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Effects of a 5-week intake of erythritol and xylitol on vascular function, abdominal fat and glucose tolerance in humans with obesity: a pilot trial

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ABSTRACT

Introduction Previous studies in humans and rats suggest that erythritol might positively affect vascular function, xylitol decrease visceral fat mass and both substances improve glycaemic control. The objective of this study was to investigate the impact of a 5-week intake of erythritol and xylitol on vascular function, abdominal fat and blood lipids, glucose tolerance, uric acid, hepatic enzymes, creatinine, gastrointestinal tolerance and dietary patterns in humans with obesity.

Methods Forty-two participants were randomised to consume either 36 g erythritol, 24 g xylitol, or no substance daily for 5 weeks. Before and after the intervention, arterial stiffness (pulse wave velocity, arteriolar-to-venular diameter ratio), abdominal fat (liver volume, liver fat percentage, visceral and subcutaneous adipose tissue, blood lipids), glucose tolerance (glucose and insulin concentrations), uric acid, hepatic enzymes, creatinine, gastrointestinal tolerance and dietary patterns were assessed. Data were analysed by linear mixed effect model.

Results The 5-week intake of erythritol and xylitol showed no statistically significant effect on vascular function. Neither the time nor the treatment effects were significantly different for pulse wave velocity (time effect: p=0.079, Cohen's D (95% CI) −0.14 (−0.54–0.25); treatment effect: p=0.792, Cohen's D (95% CI) control versus xylitol: −0.11 (−0.61–0.35), control versus erythritol: 0.05 (0.44–0.54), erythritol versus xylitol: 0.07 (−0.41–0.54)). There was no statistically significant effect on abdominal fat, glucose tolerance, uric acid, hepatic enzymes and creatinine. Gastrointestinal tolerance was good except for a few diarrhoea-related symptoms. Participants of all groups reduced their consumption of sweetened beverages and sweets compared with preintervention.

Conclusions The 5-week intake of erythritol and xylitol showed no statistically significant effects on vascular function, abdominal fat, or glucose tolerance in people with obesity.

Clinical trial registration NCT02821923.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior research indicates that among people with diabetes, erythritol consumption improves glycaemic control and vascular function. Diabetic animal models have demonstrated that both polyols enhance blood glucose control, while xylitol decreases visceral fat mass. In humans, both polyols also trigger the release of metabolically advantageous gastrointestinal hormones (incretins).

WHAT THIS STUDY ADDS

⇒ This randomised controlled trial in normoglycaemic people with obesity shows no statistically significant effect of a 5-week intake of erythritol and xylitol on vascular function, abdominal fat or glucose tolerance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study contributes valuable insights into the metabolic impacts of regular erythritol and xylitol consumption. It reveals that these sugar substitutes do not seem to exhibit adverse effects on vascular function, glycaemic control or fat metabolism and, therefore, hold promise as suitable sugar alternatives for individuals with obesity.

INTRODUCTION

Obesity is linked to reduced postprandial incretin secretion[1] and increased glucose absorption.[2] These characteristics promote hyperglycaemia.[3] Additionally, obesity is associated with increased free fatty acid and triglyceride (TG) concentrations.[4 5] Hyperglycaemia and hyperlipidaemia combined play a role in the pathogenesis of vascular dysfunction. In human endothelial cells, high glucose concentrations induce apoptosis and overproduction of reactive oxygen species, leading to endothelial dysfunction.[6 7] Moreover, in humans, high insulin and TG concentrations have a synergistic association with arterial stiffness.[8] Additionally, the retinal venular calibre—a secondary marker of vascular dysfunction—is significantly

larger in people with increased fasting glucose levels and glycated haemoglobin (HbA1C).[9]

Arterial stiffness is an early marker of cardiovascular disease[10] and a strong predictor of future cardiovascular events.[11] The retinal arteriolar narrowing is associated with hypertension, especially when combined with higher venular diameter.[12 13] An increase in the arteriolar-to-venule diameter ratio (AVR) is associated with an increased risk of coronary heart disease and acute myocardial infarction in women.[14] Therefore, assessment of the retinal and central blood vessels allows the detection of early changes in vascular function, possibly prior to type 2 diabetes mellitus (T2DM) and its complications.

Given the current obesity epidemic, the WHO recommends reducing sugar intake.[15] A possibility to achieve this recommendation is to partially replace sugar with low-calorie sweeteners such as erythritol and xylitol. These sweeteners are interesting for patients with overweight and diabetes due to their low glycemic indexes[16] and their ability to induce the secretion of gastrointestinal satiation hormones.[17–19] Additionally, erythritol has a protective effect on endothelial cell function, as shown in endothelial cell culture as well as in patients with T2DM, and a 4-week intake reduces central pulse pressure in patients with T2DM.[20 21]

A recent study suggests a potential link between plasma erythritol levels and cardiovascular events in humans.[22] However, erythritol is also produced endogenously from glucose in humans.[23] In the studied group, the origin of erythritol is not clear, which makes a causal analysis impossible. Rodent studies hint that sucrose intake may raise internal erythritol production,[24] possibly explaining higher erythritol levels.

Xylitol has beneficial effects on visceral fat mass, plasma insulin, glycaemia and lipid concentrations in non-diabetic rats.[25 26] In humans, xylitol intake for 18 days tends to decrease cholesterol levels compared with 6-day sucrose intake.[27] Finally, both substances show beneficial effects on glycaemic control in both normoglycaemic and diabetic rats.[28 29] Therefore, these two substances seem promising in preventing vascular dysfunction and its underlying mechanisms, such as endothelial cell death, hyperlipidaemia and hyperglycaemia.

The objective of this study was to investigate the impact of a 5-week intake of erythritol and xylitol on vascular function (primary objective), abdominal fat and blood lipids, glucose tolerance, uric acid, hepatic enzymes, creatinine, gastrointestinal tolerance and dietary patterns (secondary objectives) in humans with obesity.

METHODS

The study was conducted as a randomised, controlled trial and performed in accordance with the current version (V.2013) of the Declaration of Helsinki on medical research involving human subjects (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/).

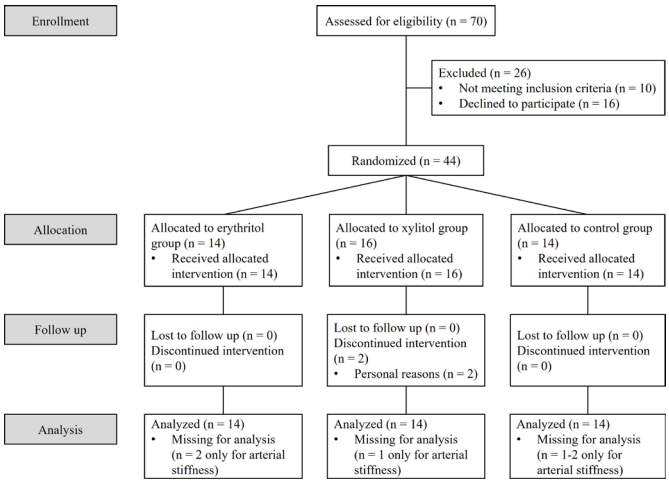

Figure 1 Participants flowchart.

A total of 44 normoglycaemic participants with obesity were recruited via advertisement between November 2016 and January 2022. Exclusion criteria included any prior medical conditions, any surgery with major changes to the gastrointestinal tract, regular medications use, pregnancy or consumption of substances in abuse. Participants did not have any dietary restrictions or regular consumption of erythritol or xylitol. Two participants dropped out for personal reasons and were replaced, resulting in 42 participants who completed the study (see participants' flowchart in figure 1). The baseline characteristics for each group are presented in table 1.

The participants were randomly assigned—by a third person, using a computer-based randomisation system—to consume either 12 g of erythritol, or 8 g of xylitol dissolved in water three times a day (together with the main meals) for 5 weeks or to the control group (no substance) in a 1:1:1 ratio.

The first week of intervention was an adaptation period: one portion per day for 2 days, then two portions per day for 3 days, finally three portions per day for two last days. Then, participants went on with three daily portions for the remaining 4 weeks. Participants in the control group did not consume any substances. In the intervention groups, the trial was double-blind, meaning that the study participants and the study personnel were blinded concerning the type of substance consumed.

Erythritol and xylitol were purchased from Mithana GmbH (Zimmerwald, Switzerland). The duration of intervention and the dosage of erythritol were based on a previous pilot study of Flint *et al*,[21] which showed reduced central pulse pressure and improved endothelial function in patients with T2DM after a 4-week intake of 36 g/day of erythritol. This quantity of erythritol is a feasible dosage to replace the daily added sugar intake in Switzerland and represents real-life conditions. Xylitol was given in an equisweet dosage to erythritol.

Before and after the intervention period, participants were invited to three study visits to assess arterial stiffness and retinal vessels diameters, abdominal fat quantification

Table 1 Baseline characteristics (mean±SD) for each group

Parameter	Erythritol group	Xylitol group	Control group	P values
Sex	n=14 (8♂; 6♀)	n=14 (9♂; 5♀)	n=14 (7♂; 7♀)	0.583*
Age (years)	31.3±8.8	30.4±10.6	30.6±10.1	0.972†
BMI (kg/m^2)	33.9±3.7	34.8±2.8	34.9±3.7	0.709†
Systolic blood pressure (mm Hg)	131.9±12.9	129.4±7.3	126.4±17.2	0.552†
Diastolic blood pressure (mm Hg)	85.9±10.9	85.6±10.2	78.7±8.6	0.107†
Pulse rate (1/min)	72.9±11.2	73.9±11.2	75.3±11.2	0.862†

♀: females, ♂: males.
*Chi-square test.
†Analysis of variance.
BMI, body mass index.

(including subcutaneous, visceral and hepatic distribution), and glycaemic control, blood lipids, uric acid, hepatic enzymes and creatinine. In addition, gastrointestinal tolerance and dietary patterns were assessed before and during the second and fourth week of intervention. Further information on the methodology is found in online supplemental appendix S1.

Statistical analysis

This study is a pilot trial. Therefore, a minimum number of 14 participants per group was chosen for reasons of comparability and practicability. Imputation of isolated missing values, which constituted less than 0.5% of the data set, except for glucose (3.3%), was performed using the median value corresponding to the respective treatment group. Therefore, the imputation did not alter the distribution of the values for the parameter in question.

For longitudinal parameters, a linear mixed effect model with subsequent Šidak test was applied using the time (pre- or post-intervention) as a within-subject factor and the treatment (erythritol, xylitol, control) as a fixed between-subject factor. Non-longitudinal parameters were analysed by general linear modelling. SPSS for Windows software, V.25.0 was used (IBM, Armonk, New York). Values are reported as means±SD and displayed in figures as means±SE of the mean (SEM) or median and IQR for boxplots. Differences were considered to be statistically significant when $p<0.05$. For the primary endpoint, effect sizes were calculated as Cohen's D with their corresponding 95% CIs in Python (V.3.11) using the modules Statsmodels (V.0.13.5)[30] and Scipy (V.1.10.1).

RESULTS

Vascular function: arterial stiffness, retinal vessel diameters

No statistically significant effect of erythritol or xylitol intake on vascular function was found. For arterial stiffness: Neither the time (preintervention or postintervention) nor the treatment (erythritol, xylitol, control) effects were significantly different for the left brachial pulse wave velocity (LB-PWV).

The effect size (Cohen's D (95% CI)) for the time effect was −0.14 (−0.54–0.25), and the effect sizes (Cohen's D (95% CIs)) for the treatment effects were control versus xylitol: −0.11 (−0.61–0.35), control versus erythritol: 0.05 (0.44–0.54) and erythritol versus xylitol: 0.07 (−0.41–0.54).

For retinal vessel diameters: neither the time nor the treatment effects were significantly different for the AVR. The effect size (Cohen's D (95% CI)) for the time effect was −0.14 (-0.034–0.01), and the effect sizes (Cohen's D (95% CIs)) for the treatment effects were control versus xylitol: −0.23 (−0.61–0.26), control versus erythritol: 0.13 (−0.11–0.16) and erythritol versus xylitol: 0.12 (0.10–0.14). The vascular parameters are reported in table 2.

Table 2 Arterial stiffness and retinal vessel diameters (mean±SD) for each group before and after intervention

Parameter	Time point	Erythritol group	Xylitol group	Control group	Time effect (P value)	Treatment effect (P value)
LB-PWV(m/s)	Preintervention	(n=12) 6.0±0.9	(n=13) 6.1±0.9	(n=13) 5.9±0.9	0.079	0.792
	Postintervention	(n=12) 5.8±0.6	(n=13) 6.0±0.9	(n=12) 5.9±0.9		
AVR (n=14)	Preintervention	0.8±0.0	0.8±0.1	0.8±0.1	0.900	0.698
	Postintervention	0.8±0.0	0.8±0.1	0.8±0.1		

Linear mixed effect model with subsequent Šidak test.
AVR, arteriolar-to-venular diameter ratio; LB-PWV, left-brachial pulse wave velocity.

Table 3 Abdominal fat and blood lipids parameters (mean±SD) for each group before and after intervention

Parameter	Time point	Erythritol group (n=14)	Xylitol group (n=14)	Control group (n=14)	Time effect (P value)	Treatment effect (P value)
Liver volume (L)	Preintervention	1.70±0.40	1.81±0.47	1.72±0.30	0.307	0.564
	Postintervention	1.70±0.47	1.89±0.52	1.70±0.32		
Liver fat percentage (%)	Preintervention	9.5±7.8	7.3±6.6	6.1±7.3	0.436	0.892
	Postintervention	8.7±7.6	7.3±7.5	6.0±6.5		
VAT volume (L)	Preintervention	4.64±2.62	3.98±1.85	4.21±1.53	0.216	0.583
	Postintervention	5.11±3.00	4.39±2.03	4.32±1.72		
SAT volume (L)	Preintervention	13.06±3.73	12.84±2.71	13.27±4.32	0.300	0.995
	Postintervention	12.96±4.22	13.07±2.71	13.48±4.57		
Triglycerides (mmol/L)	Preintervention	1.9±1.3	1.4±0.7	2.2±2.1	0.158	0.837
	Postintervention	1.6±1.0	1.7±1.0	1.2±0.5		
Total cholesterol (mmol/L)	Preintervention	5.4±1.4	4.8±0.9	4.7±1.0	0.489	0.365
	Postintervention	5.0±1.1	4.8±1.1	4.6±0.9		
HDL-cholesterol (mmol/L)	Preintervention	1.8±1.8	1.4±0.3	1.2±0.3	0.240	0.364
	Postintervention	1.3±0.4	1.3±0.2	1.2±0.3		
LDL-cholesterol (mmol/L)	Preintervention	3.0±0.9	3.0±0.5	3.1±0.7	0.038*	0.943
	Postintervention	2.9±0.7	2.9±0.6	2.9±0.9		

Linear mixed effect model with subsequent Šidak test.
*Significant with p<0.05.
HDL, high-density lipoprotein; LDL, low-density lipoprotein; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Abdominal fat: quantification and distribution, blood lipids

No statistically significant effect of erythritol or xylitol intake on abdominal fat and blood lipids was found. Abdominal fat: neither the time nor the treatment effects were significantly different for the liver volume, the liver fat percentage, the visceral adipose tissue and the subcutaneous adipose tissue volumes.

Blood lipids: neither the time nor the treatment effects were significantly different for TGs, total cholesterol levels and high-density lipoprotein cholesterol. There was a significant time, but no treatment effect for the low-density lipoprotein (LDL) cholesterol. In all treatment groups, the LDL cholesterol levels were significantly decreased after the intervention compared with before. The respective parameters are reported in table 3.

Glucose tolerance

No statistically significant effect of erythritol or xylitol intake on glucose tolerance was found. Neither the time nor the treatment effects were significantly different for the glucose and insulin concentrations during oral glucose tolerance test (see figure 2), and for the areas under the glucose and insulin concentration curves at 120 min (glucose: p=0.482 and p=0.412, respectively; insulin: p=0.902 and p=0.583, respectively).

No statistically significant effect of erythritol or xylitol intake on the Homeostatic Model Assessment index = (fasting glucose × fasting insulin)/22.5 was found. Neither the time nor the treatment effects were significantly different (p=0.339, p=0.780, respectively, see figure 3).

Uric acid, hepatic enzymes and creatinine

No statistically significant effect of erythritol or xylitol intake on uric acid, hepatic enzymes and creatinine was found. Neither the time nor the treatment effects were significantly different for uric acid, aspartate

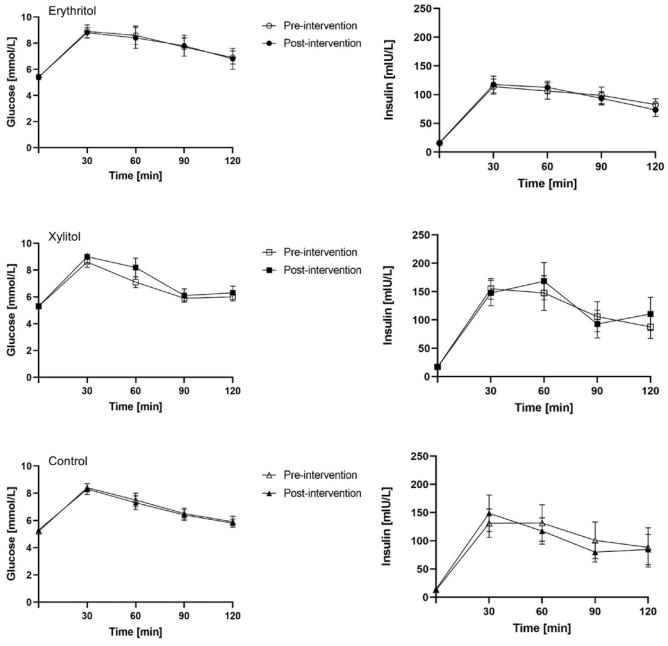

Figure 2 Glucose and insulin concentrations during glucose tolerance test for each group before and after intervention (mean±SEM).

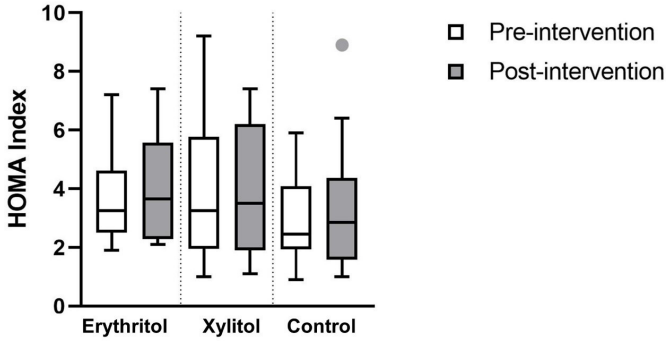

Figure 3 HOMA Index for each group before and after intervention (median and IQR). HOMA, Homeostatic Model Assessment.

aminotransferase, alanine aminotransferase and creatinine. The respective parameters are reported in table 4.

Gastrointestinal tolerance and dietary patterns

Gastrointestinal Symptoms Rating Scale (GSRS)-Question 15 (sensation of not completely emptying the bowels) was removed from the analysis due to many missing values. Overall, the gastrointestinal tolerance was good. No statistically significant effect of erythritol or xylitol intake on abdominal pain, indigestion or constipation was found. Neither the time nor the treatment effects were significantly different for the GSRS questions regarding those symptoms. There was a significant treatment effect with regard to the experience of reflux (question 2: 'Have you been bothered by heartburn during the past week (meaning retrosternal discomfort or unpleasant burning sensation in the chest)?') and loose stools (question 12: 'Have you been bothered by loose stools during the past week?'). In the control group, participants experienced significantly more reflux compared with the erythritol group, and in the xylitol group, participants have been significantly more bothered by loose stools compared with the erythritol group. In addition, there was a significant time effect with regard to sensations of an urgent need for bowel movement (question 14: 'Have you been bothered by an urgent need to have a bowel movement during the past week?'). In all treatment groups, the sensations of urgent need for bowel movement were significantly increased after the second week compared with preintervention. The mean scores of the different gastrointestinal symptoms are displayed in table 5.

For dietary pattern, there was a significant time, and a significant treatment effect regarding the consumption of dairy products. In all treatment groups, the consumption of dairy products was significantly reduced after the fourth week compared with preintervention (p=0.027). Additionally, in the erythritol group, participants consumed significantly more dairy products compared with the xylitol group (p=0.028). Otherwise, there was only a significant time, but no treatment effect on the consumption of beverages with added sugar (preintervention vs week 2, p=0.024, and preintervention vs week 4, p=0.048), sugar-sweetened beverages (preintervention vs week 4, p=0.025) and sweets (preintervention vs week 2, p=0.001, and preintervention vs week 4, p=0.022). In all treatment groups, the consumption of beverages with added sugar, sugar-sweetened beverages and sweets was significantly reduced compared with preintervention.

DISCUSSION

In this randomised controlled trial, we examined the effect of a 5-week intake of erythritol and xylitol on vascular function, abdominal fat and glucose tolerance in humans with obesity. Additionally, we examined blood lipids, uric acid, hepatic enzymes and creatinine, assessed gastrointestinal symptoms and evaluated changes in dietary patterns.

Flint *et al*[21] found a significant decrease in central pulse pressure and a trend for reduced PWV after a 4-week erythritol intake in patients with T2DM.[21] Our study found no statistically significant effect of erythritol and xylitol intake on vascular function (PWV and retinal vessel diameters) in normoglycaemic participants with obesity. This discrepancy may be due to differences in the study populations, as participants with T2DM typically

Table 4 Uric acid, hepatic enzymes and creatinine (mean±SD) for each group before and after intervention

Parameter	Time point	Erythritol group (n=14)	Xylitol group (n=14)	Control group (n=14)	Time effect (P value)	Treatment effect (P value)
Uric acid(mmol/L)	Preintervention	350.5±84.6	391.2±108.3	342.1±70.5	0.704	0.330
	Postintervention	342.9±77.4	380.6±92.4	351.9±60.2		
ASAT(U/L)	Preintervention	22.0±9.7	25.9±14.5	23.1±10.5	0.436	0.876
	Postintervention	25.6±11.7	25.7±13.0	22.3±7.3		
ALAT(U/L)	Preintervention	38.4±19.4	33.6±22.6	31.1±23.5	0.800	0.518
	Postintervention	40.5±26.9	32.2±17.9	28.6±16.1		
Creatinine (mmol/L)	Preintervention	69.3±21.8	72.9±13.0	70.8±12.9	0.611	0.491
	Postintervention	69.3±13.0	70.1±14.5	70.7±13.8		

Linear mixed effect model with subsequent Šidak test.
ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase.

Table 5 Gastrointestinal symptoms scores (mean±SD) for each group before and after intervention

Parameter	Time point	Erythritol group (n=14)	Xylitol group (n=14)	Control group (n=14)	Time effect (P value)	Treatment effect (P value)
Q1: Abdominal pain (pain or discomfort in the upper abdomen)	Preintervention	1.2±0.4	1.4±0.9	1.1±0.4	0.108	0.390
	Week 2 of intervention	1.6±1.6	1.6±1.1	1.8±0.9		
	Week 4 of intervention	1.3±0.8	1.6±1.0	1.9±1.4		
Q2: Reflux (heart burn)	Preintervention	1.1±0.4	1.7±1.3	1.4±0.6	0.560	0.015* (C *vs* E)
	Week 2 of intervention	1.3±0.5	1.5±0.9	1.3±0.6		
	Week 4 of intervention	1.1±0.5	1.6±1.0	1.8±1.2		
Q3: Reflux (acid reflux)	Preintervention	1.1±0.4	1.4±1.1	1.4±0.8	0.872	0.531
	Week 2 of intervention	1.4±0.7	1.3±0.6	1.2±0.4		
	Week 4 of intervention	1.3±0.8	1.2±0.6	1.6±0.9		
Q4: Abdominal pain (hunger pains)	Preintervention	1.9±0.9	2.7±1.4	2.2±1.5	0.813	0.141
	Week 2 of intervention	2.1±1.4	2.7±1.4	2.6±1.5		
	Week 4 of intervention	1.8±1.1	2.6±1.3	2.2±1.0		
Q5: Abdominal pain (nausea)	Preintervention	1.0±0.0	1.4±0.8	1.3±0.7	0.261	0.480
	Week 2 of intervention	1.6±1.4	1.5±1.2	1.2±0.4		
	Week 4 of intervention	1.3±0.8	1.7±1.3	1.6±1.0		
Q6: Indigestion (rumbling in the stomach)	Preintervention	1.8±1.1	2.2±1.1	2.0±1.6	0.170	0.113
	Week 2 of intervention	1.7±0.9	2.5±1.3	2.6±1.7		
	Week 4 of intervention	1.4±0.6	2.6±1.8	1.8±1.3		
Q7: Indigestion (bloating)	Preintervention	2.5±1.8	2.4±1.5	2.1±1.4	0.807	0.442
	Week 2 of intervention	2.1±1.9	2.8±1.9	2.2±1.4		
	Week 4 of intervention	1.7±1.1	2.7±1.8	2.4±1.9		
Q8: Indigestion (burping)	Preintervention	1.6±0.8	2.1±1.3	1.9±1.2	0.436	0.079
	Week 2 of intervention	1.5±0.9	1.9±1.3	2.0±1.3		
	Week 4 of intervention	1.3±0.6	2.1±1.4	2.5±2.0		
Q9: Indigestion (passing gas/flatus)	Preintervention	2.4±1.4	2.9±1.4	2.5±1.1	0.935	0.482
	Week 2 of intervention	2.6±1.7	2.9±1.7	2.4±1.5		
	Week 4 of intervention	2.2±1.2	2.9±1.9	2.8±1.9		
Q10: Constipation (reduced emptying)	Preintervention	1.0±0.0	1.5±1.3	2.1±1.4	0.701	0.159
	Week 2 of intervention	1.6±1.3	1.8±1.5	1.6±0.9		
	Week 4 of intervention	1.1±0.5	2.0±1.9	1.5±1.2		
Q11: Diarrhoea (frequent emptying)	Preintervention	1.4±0.7	1.6±0.9	1.9±1.0	0.212	0.236
	Week 2 of intervention	1.9±1.2	2.4±1.7	1.2±0.6		
	Week 4 of intervention	1.7±0.8	2.1±1.6	2.3±1.3		
Q12: Diarrhoea (loose stools)	Preintervention	1.4±0.9	1.6±0.9	2.1±1.2	0.297	0.022* (E *vs* X)
	Week 2 of intervention	1.4±0.6	2.9±2.1	1.5±0.8		
	Week 4 of intervention	1.5±0.8	2.5±2.0	2.4±1.8		
Q13: Constipation (hard stools)	Preintervention	1.2±0.8	1.7±1.4	1.9±1.3	0.563	0.630
	Week 2 of intervention	1.9±1.4	1.4±0.9	1.9±1.3		
	Week 4 of intervention	1.4±0.6	1.9±1.2	1.4±0.8		
Q14: Diarrhoea (urgent need of bowel movement)	Preintervention	1.4±0.5	1.1±0.5	1.4±0.6	0.006** (pre vs W2)	0.262
	Week 2 of intervention	1.6±0.9	2.7±1.9	1.5±0.8		
	Week 4 of intervention	1.6±1.0	2.4±2.2	2.1±1.8		
Q15: Diarrhoea (incomplete emptying)	*Removed from the analysis due to many missing values*					

Linear mixed effect model with subsequent Šidak test.
**Significant with p<0.01; *significant with p<0.05.
C, control group; E, erythritol group; W2, week 2; X, xylitol group.

have higher PWV compared with healthy individuals.[31] Participants in our study were, considering a clinically healthy upper limit for PWV of 10 m/s,[32 33] already in the normal range before the intervention. However, even if erythritol and xylitol consumption did not improve vascular function in our trial, the fact that their ingestion showed no statistically significant effect concerning vascular function in our population argues for their use as a sugar substitutes, as hyperglycaemia associated with sugar intake is known to impact vascular function.[34] Of note, a recent cohort study by Witkowski *et al*[22] showed a possible correlation between erythritol blood levels and risk of cardiovascular events in humans. Given that erythritol is also endogenously synthesised in humans via the pentose-phosphate pathway from glucose,[23] determining the source of erythritol in this particular group remains uncertain, making it impossible to establish a causal relationship. Interestingly, studies on rodents suggest that sucrose intake can stimulate the endogenous production of erythritol.[24] Consequently, the observed high plasma erythritol levels could potentially be attributed to heightened sugar consumption.

Amo *et al*[25] found that in rats fed a high-fat diet and receiving xylitol during 8 weeks, visceral fat mass was significantly lower compared with the control group.[25] In our trial, the 5-week intake of erythritol and xylitol showed no statistically significant effect on abdominal fat mass and its distribution. Of note, participants were instructed to consume their habitual diet, and, therefore, did not profit from the possible beneficial effect of xylitol found when combined with a high-fat diet. Our results concerning blood lipids are in line with a human study looking at an intake of high doses (up to 100 g/day, during 18 days) of xylitol in healthy volunteers, which found no changes in TG levels and a trend in reduction of cholesterol levels.[27] Therefore, erythritol and xylitol seem superior compared with sucrose, which is known to increase blood lipids and promote liver fat accumulation.[35 36]

Huttunen *et al*[37] found no effect of chronic xylitol intake (30 g/day) for 2 years on fasting insulin or glucose concentrations in healthy volunteers.[37] In line, we also found no statistically significant effect of a 5-week erythritol or xylitol intake on glucose tolerance. However, in another study assessing the effect of 20 g/day erythritol during 2 weeks on glucose tolerance in patients with T2DM, Ishikawa *et al*[38] found a trend for decreased fasting blood glucose and decreased HbA1C.[38] Here again, the difference in study populations might explain the discrepancy. In conclusion, we show that erythritol and xylitol do not lead to statistically significant changes in glucose tolerance, which make them promising sugar alternatives, especially in patients at risk for T2DM.

We have previously found that acute ingestion of 35 g xylitol led to an increase in uric acid, while there was no effect after 50 g erythritol.[18 19] An increase in uric acid was also found in an acute study in healthy volunteers given 35 g xylitol during physical exercise.[39] Förster *et al*[27] reported that plasma uric acid was unchanged in healthy volunteers after 18 days of up to 100 g/day xylitol consumption. Here, we did not find any statistically significant elevation in uric acid in either group. We conclude that an increase in uric acid can be observed when xylitol is given acutely in healthy volunteers, but not after a 5-week exposure in volunteers with obesity but without T2DM.

Gastrointestinal tolerance in our trial was good except for a few diarrhoea-related symptoms at the beginning of the intervention, especially in the xylitol group. This is in line with other studies, showing that the acute consumption of xylitol might cause some gastrointestinal inconvenience,[19 39] and that subjects over time adapt to chronic intake.[40]

There were some modifications in dietary patterns during the intervention. Participants of all treatment groups reduced their consumption of dairy products, sweetened beverages and sweets compared with preintervention. However, as these changes also occurred in participants of the control group, we rather interpret them as a 'study effect' than any intervention effect.

It is necessary to acknowledge some limitations of this study. First, as this is a pilot study, we cannot exclude that the sample size has been too small to detect significant changes. Second, the duration of intake was only 5 weeks. Therefore, no conclusions can be drawn for longer periods. Third, as no placebo substance is available, which would be metabolically inert and sweet in taste, the study was not placebo-controlled. Therefore, participants in the control group were not blinded. Fourth, no biomarker of intake was assessed, therefore compliance to the study intervention could not be objectively measured. Fifth, the participants consumed 36 g/day, or 24 g/day of erythritol or xylitol, respectively. Therefore, we cannot exclude that the use of higher amounts of erythritol and xylitol would have induced an effect on the parameters studied. However, higher dosages might cause more severe gastrointestinal symptoms, leading to poorer treatment adherence, and might not represent real-life settings.

In conclusion, we showed that the 5-week intake of erythritol and xylitol in people with obesity had no statistically significant effects on vascular function, abdominal fat and blood lipids, glucose tolerance, uric acid, hepatic enzymes and creatinine and was well tolerated except loose stools in the xylitol group. These results are relevant given the current recommendation to reduce sugar consumption, as the dosages and intake time points correspond to everyday-life sugar consumption. The study adds important information to the knowledge about erythritol and xylitol, showing that they are promising sugar alternatives, especially for people with obesity and, therefore, at risk of hypertension and cardiovascular diseases, hepatic steatosis and type 2 diabetes.

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Appendix S1: Detailed description of the experimental procedure, the assessment of parameters, and the laboratory analyses

Assessment of vascular function: arterial stiffness, retinal vessel diameters

Before and after the intervention period, participants were admitted to the Department of Sport, Exercise and Health of the University of Basel to assess arterial stiffness and retinal vessel diameters. To prepare for the measurements, participants were instructed to abstain from caffeine, alcohol and heavy physical activity, and to fast at least four hours.

Arterial stiffness was measured oscillometrically using a VaSera VS-1500 vascular screening system (Fukuda Denshi Co. Ltd, Tokyo, Japan). Triple measurements were taken in a supine position after resting for at least 10 minutes and 5 minutes between the measurements in a quiet room with a controlled temperature between 22-24 °C. Standard blood pressure cuffs were placed at each upper arm and above each ankle. Electrocardiogram leads were attached at each wrist, and a phonocardiogram was placed on the sternal border in the second intercostal space. The heart-ankle pulse wave velocity (PWV) was measured based on the vessel length between the heart valve and the ankle artery divided by the time taken for the pulse wave to propagate from the aortic valve to the ankle. ARCSolver algorithm was applied to pulse wave signals acquired at the left upper arm to estimate central PWV (1). The average of the three PWV-measurements was taken for statistical analysis.

A fundus camera (Topcon TRC NW) and the analyzing software Visualis (Visualis 2.80, Imedos Systems UG) were used for retinal image acquisition. Three crisp images of each eye were taken at an angle of 45 degrees with the optic disc at the center. All arterioles and venules 0.5–1 disk diameter away from the optic disk margin were marked. Retinal arteriolar and venular diameter segments were semi-automatically marked using an analysis software (Vesselmap 2®; IMEDOS Systems GmbH, Jena, Germany). Arteriolar and venular diameters

from the three images of each eye were averaged to Central Retinal Arteriolar Diameter Equivalents (CRAE) and Central Retinal Venular Diameter Equivalents (CRVE) by use of the Parr–Hubbard formula (2). The arteriolar-to-venular diameter ratio (AVR) was calculated from the CRAE and CRVE. The values of each eye were again averaged. To guarantee optimal standardization, the same vessel segments were chosen at both time points using the pre-intervention assessment as a reference.

Assessment of abdominal fat: quantification and distribution

Before and after the intervention period, participants were admitted to the Department of Radiology and Nuclear Medicine of the University Hospital of Basel for an abdominal MRI. Data for the evaluation of percentage liver fat (%-LF), total liver volume (TLV), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) were acquired using a MAGNETOM Prisma 3T scanner (Siemens Healthineers, Erlangen, Germany). A transversal T2*-IDEAL (3D spoiled gradient echo with 6 echoes) sequence was used for the liver fat measurement, and a two-point Dixon (3D spoiled gradient echo with two echoes) sequence in coronal orientation for the SAT and VAT quantification. Both scans were performed in breath holding (up to 20 seconds each). Details on data acquisition and evaluation are described elsewhere (3). In short, the T2*-IDEAL scan covered the whole liver. Those images were segmented manually to derive %-LF and TLV. The two-point Dixon scan was used for the automatic SAT and VAT volume segmentation which was subsequently manually corrected, and spatially confined to the upper end of the femoral head and the lower end of the ninth thoracic vertebra.

Assessment of glucose tolerance, blood lipids, uric acid, hepatic enzymes, and creatinine

Before and after the intervention period, participants were admitted to the St. Clara Research

Ltd. in the morning after an overnight fast for an oral glucose tolerance test (OGTT). For this purpose, they were instructed to abstain from heavy physical activity within the two days before the test, to eat meals containing carbohydrates, and to come on an empty stomach, i.e., not eat or drink (water allowed until two hours before the test) nor consume alcohol within ten hours before the test.

An antecubital catheter was inserted into a forearm vein for blood collection. After taking a fasting blood sample (t = -15 min) for assessment of fasting glucose and insulin concentrations (ethylenediaminetetraacetic acid (EDTA) tubes), blood lipids, uric acid, hepatic enzymes, creatinine concentrations (lithium heparin tubes), participants received a standardized solution containing 75 g of glucose.

Blood samples were taken at regular time intervals after administration of the solution (t = 30, 60, 90, and 120 min) for assessment of glucose and insulin concentrations. The samples were collected on ice into tubes (EDTA, 6 µmol/L blood). After centrifugation (4 °C at 3000 rpm for 10 min), plasma samples were immediately processed into different aliquots and stored at -80 °C until analysis.

Assessment of gastrointestinal tolerance and dietary patterns

Gastrointestinal tolerance was assessed using the Gastrointestinal Symptom Rating Scale (GSRS) (4) before and during the second and fourth week of intervention. The 15 items of this scale combine into five symptom clusters: reflux, abdominal pain, indigestion, diarrhea and constipation.

To assess changes in dietary patterns, participants completed dietary records seven days before the intervention and during the second and the fourth week of the intervention. The dietary records were analyzed qualitatively by categorizing the foods into 11 different groups (vegetables, fruits, cereals/bread, other carbohydrates, meat/fish/other protein sources, dairy

products, fats/nuts/seeds, beverages with added sugar (e.g., coffee with sugar), beverages with sweeteners, sugar-sweetened beverages, and sweets) and comparing the number of servings per food group.

Laboratory analysis

Plasma glucose was measured by a glucose oxidase method (Rothen Medizinische Laboratorien AG, Basel, Switzerland; range of assay, 0.6 to 45.0 mmol/L). Plasma insulin was quantified using an electro-chemiluminescent immunoassay (Rothen Medizinische Laboratorien AG, Basel, Switzerland; range of assay, 4.0 to 1000.0 mIU/L; intra- and inter-assay variability below 4.3% and 5.3%).

The laboratory of the St. Clara Hospital in Basel assessed fasting blood lipids, uric acid, hepatic enzymes, and creatinine. Serum blood lipids (serum triglyceride, cholesterol, and high density lipoprotein (HDL)) were measured with enzymatic colorimetric tests. The intra- and inter-assay variability are below 2.1% and 2.3% (triglyceride), 2.1% and 7.4% (cholesterol), and 1.1% and 1.5% (HDL). Low density lipoprotein (LDL) was calculated with the Friedewald-Formula (5). Serum uric acid was measured with an enzymatic colorimetric test with an intra- and inter-assay variability below 1.7% and 2.0%. Hepatic enzymes alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) were measured with enzymatic colorimetric tests. The intra- and inter-assay variability are below 1.8% and 1.8% (ALAT), and 1.6% and 1.8% (ASAT). Creatinine was assessed with a kinetic colorimetric test based on the Jaffe method (6) with an intra- and inter-assay variability below 2.9% and 3.4%.

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