Title

Short-term dietary supplementation with fructose accelerates gastric emptying of a fructose but not a glucose solution

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Role of authors

AMWY contributed to study design, recruited the participants, performed the data collection, biochemical analysis, data analysis, interpretation, and wrote the manuscript. GHE contributed to study design, data collection, and manuscript writing. JM, RJM and WG contributed to the study design and manuscript writing. All authors read and approved the final manuscript and none of the authors has any conflict of interest to report.

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Abstract

Objective: Short-term dietary glucose supplementation has been shown to accelerate gastric emptying rate of both glucose and fructose solutions. The aim of this study was to examine gastric emptying rate responses to monosaccharide ingestion following dietary fructose supplementation.

Methods: Gastric emptying rate of a fructose solution containing 36 g of fructose and an equicaloric glucose solution containing 39.6 g glucose monohydrate were measured in 10 healthy non-smoking men with and without prior fructose supplementation (water control) using a randomised crossover design. Gastric emptying rate was assessed for a period of 1 h using the [^{13}C]breath test with sample collections at baseline and 10 min intervals following drink ingestion. In addition, appetite ratings of hunger, fullness and prospective food consumption were recorded at baseline and every 10 min using visual analogue scales.

Results: Increased dietary fructose ingestion resulted in significantly accelerated half emptying time of a fructose solution (mean 48 (SD 6) vs. 58 (SD 14) min control, P=0.037) whilst the emptying of a glucose solution remained unchanged (mean 85 (SD 31) vs. 78 (SD 27) min control; P=0.273). Time of maximal emptying rate of fructose was also significantly accelerated following increased dietary fructose intake (mean 33 (SD 6) vs. 38 (SD 9) min control, P=0.042) whilst it remained unchanged for glucose (mean 45 (SD 14) vs. 44 (SD 14) min control, P=0.757). No effects of supplementation were observed for appetite measures.

Conclusion: Three days of supplementation with 120 g/d of fructose resulted in an acceleration of gastric emptying rate of a fructose solution but not a glucose solution.

Key Words

Diet; fructose supplementation; monosaccharide solutions; gastrointestinal adaptation; appetite

Introduction

A rate-limiting step in the delivery, and thus absorption, of nutrients and fluid in the small intestine is the rate of gastric emptying. The regulation of gastric emptying is therefore perceived as an important factor in appetite control [1]. Gastric distension induced by an intragastric balloon to simulate the mechanical presence of food in the stomach has been shown to cause both satiation and satiety [2]. Therefore, a prolonged period of gastric distension as a result of delayed emptying would lead to a prolonged satiety period [3]. Slower emptying will also delay the appearance in the circulation of nutrients that might contribute to satiety.

Carbohydrates, when ingested orally or directly administered into the stomach or small intestine result in a reduction in subsequent food intake [4]. The magnitude of this effect is however suggested to vary between different types of carbohydrate or sugars. With the recent rise in levels of obesity and its associated morbidities worldwide, research interests in carbohydrates and satiety have centred on the possible role of fructose in the pathogenesis of obesity and the metabolic syndrome [5]. This has been motivated by the widespread use of fructose, either in the form of sucrose or high fructose corn syrup, as an added ingredient in soft drinks and other sweetened beverages or foods, greatly increasing its dietary consumption [6,7]. Excessive intake of fructose and over-consumption of sugary beverages is suggested to contribute to the development of the metabolic syndrome and obesity through altering feeding patterns and the promotion of weight gain [7]. Gastric emptying rate may play an important modulatory role in these outcomes.

A small compilation of research indicates that gastric emptying in humans may be influenced by patterns of previous dietary nutrient intake. Furthermore, there is evidence to suggest that these adaptive changes are macronutrient-specific [8,9] and rapid, with adaptations occurring in only a few days [3,9]. A high-fat diet for 14 days has been shown to

accelerate gastric emptying of a high-fat test meal [10] but not a high-carbohydrate meal [8]. More recently, this adaptive response of the gastrointestinal system to the ingestion of high-fat meals has been reported to occur following only three days of high fat diet [3]. Similarly, short-term dietary supplementation with 400 g glucose per day for three days in healthy individuals has been shown to accelerate gastric emptying of a hyperosmotic glucose solution, but not of a protein solution [9]. The specificity of these effects of a high-glucose diet has not been extended to different monosaccharides, however. The emptying of a hyperosmotic fructose solution was equally accelerated following short-term supplementation with glucose solutions [11]. Whether these effects are replicated in response to short-term dietary supplementation with fructose is unknown. The aim of this study was to investigate the effect of 3 d of dietary fructose supplementation on the rate of gastric emptying of glucose and the rate of gastric emptying of fructose solutions as well as the accompanying subjective feelings of appetite.

Materials and methods

Participants

Ten healthy men completed this study (mean age 27 (SD 6) years, height 179.9 (SD 9.2) cm, body mass 81 (SD 11) kg, BMI 25 (SD 3) $kg.m^{-2}$, and estimated body fat 21 (SD 8)%). All volunteers were non-smokers, had no history of gastrointestinal symptoms or disease, were not consuming medication with any known effect on gastrointestinal function and had no other relevant medical conditions as assessed by a medical screening questionnaire. Verbal and written explanations of the experimental procedures were provided prior to participation. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the Ethical Advisory Committee of Manchester

Metropolitan University's Faculty of Science and Engineering. Written informed consent was obtained from all participants.

Preliminary trials

All participants reported to the laboratory for a preliminary familiarisation visit. Anthropometric measurements of height to the nearest 0.1 cm using a wall mounted stadiometer, body mass (BM) to the nearest 0.01 kg using electronic scales (GFK 150; Adam Equipment Co. Ltd., Milton Keynes, UK), and estimation of body fat percentage using a hand-held bioelectrical impedance device (Omron BF306; Kyoto, Japan) were made. Furthermore, participants were familiarised with the gastric emptying assessment technique and the visual analogue scales (VAS) to be used during the experimental trials. The VAS was composed of questions asking "how hungry do you feel," "how full do you feel," "how much do you think you can eat," [12] "how bloated do you feel," and "how nauseous do you feel?" Respectively, horizontal lines 100 mm in length were anchored with "I am not hungry at all- I have never been more hungry", "not at all full- totally full", "nothing at all- a lot", [12] "not at all bloated- very bloated" and "not at all nauseous- very nauseous." In addition, participants who had not previously participated in any studies in our laboratory involving fructose consumption completed a fructose tolerance test before further participation by consuming a 600 ml solution containing 36 g fructose. This procedure was used to ensure that no adverse effects would be experienced due to unknown malabsorption during supplementation and experimental trials.

Experimental protocol

Experimental trials were conducted in a single-blind, randomised crossover fashion commencing between 08.30 and 10.00 hours following an overnight fast from 21.00 hours with the exception of drinking 500 ml of water approximately 90 min before arrival at the

laboratory. Participants reported to the laboratory on four occasions to complete four experimental trials; fructose with supplementation (FS), fructose with water control (FC), glucose with supplementation (GS) and glucose with water control (GC). Experimental trials were separated by a minimum period of 7 d. Each experimental trial was preceded by a 3 d dietary and activity maintenance period where participants were asked to record their diet and activity in their first trial and then replicate them in the remaining three trials. The purpose of this was to ensure standardisation and consistency of macronutrient intake and metabolic status in the days leading up to each trial within participants. In addition to their normal dietary intake, participants were asked to consume either four 500 ml bottles of water or four 500 ml solutions each containing 30 g fructose per day over the 3 d. Participants were instructed to consume these drinks evenly throughout the day in between meals. Furthermore, participants were asked to refrain from alcohol consumption and strenuous physical activity in the 24 h preceding each experimental trial.

Upon arrival at the laboratory, participants were asked to completely empty their bladder into a container from which a 5 ml urine sample was retained for later analysis of osmolality by freezing point depression (Gonotec Osmomat 030 Cryoscopic Osmometer; Gonotec, Berlin, Germany). Body mass was subsequently recorded. Participants then ingested 595 ml of a fructose solution (36 g dissolved in 600 ml water) or an equicaloric glucose monohydrate solution (39.6 g dissolved in 600 ml water) containing 100 mg [^{13}C]sodium acetate (Cambridge Isotope Laboratories Inc., Andover MA, USA). Participants were given a maximum of two minutes to consume the test solution and instructed to consume it as quickly as they were able to. Test drink solutions were freshly prepared on the morning of the test and were given at room temperature. A 5 ml sample of the drink was retained for later analysis of osmolality. Ratings of appetite (hunger, fullness, prospective food consumption) [12] as well as ratings of bloatedness and nausea were assessed using 100-

mm VAS, as described above, at baseline and at 10 min intervals following drink ingestion for 60 min. Participants remained seated throughout the drink ingestion and 60 min sampling procedure. Following the last breath sample collection and completion of the VAS at 60 min, participants were asked again to completely empty their bladder into a container and a 5 ml urine sample was retained for osmolality analysis using the method aforementioned.

Measurement of gastric emptying

Gastric emptying was assessed using the [^{13}C]acetate breath method. This method of measurement has been shown to correlate closely to scintigraphy [13,14] and gastric aspiration [15]. Prior to ingestion of the test drink containing 100 mg [^{13}C]sodium acetate (Cambridge Isotope Laboratories Inc., Andover MA, USA), a basal end-expiratory breath sample was collected. Further end-expiratory breath samples were collected at 10 min intervals over a period of 60 min following drink ingestion. Breath samples were collected into a 100 ml foil bag (Wagner Analyzen-Technik, Bremen, Germany) on each occasion by exhalation through a mouthpiece: bags were then sealed with a plastic stopper and stored for later analysis.

Breath samples were analysed by non-dispersive IR spectroscopy (IRIS, Wagner Analyzen-Technik, Bremen, Germany) for the ratio of $^{13}CO_2$:$^{12}CO_2$. The difference in the ratio of $^{13}CO_2$:$^{12}CO_2$ from baseline breath to post breath samples are expressed as delta over baseline (DOB). Half emptying time ($T_{½}$) and time of maximum emptying rate (T_{lag}) were calculated using the manufacturer's integrated software evaluation embedded with the equations of Ghoos *et al*. [13]. Each participant's own physiologic CO_2 production assumed as 300 mmol CO_2 per m^2 body surface per hour was set as default and body surface area was calculated by the integrated software according to the formula of Haycock *et al.* [16] .

Statistical analysis

Differences in pre-ingestion body mass, pre-ingestion urine osmolality and drink osmolality were examined using one-way repeated ANOVA. Two-way repeated ANOVA were used to examine differences in gastric emptying DOB values, and subjective appetite VAS scores. Sphericity for repeated measures was assessed, and where appropriate, Greenhouse-Geisser corrections were applied for epsilon <0.75, and the Huynh-Feldt correction adopted for less severe asphericity. Significant *F*-tests were followed by repeated one-way ANOVA and bonferroni adjusted pairwise comparisons as appropriate. Gastric emptying $T_{½}$ and T_{lag} data were examined with paired Student's *t*-Tests to test the hypothesis of interest (i.e. effect of supplementation on gastric emptying rate of fructose and of glucose). All data were analysed using SPSS Statistics for Windows version 19 (IBM, New York, US). Statistical significance was accepted at the 5% level and results presented as means and standard deviations.

Results

Body mass, hydration status and drink osmolality

Body mass remained stable over the duration of the study (Table 1). Furthermore, the constancy of pre-ingestion urine osmolality indicated that hydration status prior to each experimental trial was also consistent (Table 1). Drink osmolalities were 368 (SD 3), 368 (SD 3), 370 (SD 4) and 369 (SD 3) $mOsmol.kg^{-1}$ (*P*=0.490) for FC, FS, GC and GS, respectively.

Gastric emptying

Gastric emptying $T_{½}$ for fructose was accelerated after the period of dietary supplementation with fructose than when the control drink was consumed (FC, 58 (SD 14) min vs. FS, 48 (SD 6) min; *P*=0.037). In contrast, gastric emptying $T_{½}$ for glucose did not change with fructose supplementation (GC, 78 (SD 27) min vs. GS, 85 (SD 31) min; *P*=0.273). The same pattern

was also observed for T_{lag}. Dietary fructose supplementation accelerated fructose T_{lag} (FC, 38 (SD 9) min vs. FS, 33 (SD 6) min; P=0.042) whilst glucose T_{lag} remained unchanged (GC, 44 (SD 14) min vs. GS, 45 (SD 14) min; P=0.757). Breath DOB values for fructose (Figure 1) revealed no main effect of trial (P=0.441), a significant main effect of time (P<0.001) and no interaction effect (P=0.088). Breath DOB for glucose (Figure 2) showed no main effect of trial (P=0.868), a significant main effect of time (P<0.001) and no interaction effect (P=0.680).

Appetite ratings

Hunger ratings for fructose trials remained relatively constant from baseline and over the 60 min duration after drink ingestion. No main effect of trial (P=0.820), time (P=0.160) or interaction (P=0.364) was present. Ingestion of a glucose solution, on the other hand, resulted in a slight suppression of hunger within 10 min before a steady rise back to baseline values within 60 min. No statistically significant main effect of trial (P=0.861), time (P=0.07) or interaction effect (P=0.562) were identified (Figure 3).

Ingestion of a fructose solution did not affect ratings of fullness over the 60 min (FC, P=0.130; FS, P=0.137). Prior fructose supplementation also did not affect ratings of fullness when compared with its control as no main effect of supplementation (P=0.135) and no interaction effect (P=0.706) were found. Feeling of fullness following glucose ingestion was also not different between control and supplementation trials. No main effect of supplementation (P=0.575) or interaction (P=0.285) was present, though a biphasic increase then decrease in fullness following glucose ingestion with prior supplementation was observed compared to the single increase then decrease seen with no supplementation. A significant main effect of time was indicated (P=0.004), though post-hoc analysis did not identify the location.

Prospective food consumption decreased slightly within 10 min of ingestion of a fructose solution. For the control trial, this steadily increased back to pre-ingestion value within 60 min. For the supplementation trial, an increase above pre-ingestion values was seen at 50 and 60 min. A main effect of time (P=0.011), but no significant effects of trial (P=0.344) or interaction (P=0.205), was found. Significant differences between ratings over time were not located with post-hoc analysis. A similar decrease followed by a gradual increase back to baseline scores was also seen for the ingestion of glucose for both control and supplementation conditions. Again, no effect of trial (P=0.898) nor interaction (P=0.142) was shown, but there was an effect of time (P=0.048).

Discussion

The results of this study show that a 3-d period of dietary supplementation with 120 g fructose consumed throughout the day results in an acceleration of gastric emptying of a fructose solution but not of a glucose solution. This study thus shows a monosaccharide-specific adaptation to increased fructose in the diet in contrast to the glucose supplementation results of Horowitz *et al.* [11]. Furthermore, the results of this present study demonstrate an adaptation of gastric emptying rate to a much smaller amount of additional carbohydrate consumption than that utilised in previous studies, and highlight the pertinent potential negative effects of an increase in dietary fructose consumption. An amount of 30 g of fructose is on average less than the amount that would be found in a typical 500 mL serving of commercially-available soft drinks which contain 11.0-12.5% high fructose corn syrup (55% fructose) in some countries such as the US. The fructose content in the majority of these soft drinks thus range from a little over 30 g to 34 g. Although the dose of fructose ingested in this study (120g/day) is four times the amount of this typical single serving, data shows that it is not an unrealistic amount. Estimated daily mean, 90th and 95th percentile fructose intakes

from NHANES data are reported respectively as 63 g, 103 g and 118 g for males aged 23-50 y and 75 g, 117 g and 134 g for males aged 19-22 y [17].

The increased rate of gastric emptying following fructose supplementation is highly indicative of a short-term reduction in gastric emptying inhibition resulting from small intestinal feedback. This may have been due to several possible adaptations. One possible mechanism is a decreased sensitivity to fructose by specific receptors in the small intestine. However, the existence of fructose-selective receptors has not been reported and is perhaps rather unlikely. Another possible mechanism is an enhanced absorption capacity of the small intestine for fructose, resulting in decreased intestinal exposure time and length, may have occurred. The length of intestine exposed to nutrients has been shown to be an important determinant of the extent of feedback inhibition of gastric emptying [18,19]. Alternatively, and/or in combination with this, the adaptation of enhanced absorption leading to augmented transporter activation may be responsible. This latter explanation seems more plausible in the light of the current study's monosaccharide-specific results due to the different transport pathways of fructose and glucose. Glucose is actively transported across the brush border membrane of the intestine by sodium-dependent glucose transporters (SGLT1) and across the basolateral membrane by the GLUT2 hexose transporter [20]. Fructose, however, is absorbed through facilitated transport by a sodium-independent transport system, believed to primarily be the GLUT5 transporter, and across the basolateral membrane also by GLUT2 [20,21]. The different yet inter-related monosaccharide effects of the present study and that of Horowitz *et al*. [11] are consistent with an upregulation of GLUT5 activity in response to dietary fructose supplementation and an upregulation of both glucose and fructose transport pathways (possibly involving GLUT2) following increased dietary glucose exposure. In any case, as nutrient transporters appear to have a role in nutrient sensing and gut hormone secretion [22,23], this may have led to changes in either the secretion of or sensitivity to gut hormones

such as GLP-1 or ghrelin, both of which are known to affect the rate of gastric emptying. Previous work investigating the effect of acute ingestion of fructose on gastrointestinal response is limited and with specific regards to GLP-1 and ghrelin is conflicting. Some have reported fructose to stimulate GLP-1 [24], insulin [24-26], and leptin [25] secretion, and suppress ghrelin [25], to a lesser degree than comparable amounts of glucose. Others, including recent work from our own laboratory, have reported similar GLP-1 and ghrelin responses [26,27]. No data is currently available on repeated ingestion or the effects of short-term increases or habitually high intakes of fructose in humans. Further work investigating whether any changes in gut hormone responses occur with fructose supplementation is required to elucidate the mechanism of gastrointestinal adaptation observed in this present study.

The ingestion of a single bolus of fructose results in markedly lower plasma glucose and insulin responses compared to the response following an isoenergetic amount of glucose or sucrose [11,24-26]. Whilst this may be beneficial in the short-term postprandial maintenance and control of blood glucose levels in diabetics, this also has negative appetite regulation and metabolic consequences irrespective of insulin status. Decreased insulin production and secretion results in decreased circulating levels of leptin, the long-term regulator of food intake, and reduced suppression of the orexigenic hormone ghrelin [27]. Glucagon suppression is also significantly lower following fructose ingestion leading to greater glycogenolysis and lipolysis and increased plasma triglyceride concentrations [25]. Furthermore, the complete metabolism of fructose in hepatocytes results in an unregulated source of substrates for augmented *de novo* lipogenesis and also increased uric acid concentration [28-30]. Accelerated gastric emptying of fructose would therefore lead to more rapid rises in plasma fructose and may result in both larger and earlier peaks of plasma

triglycerides and uric acid, both of which are strong independent contributors to the development of diabetes, cardiovascular disease, and obesity [29,30].

Although no significant changes to appetite ratings were observed in this present study, this is likely due to the fact that ingestion of liquids generally provides a smaller satiation effect than does ingestion of isoenergetic solids [31,32]. The effect of increased fructose ingestion on gastrointestinal adaptation and appetite should also be investigated in solid foods.

Conclusion

The results of this study reveal that three consecutive days of dietary supplementation with 120 g fructose per day accelerates gastric emptying of a fructose solution but not of a glucose solution. The mechanisms and implications of this observed gastrointestinal adaptation to increased dietary fructose should be further investigated.

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Figure legends

Fig.1: Gastric emptying breath delta over baseline (DOB) for 60 min following 595 ml of a 6% fructose solution ingestion. Treatments were control without fructose supplementation (-○-) and with 3 days supplementation of 120g fructose per day (-●-). Values are means (*n* 10) with standard deviations represented as vertical bars.

Fig. 2: Gastric emptying breath delta over baseline (DOB) for 60 min following 595 ml of a 6% glucose solution ingestion. Treatments were control without fructose supplementation (-○-) and with 3 days supplementation of 120g of glucose per day (-●-).Values are means (*n* 10) with standard deviations represented as vertical bars.

Fig. 3: Subjective feeling of hunger assessed by 100-mm visual analogue scale (VAS) for 60 min following ingestion of 595 ml of a 6% glucose solution. Treatments were control without fructose supplementation (-○-) and with 3 days supplementation of 120g of glucose per day (-●-).Values are means (*n* 10) with standard deviations represented as vertical bars.

Tables

Table 1: Pre-ingestion body mass and hydration status

(Mean values with standard deviations, *n* 10)

	Fructose				Glucose				*P*-value (one-way ANOVA)
	Control		Supplementation		Control		Supplementation		
Pre-ingestion measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Body mass (kg)	80.91	11.48	81.23	11.53	81.80	11.70	81.34	11.38	0.589
Urine osmolality (mOsmol.kg^{-1})	423	259	489	265	425	230	452	270	0.613

Figure 1.

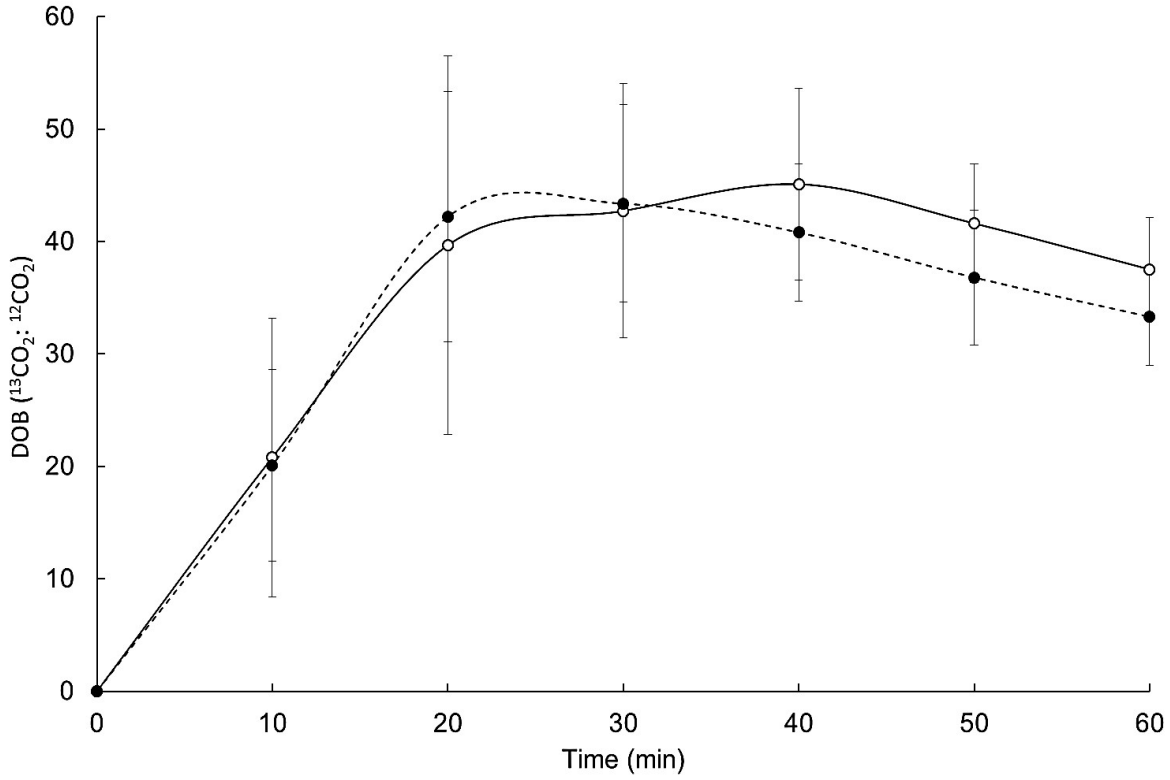
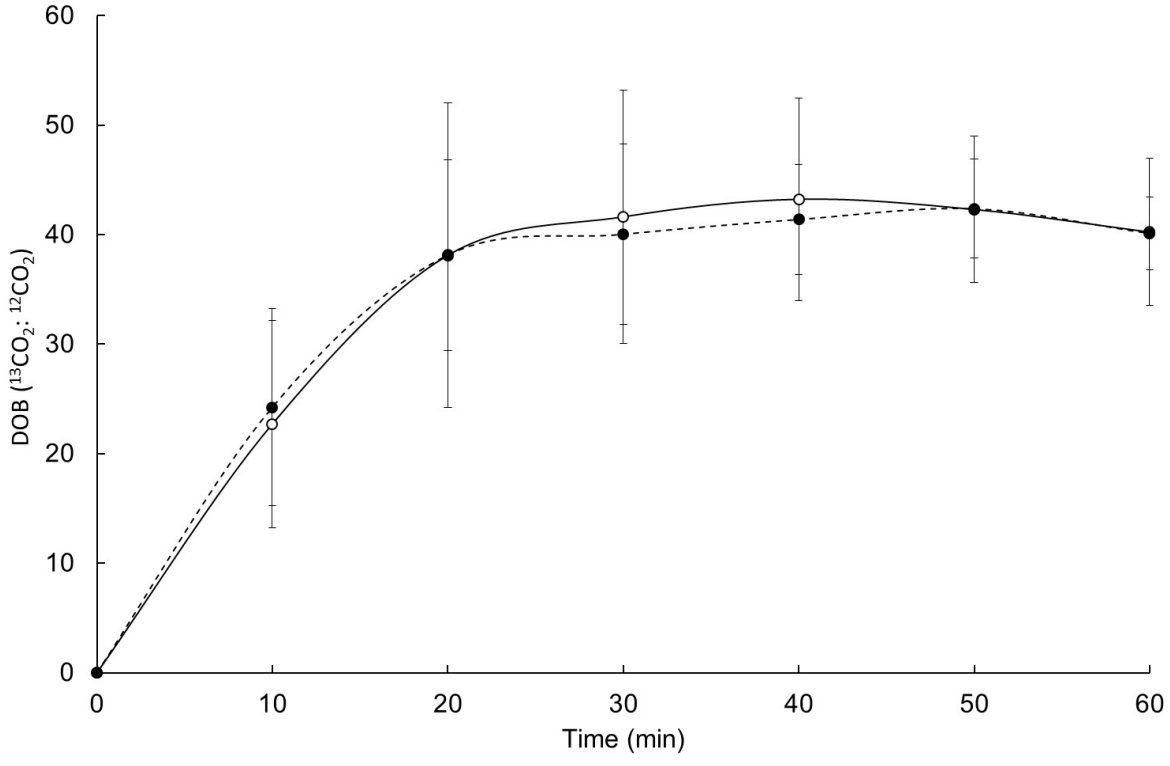


Figure 2.



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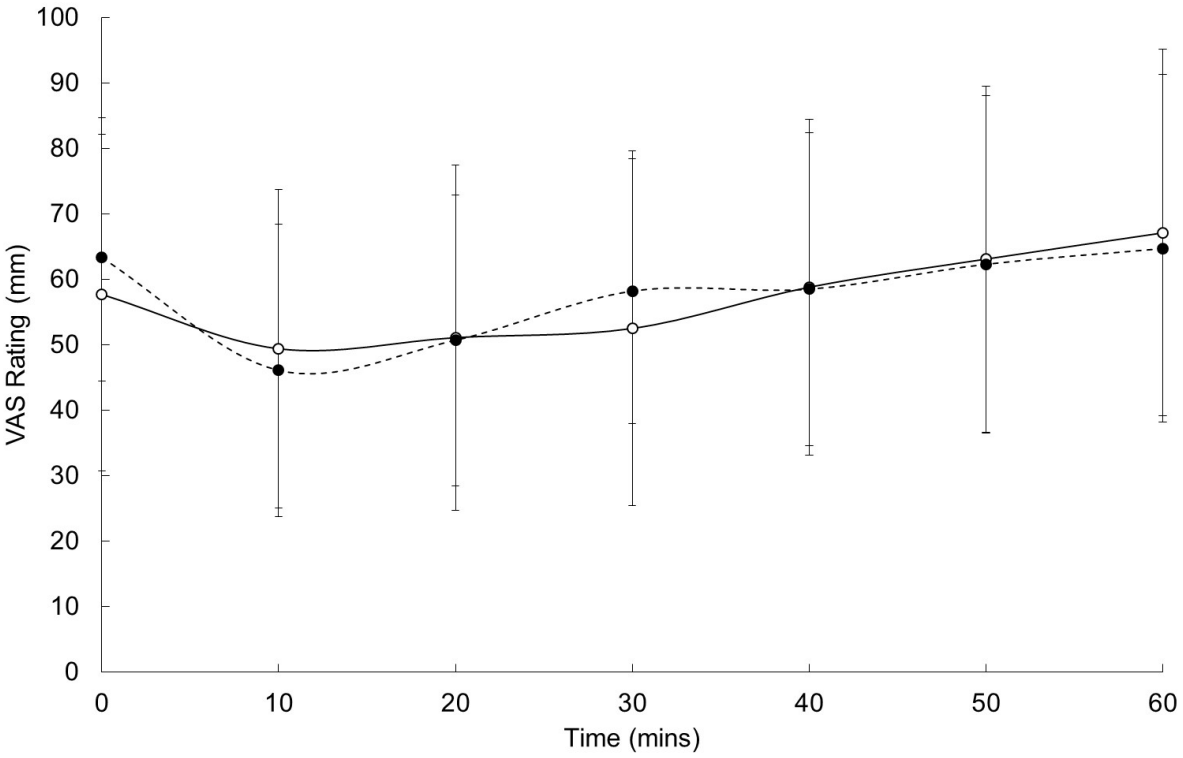
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