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Comparison of postprandial glycemic and insulinemic response of allulose when consumed alone or when added to sucrose: A randomized controlled trial

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ABSTRACT

Allulose is a naturally occurring monosaccharide with ~70% sweetness of sucrose which may blunt postprandial glucose when consumed with a carbohydrate-containing meal. Whether a higher allulose to carbohydrate ratio further inhibits both glycemic and insulinemic responses remains unclear. In an acute, double-blind, randomized design, 14 individuals without diabetes (age:51 ± 15 years, BMI:27.2 ± 4.1 kg/m^2) were studied over 120 min on three separate occasions after consuming beverages containing 15 g allulose, 15 g allulose plus 30 g sucrose, or 30 g sucrose. After allulose, allulose + sucrose, and sucrose beverages, respectively, glucose iAUC (mean ± SEM; 0.6 ± 0.2, 86.0 ± 9.5, and 118.1 ± 11.3 mmol × min/L), and peak rise (0.05 ± 0.02, 1.69 ± 0.13, and 3.15 ± 0.23 mmol/L) all differed significantly ($p < 0.05$). Similarly, insulin iAUC and peak rise were significantly different between all beverages. This study demonstrated that allulose added to sucrose attenuated both postprandial glucose and insulin responses. Thus, dietary substitution of sucrose with allulose may be advantageous, but longer-term studies are needed to confirm long term benefits.

1. Introduction

Increased consumption of dietary sugars across the developed world continues to be a serious public health concern, prompting many health organizations to call for reducing the intake of added or free sugars (Dietary Guidelines Advisory Committee, 2020; Nutrition, 2015; World Health Organization, 2015). While several sugar alternatives and low-calorie sweeteners have been developed, the continued rise in rates of obesity and cardiometabolic diseases has sparked renewed interest in exploring sugar alternatives that may have favourable effects on health beyond energy metabolism.

Allulose, also known as psicose, is a monosaccharide that is the C-3 epimer of fructose and is naturally occurring in small amounts in dried fruits, brown sugar, and maple syrup (Oshima, Kimura, & Izumori, 2006). It reportedly has a sweetness of approximately 70% of sucrose and is considered low-calorie (<0.2 kcal/g) (Hossain et al., 2015). It is currently approved for use as a sugar-substitute in the United States, as it is generally recognized as safe (GRAS) by the US Food and Drug Administration (Food & Drug Administration, 2022; Food & Drug Administration, 2022; Food & Drug Administration, 2022). While allulose occurs naturally only in small amounts, recent advances in technology have facilitated the mass manufacturing of allulose, which has renewed the interest in studying its metabolic properties (Takeshita, Suga, Takada, & Izumori, 2000).

In controlled human trials, allulose consumed alone does not appear to raise postprandial glucose or insulin (Iida et al., 2008). Moreover, evidence from 14 comparisons in 6 studies (Braunstein et al., 2018; Franchi et al., 2021; Hayashi et al., 2010; Iida et al., 2008; Kimura et al., 2017; Noronha et al., 2018) suggests that adding 2.5–15 g of allulose to 50–85 g of available carbohydrate from glucose, maltodextrin, sucrose or a mixed meal reduces the incremental area under the glucose response curve (iAUC) in individuals without diabetes, and those with prediabetes and type 2 diabetes by (mean ± SEM) 8.9 ± 2.6% ($p = 0.004$). However, the amount of allulose per gram of carbohydrate in these studies ranged from only 0.03 to 0.20 g/g and no significant dose–response is evident ($r = 0.17$, $n = 14$, $p = 0.55$). Thus, it is not clear

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if a larger effect would be obtained with a larger dose of allulose.

Therefore, the objective of the present study was to evaluate the postprandial glucose and insulin responses elicited by 15 g of a commercially available allulose, allSWEET®, when consumed alone or with 30 g sucrose in individuals without diabetes, yielding an allulose/carbohydrate ratio of 0.5 g/g.

2. Materials and methods

2.1. Participants

Participants were recruited from the pool of volunteers who had expressed interest in participating in studies at INQUIS Clinical Research and had given permission to be contacted to be recruited for future studies. Individuals who expressed interest were invited to the clinic where anthropometrics (height and weight) were taken, and questionnaires were completed to assess eligibility. Individuals were eligible if they met the following inclusion criteria: age between 20 and 70 years, BMI between 18–33 kg/m^2, no presence or known history of diabetes or other major diseases or eating disorders, not pregnant or lactating, not practicing any unusual dietary habits, and no known intolerance or sensitivities to the study products.

This trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines and was approved by Advarra Institutional Review Board (Aurora, Canada) on September 7th, 2021 (Pro00056886). All participants provided written informed consent before entry into the trial and the trial was conducted at INQUIS Clinical Research (Toronto, Canada). The study was registered at clinicaltrials.gov (NCT05185960), however please note that although the study was submitted for registration prior to the start of the study, due to an administrative oversight, the actual confirmation of the registration was not until 4 months after the completion of the study.

2.2. Design

This trial followed a double-blind, randomized, cross-over design assessing the acute postprandial glycemic and insulinemic response to three beverages sweetened with allulose, sucrose, or a combination. Randomization of the sequence of the 3 beverages was done using a random sequence generator by the study statistician who was blinded to the identity of the participants and did not have contact with the participants. All participants, the clinic staff, the statistician, investigators, and outcome assessors were blinded to the identity of the beverages. An independent staff unrelated to the study who did not have contact with participants performed the allocation concealment by providing unique codes for each of the three beverages and prepared the study beverages for the clinic staff to dispense. The blinding codes for the beverages were kept in a sealed envelop under lock and key and were not broken until all participants had completed the study and all analyses were completed.

2.3. Study beverages

The allulose used in the study beverages is commercially available as allSWEET®, a registered trademark of Anderson Advanced Ingredients, and is manufactured and provided by Anderson Advanced Ingredients (Irvine, California, US). The study beverages consisted of either 15 g of allulose, 30 g of sucrose, or 15 g of allulose combined with 30 g of sucrose dissolved in 250 mL of room temperature water. All beverages were similar in appearance (colourless and clear), texture, and odour such that neither the participants nor clinic staff could identify the beverages. Study beverages were prepared up to two weeks in advance and kept sealed and refrigerated at 4 °C prior to serving.

2.4. Procedures

Participants attended the clinic at INQUIS after a 10–14 h overnight fast on three separate mornings separated by at least 2 days over a period of 2 to 6 weeks. Upon arrival at the clinic, participants were weighed and seated in a quiet area for the remainder of the visit. Participants were asked to avoid unusual levels of food intake or physical activity and refrain from drinking alcohol for 24 h before each visit. Participants that were not compliant with study protocols were rescheduled for a different day. Thereafter, two fasting blood samples were collected separated by five minutes apart. After the second blood sample, the study beverage was administered accompanied by 125 mL of water and participants were asked to consume both beverages evenly over 10 min. Additional blood samples were collected at 15, 30, 45, 60, 90, and 120 min after the first sip of the study beverage. No other food or drink was consumed during the 120-minute blood sampling period. After the last blood sample, participants were offered a small snack before leaving the clinic.

2.5. Outcomes

The primary outcome measure was the incremental area under the curve (iAUC) over 2 h for plasma glucose. The secondary outcome measures were the iAUC over 2 h for serum insulin and the incremental change at each time point along with the incremental peak rise in plasma glucose and serum insulin.

2.6. Glucose and insulin analysis

Blood samples were collected via finger-prick by placing 6–8 drops of capillary blood into each of two collection tubes. Samples for glucose were collected in microtubes containing heparin-fluoride and were immediately centrifuged and stored at 4 °C pending analysis within 5 days using the VITROS 350 Chemistry System (Ortho Clinical Diagnostics, Raritan, NJ). The typical CV for plasma glucose analysis is $<$ 2%. Samples for insulin were collected into plain microtubes and left to clot at room temperature for 30–60 min, then centrifuged, aliquoted in separate tubes, and stored at −20 °C pending analysis using the Human Insulin EIA Kit (catalog # 80-INSHU-E10.1, Alpco Diagnostics, Salem, NJ). The lower limit of detection for this assay is 18.0 pmol/L and the typical CV for serum insulin analysis is 7%.

2.7. Statistical analysis

The incremental areas under the blood glucose and insulin response curves were calculated ignoring the area below fasting using the trapezoid rule (Wolever, Jenkins, Jenkins, & Josse, 1991). For the purpose of the iAUC and incremental changes, fasting glucose and insulin were taken as the mean of the first measurement of the glucose and insulin concentrations at times −5 and 0 min. Individual glucose and insulin values which were greater than ± 2 standard deviations were considered outliers and were replaced with the mean value. Incremental peak rise was calculated as peak height (i.e., the maximum concentration achieved) minus the fasting concentration for the sucrose and allulose + sucrose beverages.

The primary and secondary outcomes were analysed using repeated-measures analysis of variance using the general linear model. After demonstration of significant heterogeneity, individual means were compared using Tukey's test to adjust for multiple comparisons. The criterion for statistical significance was 2-tailed $P < 0.05$. Data are presented as means and standard errors unless otherwise specified.

The power calculation was based on a 25% difference in iAUC for plasma glucose between groups in a two-tailed test with a significance level of 0.05 and a power of 80%. With an attrition rate of 10%, 15 participants were to be recruited into the trial.

3. Results

3.1. Participants

Sixteen individuals were randomized and enrolled in the trial between September 2021 and October 2021. Two participants were withdrawn, one because the participant developed a fever during the trial that was unrelated to the study beverages and was not able to confirm whether the fever was related to SARS-CoV-2; the other was withdrawn because their fasting glucose concentration was in the diabetic range (7.68 mmol/L) for one of the 3 test meals. No other adverse events were reported, and all beverages were well tolerated. Table 1 presents the characteristics for the 14 participants that completed the trial and were included in the final analysis.

3.2. Plasma glucose

Glucose iAUC after allulose + sucrose was 24% less than that after sucrose alone ($p < 0.05$). The iAUC after allulose alone was significantly less than that after both other treatments (Table 2). Individual responses for glucose iAUC are presented in Fig. 2, panels A and B. Peak rise of plasma glucose after allulose + sucrose was 46% less than that after sucrose alone ($p < 0.05$). Peak rise after allulose alone was significantly less than those after both other treatments (Table 2).

Fasting plasma glucose concentrations before allulose, allulose + sucrose and sucrose were 5.41 ± 0.09, 5.35 ± 0.09, and 5.51 ± 0.09 mmol/L, respectively, and did not differ significantly from each other. At 15, 30, and 45 min, incremental plasma glucose levels after the 3 study beverages differed significantly from each other with allulose < allulose + sucrose < sucrose. At 60 min, the incremental glucose level after allulose alone was significantly less than those after the other 2 treatments and by 90 min, after allulose + sucrose, it was significantly greater than that after both other treatments (Fig. 1A).

3.3. Serum insulin

Insulin iAUC after allulose + sucrose was 33% less than that after sucrose alone ($p < 0.05$) and significantly greater than that after allulose alone (Table 2). Individual responses for insulin iAUC are presented in Fig. 2, panels C and D. Insulin peak rise after allulose + sucrose was 43% less than that after sucrose alone ($p < 0.05$) and significantly greater than that after allulose alone (Table 2).

Fasting serum insulin concentrations before allulose, allulose + sucrose and sucrose were 62.7 ± 8.1, 57.3 ± 8.0, and 65.8 ± 7.9 pmol/L, respectively, and did not differ significantly from each other. At 15 and 30 min, incremental insulin levels after the 3 study beverages differed significantly from each other with allulose < allulose + sucrose < sucrose. At 60 and 90 min, the incremental levels after allulose alone were significantly less than those after the other 2 treatments and by 90 min, after allulose + sucrose, it was significantly greater than that after allulose alone (Fig. 1B).

Table 1
Participant characteristics.

	All	Female	Male
n	14	8	6
Age (years)	50.6 ± 14.8	53.8 ± 14.1	46.5 ± 16
Height (cm)	167.9 ± 9.9	175.7 ± 9.3	162.1 ± 5.3
Weight (kg)	77.1 ± 15.8	71.6 ± 13.6	84.4 ± 16.6
BMI (kg/m^2)	27.2 ± 4.1	27.2 ± 4.6	27.2 ± 3.6
Fasting Plasma Glucose (mmol/L)	5.41 ± 0.37	5.39 ± 0.39	5.43 ± 0.37
Fasting Serum Insulin (pmol/L)	11.52 ± 5.4	11.12 ± 3.49	12.04 ± 7.63

Data presented as means ± SD for n = 14 participants.

Table 2
Glucose and insulin incremental areas under the curve and peak rises over 120 min.

Outcomes (n=14)		30 g sucrose	15 g allulose	15 g allulose + 30 g sucrose
Plasma Glucose	iAUC (mmol × min/L)	112.8 ± 10.7^a	0.6 ± 0.3^b	85.8 ± 10.2^a
	Peak Rise (mmol/L)	3.15 ± 0.23^a	0.05 ± 0.02^b	1.69 ± 0.13^c
Serum Insulin	iAUC (pmol × hr/L)	213.2 ± 30.8^a	9.4 ± 2.8^b	141.9 ± 15.4^c
	Peak Rise (pmol/L)	273 ± 26^a	25 ± 6^b	156 ± 16^c

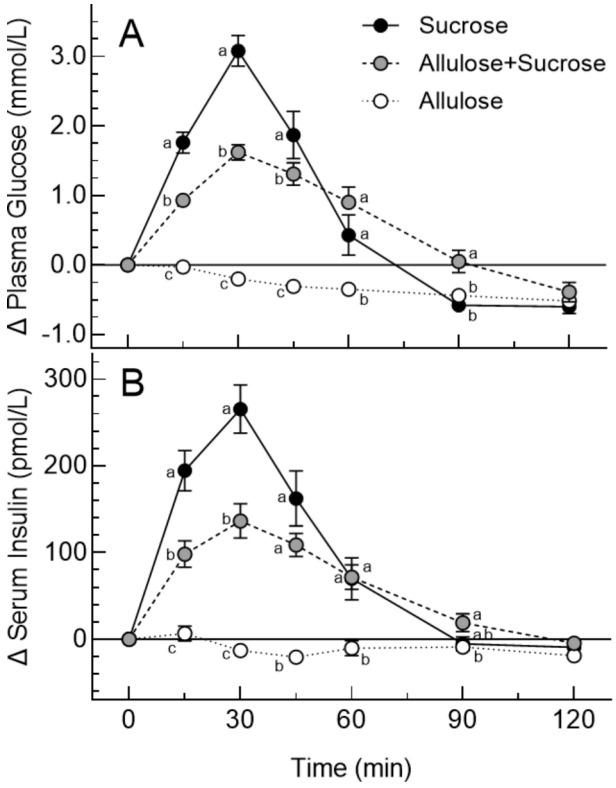

Fig. 1. Incremental plasma glucose (A) and serum insulin (B) responses in n = 14 individuals after consuming 30 g sucrose (black circles), 15 g allulose plus 30 g sucrose (grey circles), and 15 g allulose alone (white circles). Data are expressed as mean ± SEM. Means within each time point with different letter superscripts differ significantly by Tukey's test (2-tailed $p < 0.05$).

4. Discussion

Our results demonstrated that adding 15 g allulose to 30 g sucrose significantly reduced both glucose and insulin iAUCs in adults without diabetes. As anticipated, the consumption of allulose alone did not elicit any significant increase in either plasma glucose or serum insulin.

A recent systematic review and *meta*-analysis (SRMA) of the results of 10 comparisons from 5 controlled trials showed that adding 2.5–10 g allulose to test meals containing 75–87 g carbohydrate (0.03–0.13 g allulose per g carbohydrate) significantly reduced glucose iAUC by (mean [95% confidence interval]), −10 [-16, −4] % and a non-significantly reduced insulin iAUC by −7 [-17, +4]% (Braunstein et al., 2020). The 24% and 33% reductions in glucose and insulin iAUC we observed are considerably less than the SRMA's lower 95% confidence intervals suggesting that our results differ significantly from previous studies. This could be due to the fact that our study differed

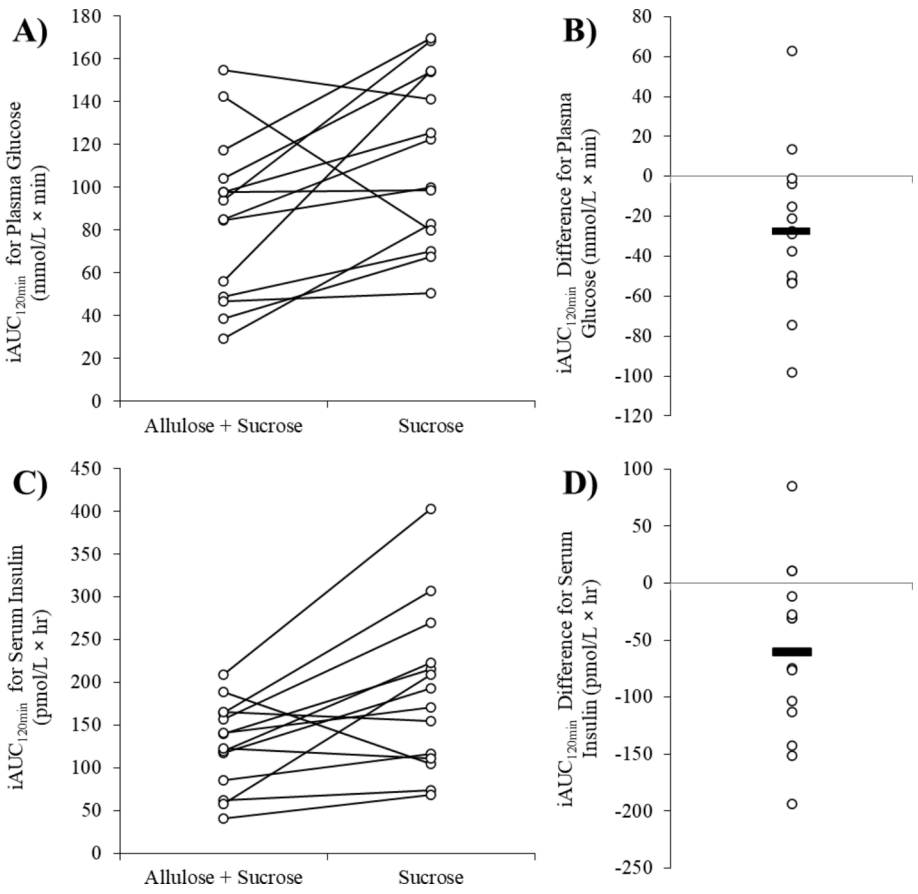

Fig. 2. Individual values in n = 14 participants for incremental area under the curve over 120 min ($iAUC_{120min}$) after allulose + sucrose or sucrose alone on A) plasma glucose or C) serum insulin and individual differences on $iAUC_{120min}$ for allulose + sucrose compared to sucrose alone on B) plasma glucose or D) serum insulin. Open white circles represent individual values within each intervention, circles connected by a black line belong to the same participant, and the black solid line in B) and D) represents the mean of all values.

from those cited in the SRMA in several respects. We included subjects without diabetes whose fasting glucose ranged from 4.97 to 5.86 mmol/L (none had pre-diabetes) whereas of the 10 allulose comparisons in the SRMA, 1 involved subjects with pre-diabetes and 2 had subjects with diabetes (Braunstein et al., 2020). However, there was no significant heterogeneity among the participant subgroups or among the 10 allulose comparisons for either glucose or insulin iAUC, suggesting that the difference in participants does not explain the larger effect we observed.

In addition, in our study allulose was added to sucrose while the SRMA studies the allulose was added to glucose (Braunstein et al., 2018; Noronha et al., 2018), maltodextrin (Iida et al., 2008), or mixed meals containing little (Hayashi et al., 2010) or no sucrose (Kimura et al., 2017) (G/MD/MM). However, there is no evidence that adding allulose to sucrose reduces postprandial glucose and insulin to a greater extent than adding it to G/MD/MM. Franchi et al. (Franchi et al., 2021) added 2.5, 5.0, 7.5, or 10 g allulose to 50 g sucrose (0.05, 0.1, 0.15, and 0.2 g allulose per gram sucrose) and resulting reductions in glucose and insulin iAUC were similar to or smaller than those from the 10 comparisons cited in the SRMA (Supplementary Fig. 1).

Our study differed also in the dosage used, we used a dose of allulose that, on a g/g carbohydrate basis, was 2.5 to 10 times greater than those in the literature. We believe this may account for the larger effect we found, but dose–response curves from the data in the literature are ambiguous in this respect. We plotted the effect size (expressed as ratio of the means, RoM) on allulose dose (expressed as g/g carbohydrate) for the 14 comparisons in the literature (Braunstein et al., 2020; Franchi et al., 2021) and found no dose–response for iAUC of glucose (r=+0.17, p = 0.55) or insulin (r=+0.02, p = 0.94) (Supplementary Fig. 1, panels A and C). Furthermore, although the effect size for iAUC in our study is larger than most comparisons in the literature, it is within their range, providing only weak evidence for a dose–response. On the other hand, there is a trend for a dose–response for peak rise of glucose (r = -0.43, p = 0.12) and insulin (r = -0.36, p = 0.21), and the larger effect sizes from our study are very close to the extrapolated regression lines (Supplementary Fig. 1, panels B and D). Further studies with a wider range of allulose doses than previously used are needed to establish whether there is a dose–response.

It is has been suggested that allulose reduces glycemic responses by enhancing hepatic glucokinase activity, a rate-limiting enzyme in glucose metabolism (Hossain et al., 2015; Shintani et al., 2017). This, in turn, would increase hepatic glucose uptake, promote glycogen synthesis, suppress hepatic glucose output, and reduce circulating glucose levels across both the early and late phases of the glycemic response, a pattern consistent with that seen when allulose was added to G/MD/MM test meals, but with our results where plasma glucose after allulose + sucrose fell more slowly after the peak and was significantly higher than after sucrose alone at 90 min. It has also been suggested that allulose increases the secretion of glucagon-like peptide 1, slowing gastric emptying and increasing insulin secretion to reduce blood glucose (Hayakawa, Hira, Nakamura, Iida, Kishimoto, & Hara, 2018; Iwasaki et al., 2018). However, if postprandial glucose was reduced by increased insulin this would lead to an insulin:glucose ratio > 1, a pattern inconsistent with our results and those in the literature showing that the slope of the regression of insulin on glucose does not differ significantly from 1 (Supplementary Fig. 2).

Allulose may reduce the rate of glucose absorption by inhibiting the activity of GLUT2 on the basolateral membrane (Hishiike et al., 2013). Treatments that reduce the rate of carbohydrate absorption such as sipping glucose slowly (Jenkins et al., 1990) or adding viscous fiber to a test meal (Wolever et al., 2018) flatten the glycemic response curve. However, if allulose competitively inhibited GLUT2, this would flatten the glucose response curve regardless of whether allulose was added to G/MD/MM or sucrose. We found that adding allulose to sucrose flattened the glycemic response, as did Franchi et al. who showed that

adding 2.5 to 10 g allulose to 50 g sucrose reduced both the peak rise and the rate of fall of plasma glucose after the peak (Franchi et al., 2021). However, the studies cited in the SRMA all showed that allulose elicited a small reduction in glucose peak rise with, if anything, a faster rate of fall of plasma glucose after the peak (Braunstein et al., 2018; Hayashi et al., 2010; Iida et al., 2008; Kimura et al., 2017; Noronha et al., 2018). Taken together, the evidence reviewed above suggests that allulose only flattens the glycemic response curve when added to sucrose. A possible mechanism to explain this is that allulose inhibits sucrase but not amylase activity, but no study to date has investigated this mechanism.

The present findings have several implications regarding the potential role of allulose as an effective sugar substitute. We demonstrated that 15 g of allulose alone was well tolerated and did not induce a glucose or insulin response, consistent with both acute and longer-term studies up to 48 weeks (Han et al., 2018; Hayashi et al., 2010; Iida et al., 2008; Tanaka, Kanasaki, Hayashi, Iida, & Murao, 2020). As allulose is 70% as sweet as sucrose with 90% less calories, partially replacing the sugars in foods and beverages with allulose would reduce their caloric and sugar content and reduce their glycemic and insulinemic impact, effects which might assist with weight management and the reduction of cardiometabolic risk factors. In a 12-week trial of 121 generally healthy individuals randomized to consume either 7 g or 14 g of allulose or a sucralose placebo daily, a modest reduction in fat mass was reported but no significant differences were observed in cardiometabolic parameters (Han et al., 2018). However, in a 48-week trial, 15 g of allulose consumed as a preload 30 min before breakfast significantly reduced fasting serum alanine aminotransferase and gamma-glutamyl transferase, and, in the subgroup of subjects with borderline diabetes, reduced 2-hour glucose AUC after a 75 g glucose challenge (Tanaka et al., 2020). It remains unclear if higher doses of allulose can be tolerated beyond the acute setting, as reports indicate gastrointestinal side effects may occur at doses beyond 30 g when consumed in a single meal (Daniel, Hauner, Hornef, & Clavel, 2021).

There are several limitations in the present trial. The acute controlled nature of this trial may not be reflective of typical consumption behaviours in a free-living population. Furthermore, this study provides no evidence that the reductions in glucose and insulin observed are sustainable with repeated administration or lead to long-term improvements in glycemic control. We only studied a single dose of allulose (0.5 g/g carbohydrate) that was $>$ 2.5 times larger than those used in previous studies and, thus, cannot conclude with certainty that a dose–response exists. Furthermore, we only explored the effect of consuming allulose with sucrose. It remains unclear if a similar dose of allulose will elicit a similar glucose blunting response when consumed with glucose, maltodextrin, or mixed meals and whether a dose–response exists with such test meals.

5. Conclusions

In conclusion, we demonstrated that 15 g of the commercially available allulose, allSWEET®, significantly lowered the overall glycemic and insulinemic response when added to a 30 g sucrose beverage. When consumed alone, 15 g of allulose did not increase postprandial glucose or insulin and all beverages were well tolerated. Our findings suggest that allulose may potentially have a beneficial role as a sugar substitute on acute glycemic control, but further studies are needed to assess the long-term effect of allulose on glycemic control in different populations.

Data statement

Due to its proprietary nature, the data described in the manuscript, code book, and analytic code will only be made available upon request pending application, approval, and confidentiality agreement.

Results are presented as means ± SEM for n = 14 subjects. Means with different lettered superscripts within each row differ significantly ($P < 0.05$, Tukey's test). iAUC – incremental area under the curve.

Registration: Clinicaltrials.gov NCT05185960.

Sources of Support

Anderson Global Group, LLC proposed the basic premise of the study and provided funding. Anderson Global Group, LLC was not involved in the collection, analysis, or interpretation of the data and had no restrictions regarding the publication of its findings.

Funding

Anderson Global Group, LLC.

Ethics Statement

As found in page 6 of the manuscript:

"This trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines and was approved by Advarra Institutional Review Board (Aurora, Canada) on September 7th, 2021 (Pro00056886). All participants provided written informed consent before entry into the trial and the trial was conducted at INQUIS Clinical Research (Toronto, Canada)."

CRediT authorship contribution statement

Fei Au-Yeung: Data curation, Formal analysis, Project administration, Writing – original draft. **Alexandra L. Jenkins:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Steve Prancevic:** Conceptualization, Resources, Writing – review & editing. **Esther Vissers:** Conceptualization, Resources, Writing – review & editing. **Janice E. Campbell:** Conceptualization, Data curation, Project administration, Writing – review & editing. **Thomas M.S. Wolever:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

Fei Au-Yeung, Alexandra L. Jenkins, Janice E. Campbell, and Thomas M.S. Wolever are employees of INQUIS Clinical Research, Ltd., Steve Prancevic is Executive Vice President of Anderson Global Group, LLC, and Esther Vissers is Managing Director of Anderson Advanced Ingredients, BV.

Data availability

Due to its proprietary nature, the data described in the manuscript, code book, and analytic code will only be made available upon request pending application, approval, and confidentiality agreement.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2023.105569.

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