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High fructose consumption with a high-protein meal is associated with decreased glycemia and increased thermogenesis but reduced fat oxidation: A randomized controlled trial

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ABSTRACT

Objectives: Fructose is often recommended due to its ability to lower glycemic response and its increased thermogenic effect. Additionally, proteins can reduce the glycemic response of carbohydrate-rich foods and have a high diet-induced thermogenesis (DIT). The aim of this study was to investigate whether the inclusion of fructose in a high-protein meal would demonstrate metabolic advantages.
Methods: Nineteen Asian women (body mass index 17–28 kg/m^2) consumed a low-glycemic index (GI; fructose) or high GI (glucose), high-protein breakfast followed by a standardized lunch in a randomized crossover design. Simultaneously, 8-h continuous glucose monitoring provided incremental area under the curve (iAUC) and 4-h indirect calorimetry provided DIT and respiratory quotient (RQ).
Results: The low GI diet resulted in a lower glucose iAUC (135 ± 25 versus 212 ± 23 mmol/L, $P < 0.05$) following breakfast, but no second-meal effect after the standardized lunch (217 ± 37 versus 228 ± 27 mmol/L, $P < 0.05$) compared with the high GI diet. Furthermore, 4-h DIT was greater (40.6 ± 2.3 versus 34.9 ± 1.8 kcal, $P < 0.05$) and RQ was increased after the fructose high-protein breakfast (0.047 ± 0.009 versus 0.028 ± 0.009, $P < 0.05$) compared with the glucose meal.
Conclusions: Fructose is an effective sweetener in reducing glycemia and increasing DIT in the presence of a high-protein diet. However, the reduced fat oxidation after high fructose consumption might present a risk for increased lipogenesis.

Introduction

Rapidly increasing rates of diabetes are a worldwide concern that is amplified in Asia where the population is more susceptible and transitions faster from prediabetes to diabetes [1–4]. The beneficial effects of low-glycemic index (GI) foods have been well recognized and evidence indicates that the consumption of these foods decreases postprandial blood glucose levels and fluctuations. As a result, two known risk factors, high insulin levels and oxidative stress, for the onset of type 2 diabetes and impaired glucose tolerance are improved with insulin levels becoming more stable and oxidative stress reduced [5–8].

Several sugar replacements have been developed in foods and drinks, as substitutes for sucrose, to reduce the GI. These include isomaltulose [9], polyols [10], soluble fibers [11], and fructose [12]. Fructose, the GI value of which ranges from 12 to 24 [13], has been incorporated into diets to lower the overall glycemic load. Because the relative sweetness of fructose is higher than glucose, the desired sweetness can be achieved with smaller amounts of fructose. Evidence is clear that fructose reduces postprandial glucose and insulin levels compared with other carbohydrates like sucrose and glucose [12,14]. Additionally, a greater postprandial thermogenesis has been observed compared with glucose, as explained by the low energy efficiency associated with fructose metabolism [15,16].

However, controversy around fructose exists and various studies have demonstrated increased postprandial triacylglycerols (TGs) in the blood after ingestion of fructose. In some acute studies where fructose was consumed as part of a fat-tolerance test or as an addition to a mixed meal, fructose increased postprandial TG

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concentrations compared with glucose or other carbohydrates [17,18]; however, other studies showed no differences [19–21]. Gallagher et al. showed that fructose in a moderate dose (<60 g) as part of a solid meal did not elevate TGs compared with sucrose and sucralose, but still lowered postprandial glucose [21]. Livesey and Taylor concluded from their meta-analysis that fructose had no adverse effects on postprandial TGs up to 50 g/d (moderate consumption) [22]. The discrepancies between these findings are likely to be due to differences in the dose of fructose consumed, duration of the diet intervention, food structure (solid or liquid form), sex, and to the use of different sugars as controls [17–21].

Given the recognition of the positive effects of fructose (i.e., decreased glycemic response and increased energy expenditure), further research is necessary to examine how fructose, when consumed with other macronutrients, notably protein and fat, may influence positive metabolic outcomes [23,24]. Proteins are known to be insulinotropic and can reduce the glycemic response of carbohydrate-rich foods [25,26]. Additionally, protein consumption results in higher diet-induced thermogenesis (DIT; 20–30%) than carbohydrates (5–10%) and fat (0–3%) [27]. To our knowledge, little research exists on the potential metabolic advantage that may accrue when fructose is consumed in the presence of a high-protein diet.

In the present study, we investigated whether the inclusion of fructose rather than glucose in a high-protein breakfast meal would result in beneficial effects over an 8-h period. To examine this, simultaneous measurements of postprandial glycemic response, DIT, and substrate oxidation were undertaken. In the present study, meal modulation focused on the addition of a high dose of fructose or glucose to create a low or high GI breakfast. The addition of 25 g of fructose to the breakfast represented a high daily fructose intake [22] and the amount of protein in the breakfast was high but in line with recent recommendations on protein intake for elderly individuals [28,29].

Materials and methods

Participants

Twenty-three healthy Chinese women between 23 and 70 y of age were recruited by a variety of methods that included flyers, online advertisements, and personal communications around the university campus. The women underwent an initial screening and measurements including anthropometry (height, weight, waist and hip circumference), fat percentage via bio impedance analysis (Tanita), blood pressure, resting heart rate, and fasting capillary blood glucose via finger stick using the HemoCue 201+Glucose analyzer (HemoCue, Ängelholm, Sweden). Additionally, a questionnaire on general health was completed. The women were not glucose-6-phospahate dehydrogenase deficient and were not allergic to the test food. Twenty-two women completed both the treatment diets; 1 dropped out because of time restraints.

The study was conducted at the Clinical Nutrition Research Centre, Singapore. Ethical approval of all procedures involving human subjects was obtained from the National Healthcare Group Domain Specific Review Board. Research procedures and trial protocols were followed in accordance with the good clinical practice guidelines and with the ethical standards in concordance to the Declaration of Helsinki, 1983. This trial was registered as NCT03309254 (clinicaltrials.gov). Written informed consent was obtained from all eligible participants before commencement.

Study protocol

The study consisted of two dietary treatments in a randomized, crossover design: A low-GI diet using fructose and high-GI diet using glucose and a high-protein breakfast followed by a standardized lunch. Participants attended two test sessions on 2 consecutive days, separated by a washout period of ≥3 d. Each test session would start at 1600 on day 1 and end on day 2 at around 1730 consisting of a 24-h continuous glucose measurement spanning the 2 d and a 5-h measurement of energy expenditure and respiratory quotient using an indirect calorimetry (IC) ventilated hood system on day 2 between 0800 and 1300. On days 1 and 2, the women were allowed to leave the research center at around 1730. The manipulated treatment meal included breakfast on day 2; whereas dinner on day 1 and lunch on day 2 were standardized over the two dietary treatments. During the test sessions, participants were only to eat the provided foods. Additionally, they had to log their total food intake on day 1 and were instructed to refrain from strenuous physical activity. Figure 1 shows a schematic overview of the study design. Online computer software was used for simple randomization of the sequence of the treatment diets (www.randomizer.org).

Treatment meals

The study consisted of a low-GI and a high-GI breakfast that was high in protein (Table 1). The glycemic load of the treatment meals was modulated by adding glucose (high GI) or fructose (low GI). The standardized dinner consisted of ready-to-eat teriyaki chicken with rice (Charoen Pokphand, Thailand), chocolate malt drink (Nestle, Singapore), and a red apple. The entire meal reflected a typical local rice-based meal accompanied by a drink and dessert (energy: 836.3 kcal; protein: 167.1 kcal; fat: 137.3 kcal; carbohydrate: 531.9 kcal). The standardized lunch consisted of two slices of plain prata (Fairprice, Malaysia) and a cup of strawberry yogurt drink (Marigold, Malaysia; energy: 455.6 kcal; protein: 37.6 kcal; fat: 111.6 kcal; carbohydrate: 306.4 kcal). High GI breakfast foods included Black Forest smoked turkey breast (Dietz & Watson, Philadelphia, PA, USA), roasted almonds (Camel, Singapore), glucose (TSP Solutions, Singapore), Gardenia white bread (Gardenia, Singapore), and chamomile tea (Dilmah, Sri Lanka). Low GI breakfast foods were Black Forest smoked turkey breast (Dietz & Watson), Gardenia low-GI multigrain bread (Gardenia), roasted cashews (Camel), fructose (KRYSTAR 300, Tate & Lyle, Dayton, OH, USA), and chamomile tea (Dilmah).

Glycemic measurements

Continuous glucose monitoring (CGM; iPro2 Professional CGM-Medtronic MiniMed, Northbridge, CA, USA) was used to measure glycemic response. The insertion of the CGM sensor was performed on day 1 at 1600 and the sensor was removed on day 2 at 1730. Data was collated and processed using online software (Medtronic Diabetes CareLink iPro; carelink.minimed.eu). The data reported in the

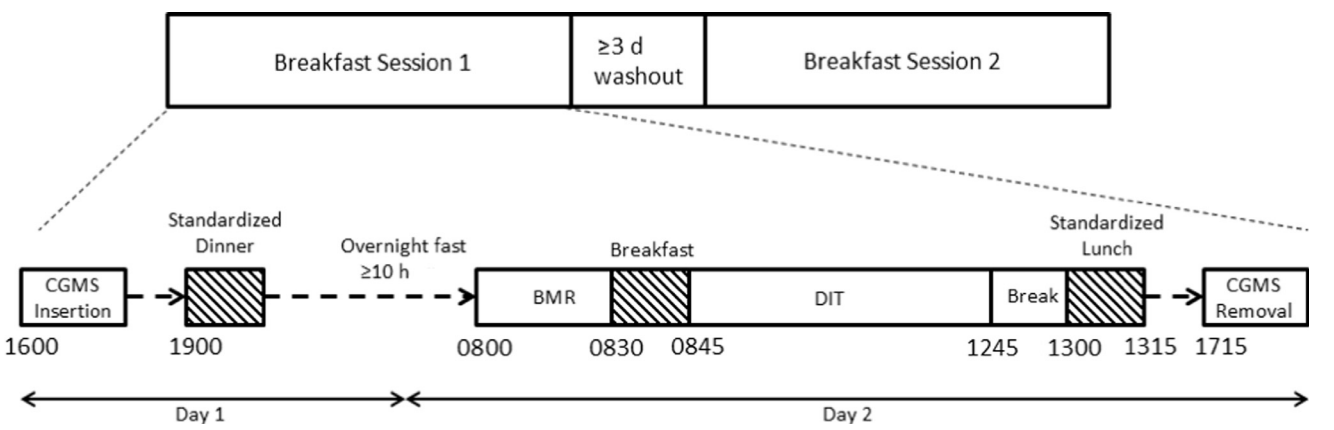

Fig. 1. Schematic overview of the study design. BMR, basal metabolic rate; CGMS, continuous glucose monitoring sensor; DIT, diet-induced thermogenesis.

Table 1
Meal composition of the low-GI and high-GI, high-protein breakfast

	Item	Serving Size	Calories (kcal)	Protein (g)	Total fat (g)	Saturated fat (g)	Carbohydrates (g)	Sugars (g)	GI	Dietary fiber (g)
High-GI breakfast	Smoked turkey breast	7 slices	117	25.7	1.2	0	0	0	0	
	Roasted almonds	15 g	87	3.6	7.8	0.6	0.6	0	0	
	White bread	2 slices	150	5.6	1.1	0.5	31.2	0	79	1.4
	Glucose	25 g	100	0	0	0	25.0	25	100	
	Chamomile tea	300 mL	0	0	0	0	0.0	0	0	
	Total		454	34.9	10	1.1	56.8	25	87	1.4
				30.8%	19.9%		50.1%			
Low-GI breakfast	Smoked turkey breast	6 slices	100	22	1	0	0	0	0	
	Roasted cashews	10 g	60	1.9	4.6	0.9	2.8	1.05	22	
	Multigrain bread	2 slices	171	9.8	3.2	0.6	25.7	2.9	55	5.1
	Fructose	25 g	100	0	0	0	25	25	25	
	Chamomile tea	300 mL	0	0	0	0	0	0	0	
	Total		431	33.7	8.8	1.5	53.5	29	39	5.1
				31.3%	18.4%		49.6%			

GI, glycemic index

present study represent interstitial glucose readings recorded every 5 min for a total of 8 h of postprandial data after the test meal. During each test session, the CGM sensor was calibrated against finger-stick blood glucose measurements before every meal and before going to bed using a blood glucose meter (OneTouchUltra2, LifeScan, Inc., Milpitas, CA, USA). A crossover design with a minimum of 8 participants would be sufficient to detect a 15% change in area under the glucose curve with a power of 0.85 at a significance level of 0.05 [30].

Energy expenditure and substrate oxidation

Basal metabolic rate (BMR), DIT, and respiratory quotient (RQ), were measured by continuous open-circuit IC using a ventilated hood system (Quark CPET, COSMED, Rome, Italy) from 0800 to 1300 on day 2. Participants were required to undergo a minimum of 10-h overnight fast and refrain from intensive physical activity for 24 h before the measurement. On day 2, the women reported to the Clinical Nutrition Research Centre at 0800. They were instructed to travel by public transport or car and to use the elevator to avoid physical activity that would increase BMR. They were then allowed to lie quietly for 15 min before measurement of BMR for 30 min via IC. For this, a transparent Perspex ventilated hood was placed over each participant's head, through which outside air was drawn by a pump. The flow rate (20–40 L/min) was measured and adjusted to keep the difference in carbon dioxide readings between inspired and expired air within the range of 0.8% to 1.2%. Air leaving the hood was analyxed for oxygen and carbon dioxide by a paramagnetic analyzer and infrared analyzer,respectively. Flow and gas analyzers were calibrated with dried standard gas mixture (16.01% oxygen, 4.98% carbon dioxide) and dried atmospheric air (20.93% oxygen, 0.03% carbon dioxide). The validity of the ventilated hood system is tested biweekly by ethanol combustion tests. All measurements were carried out in a quiet room with an ambient temperature between 23 and 25°C, barometric pressure of 750 to 770 mm Hg. and constant humidity of 60%. During the measurements, the participants were lying quietly and motionless in a semi-supine position, and were kept awake. Oxygen and carbon dioxide concentrations of the outflowing air and the airflow rate through the hood were measured every 5s to obtain oxygen consumption and carbon dioxide production. Respiratory measurements during the first 5 min were discarded to eliminate effects of subject habituation to the test procedure. Only steady-state periods of measurements of $\geq$15 min were used to calculate BMR. BMR was calculated from oxygen consumption and carbon dioxide production by the Weir equation and RQ was the ratio of oxygen over carbon dioxide [31]. Within 15 min of the completion of the BMR measurement, the participants consumed the test breakfast, followed by a 4-h measurement of DIT. During the measurement of DIT, the participants were also lying quietly and motionless in a semi-supine position, and were kept awake. They were allowed up for three 5-min toilet breaks during the measurement of DIT and data of these intervals was discarded. DIT was defined as the increase in energy expenditure above BMR and was expressed as the percentage of the energy intake for breakfast (test meal) and as kcals expended over 4 h above BMR.

Appetite

Participants were asked to rate their appetite before and every 30 min after the test breakfast by marking a vertical line on a 100-mm visual analog scale (VAS). Appetite questions included fullness, hunger, possible amount to eat, and desire to eat.

Statistical analysis

All statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). Data and figures were processed in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA). Values were presented as mean ± SD unless otherwise stated. Three women were excluded from data analysis as baseline data for energy expenditure and/or substrate oxidation were abnormal. Before statistical analysis, the normality of the data was assured using the Shapiro–Wilks test, by checking the significance, histogram, and QQ plot. The primary outcome of this study was to determine how the inclusion of fructose or glucose in a high-protein breakfast would effect postprandial blood glucose fluctuations after breakfast and lunch, as well as energy regulation after breakfast. The baseline glycemic response was calculated as the 2-h average of CGM interstitial glucose readings under the fasting state before the breakfast meal. The baseline value was then used to convert every 5-min reading of 8 postprandial hours of CGM interstitial glucose data as the "change in glucose." The other primary outcome measure was the total glucose response expressed as the incremental area under the curve (i.e., the GR iAUC) calculated using the trapezoidal rule [32,33]. The change in glucose values were important for further analyses such as the GR iAUC calculations, CGM glucose curve construction, and statistics. Baseline RQ and BMR were based on 10-min steady-state measurements in a fasted state. Subsequently, postprandial changes in RQ values and DIT were calculated for 4 h. Paired *t* test was performed to test the differences in the GR, GR iAUC, DIT, RQ, and VAS ratings between low- and high-GI treatments over 24 h and during the postprandial period. Alpha was set at 0.05 for statistical analyses.

Table 2
Baseline participant characteristics as mean ± SD (n = 19).

Characteristic (n = 19)	Mean ± SD
Age (y)	50 ± 12
Height (m)	159.9 ± 6
Weight (kg)	59.70 ± 9.76
BMI (kg/m^2)	23.3 ± 3.1
Fat percentage (%)	30.1 ± 5.8
Waist circumference (cm)	74.6 ± 9.7
Hip circumference (cm)	94 ± 8.7
Waist/hip ratio	0.79 ± 0.07
Fasting blood glucose (mmol/L)	5.2 ± 0.4
BMR (kcal/d)	1198 ± 141

BMI, body mass index; BMR, basal metabolic rate

Results

Participant characteristics at baseline are presented in Table 2.

Glycemic response was significantly lower after the low-GI fructose breakfast than after the high-GI glucose breakfast (glucose iAUC 135 ± 25 versus 212 ± 23 mmol/L, $P < 0.05$). There was no difference in glycemic response after the standardized lunch for either condition (glucose iAUC 217 ± 37 versus 228 ± 27 mmol/L, $P > 0.05$). These results are represented by the change in glucose from baseline over the 8-h measurement period (Fig. 2A) and in glucose iAUC after breakfast, lunch, and the sum (Fig. 2B).

DIT was significantly higher over 4 h after the high-protein fructose breakfast (9.4% ± 0.2%) compared to the high-protein glucose breakfast (7.7% ± 0.1%; DIT: 40.6 ± 2.3 versus 34.9 ± 1.8 kcal, $P < 0.05$). Moreover, the high-protein fructose breakfast resulted in a significantly higher 4-h increase in RQ than the high-protein glucose breakfast, indicating higher carbohydrate oxidation (d RQ: 0.047 ± 0.009 versus 0.028 ± 0.009, $P < 0.05$; Fig. 3). No relationships were observed between glycemic response after breakfast and lunch and the BMR, DIT, fasting RQ, and change in RQ. Results from the two sessions showed the following within-subject correlation for BMR ($R^2 = 0.84$; $P < 0.005$), fasting RQ ($R^2 = 0.55$; $P < 0.005$), change in RQ ($R^2 = 0.34$; $P < 0.05$), and DIT ($R^2 = 0.07$; $P < 0.05$).

No significant differences were observed over the total 4 h for mean changes in rated fullness, hunger, possible amount to eat, and desire to eat between the high-protein fructose and high-protein glucose breakfast.

Discussion

The present study investigated whether the inclusion of fructose compared with glucose in a high-protein breakfast meal resulted in beneficial effects on glycemia and energy expenditure over an 8-h period. The addition of a high dose of low-GI fructose to a high-protein breakfast compared with high-GI glucose resulted in a lower glycemic response following the 4 h after the meal. It was also accompanied by a greater DIT, a greater increase in carbohydrate oxidation, and lower fat oxidation. Interestingly, the decreased glycemic response afte the high-protein fructose breakfast did not carry over after the standardized lunch.

The present study showed that the addition of fructose to a high-protein breakfast resulted in acutely decreasing the glycemic response over the following 4 h compared with glucose and a high-protein breakfast. The results are in line with previous research indicating that fructose can be incorporated into diets to lower the overall GI of a meal [12,14]. Increased intake of protein has been shown to result in a decreased glycemic response [34,35]. The present results indicate that in addition to a high dose of protein, a high dose of fructose lowers the GI more than glucose. Some studies have shown that a reduced glycemic response as a result of a low-GI meal is able to carry over to the second meal [9,36]. However, no second-meal effect was observed in the present study. The second-meal effect may depend on the study design and also on the component used to reduce the GI of a meal as a second-meal effect has been observed with isomaltulose [9,36] but not with soluble fiber [37]. This observation suggests that not all carbohydrates used to reduce glycemia in a breakfast meal have a second-meal effect on the lunch.

In line with previous findings, a greater postprandial thermogenesis and more carbohydrate oxidation were observed after the fructose breakfast than after the glucose breakfast [15,16]. Greater DIT and carbohydrate oxidation can be explained by the lower energy efficiency and quicker metabolism of fructose. Fructose is phosphorylated by fructokinase, which is ~10 times more active than glucokinase and hexokinase, required for glucose phosphorylation [38]. Fructose also avoids phosphofructokinase, the first-rate limiting enzyme of glycolysis [39]. Glycogen formation in the liver from fructose requires cleavage of fructose to three-carbon compounds first and subsequent glycogen formation, whereas glucose can be converted directly to glycogen, doubling the required

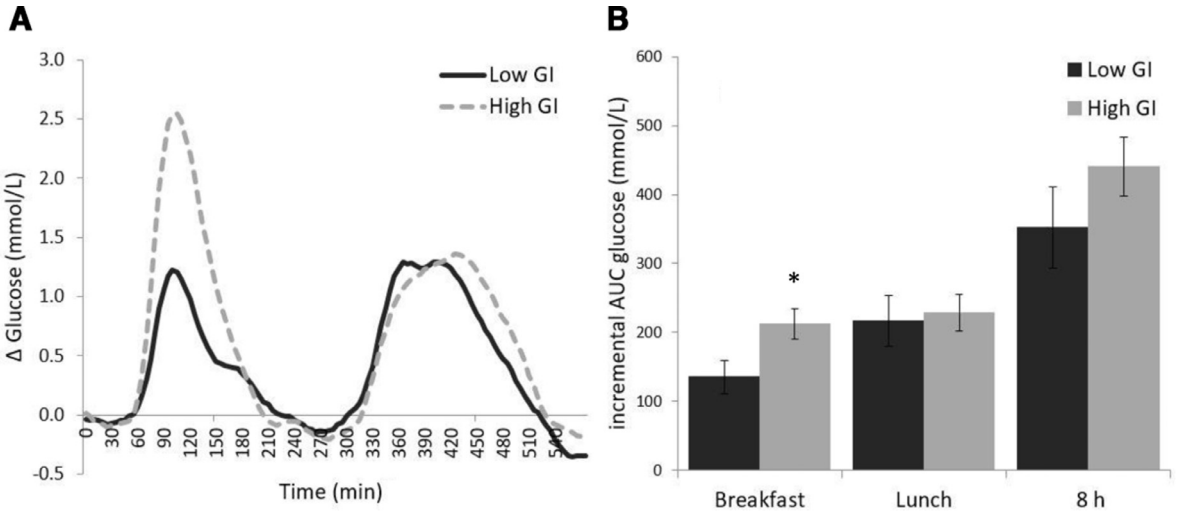

Fig. 2. Mean (± SEM) change in glucose concentration from baseline (**A**) and incremental area under the curve (± SEM) for glucose (**B**) following a low- or high-GI high-protein breakfast, a standardized lunch, and the total 8 h (n = 19). GI, glycemic index. *$P < 0.01$.

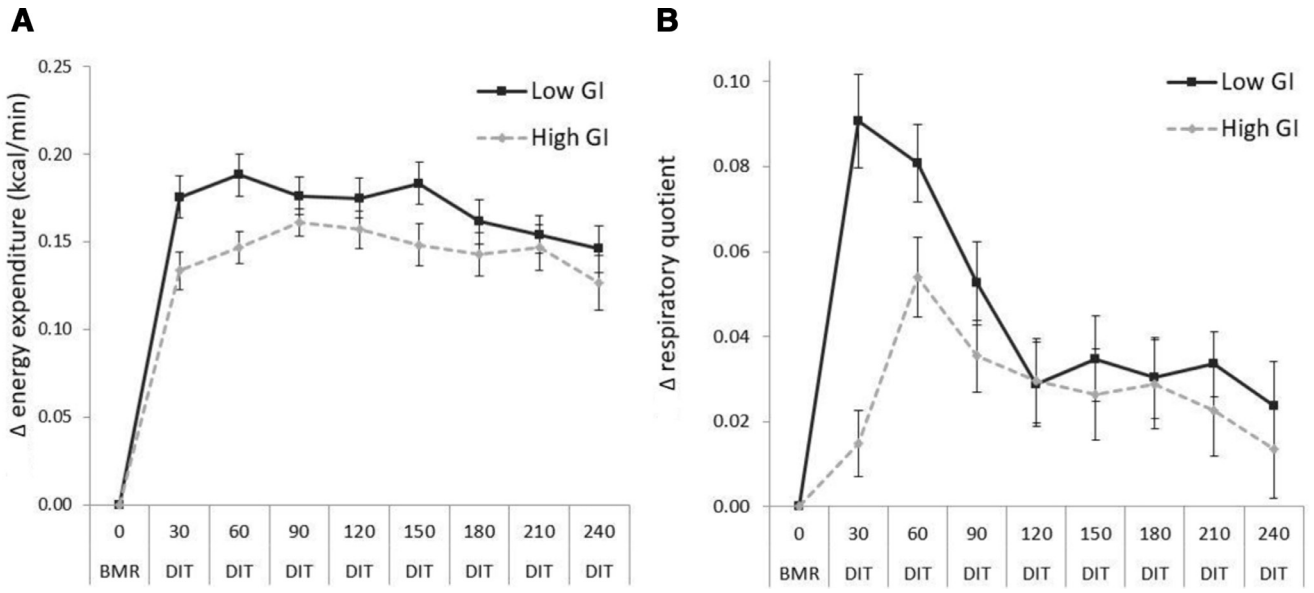

Fig. 3. Mean (± SEM) change in energy expenditure (**A**) and respiratory quotient (**B**) from baseline between the low- and high-GI breakfast over 4 h postprandially (n = 19). GI, glycemic index.

adenosine triphosphate molecules from two to four for fructose [40]. Therefore, glycogen synthesis from fructose requires more energy than formation from glucose. Consequently, fructose and sucrose result in a greater DIT response than glucose, starch, and low-GI sweeteners like isomaltulose [9,16]. Previously, Hall et al. demonstrated that the current obesogenic epidemic may be explained by only an excess of 7.5 kcal/d. Results from the present study suggested that DIT was almost 2% higher when the breakfast was supplemented with fructose rather than glucose. Hence, with its thermogenic properties on DIT, fructose might play a role in weight regulation and maintenance. However, in a study in overweight and obese men and women by Cox et al., resting energy expenditure was decreased after 10 wk of increased fructose consumption [41]. The paucity of prolonged studies warrants further research on the effect of fructose on long-term energy balance.

Contrary to other low-GI sugar replacements like isomaltulose or low-GI foods [30,36], no increased fat oxidation was observed after a low-GI breakfast with a large dose of fructose compared to the high-GI breakfast with glucose. The current results showed a greater increase in RQ afte the fructose- containing breakfast, which indicates higher carbohydrate oxidation and lower fat oxidation, similar to previous findings [16]. Our results in an acute setting are in line with a 9-d study from Schwarz et al. [23], who found increased de novo lipogenesis and decreased fat oxidation after consumption of a high-fructose diet in the absence of a positive energy balance. Schwarz et al.'s diet provided 25% of the energy from fructose, which is comparable to 23% of the energy coming from fructose in our high-protein breakfast. Furthermore, lower fasting and lower 24-h fat oxidation have been linked to prospective weight and fat gain over the following 12 to 24 mo [42,43]. As indicated by Stanhope et al., literature on the effect of fructose is not conclusive as some show a direct negative effect on health; whereas others show increased risk for weight gain as the mediator for negative effects on health [44].

No differences in appetite perception were found after the high-protein fructose and glucose breakfasts. Previous studies reported satiating effects of fructose in comparison with glucose without apparent effects on satiety peptides [45]. Other studies found increased hunger after meals with high-fructose beverages compared with glucose but only in restrained eaters [18]. Protein is well known for its satiety effect and is more satiating than fat and carbohydrates [46]. In the present study, it is probable that the high-protein component of the breakfast may have caused the effect on appetite without an additive effect of fructose or glucose.

Although the study was performed only with women, previous studies have demonstrated a similar effect in groups including both men and women [47,48]. Serum insulin, triacylglycerol, or non-esterified fatty acid measurements could have significantly strengthened the study and further supported the link between glycemic response and substrate oxidation. The CGM sensor is minimally invasive compared with an 8-h indwelling catheter. This benefit outweighed the potential lag in response of interstitial fluid glucose levels and by representing glycemic response as iAUC, lag plays a minor role. It cannot be excluded that lipogenesis contributed to greater DIT after fructose ingestion, but the contribution was probably not substantial in the present study [49]. The ratio of plant to animal protein was similar but not equal between the two diets. From literature, it is known that animal protein can potentially increase DIT more than plant protein, whereas plant protein can potentially reduce the glycemic response more [50,51]. The plant-to-animal protein ratio is unlikely to explain the current results as the difference between the two diets is minimal and f.e. the low GI diet with less animal protein resulted in higher DIT. The dose of protein during breakfast was high, ± 35 g, which translates to ~0.57 g/kg of protein. A dose of 0.57 g/kg for breakfast equates to ~1.6 g/kg per day with three meals, which is in line with recent recommendations on protein intake for elderly individuals [28,29]. The dose of fructose in the present study was 25 g during breakfast, which is considered high [22]. With equal doses during lunch and dinner, the dose would equate to 75 g/d and would be in the middle of the high range according to the classifications by Livesey and Taylor in their 2008 meta-analysis [22]. The present study focused on the consumption of fructose versus glucose in combination with a high-protein diet. Future research needs to confirm whether fructose can have an additive beneficial effect to high protein on glycemic response and DIT.

Conclusions

Unique to fructose is the combined effect of a decreased glycemic response and increased thermogenic response, distinct from general low-GI foods and low-GI sweeteners like isomaltulose [12,14–16]. However, the addition of a large dose of fructose to a high-protein meal resulted in decreased fat oxidation, which might be a risk factor for fat deposition. Results from the present study indicated that despite fructose being an effective sweetener in reducing glycemia and increasing DIT in the presence of a high-protein diet, further research is necessary to determine whether the addition of other food ingredients or different food structures also can limit the decrease of fat oxidation, thereby making fructose another ingredient that may be considered as a tool in the battle against obesity [9–11].

Acknowledgments

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