Fructose modifies the hormonal response and modulates lipid metabolism during aerobic exercise after glucose supplementation

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ABSTRACT

The metabolic response when aerobic exercise is performed after the ingestion of glucose plus fructose is unclear. In the present study, we administered two beverages containing GluF (glucose + fructose) or Glu (glucose alone) in a randomized cross-over design to 20 healthy aerobically trained volunteers to compare the hormonal and lipid responses provoked during aerobic exercise and the recovery phase. After ingesting the beverages and a 15-min resting period, volunteers performed 30 min of moderate aerobic exercise. Urinary and blood samples were taken at baseline (t−15), during the exercise (t0, t15 and t30) and during the recovery phase (t45, t75 and t105). Plasma insulin concentrations were higher halfway through the exercise period and during acute recuperation (t15 and t75; P < 0.05) following ingestion of GluF than after Glu alone, without any differences between the effects of either intervention on plasma glucose concentrations. Towards the end of the exercise period, urinary catecholamine concentrations were lower following GluF (t45; P < 0.05). Plasma triacylglycerol (triglyceride) concentrations were higher after the ingestion of GluF compared with Glu (t15, t30, t45 and t105; P < 0.05) following ingestion of GluF than after Glu alone, without any differences between the effects of either intervention on plasma glucose concentrations. Towards the end of the exercise period, urinary catecholamine concentrations were lower following GluF (t45; P < 0.05). Plasma triacylglycerol (triglyceride) concentrations were higher after the ingestion of GluF compared with Glu (t15, t30, t45 and t105; P < 0.05). Furthermore, with GluF, we observed higher levels of lipoperoxides (t15, t30, t45 and t105; P < 0.05) and oxidized LDL (low-density lipoprotein; t30; P < 0.05) compared with after the ingestion of Glu alone. In conclusion, hormonal and lipid alterations are provoked during aerobic exercise and recovery by the addition of a dose of fructose to the pre-exercise ingestion of glucose.

INTRODUCTION

The pre-exercise ingestion of carbohydrates is a common dietary supplement that delays fatigue and this is frequently consumed by sportsmen and women, and recreational practitioners [1]. However, differences in the mechanisms of absorption and the metabolic pathways taken by the ingested carbohydrate provoke a range of metabolic and hormonal responses that are still only partially understood.

Fructose is a monosaccharide that has often been studied as an ergogenic supplement in exercise conditions.

Key words: carbohydrate supplementation, exercise, fructose, glucose, hypertriacylglycerolaemia, lipid metabolism.

Abbreviations: Glu, glucose alone; GluF, glucose + fructose; HR, heart rate; NEFA, non-esterified fatty acid; LPO, lipoperoxide; LDL, low-density lipoprotein; oxLDL, oxidized LDL; PetCO2, end-tidal partial pressure of carbon dioxide; PetO2, end-tidal partial pressure of oxygen; RPE, rating of perceived exertion; TAG, triacylglycerol; VCO2, carbon dioxide production; VE, minute ventilation; VLDL, very-low-density lipoprotein; VO2, oxygen consumption; VT1, ventilatory threshold 1; VT2, ventilatory threshold 2.

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In comparison with glucose, pre-exercise ingestion of fructose did not lead to reactive hypoglycaemia and improved performance [2]. This improvement has also been reported when fructose was combined with glucose and ingested during an aerobic exercise [3,4]. Nevertheless, in these studies, the authors extensively studied mechanisms related to improved performance; for example, exogenous and endogenous rates of carbohydrate oxidation, without directly analysing the metabolic effects of glucose plus fructose on insulinaemic and glycaemic responses. Moreover, at least during rest, a reduction has been reported in the insulinaemic and glycaemic response following the combination of different doses of fructose with high glycaemic index carbohydrates [5–7]; a finding that has not been studied under exercise conditions. Such information would be of great importance, as one of the key objectives in aerobic exercise is low insulinaemia and the reduction in the vagal α-adrenergic stimulus to favour the selective use of substrates [8–10] and β-adrenergic stimulation for lipolysis [8].

On the other hand, there is growing interest in studying the effects on lipid metabolism and insulin resistance following the ingestion of fructose [11,12]. Stimulation of de novo lipogenesis [13], a defect in the clearance of VLDL (very-low-density lipoprotein) particles [14] or even the esterification of non-oxidized NEFAs (non-esterified fatty acids) in the liver [15] are among the explanations for the hypertriacylglycerolaemia induced by fructose in healthy subjects at rest. Meanwhile, the reduction in insulin sensitivity appears to be dependent on fructose-induced lipid modification [16]. Nevertheless, a high variability has been observed in the studies carried out to date, depending in part on the quantity of fructose administered [17], and the type and quantity of carbohydrate that accompanied the fructose [6]. Furthermore, other factors that have been studied less, such as the training status of the subjects [18] and exercise performed during the post-absorption phase, might also influence glycaemic and lipid metabolism after fructose ingestion. For this reason, there is no consensus regarding the ingestion of fructose either alone or in combination with high glycaemic index carbohydrates; despite this, its use as a low glycaemic index sweetener is still being recommended, and fructose is even employed in sports drinks [19].

To the best of our knowledge, no studies exist that evaluate, in trained adults, the acute hormonal and metabolic effects of the ingestion of a combination of GluF (glucose + fructose) before aerobic exercise. The aim of the present study was therefore to compare the acute hormonal response induced by the pre-exercise ingestion of Glu (glucose alone) or GluF and its effects on lipid metabolism during the course of moderate aerobic exercise and the acute recovery phase. The influence of pre-exercise ingestion of these supplements on the oxidative state of circulating lipids was also studied.

### MATERIALS AND METHODS

#### Subjects

A total of 20 healthy adult men (mean age, 26 ± 4.8 years) volunteered to participate in the study. All subjects were normoglycaemic and normolipaemic, and none had undergone pharmacological treatment or had taken vitamin or mineral supplements in the 2 months prior to the study. The subjects were aerobically trained, participating in physical exercise sessions more than three times a week. Table 1 shows their anthropometric and biological characteristics and training background. The aims of the study and the possible risks involved were explained and an informed consent form was signed by each subject before the start of the study. The ethics committee of the Reina Sofía Hospital in Córdoba approved all the procedures employed in the study.

#### Study design

As a preliminary analysis, the participants were subjected to an anthropometric study, an evaluation of their nutritional state and a pre-testing session in order to determine suitable workloads during the experimental exercise sessions \( \dot{V}O_{2\text{max}} \) (maximal \( \dot{V}O_{2} \) (oxygen consumption)) and 10RM (ten repetition maximum) tests. The subjects were thereafter randomly assigned to perform two experimental trials in consecutive order, which consisted of pre-exercise ingestion of Glu or GluF and a session of moderate aerobic exercise (Figure 1). A

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**Table 1: Characteristics and training background of the study subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>26 ± 4.85</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 ± 10.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.45 ± 1.93</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>16.96 ± 3.44</td>
</tr>
<tr>
<td>Biochemical</td>
<td></td>
</tr>
<tr>
<td>Glycaemia (mmol/l)</td>
<td>4.19 ± 0.43</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>3.60 ± 0.68</td>
</tr>
<tr>
<td>TAG (mmol/l)</td>
<td>0.70 ± 0.21</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.37 ± 0.34</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>1.88 ± 0.48</td>
</tr>
<tr>
<td>Total training</td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td>2.2 ± 1.3</td>
</tr>
<tr>
<td>Days/week</td>
<td>5.7 ± 0.5</td>
</tr>
<tr>
<td>Sessions/week</td>
<td>6.3 ± 1.2</td>
</tr>
<tr>
<td>Minutes/week</td>
<td>349.7 ± 69.2</td>
</tr>
<tr>
<td>Endurance training</td>
<td></td>
</tr>
<tr>
<td>Sessions/week</td>
<td>5.4 ± 0.8</td>
</tr>
<tr>
<td>Minutes/week</td>
<td>246.3 ± 60.6</td>
</tr>
</tbody>
</table>
1–week washout period followed each experimental trial, and the subjects were also instructed to avoid moderate-to-severe physical exercise during the 24 h before each intervention. This was controlled by means of an exercise autoself recorder and by analysing basal concentrations of Srm (standard reference material) creatine kinase, with levels > 200 units/l qualifying as an exclusion criterion. The consumption of caffeine, alcohol and carbohydrates with a high glycaemic index was also avoided during the day before each trial.

### Nutritional status and diet

A retrospective qualitative/quantitative assessment of the frequency of food intake for the 4 weeks before the preliminary evaluations was obtained from each subject by a nutritionist. The composition of the normal diet and consumption of alimentary antioxidants were calculated with the aid of tables of the chemical composition of food. This nutritional information was used to prescribe an isocaloric diet, with a moderate glycaemic load and glycaemic index [20,21]. The daily ration of vegetables and fruit was set in accordance with the recommended dietary intakes of ascorbic acid. This diet was followed by the subjects for 2 weeks before the start of the experimental trials and during the washout periods between the interventions. A 24-h food consumption diary was completed by the subjects during the week before each experimental trial on days 3 (half week) and 6 (the day before the intervention). The composition of the diet followed by the subjects was calculated and is shown in Table 2.

### Pre-testing and determination of workload

All the participants performed a progressive endurance test on an ergometer cycle (Ergometrics 800; Ergoline) in order to calculate the load of endurance exercise at the same time of day (10.00–13.00 hours) and under identical ambient conditions (21–24 °C; 45–55 % relative humidity). The protocol comprised pedalling for 2 min at 25 W and a further 2 min at 50 W as a warm-up; afterwards, the load was increased at a rate of 25 W/min.

Subjects were required to maintain a constant pedalling rate of between 60 and 70 rev./min. The test came to an end when: (i) the subject decided on his own to end it; (ii) he could no longer maintain the minimum pedalling rate of 60 rev./min; or (iii) the criteria for completion of the exercise suggested by the American College of Sports Medicine had been fulfilled [22]. HR (heart rate; in beats/min) was recorded continuously throughout the tests and for 3 min post-exercise by means of a 12-channel ECG (Viasys™; Pulse Biomedical). Gas exchange data were obtained continuously by means of an automatic breath-by-breath system (Oxycon Delta; Jaeger), which was calibrated before each test to the appropriate ambient conditions. The following parameters were acquired (average of each 15-s interval): V\textsubscript{O2} and V\textsubscript{CO2} (carbon dioxide production) [in l/min at STP (standard temperature and pressure)]; V\textsubscript{E} [minute ventilation; in l/min BPTS (backward preferred transition speed)], V\textsubscript{E}/V\textsubscript{O2}, V\textsubscript{E}/V\textsubscript{CO2}, PET\textsubscript{O2} (end-tidal partial pressure of oxygen) and PET\textsubscript{CO2} (end-tidal partial pressure of carbon dioxide). VT1 and VT2 (ventilatory thresholds 1 and 2) and the workloads (in W) corresponding to them were calculated using the methodology suggested by Davis [23]. In brief, VT1 was determined by means of an increase in both V\textsubscript{E}/V\textsubscript{O2} and PET\textsubscript{O2} without a concomitant increase in V\textsubscript{E}/V\textsubscript{CO2}. VT2 was determined by means of an increase in both V\textsubscript{E}/V\textsubscript{O2} and PET\textsubscript{O2} and a fall in PET\textsubscript{CO2}. VT1 and VT2 were calculated independently by two observers. In the event of a failure to agree, a third observer was consulted.

### Supplement and exercise protocol

The subjects arrived at the laboratory between 08.00 and 09.00 hours after 10–12 h of nocturnal fasting.

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**Table 2** Dietary composition during the week before the Glu or GluF trial

<table>
<thead>
<tr>
<th>Dietary variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Caloric distribution</td>
<td></td>
</tr>
<tr>
<td>Total calories (kJ/day)</td>
<td>7492 ± 1103</td>
</tr>
<tr>
<td>Carbohydrate (%)</td>
<td>44.56 ± 5.89</td>
</tr>
<tr>
<td>Protein (%)</td>
<td>23.85 ± 3.59</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>31.25 ± 5.54</td>
</tr>
<tr>
<td>Energy density (kJ/g)</td>
<td>5.69 ± 0.88</td>
</tr>
<tr>
<td>Dietary carbohydrate</td>
<td></td>
</tr>
<tr>
<td>Total carbohydrate (g)</td>
<td>200.01 ± 38.64</td>
</tr>
<tr>
<td>Dietary glycaemic load</td>
<td>124.41 ± 16.43</td>
</tr>
<tr>
<td>Dietary glycaemic index</td>
<td>63.51 ± 6.85</td>
</tr>
<tr>
<td>Total fibre (g)</td>
<td>23.24 ± 5.51</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td></td>
</tr>
<tr>
<td>Intake (mg/day)</td>
<td>65.54 ± 26.94</td>
</tr>
<tr>
<td>%RDI</td>
<td>109.2</td>
</tr>
</tbody>
</table>
At 15 min before the start of the exercise period, they consumed, in accordance with a cross-randomized protocol, a water-based solution (400 ml) of 50 g of glucose (glucose anhydride; C₆H₁₂O₆ 99.5%) or 50 g of glucose plus 15 g of monosaccharide fructose. The 50 g of glucose, which requires no hydrolysis for absorption, has been established as the minimal amount of glycaemic carbohydrate in the two trials, with the purpose that this may provide the same threshold for detecting changes in the glycaemic response when fructose was given simultaneously in the GluF trial. For this reason, we intentionally used two non-isocaloric supplementations, as others studies have done previously [5,6]. The Glu and GluF solutions had a total concentration of 12.5 and 16.5% respectively. The fructose provided 23.07% of the carbohydrates in the combined supplement, and this amount was determined on the basis of previous reports of its digestibility and absorption in combination with glucose under conditions of rest and exercise [24,25]. The specific concentration of fructose (3.75%) was lower than the 10% maximum reported as being capable of being absorbed without risk of gastrointestinal symptoms [26]. Under both trial conditions (Glu or GluF), aerobic exercise was performed on the ergometer cycle utilized in the preliminary tests. Each subject exercised at an intensity that corresponded to the workload value attained at a point equidistant between VT1 and VT2 during the preliminary aerobic tests. For example, an individual who had reached VT1 and VT2 with loads of 100 and 200 W respectively, would perform the exercise session against a load of 150 W. In addition, for warm-up purposes, during 1 and 2 min of the exercise sessions, we employed workloads of 25 and 50 W respectively; after 3 min, the load calculated during the preliminary test was used until a total of 30 min of exercise had been accomplished. The pedalling rate was the same as used in the preliminary tests.

Blood and urine samples, and analytical assays

On the morning of each experimental trial, a 16-gauge Vennflon cannula was inserted into the antecubital vein in order to extract blood samples. The samples were drawn immediately before the ingestion of the carbohydrates (t−15) and during the 2 h of the post-prandial period at intervals of 15, 30 and 60 min, including the exercise period (t25, t30 and t60) and during the recovery phase (t120, t150 and t240). A very small volume of sterile saline was infused immediately after the extraction of each sample in order to keep the cannula clear. The blood samples were collected into tubes containing 1 g/l EDTA and were always protected from the light. The tubes were stored on ice, and plasma was separated within 30 min of extraction by low-speed centrifugation at 1500 g for 15 min at 4°C. Glucose concentrations were determined by spectrophotometric methods using a modular analyser (ISE-4-DDPPEPP; Hoffmann-La Roche). Plasma insulin levels were measured by CMIA (chemiluminescent microparticle immunoassay) using an analyser (Architect i-4000; Abbott). Plasma TAG (triacylglycerol; ‘triglyceride’) levels were measured spectrophotometry using a modular analyser (ISE-4-DDPPEPP; Hoffmann-La Roche). Serum NEFA concentrations were determined using an enzymatic colorimetric assay (NEFA kit; Roche). The levels of LPO (lipoperoxide) were determined using a commercially available kit (LPO-586; Oxis International). Quantitative determination of oxLDL [oxidized LDL (low-density lipoprotein)] in plasma was performed by enzyme immunoassay using a commercially available kit (Biomedica). Plasma lactic acid was measured by enzymatic colorimetric assay using an analyser (Cobas 400; Hoffmann-La Roche).

Total urine production was also collected into sterile containers before the ingestion of the carbohydrates (t−15), at the end of the exercise period (t120) and the end of the recovery period (t120). The subjects were recommended to drink water ad libitum during the exercise and recovery periods in order to encourage urine production. Urinary concentrations of adrenaline (epinephrine), noradrenaline (norepinephrine) and creatinine were determined by means of HPLC, using a chromatograph (Bio-Rad Laboratories) with a reverse-phase column (flow rate of 1 ml/min) and an electrochemical detector (at 500 mV and 10 nA). Urinary concentrations of adrenaline and noradrenaline are expressed relative to urinary creatinine (nmol/mmol of creatinine). In addition, 1 day prior to collecting the urine, we encouraged the subjects to abstain from bananas, coffee, pineapples and walnuts. We also ensured they did not take any of the following drugs: pheothiazin, paracetamol, salsinol, isoproterenol or α-methyldopa.

Perceived exertion and HR

The RPE (rating of perceived exertion) was recorded according to the Borg perceived exertion scale (CR10) at three different times: mid-exercise, after completion of the exercise [27] and 30 min after completion of the exercise (see Figure 5). This last recording was used to indicate the subject’s overall perception of the session [28]. The scale had been used by the subjects during their last training year, so there was a good reproducibility and a period for such purpose was not deemed necessary. In addition, HR was recorded continuously during the study (Polar S810).

Statistical analysis

Traditional statistical methods were used to calculate means and S.D. and S.E.M. The normality of the samples was tested using the Shapiro–Wilk’s test. The effect of the different interventions (Glu and GluF as independent
Metabolic effects of fructose during exercise

Figure 2  Plasma glucose (A) and insulin (B) concentrations at rest, and throughout the exercise and recovery periods following the pre-exercise ingestion of Glu or GluF
Values are means ± S.E.M, n = 20 subjects. There were significant carbohydrate × time interactions for plasma insulin (P = 0.003) as determined by repeated-measures ANOVA. *P < 0.05 compared with Glu.

variables) on glycaemia, insulinaemia, adrenaline, noradrenaline, TAG, NEFA, oxLDL and LPO (as dependent variables) was analysed by ANOVA with repeated measures [2 (group) × 7 (time)]. A Sidak correction was used to adjust the P value in relation to the number of comparisons that were performed. P < 0.05 was adopted for statistical significance. For all of the statistical tests, we used the SPSS 11.5 package for Microsoft Windows.

RESULTS

Plasma glucose, insulin and urinary catecholamines
Plasma insulin concentrations were higher in the GluF compared with the Glu trials during the exercise and recovery phases (t15 and t75; P < 0.05), without any differences being found in the glucose concentrations between the two interventions during these phases (Figure 2). Lower urinary levels of adrenaline and noradrenaline (Figure 3) were found at the end of the exercise phase following GluF compared with Glu (t45; P < 0.05).

Plasma TAG and NEFA concentrations
Following the ingestion of GluF, TAG levels were significantly higher during the exercise phase (t15 and t30; P < 0.05) and acute recovery phase (t45 and t75; P < 0.05) compared with following Glu intake (Figure 4A). NEFA levels after GluF (Figure 4B) were lower halfway through the exercise phase (t15; P < 0.05) and during the recovery phase (t75; P < 0.05), but were higher at the end of the exercise phase (t30; P < 0.05) compared with Glu intake.

LPO and oxLDL concentrations
Following the ingestion of GluF, plasma levels of LPO were significantly higher during the exercise and recovery periods (t15, t30, t45 and t120; P < 0.05), as were those of oxLDL at the end of exercise (t150; P < 0.05), compared with following consumption of Glu alone (Table 3).

Blood lactate concentrations, perceived exertion and HR
No differences were observed in the levels of blood lactate during either the exercise or recovery periods following treatment with the supplements (Figure 5, bottom panel). RPE and HR were significantly less after GluF compared with Glu (t15, t30 and t60; P < 0.05) (Figure 5, top and middle panels respectively).
Figure 4  Plasma TAG (A) and NEFA (B) concentrations at rest, and during the exercise and recovery periods following the pre-exercise ingestion of Glu or GluF

Values are means ± S.E.M., n = 20 subjects. There were significant carbohydrate × time interactions for plasma TAG and NEFA concentrations (P = 0.001 and P = 0.03 respectively) as determined by repeated-measures ANOVA.

**DISCUSSION**

To the best of our knowledge, this is the first study in healthy sportsmen to demonstrate that the addition of a dose of fructose to the pre-exercise consumption of a glucose supplement produces a cluster of acute metabolic changes during moderate aerobic exercise and the subsequent recovery period. These fructose-induced metabolic dysregulations consist of a higher level of insulinaemia than following the ingestion of glucose alone, a greater increase in TAG and markers of lipid oxidation, and a lower urinary concentration of catecholamines and plasma NEFAs during and after aerobic exercise.

Higher levels of insulin are required for a given glucose concentration when the metabolic clearance of glucose has been reduced [29]. In our present study, insulinaemia was 37.2 and 25.8% higher during the exercise and recovery periods (t15 and t75 respectively) after GluF compared with Glu alone, without this being accompanied by differences in glycaemic behaviour between the two interventions. These findings may reflect both an improved tolerance to a higher carbohydrate intake, when an extra dose of carbohydrate was administered, such as fructose, but also a lower systemic insulin sensitivity following that fructose ingestion. Dirlewanger et al. [30] have demonstrated that the acute infusion of fructose in healthy volunteers induces hepatic and extrahepatic insulin resistance by doubling the need for insulin required to maintain a glucose steady-state. It has been suggested that an overload of lipid metabolites derived from fructose and the subsequent over-production of ROS (reactive oxygen species), able to spread outside the liver, could interfere with insulin signalling [31]. Mainly in animal models of fructose-induced insulin resistance, it has been observed that an impaired oxidative state was accompanied by an inflammatory gene response mediated by activated NF-κB (nuclear factor-κB) and the participation of inflammatory cytokines, such as muscle TNF-α (tumour necrosis factor-α) [32–34]. In the present study, both post-prandial phenomena, a greater increase in TAG and oxidative damage to lipids, as shown by LPO and oxLDL, in the GluF trial would suggest a greater amount of insulinaemia mediated by inflammatory mechanisms.

Another metabolic change that has been described after fructose consumption is an increase in TAG levels [35,36]. Elevated NEFA and TAG levels have been reported in humans even at 45 min after the ingestion of 50 g of fructose [37]. In our present study, at 30 and 45 min after the ingestion of GluF (half-way through and at the end of the exercise period) we observed TAG concentrations

<table>
<thead>
<tr>
<th>Table 3</th>
<th>LPO and oxLDL measured immediately before Glu or GluF supplementation (t−15) and at their respective exercise (t0, t15 and t30) and recovery (t45 and t105) phases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td><strong>t−15</strong></td>
</tr>
<tr>
<td>LPO (nmol/dl)</td>
<td></td>
</tr>
<tr>
<td>Glu trial</td>
<td>0.36 ± 0.01</td>
</tr>
<tr>
<td>GluF trial</td>
<td>0.36 ± 0.01</td>
</tr>
<tr>
<td>OxLDL (ng/ml)†</td>
<td></td>
</tr>
<tr>
<td>Glu trial</td>
<td>82.21 ± 13.38</td>
</tr>
<tr>
<td>GluF trial</td>
<td>82.35 ± 15.12</td>
</tr>
</tbody>
</table>

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that were 38.7 and 34.2% higher than after Glu at the same times. Moreover, TAG rapidly returned to basal levels 45 min after its peak level ($t_{75}$) following GluF, discarding the hypothesis of a delay in TAG clearance as one of the possible causes of hypertriglycerolaemia, as has been proposed by Chong et al. [15]. Furthermore, the higher level of insulin found with GluF leads us to suggest that the mechanism making the greatest contribution to the increase in TAG was not a reduction in the activation of lipoprotein lipase in adipose tissue and the subsequent delay in lipid clearance [38], but rather de novo lipogenesis, a mechanism widely explained after fructose intake [13,39].

Along these lines, several studies have reported that the fast arrival of fructose at the liver could cause an overload of the pentose phosphate pathway leading to the acute expression of lipogenic genes [40,41], and to the rapid activation of hepatic lipogenesis and the secretion of VLDL via SREBP-1c (sterol-regulatory-element-binding protein-1c) [42]. Under these conditions, the mechanisms resulting in a decrease in the glycaemic response (e.g. the hepatic uptake of glucose and glycogen synthesis) are possibly inhibited, whereas the gluconeogenic and lipogenic pathways are activated [40]. The present study was not designed to investigate the molecular mechanisms responsible for the increase in TAG after GluF ingestion; however, it is possible that the performance of aerobic exercise (non-glycolytic) may have accelerated the arrival of fructose to the portal system and the activation of the lipogenic pathway, which may be key in explaining the lipid behaviour observed.

On the other hand, it is known that the utilization of substrates during aerobic exercise is modulated by autonomic and endocrine control in response to the type and amount of carbohydrate ingested [43]. Although the present study does not provide results describing substrate oxidation, it has been reported previously that fructose by itself [44] as well as an elevated insulinemia during exercise [45] increase carbohydrate oxidation to the detriment of the contribution of lipids to energy consumption. Additionally, in agreement with MacLaren et al. [46], we have found that elevated insulinemia was accompanied by both a lower concentration of catecholamines in urine from $t_{-15}$ to $t_{30}$ of the exercise period and a low availability of NEFAs in the GluF trial. If lower activation of lipolysis followed GluF, as suggested by these findings, the addition of a dose of fructose would negate an important part of the health benefits derived from 30 min of aerobic exercise. Conversely, if GluF increased the carbohydrate oxidation rate, as reported by other studies with GluF [3,4], the use of this more rapidly available fuel would explain the minor effect on RPE and HR, without a change in blood lactate. Thus the improvement in these variables during and after exercise with GluF intake could increase the capacity to perform exercise more comfortably, but would not favour the metabolic benefits aimed at during aerobic exercise.

In conclusion, the addition of fructose to the pre-exercise ingestion of a glucose supplement triggers greater insulin secretion and lower adrenergic stimulation than the ingestion of glucose alone. This combination of carbohydrates also induces a greater increase in plasma TAGs, a deterioration in the oxidative state of circulating lipids and the suppression of circulating NEFAs during moderate-intensity aerobic exercise and the post-exercise recovery phase. Future studies in risk populations (e.g.
patients with diabetes and obese subjects) are required in order to analyse the metabolic effects of supplements containing different doses of fructose in mixed pre-exercise meals or beverages.

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