ORIGINAL ARTICLE

Effect of fructose and sucralose on flow-mediated vasodilatation in healthy, white European males

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Abstract

Objective: To assess how acute consumption of fructose affects flow-mediated dilatation in brachial artery.

Methods: The randomised cross-over study was conducted at the University of Nottingham's Medical School, Nottingham, United Kingdom in July 2009. Ten healthy, white European males visited the laboratory twice, on separate mornings. On each visit, the volunteers consumed water (3ml/kg bodyweight) and rested semi-supine on the bed. After 30 minutes, baseline diastolic brachial artery diameter and blood velocity was measured. At 60 minutes, blood velocity and five scans of brachial artery diameter were recorded before a blood pressure cuff was inflated on the forearm for 5 minutes and at 50-60-70-80 and 90 sec after cuff deflation. Fifteen minutes later, the volunteers consumed 500ml of test-drink containing either fructose (0.75 g/kg bodyweight) or sucralose (sweetness-matched with fructose drink); 45 minutes later, baseline and flow-mediated dilatation was re-measured.

Results: Pre-drink and post-drink baseline values were similar on two occasions ($p > 0.05$). Brachial artery diameter increased ($p < 0.05$) by 7±3% pre-fructose and by 6.9±3% above baseline values post-fructose with no significant difference in these responses ($p < 0.15$). It increased ($p < 0.05$) by 5.9±3% above baseline before and by 6.7±2% ($p < 0.01$) after sucralose; a significant difference was noted in these flow-mediated dilatation responses ($p < 0.02$). Responses before and after sucralose were not different from those before and after fructose ($p < 0.294$).

Conclusion: Acute ingestion of fructose or sucralose had no effect on flow-mediated dilatation measured at brachial artery.

Keywords: Endothelium, Brachial artery, Vasodilatation, Fructose, Nitric oxide, Cardiovascular. (JPMA 64: 743; 2014)

Introduction

The endothelium is a single layer of cells lining the intimal surface of blood vessels. By its production of various chemical substances in response to physical and chemical stimuli, the endothelium enables vessels to adapt to changes in the local environment by dilatation or contraction.[1-5] A normally functioning endothelium is an index of healthy cardiovascular (CV) status. Endothelial dysfunction in the brachial artery (BA) is closely related to impairment of coronary arterial endothelial function[6] and is a predictor of adverse CV health. In addition, the degree of arterial stiffness is directly related to the extent of endothelial dysfunction reflected in a reduced endothelial capacity to produce nitric oxide (NO).[7,8]

Flow-mediated dilatation (FMD) is a non-invasive method employed for the assessment of endothelial function by evaluating changes in BA diameter resulting from a sheer stress stimulus. This is achieved by the use of an occlusion cuff (typically applied for 5 minutes) on the forearm whereby release of the cuff leads to reactive hyperaemia. The resulting increase in BA diameter in response to this increase in blood flow can be measured by ultrasound imaging.[9] FMD measurements have diagnostic and prognostic value and repeated measurements are possible because of the procedure's non-invasive nature.[10]

Animal studies suggest that fructose ingestion induces hyperinsulinaemia as a consequence of the sympathetic nervous system stimulation[11] and fructose induced hypertriglyceridaemia[12] leads to the production of superoxide radicals which contributes to oxidative stress (OS) and leads to reduced amount of NO in the vasculature. This results in altered vascular function and defective vasodilatation.[13-15] Acute fructose consumption in human subjects is reported to have detrimental CV effects, such as increase in blood pressure (BP).[16-18] However, effects produced by fructose in humans remain controversial, as it has been reported that ingestion of 64g of fructose, i.e., fructose equivalent to that contained in 5 apples, may bring about beneficial effects by increasing plasma anti-oxidant levels.[19] Using sucralose (a synthetic sweetener) as a control, the purpose of the present study was to assess how acute consumption of fructose affected the FMD of the BA by employing ultrasound imaging for

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FMD measurements.

Subjects and Methods

The study of six-month duration was conducted at the University of Nottingham's Medical School, Nottingham, United Kingdom in July 2009. It was approved by the institutional ethics committee and conformed to the Declaration of Helsinki for experimentation on humans.

Ten healthy, non-smoking, white, European males were recruited for the study which involved 2 visits in a randomised, cross-over design. The volunteers fasted overnight and avoided sugar-containing soft drinks, caffeinated drinks, bakery products, fruit or fruit products, alcohol, fatty food, vitamin C supplements and strenuous exercise for 24 hours before the visit. The subjects were advised to consume the same type of meal on the night before each experimental visit. All experiments took place at the same time in the morning. Upon arrival, the volunteers were weighed and were offered water (3ml/kg bodyweight) to ensure that they were adequately hydrated. They rested on a bed, semi-recumbent in a thermo-regulated room (27°C) and their arms were positioned at the same height relative to their heart. Electrocardiogram (ECG) leads on the ultrasound machine (Toshiba Diagnostic Ultrasound System — Model SSA-770A; Toshiba Medical Systems Corporation, Japan) were attached to the volunteer to allow ECG-gating of subsequent scans, and a BP cuff was applied over a single layer of Soffban orthopaedic padding (Smith & Nephew; Hull , UK) at a pre-determined position on the right lower arm of the volunteer. After resting for 30 minutes, the BA was located and 3 baseline BA diameter measurements and blood velocity (BV) readings were taken. Cine images of all scans were stored for subsequent comparison and analysis. BA position was marked on the volunteer's skin to ensure reproducibility of measurements. A further baseline measurement was made a few minutes before the occlusion at 60 minutes; the BP cuff was inflated to 50 mmHg above the volunteer's systolic BP and it remained inflated for 5 min (occlusion period). Upon completion of the 5 minutes, the BP cuff was deflated and 15 seconds later, a BV measurement was made. Five scans of BA diameter were recorded at 50, 60, 70, 80 and 90 seconds after cuff deflation and the change in diameter was expressed as per cent change from the baseline diameter.

Fifteen min after the FMD measurement, volunteers were offered 500ml of a lemon-flavoured drink (to be consumed over 5 minutes) containing either fructose (0.75g per kg bodyweight) (Fruisana; Danisco Sweeteners OY. Kotka, Finland) or sucralose (having matched sweetness to that of the fructose drink; Splenda; McNeil Nutritionals Ltd). At 120 minutes (45 minutes after the drink), baseline diameter and BV were measured before a second FMD measurement was made. The above procedure was followed on the second study day, at least 3 days later and usually within one week, with the exception that the drink was different from the one consumed on the first experimental visit.

BA diameter change was analysed from the stored cine images and FMD was calculated by taking an average of the 3 baseline diastolic diameter measurements (A) and the average of diastolic diameter measurements taken over 3 cardiac cycles at 60, 70 and 80 sec (B) after the occlusion was released. The following equation was used to calculate the FMD:

$$B-A = C$$

$$(C/A) \times 100 = FMD\ \%$$

Intra-group statistical analyses were carried out using paired student's t-test after determination of normality of the data. Comparisons made between the 2 visits i.e., the FMD measurements before and after consumption of either sucralose or fructose, were carried out using a 2-way analyses of variance (ANOVA) with repeated measures. Statistical significance was set as $p<0.05$.

Results

Pre-drink (fructose and sucralose) and post-drink baseline values were similar on the two study visits. No significant difference was found when pre-drink baseline values were compared with those obtained after fructose ($p<0.06$) or sucralose ($p<0.07$) was consumed (Table-1).

The 5 minutes forearm occlusion resulted in a significant increase in BA diameter during the FMD measurement made both before and after fructose was consumed. A significant FMD response was observed before fructose was consumed. It was found that BA diameter changed by 0.3±0.12mm, i.e. 7±3% from the baseline. Post-drink diameter changed by 0.29±0.11mm, i.e. 6.9±3% above the baseline ($p<0.05$). There was no significant difference in these FMD responses ($p<0.15$) (Table-2; Figure-1,2).

No difference between pre- and post-drink baseline BA

Table-1: Baseline values for fructose and sucralose (pre and post-drink). Values are in mm.

	Fructose mean baseline		Sucralose mean baseline	
	Pre- drink	Post- drink	Pre- drink	Post- drink
Mean	4.26	4.31	4.24	4.29
SD	0.45	0.47	0.36	0.39

SD: Standard deviation.

Table-2: Comparison between baseline and flow-mediated dilatation values before and after fructose-containing drink was consumed.

Fructose	Pre-drink				Post-drink			
diameter	Baseline	PO diameter (FMD)	Δ diameter	% Δ diameter	Baseline	PO diameter (FMD)	Δ diameter	% Δ
Mean	4.26	4.56*	0.30	7.0	4.31	4.60**	0.29	6.9
SD	0.45	0.47	0.12	3	0.47	0.46	0.11	3
SEM	0.14	0.15	0.04	0.89	0.15	0.15	0.03	0.88

* P = 2.24139E-05 (Significant difference between PO diameter compared to baseline diameter (pre-drink))
** P= 0.000013 (Significant difference (post-drink) in PO diameter compared to post-drink baseline diameter).
PO = Post occlusion; Δ = Change; % Δ = Percent change; SD = standard deviation. Values are mean ± SD. Values are in mm.

Table-3: Comparison between baseline and flow-mediated dilatation values before and after sucralose containing drink was consumed.

Sucralose	Pre-drink				Post-drink			
diameter	Baseline	PO diameter (FMD)	Δ diameter	% Δ diameter	Baseline	PO diameter (FMD)	Δ diameter	% Δ
Mean	4.24	4.49*	0.25	5.9	4.29	4.57**	0.28***	6.7
SD	0.36	0.38	0.11	3	0.39	0.37	0.07	2
SEM	0.12	0.12	0.03	0.86	0.12	0.12	0.02	0.61

*P = 0.0000367 (Significant difference between baseline and PO diameter (before drink)).
** P = 0.01 (Significant difference (post-drink) in PO diameter of BA compared to post-drink baseline diameter)).
***P = 0.02 (Significant difference between pre and post sucralose-drink FMD response)).
Values are mean ± SD. Values are in mm. PO = Post-occlusion.

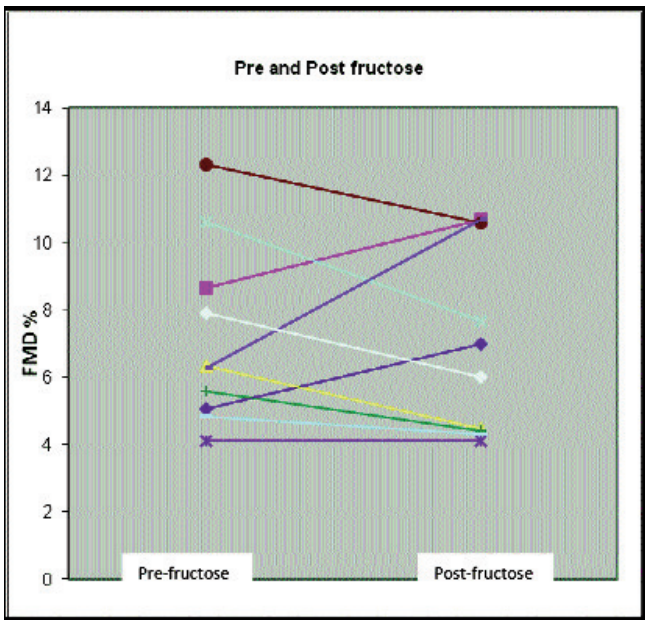
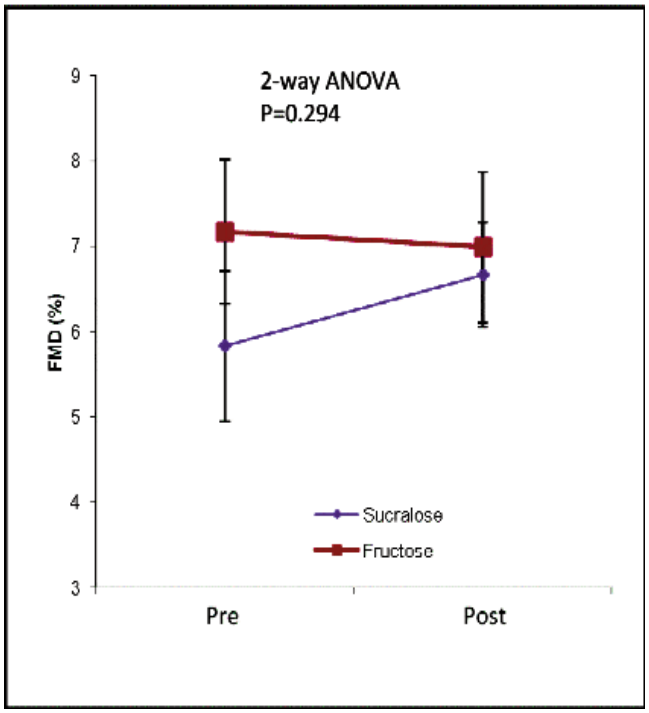


Figure-1: Flow-mediated dilatation (FMD) (per cent change in brachial arterial diameter) before and after fructose consumption in individual subjects.

diameter values was noted (p>0.05). The 5 minutes forearm occlusion resulted in a significant increase in BA diameter during the FMD measurement made both before and after sucralose was consumed. A significant FMD response occurred before sucralose was consumed



(FV (amd)MQESIM)
ANOVA: Analyses of variance
FMD: Flow-mediated dilatation.

Figure-2: Per cent flow-mediated dilatation before and after either Sucralose or Fructose consumption.

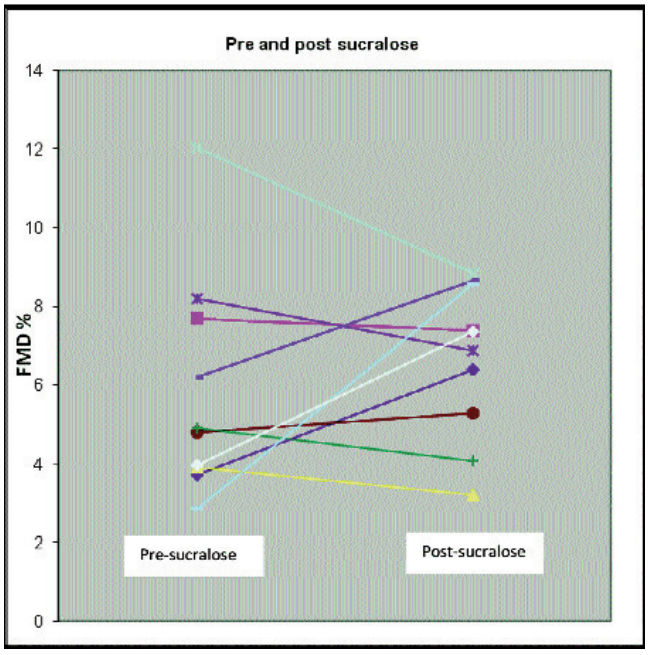


Figure-3: Flow-mediated dilatation (per cent change in brachial arterial diameter) before and after sucralose consumption in individual subjects.

($p<0.05$). It was noted that BA diameter changed by 0.25±0.11mm, i.e. 5.9±3% from the baseline. A significant FMD response was also observed after sucralose; diameter increased by 0.28±0.07mm; 6.7± 2% ($p<0.01$). A significant difference was noted in these FMD responses ($p<0.02$) (Table-3; Figure-2, 3).

FMD responses before and after sucralose were not different from those before and after fructose ($p<0.294$).

Discussion

The present study employed a randomised, cross-over, single-blind design and used non-invasive techniques, e.g., ultrasound, to assess the effects of acute consumption of fructose and that of sucralose on the FMD of BA.

FMD responses before fructose or sucralose consumption (7% and 5.9% respectively) were similar and compared well with the literature and were indicative of a healthy endothelial function.[20-22] A significant FMD response was observed before and after fructose was consumed, but there was no significant difference in these FMD responses. Other interventions reported in the literature show changes from such values — for example, both increases of FMD after flavanols, as contained in cocoa and reversal of smoking-induced endothelial dysfunction[23] and decreases after cigarette smoking[24] and saturated fat meal.[25] A possible reason for the absence of an effect of fructose is either because it does not have the purported effects proposed in the literature, that fructose induces hyperuricaemia which leads to endothelial dysfunction[26] or the dose was too small or the timing of the post-fructose measurement inappropriate. Ample time was allowed between the measurements (1h) which was sufficient for the vessel to recover and for a repeat measurement to be made and for fructose to reach peak serum level, i.e., 30-60 minutes after oral ingestion.[17] Evidence suggests that timing for post-fructose FMD measurement, i.e., 45 minutes after the drink, was appropriate for fructose effects to become apparent as a study reported CV effects of fructose to become noticeable within 30 minutes, whereas another study reported peak changes evident after 20 minutes post-drink.[18,27] The quantity of fructose used in the present study was 0.75g per kg bodyweight, which amount was determined after personal experience, which indicated that 1g per kg may cause gastrointestinal upset. Volunteers participating in this study weighed 73±9kg, so fructose used in the study ranged between 48g- 61.5g, an amount consistent with fructose dose used in a study determining fructose effects.[27]

There was a decrease in per cent diameter change of the BA after fructose was consumed compared to pre-drink in 6 of the 10 volunteers, while for the rest the values increased. Thus, it is possible that fructose may affect FMD, but the present study did not show this to be significant because of either wide variability (range of 0.20 to 19.2% between individuals) in FMD response among healthy volunteers or the sample size was too small.[20,21] Sucralose consumption resulted in decreased per cent diameter change of the BA in half of the volunteers with the other half showing an increase and sucralose responses (pre- and post-drink) were similar to fructose. The results were consistent with earlier reports that showed similarity in effects of fructose and sucralose.[18]

Conclusion

Acute ingestion of fructose and sucralose had no effects on the dilatation of the BA after 5 minutes of occlusion and the effects of sucralose were not different from that of fructose.

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