quantities of xylitol has been observed in long-term feeding trials most likely due to changes in the gut flora and enzyme induction in the liver (Mäkinen 2016), confirming observations made in the 1960s and 1970s (Mertz et al. 1972).

In summary, studies in diabetic and non-diabetic humans indicate that acute oral or intravenous administration of xylitol leads to a smaller rise in blood glucose and insulin compared to sucrose or glucose. No effect on fasting blood glucose or insulin is found upon chronic, oral intake of xylitol in non-diabetic volunteers. The gut hormones GLP-1, PYY and CCK are released upon xylitol ingestion, which leads to prolonged gastric emptying and reduces subsequent food intake. In contrast, GIP release is not stimulated. Motilin release might explain the accelerated intestinal transit observed. The stimulation of beneficial bacterial short-chain fatty acids production has been only shown in human stool inocula thus far. The effects of xylitol intake on blood lipids and uric acid remain controversial at this point: some groups found an increase in serum triglycerides and uric acid, while others found no effect at all. High doses of xylitol can lead to gastrointestinal discomfort, in particular in subjects not used to the substance. The largest safe doses range from 20 to 70 g per day or around 0.3 g/kg bw for a single bolus dose, but chronic intake increases tolerance. A summary of the effects of xylitol on glycemic and metabolic parameters is presented in Table 1.

Erythritol

In vitro, ex vivo and animal studies

Anti-oxidative properties. Yokozawa, Kim, and Cho (2002) showed that supplementation of erythritol in doses of 0.1,

0.2 or 0.4 g/kg bw for ten days significantly decreased serum glucose levels and dose-dependently reduced creatinine, thio-barbituric acid reactive substances and 5-hydroxymethylfurfural in the serum, liver and kidney in streptozotocin-induced diabetic rats (Yokozawa, Kim, and Cho 2002). The authors conclude that erythritol affects glucose metabolism and reduces lipid peroxidation, thereby improving the damage caused by oxidative stress involved in the pathogenesis of diabetes. Endothelial cell dysfunction is one of the vascular complications usually observed in diabetic condition. den Hartog et al. (2010) investigated the antioxidant properties of erythritol in vitro and subsequently determined its antioxidant activity and its vasoprotective effect in streptozotocin-induced diabetic rats vs. healthy controls. Diabetic rats and healthy controls were given up to 1 g/bw per day erythritol or plain water over 21 days. In addition, endothelial function was determined ex vivo by measuring the response of isolated aortic rings to amongst others carbachol. They found that erythritol has a strong hydroxyl radical (OH*) scavenging activity, while it was inert towards superoxide radicals (den Hartog et al. 2010). The authors conclude that erythritol acts as an antioxidant in vivo and displays an endothelium-protective effect, which may help to protect against hyperglycemia-induced vascular damage.

Boesten et al. (2013) evaluated the effects of erythritol in endothelial cells exposed to normal (7 mM) and high glucose (30 mM) or diabetic stressors (e.g. SIN-1), using targeted and transcriptomic approaches. They reported that erythritol has a strong vascular protecting effect, which is more pronounced in a diabetic rather than non-diabetic condition: Under hyperglycemic conditions, erythritol protected endothelial cells against cell death induced by diabetic stressors (i.e. high glucose, peroxynitrite and reversed increased nitric oxide release) in the in vitro trial (Boesten et al. 2013). The authors conclude that erythritol is a compound that has definite endothelium protective effects during hyperglycemia and can therefore be of great importance to a rapidly growing population of people with diabetes to reduce their risk of developing diabetic complications.

Glycemic control. Chukwuma et al. (2018) investigated the effect of erythritol on glucose absorption and glucose uptake in a series of experiments. In an ex vivo trial, isolated rat jejunum and psoas muscle were incubated in a 2.5% to 20% erythritol solution, and the glucose concentration change was monitored. Erythritol caused a concentration-dependent increase of glucose uptake in isolated psoas muscle with or without insulin. Insulin significantly enhanced the muscle glucose uptake effect of erythritol. In an in vivo trial, the acute effect of an oral dose of erythritol (with phenol red as a recovery marker) on intestinal glucose absorption, gastric emptying and postprandial blood glucose increase in a normal and T2D rat model was examined. Rats received a bolus of glucose either alone or together with erythritol or acarbose and phenol red. Glucose and phenol red were then determined in serum and GI tissue. Erythritol significantly reduced glucose absorption in the first quartile of the small intestine of normal and diabetic animals, while acarbose also reduced glucose absorption in the proximal colon of diabetic animals. Both erythritol and acarbose reduced gastric emptying in diabetic animals and prevented rise in blood glucose.

In an in vivo study, the acute effect of a single oral dose of erythritol on glucose tolerance, insulin secretion, liver and muscle gluconeogenic and glycolytic enzyme activities and mRNA expression of muscle glucose transporter type 4 (Glut-4) and insulin receptor substrate-1 (IRS-1) in normal and T2D rat models was investigated (Chukwuma et al. 2018). Erythritol had no significant effect in normal animals, but significantly improved the glucose tolerance ability of diabetic animals, especially at 30 and 60 min after glucose ingestion. Erythritol had no effect on the activities of muscle hexokinase, liver glucokinase and liver glucose-6 phosphatase in normal animals, while it markedly improved diabetes-induced reduction of muscle hexokinase and liver glucokinase activities, and significantly reduced diabetes-induced elevation of glucose-6-phosphatase activity in the liver. Erythritol treatment did not significantly influence the mRNA expression of muscle Glut-4 and IRS-1 in normal animals. Induction of diabetes decreased the mRNA expression of muscle Glut-4 and IRS-1, but increased after erythritol treatment. The authors conclude that erythritol is able to reduce small intestinal glucose absorption. It also enhances insulin secretion and insulin-mediated muscle glucose uptake and metabolism via improving glucose metabolic enzyme activity and enhancing Glut-4 and IRS-1 mRNA expression, especially in diabetic animals. They propose the antihyperglycemic potency of erythritol (reduction in small intestinal glucose absorption and enhancement insulin-mediated muscle glucose uptake and metabolism) may work in concert to improve glucose tolerance and ameliorate hyperglycemia. It also may be a useful dietary supplement for managing hyperglycemia in diabetic individuals.

Wen et al. (2018) examined the effect of 500 mg/kg erythritol or 4 mg/kg acarbose per day in an alloxan-induced diabetes mellitus mice model vs. healthy controls. They reported that in diabetic mice (but not in healthy controls), erythritol reduces postprandial blood glucose level via inhibiting α-glucosidase enzyme activity, the findings of which have also been confirmed by molecular docking studies (Wen et al. 2018).

In summary, studies in diabetic and non-diabetic rats and in vitro trials indicate that erythritol exerts anti-oxidative properties, improves glycemic control and displays an endothelium-protective effect. Gastric emptying, carbohydrate digestion and intestinal glucose absorption is decreased, while muscle glucose uptake is increased, which might explain the glucose-lowering effect.

Human studies

Glycemic control. Noda et al. (1994) examined the acute effects of oral administration of 0.3 g/kg body weight erythritol in five healthy volunteers (Noda, Nakayama, and Oku 1994). Serum levels of glucose and insulin were not affected. Wölnerhanssen et al. (2016) investigated the effect of 75 g (around 0.9 g/kg) of erythritol dissolved in 300 mL water given as a single bolus to lean and obese non-diabetic

subjects on glycemic responses. This higher dose of erythritol did not cause any rise in plasma insulin nor in glucose concentrations (Wölnerhanssen et al. 2016). The authors conclude that in non-diabetic human subjects, there is no effect on blood glucose or insulin after ingestion of erythritol.

In 1996, Ishikawa et al. investigated the effects of oral administration of erythritol in patients with diabetes. A single dose of 20 g erythritol did not cause any changes in serum glucose and insulin levels of five patients with diabetes (Ishikawa et al. 1996). In a separate clinical trial, 20 g erythritol was administered orally daily for 14 days to 11 patients with diabetes (Ishikawa et al. 1996). Fasting blood glucose (trend) and hemoglobin A1c levels decreased over the time period. The authors conclude that daily administration of erythritol may safely be a part of the diet of diabetics, and the significant decline in HbA1c (glycated hemoglobin) is an indication that erythritol may be helpful in long-term glucose control.

Gastric emptying and gut hormones. Wölnerhanssen et al. (2016) studied the effects of a single bolus of 75 g of erythritol on gut hormone secretion and gastric emptying in 12 lean and 12 obese non-diabetic subjects (Wölnerhanssen et al. 2016). Gastric emptying was measured by the ^{13}C sodium acetate breath test. Erythritol markedly increased CCK and GLP-1 release and delayed gastric emptying. The authors conclude that the significant retardation in gastric emptying is mediated by incretin stimulation, in particular CCK. Overduin et al. (2016) also investigated the effect of erythritol on gut hormone release: 10 lean and 10 obese volunteers consumed test meals with erythritol. Gut hormone levels, hunger and satiety scores, subsequent ad libitum food intake and sucrose preference and intake were measured. They found that the secretion of GLP-1 and PYY (peptide YY) was stimulated by erythritol, and levels were not different compared to a test meal with sucrose. Also, subsequent energy intake and sucrose preference was not different, indicating that the satiating effect of the different preloads were equal. The authors conclude that replacing sucrose with erythritol leads to comparable hunger and satiety scores, GLP-1 and PYY levels and subsequent sucrose preference and intake (Overduin et al. 2016).

Energy metabolism and gut microbiota. Generally, erythritol is considered as a zero-calorie sweetener since it cannot be metabolized. In 1993, Hiele et al. investigated the metabolism of erythritol in five healthy volunteer in comparison with glucose by measuring the excretion of ^{13}C and H_2 in the breath after the consumption of test materials (Hiele et al. 1993). The results of this study did not find any change in the excretion of breath $^{13}CO_2$ and H_2 after the consumption of erythritol, which was nearly completely recovered in the urine, suggesting its zero metabolism. The authors conclude that erythritol is a substrate that is readily absorbed and undergoes no metabolism by the host. However, recently Hootman et al. (2017) challenged these findings. They could demonstrate that there is a metabolism of erythritol to erythronate and that in human blood cells, whereas glucose is converted into erythritol via the pentose-phosphate pathway (Hootman et al. 2017). Furthermore, Hootman et al. (2017) collected blood samples from 264 young adults starting university and nine months thereafter, in order to investigate metabolic markers associated with central adiposity. They found a positive association between circulating levels of erythritol at the study baseline and the incidence of central adiposity gain (Hootman et al. 2017). Of note, these findings were not related to erythritol consumption, but might rather be related to hyperglycemia (which was also associated with erythritol levels at baseline) and use of the pentose-phosphate pathway as one option to reduce glucose.

Bornet et al. (1996a, 1996b) examined six healthy volunteers, who received a snack with either 0.4 or 0.8 g erythritol/kg body wt. Plasma and urine erythritol concentrations increased within 2 hours of ingestion in proportion to the amount ingested. Approximately 60% of the erythritol dose was eliminated in the urine within 22 hours. The authors conclude that although erythritol is readily absorbed following oral administration and excreted unchanged in the urine, at least 20% of it remained unabsorbed and therefore available for colonic fermentation (Bornet et al. 1996a, 1996b). Arrigoni, Brouns, and Amado (2005) carried out an in vitro experiment to study the impact of erythritol on human gut microbiota. They reported that human gut microbiota do not ferment erythritol under laboratory conditions by the measurement of total gas production, hydrogen accumulation, pH level, short chain fatty acids production and substrate degradation within 24 hours (Arrigoni, Brouns, and Amado 2005). The authors conclude that – at least in an in vitro setting – erythritol as a sole substrate is completely non-fermentable (Arrigoni, Brouns, and Amado 2005). Up to now, in vivo studies on the effect of erythritol on human gut microbiota are missing. Hence, further studies are needed to understand the effects of erythritol on gut microbiota, particularly in humans.

Endothelial function. Flint et al. (2014) evaluated the endothelial protective effects of erythritol in patients with type 2 diabetes mellitus (Flint et al. 2014). In this study, supplementation of a single bolus dose (24 g) or chronic dose (36 g per day) of erythritol for four weeks to 24 patients with type 2 diabetes significantly improved endothelial function, which was confirmed by measuring fingertip peripheral arterial tonometry. Moreover, central pulse pressure and carotid-femoral pulse wave velocity decreased. Erythritol consumption acutely improved small vessel endothelial function, and chronic treatment reduced central aortic stiffness. The authors conclude that erythritol may be a preferred sugar substitute for patients with diabetes mellitus. The above-mentioned in vitro study by Boesten et al. (2013) on endothelial cells shows that erythritol has a strong vascular protecting effect under hyperglycemic conditions most likely due to its anti-oxidative properties (Boesten et al. 2013).

Blood lipids and uric acid. Few studies have examined the effects of erythritol intake on blood lipids and uric acid in

humans. Noda, Nakayama, and Oku (1994) examined the acute effects of oral administration of 0.3 g/kg body weight erythritol in five healthy volunteers (Noda, Nakayama, and Oku 1994). They found no changes in serum cholesterol, TG and free fatty acid levels after the administration of a single oral dose of 0.3 g/kg bw erythritol after 0.5 h, 1 h, 2 h, 3 h, 8 h and 24 hours of ingestion (Noda, Nakayama, and Oku 1994). In 1996, Ishikawa et al. (1996) investigated the effects of oral administration of an erythritol single bolus of 20 g in five diabetic subjects (Ishikawa et al. 1996). In this trial, NEFA (non-esterified fatty acids) and HBA (3-hydroxy butyric acid) both gradually increased followed by decreases after ingestion of food. The authors conclude that this probably occurred because no energy was supplied under erythritol load, placing the subjects in a state of hunger. Wölnerhanssen and Meyer-Gerspach recently carried out a trial with 12 healthy volunteers where acute ingestion of 50 g of erythritol had no effect on total cholesterol, LDL, HDL, triglycerides or plasma uric acid (unpublished data).

In 1996, Oku and Okazaki examined 38 healthy volunteers after a single bolus dose of 75 g of erythritol and found no effect on uric acid (Oku and Okazaki 1996).

Tolerance. Erythritol is mostly absorbed (80–90%) and excreted by the kidneys (Bornet et al. 1996a, 1996b). Storey et al. (2007) examined gastrointestinal tolerance after a single oral bolus dose of either 20 g, 35 g or 50 g of erythritol in seven healthy young adults. Twenty grams and 35 g erythritol did not provoke any gastrointestinal symptoms, while the highest dose (50 g) only significantly increased the number of subjects reporting nausea and borborygmi (Storey et al. 2007). Tetzloff et al. (1996) studied the gastrointestinal effects of erythritol at up to 1 g/kg body weight (up to 80 g/day) in five portions over one week in 12 healthy volunteers. They did not observe any untoward intestinal side effects (Tetzloff et al. 1996). An extensive review on gastrointestinal tolerance of sugar alcohols was presented in 2016 by Mäkinen, mainly focusing on xylitol, but also mentioning erythritol (Mäkinen 2016). The author concludes that for erythritol, the largest safe dose for a single bolus lies around 0.6–0.8 g/kg bw.

Recently, a study involving 184 children aged four-six years old showed that rapid ingestion of up to 15 g (corresponding to 0.73 g/kg bw) of erythritol in a beverage was well-tolerated; children did not appear to be more sensitive to the gastrointestinal effects of erythritol than adults on a g/kg bw basis (Jacqz-Aigrain et al. 2015). Livesey even suggested a maximum total intake of 132 g erythritol per day as a tolerable dose (Livesey 2003). However, in the trial carried out by Wölnerhanssen et al. (2016), 12 out of 20 participants (60%) receiving a single bolus of 75 g of erythritol in 300 mL water experienced mild symptoms of bloating and diarrhea. The participants had not been exposed to polyols previously (Wölnerhanssen et al. 2016). Repetitive exposure appears to lead to increased tolerance even with erythritol through adaptive processes; however, literature documenting this effect in humans is lacking.

In summary, studies in diabetic and non-diabetic humans indicate that acute oral administration of erythritol leads to no rise in blood glucose and insulin while gut hormones such as GLP-1, PYY and CCK are released, which lead to prolonged gastric emptying and reduced subsequent food intake. Subchronic intake in diabetic patients showed improvement in fasting glucose, HbA1c and endothelial function. The impact of erythritol on human gut microbiota has been studied in human stool inocula so far only, and no effect was found. Erythritol intake seems to have no effect on blood lipids and uric acid. High doses of erythritol can lead to gastrointestinal discomfort, in particular in subjects not used to the substance. The largest safe doses are around 0.6–0.8 g/kg bw for a single bolus dose, but chronic intake increases tolerance. A summary of the effects of erythritol on glycemic and metabolic parameters is presented in Table 2.

Conclusions

The results of in vivo, ex vivo and animal studies confirmed that xylitol and erythritol both have potential anti-diabetic and anti-obesogenic effects, which are achieved by: 1) changes in gastrointestinal motor activity through inhibition of gastric emptying and increasing gut transit, 2) inhibition of carbohydrate digesting enzyme activity, 3) increase in muscle glucose uptake, 4) trophic effects on pancreatic islets and 5) release of favorable gut hormones such as GLP-1 (which in turn exerts trophic effects on pancreatic β-cells, increases insulin secretion as well as insulin-sensitivity in both α-cells and β-cells promoting insulin sensitivity and decreases glucagon secretion (Holst 2007).

While the trophic effects on pancreatic islets and effects on carbohydrate digesting enzymes activity have been demonstrated for xylitol in rats (Rahman and Islam 2014), data on erythritol are still lacking. In vitro studies confirmed the potency of erythritol in scavenging hydroxyl radical (OH*), a major culprit of damaging pancreatic β-cells (den Hartog et al. 2010). The pancreas is very susceptible to hydroxyl radicals (OH*), with islet cells in particular showing high vulnerability to oxidative damage, as this organ has a lower anti-oxidative defense system compared to many other organs (Acharya and Ghaskadbi 2010). Hydroxyl radicals easily pass through the membrane barriers to the nucleus of the cells compared to many other free radicals (Robertson et al. 2003), which are usually produced in our body via various metabolic processes. The anti-oxidative effects of xylitol and erythritol might also contribute to amelioration in glycemic control.

Hyperuricemia and hyperlipidemia are potential undesired side-effects associated with chronic intake of sugar alcohols. However, there are conflicting results in both animal and human trials concerning changes in blood lipids after consumption of xylitol and erythritol. In rat models, it has been shown that in normoglycemic rats, triglycerides increases, while under diabetic conditions no changes are seen. In human studies, most trials found no changes after acute, subchronic or chronic exposition (Huttunen

et al. 1976; Förster et al. 1982). This is in contrast to one acute trial with eight participants, where a xylitol-containing formula lead to a significant increase in TG and VLDL (Otto et al. 1993). Results on hyperuricemia are also inconsistent: Förster et al. (1977) found an increase in uric acid in diabetic children, but no change in non-diabetic volunteers when exposed for 2–4 weeks, while in the Turku studies no increase in uric acid was seen (Huttunen et al. 1976; Förster et al. 1977). Hence, further studies are warranted in order ascertain these discrepancies.

From our analyses, we conclude that both xylitol and erythritol have potential anti-hyperglycemic properties and suggest that more dose-response and long-term studies in normal weight, overweight, obese and diabetic individuals are needed to understand the true anti-hyperglycemic effects of xylitol and erythritol in humans. In this context, we also propose that the effects of these sugar alcohols on lipid metabolism and hyperuricemia need further investigations for their safer use as supplements in diabetic foods and food products.

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References

Acharya, J. D., and S. S. Ghaskadbi. 2010. Islets and their antioxidant defense. *Islets* 2 (4):225–35. doi: 10.4161/isl.2.4.12219.

Akerblom, H. K., T. Koivukangas, R. Puukka, and M. Mononen. 1982. The tolerance of increasing amounts of dietary xylitol in children. *International Journal for Vitamin and Nutrition Research. Supplement = Internationale Zeitschrift Fur Vitamin- Und Ernahrungsforschung*. Supplement 22:53–66.

Amo, K., H. Arai, T. Uebanso, M. Fukaya, M. Koganei, H. Sasaki, H. Yamamoto, Y. Taketani, and E. Takeda. 2011. Effects of xylitol on metabolic parameters and visceral fat accumulation. *Journal of Clinical Biochemistry and Nutrition* 49 (1):1–7. doi: 10.3164/jcbn.10-111.

Arrigoni, E., F. Brouns, and R. Amado. 2005. Human gut microbiota does not ferment erythritol. *The British Journal of Nutrition* 94 (5): 643–6.

Asano, T., M. D. Levitt, and F. C. Goetz. 1973. Xylitol absorption in healthy men. *Diabetes* 22 (4):279–81. doi: 10.2337/diab.22.4.279.

Baessler, K. H., W. Prellwitz, V. Unbehaun, and K. Lang. 1962. [Xylitol metabolism in man. On the problem of the suitability of xylitol as a sugar substitute in diabetics]. *Klinische Wochenschrift* 40:791–3.

Boesten, D. M., A. Berger, P. de Cock, H. Dong, B. D. Hammock, G. J. den Hartog, and A. Bast. 2013. Multi-targeted mechanisms underlying the endothelial protective effects of the diabetic-safe sweetener erythritol. *PLoS One* 8 (6):e65741. doi: 10.1371/journal.pone.0065741.

Bornet, F. R., A. Blayo, F. Dauchy, and G. Slama. 1996a. Gastrointestinal response and plasma and urine determinations in human subjects given erythritol. *Regulatory Toxicology and Pharmacology* 24 (2):S296–S302. doi: 10.1006/rtph.1996.0111.

Bornet, F. R., A. Blayo, F. Dauchy, and G. Slama. 1996b. Plasma and urine kinetics of erythritol after oral ingestion by healthy humans. *Regulatory Toxicology and Pharmacology* 24 (2):S280–S5. doi: 10.1006/rtph.1996.0109.

Bray, G. A., and B. M. Popkin. 2014. Dietary sugar and body weight: Have we reached a crisis in the epidemic of obesity and diabetes?: Health be damned! Pour on the sugar. *Diabetes Care* 37 (4):950–6. doi: 10.2337/dc13-2085.

Brunzell, J. D. 1978. Use of fructose, sorbitol, or xylitol as a sweetener in diabetes mellitus. *Journal of the American Dietetic Association* 73 (5):499–506.

Chan, T. F., W. T. Lin, H. L. Huang, C. Y. Lee, P. W. Wu, Y. W. Chiu, C. C. Huang, S. Tsai, C. L. Lin, and C. H. Lee. 2014. Consumption of sugar-sweetened beverages is associated with components of the metabolic syndrome in adolescents. *Nutrients* 6 (5): 2088–103. doi: 10.3390/nu6052088.

Chukwuma, C. I., and M. S. Islam. 2015. Effects of xylitol on carbohydrate digesting enzymes activity, intestinal glucose absorption and muscle glucose uptake: A multi-mode study. *Food & Function* 6 (3): 955–62. doi: 10.1039/C4FO00994K.

Chukwuma, C. I., and S. Islam. 2017. Xylitol improves anti-oxidative defense system in serum, liver, heart, kidney and pancreas of normal and type 2 diabetes model of rats. *Acta Poloniae Pharmaceutica* 74 (3):817–26.

Chukwuma, C. I., R. Mopuri, S. Nagiah, A. A. Chuturgoon, and M. S. Islam. 2018. Erythritol reduces small intestinal glucose absorption, increases muscle glucose uptake, improves glucose metabolic enzymes activities and increases expression of Glut-4 and IRS-1 in type 2 diabetic rats. *European Journal of Nutrition* 57 (7):2431–44. doi: 10.1007/s00394-017-1516-x.

de Cock, P., K. Mäkinen, E. Honkala, M. Saag, E. Kennepohl, and A. Eapen. 2016. Erythritol is more effective than xylitol and sorbitol in managing oral health endpoints. *International Journal of Dentistry* 2016:15. doi: 10.1155/2016/9868421.

den Besten, G., K. van Eunen, A. K. Groen, K. Venema, D. J. Reijngoud, and B. M. Bakker. 2013. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *Journal of Lipid Research* 54 (9):2325–40. doi: 10.1194/jlr.R036012.

den Hartog, G. J., A. W. Boots, A. Adam-Perrot, F. Brouns, I. W. Verkooijen, A. R. Weseler, G. R. Haenen, and A. Bast. 2010. Erythritol is a sweet antioxidant. *Nutrition* 26 (4):449–58. doi: 10.1016/j.nut.2009.05.004.

Domareva, I. V. 1967. [The use of xylitol in diabetes mellitus (literature survey)]. *Voprosy Pitaniia* 26 (3):46–52.

Dubach, U. C. 1976. [Comparative study of i.v. administration of xylitol and sorbitol to diabetics]. *Internationale Zeitschrift Fur Vitamin- Und Ernahrungsforschung*. Beiheft 15:81–91.

Feinman, R. D., and E. J. Fine. 2013. Fructose in perspective. *Nutrition & Metabolism* 10 (1):45. doi: 10.1186/1743-7075-10-45.

Flint, N., N. M. Hamburg, M. Holbrook, P. G. Dorsey, R. M. LeLeiko, A. Berger, P. de Cock, D. Bosscher, and J. A. Vita. 2014. Effects of erythritol on endothelial function in patients with type 2 diabetes

mellitus: A pilot study. *Acta Diabetologica* 51 (3):513–6. doi: 10.1007/s00592-013-0534-2.

Förster, H., S. Boecker, and A. Walther. 1977. [Use of xylitol as sugar substitute in diabetic children]. *Fortschritte Der Medizin* 95 (2): 99–102.

Förster, H., R. Quadbeck, and U. Gottstein. 1982. Metabolic tolerance to high doses of oral xylitol in human volunteers not previously adapted to xylitol. *International Journal for Vitamin and Nutrition Research. Supplement = Internationale Zeitschrift Fur Vitamin- Und Ernahrungsforschung*. Supplement 22:67–88.

Fowler, S. P. G. 2016. Low-calorie sweetener use and energy balance: Results from experimental studies in animals, and large-scale prospective studies in humans. *Physiology & Behavior* 164 (Pt B): 517–23. doi: 10.1016/j.physbeh.2016.04.047.

Ha, V., V. H. Jayalath, A. I. Cozma, A. Mirrahimi, R. J. de Souza, and J. L. Sievenpiper. 2013. Fructose-containing sugars, blood pressure, and cardiometabolic risk: A critical review. *Current Hypertension Reports* 15 (4):281–97. doi: 10.1007/s11906-013-0364-1.

Hassinger, W., G. Sauer, U. Cordes, U. Krause, J. Beyer, and K. H. Baessler. 1981. The effects of equal caloric amounts of xylitol, sucrose and starch on insulin requirements and blood glucose levels in insulin-dependent diabetics. *Diabetologia* 21 (1):37–40. doi: 10.1007/BF03216221.

Hiele, M., Y. Ghoos, P. Rutgeerts, and G. Vantrappen. 1993. Metabolism of erythritol in humans: Comparison with glucose and lactitol. *The British Journal of Nutrition* 69 (1):169–76.

Holst, J. J. 2007. The physiology of glucagon-like peptide 1. *Physiological Reviews* 87 (4):1409–39. doi: 10.1152/physrev.00034.2006.

Holst, J. J. 2013. Incretin hormones and the satiation signal. *International Journal of Obesity* 37 (9):1161–8. doi: 10.1038/ijo.2012.208.

Hootman, K. C., J. P. Trezzi, L. Kraemer, L. S. Burwell, X. Dong, K. A. Guertin, C. Jaeger, P. J. Stover, K. Hiller, and P. A. Cassano. 2017. Erythritol is a pentose-phosphate pathway metabolite and associated with adiposity gain in young adults. *Proceedings of the National Academy of Sciences of the United States of America* 114 (21): E4233–40. doi: 10.1073/pnas.1620079114.

Huttunen, J. K., K. K. Mäkinen, and A. Scheinin. 1976. Turku sugar studies XI. Effects of sucrose, fructose and xylitol diets on glucose, lipid and urate metabolism. *Acta Odontologica Scandinavica* 34 (6): 345–51. doi: 10.3109/00016357609004646.

Ishikawa, M., M. Miyashita, Y. Kawashima, T. Nakamura, N. Saitou, and J. Modderman. 1996. Effects of oral administration of erythritol on patients with diabetes. *Regulatory Toxicology and Pharmacology* 24 (2):S303–S8. doi: 10.1006/rtph.1996.0112.

Islam, M. S. 2011. Effects of xylitol as a sugar substitute on diabetes-related parameters in nondiabetic rats. *Journal of Medicinal Food* 14 (5):505–11. doi: 10.1089/jmf.2010.0015.

Islam, M. S. 2012. Xylitol increases serum triglyceride in normal but not in a type 2 diabetes model of rats. *Journal of Medicinal Food* 15 (8):677. doi: 10.1089/jmf.2012.0077.

Islam, M. S., and M. Indrajit. 2012. Effects of xylitol on blood glucose, glucose tolerance, serum insulin and lipid profile in a type 2 diabetes model of rats. *Annals of Nutrition and Metabolism* 61 (1): 57–64. doi: 10.1159/000338440.

Jacqz-Aigrain, E., B. Kassai, C. Cornu, J. M. Cazaubiel, B. Housez, M. Cazaubiel, J. M. Prevel, M. Bell, A. Boileau, and P. de Cock. 2015. Gastrointestinal tolerance of erythritol-containing beverage in young children: A double-blind, randomised controlled trial. *European Journal of Clinical Nutrition* 69 (6):746–51. doi: 10.1038/ejcn.2015.4.

Johnson, R. J., T. Nakagawa, L. G. Sanchez-Lozada, M. Shafiu, S. Sundaram, M. Le, T. Ishimoto, Y. Y. Sautin, and M. A. Lanaspa. 2013. Sugar, uric acid, and the etiology of diabetes and obesity. *Diabetes* 62 (10):3307–15. doi: 10.2337/db12-1814.

Kishore, P., S. Kehlenbrink, M. Hu, K. Zhang, R. Gutierrez-Juarez, S. Koppaka, M. R. El-Maghrabi, and M. Hawkins. 2012. Xylitol prevents NEFA-induced insulin resistance in rats. *Diabetologia* 55 (6): 1808–12. doi: 10.1007/s00125-012-2527-z.

Lang, K. 1971. [Xylitol, metabolism and clinical use]. *Klinische Wochenschrift* 49 (5):233–45.

Livesey, G. 2003. Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. *Nutrition Research Reviews* 16 (2):163–91. doi: 10.1079/NRR200371.

Makelainen, H. S., H. A. Makivuokko, S. J. Salminen, N. E. Rautonen, and A. C. Ouwehand. 2007. The effects of polydextrose and xylitol on microbial community and activity in a 4-stage Colon simulator. *Journal of Food Science* 72 (5):M153–9. doi: 10.1111/j.1750-3841.2007.00350.x.

Mäkinen, K. K. 1976. Long-term tolerance of healthy human subjects to high amounts of xylitol and fructose: General and biochemical findings. *Internationale Zeitschrift für Vitamin- und Ernährungsforschung. Beiheft* 15:92–104.

Mäkinen, K. K. 2011. Sugar alcohol sweeteners as alternatives to sugar with special consideration of xylitol. *Medical Principles and Practice* 20 (4):303–20. doi: 10.1159/000324534.

Mäkinen, K. K. 2016. 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. *International Journal of Dentistry* 2016:5967907. doi: 10.1155/2016/5967907.

Mäkinen, K. K., R. Ylikahri, P. L. Mäkinen, E. Soderling, and M. Hamalainen. 1982. Turku sugar studies XXIII. Comparison of metabolic tolerance in human volunteers to high oral doses of xylitol and sucrose after long-term regular consumption of xylitol. *International Journal for Vitamin and Nutrition Research. Supplement = Internationale Zeitschrift für Vitamin- und Ernährungsforschung. Supplement*. 22:29–49.

Mellinghoff, C. H. 1961. [The usefulness of xylitol as a sugar substitute in diabetics]. *Klinische Wochenschrift* 39:447

Mertz, D. P., V. Kaiser, M. Klöpfer-Zaar, and H. Beisbarth. 1972. Serumkonzentrationen verschiedener lipide und von harnsäure während 2-wöchiger verabreichung von xylit. *Klinische Wochenschrift* 50 (23):1107–11. doi: 10.1007/BF01486855.

Moon, H. J., M. Jeya, I. W. Kim, and J. K. Lee. 2010. Biotechnological production of erythritol and its applications. *Applied Microbiology and Biotechnology* 86 (4):1017–25. doi: 10.1007/s00253-010-2496-4.

Muller-Hess, R., C. A. Geser, J. P. Bonjour, E. Jequier, and J. P. Felber. 1975. Effects of oral xylitol administration on carbohydrate and lipid metabolism in normal subjects. *Transfusion Medicine and Hemotherapy* 2 (4):247–52. doi: 10.1159/000219627.

Munro, I. C., W. O. Bernt, J. F. Borzelleca, G. Flamm, B. S. Lynch, E. Kennepohl, E. A. Bär, and J. Modderman. 1998. Erythritol: An interpretive summary of biochemical, metabolic, toxicological and clinical data. *Food and Chemical Toxicology* 36 (12):1139–74. doi: 10.1016/S0278-6915(98)00091-X.

Mushtaq, Z., M. Imran, ur Rehman Salim, T. Zahoor, R. S. Ahmad, and M. U. Arshad. 2014. Biochemical perspectives of xylitol extracted from indigenous agricultural by-product mung bean (*Vigna radiata*) hulls in a rat model. *Journal of the Science of Food and Agriculture* 94 (5):969–74.

Nesterin, M. F. 1980. Xylitol. Experimental and clinical investigations conducted in the USSR (review). *Zeitschrift für Ernährungswissenschaft* 19 (2):88–94. doi: 10.1007/BF02021392.

Noda, K., K. Nakayama, and J. Modderman. 1996. Fate of erythritol after single oral administration to rats and dogs. *Regulatory Toxicology and Pharmacology* 24 (2):S206–S13. doi: 10.1006/rtph.1996.0100.

Noda, K., K. Nakayama, and T. Oku. 1994. Serum glucose and insulin levels and erythritol balance after oral administration of erythritol in healthy subjects. *European Journal of Clinical Nutrition* 48 (4): 286–92.

Oku, T., and M. Okazaki. 1996. Laxative threshold of sugar alcohol erythritol in human subjects. *Nutrition Research* 16 (4):577–89. doi: 10.1016/0271-5317(96)00036-X.

Otto, C., A. C. Sonnichsen, M. M. Ritter, W. O. Richter, and P. Schwandt. 1993. Influence of fiber, xylitol and fructose in enteral formulas on glucose and lipid metabolism in normal subjects. *Journal of Clinical Investigation* 71 (4):290–3.

Overduin, J., T. H. Collet, N. Medic, E. Henning, J. M. Keogh, F. Forsyth, C. Stephenson, M. W. Kanning, R. M. Ruijschop, I. S.

Farooqi, and A. A. van der Klaauw. 2016. Failure of sucrose replacement with the non-nutritive sweetener erythritol to alter GLP-1 or PYY release or test meal size in lean or obese people. *Appetite* 107: 596–603. doi: 10.1016/j.appet.2016.09.009.

Pfeiffer, A. F. H., and F. Keyhani-Nejad. 2018. High glycemic index metabolic damage – A pivotal role of GIP and GLP-1. *Trends in Endocrinology and Metabolism* 29 (5):289–99. doi: 10.1016/j.tem.2018.03.003.

Rahman, M. A., and M. S. Islam. 2014. Xylitol improves pancreatic islets morphology to ameliorate type 2 diabetes in rats: A dose response study. *Journal of Food Science* 79 (7):H1436–42. doi: 10.1111/1750-3841.12520.

Robertson, R. P., J. Harmon, P. O. Tran, Y. Tanaka, and H. Takahashi. 2003. Glucose toxicity in beta-cells: Type 2 diabetes, good radicals gone bad, and the glutathione connection. *Diabetes* 52 (3):581–7. doi: 10.2337/diabetes.52.3.581.

Rogala, H., and J. Sieradzki. 1971. [Xylitol and its possible clinical use]. *Przeglad Lekarski* 28 (12):802–6.

Salminen, E. K., S. J. Salminen, L. Porkka, P. Kwasowski, V. Marks, and P. E. Koivistoinen. 1989. Xylitol vs glucose: Effect on the rate of gastric emptying and motilin, insulin, and gastric inhibitory polypeptide release. *The American Journal of Clinical Nutrition* 49 (6): 1228–32. doi: 10.1093/ajcn/49.6.1228.

Shafer, R. B., A. S. Levine, J. M. Marlette, and J. E. Morley. 1987. Effects of xylitol on gastric emptying and food intake. *The American Journal of Clinical Nutrition* 45 (4):744–7. doi: 10.1093/ajcn/45.4.744.

Storey, D., A. Lee, F. Bornet, and F. Brouns. 2007. Gastrointestinal tolerance of erythritol and xylitol ingested in a liquid. *European Journal of Clinical Nutrition* 61 (3):349–54. doi: 10.1038/sj.ejcn.1602532.

Tetzloff, W., F. Dauchy, S. Medimagh, D. Carr, and A. Bar. 1996. Tolerance to subchronic, high-dose ingestion of erythritol in human volunteers. *Regulatory Toxicology and Pharmacology* 24 (2): S286–S95. doi: 10.1006/rtph.1996.0110.

Uebanso, T., S. Kano, A. Yoshimoto, C. Naito, T. Shimohata, K. Mawatari, and A. Takahashi. 2017. Effects of consuming xylitol on gut microbiota and lipid metabolism in mice. *Nutrients* 9 (7):E756. doi: 10.3390/nu9070756.

Wen, H., B. Tang, A. J. Stewart, Y. Tao, Y. Shao, Y. Cui, H. Yue, J. Pei, Z. Liu, L. Mei, et al. 2018. Erythritol attenuates postprandial blood glucose by inhibiting alpha-glucosidase. *Journal of Agricultural and Food Chemistry* 66 (6):1401–7. doi: 10.1021/acs.jafc.7b05033.

Wölnerhanssen, B. K., L. Cajacob, N. Keller, A. Doody, J. F. Rehfeld, J. Drewe, R. Peterli, C. Beglinger, and A. C. Meyer-Gerspach. 2016. Gut hormone secretion, gastric emptying, and glycemic responses to erythritol and xylitol in lean and obese subjects. *American Journal of Physiology-Endocrinology and Metabolism* 310 (11):E1053–61. doi: 10.1152/ajpendo.00037.2016.

Yamamoto, T., Y. Moriwaki, S. Takahashi, Z. Tsutsumi, J. Yamakita, and K. Higashino. 1999. Effects of fructose and xylitol on the urinary excretion of adenosine, uridine, and purine bases. *Metabolism* 48 (4):520–4. doi: 10.1016/S0026-0495(99)90114-2.

Yokozawa, T., H. Y. Kim, and E. J. Cho. 2002. Erythritol attenuates the diabetic oxidative stress through modulating glucose metabolism and lipid peroxidation in streptozotocin-induced diabetic rats. *Journal of Agricultural and Food Chemistry* 50 (19):5485–9. doi: 10.1021/jf020168z.