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Citation: Gonzalez, Javier, Barwood, Martin, Goodall, Stuart, Thomas, Kevin and Howatson, Glyn (2015) Alterations in whole-body insulin sensitivity resulting from repeated eccentric exercise of a single muscle group: a pilot investigation. *International Journal of Sport Nutrition and Exercise Metabolism*, 25 (4). pp. 405-410. ISSN 1526-484X

Published by: Human Kinetics

URL: <http://dx.doi.org/10.1123/ijsnem.2014-0211> <<http://dx.doi.org/10.1123/ijsnem.2014-0211>>

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1 **TITLE:** Alterations in whole-body insulin sensitivity resulting from repeated eccentric  
2 exercise of a single muscle group: a pilot investigation

3

4 **SHORT RUNNING TITLE:** Muscle damage and insulin resistance

5

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24 **Word Count:** 1717

## 25 **Abstract**

26 Unaccustomed eccentric exercise using large muscle groups elicits soreness, decrements in  
27 physical function and impairs markers of whole-body insulin sensitivity; although these  
28 effects are attenuated with a repeated exposure. Eccentric exercise of a small muscle group  
29 (elbow flexors) displays similar soreness and damage profiles in response to repeated  
30 exposure. However, it is unknown whether damage to small muscle groups impacts upon  
31 whole-body insulin sensitivity. This pilot investigation aimed to characterize whole-body  
32 insulin sensitivity in response to repeated bouts of eccentric exercise of the elbow flexors.  
33 Nine healthy males completed two bouts of eccentric exercise separated by 2 weeks. Insulin  
34 resistance (updated homeostasis model of insulin resistance, HOMA2-IR) and muscle  
35 damage profiles (soreness and physical function) were assessed before, and 48 h after  
36 exercise. Matsuda insulin sensitivity indices ( $ISI_{\text{Matsuda}}$ ) were also determined in 6 participants  
37 at the same time points as HOMA2-IR. Soreness was elevated, and physical function  
38 impaired, by both bouts of exercise (both  $P < 0.05$ ) but to a lesser extent following bout 2  
39 (time x bout interaction,  $P < 0.05$ ). Eccentric exercise decreased  $ISI_{\text{Matsuda}}$  after the first but  
40 not the second bout of eccentric exercise (time x bout interaction  $P < 0.05$ ). Eccentric  
41 exercise performed with an isolated upper limb impairs whole-body insulin sensitivity after  
42 the first, but not the second, bout.

43

44 **Keywords:** glucose; glycemia; insulin resistance; metabolic control; muscle damage  
45 repeated bout.

46

## 47 **Abbreviations**

48 GLUT-4: glucose transporter isoform 4

49 HOMA2-IR: updated homeostasis model of insulin resistance

- 50 iAUC: incremental area under the curve
- 51  $ISI_{\text{Matsuda}}$ : Matsuda insulin sensitivity index
- 52 MVC: maximal voluntary contraction
- 53 OGTT: oral glucose tolerance test
- 54
- 55
- 56

## 57 **Introduction**

58           Insulin sensitivity indices predict the risk of developing metabolism-related diseases  
59 i.e. type 2 diabetes and cardiovascular disease (The DECODE Study Group & The European  
60 Diabetes Epidemiology Group, 1999; Zavaroni et al., 1989), even when only the “healthy”  
61 range of indices are considered (Ning et al., 2012). Accordingly, understanding how insulin  
62 sensitivity responds to stimuli can give insight into metabolic disease risk in currently healthy  
63 populations. Whilst regular exercise alongside lifestyle interventions can prevent metabolic  
64 disease (Knowler et al., 2002), the acute effects of exercise on whole-body glucose  
65 metabolism are equivocal. Following a single bout of exercise, glucose tolerance has been  
66 shown to improve (Bonen, Ball-Burnett, & Russel, 1998), deteriorate, or remain stable  
67 (Gonzalez, Veasey, Rumbold, & Stevenson, 2013), relative to rest. Numerous factors are  
68 postulated to explain these discrepancies (including metabolic and nutritional status’ of the  
69 population, modality, volume and intensity of exercise), one of which is muscle damage  
70 induced by exercise with an eccentric component, and associated impairment of insulin  
71 sensitivity (Gonzalez, 2014).

72           Typically, the exercise paradigms employed to study muscle damage involve large  
73 muscle groups or whole-body exercise, i.e., downhill running (Cook, Myers, Kelly, &  
74 Willems, 2014; Green et al., 2010), or eccentric exercise of knee flexors (Paschalis et al.,  
75 2011). These models produce acute metabolic alterations indicative of reduced insulin  
76 sensitivity when measured at 48 h (Green et al., 2010; Paschalis et al., 2011) post-exercise.  
77 This effect is only present when exercise is unaccustomed, and is abolished or reversed with  
78 multiple bouts (Green et al., 2010; Paschalis et al., 2011). For damaging exercise of a small  
79 muscle group, similar profiles of damage, recovery and protection on repeated-bouts have  
80 been observed (Howatson, van Someren, & Hortobagyi, 2007), but the effect of damaging  
81 exercise of a small muscle group on whole-body insulin sensitivity is unknown. If whole-

82 body insulin sensitivity can be modified by acute exercise of small muscle groups, such as  
83 the elbow flexors of a single limb (constituting <6% of total lean mass (Araujo et al., 2010)),  
84 this could reveal an avenue to explore potentially beneficial adaptations with multiple bouts,  
85 which may have implications during forced inactivity or immobilization.

86 Accordingly, this pilot investigation aimed to assess whole-body insulin sensitivity  
87 during an oral glucose tolerance test (OGTT), in response to two bouts of eccentric exercise  
88 of the elbow flexors, separated by 14 days. We hypothesized that damaging exercise of a  
89 single muscle group would impair whole-body insulin sensitivity after the first, but not the  
90 second bout.

91

## 92 **Materials and methods**

### 93 *Participants*

94 Six male participants completed the full protocol, whilst a further three males provided  
95 fasting samples only. Thus, postprandial OGTT data are  $n = 6$  whilst all other data are  $n = 9$   
96 (participant characteristics are presented in Table 1). All participants were naïve to regular  
97 resistance exercise.

98

### 99 *Study design*

100 Participants visited the laboratory on 6 occasions; twice to complete the eccentric exercise  
101 protocol (separated by 2 weeks), and 4 times for blood sampling in line with assessment of  
102 physical function and soreness (muscle damage markers). Blood sampling (including OGTT)  
103 and damage marker assessments were performed prior to, and 48 h following damaging  
104 exercise. The eccentric exercise protocol was performed on an isokinetic dynamometer  
105 (System 4 Pro, Biodex Medical Systems Inc. NY, USA) and comprised  $8 \times 5$  maximal  
106 eccentric contractions of the left elbow flexors at  $30^\circ \text{d.s}^{-1}$ ; each set separated by 90 s rest.

107

108 *Subjective soreness and physical function*

109 Subjective soreness was determined using 200 mm visual analogue scales during full range of  
110 movement of the elbow flexors. Physical function was taken as the peak value attained during  
111 3 isometric maximal voluntary contractions (MVC) of the elbow flexors, each performed  
112 with 90° flexion of the elbow, separated by 120 s rest and following a standardized warm-up.

113

114 *OGTT and blood sampling*

115 Participants were asked to maintain a similar carbohydrate intake throughout to minimize  
116 effects of diet on insulin sensitivity. Blood sampling was always performed after a 12-h fast.  
117 Participants were instructed to eat their evening meal prior to trials at a standardized time, to  
118 eat the same meal before all trials, and to refrain from exercise for 24 h prior to blood  
119 sampling in accordance with standardization for postprandial glycemia testing guidelines  
120 (Brouns et al., 2005). For those who undertook the OGTT, 75 g of glucose (82 g dextrose  
121 monohydrate, corrected for moisture; Myprotein, Cheshire, UK) was dissolved in 300 ml of  
122 water and ingested within 5 min. Finger-prick blood samples were taken before (0 min), and  
123 15, 30, 45, 60, 90 and 120 min following ingestion, and analyzed immediately for blood  
124 glucose concentration (Biosen C\_line, EKF Diagnostics, Magdeberg, Germany), whilst a 250  
125 µL EDTA-microvette was filled with whole blood, before centrifugation (10 min at 3000  
126 rpm). By revisiting glucose data obtained in duplicate from one of our previous studies  
127 (Gonzalez & Stevenson, 2012), we are able to report reliability statistics, which include the  
128 combined variability of sample collection and analysis. Across 196 pairs of samples (range  
129 3.60-8.81 mmol/L), the standardized typical error was 0.12 mmol/L (95%CI: 0.11, 0.13  
130 mmol/L) and the coefficient of variation was 1.7%. Plasma was stored at -80°C for

131 subsequent determination of insulin concentrations by commercially available ELISA (IBL  
132 International GmbH, Hamburg, Germany; intra-assay coefficient of variation: 6%).

133

#### 134 *Calculations and statistics*

135 Insulin sensitivity was estimated in the fasted state, using the updated homeostasis model of  
136 insulin resistance (HOMA2-IR; reciprocal of insulin sensitivity (Levy, Matthews, &  
137 Hermans, 1998)) and in the postprandial state (OGTT), using the Matsuda insulin sensitivity  
138 index ( $ISI_{Matsuda}$  (Matsuda & DeFronzo, 1999)). Postprandial glucose and insulin  
139 concentrations were converted into time-averaged incremental areas under the curve (iAUC)  
140 as has been previously used (Gill et al., 2004). All analyses were performed using Prism v6  
141 (Graphpad Software, San Diego, CA). Data were checked for normal distribution  
142 (D'Agostino & Pearson omnibus normality test) and log transformed if appropriate, prior to  
143 analysis. The difference in work done between bout 1 and bout 2 was assessed by a paired  
144 samples t-test. Two-way [time (pre vs. post) x bout (bout 1 vs. bout 2)] repeated measures  
145 ANOVA were used to examine differences in fasting blood variables, OGTT data, MVC and  
146 soreness ratings. Data are presented as means  $\pm$  SEM unless stated otherwise, and statistical  
147 significance was set at  $P < 0.05$ .

148

#### 149 **Results**

150 Total work done during eccentric exercise was similar between bout 1 ( $2501 \pm 205$  kJ) and  
151 bout 2 ( $2527 \pm 215$  kJ;  $P = 0.738$ ). Eccentric exercise elicited increases in soreness on both  
152 bouts ( $P = 0.003$ ). Soreness was lower on the second bout vs. the first ( $P = 0.001$ ) and  
153 significantly attenuated (time  $\times$  bout interaction  $P = 0.001$ ; Figure 1A). MVC decreased after  
154 both bouts (main effect of time,  $P < 0.001$ ). No significant main effect of bout was detected



155 ( $P = 0.218$ ), but the reduction in MVC post-damaging exercise was attenuated on repeated  
156 bouts (time  $\times$  bout interaction,  $P = 0.019$ ; Figure 1B).

157 Fasting indices of insulin sensitivity (glucose and insulin concentrations, and  
158 HOMA2-IR) were unaffected by the intervention and neither was the glucose nor insulin  
159 iAUC (Table 2 and Figure 2).  $ISI_{\text{Matsuda}}$  did not display significant main effects for time or  
160 bout (both  $P > 0.05$ ) but the reduction in  $ISI_{\text{Matsuda}}$  observed after bout 1 was abolished after  
161 bout 2 (time  $\times$  bout interaction,  $P = 0.030$ , Figure 1C) indicating preserved insulin sensitivity  
162 after the second bout.

163

## 164 **Discussion**

165 These data indicate that: 1) unaccustomed eccentric exercise of a single upper-body  
166 limb reduces insulin sensitivity at the whole-body level, detectable in the postprandial state;  
167 2) the impairment in insulin sensitivity is abolished following a second bout of damaging  
168 eccentric exercise.

169 Previous work has demonstrated acute reductions in insulin sensitivity following  
170 downhill running are absent following a second bout (Green et al., 2010), and others have  
171 shown that after 8 bouts, eccentric exercise of the knee flexors *increases* fasting insulin  
172 sensitivity indices (Paschalis et al., 2011). Here we demonstrate that a single exposure to  
173 eccentric exercise of a single, small muscle group (left elbow flexors) induces an adaptive  
174 response, whereby full protection from acute impairment of insulin sensitivity is observed.  
175 Whether eccentric exercise of an upper limb has the capacity to positively influence insulin  
176 sensitivity over a longer time-course however, warrants further investigation. If this is the  
177 case, then one can envisage potential application during imposed inactivity or immobilization  
178 of lower limbs.

179           It has been suggested that due to relatively low insulin concentrations used to  
180 calculate HOMA2-IR (fasting vs. a clamp procedure or postprandial), this measure represents  
181 a different balance of sensitivity (hepatic vs. peripheral) than the  $ISI_{Matsuda}$  (Matsuda &  
182 DeFronzo, 1999; Radziuk, 2014). Accordingly, the reduction in  $ISI_{Matsuda}$  seen in the present  
183 study, when viewed in light of the lack of change in HOMA2-IR, suggests that eccentric  
184 exercise reduced peripheral (but not hepatic) insulin sensitivity.

185           Numerous mechanisms have been proposed to underlie muscle damage-induced  
186 reductions in insulin sensitivity. These include, a decrease in glucose transporter isoform 4  
187 (GLUT-4) at the plasma membrane due to reduced GLUT-4 transcription and thus GLUT-4  
188 protein content (Kristiansen, Jones, Handberg, Dohm, & Richter, 1997), associated with  
189 reduced muscle glucose transport manifest under hyperinsulinaemia but, intriguingly,  
190 elevated glucose transport when not exposed to insulin (Asp & Richter, 1996). This provides  
191 another potential explanation for the detectable reductions in  $ISI_{Matsuda}$  but not in HOMA2-IR.  
192 Secondly, systemic factors released by damaged muscle including cytokines such as tumor  
193 necrosis factor- $\alpha$  may also be implicated an impaired ability of insulin to stimulate insulin  
194 receptor substrate-1, phosphatidylinositol 3-kinase and Akt (protein kinase B) (Asp,  
195 Dugaard, Kristiansen, Kiens, & Richter, 1996; Del Aguila et al., 2000; Krogh-Madsen,  
196 Plomgaard, Moller, Mittendorfer, & Pedersen, 2006; Liao, Zhou, Ji, & Zhang, 2010). Whilst  
197 our data are unable to give insight into which of these mechanisms is responsible, given the  
198 relatively small muscle group used (<6% of total lean mass (Araujo et al., 2010)), the impact  
199 at the systemic level is noteworthy. This indicates that, either a very small decrease in total  
200 GLUT-4 content has implications for insulin sensitivity at the whole body level, and/or  
201 damage to small muscle groups produces adequate release of systemic factors (*ie.* cytokines)  
202 to impair the action of a sufficient mass of insulin sensitive tissue to influence whole-body  
203 metabolism.

204           In conclusion, these data indicate that eccentric exercise of a single upper limb,  
205 inhibits whole-body insulin sensitivity 48 h after the first bout, and such a reduction is not  
206 apparent after a second bout.

207

208 **Novelty statement:** Eccentric exercise of large muscle groups (leg flexors of both legs, or  
209 whole-body exercise) is known to impair whole-body insulin sensitivity after an initial  
210 exposure, with protection from this effect demonstrated with subsequent bouts. This is the  
211 first study to demonstrate that eccentric exercise with a single small muscle group (elbow  
212 flexors of a single arm) impairs insulin sensitivity following the first bout, but not following a  
213 second bout.

214

215 **Practical application statement:** In developing strategies to modulate insulin sensitivity,  
216 activating large muscle groups may not necessarily be required to elicit a response at the  
217 whole-body level. Eccentric exercise using upper limbs is likely sufficient to influence  
218 whole-body insulin sensitivity and this pilot work highlights a new strategy to potentially  
219 influence metabolism.

220

#### 221 **Author contributions**

222 All authors contributed to study design, data collection and analysis, drafting, editing and  
223 approved the final article.

224

#### 225 **Acknowledgements and funding**

226 This study was funded by Northumbria University.

227

#### 228 **Conflict of interest**

229 The authors declare no conflict of interest.

230

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313

314

315

316 **Figure legends**

317 **Figure 1.** Subjective soreness (A), maximal voluntary force production (B) and insulin  
318 sensitivity indices (C) before and 48 h after 2 bouts of eccentric exercise using the elbow  
319 flexors of an upper limb in males. MVC, maximum voluntary contraction force; ISI<sub>Matsuda</sub>,  
320 Matsuda insulin sensitivity index (Matsuda & DeFronzo, 1999). Data expressed as means  $\pm$   
321 SEM. \*, significant main effect of time; #, significant main effect of bout; ^, significant time  
322 x bout interaction effect ( $P < 0.05$ ).

323

324

325 **Figure 2.** Blood glucose (A, B) and plasma insulin (C, D) concentrations during an OGTT  
326 prior to and 48 h following, an initial (A, C) and second (B, D) bout of eccentric exercise  
327 using the elbow flexors of an upper limb in males. Data expressed as means  $\pm$  SEM.

## List of tables

**Table 1.** Participant characteristics.

Variable	Fasting Data <sup>1</sup>		OGTT Data <sup>2</sup>		Independent t-test ( <i>P</i> )
	Mean ± SEM	Range	Mean ± SEM	Range	
Age (y)	21 ± 1	19 – 26	21 ± 1	19 – 26	0.749
Stature (cm)	180 ± 2	173 – 188	181 ± 2	173 – 186	0.845
Body mass (kg)	76.9 ± 2.8	65 – 89.2	77.0 ± 3.1	68.7 – 86.2	0.997
Body mass index (kg/m <sup>2</sup> )	23.6 ± 0.6	19.9 – 26.0	23.5 ± 0.8	19.9 – 26.0	0.923

<sup>1</sup>, *n* = 9; <sup>2</sup>, *n* = 6.

**Table 2.** Indices of insulin sensitivity in response to acute and repeated exposure to eccentric exercise.

Variable	Bout 1		Bout 2		ANOVA time x bout interaction ( <i>P</i> )
	Pre	48 h post	Pre	48 h post	
Fasting glucose <sup>1</sup> (mmol/L)	4.45 ± 0.13	4.46 ± 0.20	4.46 ± 0.14	4.57 ± 0.18	0.756
Fasting insulin <sup>1</sup> (pmol/L)	128 ± 36	149 ± 54	147 ± 40	160 ± 46	0.910
HOMA2-IR <sup>1</sup>	2.25 ± 0.62	2.60 ± 0.92	2.54 ± 0.65	2.75 ± 0.73	0.874
Glucose iAUC <sup>2</sup> (mmol/L)	1.47 ± 0.23	1.29 ± 0.19	1.91 ± 0.22	1.27 ± 0.33	0.285
Insulin iAUC <sup>2</sup> (pmol/L)	139 ± 36	153 ± 26	158 ± 17	144 ± 38	0.160

Data expressed as means ± SEM. <sup>1</sup>, *n* = 9; <sup>2</sup>, *n* = 6; HOMA2-IR, updated homeostasis model of insulin resistance (Levy et al., 1998); iAUC, incremental time-averaged area under the curve.