Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes

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ABSTRACT

OBJECTIVE – To determine the effects of exercise order on acute glycemic responses in individuals with type 1 diabetes performing both aerobic and resistance exercise in the same session.

RESEARCH DESIGN AND METHODS - 12 physically active individuals with type 1 diabetes (HbA_{1c}=7.1±1.0%) either performed aerobic exercise (45 minutes of running at 60% $\dot{V}O_{2peak}$) prior to 45 minutes of resistance training (3 sets of 8, 7 different exercises) **(AR)**, or performed the resistance exercise prior to aerobic exercise (**RA**). Plasma glucose was measured during exercise and for 60 minutes after exercise. Interstitial glucose was measured by continuous glucose monitoring (CGM) 24 hours prior to, during and 24 hours post-exercise.

RESULTS - Significant declines in blood glucose levels were seen in **AR** but not in **RA** throughout the first exercise modality, resulting in higher glucose levels in **RA** (**AR**=5.5±0.7 mmol/l, **RA**=9.2±1.2 mmol/l, P=0.006 after 45 minutes of exercise). Glucose subsequently decreased in **RA** and increased in **AR** over the course of the second 45 minute exercise bout resulting in levels that were not significantly different by the end of exercise (**AR**=7.5±0.8 mmol/l, **RA**=6.9±1.0 mmol/l, P=0.436). While there were no differences in frequency of post-exercise hypoglycemia, the duration (105 minutes versus 48 minutes) and severity (area under the curve 112 U·min versus 59 U·min) of hypoglycemia were non-significantly greater after **AR** compared to **RA.**

CONCLUSIONS - Performing resistance exercise before aerobic exercise improves glycemic stability throughout exercise and reduces the duration and severity of post-exercise hypoglycemia for individuals with type 1 diabetes.

Key words: continuous glucose monitoring, hypoglycemia, resistance exercise, aerobic exercise, type 1 diabetes

Regular physical activity is associated with greater longevity and lower frequency and severity of diabetic complications in individuals with type 1 diabetes (1; 2). The type of exercise to recommend for potential improvements in glycemia in this population is still uncertain. Intervention studies of aerobic exercise training have not shown consistent effects on blood glucose control, as measured by HbA_{1c} (3). Two small (n=8-10) studies examining the chronic effects of resistance exercise training have found approximately one percentage point reductions in HbA_{1c} (4; 5).

Including short bursts of intense activity, where anaerobic metabolism plays a major role in providing fuel, may assist in preventing hypoglycemia during and up to 2 hours post-exercise in individuals with type 1 diabetes (6-9). However, two studies using continuous glucose monitoring systems (CGMS) suggested that the risk of nocturnal hypoglycemia after such exercise sessions is increased (10; 11) and perhaps even more than after moderate aerobic activity (11). The effects of resistance training, another form of anaerobic exercise, on acute glycemia in type 1 diabetes is currently unclear. In one study, insulin sensitivity, (measured by euglycemic clamp) was unchanged 12 and 36 hours after resistance exercise, thereby suggesting that resistance exercise may not cause as much of a post-exercise hypoglycemic response compared with aerobic exercise (12).

The American Diabetes Association Standards of Medical Care (13) encourages individuals with diabetes to follow the U.S. Department of Health and Human Services' Physical Activity Guidelines (14), which suggest including both aerobic and resistance exercise in fitness programs. Individuals who are actively engaged in training often wish to perform both types of exercise within the same session. We have previously found that aerobic exercise causes a more rapid decrease in blood glucose, and a greater need for carbohydrate supplementation during

exercise, than resistance exercise (15). We are unaware of previous research examining the acute effects of combining these exercise modalities in a single session, or whether there is an advantage related to the order in which they are undertaken, in individuals with type 1 diabetes. We sought to determine if the order of exercise in combined sessions has differential impact on blood glucose both during and post-exercise (as measured by CGM) in this population.

In individuals without diabetes, performing aerobic exercise immediately after resistance exercise results in an increased reliance on lipids as a fuel source during activity (16). We therefore hypothesized that performing resistance exercise prior to aerobic exercise would lead to less of a decline in blood glucose during exercise in individuals with type 1 diabetes than when exercise is performed in the opposite order. As performing resistance exercise first may result in a diminished reliance on carbohydrate for fuel during exercise, we anticipated that less nocturnal hypoglycemia would be found where aerobic exercise was preceded by resistance exercise.

RESEARCH DESIGN AND METHODS – The University of Ottawa and Ottawa Hospital Research Ethics Boards approved the experimental protocol. We recruited 12 non-obese adults with type 1 diabetes. Participants performed both aerobic and resistance exercise at least three times per week and had been doing so for at least 6 months (Table 1).

Experimental Design

The research took place in the Human and Environmental Physiology Research Unit at the University of Ottawa. After being informed of the purpose, protocol, and possible risks of the study, participants gave written consent and completed physical activity readiness questionnaires

(PAR-Q, AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire). Hand-held glucose meters (OneTouch® Ultra®, Lifescan, Johnson & Johnson, Milpitas, CA) and test strips (with identical code) were provided for capillary glucose tests. On a separate visit, participants underwent an incremental workload running test on a treadmill with a monitored electrocardiogram (Quinton Q4500, Quinton, Bothell, Washington) to determine peak oxygen consumption ($\dot{V}\mathbf{O_{2peak}}$). $\dot{V}O_{2peak}$ was determined by measuring the volume and concentration of expired oxygen and carbon dioxide (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry, Pittsburgh, PA). Muscular strength [(eight repetition maximum (8-RM)] was recorded as the maximum weight that participants could lift eight times with good form for the following exercises: chest press (pectoralis major), leg press (quadriceps, biceps femoris, gluteus maximus), seated row (latissimus dorsi, rhomboids), leg curl (biceps femoris), shoulder press (deltoids) and lat pulldown (latissimus dorsi). A venous blood sample was drawn for determination of HbA_{1c}, which was measured by automated heterogeneous immunoassay with latex-enhanced turbidimetric detection on a Roche Cobas Integra 800 analyzer (Roche Diagnostics Corporation, Indianapolis, IN).

Continuous Glucose Monitoring

The CGMS® System Gold™ (Medtronic, Northridge, CA) was used in this study. Participants were blinded to their glucose values and could not change their regular behavior patterns based on real-time glucose monitoring. Twenty-four hours prior to each experimental session, the CGM sensor was inserted subcutaneously in the abdomen, or in the upper gluteal area. The same insertion site was used for both trials. Training on calibration and operation of the CGM units was provided. Participants performed capillary glucose tests and calibrated the

CGMS® 4 times daily using the hand-held glucose meter provided. On the third day, 24 hours post-exercise, participants removed the sensors and the researchers retrieved the monitors. Data were downloaded using a Medtronic Com-Station and Minimed Solutions Software version 3.0 (Medtronic, Northridge, CA).

Participants maintained diaries of food intake and insulin administration while wearing the CGM sensor. They ate the same breakfast, same lunch and same supper each day of sensor wear, and kept their insulin doses the same each of these days to the greatest extent possible. Participants avoided exercise (apart from that performed in our laboratory) for 24 hours before inserting the sensor (48 hours before each study exercise session) as well as during the three days of sensor wear. They also avoided caffeine and alcohol during this time.

Experimental sessions

Participants arrived at the lab at 1600 h. Intravenous catheters were inserted soon after arrival. Exercise started at 1700 h for all participants. Each participant performed two experimental sessions in random order separated by at least 5 days:

1) Aerobic exercise before resistance exercise session (**AR**): A 45 minute bout of moderate intensity aerobic exercise (treadmill running at 60% $\dot{V}O_{2peak}$) followed by a 45 minute bout of resistance training (three sets of eight repetitions with 90 seconds rest between sets).

2) Resistance exercise before aerobic exercise session (**RA**): The same exercises as above were performed with the resistance exercise taking place before the aerobic exercise.

Sessions were followed by one hour of monitored resting recovery. Female participants were using monophasic oral contraceptives and were tested during the active pill consumption phase.

Measurements

On the days that exercise was scheduled (day 2 of each 3-day monitoring period), participants were asked to decrease their insulin doses (a 10% decrease in long or intermediate-acting for MDI patients and a 50% decrease in basal rate 1 hour pre-exercise for CSII patients). A further 25% basal rate decrease was made for CSII patients if their capillary glucose was $\leq$5 mmol/l upon arrival at the laboratory. Adjusted rates were maintained throughout exercise. Standardized snacks (Glucerna™ Chocolate Graham Snack Bars, Abbott Laboratories, Abbott Park, IL – 150 calories, 25 g of carbohydrate) were provided and consumed at 1600 h each day of monitoring.

Before starting exercise, participants were required to have blood glucose levels between 5.5 and 13.9 mmol/L. Capillary glucose tests were performed upon arrival at the laboratory, 30 minutes prior to and immediately prior to exercise. If capillary glucose levels were <4.5 mmol/l, participants were provided with 32 g of glucose (Dex4 ®, AMG Medical, Montreal, Canada) before checking levels again 15 minutes later. If initial readings were between 4.5 and 5.4 mmol/l, participants were given 16 g of glucose. These steps were repeated until a level of $\geq$5.5 mmol/l was achieved. Glucose concentrations during exercise were monitored by applying a drop of venous blood to a test strip inserted in the study hand-held glucose meter when venous blood samples were collected. When levels were <4.5 mmol/l, exercise was interrupted and participants were provided with 16 g of glucose. Capillary glucose tests were then performed every 10 minutes and an additional 16 g of glucose provided when necessary until a level of $\geq$5.5 mmol/l was achieved and exercise resumed. Oxygen consumption was measured using a

portable gas analysis system (Oxycon Mobile, Jaeger; Hoechberg, Germany). Energy expenditure was calculated as described elsewhere (17).

Blood analyses

Venous blood samples were collected at baseline, 5, 10, 15, 30, 45, 50, 55, 60, 75, and 90 minutes during exercise and at 5, 10, 15, 20, 30, 40, 50 and 60 minutes post-exercise. Blood was drawn using 5 ml sterile plastic syringes and transferred immediately into 5.4 ml plasma (K_2EDTA) BD Vacutainer® tubes (BD, Franklin Lakes, NJ, USA), mixed by inversion and centrifuged immediately. Plasma aliquots were transferred into 1.5 ml microcentrifuge tubes and stored at -80ºC until analyzed. Plasma glucose concentrations were determined using the hexokinase timed endpoint method on the Beckman Coulter Unicel ®DxC600 Synchron® Clinical Analyzer (Beckman Coulter Inc., Fullerton, CA, USA) with SYNCHRON CX® Systems GLUCOSE reagent (Cat#442640).

STATISTICAL ANALYSES

Exercise and recovery periods were examined separately. Plasma glucose concentration was compared between treatments using two-way repeated measures ANOVA with the factors of time (Exercise - 5, 10, 15, 30, 45, 50, 55, 60, 75 and 90 minutes; Recovery - 5, 10, 15, 20, 30, 40, 50, and 60 minutes) and treatment (**RA** or **AR**). Paired sample t-tests were used to perform pair-wise post-hoc comparisons between treatments for each time point to examine within treatment changes from baseline, and changes throughout recovery. The level of significance was set at 0.05. Energy expenditure during the exercise sessions (including the recovery) was compared using a paired sample t-test.

CGM data were grouped and summarized as follows: 24 hours and overnight (2400 to 0600h) pre-exercise, as well as 24 hours and overnight post-exercise. Hypoglycemia was defined as any value <3.5 mmol/l detected by CGM and values >10.9 mmol/l were categorized as hyperglycemic. Total time spent in hypoglycemia, euglycemia, and hyperglycemia for the pre-determined periods and the area under the curve (**AUC** - defined as the *absolute* distance from the described limits, multiplied by the time spent outside those limits) for time spent hypo- and hyperglycemic was determined along with the maximum, minimum and mean interstitial glucose for each time period. Variables were compared between exercise treatments, and pre- and post-exercise values were compared within treatments using related samples Wilcoxon Signed Ranks tests. These tests were also used to examine differences in insulin and carbohydrate intake (calculated from the participants' food and insulin diaries) between days within exercise treatments (day 1 versus 2), and between exercise treatments (days one through three). Pearson correlation analyses were performed comparing capillary glucose values recorded by the participants during non-exercise periods to CGM data to assess the accuracy of the sensors throughout each 3-day measuring period. Analyses were performed using SPSS 18.0 for Windows (SPSS Inc. Chicago, IL, USA). Data are presented as means±SD.

RESULTS

Energy expenditure was measured during exercise and recovery together for both sessions in 9 out of the 12 participants. There were no differences in energy expenditure between **AR** (4277±729 kJ) and **RA** (4247±589 kJ).

Plasma glucose

Plasma glucose levels for exercise and recovery (Supplemental table S-1) are plotted in Figure 1. A significant effect of time (P=0.001) and an interaction of treatment and time (P=0.004) were found in examining plasma glucose levels during exercise (Figure 1). Differences between treatments were not significant at baseline. The aerobic exercise performed in the **AR** treatment caused a substantial decline in blood glucose concentration, resulting in plasma glucose levels that were lower than baseline within the first 10 minutes of exercise, persisting until the end of aerobic exercise (9.1±2.4 at baseline; 5.5±2.4 mmol/l at 45 minutes; P<0.01) and continuing into resistance exercise. Glucose then increased during resistance exercise, producing levels that were similar to baseline by the end of exercise. Conversely, the **RA** treatment did not produce significant changes from baseline during resistance exercise. After the change in exercise modality in **RA**, glucose levels were only significantly different from baseline after 75 (p=0.044) and 90 (p=0.018) minutes of exercise. Glucose was lower in the **AR** treatment as compared to the **RA** treatment until the end of exercise, with differences achieving statistical significance between 30 and 60 minutes (P<0.05).

During the post-exercise recovery period, there was a significant effect of time (P<0.01) for changes in plasma glucose, but no effect of treatment or interaction of treatment and time. Significant increases in plasma glucose from the end of exercise were seen throughout recovery after **AR** where none were observed after exercise in **RA** (Figure 1).

Carbohydrate intake and insulin dosage

Total daily insulin doses did not differ significantly between treatments on the first two days of CGM wear prior to the experimental exercise session, or between the first and second day within each treatment. Insulin adjustments for exercise were similar between treatments

(Supplemental Table S-2). On the day after the exercise testing session insulin intake was lower after **AR** session as compared to **RA** (**AR**=36.1±16.3 U, **RA**=38.8±18.5 U, P=0.028). Ten out of twelve participants required carbohydrate supplementation during the **AR** session, as compared to only 6 out of 12 during **RA**, however there were no statistically significant differences between groups in total carbohydrate intake during exercise and recovery in the laboratory (Supplemental Table S-3), and in the 6 hours following exercise (Supplemental Table S-4).

Interstitial glucose levels

Pearson correlations between capillary glucose readings from non-exercise periods and sensor readings over the monitoring period were 0.95 and 0.91 for **AR** and **RA** respectively (P<0.001). There were no significant differences between treatments with respect to hypoglycemia and hyperglycemia (number of excursions, time, AUC) as well as mean, maximum and minimum glucose either on the night before or 24 hours prior to exercise.

Mean post-exercise overnight CGM profiles are provided in Figure 2. In the **RA** treatment, average maximum nocturnal glucose levels were significantly lower after exercise than the previous (non-exercise) night (pre-exercise=9.5±3.0 mmol/l, post-exercise maximum=8.8±4.0 mmol/l; P=0.04). Within the **AR** treatment there was a trend towards greater AUC post-exercise for nocturnal hypoglycemia (P=0.06) as compared to **RA**. While the frequency of nocturnal hypoglycemic events did not differ between the two exercise sessions the duration and depth of hypoglycemia tended to be longer and more severe after **AR** in comparison to **RA** (Table 2).

DISCUSSION

This study evaluated, in the context of a combined resistance and aerobic exercise session, the effects of exercise order on blood glucose levels in individuals with type 1 diabetes. As we had anticipated, performing resistance exercise prior to aerobic exercise rather than the reverse resulted in attenuated declines in glucose concentration during exercise, fewer exercise-induced hypoglycemic events, and less need for carbohydrate supplementation. Furthermore, we observed beneficial effects from this sequence on subsequent 12-hour glycemic trends where the duration and severity of hypoglycemia was reduced. The benefits of performing resistance exercise prior to aerobic exercise instead of the reverse were observed despite overall energy expenditure being equal between experimental sessions.

Resistance exercise is a primarily anaerobic activity. Other types of high-intensity exercise combining aerobic and anaerobic metabolism (e.g. high intensity cycling) can increase the rate of glucose appearance to a greater extent than the rate of glucose utilization (seven and four times respectively) during exercise in type 1 diabetes (18). This may cause glucose levels to increase during exercise, producing post-exercise hyperglycemia if intense exercise is sustained for 12 or more minutes (19). Shorter anaerobic exercise bouts (intermittent 4-s sprints, or 10-s sprints prior to or post-low-intensity aerobic exercise) attenuated declines in blood glucose both during and after exercise when combined with low-intensity (40% $\dot{V}O_{2peak}$) cycling (6-8). Elevated glucose production from very high-intensity exercise is generally attributed to increased levels of circulating epinephrine (known to triple with short sprints (6; 8; 9) and increase up to 14 times its resting value (18) after 12 minutes of exhaustive cycling) and norepinephrine which augment glycogenolysis throughout exercise and early recovery (18; 19).

While we did not measure catecholamines during the sessions, responses to high-intensity exercise are known to be comparable (18; 20) or slightly attenuated (19; 21) in

individuals with type 1 diabetes when compared to non-diabetic counterparts. Catecholamines can increase to three or four times resting values during moderate-intensity resistance exercise in individuals without diabetes (22) with responses increasing in proportion to exercise intensity (23). If our participants experienced similar responses to resistance exercise as individuals without diabetes, then increases in epinephrine may have contributed to the attenuated rate of decline in blood glucose during the first 15 minutes of aerobic exercise in **RA**, and to the increase in glucose during resistance exercise in **AR** (Figure 1). The latter should be interpreted with caution as most participants needed glucose supplements to prevent hypoglycemia during aerobic exercise in this session.

It is also possible that exercise-related growth hormone (GH) secretion differed between treatments potentially affecting fuel selection during exercise. Goto *et al*.(24) found that, in non-diabetic individuals, performing endurance exercise before resistance exercise produced lower GH secretion than resistance exercise alone. The same researchers also found that resistance exercise performed 20 minutes or less prior to endurance exercise produced elevated levels of GH and greater rates of lipolysis during the subsequent aerobic activity compared to endurance exercise alone (16). As higher GH levels are known to decrease muscle glucose uptake and increase lipolysis in non-diabetic individuals (25), this may have been a factor in the attenuated declines in blood glucose during aerobic activity in **RA**.

High-intensity cycling increases blood lactate levels during and up to 40 minutes post-exercise in individuals with type 1 diabetes (6; 7; 9; 18; 19). We are unaware of published data describing lactate responses to resistance exercise in this population. Resistance exercise protocols similar to the one we used have produced lactate concentrations up to four times those measured at rest, with levels remaining significantly higher than baseline until 30 minutes post-

exercise in trained non-diabetic individuals (26). As elevated lactate could serve to increase gluconeogenesis (7) it could be a contributing factor in the attenuated decline in glucose during the first 15 minutes of aerobic exercise in **RA**, as well as the increases in post-exercise glucose levels in **AR**.

Studies suggest that high-intensity exercise may be associated with a greater frequency of nocturnal hypoglycemia in type 1 diabetic individuals (10; 11). Our participants experienced nocturnal hypoglycemia as frequently post-exercise as on non-exercise nights. As nocturnal hypoglycemia has been identified as a risk inherent with intensive insulin therapy (27), it is possible that overnight hypoglycemia in our study was more related to insulin therapy than to exercise. It is noteworthy that hypoglycemic events occurring after **AR** tended to be longer and more severe than those experienced in **RA** as demonstrated by a greater AUC. Studies using glucose clamp found that counter-regulatory responses to subsequent hypoglycemia were blunted post-exercise, even in the absence of significant changes in glucose levels during exercise (28). In addition, in non-diabetic individuals, even mild hypoglycemia (3.9 mmol/l) is sufficient to elicit counter-regulatory reactions which can blunt neuroendocrine responses to subsequent hypoglycemia within 24 hours (29). As decreases in blood glucose were greater during **AR** (reaching a mean of 5.5±2.4 mmol/l as compared to 6.9±3.1 mmol/l in **RA**), it is plausible that subsequent responses to declining blood glucose could have been subject to impairment post-exercise.

Although there are advantages to admitting study subjects the night prior to testing to control participant activity and food intake, we chose a study design more reflective of real-life conditions. Participants controlled their meals and insulin, but were asked to eat the same breakfast, lunch and dinner at the same time for every day of sensor wear and to match their

insulin intake as closely as possible. Exercise took place at 1700 h when many individuals who work during the day opt to exercise, unlike several other studies where mid-morning exercise was performed (6-9; 18; 19).

Several aspects of resistance training in type 1 diabetic individuals require further scrutiny. Glucose responses may be different if exercise is performed at another time of day as both hormone and exogenous insulin concentrations are likely to be different. Our participants were fit, habitual exercisers, and the effects of exercise may be less pronounced in unfit individuals exercising at the same relative intensity, as the activity would be at a lower absolute intensity. In non-diabetic subjects running at very high relative intensity, glucose production and catecholamine concentrations increase more in athletes than in physically-untrained individuals, resulting in hyperglycemia after exercise in the former group, because glucose production falls more slowly than glucose utilization when exercise ends (30). Further research on different subpopulations of type 1 diabetic individuals, including those with lower fitness levels and poorer glycemic control is warranted.

This study is limited by its small sample size (n=12) which may have prevented us from finding all of the significant differences in plasma glucose levels during exercise. To examine our participants in a real-life scenario, we compromised a certain amount of experimental control, such as having complete control over all food and insulin intake. The ability to interpret the data would have been improved by having catecholamine, lactate and growth hormone measurements. Finally, having a relatively fit sample with moderate to good control of their diabetes makes the applicability of the outcomes to individuals who are inactive or have poor glycemic control uncertain.

In summary, our findings suggest that trained individuals with type 1 diabetes who perform both resistance and moderate aerobic exercise should consider performing their resistance exercise first if they tend to develop exercise-associated hypoglycemia, as doing so may attenuate declines in glucose levels during subsequent aerobic exercise. This order of exercise could lead to a lower reliance on glucose supplementation during exercise, and may also decrease the severity of potential nocturnal hypoglycemia. Conversely, individuals complaining of exercise-associated hyperglycemia may wish to perform aerobic exercise prior to resistance training. Both approaches should still be accompanied by careful monitoring of blood glucose levels both during, and post-exercise.

AUTHOR CONTRIBUTIONS

R.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.Y. contributed to the conception and design of the project, contributed to the discussion, collected and analyzed the data, drafted and reviewed/edited the manuscript. G.K., B.P., M.R. and RS contributed to the conception and design of the project, researched data, contributed to the discussion, and reviewed/edited the manuscript. F.K. took the lead in data analysis, contributed to the discussion, and reviewed/edited the manuscript. P.B. and J.M. contributed to the discussion and reviewed/edited the manuscript.

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REFERENCES

1. Moy CS, Songer TJ, LaPorte RE, Dorman JS, Kriska AM, Orchard TJ, Becker DJ, Drash AL: Insulin-dependent diabetes mellitus, physical activity, and death. *Am J Epidemiol* 137:74-81, 1993
2. Kriska AM, LaPorte RE, Patrick SL, Kuller LH, Orchard TJ: The association of physical activity and diabetic complications in individuals with insulin-dependent diabetes mellitus: the Epidemiology of Diabetes Complications Study--VII. *J Clin Epidemiol* 44:1207-1214, 1991
3. Kavookjian J, Elswick BM, Whetsel T: Interventions for being active among individuals with diabetes: a systematic review of the literature. *Diabetes Educ* 33:962-988; discussion 989-990, 2007
4. Durak EP, Jovanovic-Peterson L, Peterson CM: Randomized crossover study of effect of resistance training on glycemic control, muscular strength, and cholesterol in type I diabetic men. *Diabetes Care* 13:1039-1043, 1990
5. Mosher PE, Nash MS, Perry AC, LaPerriere AR, Goldberg RB: Aerobic circuit exercise training: effect on adolescents with well-controlled insulin-dependent diabetes mellitus. *Arch Phys Med Rehabil* 79:652-657, 1998
6. Bussau VA, Ferreira LD, Jones TW, Fournier PA: The 10-s maximal sprint: a novel approach to counter an exercise-mediated fall in glycemia in individuals with type 1 diabetes. *Diabetes Care* 29:601-606, 2006
7. Bussau VA, Ferreira LD, Jones TW, Fournier PA: A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes. *Diabetologia* 50:1815-1818, 2007
8. Guelfi KJ, Jones TW, Fournier PA: The decline in blood glucose levels is less with intermittent high-intensity compared with moderate exercise in individuals with type 1 diabetes. *Diabetes Care* 28:1289-1294, 2005
9. Guelfi KJ, Ratnam N, Smythe GA, Jones TW, Fournier PA: Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes. *Am J Physiol Endocrinol Metab* 292:E865-870, 2007
10. Iscoe KE, Campbell JE, Jamnik V, Perkins BA, Riddell MC: Efficacy of continuous real-time blood glucose monitoring during and after prolonged high-intensity cycling exercise: spinning with a continuous glucose monitoring system. *Diabetes Technol Ther* 8:627-635, 2006
11. Maran A, Pavan P, Bonsembiante B, Brugin E, Ermolao A, Avogaro A, Zaccaria M: Continuous Glucose Monitoring Reveals Delayed Nocturnal Hypoglycemia after Intermittent

High-Intensity Exercise in Nontrained Patients with Type 1 Diabetes. *Diabetes Technol Ther* 12:1-6, 2010
12. Jimenez C, Santiago M, Sitler M, Boden G, Homko C: Insulin-sensitivity response to a single bout of resistive exercise in type 1 diabetes mellitus. *J Sport Rehabil* 18:564-571, 2009
13. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care* 34:S11-S61, 2011
14. U.S. Department of Health and Human Services: 2008 Physical Activity Guidelines for Americans. 2008
15. Yardley J, Kenny G, Perkins B, Riddell M, Malcolm JS, RJ: Greater fluctuations in blood glucose seen both during and after aerobic exercise as compared to resistance exercise or no exercise in type 1 diabetes: A study using continuous glucose monitoring. *Appl Physiol Nutr Metab* 35 (Suppl):S112, 2010
16. Goto K, Ishii N, Sugihara S, Yoshioka T, Takamatsu K: Effects of resistance exercise on lipolysis during subsequent submaximal exercise. *Med Sci Sports Exerc* 39:308-315, 2007
17. Nishi Y: Measurement of thermal balance in man. In *Bioengineering, thermal physiology and comfort* Cena K, Clark J, Eds. New York, NY, Elsevier, 1981, p. 29-39
18. Purdon C, Brousson M, Nyveen SL, Miles PD, Halter JB, Vranic M, Marliss EB: The roles of insulin and catecholamines in the glucoregulatory response during intense exercise and early recovery in insulin-dependent diabetic and control subjects. *J Clin Endocrinol Metab* 76:566-573, 1993
19. Sigal RJ, Purdon C, Fisher SJ, Halter JB, Vranic M, Marliss EB: Hyperinsulinemia prevents prolonged hyperglycemia after intense exercise in insulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 79:1049-1057, 1994
20. Sigal RJ, Fisher SJ, Halter JB, Vranic M, Marliss EB: Glucoregulation during and after intense exercise: effects of beta-adrenergic blockade in subjects with type 1 diabetes mellitus. *J Clin Endocrinol Metab* 84:3961-3971, 1999
21. Petersen KF, Price TB, Bergeron R: Regulation of net hepatic glycogenolysis and gluconeogenesis during exercise: impact of type 1 diabetes. *J Clin Endocrinol Metab* 89:4656-4664, 2004
22. Pullinen T, Nicol C, MacDonald E, Komi PV: Plasma catecholamine responses to four resistance exercise tests in men and women. *Eur J Appl Physiol Occup Physiol* 80:125-131, 1999
23. Kraemer WJ, Ratamess NA: Hormonal responses and adaptations to resistance exercise and training. *Sports Med* 35:339-361, 2005
24. Goto K, Higashiyama M, Ishii N, Takamatsu K: Prior endurance exercise attenuates growth hormone response to subsequent resistance exercise. *Eur J Appl Physiol* 94:333-338, 2005
25. Moller N, Schmitz O, Porksen N, Moller J, Jorgensen JO: Dose-response studies on the metabolic effects of a growth hormone pulse in humans. *Metabolism* 41:172-175, 1992
26. Smilios I, Pilianidis T, Karamouzis M, Tokmakidis SP: Hormonal responses after various resistance exercise protocols. *Med Sci Sports Exerc* 35:644-654, 2003
27. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977-986, 1993
28. Sandoval DA, Guy DL, Richardson MA, Ertl AC, Davis SN: Effects of low and moderate antecedent exercise on counterregulatory responses to subsequent hypoglycemia in type 1 diabetes. *Diabetes* 53:1798-1806, 2004

29. Davis SN, Shavers C, Mosqueda-Garcia R, Costa F: Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. *Diabetes* 46:1328-1335, 1997
30. Kjaer M, Farrell PA, Christensen NJ, Galbo H: Increased epinephrine response and inaccurate glucoregulation in exercising athletes. *J Appl Physiol* 61:1693-1700, 1986

Table 1 – Participant characteristics. Data are presented as means ± SD.

N	12 (10 male, 2 female)
Age (yrs)	31.8 ± 15.3
Height (m)	1.77 ± 0.07
Weight (kg)	79.2 ± 10.4
BMI ($kg \cdot m^{-2}$)	25.3 ± 3.0
VO_{2peak} ($mLO_2 \cdot kg^{-1} \cdot min^{-1}$)	51.2 ± 10.8
Hemoglobin A_{1c} (%)	7.1 ± 1.1
Diabetes Duration (yrs)	12.5 ± 10.0
Insulin delivery	MDI = 5, CSII = 7

Table 2 – Summary of overnight (from midnight to 6 am) continuous glucose monitoring data for the night before and the night after exercise*

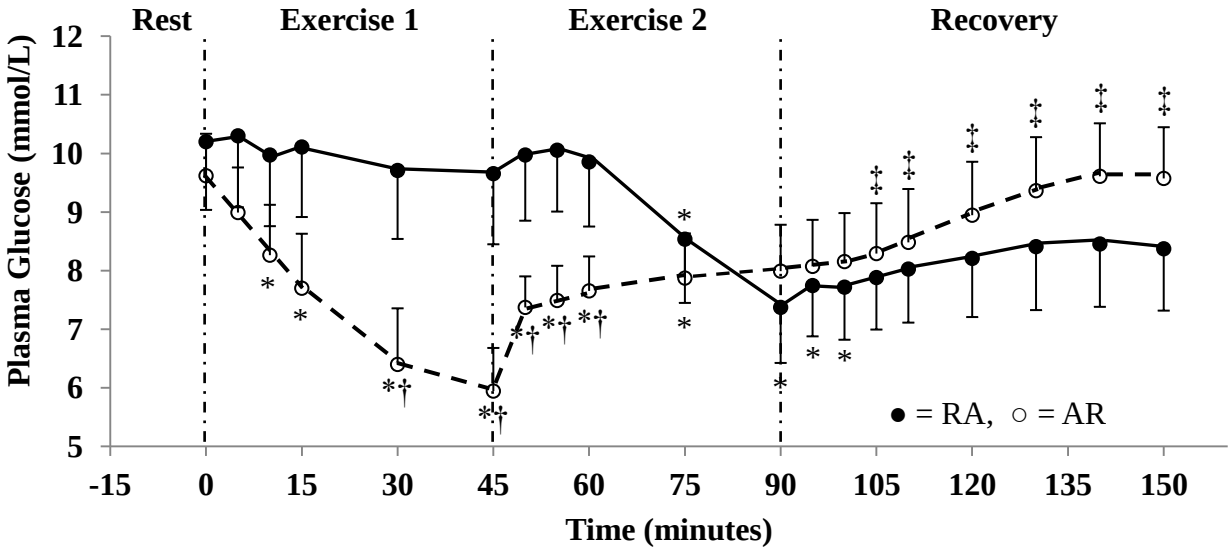
	Aerobic then Resistance	Resistance then Aerobic
Night before exercise session		
Number of participants experiencing nocturnal hypoglycemia (< 3.5 mmol/l)	4/12 (30%)	5/12 (42%)
Total number of hypoglycemic episodes	7	4
Mean duration of hypoglycemia per episode (minutes)	97.5 ± 84.9	47.1 ± 32.8
Mean area under the curve for hypoglycemia (glucose < 3.5 mmol/l) per episode (mmol·min)	112.3 ± 97.6	42.3 ± 41.9
Mean overnight glucose (mmol/l)	6.7 ± 3.2	6.9 ± 2.7
Night after exercise session		
Number of participants experiencing nocturnal hypoglycemia (< 3.5 mmol/l)	3/12 (25%)	4/12 (30%)
Total number of hypoglycemic episodes	5	6
Mean duration of hypoglycemia per episode (minutes)	105 ± 116	48 ± 68
Mean area under the curve for hypoglycemia (glucose < 3.5 mmol/l) per episode (mmol·min)	110 ± 146	59 ± 110
Mean overnight glucose (mmol/l)	6.3 ± 2.4	6.7 ± 3.1

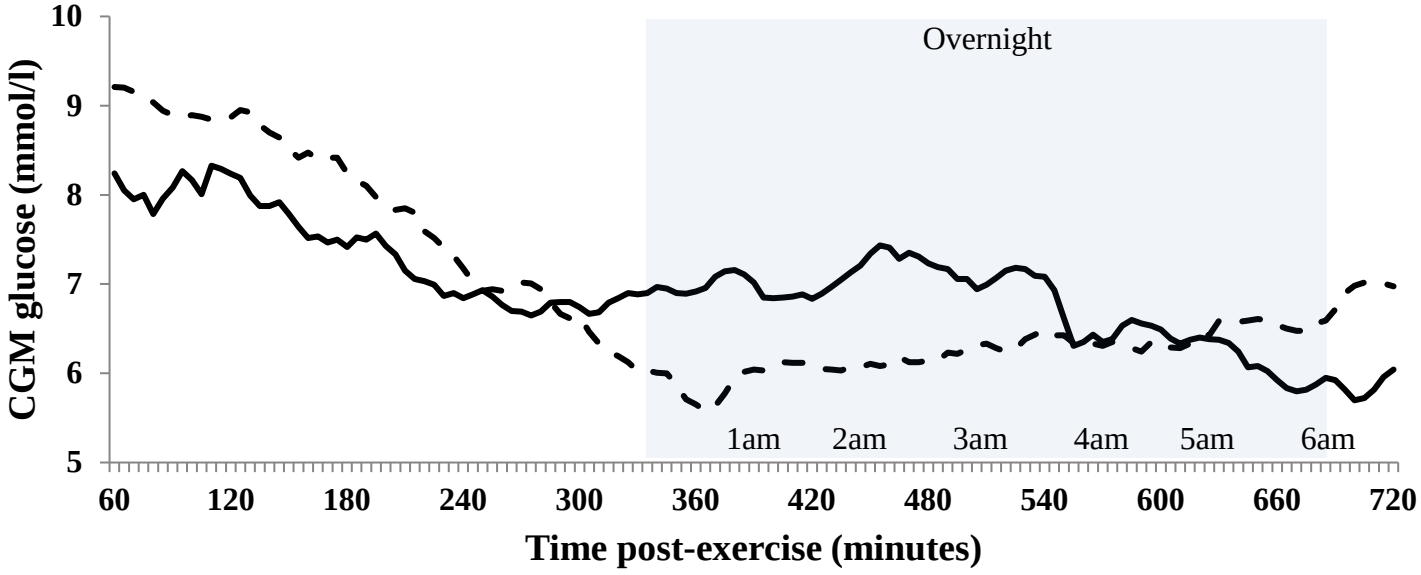
n=12. Data are presented as mean ± SD.
* no significant differences between pre and post, or between exercise conditions

FIGURE LEGENDS

Figure 1 – Mean (±SE) plasma glucose during exercise and recovery for aerobic exercise performed before resistance exercise (**AR** – dashed line with open symbols) and resistance exercise performed before aerobic exercise (**RA** – solid line with closed symbols) (n=11). * denotes difference from baseline during exercise where $P<0.05$. † denotes difference between conditions where $P<0.05$. ‡ denotes change throughout recovery from end-exercise level where $P<0.05$.

Figure 2 - Mean glucose (n=12) as measured by continuous glucose monitoring from 1 to 12 hours post-exercise following aerobic exercise performed before resistance exercise (solid line, **AR**) and resistance exercise performed before aerobic exercise (dashed line, **RA**).


Rest
Exercise 1
Exercise 2
Recovery
Plasma Glucose (mmol/L)
12
11
10
9
8
7
6
5
-15
0
15
30
45
60
75
90
105
120
135
150
Time (minutes)
● = RA, ○ = AR


Overnight
1am
2am
3am
4am
5am
6am
CGM glucose (mmol/l)
10
9
8
7
6
5
60
120
180
240
300
360
420
480
540
600
660
720
Time post-exercise (minutes)