1   **Gut hormone secretion, gastric emptying and glycemic responses to**

2   **erythritol and xylitol in lean and obese subjects**

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21 **Running Title:** Xylitol and erythritol stimulate gut peptide release

22

23 **Abstract**

24 With the increasing prevalence of obesity and a possible association with increasing sucrose

25 consumption, non-nutritive sweeteners are gaining popularity. Given that some studies indicate that

26 artificial sweeteners might have adverse effects, and alternative solutions are sought. Xylitol and

27 erythritol have been known for a long time and their beneficial effects on caries prevention and

28 potential health benefits in diabetic patients have been demonstrated in several studies. Glucagon-like

29 peptide 1 (GLP-1) and cholecystokinin (CCK) are released from the gut in response to food intake,

30 promote satiation, reduce gastric emptying (GE) and modulate glucose homeostasis. While glucose

31 ingestion stimulates sweet taste receptors in the gut, and leads to incretin and gastrointestinal hormone

32 release, the effect of xylitol and erythritol have not been well studied.

33 Ten lean and 10 obese volunteers were given 75g glucose, 50g xylitol or 75g erythritol in 300mL

34 water or placebo (water) by a nasogastric tube. We examined plasma glucose, insulin, active GLP-1,

35 CCK, and GE with a 13C-sodium acetate breath test and assessed subjective feelings of satiation.

36 Xylitol and erythritol lead to a marked increase in CCK and GLP-1, while insulin and plasma glucose

37 are not (erythritol) or only slightly (xylitol) affected. Both xylitol and erythritol induce a significant

38 retardation in GE. Subjective feelings of appetite are not significantly different after carbohydrate

39 intake compared to placebo.

40 In conclusion, acute ingestion of erythritol and xylitol stimulates gut hormone release and slows down

41 gastric emptying, while there is no or only little effect on insulin release.

42

43 *Keywords:* Xylitol; Erythritol; Incretins; Gastric emptying; Sweetener

Introduction

Obesity has increased significantly worldwide (7). Sugar consumption - in the form of sucrose or high-

fructose corn syrup (HFCS) - has partly contributed to the dramatic rise in obesity, metabolic

syndrome and diabetes (15, 35). Research on the effects of dietary sugars on health has recently

focused on fructose, given the striking parallel increases in obesity and in fructose intake over the past

decades (5). Fructose intake in diets mostly originates from sucrose (containing 50% fructose and 50%

glucose) and soft drinks containing high-fructose corn syrup (HFCS) (39). Patients with nonalcoholic

fatty liver disease (NAFLD) consume twofold more calories of HFCS from beverages than healthy

patients (26). The increasing evidence of the detrimental role of sucrose and fructose, justifies a

reduction in intake and substitution of sugar by alternative dietary sweeteners. However, several

human- and animal-based studies reported that chemically originated sugar substitutes or artificial,

non-nutritive sweeteners (including saccharine, aspartame, neotame, sucralose and acesulfame-K),

have either short- or long-term side effects (2, 38)

Xylitol and erythritol are sweeteners naturally found in low concentrations in fruits and vegetables,

and can be extracted from fibrous material such as birch. In particular, xylitol has gained popularity as

several studies were able to show a dental caries preventive effect, which was also demonstrated for

erythritol (13). Apart from the proven anticariogenic properties, xylitol seems to be effective in

reducing the accumulation of visceral fat, and in animal models, xylitol improves glycaemia (1, 6,16,

27). Polyol metabolism requires little or no insulin once they are absorbed (20, 33). The effects in

animal studies include antidiabetic properties such as improved pancreatic islets morphology and

blood glucose lowering effects in heathy and diabetic rats (17, 27). In pilot studies of patients with

diabetes, daily intake of 36g erythritol resulted in improvement of endothelial function and reduced

central aortic stiffness (9). Taken together, these studies support the concept that polyols, especially

erythritol, might be an attractive non-nutritive sweetener for the dietary management of diabetes

mellitus. Appropriately used, these products might be helpful both in weight management and

glycemic control. In conclusion, there is emerging evidence to indicate a beneficial role for dietary

polyols in either modulating insulin release or related factors, including gut hormones and attenuating

71   factors associated with the metabolic syndrome, and other potential health benefits warrant further

72   investigation (20).

73   In 1987, Shafer et al showed gastric emptying of a solid meal was markedly prolonged if 25g

74   of xylitol had been ingested prior to meal (34). Shafer could also show that a preload of 25g of xylitol

75   significantly suppressed subsequent food intake from a buffet compared to a placebo preload or 250g

76   of aspartame, which both had no effect at all (34). Decrease in gastric emptying after ingestion of a

77   30g xylitol solution was also shown by scintigraphy in 1989 by Salminen et al (32). In this study, the

78   investigators also measured GIP, insulin and motilin and demonstrated that xylitol leads to motilin

79   secretion but no GIP release. However, temporal correlation with gastric emptying and other important

80   satiation hormones such as GLP-1 and CCK were not measured (32). No data was found describing

81   the effect of erythritol on incretins and gastric emptying.

82   The aim of this study was to examine the effects of these two naturally occurring, non-nutritive

83   sweeteners on incretin release and gastric emptying.

84   **Materials and Methods**

85   *Study approval.* The protocol was approved by the Ethics Committee of Basel, Switzerland

86   (EKNZ: 2014/072) and conducted in accordance with the principles of the Declaration of Helsinki of

87   1975 as revised in 1983. Subjects were recruited by word of mouth over a period of four months (2/

88   2014 – 5/ 2014). All patients gave written informed consent. The trial is registered in the Clinical trials

89   registry of the National Institutes of Health (NCT 02563847) and was funded by the Swiss National

90   Science Foundation (SNSF: Marie Heim-Voegtlin subsidy: PMPDP3-145486/1).

91   *Subjects.* A total of 10 lean (mean BMI: 21.7 ± 0.5 kg/m^2, range 19.9 - 24.3 kg/m^2, 5 men and

92   5 women; mean age: 24.6 ± 0.2 years, range 24 - 26 years) and 10 obese (mean BMI: 40.0 ± 1.4

93   kg/m^2, range 33.8 - 48.2 kg/m^2, 5 men and 5 women; mean age: 27.2 ± 2.8 years, range 20 - 48 years)

94   volunteers were recruited. Inclusion criteria were: general good health, age between 18-50 years BMI

95   <18 and >25 kg/m^2 in the lean group and >30 kg/m^2 in the obese group. Exclusions included smoking,

96   substance abuse, regular intake of medications, psychiatric or medical illness and any abnormalities

97   detected by physical examination or laboratory screening. None of the subjects had a history of

98   gastrointestinal disorders, food allergies or dietary restrictions. Anthropometric measurements,

99   including weight, height, BMI, as well as heart rate and blood pressure, were recorded for all

100   participants. Subjects were instructed to abstain from alcohol, caffeine, black- and green- tee, coke,

101   chocolate and strenuous exercise for 24 hours before each treatment and, furthermore, to abstain from

102   sprouts, broccoli and grapefruit for the entire study duration.

103   *Study design and experimental procedures.* The study was conducted as a randomized,

104   double-blind, placebo-controlled, crossover trial. Randomization was computer-generated (computer-

105   generated random order of treatment sessions). The day before each study day, subjects consumed a

106   restricted simple carbohydrate standard dinner before 0800 PM and fasted from 1200 AM (midnight)

107   onward. On each study day, subjects were admitted to the Phase 1 Research Unit of the University

108   Hospital Basel at 0800 AM. An antecubital catheter was inserted into a forearm vein for blood

109   collection. Subjects swallowed a polyvinyl feeding tube (external diameter 8 French). The tube was

110   placed through an anesthetized nostril; its intragastric position was confirmed by rapid injection of

111   10mL of air and auscultation of the upper abdomen. The test trials were identical in design except for

112   the test solutions containing:

113   • 50g xylitol dissolved in 300mL tap water

114   • 75g erythritol dissolved in 300mL tap water

115   • 75g glucose dissolved in 300mL tap water (positive control)

116   • 300mL tap water (negative control)

117   Concentrations were chosen based on the following considerations: 75g of glucose as in a standard

118   oral glucose tolerance test (with known effects on plasma insulin, plasma glucose and gastric

119   emptying), 50g of xylitol and 75g of erythritol as the sweetness of the xylitol and erythritol

120   concentrations correspond approximately to 75g of glucose, resulting in equisweet loads. Each test

121   solution was labeled with 50mg ^{13}C-sodium acetate for determination of gastric emptying. Glucose

122   was purchased from Haenseler AG (Switzerland), xylitol and erythritol was purchased from Mithana

123   GmbH (Switzerland) and ^{13}C-sodium acetate from ReseaChem (Switzerland). The intragastric

124   infusions were freshly prepared each morning of the study and were at room temperature when

125   administered. In order to maintain the blind, differing persons prepared and administered the

126   treatment. After taking two fasting blood samples (t = -10 and -1 min) and a fasting breath sample (t =

127   -1 min), subjects received the test solution via the feeding tube within 2 minutes (t = 0-2 min). Blood

128   samples were taken at regular time intervals (15, 30, 45, 60, 90, 120 and 180 min) on ice into tubes

129   containing EDTA (6 μmol/L), a protease inhibitor cocktail (Complete®, EDTA-free, 1 tablet/50mL

130   blood; Roche, Mannheim, Germany) and a dipeptidylpeptidase IV inhibitor (10μL/mL; Millipore

131   Corporation, St. Charles, Missouri, USA). Tubes were centrifuged at 4º C at 3000 rpm for 10 min and

132   plasma samples were stored at -70º C until analysis of plasma glucose, insulin, active GLP-1 and CCK

133   was performed. For determining gastric emptying rates, end-expiratory breath samples were taken at

134   fixed time intervals (15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 min) after instillation of

135   the test solution. The subject's vital signs (blood pressure, heart rate) were measured before and after

136   each study intervention. Appetite perceptions (feelings of: a) hunger, b) satiety, c) fullness and d)

137   prospective food consumption) were assessed by visual analogue scales (VAS) (8). Visual analogue

138 scales consisted of a horizontal, unstructured, 10-cm line representing the minimum (0.0 points) to the

139 maximum rating (10.0 points). Subjects assigned a vertical mark across the line to indicate the

140 magnitude of their subjective sensation at the present time point. The measurement was quantified by

141 the distance from the left end of the line (minimum rating) to the subject's vertical mark.

142 ***Laboratory analysis.*** *Plasma glucose* concentration was measured by a glucose oxidase

143 method (Rothen Medizinische Laboratorien AG, Basel, Switzerland). The intra- and inter-assay

144 coefficient of variation is below 2.9% and 3.9%, respectively. *Plasma insulin* was measured with a

145 commercially available electrochemiluminescence immunoassay (Cobas/Roche Diagnostics GmbH,

146 Mannheim, Germany). The intra- and inter-assay coefficient of variation for this assay is below 2.0%

147 and 2.8%, respectively. *Plasma active GLP-1* was measured with a commercially available ELISA kit

148 (Millipore Inc., St. Charles, Missouri, USA). The intra- and inter-assay variability is below 9.0% and

149 13.0%, respectively.

150 *Plasma CCK* concentrations were measured with a sensitive radioimmunoassay using a highly

151 specific antiserum (No. 92128), (29). The intra- and inter-assay variability is below 15% for both.

152 ***Assessment of gastric emptying.*** The gastric emptying rate was determined using a ^{13}C-

153 sodium acetate breath test, an accurate, non-invasive method for measuring gastric emptying, without

154 radiation exposure, and a reliable alternative to scintigraphy, the current "gold standard" (10). Test

155 solutions were labeled with 50mg of ^{13}C-sodium acetate, an isotope absorbed readily in the proximal

156 small intestine, next transported to the liver where it is metabolized to $^{13}CO_2$, which is then exhaled

157 rapidly (10). At fixed time intervals, end-expiratory breath samples were taken into a 100mL foil bag.

158 The ^{13}C-exhalation was determined by non-dispersive infrared spectroscopy using an isotope ratio

159 mass spectrophotometer (IRIS®; Wagner Analysen Technik, Bremen, Germany), and expressed as the

160 relative difference (δ ‰) from the universal reference standard (carbon from Pee Dee Belemnite

161 limestone). ^{13}C-enrichment was defined as the difference between pre-prandial ^{13}C-exhalation and

162 post-prandial ^{13}C-exhalation at defined time points, δ over basal (DOB, ‰). Delta values were

163 converted into atom percent excess and then into percent of administered dose of ^{13}C excreted per hour

164 (%dose/h (%)). In this last conversion, the CO_2 production of the subjects was used, which is assumed

165   to be 300 mmol/h multiplied by the body surface area. The body surface area was calculated by the

166   weight height formula of Haycock *et al.* (11).

167   *Statistics.* The purpose of this study is to gain basic information on the physiologic role of the

168   aforementioned doses of xylitol and erythritol on incretin release and gastric emptying. The sample

169   size of this study was chosen on the basis of practical considerations rather than statistical estimation.

170   However, according to our experience, a sample size of 8-12 subjects will most likely allow us to

171   detect large differences in parameters (>50%) between the treatments groups. Descriptive statistics

172   were used for demographic variables, such as age, weight, height and BMI. Hormone and glucose

173   profiles were analyzed by calculating the area under the concentration-time curve (AUC) from

174   baseline values. The parameters were tested for normality by the Shapiro-Wilk test method. General

175   linear model repeated measures ANOVA was applied to describe differences between lean subjects

176   and obese participants in the different treatment groups (50g xylitol, 75g erythritol and 75g glucose),

177   where obesity status (yes or no) was used as between-subject factor in this analysis. Pairwise *post-hoc*

178   within-subject comparisons were done with the Šidak multicomparison test, between-subject

179   comparisons by univariate ANOVA. All statistical analysis was done using the statistical software

180   package, SPSS for Windows, Version 23.0 (SPSS Inc., Chicago, USA). Values were reported as mean

181   ± SEM. Differences were considered to be significant when $p < 0.05$. Prevalence of diarrhea

182   associated with either polyol intake was compared by use of Fisher's exact test.

183   **Results**

184   Fifty grams of xylitol ingestion led to bloating and diarrhea in 70% of all subjects and 75g of erythritol

185   had the same side effects in 60% of all subjects ($p = 0.741$). There was no statistically significant

186   difference between obese and lean subjects (obese *vs*. lean: xylitol $p = 1.0$ and erythritol $p = 1.0$) or

187   between the two polyols (xylitol *vs*. erythritol: lean $p = 1.0$, obese: $p = 1.0$) concerning side effects.

188   Despite diarrhea (which usually stopped after 1-2 bowel movements), no study session had to be

189   terminated prematurely. There were no drop-outs and complete data from 20 subjects (10 lean and 10

190   obese) were available for analysis.

191   *Plasma cholecystokinin (CCK).* In *lean subjects*, glucose and both polyols lead to a

192   significant CCK release. There was no statistically significant difference between the two polyols and

193   glucose **(Table 1)**. In *obese subjects*, only xylitol treatment increased AUC0-180min of CCK

194   compared to placebo due to a higher variability. The pattern was, however, the same as in lean

195   subjects **(Table 1)**. If *all subjects* were taken together (lean + obese, N = 20), glucose and both polyols

196   lead to a significant CCK release (F $(3, 15) = 16.15$; $p < 0.001$), and there was no statistically

197   significant difference between the two polyols and glucose **(Figure 1, Table 1)**. *Lean vs. obese:* Basal

198   CCK concentrations were higher in obese *vs*. lean subjects (obese: 1.4 ± 0.2 *vs*. lean: 0.9 ± 0.1 mmol/L

199    $p = 0.044$), but there were no statistically significant differences in integrated CCK responses (AUC0-

200   180min; F $(1, 17) = 0.009$, $p = 0.925$).

201   *Plasma glucagon like peptide-1 (GLP-1).* In *lean subjects*, glucose ingestion as well as polyol

202   intake stimulated GLP-1 release. This increase was, however, numerically smaller with polyols, only

203   borderline significant for polyols compared to placebo treatment (xylitol: $p = 0.081$, erythritol: $p =$

204   0.08) and only significantly different for glucose administration compared to placebo (AUC0-180min;

205    $p = 0.004$). Comparing glucose to xylitol administration, GLP-1 release was significantly lower after

206   xylitol (AUC0-180min; $p = 0.027$), **(Table 1).** In *obese subjects*, glucose ingestion as well as polyol

207   intake stimulated GLP-1 release. Only glucose compared to placebo treatment was statistically

208   significant (AUC0-180min; $p = 0.002$), **(Table 1).** If *all subjects* were taken together, glucose and both

209   polyols lead to a significant GLP-1 release (F $(3, 15) = 15.95$; $p < 0.001$) and no statistically

210 significant difference between the two polyols was found ($p = 0.276$), **(Figure 1, Table 1)**. *Lean vs.*

211 *obese:* Basal GLP-1 concentrations were similar in both groups. The integrated GLP-1 response to

212 glucose administration (AUC0-180min) was significantly higher in lean subjects (AUC0-180min in

213 lean: 862.3 ± 104.6 pMol*min/L and in obese: 437.1 ± 62.6 pMol*min/L; $F_{(1, 17)} = 12.775$; $p =$

214 0.002, respectively), while there were no differences after polyol intake.

215   ***Plasma glucose.*** In *lean subjects* glucose administration increased glucose AUC0-180min

216 significantly ($p = 0.045$), xylitol and erythritol compared to placebo showed no statistically significant

217 effect **(Table 2)**. In *obese subjects,* glucose ingestion led to a statistically significant increase in

218 plasma glucose AUC0-180min ($p = 0.008$). Plasma glucose response (AUC0-180min) was slightly but

219 significantly increased after administrations of xylitol ($p = 0.002$) but also erythritol ($p = 0.001$)

220 compared to placebo. We hypothesize that this is due to a decrease in plasma glucose over time after

221 placebo rather than a small increase of plasma glucose after erythritol ingestion **(Table 2)**. If *all*

222 *subjects* were taken together, glucose, xylitol and erythritol lead to a statistically significant changes in

223 plasma glucose ($F_{(1.1, 19.73)} = 27.97$; $p < 0.001$) and obesity status (yes/no) significantly modified

224 these responses ($F_{(1, 18)} = 6.79$; $p = 0.018$), **(Figure 1, Table 2)**. However, compared to placebo, the

225 increases in plasma glucose after xylitol and erythritol ingestion were minimal although statistically

226 significant ($p = 0.004$ and $p = 0.01$, respectively). There was no statistically significant difference

227 between the two polyols. *Lean vs. obese*: Fasting glucose concentrations where higher in obese

228 compared to lean subjects (5.2 ± 0.0 *vs.* 4.7 ± 0.1 mmol/L, $F_{(1,79)} = 28.5$; $p < 0.001$, respectively);

229 glucose excursions showed a higher Cmax for all carbohydrate treatments in the obese group

230 compared to lean group (6.6 ± 0.3 *vs.* 5.6 ± 0.2 mmol/L; $F_{(1,79)} = 20.2$; $p = 0.009$, Cmax xylitol lean

231 *vs.* obese: $F_{(1,19)} = 10.2$; $p = 0.005$, Cmax erythritol lean *vs.* obese: $F_{(1,19)} = 7.97$; $p = 0.011$).

232 AUC0-180min was significantly higher in the obese compared to lean subjects after glucose treatment

233 only ($F_{(1, 19)} = 6.19$; $p = 0.023$).

234   ***Plasma insulin***. In *lean subjects*, glucose ingestion led to an increase in insulin ($p < 0.001$).

235 Xylitol had a minimal but statistically significant ($p < 0.001$) enhancing effect on insulin AUC0-

236 180min. In contrast to xylitol, erythritol treatment did not stimulate insulin release. However,

237 comparing the integrated insulin response (AUC0-180min) after erythritol treatment to placebo, there

238 was a statistically significant difference ($p = 0.037$), as insulin decreased over time after the placebo

239 treatment, while insulin concentration remained stable after erythritol treatment **(Table 2)**. In *obese*

240 *subjects*, glucose ingestion led to an increase in insulin ($p = 0.005$), whereas xylitol had a minimal but

241 statistically significant effect ($p = 0.047$). In contrast to xylitol, erythritol treatment did not stimulate

242 insulin release ($p = 0.98$), **(Table 2)**. If *all subjects* were taken together, treatments lead to significant

243 changes in insulin release ($F (1.1, 19.9) = 33.4$; $p < 0.001$) which were significantly different between

244 lean and obese subjects ($F (1, 18) = 12.0$, $p = 0.003$), **(Figure 1, Table 2)**. In particular, glucose and

245 xylitol significantly increased insulin release ($p < 0.001$ and $p = 0.001$, respectively), whereas

246 erythritol had no effect on insulin release ($p = 0.57$). *Lean vs. obese*: Basal insulin concentrations were

247 higher in obese compared to lean subjects (21.9 ± 2.1 µU/mL *vs.* 6.8 ± 0.4 µU/mL, $F (1, 79)$ 50.72; $p <$

248 0.001, respectively) and insulin excursions showed a higher Cmax (78.8 ± 15.2 µU/mL *vs.* 22.8 ± 3.4

249 µU/mL, $F (1, 79)$ 12.89, $p = 0.001$) after all treatments in obese subjects. The integrated insulin

250 response (AUC0-180min) was significantly higher in the obese persons after the glucose treatment

251 (AUC0-180min lean *vs.* obese ($F (1, 19) = 11.78$; $p = 0.003$).

252   ***Gastric emptying.*** *Lean subjects:* Glucose (given as positive control) compared to placebo

253 (negative control) slowed gastric emptying (AUC 0-60min $p < 0.001$), and both polyols had a

254 decelerating effect as well (AUC 0-60min xylitol $p = 0.001$, erythritol $p = 0.008$). No statistically

255 significant difference was seen between the two polyols ($p = 0.683$). The effect of both polyols was

256 slightly smaller compared to glucose and there was a statistically significant difference in AUC0-

257 60min between erythritol and glucose ($p = 0.036$), but not between xylitol and glucose ($p = 0.361$),

258 **(Figure 2, Table 3).** *Obese subjects:* Glucose and both polyols compared to placebo slowed gastric

259 emptying within the first hour (AUC 0-60min glucose $p < 0.001$, xylitol $p = 0.004$, and erythritol $p =$

260 0.001). No statistically significant difference was seen between the two polyols and between glucose

261 vs. each polyol **(Figure 2, Table 3)**. If *all subjects* were taken together, glucose and both polyols

262 slowed gastric emptying during the first 60 min ($F (3, 54) = 46.1$; $p < 0.001$) with no significant effect

263 between lean and obese subjects **(Figure 2, Table 3)**. There was no statistically significant difference

264   between glucose and both polyols. ***Appetite scores:*** Baseline assessments were not equivalent across

265   all study sessions. Therefore, we used relative values (post-treatment values minus pre-treatment

266   value) representing changes in appetite perception. Over time, feelings of satiety and fullness

267   decreased, while feelings of hunger and prospective food consumption increased. There were no

268   statistically significant differences between the four treatments and between lean and obese subjects

269   **(Figure 3)**.

270 **Discussion**

271   The objectives of this trial were to investigate whether a) polyols can stimulate GLP-1 and

272 CCK release, b) gastric emptying is affected and c) whether polyols show these effects not only in

273 lean, but also in obese patients with impaired glucose tolerance, the "target group" for sugar

274 substitutes.

275   Polyols such as xylitol and erythritol are natural sugar substitutes and have a long history of

276 use in a wide variety of foods. Xylitol and erythritol are not completely absorbed as most of ingested

277 xylitol passes through the small intestine and is fermented by bacteria in the large intestine, whereas

278 erythritol is mostly absorbed (>90%) but then excreted by the kidneys (3, 4, 12). As a consequence,

279 erythritol is better tolerated than xylitol, provoking less gastrointestinal side effects such as diarrhea

280 and bloating. However, when erythritol is consumed as a single oral bolus exceeding 35g, undesirable

281 effects, including nausea and borborygmi are common (18, 19, 25, 37). Repetitive exposure appears to

282 lead to increased tolerance through adaptive processes (23). In our trial, subjects who had not been

283 exposed to polyols before received high loads of glucose, xylitol and erythritol to achieve equisweet

284 conditions. After polyol treatments, the majority of participants had diarrhea irrespective of which

285 polyol was used.

286   Taste signaling mechanisms identified in the oral cavity are also present in the gut and play a

287 role in both locations for sugar detection; activation of sweet taste receptors trigger regulatory circuits,

288 which in turn are important in the control of eating behavior and the regulation of energy homeostasis.

289 In the gut, nutrient detection is mainly controlled by enteroendocrine cells: upon sensing nutrients, a

290 cascade of physiological phenomena is activated, including secretion of insulin, CCK

291 (cholecystokinin), GLP-1 (glucagon like peptide-1) as well as inhibition of gastric emptying and

292 reduction in food intake (28, 30). Co-localization of GLP-1, GIP (glucose-dependent insulinotropic

293 peptide), PYY (peptide tyrosine tyrosine) and CCK with taste-signaling elements such as the sweet

294 taste receptor T1R2-T1R3, is found in human intestinal endocrine L-cells explaining part of this

295 phenomenon (14, 31). As both caloric sweeteners (e.g. glucose, fructose and sucrose) and non-

296 nutritive, artificial sweeteners (e.g. aspartame, acesulfame-K, sucralose) bind to oral sweet-taste

297   receptors, binding to sweet-taste receptors on enteroendocrine cells are likely to cause signal

298   transduction and downstream actions such as gut peptide release. However, the effect of non-nutritive

299   sweeteners on incretin release seems to be more complicated. Non-nutritive sweeteners seem to be

300   able to stimulate GLP-1 release *in vitro* (22), but in humans non-nutritive sweetener administration

301   alone had no effect on plasma incretin concentrations (21, 36). In this study, both xylitol and erythritol

302   stimulated GLP-1 release, suggesting an activation of the sweet receptor in the gut, although *in vitro*

303   support of this finding is currently lacking.

304   We and others have reported that obese subjects show an attenuated incretin response to meal

305   ingestion compared to lean persons (24, 40). In the present study, GLP-1 and CCK release could be

306   demonstrated after glucose, xylitol and erythritol treatment both in lean and obese subjects. Whereas

307   the two polyols had similar effects on CCK release in lean and obese persons, the effect on GLP-1

308   secretion seemed to be reduced in obese persons. This was apparent for glucose and polyol

309   administration; however, only after glucose administration a statistically significant difference in

310   integrated GLP-1 response could be seen. The data are in line with previous studies documenting

311   reduced nutrient stimulated GLP-1 response in obese subjects (24, 40).

312   When glucose was ingested, the GLP-1 response in the presence of increased plasma glucose

313   resulted in the expected plasma insulin response. As expected with both erythritol and xylitol when a

314   GLP-1 response is triggered, but a significant rise in plasma glucose is not simultaneously present,

315   very little insulin response will follow. The obese subjects in our trial all showed impaired glycemic

316   control as demonstrated by elevated fasting glucose and insulin concentrations and higher glucose and

317   insulin excursions after all carbohydrates. The effect of the two polyols on plasma glucose

318   concentration and insulin release – although still higher in obese compared to lean subjects - was much

319   smaller than after glucose ingestion, and this patient group might particularly profit from polyols as

320   sugar substitutes.

321   Gastric emptying is regulated by numerous feedback mechanisms, including gut peptide

322   release such as CCK and GLP-1. Prolonged gastric emptying leads to a feeling of fullness and

323   satiation, which results in meal termination. As we demonstrated in this trial, erythritol and xylitol

324 both lead to a prolonged gastric emptying. We also found a marked increase of both GLP-1 and CCK

325 after both polyol treatments. We infer from these observations that the significant retardation in gastric

326 emptying is mediated by those incretins, particularly CCK. Subjective feelings of appetite were not

327 significantly different after glucose, xylitol or erythritol intake compared to placebo.

328   Limitations: In this trial, we studied acute effects of rather high doses of erythritol and xylitol

329 in subjects who were not used to these substances. In future studies, effects of lower doses, which

330 could be used in everyday life, should be examined as well (e.g. 10g and 25g). Furthermore, effects of

331 long-term exposure on gastric emptying and stimulation of gut hormone release needs to be

332 investigated as adaptive processes cannot be ruled out.

333

334 **Conclusion**

335 We conclude that acute ingestion of the natural sweeteners erythritol and xylitol lead to stimulation of

336 gut hormone release (CCK and GLP-1) and have a decelerating effect on gastric emptying, while there

337 is no (erythritol) or only little (xylitol) effect on insulin release.

338

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477
478

479   **Legend to the figures**

480

481   **Figure 1: Plasma concentrations of cholecystokinin, active glucagon like peptide-1, glucose, and**

482   **insulin**

483   **A:** CCK (cholecystokinin), **B:** Active GLP-1 (glucagon like peptide-1), **C:** Glucose, and **D:** Insulin

484   after ingestion of 75g glucose, 50g xylitol, 75g erythritol or placebo (tap water). Data are expressed as

485   mean ± SEM. Lean and obese subjects ("all"), N = 20.

486   **Figure 2: Gastric emptying rates**

487   **A:** Lean subjects, N = 10; **B:** Obese subjects, N= 10; **C:** Lean and obese subjects ("all"), N = 20, after

488   ingestion of 75g glucose, 50g xylitol, 75g erythritol or placebo (tap water). Data are expressed as

489   mean ± SEM.

490   **Figure 3**: **Subjective Appetite Perceptions**.

491   Lean and obese subjects ("all"), N = 20, after ingestion of 75g glucose, 50g xylitol, 75g erythritol or

492   placebo (tap water).Over time, feelings of **A:** satiety, and **B:** fullness decreased, while feelings of **C**:

493   hunger, and **D:** prospective food consumption increased. There were no statistically significant

494   differences between the four treatments.

495   **Table 1: Pharmacokinetic parameters of CCK (cholecystokinin) and aGLP-1 (active glucagon**
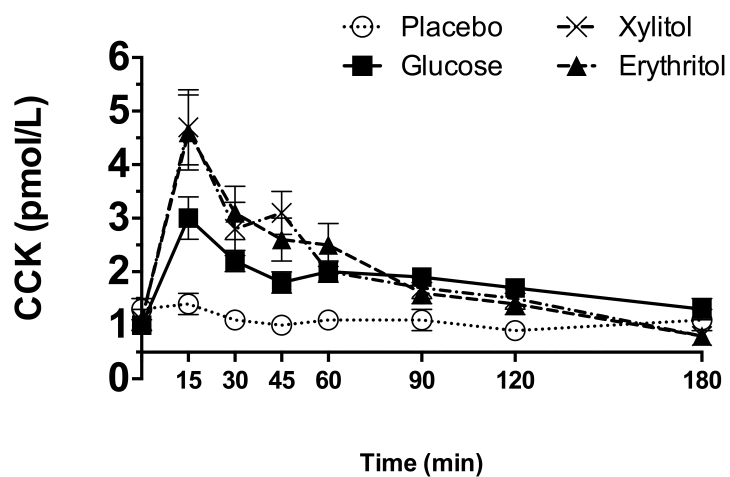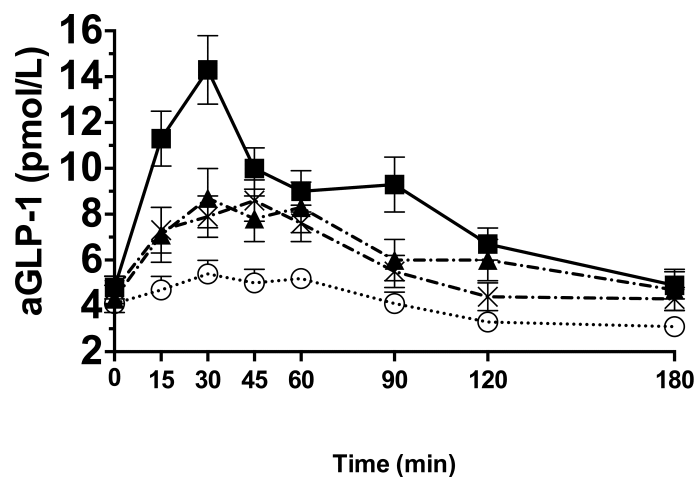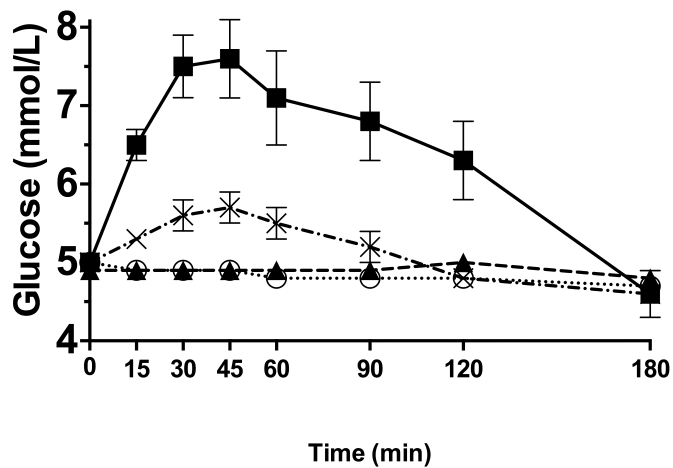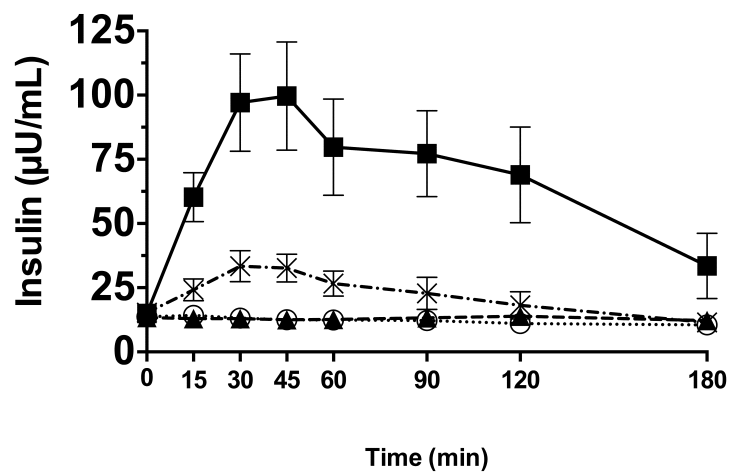
496   **like peptide-1)**

497   **A, B, C, D**: significantly different from treatment A (placebo), B (glucose), C (xylitol), D (erythritol),

498   respectively. **O**: significantly different between lean and obese subjects.

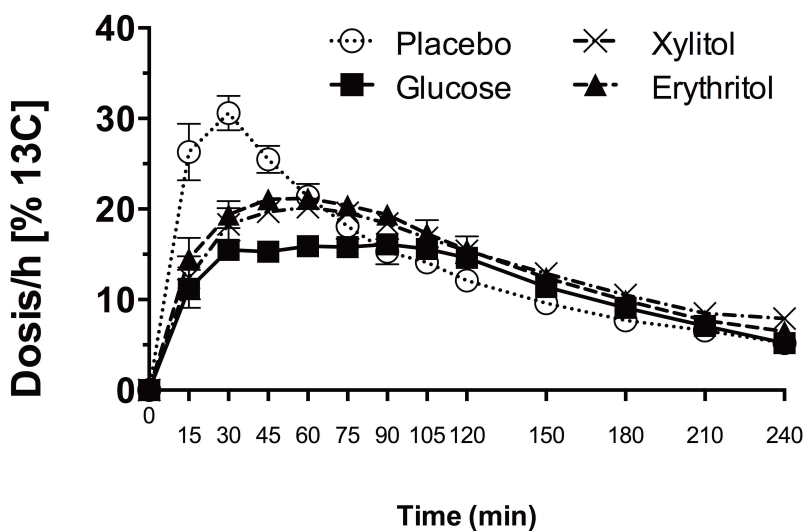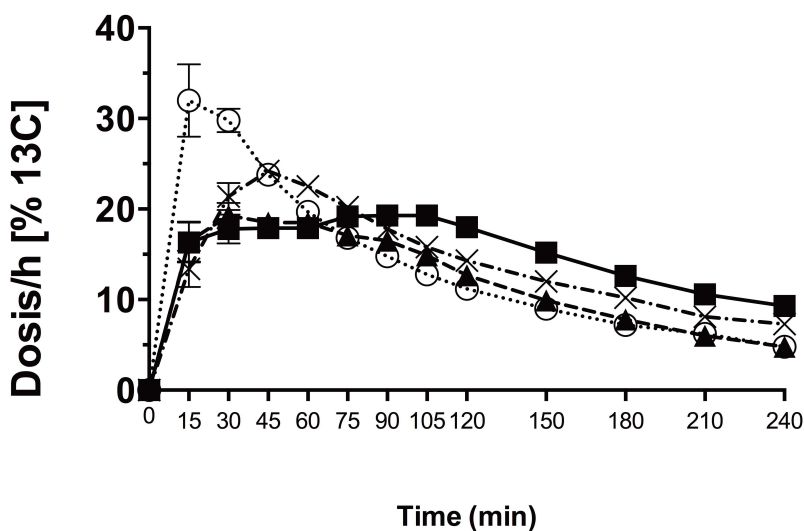499   **Table 2: Pharmacokinetic parameters of plasma glucose and insulin**

500   **A, B, C, D**: significantly different from treatment A (placebo), B (glucose), C (xylitol), D (erythritol),

501   respectively. **O**: significantly different between lean and obese subjects.

502   **Table 3: Pharmacokinetic parameters of gastric emptying**

503   **A, B, C, D**: significantly different from treatment A (placebo), B (glucose), C (xylitol), D (erythritol),

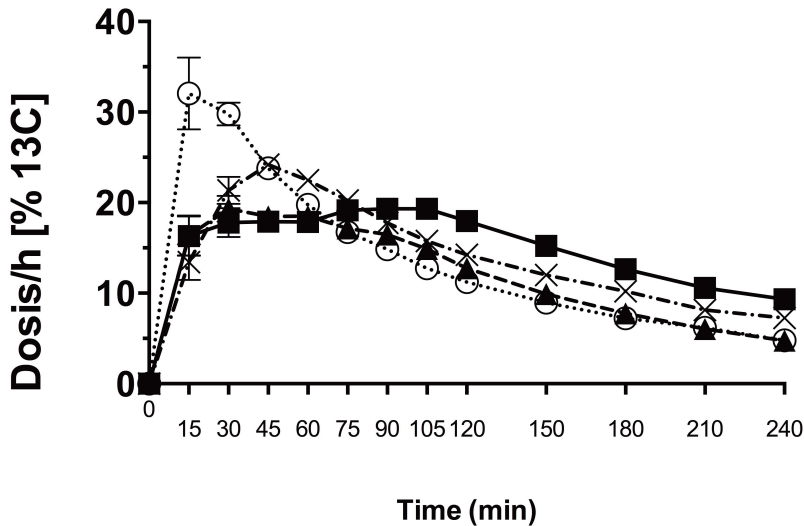504   respectively. **O**: significantly different between lean and obese subjects.

A

CCK (pmol/L)

Placebo, Xylitol, Glucose, Erythritol

Time (min)

B

aGLP-1 (pmol/L)

Time (min)

C

Glucose (mmol/L)

Time (min)

D

Insulin (µU/mL)

Time (min)

A LEAN

B OBESE

C ALL

ALL

Legend: ■ Glucose ○ Placebo ✕ Xylitol ▲ Erythritol
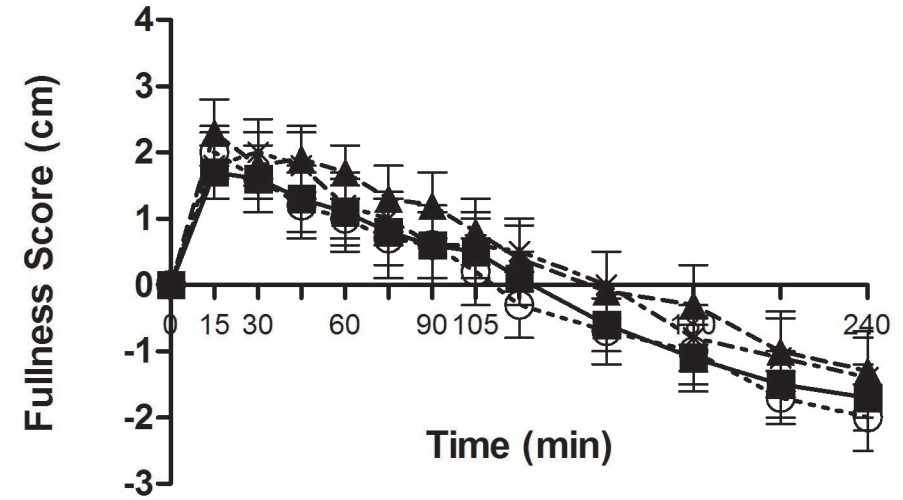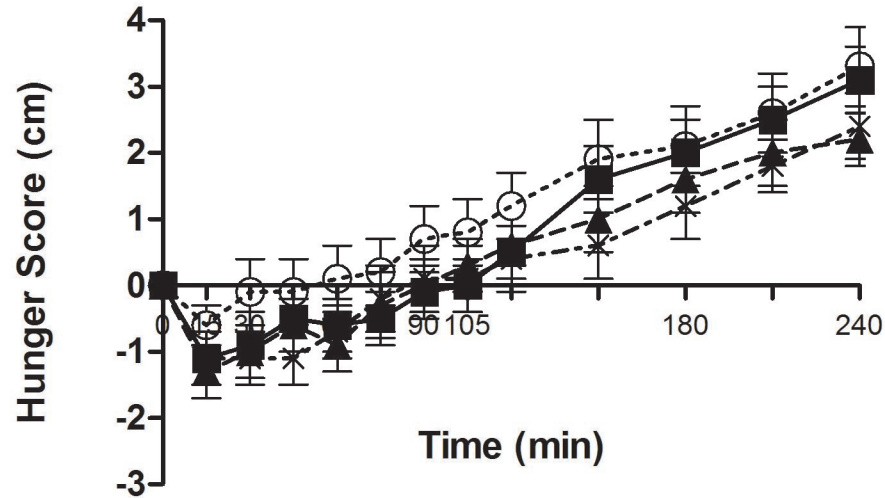
A Satiety
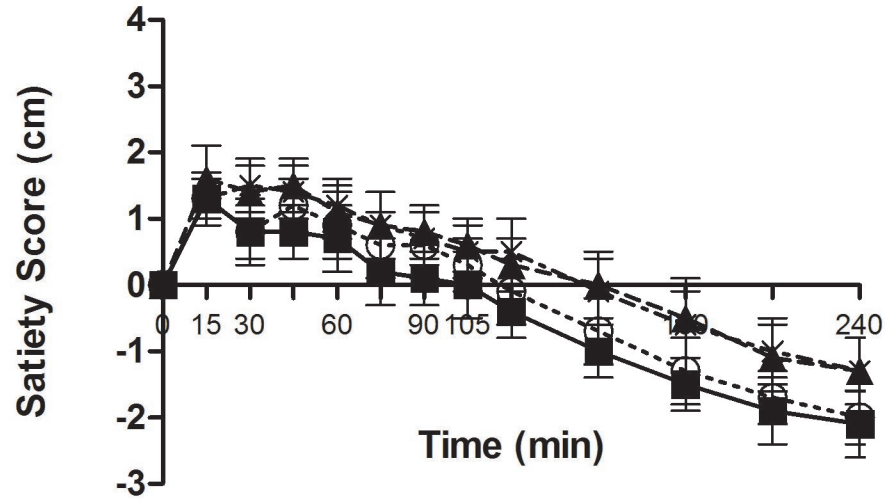
B Fullness

C Hunger
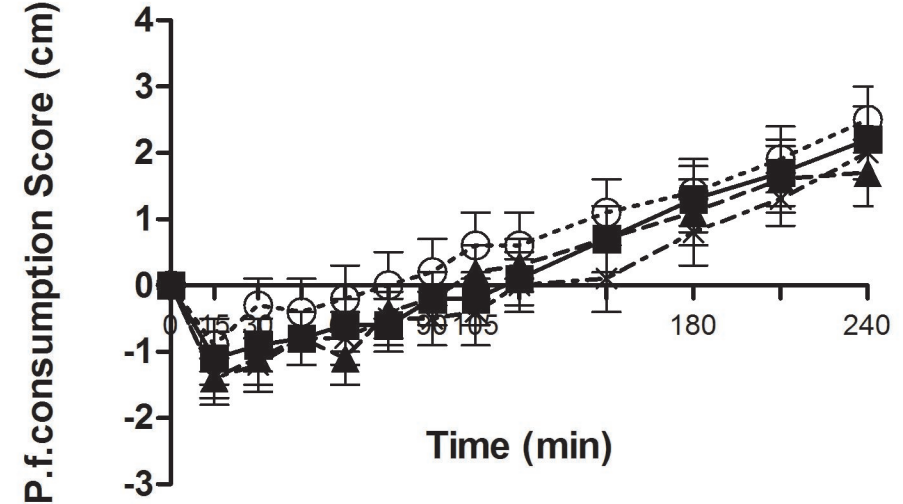
D Prospective Food Consumption

Table 1:

Pharmacokinetic parameters of CCK (cholecystokinin) and aGLP-1 (active glucagon like peptide-1)

CCK		A: Placebo	B: Glucose	C: Xylitol	D: Erythritol
Lean	Baseline (pmol/L)	1.1 ± 0.2	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.2
	Cmax (pmol/L)	1.4 ± 0.2	2.5 ± 0.3	4.6 ± 0.9	4.2 ± 0.5
		C: *p* = 0.035, D: *p* < 0.001	**D: *p* = 0.03**		
	Tmax (min)	51.7 ± 18.0	53.3 ± 15.0	21.7 ± 3.6	28.3 ± 4.6
	AUC (0-180min)	-41 ± 25	139 ± 20	159 ± 46	166 ± 42
	(pmol×min/L)	**B: *p* < 0.001, C: *p* = 0.007**			
		D: *p* = 0.004			
Obese	Baseline (pmol/L)	1.4 ± 0.3	1.3 ± 0.2	1.4 ± 0.2	1.4 ± 0.2
	Cmax (pmol/L)	2.1 ± 0.3	4.0 ± 0.5	5.6 ± 0.9	5.7 ± 1.1
		B: *p* = 0.049, C: *p* = 0.006			
	Tmax (min)	58.5 ± 22.1	37.5 ± 16.5	24.0 ± 4.0	22.5 ± 3.4
	AUC (0-180min)	-30 ± 41	138 ± 30	155 ± 37	147 ± 42
	(pmol×min/L)	**C: *p* = 0.021,** (D: *p* = 0.05)			
All	Baseline (pmol/L)	1.3 ± 0.2	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.2
				O: *p* = 0.023	
	Cmax (pmol/L)	1.8 ± 0.2	3.3 ± 0.4	5.1 ± 0.6	5.0 ± 0.6
		B: *p* = 0.002, C: *p* < 0.001	**C: *p* = 0.014**		
		D: *p* < 0.001	**O: *p* = 0.031**		
	Tmax (min)	55.3 ± 14.1	45.0 ± 11.1	22.9 ± 2.7	25.3 ± 2.8
	AUC (0-180min)	-35 ± 24	139 ± 18	157 ± 28	156 ± 29
	(pmol×min/L)	**B: *p* < 0.001, C: *p* < 0.001**			
		D: *p* < 0.001			

aGLP-1		A: Placebo	B: Glucose	C: Xylitol	D: Erythritol
Lean	Baseline (pmol/L)	4.4 ± 0.6	4.4 ± 0.8	5.0 ± 1.0	5.2 ± 1.0
	Cmax (pmol/L)	7.1 ± 1.0	17.0 ± 1.9	11.7 ± 1.5	14.5 ± 1.4
		B: *p* = 0.027, C: *p* = 0.037			
		D: *p* = 0.003			
	Tmax (min)	30.0 ± 7.1	46.7 ± 8.5	48.3 ± 6.0	46.7 ± 107
	AUC (0-180min)	-65.7 ± 92.5	862.3 ± 104.6	254.4 ± 104.3	530.5 ± 123.2
	(pmol×min/L)	**B: *p* = 0.004**	**C: *p* = 0.027**		
Obese	Baseline (pmol/L)	3.9 ± 0.4	5.2 ± 0.6	4.4 ± 0.8	3.4 ± 0.5
	Cmax (pmol/L)	6.6 ± 0.7	16.5 ± 1.7	10.2 ± 1.3	8.9 ± 1.3
		B: *p* = 0.002			
	Tmax (min)	27.0 ± 8.0	21.0 ± 2.4	34.5 ± 5.0	42.0 ± 7.0
	AUC (0-180min)	87.6 ± 68.2	437 ± 62.6	201.6 ± 58.7	288.1 ± 99.8
	(pmol×min/L)	**B: *p* = 0.002**			
All	Baseline (pmol/L)	4.1 ± 0.4	4.8 ± 0.5	4.7 ± 0.6	4.3 ± 0.6
	Cmax (pmol/L)	6.9 ± 0.6	16.7 ± 1.3	10.9 ± 1.0	11.5 ± 1.1
		B: *p* < 0.001, C: *p* = 0.001	**C: *p* = 0.03**		
		D: *p* < 0.001			
	Tmax (min)	28.4 ± 5.2	33.2 ± 5.1	41.1 ± 4.1	44.2 ± 6.1
	AUC (0-180min)	14.9 ± 57.9	638.5 ± 76.4	226.6 ± 56.8	402.9 ± 81.4
	(pmol×min/L)	**B: *p* = 0.001**	**C: *p* = 0.001**		
		C: *p* = 0.037			
		D: *p* = 0.013			

Table 2:
Pharmacokinetic parameters of glucose and insulin

Plasma glucose		A: Placebo	B: Glucose	C: Xylitol	D: Erythritol
Lean	Baseline (mmol/L)	4.8 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.8 ± 0.1
	Cmax (mmol/L)	4.9 ± 0.1	7.1 ± 0.2	5.4 ± 0.1	4.9 ± 0.1
		B: $p = 0.003$	**C: $p = 0.013$, D: $p = 0.002$**	**D: $p = 0.035$**	
	Tmax (min)	30.0 ± 13.6	69.0 ± 16.6	42.0 ± 6.6	49.5 ± 17.5
	AUC (0-180min)	-19 ± 15	135 ± 45	0 ± 15	-14 ± 7
	(mmol×min/L)	**B: $p = 0.045$**	**C: $p = 0.018$**		
Obese	Baseline (mmol/L)	5.1 ± 0.1	5.2 ± 0.1	5.3 ± 0.2	5.1 ± 0.1
	Cmax (mmol/L)	5.2 ± 0.1	9.4 ± 0.7	6.4 ± 0.3	5.3 ± 0.1
		B: $p = 0.001$, C: $p = 0.005$	**C: $p = 0.001$, D: $p = 0.001$**	**D: $p = 0.004$**	
	Tmax (min)	10.5 ± 3.9	46.5 ± 8.5	39.0 ± 3.3	58.5 ± 13.5
		B: $p = 0.026$, C: $p = 0.007$ **D: $p = 0.019$**			
	AUC (0-180min)	-44 ± 10	375 ± 86	44 + 15	2 ± 10
	(mmol×min/L)	**B: $p = 0.008$, C: $p = 0.002$** **D: $p = 0.001$**			
All	Baseline (mmol/L)	5.0 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	4.9 ± 0.1
		O: $p = 0.034$	**O: $p = 0.013$**	**O: $p = 0.006$**	**O: $p = 0.043$**
	Cmax (mmol/L)	5.0 ± 0.1	8.2 ± 0.5	5.9 ± 0.2	5.1 ± 0.1
		B: $p < 0.001$, C: $p < 0.001$	**C: $p < 0.001$, D: $p < 0.001$** **O: $p = 0.01$**	**D: $p < 0.001$** **O: $p = 0.005$**	**O: $p = 0.011$**
	Tmax (min)	20.3 ± 5.1	57.8 ± 9.1	40.5 ± 3.7	54.0 ± 10.5
		B: $p = 0.007$, D: $p = 0.004$			
	AUC (0-180min)	-32 ± 9	255 ± 56	22 ± 12	-6 ± 6
	(mmol×min/L)	**B: $p < 0.001$, C: $p = 0.004$** **D: $p = 0.01$** **O: $p = 0.023$**	**C: $p < 0.001$, D: $p < 0.001$**		

Insulin		A: Placebo	B: Glucose	C: Xylitol	D: Erythritol
Lean	Baseline (µU/mL)	7.3 ± 0.9	6.4 ± 1.0	6.5 ± 0.8	6.8 ± 0.6
	Cmax (µU/mL)	7.6 ± 0.8	54.2 ± 6.1	20.4 ± 3.0	9.0 ± 0.6
		B: $p < 0.001$, C: $p = 0.013$	**C: $p < 0.001$, D: $p < 0.001$**	**D: $p = 0.01$**	
	Tmax (min)	24.0 ± 19.8	49.5 ± 8.1	36.0 ± 5.6	73.5 ± 17.7
	AUC (0-180min)	-369 ± 93	3963 ± 428	558 ± 123	-93 ± 63
	(µU×min/mL)	**B: $p < 0.001$, C: $p < 0.001$** **D: $p = 0.037$**	**C: $p < 0.001$, D: $p < 0.001$**	**D: $p < 0.001$**	
Obese	Baseline (µU/mL)	20.0 ± 3.2	23.5 ± 6.0	24.1 ± 3.6	19.9 ± 3.8
	Cmax (µU/mL)	25.4 ± 5.6	204.1 ± 37.5	61.3 ± 11.2	24.3 ± 4.0
		B: $p = 0.005$, C: $p = 0.005$	**C: $p = 0.023$, D: $p = 0.013$**	**D: $p = 0.013$**	
	Tmax (min)	27.0 ± 9.9	66.0 ± 17.5	43.5 ± 8.2	67.5 ± 14.0
	AUC (0-180min)	-253 ± 253	15021 ± 3193	1751 ± 727	-10 ± 163
	(µU×min/mL)	**B: $p = 0.005$, C: $p = 0.047$**	**C: $p = 0.013$, D: $p = 0.006$**		
All	Baseline (µU/mL)	13.7 ± 2.2	15.0 ± 3.6	15.3 ± 2.7	13.4 ± 2.4
	Cmax (µU/mL)	16.5 ± 3.4	129.2 ± 25.8	40.8 ± 7.4	16.6 ± 2.7
		B: $p < 0.001$, C: $p < 0.001$ **O: $p = 0.005$**	**C: $p = 0.001$, D: $p < 0.001$** **O: $p = 0.001$**	**D: $p < 0.001$** **O: $p = 0.002$**	**O: $p = 0.001$**
	Tmax (min)	25.5 ± 7.2	57.6 ± 9.6	39.8 ± 5.0	16.6 ± 2.7
		B: $p = 0.046$, D: $p = 0.031$			
	AUC (0-180min)	-311 ± 135	9492 ± 2053	1154 ± 394	-52 ± 88
	(µU×min/mL)	**B: $p < 0.001$, C: $p = 0.001$**	**C: $p < 0.001$, D: $p < 0.001$** **O: $p = 0.003$**		

Table 3:
Pharmacokinetic parameters of gastric emptying

Gastric Empyting		A: Placebo	B: Glucose	C: Xylitol	D: Erythritol
Lean	Baseline (%^{13}C)	NA	NA	NA	NA
	Cmax (%^{13}C)	32.8 ± 2.0	18.4 ±1.1	22.7 ± 0.9	24.5 ± 0.9
		B: p = 0.001, C: p = 0.003	**D: p = 0.011**		
		D: p = 0.029			
	Tmax (min)	28.5 ± 4.2	63.0 ± 12.8	51.0 ± 9.5	58.5 ± 8.5
	AUC (0-60min)	1398 ± 82	750 ±52	907 ± 66	948 ± 63
	(%^{13}C×min)	**B: p < 0001, C: p = 0.001**	**D: p = 0.036**		
		D: p = 0.008			
Obese	Baseline (%^{13}C)	NA	NA	NA	NA
	Cmax (%^{13}C)	35.6 ± 2.4	22.5 ± 1.2	24.8 ± 1.1	22.8 ± 1.3
		B: p = 0.001, C: p = 0.003			
		D: p = 0.002			
	Tmax (min)	19.5 ± 2.3	66.0 ± 13.1	46.6 ± 2.7	46.5 ± 8.8
	AUC (0-60min)	1433 ± 83	914 ± 57	1054 ± 67	952 ± 54
	(%^{13}C×min)	**B: p < 0.001, C: p = 0.004**			
		D: p = 0.001			
All	Baseline (%^{13}C)	NA	NA	NA	NA
	Cmax (%^{13}C)	34.2 ± 1.6	20.4 ± 0.9	23.7 ± 0.8	23.7 ± 0.8
		B: p < 0.001, C: p < 0.001	**C: p = 0.042, D: p = 0.037**		
		D: p < 0.001	**O: p = 0.022**		
	Tmax (min)	24.0 ± 2.6	64.5 ± 8.8	48.8 ± 4.8	52.5 ± 6.2
	AUC (0-60min)	1415 ± 58	832 ± 41	980 ± 50	968 ± 42
	(%^{13}C×min)	**B: p < 0.001, C: p < 0.001**	**O: p = 0.047**		
		D: p < 0.001			