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The effect of replacing sucrose with L-arabinose in drinks and cereal foods on blood glucose and plasma insulin responses in healthy adults

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ABSTRACT

Glycaemic control is important in metabolic diseases such as diabetes and impaired glucose tolerance. L-arabinose inhibits the hydrolysis of sucrose into glucose and fructose. So far little is known about its functionality in different food matrices. We assessed the effect of replacing sucrose with L-arabinose in drinks and in cereal foods on blood glucose and insulin in healthy adults. Glucose and insulin responses were reduced when sucrose was replaced by L-arabinose in drinks. Replacement of sucrose in cereal foods did not affect glucose responses, however it reduced the insulin peak. L-arabinose without sucrose in a drink did not affect glucose responses. Therefore, replacing sucrose with L-arabinose is potentially a good strategy to lower glycaemic and insulin responses. However, the effects depend on the food matrix and the nutritional composition of the food. More research is warranted on the functionality of L-arabinose in different food matrices and in other populations.

1. Introduction

Glycaemic control is of high importance in metabolic diseases, such as diabetes and impaired glucose tolerance. Circulating blood glucose levels are controlled by insulin and glucagon. After food consumption, blood glucose levels increase, and insulin is produced by the pancreas to store the surplus of glucose in the form of glycogen and fat. It has been shown that the intake of foods that dampen glucose responses, such as high fibre foods, is associated with a lower prevalence of type 2 diabetes, coronary heart disease and health risk markers for diabetes and heart disease (Livesey, Taylor, Hulshof, & Howlett, 2008). Moreover, there are indications that foods low in glycaemic response might affect appetite feelings (Bornet, Jardy-Gennetier, Jacquet, & Stowell, 2007), although this effect depends on many factors and has yet to be proven to be causal (Alfenas & Mattes, 2005).

Foods differ in their effects on blood glucose responses. The glycaemic load of a food is amongst others affected by the nature and type of the available carbohydrates, such as mono-, di or polysaccharide, but also by other factors such as the other nutrients present, the food form, and the presence of unavailable carbohydrates, that is fibre (Brouns et al., 2005). The glycaemic responses in humans depend on many factors amongst others gastric emptying, intraluminal glucose concentration, enzymatic activity in the brush border, endogenous glucose production and glucose clearance.

Sucrose, also known as table sugar, is a disaccharide consisting of glucose and fructose monosaccharide units. Sucrose is a compound found in the human diet in fruits and is added to many products as refined beet or cane sugar. After ingestion, sucrose forms a membrane bound complex with sucrase-isomaltose in the brush border of the small intestine, which rapidly hydrolyses sucrose to its monosaccharides, which are then transported from the lumen by SGLT-1, GLUT-2, and GLUT-5. This gives a fast rise to blood glucose concentrations after sucrose consumption. A part of the circulating glucose and fructose is quickly oxidized and exhaled as CO_2, and the remainder is metabolized and stored in the form of glycogen or fat (Robayo-Torres et al., 2009).

Sweet tasting ingredients that have less or no impact on the glycaemic response may be good alternatives for sucrose. One ingredient that is currently of interest is L-arabinose. L-arabinose is a pentose which can be derived from hemicellulose by enzymatic hydrolysis (Maki-Arvela, Salmi, Holmbom, Willfor, & Murzin, 2011). Hemicellulose is naturally abundantly present in plant materials, such as sugar beet pulp (Maki-Arvela et al., 2011). L-arabinose has a sweet taste

Abbreviations: 13% Ara cereal, Cereal with 13% sucrose replaced by L-arabinose; 8% Ara cereal, Cereal with 8% sucrose replaced by L-arabinose; Ara, Drink with L-arabinose; AUC, Area Under the Curve; BMI, Body Mass Index (kg/m^2); CV, Coefficient of Variation; DEBQ, Dutch Eating Behaviour Questionnaire; GLP-1, Glucagon-Like Peptide-1; iAUC, incremental Area Under the Curve; SD, Standard Deviation; Suc, Drink with sucrose (control); Suc + Ara, Drink with sucrose replaced by L-Arabinose; VAS, Visual Analogue Scale

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(Birch & Shamil, 1988) and may therefore be easily added to sweet tasting foods, such as fruit drinks or confectionary.

Health effects of L-arabinose in food have not been studied very well. However a small number of studies have shown that consumption of 2–3 g L-arabinose together with 40-75 g sucrose reduced blood glucose (Inoue, Sanai, & Seri, 2000; Krog-Mikkelsen et al., 2011; Shibanuma, Degawa, & Houda, 2011). Also, animal studies suggest that L-arabinose together with sucrose lowers blood glucose and insulin responses (Preuss, Echard, Bagchi, & Stohs, 2007; Seri et al., 1996). It is also shown that L-arabinose moderates blood glucose response when used together with starch (Jurgoński, Krotkiewski, Juskiewicz, & Billing-Marczak, 2015; Preuss et al., 2007). To our knowledge, there have been no studies on the effects of L-arabinose in drinks without sucrose or with L-arabinose in a higher concentration than 2–3 g (e.g. > 10 g) together with sucrose. The research of L-arabinose incorporated in real foods, such as cereal foods, is even scarcer (Halschou-Jensen, Bach Knudsen, Nielsen, Bukhave, & Andersen, 2015).

Our objective was to investigate the effect of L-arabinose on glycaemic and insulin responses in healthy subjects up to 180 min after consumption. We investigated the effect of replacing sucrose with L-arabinose in two different food matrices, that is drinks and cereal foods. In addition, we explored the underlying biological mechanisms by assessing the effect on GLP-1 responses and by measuring L-arabinose in 24 h urine to see whether it was absorbed and metabolised in the body. We also assessed the effects on feelings of satiety and wellbeing during the test sessions and spontaneous food intake after the test sessions. Finally, we investigated gastro-intestinal side effects 3, 6 and 9 h after consumption.

2. Subjects and methods

2.1. Subjects

Healthy adults (both sexes, age: 18–35 years) were recruited from Wageningen and surroundings, amongst others via the recruitment database of our division. Inclusion and exclusion criteria were assessed by a questionnaire. Inclusion criteria were: apparently healthy as judged by the subject (i.e. had not reported gastro-intestinal problems, nor a history of medical surgical events that may affect the study outcome), and no use of medicines judged likely to interfere with the experimental outcomes (e.g. antibiotics for the last 2 months, or dietary supplements, such as fibre supplements and supplements including Chromium, except contraceptives). Subjects who reported weight fluctuations of > 5 kg for the last 2 months and those currently following a slimming diet or medically prescribed diet or having followed one for the last 2 months, were excluded from participation. Subjects were required to be willing to eat or drink the test products. Subjects were excluded if they were allergic, intolerant or oversensitive to any of the study foods, if they consumed on average ≥21 alcoholic drinks per week, were pregnant or breast-feeding, or were planning to change their physical activity pattern during the study.

After receiving oral and written information and signing the consent form, 66 subjects completed the inclusion questionnaire to determine eligibility. In addition, the Dutch Eating Behaviour Questionnaire (DEBQ, (Van Strien, 2005)) was completed. Then the subjects joined a screening visit in fasting state. This visit included a measurement of height and body weight and fasting glucose and haemoglobin (Hb) concentration were checked by finger prick and a nurse checked whether veins were suitable for inserting a cannula. Individuals were excluded if they had a fasting glucose concentration of > 6.1 mmol/L (World Health Organization (2006)) or fasting Hb concentration < 8.5 mmol/L for men and < 7.5 mmol/L for women (Hooijkaas et al., 2013). Eventually, twenty-four subjects did not meet the inclusion criteria. Reasons for exclusion were: unsuitable veins for inserting a cannula (n = 10), use of medicines or supplements that could interfere with the experiment (n = 9), low Hb (n = 4) and plans to change his or her physical activity pattern during the study period (n = 1). Furthermore, ten subjects could not participate because of planning problems. As we ended up with more eligible participants than expected we included the 18 subjects by drawing lots.

Table 1
Baseline characteristics of subjects that completed the study. Values are means ± SD.

	Total (n = 16)	Men (n = 7)	Women (n = 9)
Age (y)	23 ± 3	24 ± 4	22 ± 2
Body weight (kg)	70.5 ± 10.0	73.9 ± 13.0	67.9 ± 6.6
Height (m)	1.79 ± 0.10	1.87 ± 0.08	1.73 ± 0.07
BMI (kg/m^2)	22.0 ± 2.2	21.0 ± 2.2	22.7 ± 2.1

From the eighteen that started with the experiment, sixteen completed the total study and were included in the data analysis (per protocol analysis) (Table 1). Two subjects dropped out due to study procedures; one subject did not feel well at the first test day after the cannula was placed, the other subject decided to stop when he/she did not feel well on the third test day when the cannula was placed.

The study was performed according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the medical research ethics committee of Wageningen University (NL559740.081.15). Written informed consent was obtained and subjects received monetary compensation for participation. Prior to execution, the trial and its primary outcomes were registered at the Dutch public trial registry as NTR5929 (www.trialregister.nl).

2.2. Study design

The present randomized cross-over trial including a within block design, i.e. drinks and cereal foods, was carried out between May and July 2016 at the Division of Human Nutrition and Health, Wageningen University. An independent researcher generated a list with randomized sequences using balanced block randomisation. Subjects were randomized to three test products within the block of the drinks and to three test products within the block of the cereal foods by an independent researcher. The researchers allocated the included subjects in a consecutive order to the randomized sequences. A second independent researcher prepared and coded the test products. The researchers provided the test products to the subjects.

Within the cereal foods block, the test product was double-blind, within the drink block the manipulation was only blinded for the researchers (single blind), as the subjects could taste the difference between the drinks. To minimize carry-over effects, we used a washout period between treatments of one week, with a minimum of three days. The different test products provided in the first three weeks were drinks: 1) Suc: Control sucrose drink; 2) Suc + Ara: L-Arabinose sucrose drink; and 3) Ara: L-arabinose drink. In the second three weeks the test products were cereal foods: 4) Control cereal food; 5) 8% L-Arabinose cereal food; and 6) 13% L-arabinose cereal food.

The main outcomes of the study were blood glucose and plasma insulin responses. Secondary outcomes were: plasma GLP-1 responses, feelings of appetite and gastro-intestinal comfort ratings, and food intake. Furthermore, L-arabinose concentrations were measured in 24 h urine.

2.3. Test products

All control products contained 50 g available carbohydrates; sucrose was replaced by L-arabinose in all intervention products. We assumed that L-arabinose was an available carbohydrate as no data was available that it is not absorbed and metabolized. The drinks were sugar solutions in water, and the foods were grinded cereal foods (Table 2). Both the

Table 2
Sucrose, L-arabinose and macronutrient content of the test products (g per portion).

	Portion	Sucrose	L-arabinose	Description	Energy	Carbohydrate	Fat	Protein	Liking scores §
	(g)	(g)	(g)		(kcal) ‡	(g) ‡	(g) ‡	(g) ‡	
Drinks*†									
Suc drink	300	50	0	100% sucrose	200	50	0	0	5.1 ± 1.9
Suc + Ara drink	300	35	15	30% replacement of sucrose by L-arabinose	200	50	0	0	4.9 ± 1.7
Ara drink	265	0	15	Only L-arabinose	60	15	0	0	4.9 ± 1.3
Cereal foods†									
Control cereal	80	25	0	100% sucrose, no replacement	382	55	15	5	7.1 ± 0.9
8% Ara cereal	80	21	1.7	8% sucrose replacement by L-arabinose (w/w)	370	58	12	5	7.4 ± 1.0
13% Ara cereal	80	20	2.6	13% sucrose replacement by L-arabinose (w/w)	369	58	12	5	7.1 ± 0.9

* All drinks were made with 250 ml water.
† Both the drinks and the cereal foods were consumed together with 250 ml water.
‡ Energy content was calculated from the individual macronutrients; carbohydrate, fat and protein content were analysed by an independent lab.
§ Liking was rated on a 9-point scale, where 1: dislike extremely, 2: dislike very much, 3: dislike moderately, 4: dislike slightly, 5: neither like nor dislike, 6: like slightly, 7: like moderately, 8: like very much, 9: like extremely (Evaluation questionnaire).

control drink and the control cereal food only contained 100% sucrose, no replacement with L-arabinose was made. The doses of L-arabinose were chosen based on previous studies in which 15 g L-arabinose was thought to be a sufficiently high and a safe dose (Liu, Zhu, Sun, Gao, & Wang, 2013).

2.3.1. Preparation of the drinks

The drinks were freshly prepared before each test session on the test day. The sugar(s) was/were added to a 400 ml milkshake beaker in which 250 ml water was poured and stirred until all particles were dissolved. Bottles of water (500 ml, mineral water Albert Heijn, Zaandam, the Netherlands) were used. The rest of the water was provided to the subjects to drink afterwards.

2.3.2. Preparation of the cereal foods

The ingredients for the cereal foods were derived from a dry and syrup part. The dry part consisted of fine oat flakes, rough oat flakes and wheat flakes. The syrup part consisted of granulated sugar, vegetable fat, water, emulsifier (and L-arabinose). These test products were prepared at the Cosun Food Technology Centre, Roosendaal. The cereal and syrup mix was baked in a combi steamer (Crisp&Taste – option 2) at 130 °C for 19 min. Then the cereals were cooled down for 5 min, afterwards they were taken off the baking tray and the cereals were cooled for another 5 min. Then the cereals were broken down in clusters and after 45 min cooling these were packed in sealed bags. At the university, the clusters were grinded for 1 min to get fine particles, prior to weighing into portions. As complex foods, in contrast to more simple foods like drinks, may reduce the potential activity of L-arabinose to lower glycaemic response (Halschou-Jensen, 2013), the clusters were grinded such that the sucrose and L-arabinose may be more rapidly available in the intestine. The cereal foods were consumed together with 250 ml water.

2.4. Study procedures

To standardize baseline levels, subjects consumed an evening meal distributed by the study team. This evening meal consisted of noodles with vegetable and chicken filet (Bami Goreng, Iglo Roerbak Sensatie, 475 g per package; 513 kJ or 123 kcal/100 g) and one ice cream as dessert (Magnum mini classic, 50 g; 1366 kJ or 325 kcal/100 g). Besides this meal subjects were not allowed to eat anything else. On the first test day subjects estimated how much they normally ate from such an evening meal (e.g. 1 package, or 1.5 or 2 package(s) of noodles) and were instructed to eat the same amount every week again. In addition, subjects were instructed to maintain their regular diet and physical activity pattern and abstain from strenuous exercise and alcohol 24 h prior to treatments.

Each test day the subjects arrived at 7.30 a.m. at the university in a fasting state; subjects were not allowed to consume food and drinks other than water after 22.00 h the evening before. They completed a well-being, a gastro-intestinal side effects and an appetite questionnaire. Then an intravenous cannula was placed for blood collection and the first blood sample was drawn (baseline). Thereafter subjects started to consume the test product (t = 0) within 5 min. Further blood samples and appetite ratings were collected at t = 15, t = 30, t = 60, t = 90, t = 120 and t = 180 min. In between blood drawings subjects remained in the living room of the human research facilities and were allowed to do sedentary activities, that is read, watch television, or listen to music. After the last blood drawing at t = 180 the cannula was removed and subjects were directed to the eating lab where they had lunch and their food intake was measured.

After the third and after the sixth test day subjects were asked to identify the right product via an evaluation questionnaire with multiple choice answers (“the drink with sugar only”, “with arabinose and sugar”, and “with arabinose only” or “I don’t know” and “the control cereal food”, “the cereal food low in arabinose”, “the cereal food high in arabinose” and “I don’t know”). From the 48 product-subject combinations, 30 (63%) and 15 (31%) times the products were recognized correctly for the drinks and the cereal foods respectively.

2.5. Outcome measures

2.5.1. Blood glucose, plasma insulin and plasma GLP-1

Blood glucose was determined by taking a blood sample from the cannula, which was then measured immediately by a glucometer (FreeStyle Freedom Lite, Abbott Diabetes Care Inc., USA). Blood samples for insulin analysis were collected from the cannula into EDTA vacutainers. Blood samples for total GLP-1 concentrations were collected into aprotinine K3EDTA vacutainers, which we manually pretreated with 50 μl DPP-IV inhibitor (Catalog no. DPP4-010, Millipore, USA) to prevent proteolytic cleavage. Both tubes were kept in ice water for a maximum of 15 min before being centrifuged for 10 min at 1200 × g at 4 °C. Plasma was then collected in cryo vials and stored at −80 °C until analysis. Plasma concentrations of insulin were measured using enzyme-linked immunosorbent assay (ELISA) (catalog no. 10–1113-10, Mercodia Insulin ELISA, Sweden) (the lowest detectable level for insulin was 1.0 mU/L; intra-assay-coefficient of variation (CV): 4% and inter-assay CV: 4%). Plasma concentrations of total GLP-1 were measured using ELISA (catalog no. EZGLP1T-36 K, Millipore, USA) (the lowest detectable level for GLP-1 was 2 pmol/L; intra-assay CV: 1% and inter-assay CV: 12%). All ELISA’s were performed by the same lab technicians. All samples of one subject were analysed within one run or plate and contained a positive and negative control.

2.5.2. Appetite ratings and food intake

Dimensions of appetite that we measured were: hunger, fullness, prospective food consumption, desire to eat and thirst (formatted as described in (Halford et al., 2018)). A 100 mm visual analogue scale (VAS) was used with the anchors: 'not at all' (left) and 'very much' (right). Also comfort was rated in this way (how comfortable do you feel at this moment? Not at all to very much). The questionnaire was completed on a tablet (Samsung, Galaxy TabA, 9.7).

Food intake was measured by assessing the intake from an *ad libitum* lunch after the test session. Subjects were provided with a meal and instructed to eat until they were comfortably full. The lunch had a maximum duration of 30 min. During lunch subjects could not see each other and external distractions were not allowed (such as mobile phone, laptop, books).

The meal consisted of an excess of small brown wheat buns and several toppings. These toppings were low fat margarine, slices of 48 + cheese, peanut butter, jam and chocolate sprinkles. Water, coffee and tea with some coffee milk and sugar were also offered. Food was served in excess to the subject along with free choice of water, tea and coffee. Food intake was calculated by weighing all food and drinks before serving and weighing leftovers after subjects left the laboratory. Energy and macronutrient intake was estimated using the Dutch Food Composition Database (NEVO-online versie 2013/4.0 & Bilthoven, 2013/4.0). There were no subjects that ate all buns or asked for a second portion.

2.5.3. Gastro-intestinal wellbeing

Gastro-intestinal wellbeing ratings were taken 4 times: at baseline, 3, 6 and 9 h after consumption of the test product. Bloating, regurgitation, flatulence and nausea were registered on a 7-point Likert scale, where 1 was labelled "less than normal", 4 is "normal" and 7 "much more than normal".

2.5.4. L-arabinose in urine

L-arabinose was measured in 24 h urine to quantify the excretion through urine. This was only measured after the conditions in which the drinks were consumed. Directly after arrival at the university, before placing the cannula, subjects emptied their bladder. From this moment onwards subjects started to collect their urine for 24 h. Urine was collected in cans which contained 0.5 ml chlorhexidinegluconate as preservative. Subjects returned the cans the next day, urine was weighed, then homogenised and 3 ml samples were taken and stored until further analyses at −20 °C. For analysis, 200 μl of urine was purified using polymeric cation exchange solid phase extraction (SPE; Phenomenex Strata-X-C 33 μm, part no. 8B-S029-TBJ). SPE extracts (2 ml) were subsequently analyzed using High Performance Anion Exchange Chromatography using Pulsed Amperometric Detection (HPAEC-PAD, Dionex) on a CarboPac PA-1 column (250 mm × 2 mm i.d., Thermo Scientific). Calibrators (range 2-60 mg/L) were prepared by spiking arabinose (Cosun) to 10-fold diluted urine from a healthy volunteer. Quality control samples were similarly prepared by spiking arabinose at 5 and 30 mg/L to 10-fold urine. Then high-pH anion-exchange chromatography (HPAEC) coupled with pulsed amperometric detection (PAD) was performed with Dionex system and a CarboPax PA-1 column. Accuracies ranged between 103.6–110.7% and 89.0–106.0% for the QC samples spiked at 5 and 50 mg/L, respectively. Intra-assay CVs were 12.7% for unspiked urine, and 2.3% and 7.1% for the QCs spiked at 5 and 30 mg/L, respectively. Samples with arabinose concentrations that exceeded the calibration curve where re-analysed in a higher dilution. Subsequently, L-arabinose recovery in 24 h was calculated from the samples and the total amount of collected 24 h urine.

2.6. Calculations and data analyses

2.6.1. Calculations

From the individual blood glucose, plasma insulin, and plasma GLP-1 curves the following curve parameters were calculated: total area under the curve (AUC), incremental area under the curve above baseline (iAUC), peak, time-to-peak, and time to baseline were calculated. In addition, the AUC for the appetite ratings was calculated. All areas were calculated with the trapezoidal rule. Peak was defined as upper peak, so the peak above baseline level.

2.6.2. Data analyses

Results are expressed as means and standard deviations, unless stated otherwise. P-values < 0.05 were considered statistically significant. All data were analysed using SAS v9.4 (SAS Institute, Cary, NC, USA). All continuous variables were checked for normal distribution by visual inspection of Q-Q-plots. The plasma insulin values were not normally distributed and therefore all values were transformed with the natural logarithm (ln) before analyses. Baseline glucose and insulin concentrations were significant different with the cereal foods, therefore baseline concentrations were added as covariate to the model. Gastro-intestinal side effect ratings were treated as continuous variables and analysed according to a similar procedure as the continuous variables.

For the analysis, all outcome measures were compared between the treatments; drinks and cereal foods were analysed separately. Data were analysed by means of mixed model ANOVA's (PROC MIXED, SAS). Models included food product, time, and the interaction of food product and time as fixed factor and subject id as random factor. Variance Components was used as covariance structure. All post hoc tests were performed for slices of the interaction food product and time sliced by time with Tukey adjustments. The statistical analyses were performed triplicate blinded within the block of drinks and cereal foods. Only after primary analyses, the treatments were unblinded to the researchers.

2.6.3. Sample size estimation

The sample size estimation was based on the expected effect of L-arabinose on the glycaemic response, that is peak concentration of glucose (C_{max}) using data from a previous study (Pol et al., submitted). The design of that trial was similar (cross-over, with response measurements) and also the functional ingredient was identical (L-arabinose). This study tested fruit based drinks and muffins. We found effects of 7–9%, with a coefficient of variation of 20%. For the current study we used larger dosages of L-arabinose and we used simple matrices therefore we expected to find effects around 15%. We estimated that with a sample size of 12 subjects we were able to show a difference of ~15% between treatments in the C_{max} of glucose. For this calculation we assumed a power of 0.80, a two sided paired *t*-test with $\alpha = 0.05$ and a coefficient of variation in the glucose C_{max} of 20%. We included 6 extra subjects to account for drop outs or missing data.

3. Results

3.1. Drinks

3.1.1. Blood glucose responses

Mean blood glucose response curves and curve parameters are presented in Fig. 1 and Table 3. Blood glucose concentrations were significantly lower at 15 and 30 min after the Suc + Ara drink than after the Suc drink and more close to baseline after 90 min. The glucose peak was also 1.6 mmol/L (–22%) lower after the Suc + Ara drink compared to the Suc drink (Tukey; $t_{23} = -5.96$; $p < 0.001$). Moreover, from the blood glucose response curve it can be seen that after the Suc drink the blood glucose levels reached baseline levels around 65 min, and showed a nadir around 90 min and then came back to baseline levels around 180 min, while the Suc + Ara curves did not show a nadir before 180 min. This observation was supported by the higher iAUC after the Suc drink compared to Ara + Suc drink, despite this observation not being statistically significant (Tukey; $t_{30} = -1.80$; $p = 0.19$). Thus, drinking L-arabinose in combination with sucrose,

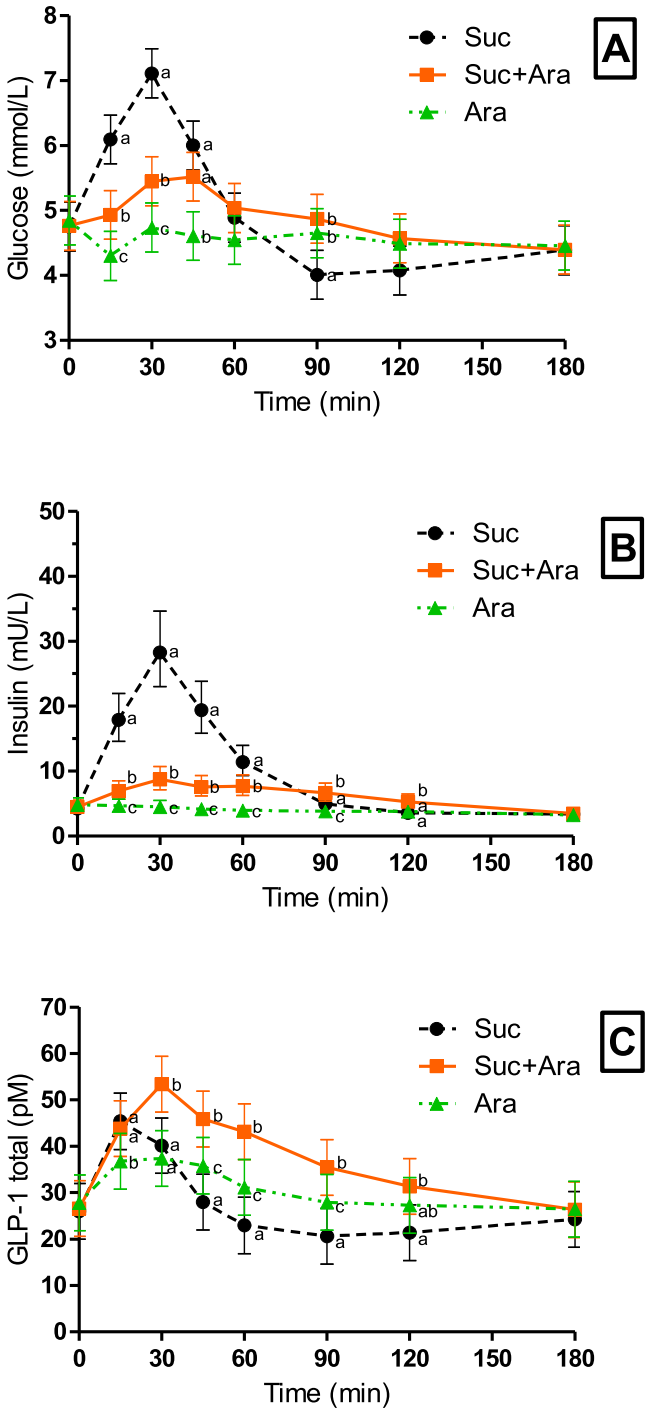

Fig. 1. Least square means (± 95% confidence interval) concentrations of blood glucose measured with a glucometer (A), plasma insulin (B), and plasma GLP-1 (C), after consumption of the drinks containing either: (i) 50 g sucrose (circles with dashed line), (ii) 35 g sucrose and 15 g L-arabinose (squares with solid line), (iii) 15 g L-arabinose (triangle with dashed line) in healthy subjects (n = 16). (B) Data represent lsmeans (95%CI) of the ln transformed and backtransformed data. (A and C) are untransformed. [a,b,c] Different letters indicate significant differences between test drinks at certain time points (predefined slices treatment*time; Posthoc Tukey, $p < 0.05$).

reduced and smoothened the blood glucose response in comparison to sucrose.

After drinking the Ara drink, at 15 min a small, but statistically significant decrease, in blood glucose was observed ($t_{105} = 3.53$; $p = 0.01$). At 30 min this was again similar to baseline levels and no further changes in blood glucose were observed. Six subjects did not show an increase from their fasting glucose levels at all after the Ara drink.

3.1.2. Plasma insulin responses

The insulin response curve and curve parameters following the consumption of the drinks are presented in Fig. 1 and Table 3. After the Suc + Ara drink statistically significant lower plasma insulin concentrations were observed after 15, 30, 45 and 60 min compared to the Suc drink (all p's < 0.05). After 90 and 120 min plasma insulin remained increased compared to the Suc drink (all p's < 0.05). Similar results were shown when looking at iAUC and average peak level, these were significantly lower for the Suc + Ara drink compared to the Suc drink. Sixty minutes after consumption insulin concentrations were again similar to the control Suc drink. To summarize, L-arabinose in combination with sucrose resulted in a lower insulinemic response compared to sucrose alone.

A negligible effect of the Ara drink was found on plasma insulin concentrations; 7 subjects (44%) showed no peak at all, meaning that there was no response. Overall, no main effect of time was observed for the Ara drink ($F_{3,345} = 0.88$; $p = 0.55$).

3.1.3. Plasma GLP-1 responses

The plasma GLP-1 response and response curve parameters after drinking the different drinks are shown in Fig. 1 and Table 3. GLP-1 concentrations were significantly higher after consumption at 30, 45, 60, 90 and 120 min after the Suc + Ara drink compared to the Suc drink (all p-values < 0.0001). This is also shown by the increased AUC and iAUC ($p < 0.001$). In summary, partly replacing L-arabinose with sucrose increases plasma GLP-1 responses; it showed a large increase in GLP-1 which sustained for 2 h.

Consumption of the Ara only drink increased GLP-1 levels (main time effect: $F_{7,342} = 4.68$; $p < 0.0001$); levels were increased at 15 min (borderline significant $t_{342} = -2.98$; $p = 0.06$) and 30 min ($t_{342} = -3.18$; $p = 0.03$) compared to baseline. Compared to the Suc drink the response was lower at 15 min and higher at 45, 60 and 90 min (all p-values < 0.05).

3.1.4. Appetite ratings and food intake

See the **Supplementary data** for the ratings of hunger, fullness, desire to eat, prospective food consumption, thirst and comfort. No significant differences in appetite ratings were seen at specific time points (all p-values > 0.05). Subjects ate on average 1072 ± 351 kcal (4.5 ± 1.5 MJ, 41.3% carbohydrates, 40.0% fat, 15.8% protein) during the lunch that was offered *ad libitum*. None of the subjects finished the total offered meal. There was no effect of test product on food intake after the test session.

3.1.5. Gastro-intestinal side effects

Ratings for bloating were somewhat higher after 3 and 6 h compared to levels in the fasting state; this rise was similar for all three drinks (data not shown). Ratings for flatulence and regurgitation also increased 6 h after consumption; this was also not different between drinks. Nausea ratings did not change during the course of the test sessions.

3.1.6. L-arabinose in urine analysis

Fig. 2 shows the recovery of L-arabinose in urine. On average ~8.0–8.5% was recovered of the 15 g supplemented; this was similar for the Suc + Ara drink and the Ara drink. The recovery showed a large between subject variation; the amount recovered varied from 1.4% to 15%. After consumption of the sucrose drink only very low amounts of arabinose were measured in urine (see Fig. 2).

Table 3
Blood glucose, plasma insulin and plasma GLP-1 response parameters after consumption of the drinks in healthy subjects.

	Suc	Suc + Ara	Ara	p-value*
Blood glucose response parameters *				
iAUC (mmol/l*min)	94 (63–124) [a]	57 (27–87) [ab]	8 (–22–38) [b]	0.001
Peak (mmol/L)	7.4 (6.9–7.8) [a]	5.8 (5.3–6.3) [b]	5.2 (4.7–5.8) [b]	< 0.001
Peak increase from baseline (mmol/L)	2.6 (2.1–3.1) [a]	1.1 (0.6–1.6) [b]	0.4 (-0.2–1.0) [b]	< 0.001
Time-to-peak (min)	30 (15–45) [a]	39 (24–54) [ab]	60 (41–79) [b]	0.05
Plasma insulin response parameters**†				
AUC (mU/L*min)	1906 (1655–2157) [a]	1179 (927–1430) [b]	743 (492–994) [c]	< 0.001
iAUC (mU/L*min) †	1166 (976–1356) [a]	408 (213–603) [b]	121 (-116–359) [c]	< 0.001
Peak (mU/L) †^	29.6 (24.1–36.3) [a]	10.1 (8.2–12.4) [b]	5.4 (4.2–6.8) [c]	< 0.001
Peak increase from baseline (mU/L) †^	25.2 (18.1–35.1) [a]	5.3 (3.8–7.5) [b]	1.0 (0.7–1.5) [c]	< 0.001
Time-to-peak (min) †	33 (24–42) [a]	46 (36–55) [b]	28 (17–40) [a]	0.02
Plasma GLP-1 response parameters***				
AUC (pM*min.)	4597 (3678–5516) [a]	6580 (5661–7500) [b]	5374 (4455–6293) [a]	< 0.001
iAUC (pM*min.) †	676 (351–1001) [a]	1870 (1554–2185) [b]	820 (495–1145) [a]	< 0.001
Peak (pM) †	49.0 (41.2–56.9) [ab]	57.3 (49.6–65.0) [a]	42.3 (34.4–50.1) [b]	0.006
Peak increase from baseline (pM) †	23.0 (16.7–29.3) [ab]	30.7 (24.6–36.8) [a]	15.6 (9.2–21.9) [b]	0.002
Time-to-peak (min) †	31 (16–46)	34 (20–48)	33 (18–48)	0.93

Least square means (± 95% confidence interval) response parameters of blood glucose measured with a glucometer (A), plasma insulin (B), and plasma GLP-1 (C), after consumption of the drinks containing either: (i) 50 g sucrose, (ii) 35 g sucrose and 15 g L-arabinose, (iii) 15 g L-arabinose in healthy subjects (n = 16).
* Only for subjects that had positive glucose peaks: Suc n = 16, Suc + Ara n = 15, Ara n = 10.
** † Only for subjects that had positive insulin peaks: Suc n = 16, Suc + Ara n = 15, Ara n = 9.
*** † Only for subjects that had positive GLP-1 peaks: Suc n = 15, Suc + Ara n = 16, Ara n = 15.
iAUC = incremental Area Under the Curve for 180 min (area by definition, all peaks must go above the baseline).
AUC = Area Under the Curve.
* Tested with MIXED model ANOVA.
[a, b, c] Different superscript letters indicate significant differences between test products (Tukey, p < 0.05).
^ Insulin data was analysed using natural logarithm transformed data and back transformed data is reported here.

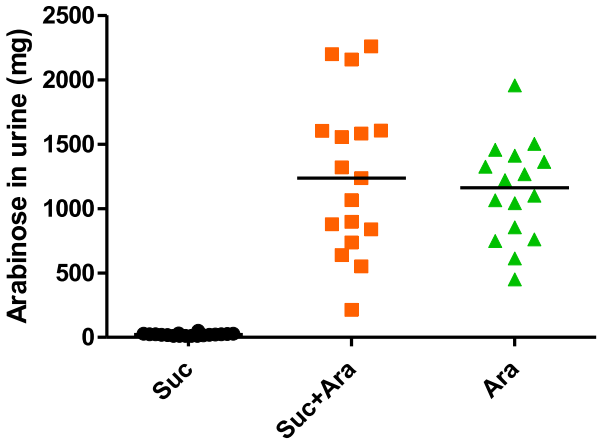

Fig. 2. Arabinose recovered from 24 h urine samples (horizontal line represents the median).

3.2. Cereal foods

3.2.1. Blood glucose responses

Glycaemic response curves and parameters are depicted in Fig. 3 and Table 4. Glycaemic responses were not different at any time point after cereal food consumption with or without L-arabinose (all p-values > 0.05). In addition, all curve parameters were similar between treatments (all p-values > 0.05). Thus replacement of L-arabinose to cereal foods did not affect glucose responses.

3.2.2. Plasma insulin responses

Insulin response curves after consumption of the cereal foods are depicted in Fig. 3 and Table 4. Thirty minutes after consumption of the 8% and 13% Ara cereal foods, insulin levels were significantly lower compared to the control cereal foods (t_{344} = 2.74; p = 0.02 and t_{344} = 2.81; p = 0.02, respectively). This is also shown by the lower peak insulin level of 8% Ara cereal, which was 24% lower compared to the control cereal (t_{29} = 2.69; p = 0.03). The peak insulin level of the 13% Ara cereal was also 19% lower, but this did not reach statistical significance (t_{29} = 2.23; p = 0.08). The rest of the time curve parameters did not show significant differences between the different cereal foods (all p-values > 0.05). Overall, no statistically significant differences were observed between the 8% Ara and 13% Ara cereal foods. In summary, addition of 8% L-arabinose in these cereal foods lowered the insulin peak, and this trend was also seen for the 13% replacement, although this was a smaller effect that did not reach significance.

3.2.3. Plasma GLP-1 responses

The plasma GLP-1 responses and curve parameters can be found in Fig. 3 and Table 4. All three cereal foods resulted in a GLP-1 response, however no differences were observed between the three cereal foods (all p-values > 0.05).

3.2.4. Appetite ratings and food intake

The ratings for hunger, fullness, desire to eat, prospective food consumption, thirst and comfort are shown in the **Supplementary data**. No significant differences in appetite ratings were seen between cereal foods at specific time points (all p-values > 0.05). Subjects ate on average 1018 ± 325 kcal (4.3 ± 1.4 MJ, 40.8% carbohydrates, 40.4% fat, 16.0% protein) during the lunch that was offered *ad libitum*. No subjects finished the total offered meal. There were no effects of the type of cereal foods on food intake (all p-values > 0.05).

3.2.5. Gastro-intestinal comfort

Ratings for regurgitation were higher 6 h after consumption compared to fasting, these were not different after consumption of the three different cereal foods. Ratings for bloating, flatulence and nausea did not change over time.

4. Discussion and conclusion

The current study is the first well controlled study that investigated the effect of L-arabinose on glycaemic responses in healthy subjects up to 180 min after consumption. We measured blood glucose, plasma

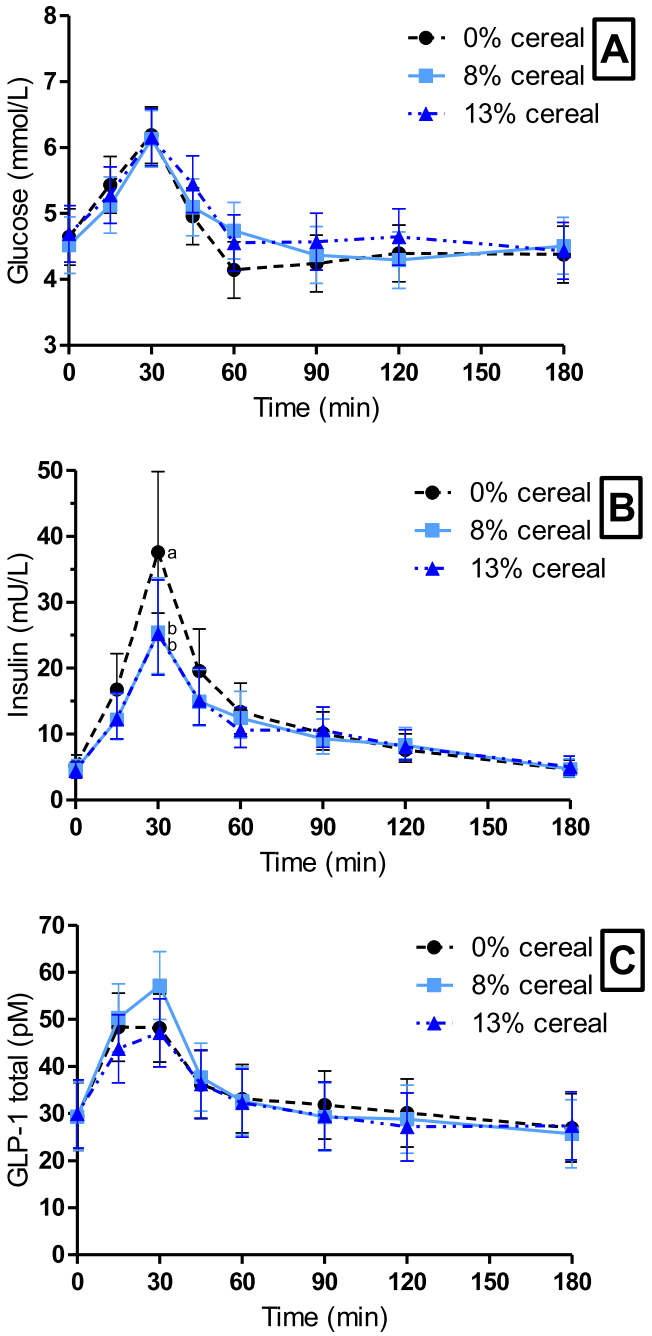

Fig. 3. Least square means (± 95% confidence interval) concentrations of blood glucose measured with a glucometer (A), plasma insulin (B), and plasma GLP-1 (C), after consumption of the cereal foods containing either: (i) 0% L-arabinose (circles with dashed line), (ii) 8% L-arabinose (square with solid line), or (iii) 13% L-arabinose (triangle with dashed line) in healthy subjects (n = 16). (B) Data represent lsmeans (95%CI) of the ln transformed and backtransformed data. (A and C) are untransformed. [a,b,c] Different letters indicate significant differences between test foods at certain time points (predefined slices treatment*time; Posthoc Tukey, $p < 0.05$).

insulin and plasma GLP-1 responses after consumption of drinks and cereal foods in which sucrose was (partly) replaced with L-arabinose. We observed that in a drink replacement of 30% sucrose for L-arabinose (15 g) significantly lowered and dampened the blood glucose responses, it lowered insulin responses and affected GLP-1 responses. In cereal foods, no effects of 8% and 13% replacement of sugar by L-arabinose were observed on glucose and GLP-1 responses. However, it lowered peak insulin concentrations with 24% after consumption of the 8% replacement cereal. This trend was also seen for the 13% replacement cereal, however this was a smaller effect (19%) that did not reach significance ($p = 0.08$). Replacing sucrose by L-arabinose had no effect on appetite responses and subsequent food intake.

In drinks, glucose and insulin peaks were lower and responses were reduced when 15 g sucrose was replaced by L-arabinose in drinks containing 50 g sucrose (30% replacement). This replacement also resulted in lower insulin levels and a smaller rebound, that is the nadir after the insulin peak. Similarly, significant reductions were observed after several combinations of sucrose with L-arabinose in drinks ranging from 40 to 75 g sucrose and 1 to 3 g L-arabinose in healthy subjects (Inoue et al., 2000; Krog-Mikkelsen et al., 2011; Shibanuma et al., 2011). This effect in our study is presumably the result of both removing sucrose from the drink as from the addition of L-arabinose. However, with the current design it is difficult to disentangle these two effects. To disentangle these effects we should have added a treatment of 35 g sucrose only to the design. A drink with L-arabinose alone did not induce a blood glucose or insulin response, however it did initiate a postprandial response in GLP-1. In summary, partly replacing L-arabinose with sucrose increases plasma GLP-1 responses; it showed a large increase in GLP-1 which sustained for 2 h.

Replacement of sucrose in cereal foods, both 8 and 13%, did not affect blood glucose responses. We did expect that L-arabinose would be less effective in the solid, more complex food, compared to the drinks. Similar to the drinks, the cereal foods contained 50 g digestible carbohydrates, however, in contrast to the drinks, a large part of the carbohydrates were present in the form of starch. As L-arabinose only affects the enzyme sucrase, the glucose response due to breakdown of starch could have been overshadowing the only small effect of the sucrose replacement with L-arabinose. Notably, L-arabinose has been shown before to affect blood glucose response after starch in drinks (Jurgoński, Krotkiewski, Juskiewicz, & Billing-Marczak, 2015). However, the type of starch may be important, since this was the only study that found an effect of starch with L-arabinose. Another study also incorporated L-arabinose in a more complex meal which was a lunch containing buns with fatty toppings or buns and muffins with sugary toppings. Here, no differences in plasma glucose, serum insulin or c-peptide were found (Halschou-Jensen et al., 2015). In our study, the replacement of sucrose for L-arabinose did reduce the insulin peak by 20–25%, which is a clinically relevant effect. This effect was 24% after the 8% cereal, and, although not significant, a similarly sized trend of 19% was also observed after the 13% replacement cereal. This means that less insulin was circulating to get similar glucose responses, which can be seen as a beneficial health effect in populations with problems with blood glucose regulation, such as (pre)diabetes. Although replacement of sucrose for L-arabinose had no effect on postprandial glucose responses, the reduction of insulin response may have potential for beneficial effects in cereal foods.

In this study, we also measured GLP-1 responses. These responses were enhanced when sucrose was replaced by L-arabinose in the drinks. These results are similar to previous literature demonstrating an increase in iAUC of GLP-1 after 3 g L-arabinose addition to 75 g sucrose in water (Krog-Mikkelsen et al., 2011). A suggested mechanism may be the delayed sucrose digestion in the upper part of the duodenum caused by the inhibition of sucrase by L-arabinose. As a result more intact sucrose moves to a more distal site of the intestines, where the density of GLP-1 secreting L-cells is the highest.

To get a better understanding of the metabolism of L-arabinose in the body we measured L-arabinose excretion in urine 24 h after consumption. So far, little is known about the metabolism of L-arabinose. Around 8% of the ingested dose was recovered in urine after 24 h, and more importantly no L-arabinose was found in urine when subjects did not drink L-arabinose. This may mean that only small amounts are absorbed and the rest is excreted through faeces. However, it may very well be that L-arabinose is metabolised in the liver into compounds that were not excreted of which we did not detect in urine. A study in

Table 4
Blood glucose, plasma insulin and plasma GLP-1 response parameters after consumption of the cereal foods in healthy subjects (n = 16).

	0% cereal	8% cereal	13% cereal	p-value*
Blood glucose response parameters *				
iAUC (mmol/l*min)	63 (32–94)	79 (48–111)	77 (46–108)	0.39
Peak (mmol/L)	6.3 (5.9–6.6)	6.3 (6.0–6.7)	6.5 (6.2–6.9)	0.29
Peak increase from baseline (mmol/L)	1.7 (1.3–2.0)	1.7 (1.3–2.1)	1.9 (1.6–2.3)	0.29
Time-to-peak (min)	31 (26–36)	32 (26–37)	33 (28–38)	0.85
Plasma insulin response parameters				
AUC (mU/L*min)	1619 (1138–2099)	1369 (892–1845)	1493 (1015–1972)	0.20
iAUC (mU/L*min) †	1603 (1107–2099)	1345 (852–1837)	1467 (972–1961)	0.19
Peak (mU/L) †^	42 (33–51) [a]	32 (23–41) [b]	34 (25–42) [ab]	0.03
Peak increase from baseline (mU/L) †^	37 (28–46) [a]	27 (18–36) [b]	28 (20–37) [ab]	0.03
Time-to-peak (min) †	33 (26–39)	34 (27–40)	36 (30–43)	0.58
Plasma GLP-1 response parameters				
AUC (pM*min.)	6076 (5092–7061)	6080 (5096–7065)	5787 (4803–6771)	0.67
iAUC (pM*min.) †	1134 (679–1589)	1240 (785–1695)	819 (365–1274)	0.21
Peak (pM) †	52 (41–64)	58 (46–69)	50 (38–62)	0.31
Peak increase from baseline (pM) †	23 (14–32)	28 (19–37)	20 (11–29)	0.16
Time-to-peak (min) †	27 (18–36)	28 (19–37)	30 (21–39)	0.89

Least square means (± 95% confidence interval) response parameters of blood glucose measured with a glucometer (A), plasma insulin (B), and plasma GLP-1 (C), after consumption of the cereal foods containing either: (i) 0% L-arabinose, (ii) 8% L-arabinose, or (iii) 13% L-arabinose in healthy subjects (n = 16).
* Only for subjects that had positive glucose peaks: 0% Ara n = 16, 8% Ara n = 16, 13% Ara n = 15.
iAUC = incremental Area Under the Curve for 180 min (area by definition, all peaks must go above the baseline).
AUC = Area Under the Curve.
* Tested with MIXED model ANOVA.
[a, b, c] Different superscript letters indicate significant differences between test products (Tukey, $p < 0.05$).
^ Insulin data was analysed using natural logarithm transformed data and back transformed data is reported here.

eviscerated-nephrectomized dogs, showed that under influence of insulin, L-arabinose in blood may enter the cell, probably skeletal muscle cells, and is finally distributed in total body water (Goldstein, Henry, Huddlestun, & Levine, 1953). Until now, no utilization data of L-arabinose are available. Our measurements were only explorative and further metabolic research, for example with stable isotopes has to be done to further understand the metabolism of L-arabinose.

Furthermore, we assessed effects on satiety feelings and comfort during the test. Some effects on appetite were seen, but no consistent pattern could be observed. Moreover, no differences were observed in spontaneous food intake after the sessions. Finally, we investigated gastro-intestinal side effects 3, 6 and 9 h after consumption. It may be hypothesized that when more carbohydrates enter the colon, an increase in fermentation occurs, with the result that more gases are formed, which may cause gastro-intestinal side effects. In our study, replacing sucrose with L-arabinose did not give any additional gastro-intestinal side effects. These data show that a dosage of 15 g L-arabinose did not induce gastro-intestinal effects such as bloating, flatulence or nausea.

In this study, the drinks part was considered single blind for researchers only, since 63% of the product-subject combinations were indicated correctly, which shows that subjects could have recognized the different drinks. At the cereal part of the study 31% product-subject combinations were indicated correctly, which result would be expected by chance. Despite the drinks part was not double blind, we think it is unlikely that cognition could have an impact on glucose or insulin levels.

In the current set-up we removed sucrose and added L-arabinose. As such it is not possible to distinguish between direct effects of L-arabinose and the reduction of sucrose. However, in food applications this may very well be a realistic approach as L-arabinose is a sweet tasting compound. This may mean that there is an opportunity to reduce sucrose without compromising taste. There are however also some limitations for the use of this compound; L-arabinose is found to be very reactive under high temperatures (Gairola & Smirnova, 2012) which limits the type of applications. Moreover, as it is only functional in the presence of sucrose, it is hypothesized that in foods with low pH – in which sucrose gradually hydrolyses into glucose and fructose – are less suitable. Also other factors like the nutrient composition and food matrix may hinder the functionality, as also shown by the current study. Therefore, more different food applications need to be explored to get indications on the boundaries of the types of applications. In addition, it may be valuable to develop in silico models to predict the functionality of the compound under different circumstances and dosages, before in human intervention studies are set up.

Lastly, the current population comprised healthy lean normo-glycaemic males and females. Moreover, this study was a powerful strictly controlled randomized cross-over design in which every individual was its own control. Despite their well-regulated glucose levels we could show effects of L-arabinose on glucose and insulin responses. One may speculate that these effect may be stronger in individuals that have poor glucose homeostasis such as (pre)diabetic patients. Therefore further research may investigate whether there are beneficial effects of L-arabinose in populations with poor glycaemic control.

5. Conclusion

This study shows that replacement of sucrose by L-arabinose in a drink, or L-arabinose alone lowers the effect on glycaemic responses in healthy subjects. A dosage of 15 g L-arabinose is a safe and successful dosage in a drink. However in the cereal foods, no effect of L-arabinose on the glycaemic response was observed, although there was an effect on insulin levels. Further research in other drinks and food matrices with different composition in macronutrients, being starch, fat and protein, may indicate the boundaries of effects of food matrices on the glycaemic and insulin effects of L-arabinose in complex drinks and foods. Moreover, more research is warranted on the exact metabolism of this compound, to see whether it yields energy and can be implemented as a non-caloric sweetener. Last, further research, for example with different study populations, such as (pre)diabetics, and longer intervention periods, may reveal evidence for postprandial effects of L-arabinose under other conditions.

6. Ethics statement

The study was performed according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the medical research ethics committee of Wageningen University (ABR NL559740.081.15). Written informed consent was obtained and subjects received monetary compensation for participation. Prior to execution, the trial and its primary outcomes were registered at the Dutch public trial registry as NTR 5929 (www.trialregister.nl).

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2020.104114.

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