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# **A comparison of the appetite responses to high and low glycemic index post-exercise meals under matched insulinemia and fiber in type 1 diabetes**

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**RUNNING TITLE:** Postexercise appetite in Type 1 diabetes

**ABBREVIATIONS:** GI (glycemic index), LGI (low glycemic index), HGI (high glycemic index), GLP-1 (glucagon-like peptide 1).

**CLINICAL TRIAL REGISTRY:** ClinicalTrials.gov (NCT02208115).

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1 **ABSTRACT**

2 **Background:** Type 1 diabetes patients face a heightened risk of hypoglycemia following  
3 exercise. Subsequent overfeeding, as a preventative measure against hypoglycemia, negates  
4 the energy deficit following exercise. Patients are also required to reduce the insulin dose  
5 administered with post-exercise foods to further combat hypoglycemia. However, insulin  
6 dose is dictated solely by carbohydrate content, even though post-prandial glycemia is vastly  
7 influenced by glycemic index (GI). With a need to control post-exercise energy balance, the  
8 appetite responses following meals differing in GI are of particular interest. **Objective:** This  
9 study assessed the appetite response to a low (LGI) and high GI (HGI) post-exercise meal in  
10 type 1 diabetes patients. This also offered an opportunity to assess the influence of GI on  
11 appetite responses independent of insulinemia, which confounds findings in individuals  
12 without diabetes. **Design:** Ten physically-active men with type 1 diabetes completed two  
13 trials in a randomized crossover design. Following 45-min of treadmill-exercise at 70% of  
14 peak oxygen uptake, participants consumed a low (**LGI:** GI = ~37) or high GI (**HGI:** GI =  
15 ~92) meal, with matched macronutrient composition, negligible fiber content, and with  
16 insulin dose administration standardized. The postprandial appetite response was determined  
17 for 180-min post-meal. During this time, circulating glucose, insulin, glucagon and glucagon-  
18 like peptide-1 (GLP-1) concentrations, and subjective appetite ratings were determined.  
19 **Results:** **HGI** meals produced ~60% greater postprandial glucose AUC compared to **LGI** ( $p$   
20 = 0.008). Insulin, glucagon and GLP-1 did not significantly differ between trials ( $p > 0.05$ ).  
21 Fullness AUC was ~25% greater following **HGI** vs. **LGI** ( $p < 0.001$ ), whereas hunger  
22 sensations were ~9% lower following **HGI** vs. **LGI** ( $p = 0.001$ ). **Conclusions:** Under  
23 conditions of matched insulinemia and fiber, a HGI post-exercise meal suppresses feelings of  
24 hunger and augments postprandial fullness sensations more so than an otherwise equivalent  
25 LGI meal, in type 1 diabetes patients.

## 26 INTRODUCTION

27 Regular exercise brings a vast array of health benefits for patients with type 1 diabetes (1).  
28 However, managing diabetes, whilst integrating exercise into the lives of patients, is both  
29 complex and challenging. A heightened risk of exercise-induced and iatrogenic  
30 hypoglycemia (i.e. a fall in blood glucose concentrations below the normal physiological  
31 range) (2), often results in over-consumption of carbohydrate (3), and ultimately excessive  
32 energy intake (4) as a preventative measure. This may negate the benefits exercise offers for  
33 weight management and body composition, and could potentially contribute to a deterioration  
34 in wider diabetes management (5).

35

36 Research has shown that insufficient exercise and excessive energy intake can confer  
37 detrimental long-term implications for glycemic control and cardiovascular risk in patients (6,  
38 7). Conversely, elevating energy expenditure through regularly exercising, and thus inducing  
39 a negative energy balance could be advantageous to glycemic control; reduced energy and  
40 carbohydrate intake may assist in the prevention of adiposity accumulation and the associated  
41 insulin resistance which occurs following diagnosis of type 1 diabetes (8). However, even in  
42 people without diabetes there is a risk of over-compensation of energy intake in response to  
43 energy expenditure (9), potentially due to increased appetite (9,10). Indeed, modulating post-  
44 exercise appetite through nutritional strategies could be advantageous for type 1 diabetes  
45 patients, thus appetite regulation following exercise is emerging as an important component  
46 of diabetes care (3, 11).

47

48 The composition of the foods consumed following exercise is of importance to type 1  
49 diabetes patients. Work from our group illustrates reduced hyperglycemia in the acute peri-  
50 and post-exercise period when low GI (LGI) carbohydrates are consumed before and after

51 exercise, compared with high GI carbohydrates (HGI) (12-14). This is important, as patients  
52 with type 1 diabetes are faced with particular difficulty in normalizing glycemia around the  
53 time of exercise and more so following exercise (15). Repeated exposure to severe glycemic  
54 variability on a regular basis may be detrimental to diabetes management (5, 16). However,  
55 the impact of food composition on appetite in type 1 diabetes is less well understood.

56

57 In people without type 1 diabetes, diets that contain LGI carbohydrates are associated with  
58 reductions in appetite (17), however this may not be the case when fiber content is matched  
59 (18). The acute impact of glycemic index on appetite in a healthy population may be largely  
60 driven by insulinemia rather than glycemia, as postprandial insulin concentrations are  
61 inversely related to hunger, whereas postprandial glycemia is not (19), and gastrointestinal  
62 incretins may also play a role (20-22). Therefore, studying appetite responses following HGI  
63 and LGI meals in patients with type 1 diabetes offers a unique insight into the impact of meal  
64 glycemic index, whereby insulin-induced satiety is not confounded by dissimilar insulinemia  
65 (23), as administration of insulin dose is typically based on carbohydrate amount and not  
66 type.

67 Accordingly, this study had two main aims: 1) to investigate the appetite and GLP-1 response  
68 to HGI and LGI post-exercise meals in type 1 diabetes patients, thereby reflecting a typical  
69 daily situation in which exercise recommendations for minimising the risk of hypoglycemia  
70 are adhered; 2) to examine the influence of the glycemic index on appetite independent of  
71 insulinemia and fiber content.

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## 76 PARTICIPANTS AND METHODS

### 77 Patients

78 The protocol was approved by local National Health Service Research Ethics Committee  
79 (13/NE/0016, ClinicalTrials.gov (NCT02208115). All patients provided written informed  
80 consent.

81 Ten type 1 diabetic men ([mean  $\pm$  SEM] age  $27 \pm 1$  years,  $VO_{2peak}$   $51.3 \pm 2.1$  ml.kg<sup>-1</sup>.min<sup>-1</sup>,  
82 BMI  $25.5 \pm 0.3$  kg.m<sup>-2</sup>, HbA<sub>1c</sub>  $6.7 \pm 0.2\%$ ,  $49.9 \pm 2.4$  mmol/mol) attended the Newcastle  
83 NIHR Clinical Research Facility on two occasions, separated by a minimum of seven days.  
84 All patients had long standing diabetes (duration of diabetes  $15 \pm 2$  years), and were treated  
85 on a stable basal-bolus regimen composed of insulin aspart and once-daily insulin glargine.  
86 All patients were familiar with carbohydrate counting and were administering  $1.0 \pm 0.1$  units  
87 of insulin aspart per 10 g of carbohydrate. Patients were not eligible if taking medication  
88 other than insulin, or supplements known to affect appetite or gastrointestinal motor function.  
89 Furthermore, patients were free of gastrointestinal disease, had not undergone gastrointestinal  
90 surgery, and were free of diabetes-related complications. In addition, all patients were  
91 regularly active participating in running-based activities a minimum of 3 times per week for  
92 at least 30 minutes on each occasion.

93

### 94 Experimental design

95 This was a randomised, counter-balanced cross-over design with two experimental arms: a  
96 LGI and HGI trial which commenced at ~17:00PM. A schematic of the experimental trial  
97 design is presented in **Supplemental Figure 1**. Patients replicated their diet (assessed using  
98 weighed dietary recording sheets) and maintained their usual insulin regimen in the 24 hours  
99 prior to each main trial. Basal insulin dose was standardised (dose, injection site, and time of  
100 injection) across trials. Moreover, real-time continuous glucose monitoring (Paradigm Veo,

101 Medtronic diabetes, USA) was used prior to main trials to normalise glycemia in the  
102 preceding 24 hours (for details see (12)). Patients were asked to replicate activity patterns and  
103 refrain from strenuous physical activity 48 hours before each trial. Trials were rescheduled if  
104 a patient experienced a symptomatic hypoglycemic episode or periods of severe or prolonged  
105 hyperglycemia. On each trial day, patients were provided with two standardised meals which  
106 were based on the habitual dietary patterns of type 1 diabetes patients and current  
107 recommendations for exercise in diabetic patients (4, 24). This postprandial design allows for  
108 greater translation of findings into daily life (25). The meals consisted of a cereal-based  
109 breakfast (frosted flakes, semi-skimmed milk, and peaches) equating to  $1.3\text{g}\cdot\text{carbohydrate}\cdot\text{kg}^{-1}\text{BM}$   
110  $(549 \pm 20 \text{ kcal})$  and a pasta-based lunch (pasta, tomato-based sauce, cheddar cheese,  
111 olive oil) equating to  $1.3\text{g}\cdot\text{carbohydrate}\cdot\text{kg}^{-1}\text{BM}$   $(968 \pm 35 \text{ kcal})$ . The breakfast meal was  
112 consumed at  $\sim 08:00\text{AM}$ , and a lunch meal consumed at  $\sim 13:00\text{PM}$ . Both meals were  
113 provided to patients by the research team, and consumed at home, with meal times  
114 standardised across trials. Carbohydrate intake across the experimental trial day was based on  
115 recommendations for exercising type 1 diabetes patients (2), and was calculated to be  
116 sufficient to cover the cost of the exercise bout, as determined via indirect calorimetry from  
117 predicted  $\text{VO}_2$  and  $\text{VCO}_2$  concentrations during exercise.

118

119 Transport was provided to patients for each laboratory attendance and trial start time was  
120 replicated. Following arrival, a resting venous blood sample was taken (see blood sampling  
121 and analysis), and patients administered a 75% reduced dose ( $2.0 \pm 0.1$  units) of rapid-acting  
122 insulin aspart, into the subcutis of the abdomen (12, 13). Injection site was taken as  
123 equidistant between the iliac crest and naval as currently recommended (15, 26, 27), and was  
124 standardized on each visit using indelible ink. With this insulin administration, patients  
125 consumed an exercise carbohydrate-based bolus (frosted flakes, semi-skimmed milk, and

126 peaches) equating to  $1.0\text{g}\cdot\text{carbohydrate}\cdot\text{kg}^{-1}\text{BM}$  ( $423 \pm 15$  kcal), calculated to be of medium  
127 GI (GI = 57), as per current pre-exercise recommendations (15). Sixty minutes following  
128 rapid-acting insulin administration / carbohydrate bolus ingestion, a blood sample was drawn  
129 before patients performed 45 minutes of treadmill running at an intensity to elicit 70% of  
130  $\text{VO}_{2\text{peak}}$ . Running speed was calculated during a preliminary visit where a maximal  
131 incremental treadmill test was performed, as previously described by our group (15). For the  
132 performance of exercise, ambient temperature and humidity was controlled across trials.  
133 Blood samples were taken immediately after exercise and at 60 minutes post-exercise. At 60  
134 minutes post-exercise, patients administered a 50% reduced dose of rapid-acting insulin  
135 aspart in anticipation of the test meals (15). Immediately following insulin administration  
136 patients consumed one of two test meals matched for energy (**HGI**  $1.7 \pm 0.1$  MJ /  $413 \pm 16$   
137 kcal vs. **LGI**  $1.7 \pm 0.1$  MJ /  $409 \pm 15$  kcal) and carbohydrate content ( $1.0\text{g}\cdot\text{carbohydrate}\cdot\text{kg}^{-1}$   
138  $\text{BM}$ ) but differing in GI (**HGI** = 37 vs. **LGI** = 92) (**Table 1**). Meals were matched for  
139 macronutrient content (Table 1), and contained negligible amounts of fiber (**HGI** =  $1.0 \pm 0.1$   
140 vs. **LGI** =  $0.5 \pm 0.1$  g). The order in which test meals were consumed was randomized and  
141 counter-balanced, determined using a computer program. We calculated the GI of each meal  
142 using methods described by Brouns et al (28) in 10 non-diabetic control participants; meal  
143 composition and energy content were determined using a computer software package  
144 (Microdiet, Downlee Systems LTD, UK). Following the consumption of each test meal,  
145 patients remained rested for 180 minutes with periodic blood sampling every 30 minutes. As  
146 each meal composed of food and a beverage (standardised volume), water was withheld  
147 during the post-prandial period to control for mechanoreceptor-mediated suppression of  
148 appetite. Perceptions of appetite (hunger and fullness) were assessed across the duration of  
149 each trial, measured immediately before each blood sample point using visual analogue  
150 scales (29).



151 \*\*\* INSERT TABLE 1 \*\*\*

### 152 **Blood sampling and analysis**

153 At each sample point a 6-ml venous blood sample was taken of which 20 $\mu$ l was used for the  
154 immediate quantification of blood glucose (BG: Biosen C-Line; EKF Diagnostic GmbH,  
155 London, UK) and 10  $\mu$ l analyzed for hemoglobin and hematocrit (Hemo Control; EKF  
156 Diagnostic GmbH, UK), which was used to correct for changes in plasma volume following  
157 exercise (30). The remaining sample was aliquoted evenly into serum separation (Vacuette,  
158 Greiner Bio-One GmbH, Austria) and Lithium-heparin tubes (Vacuette, Greiner Bio-One  
159 GmbH, Austria) before being centrifuged at 3000 rev.min<sup>-1</sup> for 15 minutes at 4°C and stored  
160 at -80°C for retrospective analysis of serum rapid-acting insulin analogue (Invitron Insulin  
161 Assay; Invitron, Monmouth, UK) and plasma glucagon (Glucagon EIA, Sigma-Aldrich,  
162 USA) and total GLP-1 (Epitope Diagnostics, San Diego, CA). Further blood samples were  
163 taken at 60 minutes following pre-exercise meal / rapid-acting insulin administration  
164 (immediately before exercise), at 60 minutes post-exercise (immediately before the post-  
165 exercise-meal / rapid-acting insulin administration), and at 30, 60, 90, 120, 150, and 180  
166 minutes following the post-exercise meal / rapid-acting insulin administration. As patients in  
167 this study had long-standing diabetes and were solely dependent upon exogenous insulin, the  
168 influence of endogenous insulin secretion from residual  $\beta$ -cell function was considered  
169 negligible (31). Therefore, any changes in insulin concentrations detected by this assay were  
170 considered to be due to changes in the appearance or disappearance of insulin aspart. The  
171 coefficient of variation for the biochemical analysis of serum insulin, plasma glucagon and  
172 plasma GLP-1 was <10%.

### 173 **Statistical analysis**

174 All data are presented as mean  $\pm$  SEM. Data presented as Area Under the Curve (AUC) was  
175 calculated using methods described by Wolever and Jenkins (32). Delta changes in AUC

176 from pre-test meal scores / concentrations were calculated by subtracting subsequent values  
177 from pre-test meal scores. PASW *Statistics* software (IBM PASW version 18; IBM, Armonk,  
178 NY, USA) was used to analyse data. Within and between condition responses were examined  
179 using repeated measures ANOVA on two levels (time\*condition). Where significant  $p$ -values  
180 were identified for interaction effects (time\*condition), GI was deemed to have influenced  
181 the response, and simple main effects analyses were performed. Significant main effects of  
182 time were further investigated using Bonferroni adjusted pairwise comparisons. Relationships  
183 were explored using Pearson's product moment correlation coefficient. Paired samples t-tests  
184 were conducted as relevant. Statistical significance was accepted at  $p \leq 0.05$ .

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201 **RESULTS**

202 Glycemic control was comparable over the 24 hours prior to patients' arrival at the laboratory  
203 for both experimental trials (CGM mean glucose: **HGI**  $10.4 \pm 1.0$ , **LGI**  $9.4 \pm 1.1$  mmol.l<sup>-1</sup>;  $p$   
204 = 0.534; and total interstitial glucose AUC<sub>0-24hrs</sub>: **HGI**  $11324 \pm 1056$ , **LGI**  $10212 \pm 1228$   
205 mmol.l<sup>-1</sup> over 24 hours;  $p = 0.382$ ). In addition, there were no differences in dietary intake,  
206 insulin administration, or levels of physical activity during this time (**Table 2.0**).

207 \*\*\*INSERT TABLE 2\*\*\*

208

209 There were no differences in glycemia, serum insulin, plasma glucagon concentrations or  
210 appetite scores prior to the consumption of the post-exercise test meals ( $p > 0.05$ ), such that  
211 immediately before administration, patients displayed similar blood glucose (BG: **HGI**  $6.2 \pm$   
212  $0.7$  vs. **LGI**  $5.8 \pm 0.5$  mmol.l<sup>-1</sup>,  $p = 0.169$ ), serum insulin (**HGI**  $106 \pm 15$  vs. **LGI**  $102 \pm 14$   
213 pmol.l<sup>-1</sup>,  $p = 0.986$ ), plasma glucagon concentrations (**HGI**  $732 \pm 99$  vs. **LGI**  $735 \pm 103$   
214 pg.ml<sup>-1</sup>,  $p = 0.884$ ) and total GLP-1 (**HGI**  $1.95 \pm 0.21$  vs. **LGI**  $2.47 \pm 0.87$  pmol.l<sup>-1</sup>,  $p =$   
215  $0.620$ ). At this time, sensations of hunger (**HGI**  $68 \pm 3$  vs. **LGI**  $67 \pm 2$ ,  $p = 0.925$ ) and  
216 fullness (**HGI**  $60 \pm 2$  vs. **LGI**  $61 \pm 2$ ,  $p = 0.791$ ) were similar between conditions.

217

218 Following administration of rapid-acting insulin and post-exercise test meals, serum insulin  
219 peaked similarly at 30 to 60 minutes under both conditions (**HGI**  $181 \pm 26$  vs. **LGI**  $175 \pm 30$   
220 pmol.l<sup>-1</sup>,  $p = 0.773$ ; **Figure 1A**). Temporal changes in serum insulin remained similar beyond  
221 this time ( $p > 0.05$ ), with concentrations returning to periprandial measures at 180 minutes ( $p$   
222  $> 0.05$ ). Moreover, total insulin AUC were similar between conditions over the postprandial  
223 period (AUC<sub>0-180mins</sub>: **HGI**  $49576 \pm 6786$  vs. **LGI**  $43924 \pm 6196$  pmol.l<sup>-1</sup> over 180 min,  $p =$   
224  $0.332$ ). BG increased from periprandial concentrations over the postprandial period under  
225 both conditions, but elevations were significantly more pronounced under **HGI**, with higher

226 mean peaks (**HGI**  $+10.2 \pm 0.5$  vs. **LGI**  $+3.2 \pm 0.6$  mmol.l<sup>-1</sup>,  $p < 0.001$ ; **Figure 1B**) and  
227 individualized peaks (**HGI** 15.8 vs. **LGI** 12.9 mmol.l<sup>-1</sup>). Total BG AUC was significantly  
228 greater under **HGI** (AUC<sub>0-180mins</sub>: **HGI**  $2205 \pm 90$  vs. **LGI**  $1437 \pm 107$  mmol.l<sup>-1</sup> over 180 min,  
229  $p = 0.002$ ), displaying a significantly greater average change in absolute BG concentrations  
230 over the post-meal period compared to the average change under **LGI** (**HGI**  $+6.6 \pm 0.9$  vs.  
231 **LGI**  $+1.7 \pm 0.4$  mmol.l<sup>-1</sup>,  $p < 0.001$ ). As such, patients under **HGI** were, on average,  
232 hyperglycemic (**HGI**  $12.8 \pm 0.5$  mmol.l<sup>-1</sup>; Figure 1B), whereas patients under **LGI** typically  
233 remained within euglycemic ranges (**LGI**  $7.6 \pm 0.6$  mmol.l<sup>-1</sup>,  $p = 0.002$ ). Glucagon  
234 concentrations were significantly increased following the administration of both meals  
235 peaking similarly 30 minutes after consumption (**Figure 2A**). Following this, concentrations  
236 declined under **HGI** such that at 180 minutes concentrations were significantly lower than  
237 pre-meal, whereas the decline under **LGI** was largely attenuated (Figure 2A). However, total  
238 glucagon AUC was not statistically different between **LGI** and **HGI** (AUC<sub>0-180mins</sub>: **LGI**  
239  $264150 \pm 98209$  vs. **HGI**  $247054 \pm 79042$  pg.ml<sup>-1</sup> over 180 min,  $p = 0.141$ ). Temporal  
240 increases in total GLP-1 at 60 minutes following the meal were not statistically significant ( $p$   
241  $= 0.223$ ) with concentrations similar to baseline under both conditions throughout the  
242 remaining post-prandial period (**Figure 2B**).

243

244 \*\*\*INSERT FIGURE 1A-B\*\*\*

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246 \*\*\*INSERT FIGURE 2A-B\*\*\*

247

248 \*\*\*INSERT FIGURE 3A-B\*\*\*

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250 Sensations of hunger peaked at 60 minutes following consumption under both conditions,  
251 (**Figure 3AB**). Over the remaining 120 minutes hunger sensations decreased under **HGI**,  
252 (Figure 3AB). Inversely under **LGI**, no further increases in hunger were apparent, meaning  
253 total AUC for feelings of hunger and fullness were significantly higher ( $AUC_{0-180\text{mins}}$ : **LGI**  
254  $7619 \pm 1130$  vs. **HGI**  $6961 \pm 1050$   $\text{mmol.l}^{-1}$  over 180 min,  $p < 0.001$ ) and lower under the  
255 **LGI** trial ( $AUC_{0-180\text{mins}}$ : **LGI**  $2669 \pm 421$  vs. **HGI**  $3345 \pm 561$   $\text{mmol.l}^{-1}$  over 180 min,  $p$   
256  $< 0.001$ ).

257

258 In the **LGI** trial, a negative relationship was observed between total post-meal BG AUC and  
259 hunger AUC ( $r^2 = 0.420$ ,  $p = 0.039$ ), but not fullness AUC ( $r^2 = 0.003$ ,  $p = 0.910$ ) or serum  
260 insulin AUC ( $r^2 < 0.001$ ,  $p = 0.977$ ), plasma total GLP-1 ( $r^2 = 0.009$ ,  $p = 0.543$ ). Neither  
261 hunger ( $r^2 = 0.002$ ,  $p = 0.900$ ) nor fullness ( $r^2 = 0.020$ ,  $p = 0.699$ ) were associated with  
262 changes in serum insulin AUC. Glucagon AUC and total GLP-1 were not associated with any  
263 other variable under **LGI**. No other correlations were observed between measures under **HGI**  
264 ( $p > 0.05$ ; see **supplemental figure 2AD and 3AD** for correlations).

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275 **DISCUSSION**

276 The aims of this study were two-fold, 1) to investigate the influence of manipulating the  
277 glycemic index of meals consumed following exercise on appetite responses in patients with  
278 type 1 diabetes, and 2) examine the influence of glycemic index on appetite independent of  
279 insulinemia and fiber content. We demonstrate for the first time that a HGI meal consumed  
280 following exercise elevates subjective feelings of fullness and suppresses sensations of hunger  
281 in patients with type 1 diabetes, compared to an isoenergetic LGI meal. It is important to note  
282 that these responses were observed under comparable insulinemia, plasma glucagon and  
283 GLP-1 concentrations, and when meals were matched for macronutrient composition and  
284 fiber content.

285

286 Work from our group illustrates the clinical utility of consuming meals with a LGI around the  
287 time of exercise; specifically, LGI meals before and after exercise offer more favourable  
288 postprandial glycemic profiles without increasing risk of post-exercise hypoglycemia in type  
289 1 diabetes patients (12-14). This is important because the inclusion of exercise into the lives  
290 of patients is severely hampered by difficulties in managing post-exercise glycemia. From  
291 this present study however, we now reveal that patients may experience lower levels of  
292 satiety following LGI consumption in the post-exercise recovery period. Although it would  
293 be naïve to infer these findings to longer-term observations, our data may indicate likelihood  
294 for increased calorie intake following exercise due to increased appetite rather than avoidance  
295 of hypoglycemia *per se*. This may have important implications for long-term weight  
296 management in this population, and may contrast data in non-diabetic individuals which  
297 demonstrate an improvement in weight management following LGI carbohydrate diets (33).  
298 Of note however, we did not assess ad libitum energy intake in this present study. Therefore  
299 it is possible that perceived ratings of hunger or fullness may not directly translate to changes

300 in energy intake. However, we provide the first evidence of altered appetite responses to meal  
301 GI following exercise in type 1 diabetes.

302

303 We have previously demonstrated that with fiber-matched meals, a higher glycemic response  
304 is associated with greater postprandial feelings of fullness in a non-diabetic population (18).  
305 Based on strong positive correlations of fullness and postprandial insulinemia in humans  
306 (19), taken in concert with the acute induction of satiety with intracerebroventricular  
307 administration of insulin in baboons (23), we hypothesised that insulin was a confounding  
308 factor in their appetite responses. In the present study, we provided HGI and LGI meals in the  
309 post-exercise period in people with type 1 diabetes, therefore we were able to manually  
310 control for insulin concentrations due to an absolute deficiency in endogenous insulin  
311 appearance. Accordingly, insulin concentrations were similar at every time point in the  
312 postprandial period (Figure 1A), whereas marked increases in postprandial glucose  
313 concentrations were evident with HGI vs. LGI (Figure 1B) as expected. This observation in  
314 concordance with pre-trial GI testing confirmed that the meals significantly differed in  
315 glycemic index. Therefore the results of the present study indicate that HGI meals induce  
316 greater satiety independent of the insulin response that is typical of these meals (34).

317

318 These findings are consistent with previous infusion studies in people with and without type 1  
319 diabetes, whereby hyperglycemic ( $\sim 14$  and  $\sim 10$  mmol.l<sup>-1</sup>) intravenous infusion reduced  
320 hunger sensations compared to euglycemia ( $\sim 6$  mmol.l<sup>-1</sup>) (35, 36). Interestingly, these effects  
321 are more apparent in the postprandial state (35), suggesting an interaction with the  
322 gastrointestinal tract. Using <sup>13</sup>C octanoic acid, Russell et al (35). attempted to assess whether  
323 gastric emptying could explain the reduction in hunger seen under postprandial  
324 hyperglycemia (35). The gastric emptying coefficient (representing global gastric emptying

325 rate) tended ( $p = 0.052$ ,  $n = 6$ ) to be ~9% greater (i.e. slower gastric emptying) with  
326 postprandial hyperglycemia vs. euglycemia (35), which has also been shown by others (37-  
327 39). Taken together, hyperglycemic-induced delayed gastric emptying and the associated  
328 mechanoreceptor-mediated suppression of appetite (40) could be a possible contributory  
329 mechanism to explain the effect we have observed.

330

331 Another potential mechanism to explain the reduced hunger sensations with HGI vs LGI  
332 could be through portal vein signalling (41). With HGI, high glucose concentrations would  
333 likely be present in the portal vein. Since portal glucose infusions in postabsorptive rodents  
334 decreases food consumption and increases the number of *c-fos*-like immunoreactive neurons  
335 in the arcuate nucleus (41), this suggests that portal glucose enhances the activity of  
336 hypothalamic nuclei associated with appetite suppression. Furthermore, this response is  
337 attenuated by portal vein denervation (41), demonstrating the importance of this pathway for  
338 glucose sensing and appetite. Whilst glucagon displays anorectic properties (42), it is  
339 implausible that this explains the appetite response we observed in this study, since glucagon  
340 concentrations did not significantly differ between trials.

341

342 GLP-1 may play a role in the appetite response to HGI and LGI meals in healthy populations  
343 (21, 43), although the evidence for a differential GLP-1 response to HGI vs. LGI mixed-  
344 meals is equivocal (17). We chose to measure GLP-1 because it is considered at least partly  
345 active in type 1 diabetes patients (22), whereas other incretins such as gastric inhibitory  
346 polypeptide are largely absent (44). Postprandial responses in GLP-1 are thought to differ to  
347 those elicited by healthy non-diabetic individuals (22), and we now demonstrate that there is  
348 no significant difference in the GLP-1 response to HGI vs. LGI meals, consumed following



349 exercise in type 1 diabetes patients. We encourage further work to explore the wider role that  
350 incretins play in modulating appetite responses in this population.

351

352 The difference in fiber content between the HGI and LGI meals was small (0.5 g). Meta-  
353 analyses indicate that fiber reduces subjective sensations of hunger and subsequent energy  
354 intake (45). The difference between meals in the present study however, is not likely to have  
355 played a role in the response we have observed, as a 1 g increase in fiber intake suppresses  
356 appetite by ~0.18% (45). In the current investigation we observed a ~9% and ~25%  
357 difference in the postprandial AUC for hunger and fullness, respectively. Given the ~0.5 g  
358 difference in fiber would influence these responses by at least 2 orders of magnitude less  
359 (~0.09%) we consider this a negligible difference.

360

361 These findings should be considered in the context of more global diabetes care, as LGI post-  
362 exercise meals produce more suitable glycemic control than HGI (14). However, we  
363 demonstrate that a post-exercise HGI meal acutely induces greater fullness and less hunger,  
364 independent of insulin, in patients with type 1 diabetes. The clinical application of these  
365 findings should not be underestimated; interventions were carried out in the evening, in a  
366 non-fasted state, thereby facilitating greater translation to daily life (46). It is important to  
367 consider that our patients were young, physically fit, and well-controlled, and that responses  
368 observed herein may not be directly transferable to the wider type 1 diabetes population who  
369 may to be less physically active, in poorer glycaemic control and who may be treated on  
370 different insulin regimens. Further work is needed to clarify the mechanisms of this effect in  
371 well-controlled and physically-active patients and to establish the long-term implications of  
372 this response in a wider cohort of patients regularly participating in exercise. In addition we  
373 advise that future investigations feature assessment of prospective ad libitum dietary intake to

374 determine whether changes in appetite are matched with increased energy intake. In  
375 conclusion, HGI post-exercise meals induce greater postprandial feelings of fullness and  
376 lower postprandial hunger sensations in type 1 diabetes patients, under conditions of similar  
377 insulinemia and plasma GLP-1 concentrations.

378

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384

### 385 **AUTHORS' CONTRIBUTIONS**

386 **MDC** designed research, conducted research, analysed data and wrote the manuscript. **JTG**  
387 conducted research analysed data and wrote the manuscript. **PLSR** reviewed the manuscript  
388 and contributed to its preparation. **MW** conducted research, provided essential materials, and  
389 reviewed the manuscript. **JAS** conducted research, provided essential materials, and reviewed  
390 the manuscript. **DJW** designed research, conducted research and contributed to the  
391 preparation and write up of the manuscript. **EJS** designed research, conducted research,  
392 contributed to the preparation and write up of the manuscript, and has responsibility for final  
393 content.

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## TABLES

**Table 1.** Meal composition and glycemic index

	<b>GI</b>	<b>Energy (kcal)</b>	<b>CHO (g)</b>	<b>Fat (g)</b>	<b>Protein (g)</b>	<b>Fiber (g)</b>
<i>Evening meal</i>						
<b>LGI</b>	37	409±15	85±1	12±1	2±0.4	0.5±0.1
<b>HGI</b>	92	413±16	85±1	12±1	2±0.4	1±0.1

NOTE: test meals were based on 1.0g.carbohydrate.kg<sup>-1</sup> body mass (BM). LGI evening meal: basmati rice, tomato-based sauce, turkey breast, isomaltulose orange flavoured drink [10% solution]; HGI evening meal: jasmine rice, tomato-based sauce, turkey breast, maltodextrin orange flavoured drink [10% solution].



**Table 2.** Pre-trial dietary intake, insulin administration, and physical activity

	<b>HGI</b>	<b>LGI</b>	<b><i>p</i> value</b>
<b>Energy intake (MJ)</b>	9.5 ± 0.9	9.4 ± 0.8	0.776
<b>Carbohydrate (%)</b>	49 ± 3	49 ± 3	0.999
<b>Fat (%)</b>	32 ± 3	32 ± 3	0.879
<b>Protein (%)</b>	19 ± 2	20 ± 3	0.887
<b>Rapid-acting insulin (IU)</b>	24 ± 4	25 ± 4	0.803
<b>Levels of activity (steps)</b>	7492 ± 140	7325 ± 129	0.202

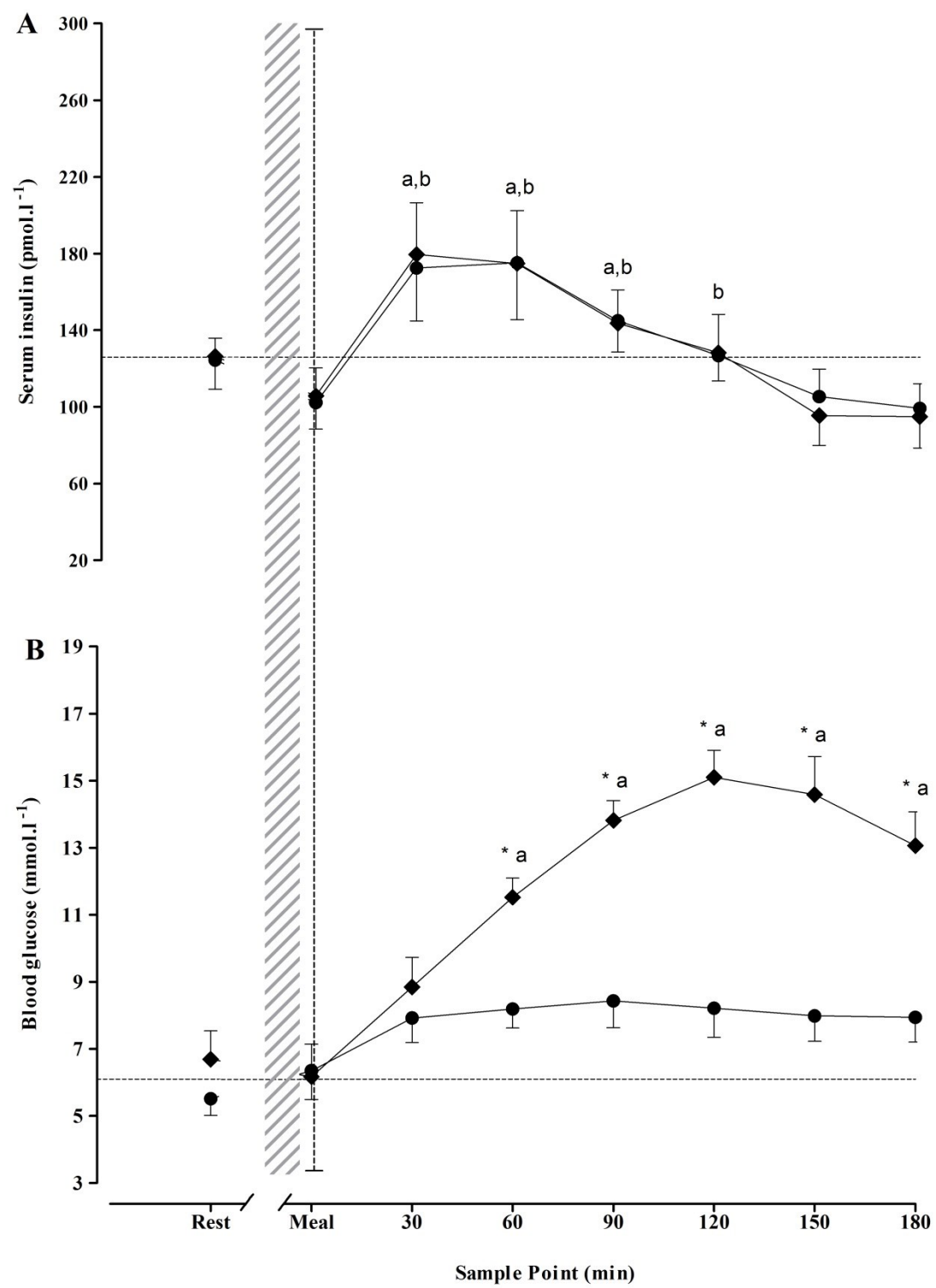
Note: Data collected over 48 hours prior to laboratory attendance and presented as mean ± SEM (n=10). Data were analyzed using paired samples t-tests. IU = insulin units. Steps recorded via pedometer.

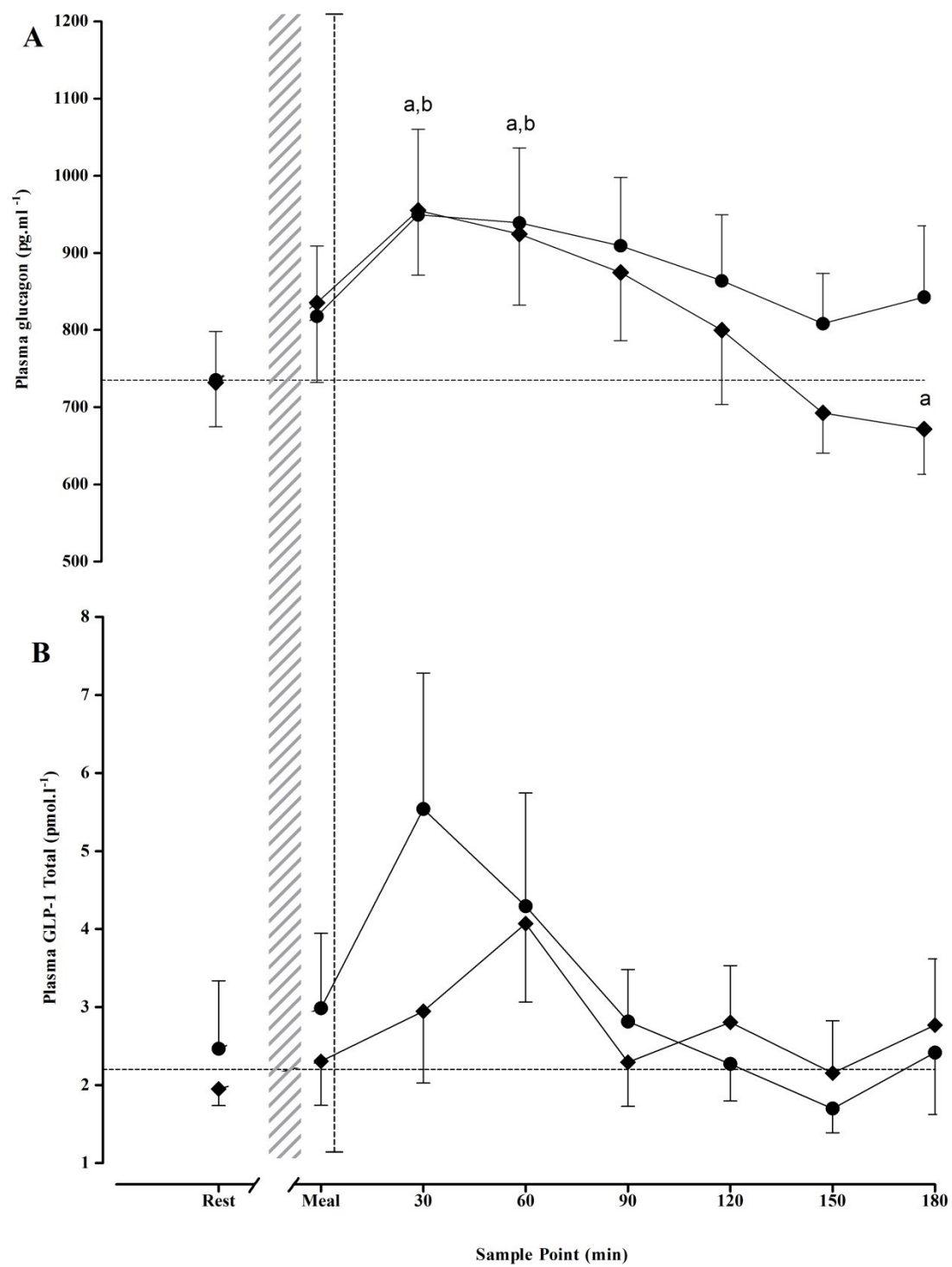
## FIGURES

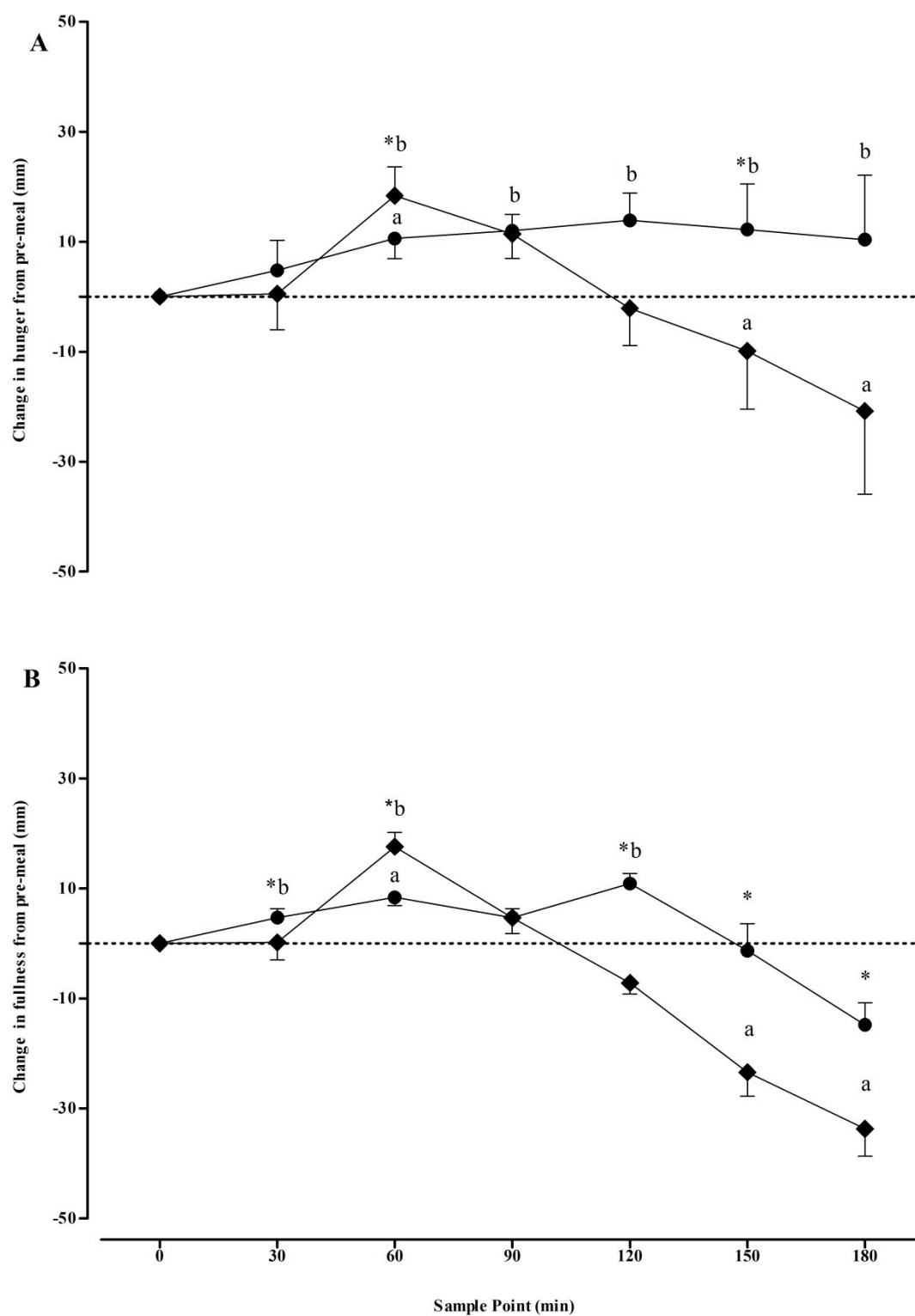
**Figure 1 A-B.** Time-course changes in (A) serum insulin and (B) blood glucose. Data presented as mean  $\pm$  SEM (n=10). Data were analysed using repeated measures ANOVA and subsequent Bonferroni adjusted pairwise comparisons. Black diamonds = **HGI**, black circles = **LGI**. \* indicates a difference between **LGI** and **HGI** ( $p \leq 0.05$ ). *a* indicates a significant difference from pre-test meal concentrations under **HGI**, *b* indicates a significant difference from pre-test meal concentrations under **LGI**. Vertical dashed line break indicates post-exercise intervention, which occurred 60 minutes post-exercise. Thatched area indicates exercise.

**Figure 2 A-B.** Time-course changes in (A) plasma glucagon and (B) plasma GLP-1 total. Data presented as mean  $\pm$  SEM (n=10). Data were analysed using repeated measures ANOVA and subsequent Bonferroni adjusted pairwise comparisons. Black diamonds = **HGI**, black circles = **LGI**. \* indicates a difference between **LGI** and **HGI** ( $p \leq 0.05$ ). *a* indicates a significant difference from pre-test meal concentrations under **HGI**, *b* indicates a significant difference from pre-test meal concentrations under **LGI**. Vertical dashed line break indicates post-exercise intervention, which occurred 60 minutes post-exercise. Thatched area indicates exercise.

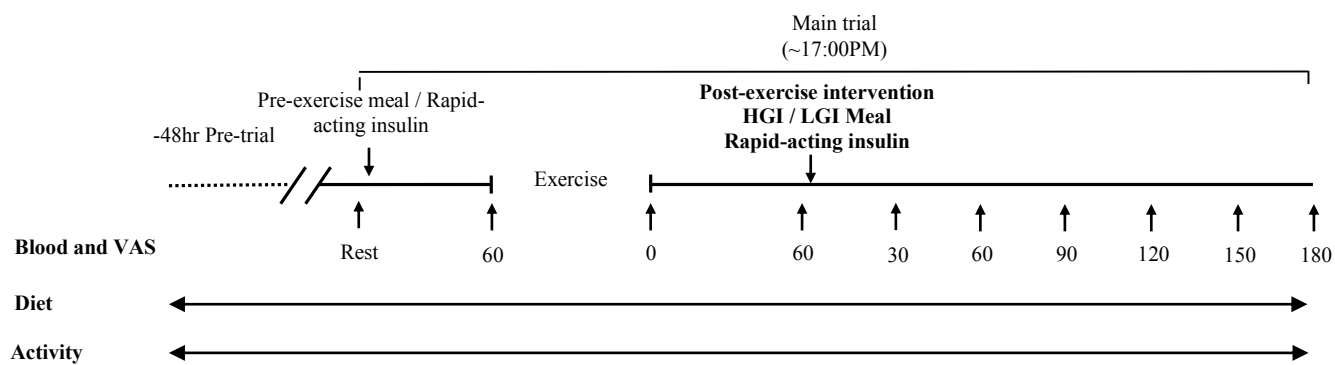
**Figure 3A-B.** Time courses in (A) hunger and (B) fullness following the consumption of the post-exercise test meals. Data presented as mean  $\pm$  SEM (n=10). Data were analysed using repeated measures ANOVA and subsequent Bonferroni adjusted pairwise comparisons. Black diamonds = **HGI**, black circles = **LGI**. \* indicates a difference between **LGI** and **HGI** ( $p \leq 0.05$ ). *a* indicates a significant difference from pre-test meal concentrations under **HGI**, *b* indicates a significant difference from pre-test meal concentrations under **LGI**.







## SUPPLEMENTAL Figure 1.



**Suppl. Figure 1** Schematic of trial design. Note: Blood glucose, serum insulin, plasma glucagon, plasma GLP-1, and VAS were analyzed at each respective blood sample time point.