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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).

PUBMED INDEXING: Campbell, Gonzalez, Rumbold, Walker, Shaw, Stevenson, West

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.

INTRODUCTION

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

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

The composition of the foods consumed following exercise is of importance to type 1 diabetes patients. Work from our group illustrates reduced hyperglycemia in the acute peri- 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^{-1}.min^{-1},

82   BMI 25.5 $\pm$ 0.3 kg.m^{-2}, HbA$_{1c}$ 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 $1.3g.carbohdyrate.kg^{-1}BM$

110 (549 ± 20 kcal) and a pasta-based lunch (pasta, tomato-based sauce, cheddar cheese,

111 olive oil) equating to $1.3g.carbohdyrate.kg^{-1}BM$ (968 ± 35 kcal). The breakfast meal was

112 consumed at ~08:00AM, and a lunch meal consumed at ~13:00PM. 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 VO_2 and 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 ± 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 1.0g.carbohdyrate.kg^{-1}BM (423 ± 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   VO$_{2peak}$. 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 ± 0.1 MJ / 413 ± 16

137   kcal vs. **LGI** 1.7 ± 0.1 MJ / 409 ± 15 kcal) and carbohydrate content (1.0g.carbohydrate.kg^{-}

138   ^{1}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 ± 0.1

140   vs. **LGI** = 0.5 ± 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 20μl was used for the

154   immediate quantification of blood glucose (BG: Biosen C-Line; EKF Diagnostic GmbH,

155   London, UK) and 10 μl 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^{-1} 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 β-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 ± 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 ± 1.0, **LGI** 9.4 ± 1.1 mmol.l^{-1}; p

204 $= 0.534$; and total interstitial glucose AUC$_{0-24hrs}$: **HGI** 11324 ± 1056, **LGI** 10212 ± 1228

205 mmol.l^{-1} 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 ± 0.5 mmol.l^{-1}, $p = 0.169$), serum insulin (**HGI** 106 ± 15 vs. **LGI** 102 ± 14

213 pmol.l^{-1}, $p = 0.986$), plasma glucagon concentrations (**HGI** 732 ± 99 vs. **LGI** 735 ± 103

214 pg.ml^{-1}, $p = 0.884$) and total GLP-1 (**HGI** 1.95 ± 0.21 vs. **LGI** 2.47 ± 0.87 pmol.l^{-1}, $p =$

215 0.620). At this time, sensations of hunger (**HGI** 68 ± 3 vs. **LGI** 67 ± 2, $p = 0.925$) and

216 fullness (**HGI** 60 ± 2 vs. **LGI** 61 ± 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 ± 26 vs. **LGI** 175 ± 30

220 pmol.l^{-1}, $p = 0.773$; **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$_{0-180mins}$: **HGI** 49576 ± 6786 vs. **LGI** 43924 ± 6196 pmol.l^{-1} 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 ± 0.5 vs. **LGI** +3.2 ± 0.6 mmol.l^{-1}, $p < 0.001$; **Figure 1B**) and

227 individualized peaks (**HGI** 15.8 vs. **LGI** 12.9 mmol.l^{-1}). Total BG AUC was significantly

228 greater under **HGI** (AUC$_{0-180mins}$: **HGI** 2205 ± 90 vs. **LGI** 1437 ± 107 mmol.l^{-1} 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 ± 0.9 vs.

231 **LGI** +1.7 ± 0.4 mmol.l^{-1}, $p < 0.001$). As such, patients under **HGI** were, on average,

232 hyperglycemic (**HGI** 12.8 ± 0.5 mmol.l^{-1}; Figure 1B), whereas patients under **LGI** typically

233 remained within euglycemic ranges (**LGI** 7.6 ± 0.6 mmol.l^{-1}, $p = 0.002$). 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$_{0-180mins}$: **LGI**

239 264150 ± 98209 vs. **HGI** 247054 ± 79042 pg.ml^{-1} 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***

245

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

247

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

249

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$_{0\text{-}180\text{mins}}$: **LGI**

254   7619 ± 1130 vs. **HGI** 6961 ± 1050 mmol.l^{-1} over 180 min, p <0.001) and lower under the

255   **LGI** trial (AUC$_{0\text{-}180\text{mins}}$: **LGI** 2669 ± 421 vs. **HGI** 3345 ± 561 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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DISCUSSION

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

Work from our group illustrates the clinical utility of consuming meals with a LGI around the time of exercise; specifically, LGI meals before and after exercise offer more favourable postprandial glycemic profiles without increasing risk of post-exercise hypoglycemia in type 1 diabetes patients (12-14). This is important because the inclusion of exercise into the lives of patients is severely hampered by difficulties in managing post-exercise glycemia. From this present study however, we now reveal that patients may experience lower levels of satiety following LGI consumption in the post-exercise recovery period. Although it would be naïve to infer these findings to longer-term observations, our data may indicate likelihood for increased calorie intake following exercise due to increased appetite rather than avoidance of hypoglycemia *per se*. This may have important implications for long-term weight management in this population, and may contrast data in non-diabetic individuals which demonstrate an improvement in weight management following LGI carbohydrate diets (33). Of note however, we did not assess ad libitum energy intake in this present study. Therefore 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 (~14 and ~10 $mmol.l^{-1}$) intravenous infusion reduced

320   hunger sensations compared to euglycemia (~6 $mmol.l^{-1}$) (35, 36). Interestingly, these effects

321   are more apparent in the postprandial state (35), suggesting an interaction with the

322   gastrointestinal tract. Using ^{13}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 in 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.

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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

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

NOTE: test meals were based on 1.0g.carbohydrate.kg^{-1} 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

	HGI	LGI	*p* value
Energy intake (MJ)	9.5 ± 0.9	9.4 ± 0.8	0.776
Carbohydrate (%)	49 ± 3	49 ± 3	0.999
Fat (%)	32 ± 3	32 ± 3	0.879
Protein (%)	19 ± 2	20 ± 3	0.887
Rapid-acting insulin (IU)	24 ± 4	25 ± 4	0.803
Levels of activity (steps)	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.
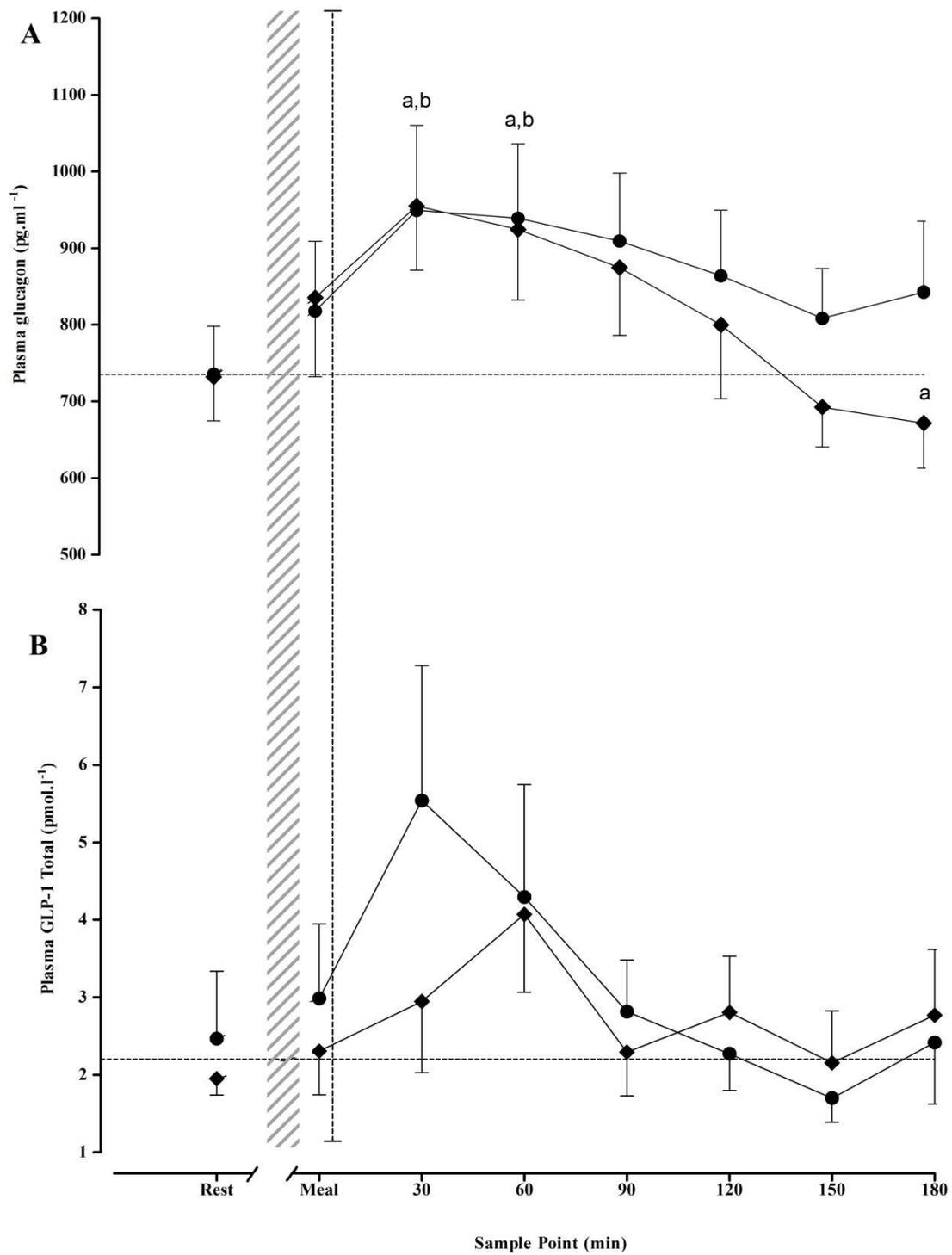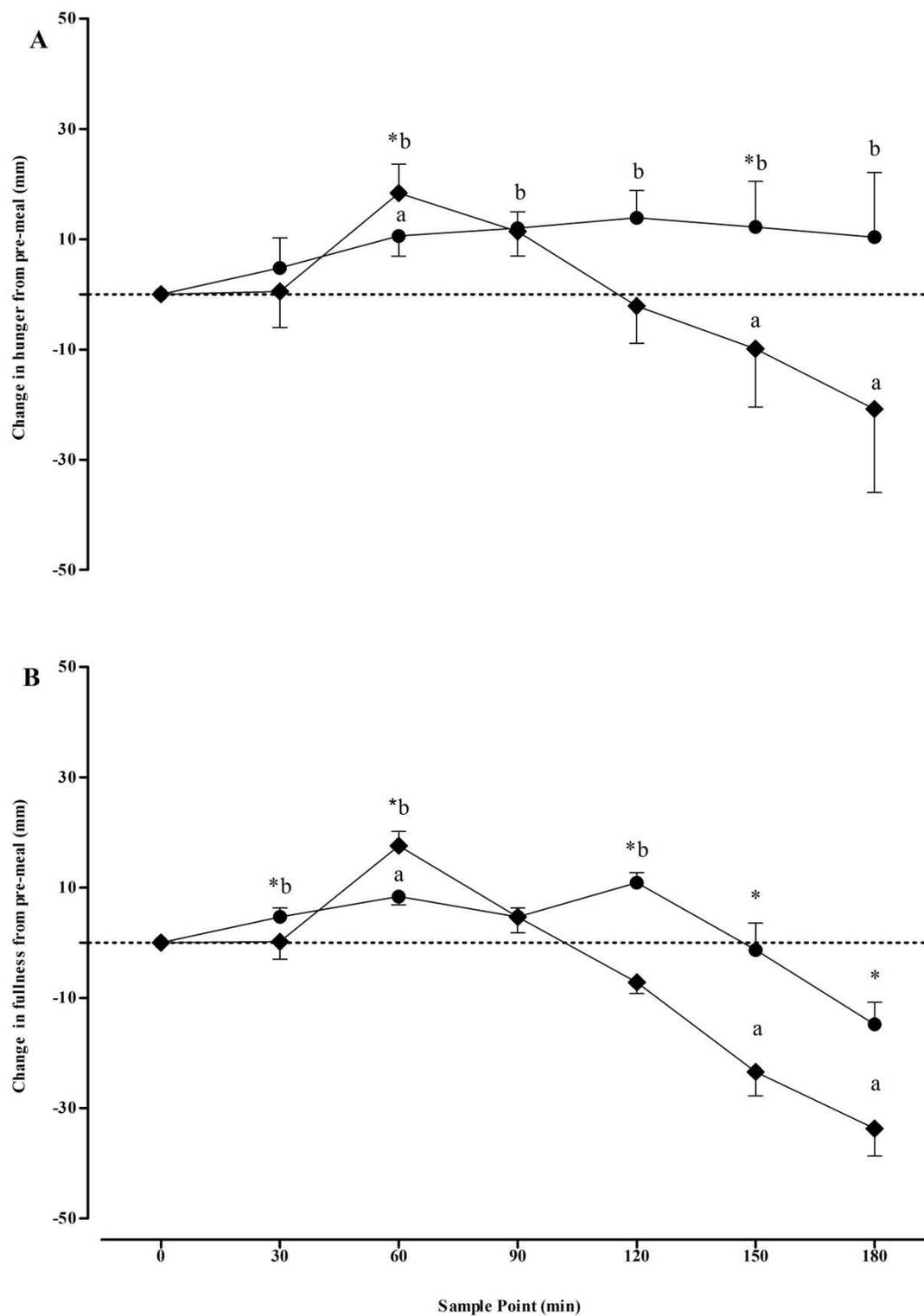
FIGURES

Figure 1 A-B. Time-course changes in (**A**) serum insulin and (**B**) blood glucose. Data presented as mean ± 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 ± 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 ± 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**.
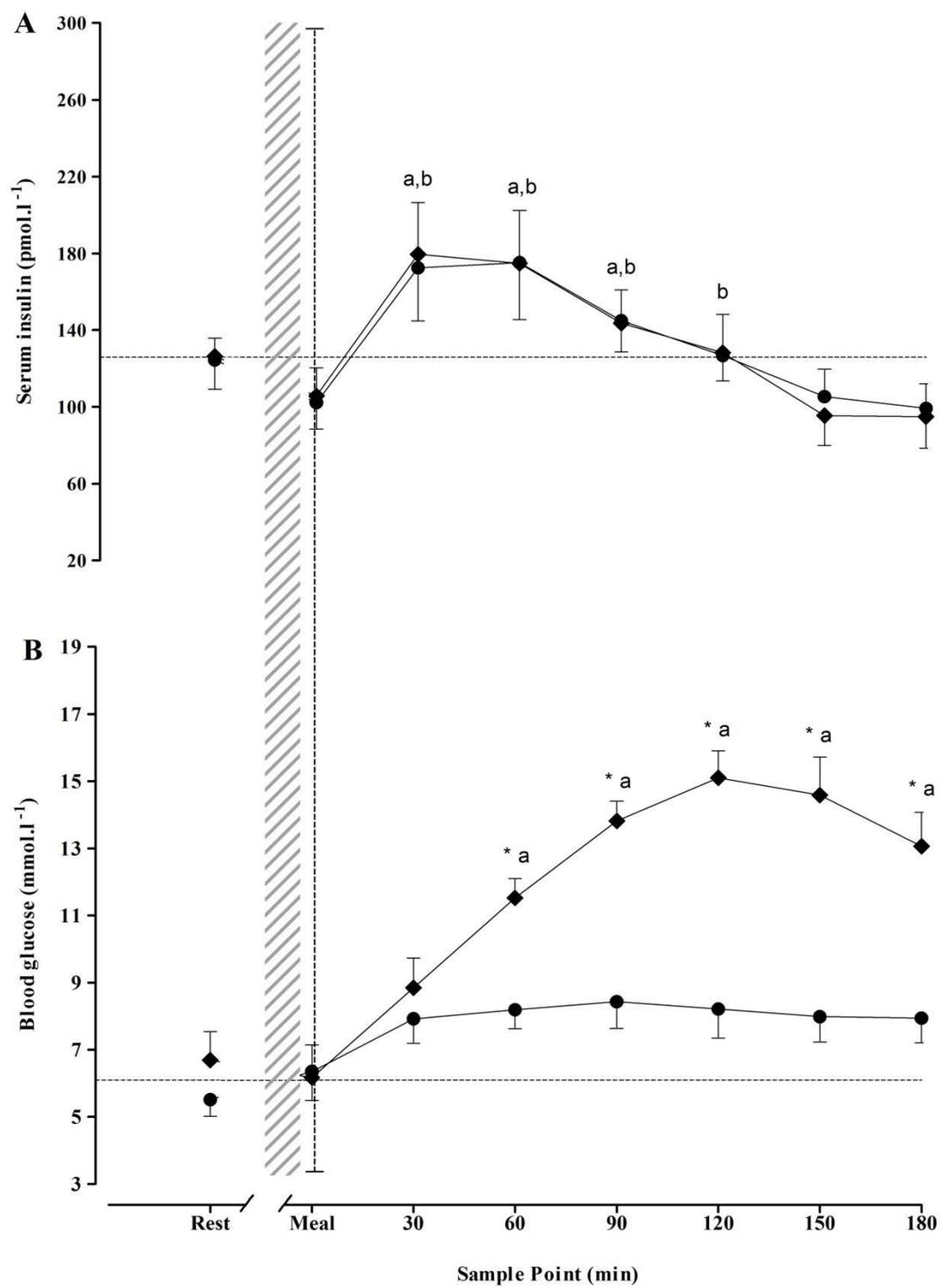
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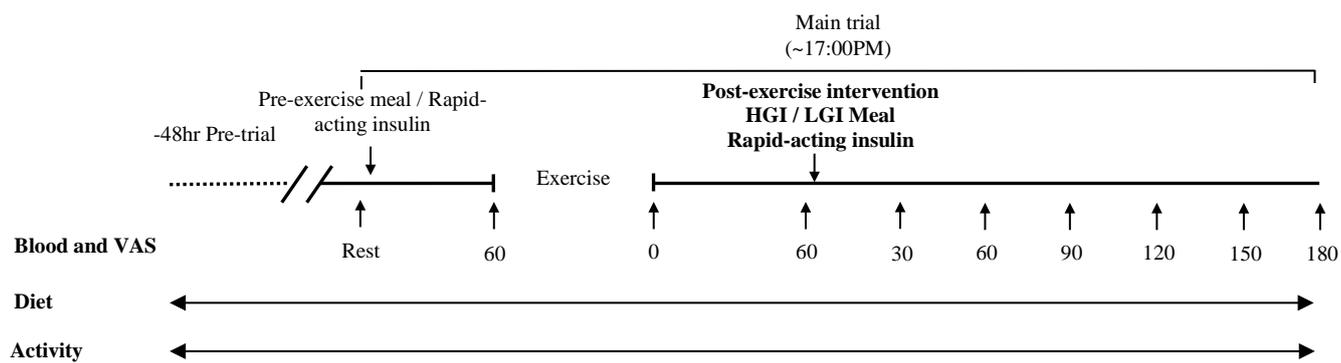
Suppl. Figure 1 Schematic of trial design. Note: Blood glucose, serum insulin, plasma glucagon, plasma GLP-1, and VAS were analyzed at each respective blood sample time point.