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Effect of a moderate dose of fructose in solid foods on TAG, glucose and uric acid before and after a 1-month moderate sugar-feeding period

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Abstract

There are few data on the effects on TAG, glucose and uric acid of chronic consumption of a moderate dose of fructose in solid foods. Twenty-eight participants with prediabetes and/or obesity and overweight commenced the study (BMI 32·3 kg/m^2, age 44·7 years, fasting glucose 5·3 (SD 0·89) mmol/l and 2-h glucose 6·6 (SD 1·8) mmol/l). Twenty-four men and women who completed the study consumed, in random order, two acute test meals of muffins sweetened with either fructose or sucrose. This was followed by 4-week chronic consumption of 42 g/d of either fructose or sucrose in low-fat muffins after which the two meal tests were repeated. The sugar type in the chronic feeding period was also randomised. Fasting TAG increased after chronic consumption of fructose by 0·31 (SD 0·37) mmol/l compared with sucrose in those participants with impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) ($P = 0·004$). Total cholesterol (0·33 mmol/l), LDL-cholesterol (0·24 mmol/l) and HDL-cholesterol (0·08 mmol/l) increased significantly over the 1- month feeding period with no differences between muffin types. Fasting glucose was not different after 1 month of muffin consumption. Uric acid response was not different between the two sugar types either baseline or 1 month, and there were no differences between baseline and 1 month. The increase in fasting TAG in participants with IFG/IGT suggests the need for caution in people at increased risk of type 2 diabetes.

Key words: **TAG: Uric acid: Glucose: Fructose: Sucrose: Solid foods**

In meta-analyses of prospective studies, greater weight gain and increased type 2 diabetes and CHD have been linked with the consumption of beverages containing either sucrose or high-fructose maize syrup[1–3]. It has been shown that fructose in sweetened beverages providing 25 % of energy requirements that induces weight gain increases serum TAG more than a similar amount of glucose over 10 weeks[4]. In contrast, fructose did not have any disparate effects compared with other types of carbohydrate in a meta-analysis of short-term isoenergetic studies, provided weight gain did not occur[5]. Despite the increase in TAG, fructose intake in excess of requirements does not increase liver or muscle fat or enhance insulin resistance in liver, muscle or adipose tissue compared with glucose[6,7]. Fructose as part of a fat tolerance test[8,9] or with a mixed meal increased postprandial TAG levels in some[10–12] but not all studies[13,14]. Substitution of fructose for starch in type 2 diabetes lowers HbA1c and fasting glucose when the amount is low, usually <40 g/d[15]. This occurs because fructose stimulates glucokinase regulatory protein-1[16] and increases glycogen synthesis 4-fold[17] leading to a lower glucose response in an oral glucose tolerance test to which 7·5 g fructose has been added. However, it has been observed that chronic fructose feeding in beverages for 10 weeks increases daily uric acid profiles in overweight and obese men and women compared with isoenergetic glucose feeding[18]. The American Diabetes Association recommends that free fructose (naturally occurring in foods such as fruit) be kept below 12 % of energy to minimise TAG elevation[19]. Non-energetic sweeteners are currently under scrutiny because of their association with type 2 diabetes[1] and with enhanced glucose absorption in healthy volunteers[20] so there may be a potential role for low dose fructose as a sweetener at levels that do not exceed recommendations.

There is a lack of data on the effects of fructose consumed added to solid foods at <12 % of energy. In the present study, we aimed to assess the metabolic responses to muffins containing 42 g sucrose or 42 g fructose before and after a 1-month chronic consumption period in which muffins are added to the normal diet. We aimed to see if fructose could substitute for sucrose in people with obesity and prediabetes without adverse metabolic effects. To our knowledge, no study has previously used fructose solely in a solid form and compared it with sucrose which is the most commonly used table sugar.

Abbreviations: iAUC, incremental AUC; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

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Materials and methods

Participants

Participants were recruited from the University of South Australia's database of volunteers.

Selection criteria

Participants were either overweight or obese (BMI > 25 kg/m^2), over 18 years and not pregnant or breast-feeding. People with impaired fasting glucose (IFG glucose > 5·5 mmol/l) or impaired glucose tolerance (IGT 2-h glucose 8–11·1 mmol/l) after 75 g oral glucose tolerance testing using finger prick glucose values were included. Exclusion criteria were known type 2 diabetes, known kidney, liver or heart disease and cancer in treatment phase. Subjects on any medication were also excluded. Participants self-reported their health status.

Study plan

Participants attended the research clinic at the University of South Australia from February to June 2016 for baseline visits on two mornings 1 week apart and were randomised to consume after an 8 h fast, two muffins over a period of 15 min (muffin S – sucrose 1 week, followed by muffin F – fructose the following week or vice versa). Subjects were asked to avoid alcohol and strenuous exercise in the 24 h preceding the tests. Following the baseline tests, participants were asked to consume two low-fat muffins/d for 4 weeks before repeating the acute studies (again in random order) on two mornings 1 week apart. They were randomly allocated to consume either sucrose or fructose muffins for this month using a computerised randomisation programme by a technician not involved in measurement or analysis of results. The research personnel enrolling the participants and providing the muffins were unaware of the muffin code as were the participants.

At each of the visits, before and following the consumption of the test muffins, we took venous blood samples at regular interval (every 30 min for 180 min) and measured glucose, TAG and uric acid levels on a Konelab using standard commercial kits.

Composition of muffins

Muffins were cooked in the research kitchens at the University of South Australia. The muffins for the acute studies (before and after the chronic phase) each contained 21 g sucrose or fructose and 21 g of polyunsaturated fat while the muffins for the chronic phase contained the same amount of sugar but had a lower amount of fat at 11 g per muffin to minimise the energy load. The two muffins/d for the chronic phase represented a total of 17–25 % of daily energy intake depending on sex with the sugar at 6–8 % of energy. No instructions were given about replacement of foods with muffins and it is possible energy intake could have increased by 17–25 % for 1 month and induced measurable weight gain. No measurement of energy or sugar intake was made before or during the intervention to ensure the intervention was as free-living as possible. No food records were collected.

Ethics

The research was conducted according to the Declaration of Helsinki. The protocol was approved by the Human Ethics Committee of the University of South Australia (application ID 200757) and all volunteers gave written informed consent. The trial was registered by the Australian New Zealand Clinical Trials Registry (ANZCTR www.anzctr.org.au/) ACTRN12 618000125224.

Statistical analysis plan

Data shown are means and standard deviations unless stated otherwise. Data were analysed by repeated-measures ANOVA of incremental AUC (iAUC) of TAG and uric acid with type of chronic sugar as a between subject factor and weight as a covariate in a secondary analysis. Statistics were obtained for acute sugar type separately at baseline and at 1 month, and month by acute sugar in a final model which also examined the between subject factor of chronic sugar type. Data were significant if P was <0·05. No adjustment was made for multiple tests. *Post hoc* analysis was performed contrasting people with IFG/IGT and those without, and weight was included as a covariate in secondary analysis. The data analyst was blinded to the code for acute and chronic sugar until analysis was completed.

Power analysis

Power analysis was based on our previous publication[21] and showed that twenty-four subjects were required to complete the study to detect a difference in TAG iAUC of 30 % (80 % power, $P < 0·05$, SD of difference 1·2 mmol/l 3 h). The primary endpoints were the contrasts between sugars for incremental TAG AUC and uric acid AUC at baseline and 1 month. Secondary endpoints were fasting TAG levels at 1 month as well as sugar, sugar by time and sugar by time by month for each individual time point value for TAG, glucose and uric acid. For the secondary endpoint, the study had enough power to detect a 35 % difference in fasting TAG between sugars with a SD of 30 %.

There was no statistical difference in characteristics between the forty eligible for the study as assessed by email questionnaires and the twenty-four who completed and whose data were analysed. Thirty-one of those invited to participate accepted the invitation and were randomised, three failed to commence and four dropped out. The characteristics of those invited to participate who declined initially (n 9) or dropped out (n 3 did not attend the first visit after randomisation, n 4 did not complete the intervention) were similar to the completers: age 56 years, BMI 31 kg/m^2, fasting glucose 6·0 mmol/l and 2-h glucose 8·3 mmol/l.

Results

Forty potential participants from the University of South Australia's database of volunteers were invited to participate. They had previously provided consent to be contacted about upcoming studies. Thirty-one volunteers accepted the invitation and were enrolled in the study, twenty-eight commenced the study and three failed to attend their first appointment.

Twenty-four participants completed the study. The drop-out rate was *n* 4, 14 %. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in Fig. 1.

Fifteen men and thirteen women commenced the study (Table 1). Fifteen participants had IFG (>5·5 mmol/l) or IGT and three had both; ten had normal glucose tolerance and seventeen were obese. The twenty-eight participants who commenced had an average BMI of 32·3 kg/m^2, age of 44·7 years, a fasting glucose of 5·3 (SD 0·89) mmol/l and a 2-h glucose of 6·6 (SD 1·8) mmol/l. There was no statistical difference between those allocated to fructose muffins and those allocated to sucrose muffins. Four dropped out after the first two acute meal studies. Seventeen people with IFG/IGT and seven with normal glucose tolerance completed the study. Weight gain over

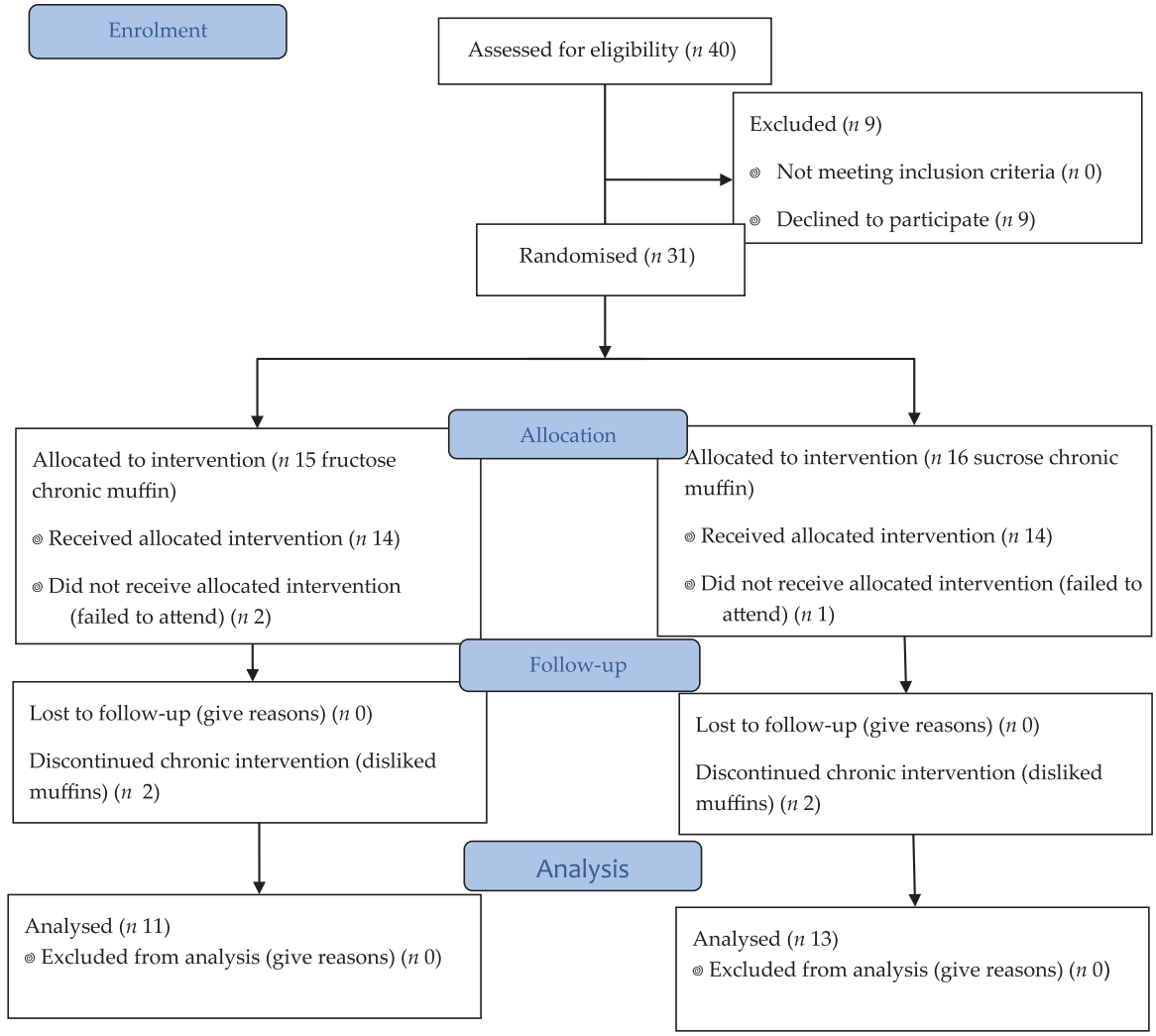

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Table 1. Baseline characteristics of completers
(Mean values and standard deviations; numbers of participants)

	Normal glucose tolerance		Impaired glucose tolerance		Chronic sugar fructose		Chronic sugar sucrose	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
IFG/IGT (*n*)			17		8		9	
Normal glucose (*n*)	7				3		4	
Sex (*n*)	3 M, 4 F		10 M, 7 F		6 M, 5 F		5 M, 8 F	
Age (years)	48·5	18·2	53·1	16·5	55	18	47	15
BMI (kg/m^2)	31·2	3·3	32·1	4·9	31·3	4·9	32·5	3·9
Fasting glucose (mmol/l)	5·0	0·5	6·0	0·8	5·6	0·8	5·8	0·9
2-h glucose (mmol/l)	6·1	1·2	7·9	1·7	7·8	2·0	7·0	1·5
Fasting TAG (mmol/l)	1·14	0·26	1·47	0·92	1·37	0·92	1·32	0·64

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; M, male; F, female.

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1 month in the twenty-four (eleven fructose, thirteen sucrose) who completed this section was 0·53 kg ($P = 0·2$) with six of this group losing weight. Volunteers could not distinguish the type of sugar in the muffins as assessed by a questionnaire on completion of the study.

TAG

Fasting TAG. Data were analysed using repeated-measures ANOVA with month (0, 1), sugar (fructose or sucrose) and IFG/IGT (yes/no) as factors. There was a strong interaction between IFG/IGT and month ($P = 0·001$) and a weak interaction between month and chronic sugar ($P = 0·036$) with higher values seen in the IFG/IGT group. Analysing only those with IFG/IGT (n 17), there was a strong effect of month ($P < 0·001$) with an increase from month 0 to month 1 and an interaction between month and chronic sugar ($P = 0·004$) with increases at month 1 seen with fructose. Change in weight over the month was a significant covariate ($P = 0·014$), but the effect of weight gain was seen only in those with IFG/IGT (an increase of 0·8 kg) where there was no difference seen between the chronic sugars. There was no effect seen in those without IFG/IGT (n 8).

Incremental AUC TAG. Following the acute meal tests, there was no difference between fructose and sucrose-containing muffins in TAG iAUC with an increase in TAG from 1·46 mmol/l at baseline to 2·53 mmol/l at 180 min after fructose and an increase from 1·43 to 2·25 mmol/l at 180 min after sucrose ($P = 0·14$ for iAUC TAG). There was a time by sugar interaction with a slightly delayed response after fructose with a peak at 180 min while after sucrose it was higher from 30 min onwards with a peak at 150 min followed by a slight fall at 180 min ($P < 0·001$ time by sugar) (Fig. 2). Average TAG over 3 h was 1·83 mmol/l after fructose and 1·89 mmol/l after sucrose (NS).

These acute tests were repeated after 1 month of consumption of muffins containing either sucrose or fructose, and iAUC TAG was not different between the sugars ($P = 0·5$). The same pattern was seen with fructose increasing from 1·55 to 2·71 mmol/l (mean 1·97 mmol/l) and sucrose increasing from 1·58 to 2·49 mmol/l (mean 2·02 mmol/l).

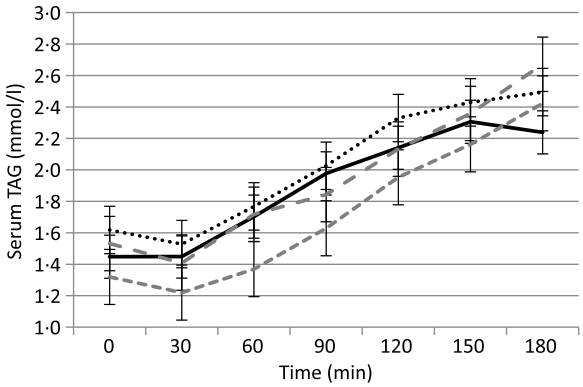

Fig. 2. Effect of acute feeding of fructose and glucose on serum TAG before (1) and after (2) 4 weeks of 42 g/d of sugar. Analysed by repeated-measures ANOVA of incremental AUC with acute sugar and month as repeated measures and chronic sugar as a between-subject factor. Fructose 1 and sucrose 1: ($P = 0·14$). Fructose 2 and sucrose 2: ($P = 0·5$). Overall $P = 0·3$ for acute sugar, $P = 0·2$ for acute sugar by month, $P = 0·5$ for acute sugar by month by chronic sugar. n 24 for each line. Data are mean values with their standard errors of the mean. ——, Sucrose 1; ·····, sucrose 2; - - -, fructose 1; – –, fructose 2.

The iAUC TAG was not different between the two sugar types at either month 0 or month 1 or both together ($P = 0·3$). There was no difference in overall iAUC TAG between month 0 and month 1 ($P = 0·5$) nor did chronic sugar type have an effect ($P = 0·5$). People consuming sucrose muffins for a month had an overall mean TAG of 2·0 mmol/l (across all time points) at month 0 and 1·99 at month 1. With the fructose chronic muffins, overall TAG was 1·70 mmol/l at month 0 and 1·87 mmol/l at month 1 (NS).

For the secondary endpoint of fasting TAG overall there was no significant effect of chronic sugar. However, when IFG/IGT was added as a factor a strong interaction with month ($P = 0·001$) was present. Analysing only those with IFG/IGT (n 17), there was a strong effect of month ($P < 0·001$) and an interaction between month and chronic sugar ($P = 0·004$). Fasting TAG was 1·51 and 1·59 mmol/l for chronic sucrose and 1·55 and 1·95 mmol/l for chronic fructose at month 0 and month 1, respectively (Table 2). The difference in this group in the effect of chronic sugar was an increase over the month of 0·40 (SD 0·21) mmol/l for fructose and 0·09 (SD 0·17) mmol/l for sucrose with a difference between the two sugars of 0·31 (SD 0·37) mmol/l (95 % CI 0·11, 0·51). Change in weight over a month was a significant covariate ($P = 0·014$). However, weight gain was seen only in those with IFG/IGT (an increase of 0·8 kg). There was no significant difference in weight gain between the chronic sugars. There was no effect of weight seen in those without IFG/IGT (n 8).

Total cholesterol, HDL-cholesterol, uric acid and glucose. Total cholesterol (0·33 mmol/l), LDL-cholesterol (0·24 mmol/l) and HDL-cholesterol (0·08 mmol/l) increased significantly over the 1-month feeding period with no differences between muffin types.

Uric acid decreased after each muffin acutely ($P < 0·001$) and iAUC was not different between the two sugar types ($P = 0·9$) at either baseline or 1 month with no differences between baseline and 1 month (Fig. 3).

Glucose profiles as expected were quite different between the two muffin types with a time by sugar P value of $P < 0·001$ for iAUC over 180 min (Fig. 4). The mean difference in glucose was 0·41 mmol/l. Blood glucose increased from 5·5 to 5·9 mmol/l after fructose muffins and from 5·6 to 6·8 mmol/l after sucrose muffins. On repeat testing after 1 month of muffin consumption, glucose after fructose muffins increased from 5·5 to 6·4 mmol/l and from 5·5 to 6·6 mmol/l after sucrose muffins with an overall significance between sugars of $P < 0·001$ (iAUC over 180 min) with no significant difference between the baseline and 1-month tests ($P = 0·14$). Fasting glucose was not different after 1 month of muffin consumption.

Discussion

Overall, there was no difference in iAUC TAG or uric acid between the two sugar types at baseline or after 1 month of sugar

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Table 2. Fasting TAG and weight before and after 4 weeks of muffin consumption (Mean values and standard deviations)

	Fasting TAG (mmol/l)								Weight (kg)							
	Chronic fructose				Chronic sucrose				Chronic fructose				Chronic sucrose			
	Baseline			1 month					Baseline			1 month				
	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*
IFG/IGT	1·55	1·03	8	1·95	1·12	8	1·51	1·04	9	1·59	0·97	9	85·2	13·5	8	86·2	13·7	8	97·1	14·4	9	97·8	14·3	9
Normal	1·03	0·18	3	1·09	0·26	3	1·31	0·52	4	1·11	0·34	4	86·8	14·5	3	87·3	14·5	3	95·6	8·7	4	94·2	9·3	4

IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

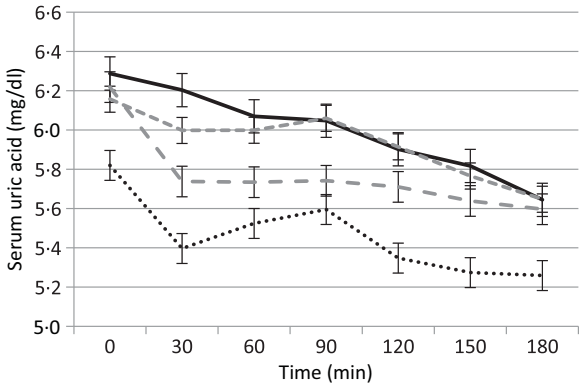

Fig. 3. Effect of acute feeding of fructose and glucose on serum uric acid before and after 4 weeks of 42 g/d of sugar. Analysed by repeated-measures ANOVA of incremental AUC with acute sugar and month as repeated measures and chronic sugar as a between-subject factor. No effect of acute sugar or acute sugar by month ($P = 0{\cdot}6$–$0{\cdot}9$). Interaction between acute sugar, month and chronic sugar feeding ($P = 0{\cdot}09$). *n* 24 for each line. Data are mean values with their standard errors of the mean. ——, Sucrose 1; ·····, Sucrose 2; – – –, fructose 1; – –, fructose 2.

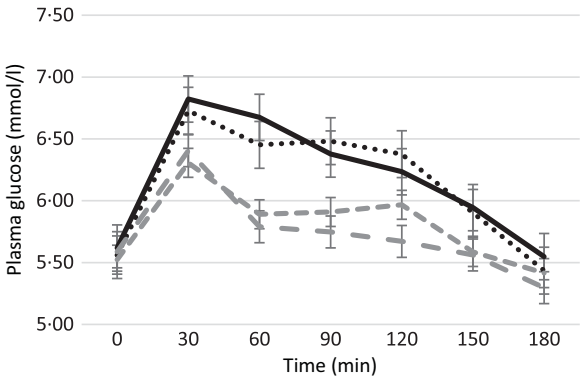

Fig. 4. Effect of acute feeding of fructose and glucose on plasma glucose before and after 4 weeks of 42 g/d of sugar. Analysed by repeated-measures ANOVA with acute sugar, time and month as repeated measures and chronic sugar as a between-subject factor. Fructose 1 and sucrose 1. $P < 0{\cdot}001$ for main effect of sugar. $P < 0{\cdot}001$ for time by sugar. Fructose 2 and sucrose 2. Main effect of sugar $P = 0{\cdot}001$, time by sugar $P = 0{\cdot}007$. No effect of chronic sugar feeding ($P = 0{\cdot}5$). Overall time by sugar $P < 0{\cdot}001$. *n* 24 for each line. Data are mean values with their standard errors of the mean. ——, Sucrose 1; ·····, sucrose 2; – – –, fructose 1; – –, fructose 2.

feeding regardless of the sugar fed chronically. One important finding of the present study was that fasting TAG increased after chronic consumption of 42 g fructose by 0·31 (SD 0·37) mmol/l compared with sucrose in those participants with IFG/IGT ($P = 0{\cdot}004$). Overall, in this group of overweight/obese individuals, this amount of fructose as part of solid food containing fat, starch and protein had no effect on postprandial plasma TAG over 3 h compared with sucrose. Fructose led to a lower glucose level compared with the sucrose-sweetened muffin meal. This may have advantages in this population at risk of progression to diabetes by minimising the demand for insulin, but the adverse effects on fasting TAG in high-risk individuals need to be borne in mind. These results differ dramatically from acute studies of fructose in liquids containing sugar and fat only with

no protein or fibre[8,9]. One study[9] in lean healthy subjects showed that fructose fed at 0·75 g/kg combined with fat at 0·5 g/kg in beverage form but with no starch or protein increased postprandial TAG with a maximum difference of 0·8 mmol/l at both 300 and 360 min compared with the glucose meal. The fat load in the current study was much lower at an average of 0·22 g/kg (varying from 0·18 to 0·28) but this represents a much more normal fat load. In agreement with our study, Singleton *et al.*[13] found that there was no difference between glucose and fructose in the TAG response to a fat load compared with no added sugar.

When a sugar-containing beverage is consumed with a solid meal, fructose augments plasma TAG compared with glucose[10,11]. Teff *et al.*[11] compared the effects of a high fructose or a high glucose beverage added to meals over 24 h in twelve normal weight women. With 130 g/d of fructose, serum TAG increased by 30–60 % compared with glucose at the same time point with a 35 % increase in fasting TAG the next day. Similar but greater effects were seen in overweight men and women[12]. These intakes of fructose are very large and represent a hyperenergetic state. Previously, we performed a study in healthy lean subjects examining 55 g of fructose in solid muffins containing protein and fat and found no difference between fructose and sucrose or sucralose in TAG levels over 5 h[21]. Both glucose and insulin levels were lower with fructose. In the present study despite the presence of prediabetes or obesity, there was still no difference between fructose and sucrose muffins on postprandial TAG levels up to 3 h and glucose was lower as expected with the fructose muffin. These data are very similar to a recent meta-analysis[22]. It is possible greater effects could be seen on TAG levels after 5 h.

In the present study, participants consumed two muffins/d containing 42 g of fructose or sucrose for 1 month and then the acute tests were repeated. Fasting TAG and glucose overall were not altered by a month of muffin consumption, and the repeat acute response was the same as the first one regardless of chronic muffin type. However, in people with IFG/IGT fasting TAG at 1 month was increased with a moderate difference between sucrose muffins and fructose muffins of 0·36 mmol/l, but numbers were small in each group. Body weight increased non-significantly by 0·5 kg which is similar to the Stanhope study[4] in which a weight gain of 1·8 kg for the glucose group and 1·4 kg for the fructose group was seen after 10 weeks with a larger daily sugar load. However, in the IFG/IGT group body weight increased significantly by 0·8 kg with no differences between chronic sugar types. The postprandial TAG peak in the Stanhope study[4] was 1·5–2 times greater with fructose than with glucose as was fasting apoB and fasting LDL. However, fasting TAG increased only after glucose and not after fructose which contrasts with our study and is difficult to explain and is in contrast to their previous 24 h studies. Fasting glucose and insulin increased 4-fold from baseline with fructose compared with glucose while AUC glucose and insulin in the oral glucose tolerance test doubled, consistent with increased insulin resistance. In our study, we saw no changes in fasting glucose, suggesting no changes in insulin resistance with this amount of fructose chronically although a meta-analysis suggested small doses of fructose could lower fasting glucose[19]; a more recent meta-analysis of eleven chronic studies (2–10 weeks) with fourteen treatment arms found no differences in fasting glucose overall or with fructose substituted for sucrose[23]. Our results in people with IFG/IGT who experienced weight gain with chronic muffin feeding partially agree with the systematic review and meta-analysis of Chiavaroli *et al.*[5] who found fructose only had adverse effects on lipids when fed at an energy level of 21–35 % with energy in excess of requirements. Isoenergetic substitution of glucose with fructose in chronic studies has no effect on fasting TAG while substitution for sucrose lowers fasting TAG but there were only three studies in this latter group. Overall, TAG was lowered by 0·08 mmol/l[22] while in isoenergetic acute studies fructose was not different to other carbohydrates in its effect on postprandial TAG[22]; although in studies that follow TAG levels over 24 h, the level tends to increase with fructose later in the day. Overall, the most important determinant of the responses to fructose is whether it is fed in excess to energetic requirements which is more likely with very large amounts fed in an easy to consume liquid form.

Teff *et al.*[12] found no effect of either glucose or fructose containing drinks with food on uric acid over 23 h in obese men and women, while Cai *et al.*[24] found that 75 g of fructose alone increased uric acid over 3 h compared with glucose. Le *et al.*[25] demonstrated a similar effect with 70 g of high fructose maize syrup over 6 h as did Stanhope *et al.*[26] over 24 h with beverages contributing 17·5 and 25 % of energy as fructose fed for 2 weeks. In the present study, beverages contributing only 10 % of energy elevated postprandial TAG, while the two higher doses increased fasting LDL-cholesterol, apoB, non-HDL cholesterol. Fasting uric acid was increased only if fed in a 35 % of energy excess[27] although this article has been criticised[28].

Conclusions

Compared with sucrose, fructose at a moderate intake of approximately 6–8 % of energy as part of a solid meal has no adverse effects nor any beneficial effects on postprandial TAG and uric acid over 3 h at baseline or after a 4-week feeding period in which no overall weight gain occurred. People with IFG/IGT have a moderate increase in fasting TAG after 1 month of eating fructose muffins and gaining weight but this needs confirmation with larger numbers, but caution in using this amount of fructose chronically is required in this particular group of high-risk individuals.

Limitations

Limitations of the present study are that we did not extend our acute studies to 5–6 h as differences may have appeared later and we did not compare fructose in solid foods to fructose in liquid form, nor did we perform acute meal tests without sugars. We did not control or assess background dietary intake which may have been differentially altered by the two muffin types by chance alone. The conclusions of the present study are limited to a moderate intake of fructose and may not apply to much larger amounts for longer periods of time.

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P C. designed the research, analysed the data and wrote paper and has primary responsibility for the final content. J. K. contributed to the design and critically reviewed the paper.

The authors have no conflicts of interest.

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