Sex-Related Differences in Blood Glucose Responses to Resistance Exercise in Type 1 Diabetes:

A Secondary Data Analysis

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Key Messages

- In individuals without diabetes, sex-related differences in hormonal responses to exercise exist, which impact fuel selection during different types of activity
- Existing exercise studies in individuals with type 1 diabetes have involved either all male, or mostly male participants
- -Sex-related differences may alter blood glucose responses to exercise between the sexes in individuals with type 1 diabetes

Key words – weight lifting; continuous glucose monitoring; male; female;

ABSTRACT

OBJECTIVE: In adults with type 1 diabetes, resistance exercise (RE) is associated with more stable blood glucose (BG) levels than aerobic exercise, both during and after exercise. In nondiabetic individuals, growth hormone and epinephrine responses to RE differ between the sexes. These hormones are known to affect BG levels in individuals with type 1 diabetes. This study explored whether sex-related differences might exist in BG responses to RE in individuals with type 1 diabetes.

METHODS: A secondary data analysis was conducted on pooled data from two studies with identical RE protocols for individuals with type 1 diabetes [n=13 male (16-63 years), 10 female ages (19-45 years)]. The RE session consisted of seven resistance-based exercises performed at 5 pm. Plasma glucose samples were collected pre-, immediately post-, and one hour post-exercise. Interstitial glucose levels were recorded through blinded continuous glucose monitoring (CGM) 24 hours pre-, during and 24 hours post-exercise.

RESULTS: There was a significant sex by time interaction (P<0.001) in plasma glucose responses to RE. Plasma glucose decreased significantly in males from 8.6 ± 2.5 to 6.3 ± 2.1 mmol/L (P<0.001) during exercise, whereas females experienced no significant change (7.2±1.3 to 7.3±1.3 mmol/L, P= 0.999). In the 6 hours following RE, males developed significantly more hypoglycemia, as measured by CGM (P=0.048).

CONCLUSIONS: Males may have a greater risk of hypoglycemia with an acute bout of RE than females. Further research is needed to examine this phenomenon more closely, as sexspecific recommendations for preventing hypoglycemia around RE may be necessary in type 1 diabetes.

INTRODUCTION

Regular physical activity and structured exercise training have many benefits for individuals with type 1 diabetes, including improved cardiovascular health, insulin sensitivity and body composition (1). Activity comes in several forms each of which has unique cardiometabolic responses that can cause acute dysregulation of glycemia in people with type 1 diabetes (2). Acutely, compared to purely aerobic activities (walking, jogging, cycling), resistance exercise and/or weight training activities are associated with more stable blood glucose levels during the activity and in early recovery (3). Studies to date, however, have not accounted for physiological factors that could impact the effect of resistance exercise on blood glucose levels in individuals with type 1 diabetes, including age, fitness level, and sex.

In the past, studies of fuel selection and hormonal responses to exercise have excluded females due to the potential impact of fluctuating sex hormone levels resulting from the menstrual cycle (4, 5). Recently, a growing number of studies have included both males and females, and sex-related differences in metabolic and neuroendocrine response to exercise have been well-established in individuals without diabetes (6). Males and females differ in fuel selection during exercise, with males exhibiting more carbohydrate use and females more fat oxidation to produce energy for activity at the same relative exercise intensity (4, 5, 7-9). Furthermore, compared with females, males generally exhibit amplified counter-regulatory responses with elevated levels of catecholamines during resistance exercise (10), high-intensity (anaerobic) exercise (11) and endurance exercise (12) at the same relative intensity. This could potentially drive a higher glycemic response to resistance exercise in males with diabetes compared to females with diabetes. Other hormonal responses that differ between males and females include higher estrogen responses (13-15), lower testosterone increases (16, 17) and

higher peak growth hormone levels (18-20) in females compared to males during various types of exercise.

Little research has been conducted on sex-related differences in glycemic response to exercise in those with type 1 diabetes. A single study investigating sex-related differences in type 1 diabetes involved 90 minutes of submaximal aerobic exercise on a cycle ergometer at moderate intensity (50% of the participants' pre-determined maximal aerobic capacity (VO₂max)) (21). Similarly to people without diabetes, female participants in this study had significantly smaller increases in epinephrine and norepinephrine and higher levels of lipolysis compared to male participants in response to exercise. In spite of these differences, endogenous glucose production and exogenous glucose infusion rates during exercise (which was performed under a euglycemic clamp) were similar between the sexes.

To our knowledge, no study to date has examined the impact of sex on blood glucose changes during resistance exercise in individuals with type 1 diabetes. Therefore, the purpose of this study was to examine whether sex-related differences might exist in blood glucose responses to an acute bout of resistance exercise in habitually physically active adults with type 1 diabetes. We hypothesized that males would have smaller declines in blood glucose during exercise (due to a higher epinephrine response) but their higher reliance on muscle glycogen as a fuel source would increase their risk of post-exercise hypoglycemia when compared to females.

METHODS

We performed a secondary analysis of data from two separate studies, conducted in Ottawa, Canada (2012) and in Edmonton, Canada (2017) to compare changes in blood glucose concentration during exercise between the sexes. The Ottawa study (3) was approved by the research ethics boards (REB) of the University of Ottawa and the Ottawa Hospitals. The

Edmonton study (22) was approved by the University of Alberta's Human REB. Informed consent for secondary use of previously collected data was obtained from all participants. This secondary data analysis received ethics approval from the University of Alberta's REB2 for use of data collected from the two completed studies. Both initial studies contained identical protocols for their inclusion/exclusion criteria, baseline strength testing, and afternoon resistance exercise sessions.

Participants

Data were collected and analysed from 23 (13 male aged 16-63 years and 10 females aged 19-45 years) participants pooled from the Ottawa and Edmonton studies. Participants were recruited by word of mouth, social media and recruitment posters placed around university campuses, medical clinics and gyms. Participants were required to be non-obese, habitually active (perform both aerobic and resistance-type activities at least three times weekly for a minimum of six months), non-smoking adults with complication-free type 1 diabetes. Participants were excluded if they had $HbA_{1c} > 10\%$, were taking any medication (other than insulin) that would impact glucose metabolism, had frequent and/or severe hypoglycemia or hyperglycemia, or any condition that would contraindicate lifting weight. Participants used either continuous subcutaneous insulin infusion (CSII) with an insulin pump (n= 7 males, 7 females), or multiple daily injections (MDI) of insulin (n= 6 males, 3 females). Participants were asked to refrain from exercise for 24 h before sensor insertion (48 h before the experimental session). Table 1 lists participant characteristics. Females using oral contraceptives were tested during the active pill consumption phase and those not on birth control were tested in the early follicular phase of the menstrual cycle (self-reported menses). Menstrual cycle phase was unconfirmed for three female participants.

Baseline Session

Participants were informed of the purpose, protocol and possible risks of the study before providing written consent. Muscular strength was determined using an eight-repetition maximum (8-RM) strength test, which determines the maximum weight that can be lifted eight times while maintaining proper form. The outcome of the 8-RM tests was recorded for the following exercises: chest press (pectoralis major), shoulder press (deltoids), seated row (latissimus dorsi, rhomboids, trapezius), lat pulldown (latissimus dorsi), leg press (quadriceps, biceps femris, gluteus maximus) and leg curl (biceps femoris). Baseline sessions were performed at least 48 hours before testing sessions. Participants were instructed not to partake in any strenuous physical activity for 24 hours preceding testing sessions.

Experimental Sessions

Participants arrived at the laboratory at 4 pm for the pre-exercise preparations. Exercise began at 5 pm. The session consisted of performing 3 sets of 8 repetitions (8 RM) of seven difference exercises (bench press, leg press, shoulder press, leg curl, lat pull down, abdominal crunches, seated row). Participants were prompted to maintain consistent timing in the eccentric and concentric motions of the exercise with a two-second count in each direction. Sets were separated by a 90-second rest period.

Continuous Glucose Monitoring

Continuous glucose monitoring sensors (CGM) were inserted subcutaneously into the anterior abdominal or upper posterior area of the participants on the day before the first testing session. The Ottawa study (10 males, 2 females) used CGMS System Gold with SofSensors (Medtronic, Northridge, CA), while the Edmonton study (3 males, 8 females) used the iPro2 CGM with Enlite sensors (Medtronic, Northridge, CA). Participants were blind to the sensors readings with both of these systems. OneTouch UltraSmart handheld glucose meters (LifeScan; Johnson & Johnson, Milpitas, CA) and coded strips (same code throughout the study) were

provided during both studies for participants to test their capillary glucose four times daily for CGM calibration purposes. For each day of CGM use, participants kept log sheets of food and insulin intake, and avoided caffeine/alcohol consumption. Twenty-four hours after the participants' exercise session, CGM were removed and data were uploaded.

Insulin adjustments and glucose supplementation

Consistent with recent recommendations (2, 23), and similar to previous studies (24), participants reduced their insulin dose on exercise days by either making a 10% reduction in intermediate or long-acting insulin (MDI) the night before/morning of exercise or a 50% reduction in basal rate (CSII participants) beginning one hour before exercise and maintained until the end of exercise. Our pre-exercise recommendations involved a further 25% reduction in basal rate for those using CSII if the participant's blood glucose was <5mmol/L upon arrival to the lab. All participants consumed a Glucerna Chocolate Graham Snack Bar (150 calories, 25 g carbohydrate; Abbott Laboratories, Abbott Park, IL) without bolus insulin upon arrival at the lab (4 pm).

Capillary glucose was checked 30 minutes and immediately before exercise to ensure glucose levels were between 5.5 and 13.9 mmol/L. If glucose levels immediately before exercise were below 4.5 mmol/L, participants were provided with glucose tablets containing 32 g of glucose (Dex4, AMG Medical, Montreal, QC). If readings were between 4.5 and 5.4 mmol/L, it was recommended that participants take 16 g of glucose. Levels were checked again 15 min later, and if readings were still between 4.5 and 5.4, a further 16 g of glucose was recommended for participants. These steps were repeated until blood glucose levels reached a value \geq 5.5 mmol/L before exercise start time. This protocol was only required for one (male) participant, who required 32 grams of carbohydrate prior to exercise.

During exercise, glucose concentrations were monitored by applying a drop of venous blood to a glucose meter when venous blood samples were collected. If levels were below 4.5 mmol/L, it was recommended that participants take 16 g of glucose. Capillary glucose tests were performed every 10 min, and glucose was provided when necessary until participants reached \geq 5.5 mmol/L. This protocol was only required for one female participant (16 g), and one male participants (8 g) who chose not to comply with the suggested 16 g carbohydrate supplement.

Blood sampling and analysis

For both studies, blood samples were drawn by IV catheter at baseline, the end of exercise, and one hour post-exercise. Samples were mixed by inversion, separated by centrifuge immediately, and transferred to snap top microtubes for storage in a -80°C freezer. Batch analysis was performed using the hexokinase timed end point method in a commercial laboratory to determine plasma glucose levels. The analyses for the original studies were performed in separate laboratories, but used the same methods.

Statistical Methods

Analyses were performed using SPSS 25.0 software (SPSS Inc., Chicago, IL).

Descriptive statistics, including mean and standard deviation, were calculated to describe participant characteristics. Independent *t* tests were used to determine if characteristics were significantly different. The level of significance was set at 0.05.

Plasma glucose concentration was compared between sexes using two-way repeated-measures ANOVA with the factors of time (0, 45, and 105 min) and sex. Paired sample *t* tests were used to perform pair-wise post hoc comparisons between sexes for each time point to examine within-sex changes from baseline to immediately post and 1 hour post-exercise. The level of significance was set at 0.05. Differences were only considered statistically significant after Tukey-Kramer corrections were made for multiple comparisons. Based on the current

sample size and an estimated standard deviation of 1.0 mmol/L for both groups, these analysis would be powered to detect a difference of means of 1.245 mmol/L in the primary outcome (the change in plasma glucose concentration).

CGM data were grouped and summarized as follows using EasyGV (Nathan R. Hill, University of Oxford, UK): 24 h pre-exercise, as well as 6 h and 12 h post-exercise. Hypoglycemia was defined as any value detected by CGM \leq 3.9 mmol/L, and severe hypoglycemia was any value detected by CGM \leq 2.9 mmol/L. Mild hyperglycemia was defined as values >7.8 and <10.9 mmol/L, and severe hyperglycemia was defined as values \geq 10.9 mmol/L. Number of episodes, total time and percentage of time spent in hypoglycemia, euglycemia and hyperglycemia for the predetermined periods and the area under the curve (AUC, defined as the absolute distance from the described limits, multiplied by the time spent outside these limits) for time spent in hypo- and hyperglycemia was determined for each time period. Hypo- or hyperglycemic episodes were defined as events lasting at least 15 minutes and separated by at least 30 minutes as recommended by Schnell et al. (25). Independent t tests were used to compare between the sexes during each time frame. Significance was set at 0.05.

RESULTS

Work load

Males lifted 40% more weight for upper body (P=0.000) and 64% more weight for lower body (P=0.001) resistance exercises than females. However, it should also be acknowledged that the relative resistance exercise workload was identical between females and males since both groups were lifting weight equivalent to their own personal eight-repetition maximum (8RM).

Plasma glucose

Plasma glucose data are expressed as mean \pm SD. Due to the inability to successfully insert an IV catheter in one female participant, plasma glucose levels were collected for 22 of the 23 participants (13 males, 9 females). There was a significant sex by time interaction (P<0.001) for mean exercise plasma glucose levels, indicating a difference between the sexes for the total changes and rates of changes in plasma glucose levels (Figure 1). During exercise, plasma glucose levels decreased significantly for males (p < 0.001) from 8.6 ± 2.5 to 6.3 ± 2.1 mmol/L, but not for females (7.2 ± 1.3 to 7.3 ± 1.3 mmol/L, P= 0.999). One hour post-exercise, plasma glucose values in males remained significantly lower than pre-exercise values (P < 0.001). Plasma glucose levels one hour post-exercise were similar to pre-exercise (P=0.66) or immediately post-exercise (0.862) values in females. There was no significant difference in plasma glucose levels between the sexes before (p=0.753), immediately after (P=0.708), or one hour post-exercise (P=0.178).

Dietary intake and insulin dosage

Total daily carbohydrate intake and insulin dosage (Appendix Table A.1) was calculated from participant food diaries for the day prior, day of, and day after the exercise session. During the day of the exercise session, males consumed significantly more carbohydrates than females (p=0.014). Daily insulin was also higher in males compared to females during the days of sensor wear (P=0.019). However, per kg of body mass, insulin intake was not significantly different between groups. In addition, the ratio between grams of carbohydrates to insulin units did not differ between the sexes on the day before, day of, or day after resistance exercise (P=0.97). One male (8g) and one female (32 g) participant required carbohydrate supplements during exercise. Neither the absolute protein intake, nor the grams of protein intake per kilogram of body mass were significantly different between males and females in the 12 hours preceding or 12 hours following exercise.

CGM data

CGM data are expressed as mean \pm SD. Due to sensor failure in one male and one female participant, data were collected from 21 of the 23 participants (9 females, 12 males). In the 24 hours preceding exercise, there was no significant difference between the sexes in the total time spent in hypo- or hyperglycemia, area under the curve (AUC) for hypo- or hyperglycemia, or number of hypo- or hyperglycemic events. During this time, 4 females and 8 males experienced antecedent hypoglycemia (defined as blood glucose levels <3.9 mmol/L for >2 hours in the 24-hour pre-exercise).

In the 6 hours following exercise, males experienced significantly more hypoglycemia (AUC, P< 0.05) than females (Table 2). Males also experienced a significantly greater AUC per hypoglycemic episode (P=0.008) compared to females. In addition, males tended to have a lower mean glucose level in recovery compared to females $[6.4 \pm 1.3 \text{ mmol/L vs. } 8.0 \pm 2.1 \text{ for females}]$ (P=0.06), respectively] during this time (Figure 2). This time frame was chosen because it is when the impact of exercise is most apparent on blood glucose levels (3, 26). There were no differences between the sexes overnight (6-12 hours post-exercise), or in the 12 hours post-exercise with respect to time spent in hypo or hyperglycemia (duration and AUC), or number of hypo or hyperglycemic events.

DISCUSSION

This study suggests that sex-related differences may exist in habitually active individuals with type 1 diabetes in response to an acute bout of afternoon resistance exercise. Specifically, we found that compared to males, females with type 1 diabetes have a lower blood glucose response to a ~42 minutes bout of resistance exercise. Moreover, in the six hours following exercise, males experienced more hypoglycemia than females with respect to area under the

curve as measured by CGM. Thus, females with type 1 diabetes appeared to display better glycemic control than males following an acute bout of resistance exercise. These differences were observed in spite of no significant differences in the ratio of insulin dosage to carbohydrate intake or carbohydrate intake and insulin dosage per kilogram of body mass between the sexes.

The mechanisms behind these apparent sex-related differences are unclear. On the one hand, females generally have a lower adrenergic response to resistance exercise than males, at least in those without diabetes (10), which should result in greater blood glucose declines during resistance exercise in females living with type 1 diabetes. Conversely, compared to males, females tend to rely more on lipid oxidation during both aerobic (4, 5, 7, 12) and resistance (8) exercise. This may be partly due to higher estrogen, specifically 17B-estradiol, levels which are known to decrease carbohydrate oxidation and promote lipid oxidation during exercise (5, 12, 15, 27). During the follicular phase of the menstrual cycle, during which most of the female type 1 diabetes participants were tested, estrogen concentrations do not differ markedly between males and females (17). Females do, however, experience an increase in circulating estrogen levels after an acute resistance exercise bout, whereas males do not (17, 28). If this were the case in the type 1 diabetes participants in this analysis, the elevated estradiol could result in a greater contribution of fat oxidation in females, thereby sparing blood glucose and consequently glycogen stores. Additionally, it has been reported that females maintain higher levels of estrogen receptor mRNA content and percent estrogen-positive nuclei compared to males (29). Thus, while estrogen levels do not differ markedly between males and females in the follicular phase, it has been suggested that estrogen may exert its metabolic effects more readily in females, thus promoting higher levels of fat oxidation in females than in males (27).

The greater reliance on glycogen during exercise may increase post-exercise hypoglycemia risk in males with type 1 diabetes as a greater need for glucose uptake into the

liver and muscle will occur during recovery to replenish lost stores (27, 30). While one study found greater post-exercise glucose uptake in females compared to males (31), other studies found that females without diabetes defend blood glucose homeostasis better post-exercise than males (32, 33) due to their greater capacity for lipid oxidation during exercise, and overall conservation of glycogen stores. This is consistent with our observations in the present study where blood glucose levels remained more stable in the females during and after exercise. This phenomenon may have also contributed to the relatively greater amount of hypoglycemia experienced by the males (AUC) compared to the females in the six hours post-exercise. It is also important to note that antecedent hypoglycemia may have played a role: males in this analysis experienced more hypoglycemia in the 24 hours before exercise compared to females. Antecedent hypoglycemia is associated with a greater blunting of counter-regulatory responses and increased suppression of endogenous glucose production, increasing the risk of hypoglycemia during subsequent exercise (34).

Growth hormone is known to stimulate lipolysis and lipid oxidation, and thus a higher growth hormone concentration could decrease reliance on glucose oxidation, subsequently sparing plasma glucose (35). Indeed, our research team has previously linked the glucose stabilizing effect of resistance exercise in type 1 diabetes to a rise in growth hormone levels that was sustained in early recovery (36). Females have higher resting growth hormone levels than males (37, 38), particularly in the follicular phase of the menstrual cycle (35), and monophasic oral contraceptive use by females is also associated with higher levels of growth hormone (39). Furthermore, estrogen may be a factor in elevated growth hormone levels, as estrogen is known to release a growth hormone stimulating factor (37). However, studies investigating growth hormone responses to resistance exercise have conflicting results. A study by Luk et al. (20) observed significantly greater growth hormone levels in females both at rest and during

resistance exercise. Their growth hormone profile also showed a faster, higher peak and quicker return to baseline compared to males, who produced a more sustained response (20). However, other studies have shown a similar response in growth hormone levels to resistance exercise between males and females (16, 38), or even greater responses in males (40). Regardless of growth hormone changes in response to exercise, it has been suggested that females have greater tissue sensitivity to growth hormone than males, which may also preserve glucose levels (6, 21).

While novel, this is an observational study with several limitations. In addition to a lack of clear mechanisms for the differences in the glycemic response to resistance exercise, this study contains many uncontrolled variables that could have influenced the results. Because this was a secondary data analysis, we were unable to match males and females for physical characteristics that could impact the glycemic responses to exercise. For example, males in the present study had significantly higher mean height and weight, and relative fitness as measured by VO_{2max}. Furthermore, while we did not measure body composition. Males generally have more muscle mass and lower fat mass, and thus higher relative strength compared to females. The male participants in our analysis lifted significantly more weight than the females, and therefore the greater depletion of blood glucose levels could have been due to the higher workload of males. Indeed, a recent study of prolonged aerobic exercise suggests that a higher amount of working muscle mass and greater aerobic fitness is associated with a lower glucose nadir during exercise in individuals with type 1 diabetes (41). In line with our observations and with those of Khalifah et al.(41), higher physical fitness (as demonstrated by a higher VO_{2max}), is associated with a greater reliance on carbohydrate oxidation during high intensity exercise (7, 10). Consequently, body composition, fitness levels and work load may have contributed to the observed lower blood glucose values in males, rather than solely sex-related differences. Future studies should match male and female participants for aerobic capacity relative to fat free mass,

as this may be the most appropriate way to normalize aerobic fitness among participants of different body shapes (42).

Another potential limitation of this analysis includes a lack of statistical power to detect differences in the study's secondary outcomes (hypoglycemia/hyperglycemia duration, AUC and percentage of time spent in hypo/hyperglycemia determined by CGM). The data presented in this analysis may still have clinical significance and could have important implications for individuals with type 1 diabetes. Future studies with large sample sizes powered for these analyses are warranted.

CONCLUSION

Overall, these data suggest that sex-related differences may exist in blood glucose responses to resistance exercise in habitually active individuals with type 1 diabetes. As such, males may have a greater risk of hypoglycemia during and following resistance exercise than females. These findings highlight the need for future studies examining sex-related differences in responses to exercise in type 1 diabetes, as sex-specific recommendations for insulin dosage adjustments and carbohydrate intake may be warranted.

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Author Contributions

NKB analyzed data and wrote the manuscript. JEY designed the study, collected the data, and reviewed/edited the manuscript. RJS, GPK, MCR and BAP assisted in the design of the study, advised on data collection and analysis, and reviewed/edited the manuscript.

REFERENCES

- 1. Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. Diabetologia. 2012;55:542-51.
- 2. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017;5:377-90.
- 3. Yardley JE, Kenny GP, Perkins BA, Riddell MC, Balaa N, Malcolm J, et al. Resistance versus aerobic exercise: acute effects on glycemia in type 1 diabetes. Diabetes Care. 2013;36:537-42.
- 4. Devries MC. Sex-based differences in endurance exercise muscle metabolism: impact on exercise and nutritional strategies to optimize health and performance in women. Exp Physiol. 2016;101:243-9.
- 5. Isacco L, Duche P, Boisseau N. Influence of hormonal status on substrate utilization at rest and during exercise in the female population. Sports Med. 2012;42:327-42.
- 6. Brockman NK, Yardley JE. Sex-related differences in fuel utilization and hormonal response to exercise: implications for individuals with type 1 diabetes. Appl Physiol Nutr Metab. 2018;43:541-52.
- 7. Hedrington MS, Davis SN. Sexual dimorphism in glucose and lipid metabolism during fasting, hypoglycemia, and exercise. Front Endocrinol. 2015;6:61.
- 8. Sarafian D, Schutz Y, Montani JP, Dulloo AG, Miles-Chan JL. Sex difference in substrate oxidation during low-intensity isometric exercise in young adults. Appl Physiol Nutr Metab. 2016;41:977-84.
- 9. Riddell MC, Partington SL, Stupka N, Armstrong D, Rennie C, Tarnopolsky MA. Substrate utilization during exercise performed with and without glucose ingestion in female and male endurance trained athletes. Int J Sport Nutr Exerc Metab. 2003;13:407-21.
- 10. Pullinen T, Mero A, Huttunen P, Pakarinen A, Komi PV. Resistance exercise-induced hormonal responses in men, women, and pubescent boys. Med Sci Sports Exerc. 2002;34:806-13.
- 11. Gratas-Delamarche A, Le Cam R, Delamarche P, Monnier M, Koubi H. Lactate and catecholamine responses in male and female sprinters during a Wingate test. Eur J Appl Physiol Occup Physiol. 1994;68:362-6.
- 12. Horton TJ, Pagliassotti MJ, Hobbs K, Hill JO. Fuel metabolism in men and women during and after long-duration exercise. J Appl Physiol. 1998;85:1823-32.
- 13. Horton TJ, Miller EK, Bourret K. No effect of menstrual cycle phase on glycerol or palmitate kinetics during 90 min of moderate exercise. J Appl Physiol. 2006;100:917-25.
- 14. Devries MC, Hamadeh MJ, Graham TE, Tarnopolsky MA. 17beta-estradiol supplementation decreases glucose rate of appearance and disappearance with no effect on glycogen utilization during moderate intensity exercise in men. J Clin Endocrinol Metab. 2005;90:6218-25.
- 15. Hamadeh MJ, Devries MC, Tarnopolsky MA. Estrogen supplementation reduces whole body leucine and carbohydrate oxidation and increases lipid oxidation in men during endurance exercise. J Clin Endocrinol Metab. 2005;90:3592-9.
- 16. Benini R, Prado Nunes PR, Orsatti CL, Barcelos LC, Orsatti FL. Effects of acute total body resistance exercise on hormonal and cytokines changes in men and women. J Sports Med Phys Fit. 2015;55:337-44.

- 17. Fragala MS, Kraemer WJ, Denegar CR, Maresh CM, Mastro AM, Volek JS. Neuroendocrine-immune interactions and responses to exercise. Sports Med. 2011;41:621-39.
- 18. Esbjornsson M, Norman B, Suchdev S, Viru M, Lindhgren A, Jansson E. Greater growth hormone and insulin response in women than in men during repeated bouts of sprint exercise. Acta Physiol. 2009;197:107-15.
- 19. Eliakim A, Nemet D, Most G, Rakover N, Pantanowitz M, Meckel Y. Effect of gender on the GH-IGF-I response to anaerobic exercise in young adults. J Strength Cond Res. 2014;28:3411-5.
- 20. Luk HY, Kraemer WJ, Szivak TK, Flanagan SD, Hooper DR, Kupchak BR, et al. Acute resistance exercise stimulates sex-specific dimeric immunoreactive growth hormone responses. Growth Horm IGF Res. 2015;25:136-40.
- 21. Galassetti P, Tate D, Neill RA, Morrey S, Davis SN. Effect of gender on counterregulatory responses to euglycemic exercise in type 1 diabetes. J Clin Endocrinol Metab. 2002;87:5144-50.
- 22. Eshghi SRT, Yardley JE. Morning (fasting) versus afternoon resistance exercise in individuals with type 1 diabetes: A randomized cross-over study. J Clin Endocrinol Metab. 2019. [Epub ahead of print].
- 23. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care. 2016;39:2065-79.
- 24. Yardley JE, Kenny GP, Perkins BA, Riddell MC, Malcolm J, Boulay P, et al. Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes. Diabetes Care. 2012;35:669-75.
- 25. Schnell O, Barnard K, Bergenstal R, Bosi E, Garg S, Guerci B, et al. Role of Continuous Glucose Monitoring in Clinical Trials: Recommendations on Reporting. Diabetes Technol Ther. 2017;19:391-9.
- 26. Yardley JE, Iscoe KE, Sigal RJ, Kenny GP, Perkins BA, Riddell MC. Insulin pump therapy is associated with less post-exercise hyperglycemia than multiple daily injections: an observational study of physically active type 1 diabetes patients. Diabetes Technol Ther. 2013;15:84-8.
- 27. Devries MC, Hamadeh MJ, Phillips SM, Tarnopolsky MA. Menstrual cycle phase and sex influence muscle glycogen utilization and glucose turnover during moderate-intensity endurance exercise. Am J Physiol Reg Integ Comp Physiol. 2006;291:R1120-8.
- 28. Kraemer RR, Heleniak RJ, Tryniecki JL, Kraemer GR, Okazaki NJ, Castracane VD. Follicular and luteal phase hormonal responses to low-volume resistive exercise. Med Sci Sports Exerc. 1995;27:809-17.
- 29. Wiik A, Glenmark B, Ekman M, Esbjornsson-Liljedahl M, Johansson O, Bodin K, et al. Oestrogen receptor beta is expressed in adult human skeletal muscle both at the mRNA and protein level. Acta Physiol Scand. 2003;179:381-7.
- 30. Zachwieja JJ, Costill DL, Pascoe DD, Robergs RA, Fink WJ. Influence of muscle glycogen depletion on the rate of resynthesis. Med Sci Sports Exerc. 1991;23:44-8.
- 31. Marliss EB, Kreisman SH, Manzon A, Halter JB, Vranic M, Nessim SJ. Gender differences in glucoregulatory responses to intense exercise. J Appl Physiol. 2000;88:457-66.
- 32. Henderson GC. Sexual dimorphism in the effects of exercise on metabolism of lipids to support resting metabolism. Front Endocrinol. 2014;5:162.

- 33. Henderson GC, Fattor JA, Horning MA, Faghihnia N, Johnson ML, Luke-Zeitoun M, et al. Glucoregulation is more precise in women than in men during postexercise recovery. Am J Clin Nutr. 2008;87:1686-94.
- 34. Galassetti P, Tate D, Neill RA, Morrey S, Wasserman DH, Davis SN. Effect of sex on counterregulatory responses to exercise after antecedent hypoglycemia in type 1 diabetes. Am J Physiol Endocrinol Metab. 2004;287:E16-24.
- 35. Kraemer WJ, Gordon SE, Fleck SJ, Marchitelli LJ, Mello R, Dziados JE, et al. Endogenous anabolic hormonal and growth factor responses to heavy resistance exercise in males and females. Int J Sports Med. 1991;12:228-35.
- 36. Yardley JE, Sigal RJ, Riddell MC, Perkins BA, Kenny GP. Performing resistance exercise before versus after aerobic exercise influences growth hormone secretion in type 1 diabetes. Appl Physiol Nutr Metab. 2014;39:262-5.
- 37. Consitt LA, Copeland JL, Tremblay MS. Endogenous anabolic hormone responses to endurance versus resistance exercise and training in women. Sports Med. 2002;32:1-22.
- 38. Kraemer WJ, Staron RS, Hagerman FC, Hikida RS, Fry AC, Gordon SE, et al. The effects of short-term resistance training on endocrine function in men and women. Eur J Physiol Appl Physiol Occup Physiol. 1998;78:69-76.
- 39. Bonen A, Haynes FW, Graham TE. Substrate and hormonal responses to exercise in women using oral contraceptives. J Appl Physiol (1985). 1991;70:1917-27.
- 40. Linnamo V, Pakarinen A, Komi PV, Kraemer WJ, Hakkinen K. Acute hormonal responses to submaximal and maximal heavy resistance and explosive exercises in men and women. J Strength Condition Res. 2005;19:566-71.
- 41. Al Khalifah RA, Suppere C, Haidar A, Rabasa-Lhoret R, Ladouceur M, Legault L. Association of aerobic fitness level with exercise-induced hypoglycaemia in type 1 diabetes. Diabet Med. 2016;33:1686-90.
- 42. Kohler A, King R, Bahls M, Gross S, Steveling A, Gartner S, et al. Cardiopulmonary fitness is strongly associated with body cell mass and fat-free mass: The Study of Health in Pomerania (SHIP). Scand J Med Sci Sports. 2018;28:1628-35.

TABLES

Table 1. Participant characteristics

	Males (n=13)	Females (n=10)
Age (yr)	34 ± 15	29 ± 8
Height (m)	1.79 ± 0.05	1.68 ± 0.05 *
Weight (kg)	84 ± 11	$71 \pm 12*$
BMI	26 ± 3	25 ± 4
VO ₂ max (ml/kg·min)	51 ± 10	$40 \pm 8*$
HbA _{1C} (%)	7.1 ± 1.0	7.3 ± 0.7
Diabetes duration (yr)	15 ± 12	16 ± 7

Data are group means \pm SD, *P<0.05 vs. males, as determined by independent t-tests.

Table 2. Summary of CGM data for 6 hours post resistance exercise for males and females.

•	Males	Females	P
	(n=12)	(n=9)	
Participants experiencing hypoglycemia (2.9 - 3.9 mmol/L)	6/12 (50%)	3/9 (33%)	N/A
Duration of hypoglycemia (min)	48.3 ± 52.8	12.8 ± 21.1	0.051
AUC for hypoglycemia	21.6 ± 26.0	3.78 ± 8.03	0.042*
Participants experiencing severe hypoglycemia (<2.9 mmol/L)	0/12 (0%)	1/9 (11%)	N/A
Duration of severe hypoglycemia (min)	0	1.67 ± 5.00	0.347
AUC for severe hypoglycemia	0	0.22 ± 0.67	0.277
Participants experiencing hyperglycemia (7.8 – 10.9 mmol/L)	8/12 (67%)	8/9 (89%)	N/A
Duration of hyperglycemia (min)	77.5 ± 75.8	105 ± 89.5	0.469
AUC for hyperglycemia	93.5 ± 86.5	1501 ± 118	0.241
Participants experiencing severe hyperglycemia (>10.9 mmol/L)	2/12 (17%)	4/9 (44%)	N/A
Duration of severe hyperglycemia (min)	12.1 ± 29.1	61.7 ± 99.4	0.181
AUC for severe hyperglycemia	9.79 ± 22.7	107 ± 201	0.187
Percent of time spent in hypoglycemia (<3.9 mmol/L)	13.6 ± 15.2	3.96 ± 6.86	0.068
Percent of time spent in hyperglycemia (>7.8 mmol/L)	24.5 ± 21.3	45.7 ± 31.3	0.104
Percent of time spent in euglycemia (3.9-7.8 mmol/L)	61.8 ± 18.1	50.4 ± 28.8	0.314

Data are group means \pm SD, *P<0.05, as determined by independent t tests.

FIGURE LEGENDS

Figure 1 - Changes in mean (\pm SEM) blood glucose during 45 minutes of exercise, and 60 minutes of recovery between males (open circles) and females (closed circles) with type 1 diabetes. * indicates difference (p<0.05) from pre-exercise blood glucose values.

Figure 2 - Mean (±SEM) interstitial glucose (measured by continuous glucose monitoring) for 12 hours post-exercise in males (open circles) and females (closed circles) with type 1 diabetes.

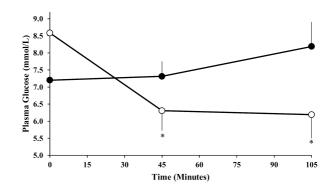


Figure 1. Mean ± SE plasma glucose during the resistance exercise session and 1 hour of recovery (n= 9 females and 13 males). White circle = males; black circle= females. *Statistically significant change from baseline in males. Differences were only considered statistically significant if still significant after Tukey-Kramer corrections for multiple comparisons.

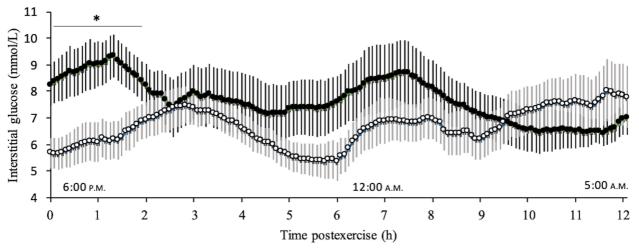


Figure 2. Mean \pm SE interstitial glucose as measured by CGM from 0 to 12 h post-exercise (n= 9 females and 10 males). Black circles = females; white circles = males. *Represents the period of time where mean interstitial glucose was significantly higher in females than males (P<0.05).