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Ingesting isomaltulose versus fructose-maltodextrin during prolonged moderate-heavy exercise increases fat oxidation but impairs gastrointestinal comfort and cycling performance

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Running title: Isomaltulose ingestion during endurance exercise

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Abstract

Certain commercial carbohydrate replacement products include slowly absorbed carbohydrates such as isomaltulose. Few studies have investigated the metabolic effects of ingesting isomaltulose during exercise and none have evaluated exercise performance and gastrointestinal comfort. Nine male cyclists participated postprandially during three trials of 2-h steady-state (S-S) exercise (60%W_max) followed by a 16 km time trial (TT) while ingesting 63 g·h⁻¹ of either, 0.8:1 fructose: maltodextrin (F:M) or isomaltulose (ISO) or placebo-flavoured water (PL). Data were analysed by magnitude-based inferences. During S-S exercise, ISO and PL similarly increased plasma non-esterified fatty acid (NEFA) concentration (mean change ISO versus F:M: 0.18, 90%CI ±0.21 mmol·L⁻¹, 88% likelihood) and fat oxidation (10, 90%CI ±9 g, 89% likelihood) while decreasing carbohydrate oxidation (-36, 90%CI ±30.2 g, 91% likelihood) compared with F:M, despite equal elevations in blood glucose concentration with ISO and F:M. Rating of stomach cramps and bloating increased progressively with ISO (rating: 0-90 min S-S, weak; 120 min S-S, moderate; TT, strong) compared with F:M and PL (0-120 min S-S and TT, very weak). TT performance was substantially slower with ISO (mean change: 1.5, 90%CI ±1.4 min, 94% likely harmful) compared with F:M. The metabolic response of ISO ingestion during moderate exercise to increase NEFA availability and fat oxidation despite elevating blood glucose concentration is anomalous for a carbohydrate supplement. However, ingesting isomaltulose at a continuous high frequency to meet the recommended carbohydrate replacement dose, results in severe gastrointestinal symptoms during prolonged or high intensity exercise and negatively affects exercise performance compared to fructose-maltodextrin supplementation.

Keywords: Low glycaemic index carbohydrates, multiple transportable carbohydrates, carbohydrate supplements
Introduction

The need for carbohydrate supplementation during endurance sports has been established (Bosch et al., 1996; Rauch et al., 1995). Previous studies have experimented with various types of carbohydrate supplements to establish which is most suitable for ingestion during endurance exercise (Achten et al., 2007; Azevedo et al., 2007; Jentjens & Jeukendrup, 2003; Moodley et al., 1992). Recent consensus supports the consumption of multiple-transportable carbohydrates (as a mix of fructose and glucose) in the region of 60-90 g·h⁻¹ during exercise lasting 2.5 hours or more (Burke et al., 2011; Jeukendrup, 2014), as the rate of exogenous carbohydrate oxidation is limited mainly by saturation kinetics of the respective intestinal transporters (Jentjens et al., 2004). Moreover, ingestion of fructose: glucose in ratios approaching unity (0.8-1.0) appears to represent the optimal approach to address the need to collectively promote exogenous carbohydrate oxidation, gastrointestinal comfort and the hydration properties of an ingested carbohydrate beverage in order to maximize performance benefits (O’Brein & Rowlands, 2011; Rowlands et al., 2008; Rowlands et al., 2013; Wallis & Wittekind, 2013). Despite the extensive evidence supporting the superiority of rapidly absorbed carbohydrates for ingestion during exercise, some sports nutrition companies fervently market products composed of slowly absorbed carbohydrates for use during endurance sports. One such slowly absorbed carbohydrate is isomaltulose.

Isomaltulose is a disaccharide synthesized by the enzymatic conversion of sucrose to alter the glycosidic bond between the glucose and fructose from α1-2 to α1-6 (Lina, 2002). While isomaltulose is completely digestible (Holub et al., 2010), the rate of hydrolysis of the α1-6 glycosidic bond of isomaltulose is considerably reduced compared to sucrose and has been reported to be up to 85% slower (Lina, 2002). Consequently, the glucose and fructose from the digestion of isomaltulose are absorbed slowly, resulting in a glycaemic index of 32 (Atkinson et al., 2008).

Ingesting isomaltulose (42-75 g) as a 2-h pre-exercise bolus is effective for maintenance of euglycaemia during short duration exercise (30-45 min) (Bracken et al., 2012; West et al., 2011) without any affect on exercise performance measured as distance completed in 10 min compared with a dextrose bolus, in untrained type 1 diabetics (Bracken et al., 2012). Only one previous study has
compared the metabolic effects of ingesting isomaltulose and sucrose (66 g·h⁻¹) during prolonged endurance exercise (150 min at 59% VO₂max) in overnight fasted healthy athletes and reported that 28% of the ingested isomaltulose was oxidised during 150 min of exercise, compared with 63% of ingested sucrose being oxidised (Achten et al., 2007). Thus, the exogenous carbohydrate oxidation rate of the ingested isomaltulose was notably reduced to ~50% of that observed with sucrose, resulting in similar substrate partitioning to when placebo-flavoured water was ingested where reliance on endogenous carbohydrate stores was greater than when ingesting sucrose (Achten et al., 2007). The metabolic findings from this study may suggest that isomaltulose is not suitable as a carbohydrate replacement for promoting endurance performance. However, this study failed to assess exercise performance and did not report on gastrointestinal comfort.

The severely restricted rate of exogenous carbohydrate oxidation when ingesting isomaltulose, may be expected to negatively affect endurance performance in overnight-fasted (Smith et al., 2010) or glycogen-depleted conditions (Bosch et al., 1996; Rauch et al., 1995). However, it may have less of an impact in athletes exercising postprandially (Correia-Oliveira et al., 2013; Madsen et al., 1996) when the duration of the exercise is not long enough to critically deplete endogenous carbohydrate stores. In such circumstances, stimulation of reward and motivation and maintenance of euglycaemia, which prevents central fatigue (Karelis et al., 2010), may be major mechanisms explaining the ergogenic effects of carbohydrate replacement. Thus, further investigation is warranted to elucidate whether ingestion of isomaltulose during endurance exercise may equally promote a favourable performance outcome comparable to the recommended multiple transportable carbohydrate supplement of 0.8:1 fructose: maltodextrin, when athletes exercise postprandially.

Therefore, the aims of the current study are to compare the metabolic, performance and the gastrointestinal comfort response when ingesting equal amounts of either isomaltulose or 0.8:1 fructose: maltodextrin as a 7% solution within the recommended carbohydrate replacement rate (63 g·h⁻¹) or placebo flavoured-water during prolonged strenuous steady-state exercise followed by a cycling time trial in healthy athletes who participated 2 h after a standard breakfast. Furthermore, we aimed to compare the glycaemic and insulinaemic response following the initial 30 min recovery.
period. We hypothesize that continual supplementation of isomaltulose or 0.8:1 fructose: maltodextrin at the recommended dose during prolonged endurance exercise will equally improve exercise performance compared with placebo-water in athletes participating postprandially. Furthermore, we hypothesize that ingestion of slowly absorbed isomaltulose will produce a more consistent blood glucose concentration during exercise and following a short recovery period than placebo-water or rapidly absorbed 0.8:1 fructose: maltodextrin.

**Methods**

**Participants**

Nine trained, male cyclists aged 38.0 ± 6.5 years, body mass 78.9 ± 6.8 kg, height 180.7 ± 4.3 cm and percentage body fat 16.9 ± 3.2% took part in this study (mean ± SD). The cyclists had 7.5 ± 2.7 years of competitive cycling experience, trained for 11.1 ± 2.6 h·week⁻¹, a VO₂max of 60.8 ± 4.8 mL·kg⁻¹·min⁻¹ and peak aerobic power output (Wmax) 4.2 ± 0.4 W·kg⁻¹. All cyclists completed a general health questionnaire to confirm that they were healthy, not on any medication and were non-smokers. All cyclists provided written consent to participate after all risks and procedures had been explained. Ethical clearance was obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand, Johannesburg, South Africa (M110241).

**Preliminary test and familiarisation**

All cyclists performed a standard incremental test to exhaustion for the determination of VO₂max and Wmax, as previously described (Oosthuysen et al., 2012). The cyclists were allowed as much time as needed to recover before completing a 16-km cycling time trial (TT) for the purpose of familiarising the cyclist with the TT course to be used during the experimental trials to evaluate cycling performance. The conditions of the familiarisation TT were identical to that used in the experimental trials as described later.

**Pre-experimental controls**

Cyclists kept a weekly training log and maintained a similar training and dietary routine for the duration of their participation in the study. The cyclists were instructed on how to keep a food
diary using explained descriptors for recording quantities of food items and composition of meals. For the 48 h period before the experimental trial the cyclists recorded their dietary intake and replicated these records before each subsequent experimental trial. The dietary records were checked for compliance before each experimental trial. No alcohol was permitted during this 48 h period. On the morning of each experimental trial, the cyclists ingested a pre-packed breakfast of bran flakes, raisins and skim milk (1774 kJ; 71 g carbohydrate, 7.3 g fat, 17.7 g protein) 2 h before arrival and were told to avoid caffeine.

**Experimental trials**

The experimental trials were performed using a randomised, double-blind, three-way crossover design where each cyclist ingested an equal volume of either a non-caloric placebo drink (PL) or 1 of 2 experimental 7% carbohydrate beverages composed of either: slowly absorbed, isomaltulose (ISO) or rapidly absorbed, 0.8:1 fructose: maltodextrin (F:M).

Cyclists arrived at the laboratory at 0700 hours and after voiding urine, body mass was recorded wearing only cycling shorts. After 20 min of supine resting a 5 mL blood sample was obtained from an antecubital vein. Indirect calorimetry measurements (Oxycon 4, Erich Jaeger, Hoechberg, Germany) were taken for 5 min with the cyclists seated at rest on a fixed-load stationary ergometer (Lode Excalibur, Groningen, Netherlands). The cyclists then ingested 400 mL of one of the test beverages (PL; ISO; or F:M) before commencing exercise at a 60% $W_{max}$ for 2 h. Heart rate was recorded by telemetry at 5 s intervals (RS-800CX, Polar, Kempele, Finland). Indirect calorimetry measures were recorded for 3 min durations prior to the end of every 15 minute interval during the steady-state exercise and 200 mL of the test beverage was then ingested at every 15 min time-point. The cyclists reported their rate of perceived exertion using a 10-point scale Borg every 30 min. Gastrointestinal discomfort for thirst, bloating, nausea, stomach cramps and sweetness of the drink was rated every 30 min by a 10-point scale, as used previously (Rowlands et al., 2008), where 0 corresponds to nothing, 1 very weak/ mild; 2 weak; 3 moderate; 5 strong; 7 very strong; and 10 extremely strong. At 60 and 90 min a finger-prick blood sample was obtained for automated measurements of blood glucose and lactate concentration. On completion of the 2-h of steady-state
cycling a 5 mL blood sample was obtained. Thereafter the cyclists immediately commenced a 16-km cycling TT.

For all TT, the cyclists rode on their own bicycles setup on a Tacx i-Magic ergometer (Tacx bv, Wassenaar, Netherlands) that was interfaced with computer software to simulate a 16 km route with an undulating gradient. The ergometer was calibrated before each TT to ensure that a constant resistance was applied to the rear bicycle wheel during all tests. Tyre pressure and bicycle setup were maintained constant between each TT. The cyclists were instructed to apply their best effort to complete the 16-km course as quickly as possible. The cyclists could follow their progression via animated video footage of the course, which also provided continuous feedback of the distance completed. However, the speed and time elapsed were concealed from the cyclist. Time to complete the TT was used as a measure of performance. The cyclists drank a 200 mL aliquot of the test beverage immediately before commencing the time trial and a further 200 mL at 8 km during the TT (of which the cyclists were made aware of at the start of the TT). On completion of the TT gastrointestinal comfort ratings were reported. The cyclists recovered in a supine position for 30 min before a final 5 mL blood sample was obtained. Throughout all exercise tests the cyclists were cooled by a fan and ambient conditions were kept constant (17-19 °C) by air-conditioning.

Experimental beverages

All beverages besides the placebo were prepared as a 7% carbohydrate solution and ingested according to the drinking routine already described, which equated to 900 mL·h⁻¹ and carbohydrate ingestion rate of 63 g·h⁻¹. In the ISO beverage, the only source of carbohydrate was isomaltulose (Palatinose, Beneo-Palatinit GmbH, Mannheim, Germany). In the F:M beverage, the source of carbohydrate consisted of a 0.8:1 ratio of fructose: maltodextrin providing 27.7 g·h⁻¹ from fructose (Krystal 300 crystalline fructose, Tate and Lyle, Decatur, IL, USA) and 35.3 g·h⁻¹ from maltodextrin (Glucidex 12, Roquette Frères, Lestrem Cedex, France). All beverages including the non-caloric placebo (PL) were matched for sweetness, colour and flavour by the addition of non-nutritive sweeteners, citric acid, β carotene, flavourants and sodium chloride. The osmolality of the beverages
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determined by vapour pressure depression (Vapro model 5600, Wescor, Logan, Utah, USA) were 62.5, 245 and 212 mOsm·kg⁻¹ for the PL, ISO and F:M drinks, respectively.

**Sample analysis and calculations**

Blood samples were collected into a vacutainer containing EDTA and kept on ice until centrifugation at 1500 x g for 10 min at 4°C. Plasma glucose (Ascensia Elite, Bayer Consumer Care, Basel, Switzerland) and lactate concentration (Lactate Pro, Arkray Europe, Amstelveen, The Netherlands) were determined enzymatically by automated analysers. Plasma was stored at -20 °C until analysis for insulin concentration by enzyme-linked immune specific assay (EIA-2935, DRG International, New Jersey, USA) and non-esterified fatty acid (NEFA) concentration by spectrophotometric enzyme assay (Cat. No. 11383175001, Roche Diagnostics, Penzberg, Germany). Samples were assayed in duplicate and all samples from each cyclist were included in the same assay.

Total carbohydrate and fat oxidation rates (g·min⁻¹) were calculated using stoichiometric equations for moderate to high intensity exercise (Jeukendrup & Wallis, 2005).

**Statistical analysis**

To allow comparison with a large proportion of the recently published studies in this field, data were analysed using probabilistic magnitude-based inferential analysis, which has been recommended (Atkinson et al., 2012; Hopkins et al., 2009) and described previously (O’Brien & Rowlands 2011; O’Brien et al., 2013; Rowlands et al., 2008, 2012; Smith et al., 2010) to analyze the physiological magnitude of effect.

Inferential analysis was done using a published spreadsheet (Hopkins, 2007). Metabolic and performance data were log-transformed to reduce non-uniformity of error and to express outcomes as a percentage. The metabolic and psychometric data were described by mechanistic inferences where the magnitude of effect was tested for substantiveness against the standardised (Cohen) change of 0.2 times the between-subject standard deviation for the reference condition (namely, PL) and uncertainty was described by 90% confidence intervals. Performance data were described by clinical inferences where the threshold for substantial change was given by 0.3 times the within-subject variability.
between trials to test for a small effect (0.7% change), while moderate and large performance effects
were described by 0.9 and 1.6 of the within-subject variability (2% and 3.5% change), respectively, as
previously described (O’Brien et al., 2013). The likelihood of a substantial increase or decrease was
calculated from the two-tailed Student’s t distribution and classified as follows: <1%, almost certainly
not; 1-5%, very unlikely; 5-25%, unlikely; 25-75%; possibly, 75-95%; likely; 95-99%, very likely;
>99%, almost certainly (Hopkins, 2007; Hopkins et al., 2009). An effect is unclear if the uncertainty
(confidence interval) includes both a positive and negative effect of >5%. Furthermore, Cohen’s effect
size scores (ES) were presented and interpretation of the magnitude of the standardised change was as
follows: trivial, 0.0-0.2; small, 0.2-0.6; moderate, 0.6-1.2; large, 1.2-2.0; very large, >2.0. Data are
presented as mean ± SD and the results describing the magnitude of change between treatments are
presented as mean percentage change (± 90%CI), ES and qualitative inference (Hopkins et al., 2009).

Results

2-h steady-state exercise

The exercise intensity during the 2-h steady-state exercise was 194 ± 13 W (58.9 ± 1.6
%W_{max}) for all trials and the average intensity as measured by indirect calorimetry equated to 65.6 ±
2.6, 63.8 ± 7.0, and 65.2 ± 3.3 %VO_{2max} during the PL, ISO and F:M trials, respectively. There were
no substantial differences in heart rate between trials during the first hour of steady-state exercise or
during TT. However, heart rate was substantially higher (82% likely increase; ES = 0.49) during the
2nd hour of steady-state exercise in ISO compared with PL (Table 1).

Substrate utilisation

The average carbohydrate oxidation rate in the first and second hour of steady-state exercise
and therefore total carbohydrate oxidised was substantially less when ingesting the ISO beverage than
when ingesting the F:M beverages (Table 2). Furthermore, the rate of fat oxidation, when ingesting
the ISO beverage compared with the F:M beverage, was likely greater in the first, and possibly greater
in second hour of exercise resulting in a likely greater total amount of fat oxidised. No substantial
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Differences in substrate partitioning were evident between the ISO and PL trials, while carbohydrate oxidation was greater and fat oxidation was less in the F:M trial compared to PL trial (Table 2).

**Blood metabolites**

During 2 h steady-state exercise, ingestion of F:M and ISO substantially increased plasma glucose concentration similarly compared with ingestion of PL at all time points (ES = 1.09-2.19) (Figure 1a). However, euglycaemia was maintained throughout exercise in the PL trial; where hypoglycaemia is regarded as a blood glucose concentration ≤ 3.5 mmol·L⁻¹ (Bracken et al., 2012). After 30 min of recovery following the TT, plasma glucose concentration was substantially greater in ISO than F:M (84% likelihood; ES = 0.84). Interestingly, plasma lactate concentration was substantially higher with ISO at 90 min of steady-state exercise compared with F:M (97% likelihood; ES = 0.8) and PL (96% likelihood; ES = 1.17) and greater following 120 min of steady-state exercise compared with PL (91% likelihood; ES = 2.13) (Figure 1b). Plasma insulin concentration was similar between trials, besides following 120 min of steady-state exercise, where plasma insulin was greater in the F:M trial than PL trial (93% likelihood; ES = 0.83) (Figure 1c). Plasma NEFA concentration was substantially lower during the F:M trial following 120 min of steady-state exercise compared with the ISO (88% likelihood; ES = -0.60) and PL (99% likelihood; ES = -0.76) and after 30 min of recovery following the TT compared with ISO (97% likelihood; ES = -1.03) (Figure 1d).

**Perceived exertion and gastrointestinal discomfort**

Following 30 min of steady-state exercise the cyclists rated their perceived exertion as less during the F:M (85% likelihood) and ISO (92% likelihood) trials compared with PL (Figure 2). However, by 120 min of steady-state exercise, perceived exertion was substantially greater during the ISO trial than F:M (93% likelihood).

When ranked on a scale of 0-10, both the PL and ISO drinks were perceived as moderately sweet (mean ± SD: PL, 3.5 ± 1.4; and ISO, 3.7 ± 1.1) but were substantially less sweet (99% likelihood) than the F:M drink (mean ± SD: F:M, 6.6 ± 2.2). However, when asked none of the participants were able to correctly identify the respective beverages. Cyclists reported similar
perception of thirst in all three trials (Figure 3). The ISO drink resulted in substantially greater symptoms of gastrointestinal discomfort than the PL and F:M drinks during both steady-state exercise and TT (Figure 3). While gastrointestinal discomfort during the ISO trial was rated as weak-moderate until 90 min of steady-state exercise, it progressed to moderate-strong discomfort by 120 min of steady-state exercise and strong-very strong during the TT, with bloating and gastrointestinal cramps being the main complaints. Furthermore, all subjects reported severe gastrointestinal discomfort during the remainder of the day following the ISO trial that in some instances included diarrhoea.

**TT performance**

The mean ± SD time to complete the 16-km TT was, 28:39 ± 2:49; 29:39 ± 3:17; and 28:27 ± 2:41 (min:s) for the PL; ISO; and F:M, respectively. Time to complete the TT was substantially slower (mean change: 1.5 min, 90%CI ±1.4 min; ES = 0.53) when ingesting the ISO beverage compared with the F:M beverage that corresponds to a small (94% likelihood) to moderate (87% likelihood) harmful effect (Figure 4). There were no other substantial differences in performance.

**Discussion**

The main findings of the current study are: firstly, contrary to our hypothesis, the ingestion of the slowly absorbed carbohydrate, isomaltulose, within the recommended rate for endurance exercise, during 2-h of moderate-heavy steady-state exercise followed by a cycling TT resulted in gastrointestinal distress and impeded exercise performance compared to ingestion of an equivalent amount of rapidly absorbed carbohydrate, 0.8:1 fructose: maltodextrin (F:M). Secondly, ingestion of isomaltulose did not, however, suppress NEFA availability and fat oxidation, which was evident with ingestion of F:M, despite plasma glucose concentration being equally elevated during exercise with both ISO and F:M ingestion compared with PL. Lastly, contrary to our hypothesis, ingestion of ISO produced a substantially higher 30 min recovery blood glucose concentration compared with F:M.

The findings of the current study concur with previous studies that reported a lower total carbohydrate oxidation and greater fat oxidation during short duration exercise (< 1 h) when ISO is ingested as a 2-h pre-exercise bolus compared with dextrose in type 1 diabetics (West et al., 2011) and
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when ISO was compared with sucrose and ingested by athletes at a similar dose to the current study during prolonged exercise (2.5 h) (Achten et al., 2007). However, these previous studies employed overnight fasted participants (Achten et al., 2007; West et al., 2011) and the latter exercised at a slightly lower exercise intensity (50% $W_{\text{max}}$) (Achten et al., 2007) compared to the current study (60% $W_{\text{max}}$). Therefore, the ingestion of ISO during exercise reduces carbohydrate oxidation while increasing fat oxidation compared with the ingestion of a high glycemic carbohydrate and based on the findings of the current study this also occurs in fed athletes, exercising at moderate-heavy intensities and when compared to a more typical carbohydrate supplement reference (0.8:1 fructose: maltodextrin). While isomaltulose is traditionally produced from the C3 photosynthetic beet plant, it is assumed that Achten et al. (2007) used ISO that had been specially synthesized from C4 photosynthetic-derived cane sugar, as these authors depended on the natural carbon-13 enrichment of the ISO to quantify exogenous carbohydrate oxidation. Using this method, Achten et al. (2007) were able to show that the greater rate of total carbohydrate oxidation with ingestion of sucrose compared to ISO, occurs only because of a greater rate of exogenous carbohydrate oxidation, when athletes followed a similar rate of carbohydrate ingestion (66 g·h$^{-1}$) to that applied in the current study. Moreover, despite the lower rate of total carbohydrate oxidation with ingestion of ISO compared to sucrose, they found that the rate of endogenous carbohydrate oxidation was greater with ISO (Achten et al., 2007).

The finding of the current study, that blood glucose concentration was similarly elevated throughout steady-state exercise with ISO and F:M (0.8:1 fructose: maltodextrin) ingestion compared to PL in fed athletes where the various carbohydrate beverages were continually supplemented throughout exercise, also agrees with the study of Achten et al. (2007) where ISO was compared with sucrose ingestion in overnight-fasted athletes. This may be surprising considering the slower digestion of ISO (Lina et al., 2002). However, it is known that 90-95% of all glucose appearing in circulation is taken up and oxidised (Jeukendrup et al., 1999a). Therefore, the quickly absorbed glucose following ingestion of F:M can be expected to be immediately taken up and metabolised by metabolic tissues, thereby resulting in a similar blood glucose response to ISO despite distinctly different rates of
glucose absorption. Conversely, ingestion of ISO as a pre-exercise bolus 2 h before exercise (~42 g) in overnight fasted type 1 diabetics produced a consistently lower blood glucose concentration throughout exercise and in the initial 15 min of recovery, compared to pre-exercise ingestion of dextrose (Bracken et al., 2012). However, comparison with this latter study is limited as in the current study athletes participated following a pre-exercise carbohydrate meal and received continual carbohydrate supplements throughout exercise. In contrast, the overnight fasted type 1 diabetics who ingested only a small carbohydrate bolus 2 h before exercise may likely have participated with low hepatic glycogen stores, particularly in the ISO trial where slow digestion may have precluded replenishment of hepatic stores prior to exercise. In fact, in the current study, blood glucose concentration was not only similarly elevated throughout steady-state exercise with ingestion of ISO and F:M, but after subsequently completing a high intensity TT, at 30 min into recovery, blood glucose concentration was substantially higher in the ISO compared to F:M. Post exercise hyperglycaemia is common following high intensity exercise of >80%VO2max owing to a high rate of catecholamine-stimulated hepatic glycogenolysis and gluconeogenesis during such exercise that may continue to persist into recovery despite a rapid decrease in skeletal muscle glycolytic rate on exercise cessation (Marliss & Vranic, 2002). The increase in hepatic glucose production during and after intense exercise is driven by catecholamines (Marliss & Vranic, 2002). Therefore, the greater 30 min post exercise blood glucose concentration in ISO may be suggestive of such continued over-solicitation of hepatic stores. This was not evident in the F:M trial possibly owing to a sufficient supply of exogenous carbohydrate reducing the metabolic stress, catecholamine response (Lee-Young et al., 2006) and hepatic glucose demand (Jeukendrup et al., 1999b) of the high intensity exercise. Furthermore, the ISO trial may have also induced a larger catecholamine stress response as a consequence of the increasingly severe gastrointestinal discomfort that was more pronounced during the TT than during steady-state exercise. In addition, as the digestion and absorption of ISO is delayed, some ISO ingested during exercise may have continued to be absorbed during recovery—particularly once blood flow to splanchnic regions had returned to normal, and thereby also contribute towards the higher recovery blood glucose concentration noted in ISO compared with F:M. The
finding from the current study suggest that ISO is suitable for maintaining euglycaemia during moderate-heavy steady-state exercise in healthy athletes, however, following a subsequent bout of high intensity exercise, an ensuing post exercise hyperglycaemic response may occur. Whether the same response would occur in type 1 diabetics remains to be determined.

Although, plasma insulin concentration was not measured throughout exercise, but only pre-exercise, immediately on completion of 2 h steady-state exercise and after 30 min recovery following the TT, insulin concentration was not notably different between ISO and F:M and only higher during F:M than PL at 120 min of steady-state exercise. Previously, Achten et al. (2007) who measured insulin concentration at earlier time points during exercise, reported insulin to be consistently higher with sucrose ingestion than placebo but only significantly greater than ISO at 30 min of exercise. Nevertheless, the higher insulin concentrations during exercise with ingestion of sucrose resulted in lower plasma NEFA concentrations, supposedly owing to insulin-induced suppression of lipolysis (Achten et al. 2007). Similarly, in the current study plasma NEFA concentration was also lower at 120 min of steady-state exercise with F:M ingestion compared to ISO and PL and this difference persisted 30 min post TT exercise. The greater NEFA availability during ISO and PL may partly explain the greater total fat oxidation that occurred during those trials (Horowitz et al., 1997). Thus, the current findings further support that ingestion of ISO during prolonged endurance exercise that includes high intensity exercise allows for the maintenance of euglycaemia without suppression of plasma NEFA concentration and fat oxidation; which typically occurs when ingesting rapidly absorbed carbohydrates (De Gliseizinski et al., 1998; Horowitz et al., 1997). Future studies should explore conditions where this atypical metabolic response with ISO ingestion as a carbohydrate supplement may be beneficial.

Interestingly, blood lactate concentration was modestly yet substantively higher in the latter stages of 2 h steady-state exercise during ISO compared to F:M and PL. Fructose is rapidly metabolised in enterocytes and hepatic cells via phosphorylation by fructokinase to form fructose-1-phosphate which subsequently feeds into the glycolytic pathway after phosphofructokinase resulting in a rapid glycolytic flux that increases lactate production (Tappy & Lê, 2010). Therefore fructose
ingestion is characterised by an increased blood lactate concentration and oxidation (Lecoultre et al., 2010). While both ISO and the F:M drinks in the current study comprise a high fructose portion, ISO being a disaccharide similar to sucrose has a 1:1 ratio of fructose:glucose, whereas the F:M beverage was specifically formulated to include the recommended 0.8:1 fructose: maltodextrin ratio. Thus, the amount of fructose ingested was modestly greater with ISO (31.5 g·h⁻¹) than F:M (27.7 g·h⁻¹).

Nevertheless, it may be unlikely that this difference in fructose ingestion would account for the higher blood lactate concentration in the latter stages of 2 h steady-state exercise of the ISO trial because the severely restricted rate of digestion of ISO would have reduced the rate of absorption and therefore metabolism of the fructose compared to when F:M was ingested. Rather, the incidence of gastrointestinal discomfort increased progressively with exercise duration and by the second hour may have imposed a sympathetic stress response that would stimulate a less efficient increase in glycolytic flux as suggested by the higher blood lactate concentrations. While catecholamine concentrations were not measured in the current study, the higher heart rate during the 2nd hour of steady-state exercise in ISO compared with PL and higher rating of perceived exertion near the end of the 2nd hour in ISO compared with F:M further supports the argument for a greater sympathetic stress response with ISO. Previously, Achten et al. (2007) reported no difference in blood lactate concentration during steady-state exercise with ingestion of ISO and sucrose. However, exercise intensity was marginally less in that previous study (50%\(W_{\text{max}}\)) (Achten et al., 2007) than in the current study (60%\(W_{\text{max}}\)). Although not reported, the lower exercise intensity in the former study may have resulted in less of an effect on gastrointestinal discomfort that is compounded by splanchnic blood flow restriction, which is intensity dependent and regulated by sympathetic \(\alpha\)-adrenergic stimulation (de Oliveira et al., 2014).

The compromised cycling TT performance in the ISO trial compared with the F:M trial is likely related to the strong gastrointestinal symptoms experienced in the ISO trial during the high intensity effort of the TT. Gastrointestinal discomfort has previously been related to performance decrements (Rowlands et al., 2012). Over the time-frame of exercise in the current study (~2.5 h), it is unlikely that the previously demonstrated greater rate of endogenous carbohydrate utilisation with
ISO ingestion (Acthen et al., 2007) would have notably compromised performance in our cyclists who participated postprandially. Furthermore, as F:M did not substantially improve TT performance compared to PL, this further argues against a metabolic-link to explain the performance decrement observed during the ISO trial. The ergogenic effect of a carbohydrate supplement is bigger following an overnight fast than in a fed condition (Correia-Oliveira et al., 2013). Therefore, the lack of effect of F:M to improve TT performance compared to PL is likely mainly owing to the participants exercising 2 h following a carbohydrate-rich meal and exercise duration being sufficiently short (~2.5 h) to precede hepatic glycogen depletion as supported by maintained blood glucose concentrations. Similar findings have been reported previously (Madsen et al., 1996). Differences may possibly become more apparent should exercise duration be increased as supported by a recent postprandial study where the total exercise duration was ~3 h (2 h exercise at 55% Wmax and 30 km TT) and TT performance was likely improved with a 62 g·h⁻¹ glucose supplement compared to the placebo trial during which blood glucose concentration dropped critically low (~65 mg·dL⁻¹ or 3.6 mmol·L⁻¹) (Baur et al., 2014).

In the current study, the metabolic response to exercise in the ISO trial was similar to PL, besides a higher blood glucose response in ISO. However, the positive effect of the higher blood glucose concentration and possible oral stimulation of reward and motivation in the ISO trial may have been offset against the greater gastrointestinal distress experienced in ISO than PL and thereby explain the lack of substantial difference in TT performance between these trials.

The moderate-to-severe gastrointestinal discomfort that occurred with the continual ingestion of ISO throughout exercise may be explained by the slow digestion of the α1-6 glycosidic bond (Lina et al., 2002) that would result in prolonged retention of ISO and possibly fluid in the small intestine. Furthermore, the symptoms became progressively worse due to the continual drinking routine that may have caused saturation of the maltase-isomaltase enzyme and a summative build up of undigested ISO. The reported incidence of diarrhoea would support the likelihood for intestinal fluid retention to have occurred. For this reason, future studies should consider the capacity for an ISO beverage to promote rehydration during exercise when using a frequent drinking strategy. Furthermore, it is indeterminate whether the extent of gastrointestinal symptoms observed in the
current study would also be observed at lower exercise intensities or with a lower hourly rate of carbohydrate ingestion or possibly when ingested in smaller fluid volumes. Such questions should be considered in order to thoroughly determine the value of ISO as a carbohydrate replacement during exercise.

Conclusions

The novel findings of this study are that ingestion of isomaltulose throughout prolonged moderate-high intensity endurance exercise within the recommended dose for carbohydrate replacement imposes gastrointestinal distress and impairs cycling TT performance compared to the recommended multiple transportable carbohydrate supplement of 0.8:1 fructose: maltodextrin. Furthermore, regular ingestion of isomaltulose during exercise promotes the incidence of higher blood glucose concentration during recovery following high intensity TT exercise in healthy athletes that should be investigated further if isomaltulose is to be considered for type 1 diabetics during prolonged exercise that includes high intensities. However, the ability of isomaltulose to maintain euglycaemia during prolonged exercise, equal to when ingesting 0.8:1 fructose: maltodextrin, and still promote an increase in plasma NEFA concentration and fat oxidation equal to placebo-water is unique for a carbohydrate supplement and circumstances where this may be beneficial should be explored.

Acknowledgements

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The authors have no conflict of interest. The study was designed by TO and AMEM; data were collected and analysed by TO, MC, and AMEM; data interpretation and manuscript preparation were undertaken by TO, MC and AMEM. All authors approved the final version of the paper.
References


“Ingesting Isomaltulose Versus Fructose-Maltodextrin During Prolonged Moderate-Heavy Exercise Increases Fat Oxidation But Impairs Gastrointestinal Comfort and Cycling Performance” by Oosthuyse T, Carstens M, Millen AM
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**Figure 1.** Comparison of plasma glucose (A), lactate (B), insulin (C) and non-esterified fatty acids (NEFA) (D) concentration during 2 h of steady-state exercise and after 30 min of recovery following a 16 km time trial (30 post) with ingestion of placebo-flavoured water (PL), isomaltulose (ISO) or 0.8:1 fructose: maltodextrin (F:M) presented as mean and SD. The symbol ††, ††† and †††† denotes ISO likely, very likely and almost certainly greater than PL at that time, respectively. The symbol §§, §§§ and §§§§ denotes F:M likely, very likely and almost certainly different to PL at that time, respectively. The symbol ** and *** denotes ISO likely and very likely greater than F:M at that time, respectively.
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**Figure 2.** Comparison of rate of perceived exertion during 2 h of steady-state exercise with ingestion of placebo-flavoured water (PL), isomaltulose (ISO) or 0.8:1 fructose: maltodextrin (F:M) presented as mean and SD. The symbol †† denotes ISO likely lower than PL. The symbol §§ denotes FMD likely lower than PL. The symbol ** denotes ISO likely greater than F:M.
Figure 3. Comparison of gastrointestinal discomfort during 2 h of steady-state exercise and after 30 min of recovery following a 16 km time trial (30 post) with ingestion of placebo-flavoured water (PL), isomaltulose (ISO) or 0.8:1 fructose: maltodextrin (F:M) presented as mean and SD. The symbol ††, ††† and †††† denotes ISO likely, very likely and almost certainly greater than PL at that time, respectively. The symbol **, *** and **** denotes ISO likely, very likely and almost certainly greater than F:M at that time, respectively.
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**Figure 4.** Percentage change and 90% CI of cycling time trial finishing time with ingestion of placebo-flavoured water (PL), isomaltulose (ISO) or 0.8:1 fructose: maltodextrin (F:M); where a trivial, small, moderate and large threshold for effect is indicated by dashed gridlines. ISO-PL indicates the differences between ISO and PL, F:M-PL indicates the difference between F:M and PL and ISO-F:M indicates the difference between ISO and F:M. The symbol ** denotes a small to moderate likely slower time for ISO compared to F:M.
Table 1 Comparison of the heart rate response during 2-h steady-state exercise and 16-km time trial when ingesting placebo (PL), low glycaemic index, isomaltulose (ISO), or high glycaemic index, 0.8:1 fructose: maltodextrin (F:M) beverages.

<table>
<thead>
<tr>
<th>Heart rate (bpm)</th>
<th>PL</th>
<th>ISO</th>
<th>F:M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady-state exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st hour</td>
<td>140 ± 12</td>
<td>146 ± 13</td>
<td>142 ±12</td>
</tr>
<tr>
<td>2nd hour</td>
<td>139 ±15</td>
<td>149 ±17†</td>
<td>143 ± 15</td>
</tr>
<tr>
<td>Time-trial</td>
<td>165 ± 16</td>
<td>168 ±11</td>
<td>166 ±15</td>
</tr>
</tbody>
</table>

Note. Data are presented as mean ± SD. †† denotes that heart rate is likely higher in ISO than PL at that time.
**Table 2** Comparison of substrate utilisation during steady-state exercise while ingesting placebo (PL), isomaltulose (ISO) or 0.8:1 fructose:maltodextrin (F:M) carbohydrate beverages

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effect (percent change ±90%CI)</th>
<th>Effect size (ES)</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F:M - PL</td>
<td>ISO - PL</td>
<td>ISO F:M</td>
</tr>
<tr>
<td>CHO oxidation rate (g·min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1st hour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td>2.41 ± 0.37</td>
<td>11.6% ± 9.0%</td>
<td>ES = 0.49 (small)</td>
</tr>
<tr>
<td>ISO</td>
<td>2.30 ± 0.34</td>
<td>-4.6% ± 14.1%</td>
<td>ES = -0.31 (small)</td>
</tr>
<tr>
<td>F:M</td>
<td>2.6 ± 0.23</td>
<td>-13.9% ± 12.2%</td>
<td>ES = -0.83 (mod)</td>
</tr>
<tr>
<td></td>
<td>90% likely increased</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>93% likely decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2nd hour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td>1.95 ± 0.21</td>
<td>17.1% ± 17.6%</td>
<td>ES = 0.59 (small)</td>
</tr>
<tr>
<td>ISO</td>
<td>1.88 ± 0.23</td>
<td>-3.3% ± 6.2%</td>
<td>ES = -0.30 (small)</td>
</tr>
<tr>
<td>F:M</td>
<td>2.17 ± 0.19</td>
<td>-15% ± 13.4%</td>
<td>ES = -1.38 (large)</td>
</tr>
<tr>
<td></td>
<td>85% likely increased</td>
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<tr>
<td></td>
<td>unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% likely decreased</td>
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<td></td>
</tr>
<tr>
<td>Total CHO oxidation (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td>261.4 ± 31.4</td>
<td>13.8% ± 12.3%</td>
<td>ES = 0.56 (mod)</td>
</tr>
<tr>
<td>ISO</td>
<td>250.9 ± 33.2</td>
<td>-4.1% ± 9.9%</td>
<td>ES = -0.33 (small)</td>
</tr>
<tr>
<td>F:M</td>
<td>286.4 ± 20.5</td>
<td>-14.7% ± 11.7%</td>
<td>ES = -1.13 (mod)</td>
</tr>
<tr>
<td></td>
<td>88% likely increased</td>
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<tr>
<td></td>
<td>unclear</td>
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<tr>
<td></td>
<td>95% likely decreased</td>
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<tr>
<td>Fat oxidation rate (g·min⁻¹)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>1st hour</strong></td>
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</tr>
<tr>
<td>PL</td>
<td>0.60 ± 0.15</td>
<td>-17.1% ± 16.7%</td>
<td>ES = -0.58 (small)</td>
</tr>
<tr>
<td>ISO</td>
<td>0.61 ± 0.20</td>
<td>0.7% ± 31.2%</td>
<td>ES = 0.09 (trivial)</td>
</tr>
<tr>
<td>F:M</td>
<td>0.50 ± 0.15</td>
<td>18.4% ± 18.2%</td>
<td>ES = 0.76 (mod)</td>
</tr>
<tr>
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<td>92% likely decreased</td>
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<td>unclear</td>
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<td></td>
<td>93% likely increased</td>
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</tr>
<tr>
<td><strong>2nd hour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td>0.76 ± 0.13</td>
<td>-14.2% ± 20.1%</td>
<td>ES = -0.61 (mod)</td>
</tr>
<tr>
<td>ISO</td>
<td>0.72 ± 0.21</td>
<td>-8.1% ± 22.9%</td>
<td>ES = -0.34 (small)</td>
</tr>
<tr>
<td>F:M</td>
<td>0.67 ± 0.16</td>
<td>6.7% ± 10.5%</td>
<td>ES = 0.41 (small)</td>
</tr>
<tr>
<td></td>
<td>85% likely decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>unclear</td>
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<tr>
<td></td>
<td>74% possibly increased</td>
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<td></td>
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<tr>
<td>Total fat oxidation (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td>81.8 ± 16.5</td>
<td>-15.1 ± 18.4%</td>
<td>ES = -0.60 (mod)</td>
</tr>
<tr>
<td>ISO</td>
<td>79.9 ± 24.3</td>
<td>-4.3% ± 26%</td>
<td>ES = -0.11 (trivial)</td>
</tr>
<tr>
<td>F:M</td>
<td>69.9 ± 17.7</td>
<td>11.8% ± 11.1%</td>
<td>ES = 0.61 (mod)</td>
</tr>
<tr>
<td></td>
<td>88% likely decreased</td>
<td></td>
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<tr>
<td></td>
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</table>
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*Note.* CHO- carbohydrate;

*a* Average for each treatment are presented as mean ± SD;

*b* Mean effect is measured as percentage change between treatments and 90% confidence interval of the change;

*c* Effect size (ES) expresses the magnitude of the standardised difference where 0.0-0.2 is trivial; 0.2-0.6 is moderate; 0.6-1.2 is large, and 1.2-2.0 is very large.

*d* Inference refers to the likelihood of a substantial effect being positive, trivial or negative based on probability thresholds derived from the *t* distribution and are assigned the following qualitative terms: <1% is *almost certainly not*; 1-5%, *very unlikely*; 5-25%, *unlikely*; 25-75%, *possibly*; 75-95%, *likely*; 95-99%, *very likely*; >99%, *almost certainly* (Hopkins 2007). An effect is unclear if the uncertainty (confidence interval) includes both a positive and negative effect of >5%.