Performing resistance exercise before versus after aerobic exercise influences growth hormone secretion in type 1 diabetes

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ABSTRACT

We compared growth hormone (GH) and plasma glucose (PG) levels in type 1 diabetic individuals performing aerobic before resistance exercise (**AR**) to when resistance exercise was performed first (**RA**). In **AR**, GH secretion declined in late exercise while it rose throughout exercise in **RA** resulting in higher GH in **RA** versus **AR** at exercise completion. Higher GH during **RA** could support PG by increasing hepatic glucose production and lipid mobilization.

Key words: hypoglycemia, exercise, diabetes, growth hormone

We recently found that performing resistance exercise before aerobic exercise (**RA**), rather than the reverse (**AR**), in a combined exercise session attenuates the drop in plasma glucose during exercise in individuals with type 1 diabetes (Yardley et al. 2012). During physical activity, growth hormone (GH) stimulates lipolysis, increases hepatic glucose release and indirectly suppresses glucose uptake into skeletal muscle (Galbo et al. 1977). In non-diabetic individuals, performing endurance exercise first blunts the GH response to subsequent resistance exercise (Goto et al. 2005) while performing resistance exercise first increases GH levels and consequently lipolysis during subsequent aerobic exercise (Goto et al. 2007). It is unknown if this phenomenon exists in individuals with type 1 diabetes and whether it may impact plasma glucose responses to exercise.

MATERIALS AND METHODS

Participants

The experimental protocol was approved by the Ottawa Hospitals Research Ethics Board and the University of Ottawa Health Sciences and Science Research Ethics Board, in accordance with the Declaration of Helsinki. Participants were required to have type 1 diabetes (Canadian Diabetes Association 2013), be habitually physically active (performing both aerobic and resistance exercise at least three times per week), non-smoking, at least 16 years of age, having $HbA_{1c} < 9.0\%$, and free from severe diabetes-related complications. Participants could receive insulin administered by multiple daily injections or by continuous subcutaneous insulin infusion. A full list of participant characteristics can be found in Table 1. The female participant in the study was using monophasic oral contraceptives and performed both testing sessions during the pill consumption (high exogenous hormone) phase.

Experimental Design

Prior to the testing sessions participants underwent an incremental workload test on a treadmill with a monitored electrocardiogram (Quinton Q4500, Quinton, Bothell, Washington) to determine peak oxygen consumption (VO_{2peak}). Strength tests were also performed to determine the maximum weight that participants could lift eight times (8 RM) while maintaining proper form. The following exercises were used in the testing protocol: chest press, leg press, seated row, leg curl, shoulder press, abdominal crunches and lat pulldown.

Participants maintained detailed diaries of food intake and insulin dosage prior to each testing session and were asked to avoid caffeine and alcohol for 24 hours prior to the testing session. They were asked to eat the same breakfast, same lunch and same supper each day they were being studied, and to keep their insulin doses and sleep patterns as consistent as possible. Participants were also asked to avoid strenuous exercise in the 24 hours leading up to the testing session.

Experimental sessions

Each participant performed two experimental sessions in random order, at the same time of day (5 pm), separated by at least 5 days:

1) Aerobic exercise before resistance exercise (**AR**): 45 minutes of moderate aerobic exercise (treadmill running at 60% VO_{2peak}) followed by 45 minutes of resistance training (3 sets of 8 repetitions at 8 RM),

2) Resistance exercise before aerobic exercise (**RA**): 45 minutes of resistance exercise followed by 45 minutes of aerobic training.

Treadmill speeds and the amount of weight lifted were kept consistent between sessions for each participant. To ensure consistency between sessions for energy expenditure, oxygen consumption was measured during exercise by means of an automated portable gas analysis system (Oxycon Mobile, Jaeger; Hoechberg, Germany). Energy expenditure was calculated as described elsewhere (Nishi 1981). Participants were monitored for one hour post-exercise.

Measurements

Pre-exercise glucose and insulin adjustments

On the days when exercise was scheduled, participants administering insulin by MDI were asked to decrease their long or intermediate-acting doses by 10% and those using CSII were asked to decrease their basal rates by 50% one hour before exercise. Capillary glucose levels between 5.5 and 13.9 mmol/L were required before starting exercise. If capillary glucose levels were less than 4.5 mmol/l during the tests participants were provided with glucose in tablet form (Dex4 ®, AMG Medical, Montreal, Canada).

Blood sampling and analyses

Venous blood samples were collected at baseline, every 15 minutes during exercise, and 15, 30 and 60 minutes post-exercise. Blood was drawn through an IV catheter using 5-ml sterile plastic syringes and transferred immediately into 5.4 ml serum (no additive) and plasma (K_2EDTA) BD Vacutainer® tubes (BD, Franklin Lakes, NJ, USA). Plasma samples were processed immediately while serum samples sat at room temperature to clot for 20 minutes before centrifugation at 4000 rev/min for 4 minutes. Aliquots were stored at -80ºC until analyzed.

The hexokinase timed endpoint method was used to determine plasma glucose concentration using a Beckman Coulter Unicel ®DxC600 Synchron® Clinical Analyzer (Beckman Coulter Inc., Fullerton, CA, USA) with SYNCHRON CX® Systems GLUCOSE reagent (Cat#442640). Serum GH concentrations were determined by enzyme immunoassay (Alpco Diagnostics ™, Salem, NH, USA). The sensitivity of the EIA kit was 1.13 $\mu g \cdot L^{-1}$. Serum free fatty acids (FFA) were measured by enzymatic assay (Wako Diagnostics, Richmond, VA), on a subsample of participants (n=6). Serum cortisol and plasma synthetic insulin were also analyzed on a subsample of participants (n=6) using enzyme immunoassay (Alpco Diagnostics TM, Salem, NH, USA) with sensitivities of 11.04 nmol/l for cortisol and 32.99 ρmol/l for insulin.

Statistical Analyses

Differences in plasma insulin, as well as serum GH, cortisol and FFA concentration were compared between conditions using two-way repeated measures ANOVA with the factors of time (0, 15, 30, 45, 60, 75, 90, 105, 120 and 150 minutes) and condition (**RA** and **AR**). Paired sample t-tests were also used to perform pair-wise post-hoc comparisons between conditions for each time point, to examine within condition changes from baseline, to compare area under the curve (AUC) for GH and to compare energy expenditure between sessions. Daily insulin and carbohydrate intake was calculated for each session (from the participants' food and insulin diaries) and compared using related-samples Wilcoxon signed rank tests. All analyses were performed using GraphPad Prism version 6.01 (GraphPad Software, San Diego, CA). Data are presented as means±SD.

RESULTS

There was no significant difference between the two exercise sessions in terms of energy expenditure and insulin dosage. While differences in total carbohydrate intake between sessions were not statistically significant, nine out of 11 participants required carbohydrate supplements during the **AR** session as compared to six out of 11 in the **RA** session. A significant effect of time ($P<0.001$) and an interaction of condition and time ($P<0.001$) was found in examining GH levels (Figure 1a). Baseline values were similar between conditions (**AR**= 1.67±3.15 vs. **RA**= 1.20±1.99 $\mu g \cdot L^{-1}$; P=0.68). GH levels increased at the onset of exercise in both sessions and were higher than baseline at 30 and 45 min during the **AR** session and from 60 to 105 min (i.e. during aerobic exercise) in the **RA** session (Figure 1). Resulting GH levels were not significantly different between conditions at the end of the first exercise bout (45 minutes: **AR**= 8.15±1.61 vs. **RA**= 5.44±2.28 $\mu g \cdot L^{-1}$; P=0.34). During **AR**, GH secretion declined during the resistance exercise phase, resulting in levels that were not different from baseline by 60 minutes (15 minutes into the resistance exercise portion of the testing session). During **RA,** GH levels continued to increase throughout the aerobic phase (45 to 90 minutes in Figure 1), peaking at the end of exercise (90 min). Accordingly, GH concentrations were higher in **RA** than in **AR** from 75 to 120 min (last 15 minutes of exercise, and first 30 minutes of recovery for both sessions). Differences between sessions with respect to area under the curve were not significant (**AR**= 467.9±301.8 vs. **RA**= 710.5±695.4 $\mu g \cdot L^{-1} \cdot min$, P=0.20). Under both conditions, the nadirs in plasma glucose were associated with peaks in GH concentrations (Figure 1). Serum FFAs were similar during the exercise period between **AR** and **RA**, but were higher in recovery in **AR** (Figure 1). Though we observed trends toward lower cortisol and insulin levels with AR compared to RA, these were not statistically significant between the two sessions.

DISCUSSION

Performing aerobic exercise blunts GH secretion during subsequent resistance exercise in individuals with type 1 diabetes. During the **AR** session, GH levels increased throughout aerobic exercise and then gradually returned to baseline during the resistance exercise portion of the session. Conversely, in the **RA** session a consistent increase in GH was seen throughout exercise, resulting in higher GH levels in **RA** compared to **AR** during the latter portion of the session. These results are consistent with the finding from similar studies involving non-diabetic subjects (Goto et al. 2005, Goto et al. 2007). The fact that similar cortisol and synthetic insulin levels were found between sessions in a subsample of participants would also suggest that neither of these hormones played a substantial role in the differences found in blood glucose responses during these exercise sessions.

The strength of the study lies in the within-subject crossover design where exercise timing, duration and intensity were kept constant, as were food and insulin intake. It should be noted, however, that the sample size was small and consisted of participants with good blood glucose control who were regularly physically active, which limits our ability to generalize the outcomes. Had it not been for the heterogeneity of the test group in terms of age and fitness levels [GH responses to exercise decline with increasing age (Kraemer et al. 1998) and are more pronounced with increasing fitness (Bunt et al. 1986)], it is possible that more differences would have reached statistical significance. The sample itself also contained one female volunteer which may have contributed to additional variability in the data, due to sex-related differences in growth hormone response (Bunt et al. 1986). Unfortunately, due to the lack of further female volunteers, it was impossible to determine from our data whether sex-related differences in GH

response to exercise order exist in participants with type 1 diabetes. We were unable to measure catecholamines during the study, and thus cannot rule out that catecholamines might have also played a role in stabilizing blood glucose by promoting hepatic gluconeogenesis during exercise. In addition, it is not possible to rule out that the additional carbohydrate supplementation required during the **AR** session played a role in decreasing GH secretion during exercise.

Due to the lack of control of endogenous insulin secretion, metabolism during and after exercise in individuals with type 1 diabetes differs from those without diabetes and remains to be fully understood. A more complete understanding of the interaction of metabolites and hormones during different exercise modalities and intensities will assist in developing age- and fitness level-appropriate evidence-based exercise recommendations for this population. Our finding that higher GH levels occur during the last 45 minutes of exercise in the **RA** compared to the **AR** session may help to explain the attenuated drop in glycemia previously reported in **AR** from that trial (Yardley et al. 2012). Higher GH levels have also been found with intermittent high intensity exercise (compared to moderate aerobic exercise), which also seems to have a glucose stabilizing effect (Guelfi et al. 2005, Guelfi et al. 2007). This is likely due to the effect of a GH peak promoting hepatic glucose production and increasing lipid mobilization (Moller and Jorgensen 2009) which can result in less glucose disposal in the subsequent hours. These novel GH findings support the notion that including anaerobic activities, such as weight lifting, before or throughout a moderate aerobic exercise session may reduce the risk of exercise-induced hypoglycemia in type 1 diabetic individuals. Further research involving a larger sample size of participants including different ages, fitness levels, and degrees of blood glucose control will be necessary to confirm the general applicability of this notion.

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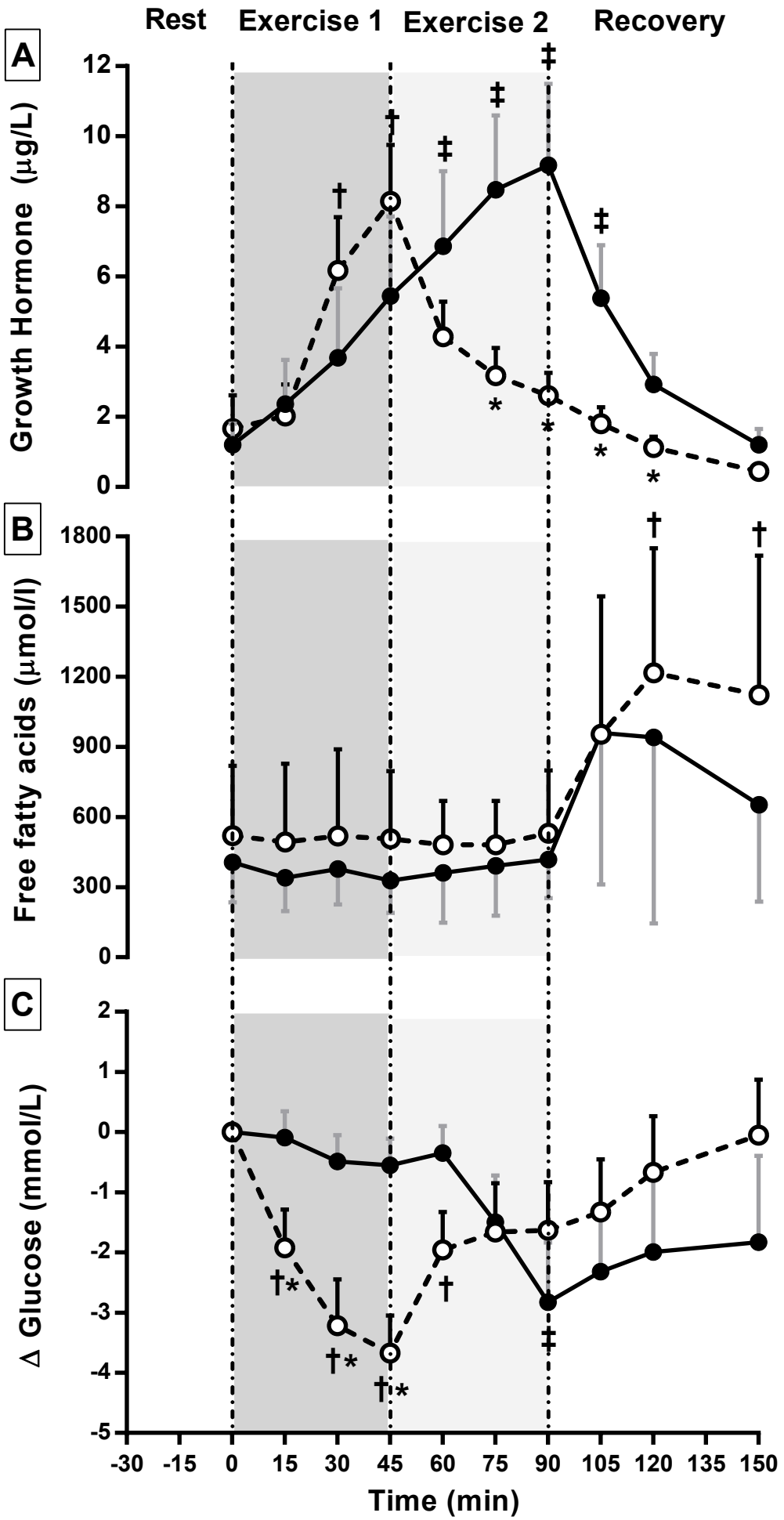
TABLES

Table 1 – Participant characteristics

N	11 (10 male, 1 female)
Age	33.0 ± 15.5 years
Height	178 ± 6 cm
Weight	80.6 ± 9.8 kg
BMI	25.4 ± 3.1 $kg \cdot m^{-2}$
HbA_{1c}	7.1 ± 1.1%
VO_{2peak}	51.3 ± 11.4 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$
Diabetes duration	12.4 ± 10.2 years
Insulin delivery	MDI = 4, CSII = 7

FIGURES

Figure 1. Changes in serum growth hormone concentration (Panel A, n=11), serum free fatty acid concentration (Panel B, n=6) and plasma glucose concentration (Panel C, n=11) during exercise when resistance exercise was performed before aerobic exercise (**RA** – black circles with solid line) and when aerobic exercise was performed first (**AR** – white circles with dashed line). * represents significant difference between **AR** and **RA** ($P<0.05$). † denotes significant change from baseline in **AR**; ‡ represents significant change from baseline in **RA.** Data are presented as mean ± SEM.


Rest
Exercise 1
Exercise 2
Recovery
A
Growth Hormone (μg/L)
B
Free fatty acids (μmol/l)
C
Δ Glucose (mmol/L)
Time (min)