Evaluating the Effect of a Ten-Minute Aerobic Cooldown on the Blood Glucose Response of Adults with Type 1 Diabetes Following Fasted Resistance Exercise

by

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Abstract

Introduction: Despite the health promoting effects of physical activity and exercise, people with type 1 diabetes (T1D) are less active than people without diabetes. This disparity is partly due to the risk of hypoglycemia and the tedious steps required to prevent or treat hyperglycemia during activity, as well as a corresponding fear of hypoglycemia and potentially severe adverse outcomes. One strategy to prevent hypoglycemia from activity is to perform moderate to high intensity resistance exercise, while fasted in the morning, as it is associated with blood glucose concentration increases. However, increasing blood glucose concentration can lead to hyperglycemia, which could increase the risk of developing diabetes-related complications and typically requires food intake to be delayed until glucose concentration has returned to target range. One potential strategy to treat exercise-induced hyperglycemia, which is currently recommended in international guidelines, is to perform a brief aerobic cooldown, but has never been empirically tested. Our objective was to investigate the effect on blood glucose concentration from performing a cooldown after fasted resistance exercise by comparing the change in capillary glucose that occurs when a 10-minute aerobic cooldown is performed immediately after fasted resistance exercise compared to no cooldown.

Methods: Sixteen participants with T1D completed two 45-minute fasted resistance exercise sessions consisting of 7 exercises performed for 3 sets of 8 repetitions at 8 repetition maximum. One session was followed immediately by a 10-minute cycle ergometer cooldown at 30% of $VO2_{peak}$ before 20 minutes of seated recovery, and the other was followed by 30 minutes of seated recovery. We measured capillary glucose before, during, and after exercise, and used 2x3 repeated measures ANOVA to determine the effect of the cooldown during the 30-minute recovery period. We investigated post-exercise glucose trends using continuous glucose monitoring (CGM) data from the 6- and 24-hour post-exercise as well as overnight period. We compared CGM data by Wilcoxon signed rank test.

Results: ANOVA analysis detected a significant interaction of time and treatment during the 30 minute recovery period due to a brief decline in capillary glucose of -0.6 ± 1.0 mmol/l during the 10-minute cooldown, but an increase of 0.7 ± 1.3mmol/l during the same period when no cooldown was completed. However, the decrease from the cooldown was not sufficient or long-lasting

enough to prevent glucose concentration from increasing, as during the last 20 minutes of the 30-minute recovery period, capillary glucose increased in both conditions. CGM data showed no significant differences when comparing conditions with 24-hour mean glucose of 8.7 mmol/l (7.46, 9.36) and 9.2 mmol/l (8.21, 10.68) during cooldown and no cooldown conditions, respectively. The time in hyperglycemic range was high for 6 hours after both conditions when compared to the guideline recommended targets of 25%, with 35% (10, 60) and 36% (10, 61) for cooldown and no cooldown respectively.

Conclusion: Performing a cooldown decreases post-exercise glucose concentration, but alone does not effectively treat or prevent hyperglycemia in the post-exercise period. Future studies should investigate the use of a cooldown as an adjunct to insulin correction to treat hyperglycemia following fasted exercise.

Preface

This thesis is an original work by Reid Desmond McClure. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Effectiveness of Aerobic Exercise to Mitigate Hyperglycemia after Fasted Resistance Exercise”, No. 00115197, 18/12/2021.

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Chapter 1 - Introduction:

Background

Type 1 diabetes (T1D) is an autoimmune condition characterized by an inability to produce insulin. If left untreated, those with T1D will experience elevated blood glucose concentration due to inadequate amounts of insulin (1). There is currently no cure for T1D, but it can be treated with exogenous insulin delivery. Management of T1D involves regular monitoring of blood glucose concentration and appropriate insulin dosing in order to maintain blood glucose as near to normal physiological values as possible via the administration of exogenous insulin. When blood glucose falls below target to hypoglycemia, or rises above target range to hyperglycemia patients experience negative symptoms in addition to increasing the likelihood of developing long-term, diabetes-related complications (1). Diabetes is difficult to manage and many challenges exist when trying to manage blood glucose values while simultaneously responding to the demands of life. With limited treatment options, those with T1D must constantly manage their blood glucose concentration, and as a result, experience psychosocial (2) and physiological barriers to participation in health promoting activities (3, 4, 5). One specific area where those with T1D continue to experience significant barriers to participation is physical activity.

Physical activity provides numerous benefits for a variety of measures of health, and these benefits extend to those living with T1D. A recent study found that individuals living with T1D for longer than 50 years who meet or exceed weekly exercise recommendations have lower rates of neuropathy and better nerve function than those who do not meet the recommendations (6). Additionally, a seven-year observational study found that males with T1D who exercised three or fewer hours per week had three times the all-cause mortality than those who exercised six or more hours per week (7). Physical activity during leisure time, particularly when performed regularly at

high intensity, has been proven to lower the risk of cardiovascular disease for those with T1D (8). Aerobic and anerobic training improves cardiorespiratory fitness, lipid levels, and endothelial function, while decreasing insulin resistance in individuals with T1D (9).

Resistance exercise improves muscle mass, body composition, strength, physical function, mental health, bone mineral density, insulin sensitivity, blood pressure, lipid profiles, and cardiovascular health for all adults (10). Regular resistance training improves strength, and reduces abdominal fat stores with no increase in hypoglycemia frequency for already active adults with T1D, with optimized glycemic management (11). Improvements in muscle mass and strength may be particularly relevant as T1D is associated with early onset of deterioration in muscle morphology, function and strength (12, 13). Furthermore, exercise improves well-being and decreases levels of anxiety and depression in individuals with type 1 diabetes (14, 15). The extent of these benefits, combined with the low rates of adherence to physical activity recommendations previously described, further support the need to identify exercise strategies that minimize physiological barriers to physical activity.

During physical activity of all modalities, the energy demands of the body increase to fuel movement. To meet this demand, mechanisms that facilitate the uptake of glucose by exercising muscle are activated. This increase in glucose uptake can cause blood glucose to decline, which, for individuals without diabetes, causes a decrease in insulin secretion to maintain blood glucose concentrations. Individuals with T1D do not experience an automatic decline in insulin release because their insulin delivery is externally managed, and as a result, are more likely to experience hypoglycemia due to hyperinsulinemia during exercise. The need for subcutaneous delivery of synthetic insulin in T1D further complicates pre-exercise preparation, as the glucose lowering

effects may persist for several hours, as opposed to several minutes for natural insulin secreted directly from the pancreas into circulation for those without T1D (16).

Self-managed, exogenous insulin delivery necessitates a preplanned strategy to modify insulin dosage or carbohydrate supplementation before or during exercise to prevent initiating exercise with excessive insulin in circulation. If adjustments to insulin dosage are not made, the combined effect of hyperinsulinemia and exercise can cause glucose utilization to outpace glucose appearance (17, 18) causing blood glucose to decrease to the point of hypoglycemia. A 2008 study found that fear of hypoglycemia and a loss of agency over diabetes management both create important barriers to physical activity in individuals with T1D (3). Considering that only 36.3% of individuals with T1D in Canada are successful in completing Diabetes Canada's recommendations for amount of physical activity per week (19, 20) it is worthwhile to investigate potential exercise strategies that have limited effects on blood glucose, particularly with respect to hypoglycemia avoidance.

The potential for blood glucose to increase as a result of engaging in certain types of exercise is recognized in current North American clinical guidelines for physical activity and diabetes (20, 21). Research on the role of prandial status in the blood glucose response to high-intensity intermittent exercise (22, 23, 24) and resistance exercise (25) has demonstrated a regular increase in blood glucose during and after exercise when performed in the morning in a fasted state. Additionally, these results have prompted review of fundamental studies in T1D and exercise, revealing that when performed fasted, blood glucose increased during and after continuous aerobic exercise (26, 27) as well as during incremental exercise to exhaustion (28). These results are promising for those with T1D who struggle with exercise-related hypoglycemia, as they offer a potential alternative exercise strategy with reduced risk of hypoglycemia.

Nonetheless, strategies should also attempt to reduce the risk of hyperglycemia in order to facilitate maintenance of blood glucose within target ranges. Fasted exercise reduces the risk of hypoglycemia, but also increases the risk of hyperglycemia during and after exercise (25, 29). In order to optimize blood glucose management for fasted exercise, strategies for reducing blood glucose post-exercise should be investigated. The current clinical recommendations suggest the use of a post-exercise corrective insulin dose or an aerobic cooldown (21). However, the efficacy of an aerobic cooldown as a technique to reduce blood glucose or prevent hyperglycemia after fasted morning exercise has never been tested, and is currently supported by limited anecdotal experience.

Aronson et al. sought to determine the optimal post-fasted exercise insulin dosage factor to treat hyperglycemia (24). Even the most effective insulin correction factor, 150% of normal, resulted in elevated time in hyperglycemia (44 and 52%), for three and twenty-one hours after exercise respectively, and was associated with increased frequency of post-exercise hypoglycemic events. Their results suggest a prolonged time to restore elevated blood glucose concentrations to target range in the 3 hours after exercise, as well as general trends toward hyperglycemia during the 21 hours after fasted exercise. It is worth considering that even in this clinical trial setting, where dosage was carefully calculated and patients were closely monitored that there were instances of hypoglycemia in the three hours after exercise. The risk of potentially miscalculating insulin dosage, and subsequently causing hypoglycemia is likely higher in free-living conditions which can have severe adverse outcomes, especially when occurring overnight (21, 30). In summary, the strategies and recommendations available for managing post-exercise hyperglycemia are effective but not perfect in the case of post-exercise insulin corrections, or

completely untested in the case of aerobic cooldowns. Both warrant further investigation to create better strategies for people with T1D.

Objective

The objective of this study was to evaluate the effect of a 10-minute aerobic cooldown on blood glucose response following fasted resistance exercise. We hypothesized that an aerobic cooldown would attenuate the increases in blood glucose resulting from fasted resistance exercise. Specifically, we hypothesized that participants would have less time in hyperglycemia with increased time in target range and lower glycemic variability during the six hours after exercise. We also hypothesized that participants would experience less of an increase in capillary glucose concentration during the 30-minute acute post-exercise period when an aerobic cooldown was included.

Chapter 2 – Literature Review

Type 1 Diabetes Pathology and Treatment

Relating to T1D management, insulin serves two primary roles. One of these roles is to act as a regulator for the endocrine hormone glucagon, which has the opposing function to insulin. Glucagon is primarily secreted by pancreatic alpha cells, which, like beta cells, are found within the islets of Langerhans, an endocrine micro-organ of the pancreas (31). Glucagon has several global effects, but of particular relevance is an increased rate of hepatic glucose production during times of elevated glucagon concentration. These increases are achieved by elevating hepatic gluconeogenesis, as well as inhibiting glycogen production and glycolysis (32) to increase blood glucose concentration. When elevated glucagon occurs without the regulatory action of insulin in the case of T1D, hyperglycemia results. The other function of insulin is to facilitate the uptake of glucose into muscle cells. When insulin binds to its membrane receptor it increases translocation of the glucose transporter type 4 from within the cell to the cellular membrane. Here, it acts to allow glucose to enter the cell, while also removing glucose from the blood.

The goal of diabetes management is to maintain blood glucose at the normal physiological values seen in those without T1D. Due to the variable nature of insulin sensitivity and the difficulty of optimal dosage calculations, it is extremely challenging for most people with T1D to replicate normal physiological glucose control. Therefore, treatment aims to maintain blood glucose concentration within a range of 4-10 mmol/L (target range) for 70% of time (33). Consistently maintaining this target glucose remains an unachievable goal for many people with T1D. Long-term management has traditionally been evaluated by the percentage of glycated hemoglobin in circulation (HbA1c), with a 7% HbA1c result serving as the upper threshold of optimal management (34).

The most common model of insulin therapy involves multiple daily injections (MDI) of insulin in conjunction with regular monitoring of capillary blood glucose by finger prick blood samples. This therapy model involves the use of a long-acting, basal insulin analogue, which is typically injected once or twice daily, and a short-acting, bolus insulin analogue, which is injected throughout the day to correct hyperglycemia and to manage blood glucose increases from carbohydrate consumption. Long-acting insulins, like glargine, detemir, and degludec, generally take effect 1.5 hours after injection and remain in circulation for 16 – 42 hours (35). The primary function of long-acting or basal insulin is to moderate glucagon secretion, by creating a counterregulatory blockade. Rapid-acting insulins, like glulisine, aspart and lispro, generally take effect within 5-20 minutes, and remain in circulation for 3-5 hours (35). The primary function of rapid-acting or bolus insulin is to respond to carbohydrate consumption to prevent hyperglycemia as a result of a meal or snack.

The alternative to MDI, continuous subcutaneous insulin infusion (CSII), does away with long-acting insulin and replaces it with continuous infusion of rapid acting insulin. In CSII, rapid-acting insulin is used as both a bolus insulin when administered to account for food consumption, and as a basal insulin through the continuous infusion of insulin throughout the day. Due to the shorter clearance time for rapid-acting insulin, the rates of infusion of basal insulin can be adjusted throughout the day in anticipation of increased or decreased insulin requirement. The need for continuous infusion requires patients using CSII to be tethered to the source of their insulin, in the form of an insulin pump. The pump contains a reservoir, from which insulin is slowly infused under the skin by means of a small plastic cannula. Like MDI, CSII maintains the use of rapid acting insulin to manage blood glucose fluctuations resulting from carbohydrate consumption.

Compared to MDI, CSII offers patients greater flexibility in terms of lifestyle and eating habits, in addition to improved sleep quality (36). This difference in perceived flexibility is likely due to the exclusive use of rapid acting insulin, which requires much less lead time to modify insulin dosage in anticipation of a change in insulin requirement compared to long-acting insulin. For example, to prevent hypoglycemia in preparation for exercise, an individual using CSII may reduce their basal insulin 1-1.5 hours prior to exercise. An individual using MDI may have to reduce their long-acting insulin dosage the night before they plan to exercise, which may lead to hyperglycemia prior to exercise, or can choose to consume a pre-exercise snack with a decreased insulin dose to prevent hypoglycemia. The latter strategy may prevent some hypoglycemia but could limit the utility of exercise for weight management and does not prevent eventual declines during prolonged exercise (37). While there are numerous benefits to CSII including lower HbA1c, MDI is more common in the Canadian population (38). These numbers are likely due to the significantly elevated cost, as well as physical and psychological stresses associated with constant device attachment.

The other major advancement in technology involves the monitoring of blood glucose. To determine optimal insulin dosage, current blood glucose concentration must be known. Otherwise, hypoglycemia or hyperglycemia may occur from inaccurate dosage. Traditional capillary glucose monitors require a finger-prick blood sample, which is then analyzed by a handheld blood glucose monitor. While these monitors can produce a result in five seconds, they typically require all other activity to be stopped while the sample is taken and the result is being analysed.

Continuous glucose monitors (CGMs) involve a sensor that is fixed to the skin via a small adhesive patch. The sensor consists of a subcutaneous filament capable of sampling the glucose concentration of interstitial fluid at regular intervals as an estimate of blood glucose concentration.

The sensor transmits the signal to a handheld receiver, which displays a reading of estimated blood glucose concentration. Without the need to collect a blood sample and the convenience of knowing blood glucose levels by looking at the receiver, using CGM facilitates more frequent and consistent monitoring (39). The use of CGM technology decreases the frequency of hyperglycemia and hypoglycemia (40), lowers diabetes-related stress (41, 42) and decreases HbA1c (39). Analysis of long-term CGM data can provide specific information about average glucose, as well as specific daily blood glucose trends and variability making it a useful tool for precisely evaluating details of long-term management that are missed with HbA1c (33). CGMs are also particularly relevant for the treatment and prevention of hypoglycemia. These devices may alert patients to asymptomatic hypoglycemia and pending hypoglycemia during rapid blood glucose declines, may awaken patients during nocturnal hypoglycemia, reduce the incidence of hypoglycemia, and attenuate diabetes-related stress and fear of hypoglycemia (43).

Hybrid, closed-loop insulin delivery combines CGM and insulin pump technologies to make automated adjustments to basal insulin delivery, and in some cases allows for delivery of conservative correction doses, to prevent and/or treat hypo- or hyperglycemia based on CGM readings. Automated insulin delivery, including hybrid closed-loop, closed-loop, and dual hormone/medication closed loop systems, is one of the most quickly developing areas of T1D therapy and research. Single-hormone, hybrid closed loop systems have recently become commercially available and are effective for improving the amount of time spent in target range (44). Patient-made and managed, do-it-yourself systems have not been tested in a randomized trial, but were associated with greater time in range compared to commercially available systems in an observational retrospective study (45).

While these systems are effective at improving overall glucose management, exercise is one area where hybrid open-loop delivery continues to require patient decisions to prevent dysglycemia. A comparison of hybrid, closed-loop delivery to open-loop pump or MDI found improved time in range during the 24 hours after exercise when a closed-loop system was used (46). However, when using an insulin-only system, a pre-planned reduction in insulin delivery is still required to prevent hypoglycemia, which is usually achieved by increasing the target glucose of the automated delivery system. In a study comparing single hormone (insulin) to dual hormone (insulin + glucagon) automated systems, there was prevalent hypoglycemia when the glucose target was only raised 20 minutes before exercise in the insulin only group, with minimal hypoglycemia in the dual hormone group due to the administration of glucagon (47). Closed-loop delivery likely represents the future of T1D therapy, and while it currently provides benefits to glucose management in the post-exercise overnight period (48), it continues to require a pre-planned strategy to prevent hypoglycemia during exercise.

Fasted Exercise and Rising Blood Glucose: Mechanisms of Action

While many studies have found blood glucose increases during and after fasted exercise (49), the physiological mechanisms responsible for causing blood glucose to increase during this type of activity are unclear. Like all cases of hyperglycemia in the context of T1D, blood glucose increases because of an imbalance: the rate of glucose appearance exceeds disposal, due to an absence of endogenous insulin and corresponding glucose regulation. Unlike afternoon, fed exercise, when glucose utilization typically exceeds glucose appearance leading to a decrease in blood glucose, we expect that a combination of physiological factors is responsible for increasing the rate of glucose appearance to the point of exceeding glucose utilization during morning, fasted exercise. However, studies investigating the factors which cause blood glucose to increase during

morning, fasted exercise have not compared their results to an afternoon, fed comparison group, so are currently limited to observational data. Some explanations have been suggested (25), including hormonal, pharmacologic and metabolic factors which may increase glucose appearance or decrease glucose utilization during morning, fasted exercise relative to afternoon, fed exercise.

During the early morning hours, the natural release of cortisol and growth hormone increase gluconeogenesis and encourage glucose sparing, leading to elevated blood glucose levels. Elevated morning blood glucose is well-documented in non-exercise related T1D literature. It is often referred to as the "dawn phenomenon", and can cause hyperglycemia without consumption of food or modification to insulin dosage (50). In a study of fasted, morning resistance exercise in adults with T1D, Turner et al. (29) measured growth hormone and cortisol, as well as adrenaline, noradrenaline and interleukin-6, and found that growth hormone, adrenalin and noradrenaline increased significantly from rest to the first five minutes of exercise. It seems likely that a combination of natural increases in growth hormone and cortisol due to time of day, as well as exercise mediated increases in catecholamines may be contributing to increases in blood glucose seen during exercise in this study.

Hypercortisolism can induce insulin resistance by promoting skeletal muscle insulin resistance, and activating lipolysis and free fatty acid release (51). In the trial by Turner et al., (51) cortisol decreased from the beginning to end of exercise. However, salivary cortisol levels naturally decline during the 30 minutes to 2 hours after waking up, so it is possible that cortisol may have been elevated during this trial but went undetected due to a lack of a baseline measurement. In a study of non-T1D individuals, which examined the effect of a maximal incremental step test on cortisol and growth hormone at 7:00, 19:00, and 24:00, cortisol levels reached peak values during exercise at 7:00 (52). Without a measurement at baseline to compare,

the role of cortisol in post-exercise hyperglycemia is unknown, but remains a potential explanation for post-exercise hyperglycemia during and following morning exercise in individuals with T1D.

Concentration of growth hormone increased during fasted morning resistance exercise in the same trial by Turner et al. (29). Growth hormone contributes to hyperglycemia by increasing rates of hepatic glucose production and glycogenolysis, suppressing glucose uptake in adipose tissue and increasing hormone-sensitive lipase leading to elevated free fatty acid concentration in the blood (53). Growth hormone is known to increase in response to resistance exercise (54), and could therefore be involved in the hyperglycemic response to exercise.

The same trial by Turner et al. (29) found that concentrations of adrenaline and noradrenaline increased during fasted resistance exercise in adults with T1D (55). These findings were similar to earlier work from Sigal et al. (56, 57) who also found increased catecholamine secretion in T1D individuals during an incremental cycle ergometer test when performed fasted. These trials used a pharmacological block of adrenergic receptors to determine that catecholamines contribute to hyperglycemia by both increasing rates of glucose appearance, as well as reducing the rate of glucose uptake. By the completion of the intervention by Turner et al., (29) concentrations of growth hormone, noradrenaline and adrenaline returned to resting levels, but the initial rise in these hormones may have contributed to the initial increase in blood glucose. These results suggest that growth hormone and catecholamines may be contributing to increasing blood glucose levels during fasted, morning resistance exercise. As this is the only study where these hormones have been measured during fasted morning resistance exercise, additional studies should be carried out to confirm these results and determine what other hormones could also be contributing to the hyperglycemic effect.

Another possible explanation for the discrepancy in blood glucose responses to morning and afternoon exercise is the potential for different levels of circulating insulin. Studies in which morning and afternoon exercise were directly compared using a repeated measures study design found that blood glucose followed different trajectories during and after exercise, with morning fasted exercise producing blood glucose increases, while afternoon exercise led to blood glucose decreases (22, 25). During afternoon exercise in these studies, the participants' last meal and bolus insulin occurred 4 hours prior to exercise to limit remaining insulin in circulation during exercise. However, for fasted morning exercise, the previous bolus was administered at least 8 hours prior, so it is possible that a difference in the amount of insulin in circulation caused different blood glucose outcomes during morning and afternoon exercise. Insulin levels were not measured during these studies. Consequently, this idea also remains speculative.

The final potential explanation is that elevated insulin resistance during morning hours and elevated production of free fatty acids during fasted exercise contribute to elevated insulin resistance during and after exercise (58). Insulin sensitivity is lower and glucose production is higher in the morning than in the afternoon for those with T1D (59). Additionally, while elevated free fatty acids do not directly increase blood glucose, the insulin resistance they induce (60) could diminish its efficacy and increase the required dosage needed to maintain blood glucose in target range. The combined effect of elevated free fatty acids, increased glucose production, and decreased insulin sensitivity could act together to increase blood glucose. This idea is strengthened by evidence of elevated blood glucose persisting during the post-exercise period when free fatty acid concentration remains elevated in studies of both resistance (25) and aerobic exercise (61). However, free fatty acid concentration has not been measured in any study of fasted morning

exercise for individuals with T1D. As with the first two options, this explanation also remains speculative.

Post-Exercise Hyperglycemia Treatments: Correction Dose and Cooldown

The difference in risk for hypoglycemia between a post-exercise insulin dose and an aerobic cooldown to manage post-exercise blood glucose has not been measured, but it is reasonable to assume that a cooldown will have a lower risk for hypoglycemia for two reasons. The first is that an aerobic cooldown, defined in this study as 10 minutes of light cycling, at an intensity of 30% of VO_{2max}, is unlikely to constitute a significant portion of the energy expenditure of an entire session. As energy expenditure is directly linked to the risk of hypoglycemia (62), we believe that the additional energy cost of the cooldown will not significantly increase the risk of hypoglycemia.

The second is related to the potential to overcorrect with insulin for post-exercise hyperglycemia. The degree of change in insulin sensitivity during and after physical activity is dependent on many factors, which creates uncertainty when determining optimal dosage. This uncertainty could increase the risk of an over-corrective insulin dose after exercise and subsequent hypoglycemia. In a trial by Aronson et al., (24) which evaluated the efficacy of post-fasted exercise correction doses, there was increased frequency of hypoglycemia following the experimental arms which were effective for correcting hyperglycemia. A study evaluating the effect of exercise order when combining these two exercise modalities, found that blood glucose declined during aerobic exercise when it was performed after resistance exercise, but was associated with post-exercise hypoglycemia (63). However, the protocol of that study was different to the protocol in this proposal, as they tested participants in the afternoon (5pm), after having eaten one hour prior. They

also performed aerobic exercise at a higher intensity (60%VO_2peak) and for much longer than proposed in this study (45 minutes vs 10 minutes) (63).

Evidence of enhanced recovery from a post-resistance exercise cooldown is mixed for a general population. Definite benefits have been identified, however, including the removal of metabolic biproducts, such as lactate, and restoring pH to baseline levels (64). For a general population, this may have minimal effect on subsequent exercise performance more than four hours after the first session, but this effect could be more meaningful for a T1D population. It has been proposed that the glucose sparing and gluconeogenic properties of lactate contribute to elevated blood glucose levels during exercise (62). As such, lactate could also have an indirect role in elevating post-exercise blood glucose.

Chapter 3 - Methods:

The study was conducted in compliance with the ethics principles of the Declaration of Helsinki. The University of Alberta Biomedical Research Ethics Board approved the protocol (ARISE: Pro00115197; NCT05203653, clinicaltrials.gov), and written informed consent was obtained from all study participants. This study used an open label, randomized, repeated-measures crossover design comparing the acute capillary glucose and post-exercise CGM response to fasted resistance exercise followed by a 10-minute aerobic cooldown to no cooldown in 16 adults with T1D.

A sample size of 16 was selected to ensure that the sample size would provide sufficient statistical power and be feasible based on previous studies of exercise and T1D performed in Edmonton (22, 25). As this is the first study to evaluate the effect of a cooldown on blood glucose, there were no data to perform accurate effect size or power calculations. In 2012, Yardley et al. (63) examined the effect of performing 45 minutes of aerobic exercise (running at 60% of VO_2peak) after 45 minutes of resistance exercise and found that blood glucose declined by 2.3 ± 1.1 mmol/L from the beginning to the end of the aerobic exercise part of the intervention, in participants with T1D (63). For the sample size calculation of this study, we assumed that a lower intensity, 10-minute cooldown will result in one quarter of the blood glucose reduction (-0.6 mmol/L) that 45 minutes of aerobic exercise caused when performed immediately following the same resistance exercise protocol in the study by Yardley et al., 2012 (63). Additionally, despite evidence to suggest that blood glucose might increase in the 10 minutes following resistance exercise (25, 29, 65), we chose to be conservative and assumed that blood glucose would remain unchanged in the control condition during the 10 minutes post resistance exercise. Estimates for the variability of the change between treatment and control were performed with data from Toghi-

Eshghi & Yardley (25) who compared the effect of fasted morning exercise to non-fasted afternoon exercise. The standard deviation of the change in blood glucose during a 60-minute recovery between the two sessions in that study was ±1.8 mmol/L. Given the much shorter duration of the cooldown in the proposed study, we expect to see one third of the variability in change with expected standard deviation set to ± 0.6 mmol/L. With these expected effect sizes, a sample size of 16 will provide sufficient statistical power (ß=0.94).

A resistance exercise intervention was selected instead of other exercise types for three reasons. The first, is that near maximal rates of perceived exertion (18.8/20), indicating extreme discomfort, reported in a study of fasted high intensity interval exercise in individuals with T1D (22) could make it unfeasible as a regular training protocol. The second reason is a lack of confidence in the consistency of continuous exercise to increase blood glucose (26, 27, 66). The third and final reason is the reliability of fasted resistance exercise to increase blood glucose seen in previous testing in our lab group (25).

We recruited habitually active individuals with T1D aged between 18 and 55 years. We excluded individuals who had been diagnosed with T1D for less than 1 year as they may experience a honeymoon phase in their beta cell function, where little insulin is required to maintain glycaemia. Residual insulin production during the honeymoon phase (the period up to 2 years after initial diagnosis), when combined with the initiation of insulin therapy in the case of newly diagnosed individuals, can increase the risk of exercise-induced hypoglycemia (67). Participants using MDI or CSII were eligible for inclusion in this study, but participants were asked to replicate any modifications to insulin dosage for both experimental sessions of this study. We excluded those who use closed-loop automated insulin delivery as these systems could make automated modifications to insulin dosage from session to session. We excluded those with an HbA1c > 9.9%

as higher levels of HbA1c are indicative of inconsistent blood glucose management which may cause the participant to have an unpredictable blood glucose response and a higher risk of hypoglycemia. Additionally, an HbA1c >9.9% indicates they may not be able to maintain consistent dietary intake and/or insulin dosage required during this study. We excluded those taking certain medications that could affect glucose metabolism, including but not limited to sodium-glucose transporter type 2 inhibitors, beta-blockers, corticosteroids, alpha-glucosidase inhibitors, and thiazolidinediones. We excluded participants who consume a moderate to high alcohol intake (> 2 drinks/day), and those who smoke. These factors are known to increase the risk of adverse outcomes such as ketoacidosis (68) or severe hypoglycemia (69), and would therefore increase the overall risk involved for participants. Baseline activity levels and previous experience with resistance exercise were measured using a modified Baecke Sport Index and modified Kohl's Physical Activity Questionnaire (70, 71). Finally, we excluded those with conditions that would contraindicate resistance exercise, such as blood pressure >160/90 (72), severe peripheral neuropathy, severe proliferative retinopathy, advanced nephropathy or a history of cardiovascular disease to maintain participant safety.

Measures

Participants wore a Polar H7 Bluetooth Smart Heart Rate Sensor (Polar Electro; Kempele, Finland) during all exercise testing sessions involved in this study. Heart rate to estimate and compare the intensity of each session. OneTouch Ultra2 (LifeScan; Johnson & Johnson, Milpitas, CA) glucose meters were used to measure capillary glucose concentration when participants were at the laboratory. The timing of capillary glucose measurements was standardized in both conditions. A capillary glucose measurement was collected immediately before the beginning of the test, at the end of the resistance exercise test, as well as 10 and 30 minutes after the end of

resistance exercise in the recovery portion of both conditions. Dexcom G6 (Dexcom, San Diego, CA) CGMs were used to measure post-exercise interstitial glucose data for 24 hours after exercise. CGMs were blinded to participants who did not regularly use a CGM to prevent modifications to their regular treatment regimen due to the novel device. CGMs were worn on the day before, the day of, and the day after each testing session. Post-exercise CGM data, specifically variables of time in range (blood glucose between 4.0 and 10.0), time in hyperglycemia (>10.0), type in hypoglycemia (<4.0) and coefficient of variation, were analyzed for the independent time periods of 6 hours, overnight (midnight-6am), 12 hours, and 24 hours post-exercise, and compared between sessions (73).

Participants were asked to match and record their daily food intake, physical activity and insulin dosage as closely as possible between conditions on the day before, day of and day after the testing sessions. Modifications to basal insulin dosage in anticipation of or after exercise were determined by the participant, but participants were asked to repeat any modifications for both sessions. Participants were asked to avoid strenuous physical activity and alcohol intake during these days. On the same days, participants were asked to wear an ActiGraph WGT3X-BT (ActiGraph, Pensacola, FL) activity monitor, to determine the amount of energy expenditure from activity each participant performed outside of the laboratory. In addition to wearing the activity monitor, participants were asked to record the time of day they went to sleep and woke up, as well as when they removed the activity monitor for activities such as bathing. A modified Astrand-Rhyming cycle ergometer sub-maximal aerobic fitness test was performed on a Monarch 894e cycle ergometer (Monarch, Varsbro, Sweden), which was used to assess the fitness and estimate the VO_{2peak} of the participants. The estimated VO_{2peak} was used to calculate the resistance for the

cooldown. Intensity for the cooldown was 30% of the estimated power at estimated VO_{peak}. The specific protocol and calculations can be seen in Appendix I.

Design

We performed all testing in the Physical Activity and Diabetes Laboratory at the Alberta Diabetes Institute in Edmonton, Alberta. Participants attended one preliminary visit and two experimental trials. The timeline of these visits is found in figure 1. During baseline tests participants gave informed consent, completed anthropometric measurements, questionnaires to assess habitual physical activity, sleep quality, barriers to physical activity, and diabetes distress, as well as completed aerobic and resistance fitness testing. Participants were familiarized with and instructed on how to use the CGM and activity monitor, as well as when and how to record their food intake and insulin dosage. During the resistance exercise portion of the baseline session participants were guided through each exercise in order to familiarize them with the testing equipment, as well as to determine the maximum amount of weight they were able to lift for 8 repetitions while maintaining proper form (8RM). We determined 8RM by asking participants if they could complete a ninth repetition during 8-repetition sets with 90-second rest. During baseline testing participants completed the exercises in circuit, where each exercise was performed for one set before moving to the next, with a minimum of five minutes between sets of the same exercise to limit the effect of fatigue. This resistance was used for all three sets of the intervention.

The experimental sessions consisted of a control session (resistance exercise without cooldown after the final exercise) and a treatment session (resistance exercise followed by a cooldown) the order of which was determined by Microsoft Excel randomize function. The second session occurred no less that 48 hours after the first. The cooldown included 10 minutes of easy

cycling on a cycle-ergometer at an intensity of 30% of estimated VO_{2max}. The control session included 10 minutes of seated rest after resistance exercise to maintain the same timeframe.

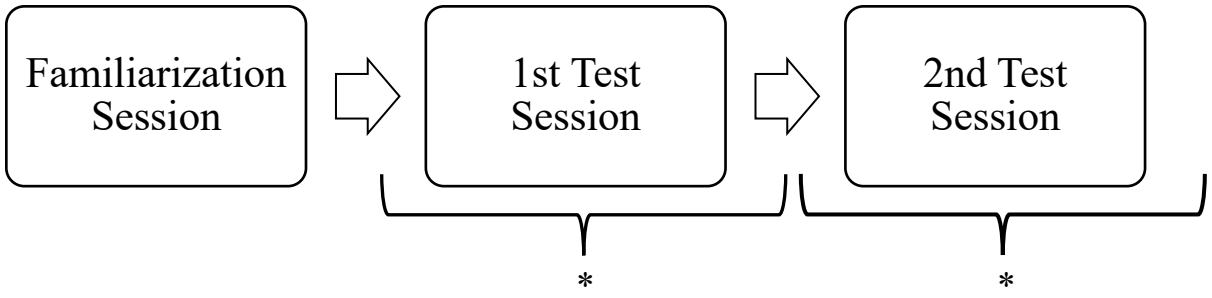

Figure 1. Timeline of the study. The timeframe represented by * is from 24 hours before to 24 hours after each exercise testing session. CGM and activity monitor data were collected for analysis during this time. The second testing session occurred no less than 48 hours after the first testing session.

On testing days participants arrived at the lab between 6:00 and 9:00 am, without having eaten or given fast-acting/bolus insulin for 8 hours. No specific modifications to basal insulin were made for the purposes of the study, but participants were able to modify their dosage freely, as long as modifications were replicated between sessions. During both testing sessions, participants performed the same protocol of seven resistance exercises [leg press, chest press, leg curls, lat pulldowns, seated row, shoulder press (modified to either dumbbell shoulder press or front shoulder raise for two participants with past shoulder injury), and abdominal crunches] with the same resistance. The protocol was three sets of eight repetitions at the participant's pre-determined 8RM, apart from abdominal crunches which were performed for 15 repetitions for all participants, with 90 seconds rest between sets, as used in previous studies of people with T1D (25, 63, 74). Movements were performed using a specific timing sequence (2,0,2,0 - two seconds for the eccentric phase, zero second hold, two seconds for the concentric phase, zero second hold) to

ensure consistent force and power production. If participants were unable to complete all eight repetitions, a member of the research team provided assistance on the final repetitions to completion of the set. Two members of the research team were present to monitor every session to ensure safety and consistent timing and form.

Outcome Measures & Statistical Plan

The primary outcome measure used to compare the glycemic effect of a post-fasted resistance exercise 10-minute cycle ergometer cooldown to no cooldown was the change in capillary glucose during the 30-minute recovery period. We compared the capillary glucose concentration at the end of resistance exercise, as well as 10 and 30 minutes after the end of resistance exercise by 2x3 repeated measures ANOVA with the alpha set at 0.05. We tested the effects of the potential time independent covariates of sex (male vs female), mode of insulin delivery (MDI vs CSII), and session order (cooldown – no cooldown vs no cooldown - cooldown) using general linear model repeated measures ANOVAs. We compared the capillary glucose concentration immediately prior to exercise, as well as the change in capillary glucose during exercise by paired samples t-tests. Secondary outcome measures of CGM glucose, including time in hyperglycemia, time in range and time in hypoglycemia, mean CGM glucose, coefficient of variability, standard deviation, area under the curve, and risk of hyperglycemia and hypoglycemia (HBGI and LBGI) during the 6-hour, 24-hour and overnight post-exercise period (midnight-6am) were compared by Wilcoxon signed rank tests. All CGM outcomes are reported as median (IQR) as per international guideline recommendations (75). HBGI and LBGI indicate the risk of hypoglycemia, and hyperglycemia and are calculated using the formulas described in Kovatchev et al. (76, 77). For LBGI the cut points of low- (LBGI <2.5), moderate- (LBGI 2.5-5), and high- (LBGI >5) indicate risk of severe hypoglycemia requiring external assistance. For HBGI the cut

points of low- (HBGI <4.5), moderate- (HBGI 4.5-9), and high- (HBGI >9), indicates the risk of hyperglycemia (BG >9.9mmol/l) (76).

Tri-axial accelerometry data were analysed on Actilife 6.13.3 software (ActiGraph, Pensacola, FL). Completion of log books was inconsistent, so periods of wear and nonwear time were determined using the algorithm proposed by Choi et al. (78). The Freedson algorithm (79) was used to determine energy expenditure from activity. Data were recorded at a 60Hz frequency. We compared insulin dosage, energy intake, and energy expenditure from activity on days before, days of and days after each session by paired-t test, as well as intraclass correlation coefficient using a two-way mixed effects model. Intra-class correlation coefficient tests use the threshold of values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 to indicate poor, moderate, strong, and excellent reliability, respectively (80). For increased precision, insulin dosage and energy intake were analysed during the morning, afternoon, and evening hours as well as full day to measure reliability in timing and source of energy intake and insulin dosage. Additionally, we performed nutrient specific comparison of the daily carbohydrate, fat and protein intake by paired t-test and ICC. For these multiple comparisons of specific outcomes, we applied a Bonferroni correction when determining significance for the results of the t-tests.

Chapter 4: Results

Participant Characteristics

Recruitment spanned from January 2022 to March 2023. We used posters and word of mouth to advertise our study. Candidates were also informed about the study through the Alberta Diabetes Institute's Clinical Research Unit who screened and provided contact details for interested candidates. A total of 57 potential candidates were identified and were contacted by email or phone. We successfully recruited 17 participants with one withdrawal due to inability to remain fasted for 8 hours, for a study sample of 16 (figure 2).

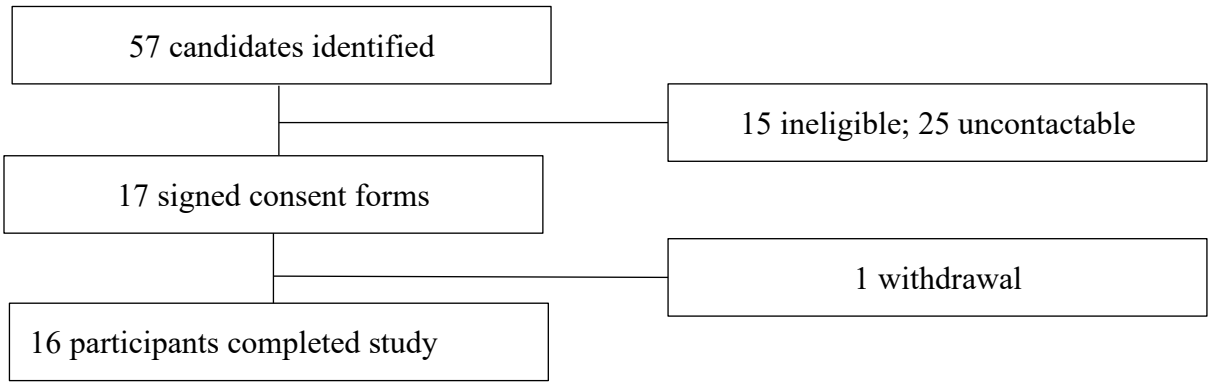

Figure 2. Flow diagram of participant recruitment.

The sample was habitually active and young, with the majority being undergraduate students at the University of Alberta living in the surrounding Edmonton area. Overall, our sample had well-managed diabetes, with a majority using CGMs as a part of their normal care (15/16). Mean HbA1c was slightly above the recommended target of 7.0% with a majority (9/16) of our sample above this target. Fitness and current activity levels were highly variable within the sample. Fourteen participants were engaged in some type of regular aerobic training but the overall sample ranged in levels from current varsity athletes to sedentary individuals. Twelve participants had

some experience with resistance exercise, but at the time of testing only 4/16 participants were actively following a resistance training program ranging from 1 session per week to 6 sessions per week. Additional participant characteristics are found in table 1.

Table 1. Participant characteristics.

	Mean	Standard Deviation
Number of participants	16	-
Male/Female	9/ 7	-
Age (years)	26.9	9.1
Weight (kg)	78.1	10.8
BMI ($kg \cdot m^{-2}$)	26.1	3.9
Estimated VO_{2max}($ml \cdot kg^{-1} \cdot min^{-1}$)	41.8	14.1
HbA1c % (mmol/mol)	7.3 (56)	0.7 (7.7)
Diabetes Duration	11.3	8.8
Method of delivery	10 MDI 6 CSII	-
CGM use (yes/no)	15 / 1	-
Baecke Sport Index Score	3.0	1.0

Resistance exercise had similar duration and mean heart rate during both conditions (table 2). Resistance exercise took just under 45 minutes to complete, including the time spent to test intra-exercise capillary glucose.

Table 2. Exercise characteristics; data presented as mean ± SD. P-values are from paired t-tests of cooldown and no cooldown conditions. bpm: beats per minute.

	No Cooldown	Cooldown	p
Heart rate during resistance exercise (bpm)	111 ± 16.1	112 ± 17.0	0.9
Resistance exercise duration (min)	43.7 ± 1.3	43.4 ± 1.2	0.9
Heart rate during cooldown (bpm)	-	132.6 ± 16.4	
Power output during cooldown (watts)	-	71.2 ± 31.2	

Primary Outcome: Capillary Glucose

Comparison by paired t-test found that prior to the start of exercise, capillary glucose (mean ± SD) was similar in cooldown (8.7 ± 3.1 mmol/l) and no cooldown conditions (7.9 ± 3.0 mmol/l; p=0.07). During the first 45 minutes of each session, which represents the time frame during which resistance exercise was performed, capillary glucose increased during cooldown (0.9 ± 1.7 mmol/l) and no cooldown (1.3 ± 1.9 mmol/l; p=0.3 for between conditions comparison by paired t-test). The 2x3 ANOVA analysis found that from the end of resistance exercise until the end of the testing session, capillary glucose increased by 0.2 ± 0.7 mmol/l and 1.0 ± 1.8 mmol/l in cooldown and no cooldown conditions (effect of time p = 0.02; effect of treatment p = 0.7), respectively. During the immediate 10-minute period after the cooldown, capillary glucose briefly declined by -0.6 ± 1.0 mmol/l in the cooldown session, whereas it increased by 0.7 ± 1.3 mmol/l when no cooldown was performed (figure 3). The resulting difference in capillary glucose trajectory during the 30 minute recovery represented a significant time by treatment interaction (p=0.02). No interactions were detected for any of the covariates.

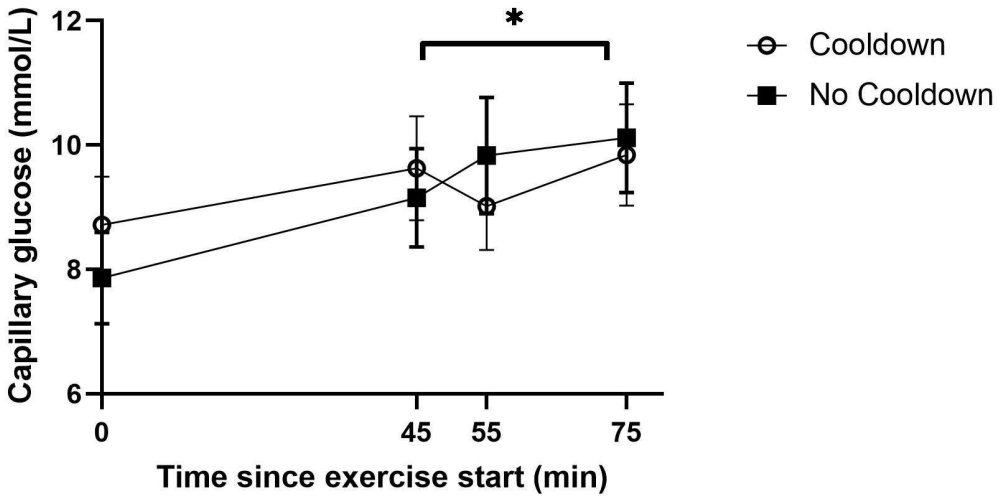

Figure 3. Capillary glucose (mean ± SEM) from the beginning to end of exercise. * indicates time by treatment interaction, p = 0.02.

Two participants required carbohydrate supplementation during resistance exercise. One required carbohydrates in the cooldown condition and the other in the no cooldown session. Both participants consumed 16g of glucose and were able to continue with exercise after a 15-minute pause when capillary glucose had returned to target range. It is likely that this treatment contributed to glucose increasing in the post exercise period of these sessions, as these participants experienced post exercise decreases in capillary glucose when no supplementation occurred in their other testing session.

Secondary Outcomes: CGM Glucose

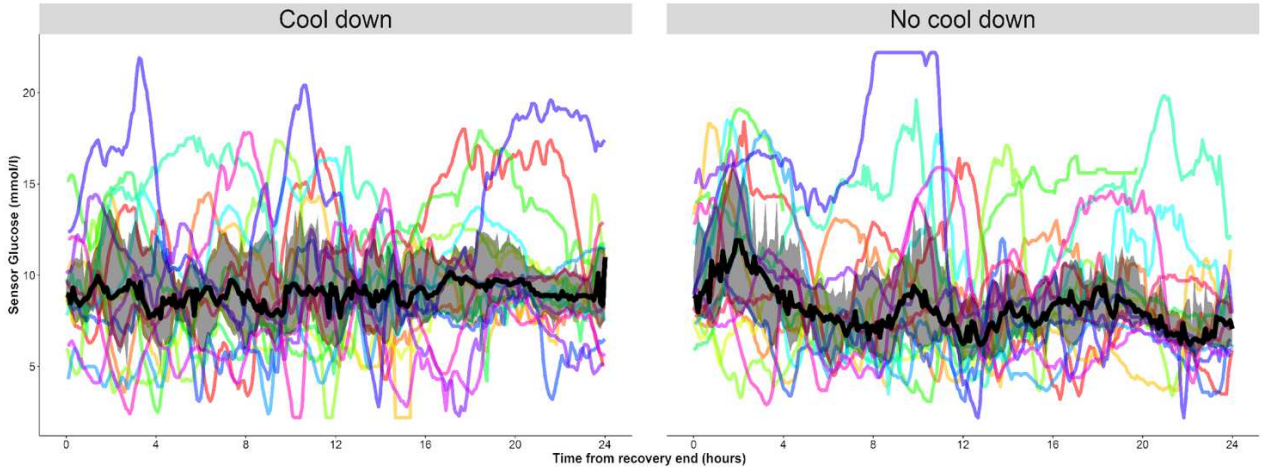

Figure 4. 24-hour post-exercise CGM glucose. Black line represents median, shaded area represents interquartile range (IQR). Each color represents one participant's CGM trace for the 24-hour post-exercise period.

Data were compared over the 6-hour, overnight, and 24-hour post-exercise (figure 4) periods by Wilcoxon signed rank test. Data are expressed as median (IQR). No comparisons of CGM variables were significant, apart from the 24-hour area under the curve, which was lower for no cooldown compared to cooldown [12,415 (10,712, 13,416) vs 13,207 (11,748, 15,310); p=0.018]. Compared to recommendations in international guidelines for T1D management (25% time in hyperglycemia), the percent time in hyperglycemia was elevated during the 6-hour post-exercise period [35 (10, 51) vs 37 (10, 61); p=0.5] in cooldown and no cooldown, respectively (75). Hypoglycemia was minimal in the post-exercise period with zero percent median time in hypoglycemia during the 6-hour post-exercise and overnight periods in both conditions. Variables from the 6-hour post-exercise period are displayed in table 3. Results from the overnight and 24-hour period can be found in Appendix II.

Table 3. CGM variables from 6 hours post-exercise.

	Cooldown[1]	**No Cooldown**[1]	**p-value**[2]
Total time analysed (mins)	360 (360, 360)	360 (360, 360)	>0.9
Average sensor glucose (mmol/l)	8.8 (7.93, 10.34)	9.3 (7.90, 12.00)	0.4
Standard deviation (mmol/l)	2.4 (1.85, 2.93)	2.1 (1.61, 3.37)	0.9
Coefficient of variation (%)	0.27 (0.21, 0.32)	0.24 (0.13, 0.32)	0.7
Percentage time 3.9-10 (mmol/l)	59 (49, 88)	54 (37, 83)	0.3
Percentage time 7-15 (mmol/l)	94 (56, 100)	94 (79, 100)	0.8
Percentage time level 1 hypoglycemia (3-3.9 mmol/l)	0.00 (0.00, 2.78)	0.00 (0.00, 0.00)	0.8
Percentage time level 2 hypoglycemia (<3 mmol/l)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.3
Percentage time level 1 hyperglycemia (>10 mmol/l)	35 (10, 50)	36 (10, 61)	0.5
Percentage time level 2 hyperglycemia (>13.9 mmol/l)	1 (0, 10)	2 (0, 37)	0.2
LBGI	1.15 (0.00, 3.59)	0.40 (0.00, 2.24)	0.08
HBGI	8 (5, 12)	13 (5, 17)	0.3
AUC	3,132 (2,779, 3,680)	3,306 (2,801, 4,251)	0.5

[1]Median (IQR)
[2]Wilcoxon signed rank test with continuity correction; Wilcoxon signed rank exact test

LBGI: Risk of hypoglycemia; HBGI: Risk of hyperglycemia; AUC: Area under curve

Food Intake

Participants recorded food intake and insulin dosage on study-provided paper logbooks. One participant's food record was lacking sufficient detail to be included. As such, data from 15 participants were included in analyses of energy intake and insulin dosage. Participants provided the volume or mass of the food items in their diet, and the time they were consumed which was entered into Food Processor® Nutrition Analysis software (ESHA, Oregon, USA). The software

provided descriptive statistics including total calories, and calories from fat, protein and carbohydrates (table 4). Comparison of energy intake by paired t-test showed energy intake was similar on the days before (2242 ± 1164 kcal and 2427 ± 1095 kcal; p=0.3), days of (2161 ± 692 kcal and 2071 ± 662 kcal; p=0.6) and days after (2099 ± 695 kcal and 1942 ± 602 kcal; p = 0.29) testing for cooldown and no cooldown sessions, respectively. Comparison of carbohydrate intake showed similar carbohydrate intake of the days before (274 ± 148g and 291 ± 152g; p=0.3), of (269 ± 86g and 256 ± 83g; p=0.6), and after (243 ± 81g and 241 ± 80g; p=0.9) testing for cooldown and no cooldown, respectively. Intake of fat and protein was also similar on the corresponding days of each condition.

Comparison of energy intake by intra-class correlation coefficients found that energy intake was moderately correlated on the days of and after the testing sessions, but was strong/excellently correlated on the day before the sessions. In addition to overall energy intake, we also performed intra-class correlation tests on energy intake from carbohydrate, fat and protein (table 4), as well as energy intake at breakfast, lunch and dinner (table 5) to investigate potential effects from macronutrient intake and meal timing. Compared to total energy intake, these more detailed analyses showed weaker correlations suggesting that participants may have been compensating for variable food intake, where participants may consume a larger meal to account for lower energy intake earlier in the day, or vice-versa.

Table 4. Daily intake of total energy, and energy from carbohydrate, fat and protein on the days before, of and after testing sessions (mean ± SD). P-values are result of paired samples t-test, with Bonferroni correction applied for nutrient specific comparison of cooldown to no cooldown ($\alpha = 0.05/3$). For daily total analyses significance was set at $\alpha = 0.05$. Intraclass correlation coefficients (ICC) are the results of correlational tests of cooldown and no cooldown conditions.

	Cooldown	No Cooldown	p-value	ICC
Day Before Session				
Total calories (kcal)	2426.5 ± 1095.1	2241.6 ± 1163.9	0.28	0.92
Carbohydrate (kcal)	1165.0 ± 609.9	1097.2 ± 590.3	0.28	0.96
Fat (kcal)	833.9 ± 423.3	785.2 ± 476.3	0.59	0.86
Protein (kcal)	422.4 ± 161.6	378.5 ± 160.3	0.09	0.91
Day Of Session				
Total calories (kcal)	2070.8 ± 661.9	2160.6 ± 691.5	0.67	0.56
Carbohydrate (kcal)	1025.4 ± 330.6	1074.6 ± 344.4	0.58	0.69
Fat (kcal)	668.2 ± 326.5	716.8 ± 331.4	0.63	0.57
Protein (kcal)	335.6 ± 90.1	370.7 ± 129.0	0.32	0.53
Day After Session				
Total calories (kcal)	1941.7 ± 601.6	2098.5 ± 695.1	0.29	0.80
Carbohydrate (kcal)	963.7 ± 321.3	973.7 ± 323.4	0.91	0.68
Fat (kcal)	650.7 ± 277.5	767.6 ± 392.8	0.21	0.67
Protein (kcal)	337.0 ± 114.7	353.6 ± 127.9	0.63	0.64

Table 5. Energy intake (kcal) from breakfast, lunch and dinner on the days before, of and after testing sessions (mean ± SD). P-values are result of paired t-test with Bonferroni correction applied for time specific results comparison of cooldown to no cooldown conditions (alpha = 0.05/3). Intra-class correlation coefficients (ICC) are the results of correlational reliability tests of cooldown and no cooldown conditions.

	Cooldown	**No Cooldown**	**p-value**	**ICC**
Day before session				
Breakfast	365.3 ± 97.2	350.2 ± 179.8	0.8	0.24
Lunch	571.3 ± 277.9	484.7 ± 334.9	0.4	0.15
Dinner	976.1 ± 566.9	882.0 ± 506.0	0.4	0.24
Day of session				
Breakfast	561.0 ± 435.8	503.5 ± 308.6	0.5	0.66
Lunch	432.5 ± 268.8	552.9 ± 343.5	0.2	0.47
Dinner	877.0 ± 482.9	843.0 ± 389.1	0.8	0.66
Day after session				
Breakfast	414.3 ± 197.7	466.2 ± 339.4	0.6	0.34
Lunch	378.9 ± 211.0	421.3 ± 287.1	0.5	0.64
Dinner	843.4 ± 412.7	958.7 ± 502.0	0.2	0.34

Rapid-acting/bolus insulin dosage

Participants recorded their insulin dosage in provided food logs on the days before, of and after each testing session. No changes were made to long-acting insulin dosage on any days that insulin dosage was tracked. For analyses of rapid-acting/bolus insulin, we divided days into three time periods, with each period corresponding to a major meal (table 6). We compared the total rapid-acting/bolus insulin dosage as well as insulin administered for breakfast, lunch and dinner times by paired t-test and intra-class correlation tests. Participants administered (18.4 ± 11.4 units vs 17.9 ± 11.9 units; p=0.4) the day before testing, (17.8 ± 8.4 units vs 18.6 ± 12.8 units; p=0.9)

the day of testing, and (20.1 ± 12.1 units vs 18.8 ± 12.5 units; p=0.3) the day after testing, on cooldown compared to no cooldown respectively. Insulin dosages were similar and had moderate-strong correlations for total daily, breakfast, and dinner insulin on all days of comparison. On the day after exercise, insulin dosage for lunch had the lowest correlation of any meal with a correlation coefficient of 0.57. We are unable to identify the source of this difference as there was no difference in energy or macronutrient intake at this meal. Insulin dosage for breakfast and dinner were similar despite the challenge that fasted exercise can pose for maintaining habitual food intake early in the day. Similar to food intake, correlation of daily energy intake was strong/excellent, but when analysed for individual meal times correlation coefficients indicated moderate correlation.

Table 6. Insulin dosage in units for breakfast, lunch and dinner, as well as total daily fast-acting/bolus dosage. P-value results are from paired t-tests, with a Bonferroni correction applied to mealtime specific insulin dosages, for the comparison of cooldown to no cooldown conditions (alpha = 0.05/3). For daily total analyses significance was set at $\alpha = 0.05$. Intra-class correlation coefficients (ICC) values are the results of correlational reliability tests of cooldown and no cooldown conditions.

	BREAKFAST				**LUNCH**			
	Cooldown	No Cooldown	p-value	ICC	Cooldown	No Cooldown	p-value	ICC
Day before	6.0 ± 3.3	5.9 ± 3.6	0.97	0.81	5.0 ± 5.1	6.1 ± 5.1	0.37	0.82
Day of	6.9 ± 4.2	6.3 ± 4.7	0.52	0.60	4.8 ± 3.6	4.8 ± 4.1	0.58	0.70
Day after	6.3 ± 3.7	5.8 ± 4.2	0.62	0.72	6.6 ± 6.1	4.6 ± 5.7	0.05	0.57
	DINNER				**DAILY TOTAL**			
	Cooldown	No Cooldown	p-value	ICC	Cooldown	No Cooldown	p-value	ICC
Day before	6.7 ± 5.3	5.9 ± 4.6	0.06	0.82	18.4 ± 11.4	17.9 ± 11.9	0.35	0.96
Day of	6.2 ± 3.8	7.9 ± 5.2	0.24	0.58	18.4 ± 8.4	18.6 ± 12.8	0.92	0.75
Day after	7.2 ± 4.0	8.5 ± 5.5	0.28	0.58	20.1 ± 12.1	18.8 ± 12.5	0.31	0.75

Energy Expenditure

Participants were asked to record when they went to sleep, woke up and when they removed the activity monitor for activities where the device could be exposed to water such as showering or swimming. Data from four participants on the day before and after exercise, and three on the day of exercise were excluded due to low wear time of less than eight hours per day (81). One participant competed in aquatic sports, and engaged in these activities during the study period. As a result, their energy expenditure is under reported. For this case they were asked to ensure that the same water-based activities were performed on the same corresponding days of the conditions to decrease the potential for confounding from different levels of energy expenditure. No comparisons of energy expenditure were significant when compared by t-test, and the intra-class correlation coefficients indicated strong, weak and moderate correlations (table 7) for the day before, day of, and day after the testing session respectively.

Table 7. Energy expenditure (kcals) from activity on the days before, of and after the testing session of each respective condition. P-values are the result of paired t-test. ICC are the results of correlation reliability tests.

	Cooldown	**No Cooldown**	**p-value**	**ICC**
Day Before	541.7 ± 275.8	557.7 ± 275.8	0.73	0.84
Day Of	598.9 ± 247.1	599.1 ± 247.1	0.99	0.49
Day After	527.2 ± 247.1	527.2 ± 217.1	0.74	0.55

Chapter 5: Discussion

Treatment of Post-Exercise Hyperglycemia

Our results suggest that an aerobic cooldown reduces blood glucose post-exercise, but the magnitude and duration of the reduction is not effective for preventing post-exercise increases in blood glucose, so alone is unlikely to be an effective treatment for post-exercise hyperglycemia. However, post-exercise cooldowns may have some clinical utility for the treatment of hyperglycemia, as an adjunct to insulin. In the cooldown condition of this trial, we observed a brief downward deflection in blood glucose trajectory during the immediate cooldown period. It is noteworthy that in studies when correction doses of insulin were administered immediately after exercise, blood glucose did not immediately decrease and continued to increase or remain elevated for 1-2 hours into the post-exercise period (24, 29). Combined with a post-exercise correction, an aerobic cooldown may be an effective adjunct treatment for post-exercise hyperglycemia due to its immediate glucose lowering effect.

Previous trials of post-exercise insulin corrections found that although blood glucose eventually returned to pre-exercise levels, it took nearly 2 hours to do so, even with 100% and 150% percent of their insulin correction factor (24, 29). We observed an immediate decrease in blood glucose during the cooldown, yet participants did not take any correction insulin until at least 30 minutes after the end of exercise. At this point several participants administered corrections, while others preferred to wait, under the expectation that exercise would eventually cause their blood glucose to decrease. This delay in insulin administration may explain why we

observed high amounts of hyperglycemia in the post-exercise period, even in the cooldown condition.

We found that mean glucose declined by -0.6 ± 1.0 mmol/L during the ten-minute cooldown period. This small decline is likely explained by the short duration and low intensity of the cooldown. A study which investigated mixed exercise where 45 minutes of resistance exercise was followed by 45 minutes of aerobic exercise, observed a decrease of 2.5 mmol/L in mean glucose concentration during the aerobic exercise portion of the session (63). In that trial, participants also exercised at 60% of VO_{2peak}, which would also contribute to the larger decrease in glucose concentration due to a higher intensity and rate of energy expenditure. Considering these results, a longer duration cooldown seems likely to cause a larger decrease in glucose concentration.

However, the benefits of a cooldown may extend beyond the decrease in glycemia. When people with type 1 diabetes experience hyperglycemia or increasing blood glucose, treatment involves administering insulin to decrease glucose concentration. Following fasted exercise, glucose can remain elevated for up to one hour despite insulin administration. Prolonged hyperglycemia despite a prior insulin dosage can lead to anxiety and questioning of whether there may be a malfunction in diabetes technology (*is my insulin pump cannula or line kinked?)* or questioning of the efficiency of the administered insulin (*did my insulin get too hot or was there air in the infusion?*) which can encourage the administration of an additional bolus dose, a clinical behaviour referred to as 'insulin stacking'. Insulin stacking eventually leads to hypoglycemia and/or severe decreases in glucose concentration due to the delayed, but eventual effects of combined insulin doses, which can be fatal. The brief downward deflection caused by a cooldown

may discourage insulin stacking behaviours as glucose concentration has decreased during the post-exercise period.

Why Would Blood Glucose Decrease During a Cooldown?

A cooldown may be a useful tool for managing post-exercise hyperglycemia, but we are unsure of the specific physiological mechanism(s) responsible for the change in glucose trajectory. Previous investigations of fasted low-moderate intensity aerobic exercise in people with T1D showed that exercise caused blood glucose increases (26, 27), as well as decreases (66), so initially our confidence in our hypothesized outcome was low. There have been no investigations of metabolic outcomes associated with fasted exercise for people with T1D, such as changes in free fatty acid or triglyceride levels, and only three trials have investigated the change in glucose from fasted low-moderate intensity aerobic exercise in people with T1D (26, 27, 66).

These trials investigated the change blood glucose during 30 minutes of walking at 50% (27) and 60% (26, 66) of VO_{2peak}. Two trials (26, 27) found glucose increased, while one found glucose decreased (66). The variability in these glucose outcomes can be attributed to a number of sources. The two trials which found glucose increased were performed 21 and 30 years ago, so participants were treated with less advanced long-acting insulin analogues (NPH and ultralente) which are more variable in their glucose lowering effect than modern long-acting analogues. If exercise occurred during a period when these long-acting analogues were becoming less active it could contribute to increasing blood glucose during and after exercise. Considering that these insulins have a 12-hour active period, patients typically administer them at morning and bedtime, so the effect of these insulins may be decreased during the morning as the previous night's dose wears off, and the morning's insulin has not taken effect. The more recent trial, published in 2023

found blood glucose decreased during fasted aerobic exercise despite nearly identical exercise timing, type and intensity. Additionally, these trials used higher intensity interventions (50-60% VO_{2peak}) which are likely promoting catecholamine secretion relative to the 30% VO_{2peak} used in this trial. In their study of fasted aerobic exercise, Ruegemer et al. (26) found that levels of catecholamines significantly elevated during exercise, likely due to the higher intensity (60% VO_{2peak}) intervention.

We expect that the glucose lowering effect of a cooldown is due to a relative decrease in counter regulatory hormone release, yet a maintained level of glucose utilization due to the low intensity aerobic exercise. After intense exercise is stopped, levels of epinephrine and norepinephrine in the blood decrease rapidly (82), which would likely lead to a decrease in the rate of liver glucose production. If during this time, the rate of energy expenditure and glucose utilization is maintained via a low intensity cooldown, blood glucose concentration may tend to decrease.

We had expected that there may be a delayed glucose lowering effect from performing a cooldown due to a potential increase in free fatty acid oxidation during the low intensity aerobic cooldown. Fasted exercise is known to increase levels of free fatty acids in circulation which can contribute to insulin resistance. We expected insulin resistance could contribute to post-exercise blood glucose increases and the persistent hyperglycemia observed in the six hours after fasted exercise. We hypothesized that a cooldown could facilitate clearance of free fatty acids produced during fasted exercise thereby increasing insulin sensitivity in the post-exercise period leading to a relative reduction in the frequency or severity of hyperglycemia. However, we did not detect any difference in the 6-hour post exercise CGM glucose which is where any effect from the lowering of free fatty acids in concentration would likely be detected. While a cooldown may increase the

rate of fat oxidation, the cooldown in this study was likely not long enough to cause a meaningful reduction in blood lipid levels during the post-exercise period.

Outpatient CGM Glucose Trends

Glucose concentration is affected by an extensive list of potential variables, and food intake, insulin dosage and physical activity represent three of the most important variables not already controlled through our study design (83). Accordingly, to determine the effect of a brief aerobic cooldown on CGM glucose in the post-exercise period, we asked participants to replicate their physical activity, food intake and insulin dosage on the corresponding days of each condition during study. By using a repeated measures design, replicating behaviours allows for differences in glucose to be attributed to the intervention, while also increasing the power of statistical tests.

Our analyses showed that at the sample level, participants were successful in repeating their food intake. However, variability within the sample may limit our ability to claim that these behaviours were replicated based on t-tests alone. To address this discrepancy, we performed intra-class correlation tests to identify the intra-class correlation coefficients for energy intake, insulin dosage and energy expenditure from activity on the corresponding days (before, of, and after) of cooldown and no cooldown. These tests are traditionally used to assess inter-rater reliability to ensure similarity between groups measured by different raters. Correlation analyses showed moderate-strong correlations for full day energy intake, but only low to moderate correlations when compared by single meal energy intake (table 4). Comparison of insulin administration to ensure similarity was equally challenging. At the daily total level, conditions were similar by t-test comparison, and strongly and excellently correlated, but when compared at the single meal level, there was one case of a statistically significant difference, and moderate correlations in insulin

dosage at the three major meals of the day. Energy expenditure from activity was only considered over full day periods, with no difference detected by the paired t-tests but had low, moderate and strong levels of correlation.

These results demonstrate the challenge of ensuring a similar baseline between conditions upon which the change in glucose concentration from exercise can be compared. This is likely because the allowable difference between groups with respect to these variables that ensures a similar baseline is unknown. Considering the scale of change in glucose concentration that a small difference in insulin dosage may bring, the tests used to compare the difference and similarity between conditions may not be sensitive enough to ensure similar glycemic sensitivity and outcomes from an exercise session. We were unable to control or account for differences in glucose because our model of glucose regulation in T1D only includes three variables, physical activity (kcal), energy intake (kcal), and insulin dosage (units). There are likely dozens of other important variables in an accurate model of glucose regulation in T1D for which our model does not account. As such, these similarity tests cannot account for the additional, expected variability within our results, particularly during the post-exercise period.

Figure 5A displays CGM data from a participant on the day of their no cooldown condition. This participant experienced a significantly prolonged period of hyperglycemia after exercise, which was exacerbated by meal consumption around 13:00. After 10 hours in hyperglycemia the effect of insulin stacking is evident at 7pm, leading glucose concentration to drop from above 22.2mmol/l to 2.7 mmol/l in 1h25m. In their cooldown condition (figure 5B), this participant's CGM glucose follows a similar trend, with hyperglycemia that began in the post-exercise period and continued to increase after the morning meal. However, on this day they chose to delay their lunch to 15:45 to allow time for their correction dose to actively lower glucose. This delay allowed

glucose to return to target range, but an underestimation of carbohydrate intake for lunch lead to hyperglycemia in the hours after lunch. This example shows the scale of the effect of exercise, relative to the scale of insulin, as well as how slight differences in food intake, and mis-timing or miscalculating insulin dosage can drastically affect CGM glucose concentration. These drastic effects make any trends in CGM outcomes during the post-exercise period difficult to attribute to exercise alone considering the large scale in glucose change that can come from potentially small differences in insulin dosage.

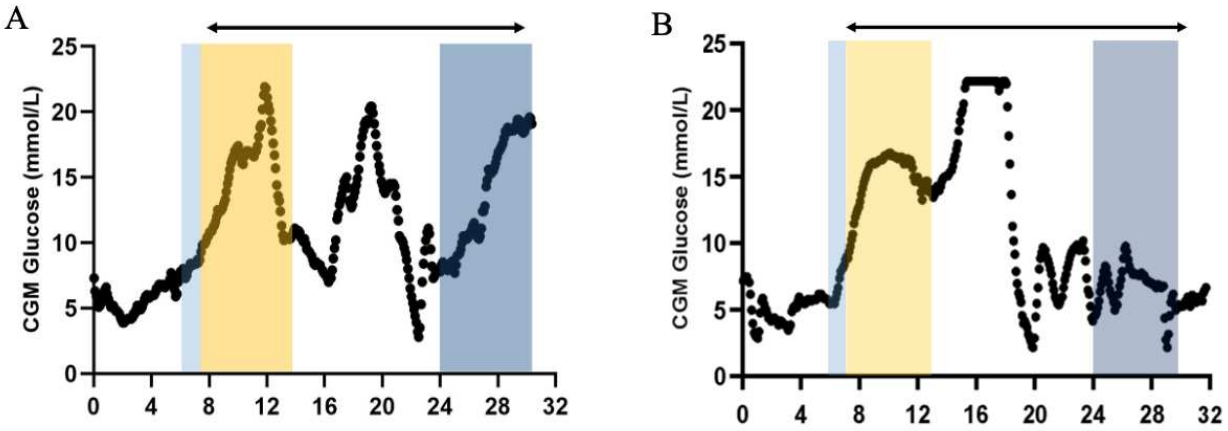

Figure 5. Single participant 32-hour trace of CGM glucose on a A) no cooldown testing day and B) cooldown testing day. Light blue represents exercise, yellow represents 6 hours post-exercise, dark blue represents overnight period, arrow represents 24-hour post exercise period.

Limitations

Our study was limited in its ability to assess trends in the post-exercise period. We attempted to control for confounders by replicating and comparing food intake, physical activity and insulin dosage on the days surrounding testing, as these variables are known to affect the glucose response to exercise. By using a repeated measures design we attempted to control for these confounding variables by replicating behaviours so that their effects on blood glucose were maintained, and therefore not contributing to differences between conditions. Despite statistical

similarity in these potentially confounding variables, individual CGM glucose traces were unpredictable and inconsistent. This inconsistency prevented our ability to detect trends in post-exercise CGM glucose, which are likely to be undetectable without a much larger sample. A larger sample may provide the sufficient statistical power to detect the delayed effects of exercise, even with high amounts of variability in post-exercise glycemia. However, the sample of this study is already larger than the majority of inpatient exercise trials people in T1D (49).

One strategy to increase the statistical power and sample size to detect a difference in post-exercise CGM trends may be an outpatient setting trial. Recently, the T1-DEXI trial implemented remote monitoring and data collection in a four-week, at-home exercise trial in 497 adults (84). Trials of at-home exercise with remote monitoring are likely to be more accessible, and may provide greater external validity in comparison to controlled in-patient settings. However, in trials of specific interventions such as the one investigated here, it is difficult to maintain the required internal validity due to the specificity of details such as timing of exercise, adherence to the criteria for remaining fasted, and consistency of exercise intensity.

Conclusions

The results of this study indicate that a 10-minute aerobic cooldown causes a temporary, small reduction in blood glucose concentration, but is not effective for preventing post-fasted exercise blood glucose increases. A longer cooldown or a 10-minute cooldown used as an adjunct to a corrective insulin dose may be more effective but additional trials of these strategies are needed to confirm efficacy and safety. The current recommendation of an aerobic cooldown used to treat post-exercise hyperglycemia (21) should be modified to recognize that a cooldown alone is unlikely to be an effective treatment for hyperglycemia.

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APPENDIX I

Modified Astrand-Rhyming Submaximal Cycle Ergometer Test

Purpose: to predict maximal oxygen uptake with submaximal exercise response (power output and HR) which is a measure of cardiorespiratory fitness.

Equipment: Monark Cycle ergometer, HR belt and watch, blood pressure cuff and stethoscope.

Overview: The test will be 2 x 4-minute exercise stages. Blood pressure will be measured and recorded between the 3 & 4-minute mark and 7 & 8-minute mark. HR will be measured at the end of each minute. The test will start out quite easy and will be slightly more difficult the last 4 minutes so that we can achieve a HR between 125 and 170 bpm.

Instructions:

1. Have the subject put the HR chest strap on just above the abdominal muscular so that it sits on top of the lower rib cage. Check to make sure the HR is being transmitted to the watch receiver (water under the rubber electrodes assists in HR detection).

2. Have the subject sit on the bike, pedal for 10 seconds, check sear height, adjust so the person has slight knee flexion at the bottom of the pedal stroke without shifting the hips on the seat.

3. Place a blood pressure cuff around the left arm. Measure BP between minutes 3 & 4 and 7 & 8. Things to watch for: SBP does not increase, or SBP goes very high during exercise > 200 mmHg. Continually monitor the person and ask them how they are feeling.

4. Always pedal at 50 rpm. Males start at 1.5 Kp (450 kp.m/min) and females start at 1.0 Kp (300 kp.m/min) the first 4 minutes serve as a warm-up. If HR < 120 bpm then increase the resistance by 1.0 – 2.0 Kp. If HR > 130 bpm increase the resistance by 0.5-1.0 Kp based on the HR response. Want HR between 125-170 bpm.

5. You can have the subject do light exercise (easy spinning at 0.5 Kp) for 1 minute following the test.

6. Use the Astrand-Rhyming tables for workload, sex, HR and age correction to complete the calculations.

Note:

1 Watt = 6.12 kg . m . min-1 = 6.12 kp . m . min-1

1 kg . m . min-1 = 0.1635 Watt (to convert kp.m/min to Watts multiply kp.m/min by 0.1635)

(1kg=1kp)

Prediction of Maximal Oxygen Consumption from Heart Rate (HR) and Cycling Power (MEN)

Maximal Oxygen Consumption ($L \cdot min^{-1}$)						Maximal Oxygen Consumption ($L \cdot min^{-1}$)				
Men's HR ($b \cdot min^{-1}$)	Power ($kgm \cdot min^{-1}$)					Men's HR ($b \cdot min^{-1}$)	Power ($kgm \cdot min^{-1}$)			
	300	600	900	1200	1500		600	900	1200	1500
120	2.2	3.5	4.8			146	2.4	3.3	4.4	5.5
121	2.2	3.4	4.7			147	2.4	3.3	4.4	5.5
122	2.2	3.4	4.6			148	2.4	3.2	4.3	5.4
123	2.1	3.4	4.6			149	2.3	3.2	4.3	5.4
124	2.1	3.3	4.5	6.0		150	2.3	3.2	4.2	5.3
125	2.0	3.2	4.4	5.9		151	2.3	3.1	4.2	5.2
126	2.0	3.2	4.4	5.8		152	2.3	3.1	4.1	5.2
127	2.0	3.1	4.3	5.7		153	2.2	3.0	4.1	5.1
128	2.0	3.1	4.2	5.6		154	2.2	3.0	4.0	5.1
129	1.9	3.0	4.2	5.6		155	2.2	3.0	4.0	5.0
130	1.9	3.0	4.1	5.5		156	2.2	2.9	4.0	5.0
131	1.9	2.9	4.0	5.4		157	2.1	2.9	3.9	4.9
132	1.8	2.9	4.0	5.3		158	2.1	2.9	3.9	4.9
133	1.8	2.8	3.9	5.3		159	2.1	2.8	3.8	4.8
134	1.8	2.8	3.9	5.2		160	2.1	2.8	3.8	4.8
135	1.7	2.8	3.8	5.1		161	2.0	2.8	3.7	4.7
136	1.7	2.7	3.8	5.0		162	2.0	2.8	3.7	4.6
137	1.7	2.7	3.7	5.0		163	2.0	2.8	3.7	4.6
138	1.6	2.7	3.7	4.9		164	2.0	2.7	3.6	4.5
139	1.6	2.6	3.6	4.8		165	2.0	2.7	3.6	4.5
140	1.6	2.6	3.6	4.8	6.0	166	1.9	2.7	3.6	4.4
141		2.6	3.5	4.7	5.9	167	1.9	2.6	3.5	4.4
142		2.5	3.5	4.6	5.8	168	1.9	2.6	3.5	4.3
143		2.5	3.4	4.6	5.7	169	1.9	2.6	3.5	4.3
144		2.5	3.4	4.5	5.7	170	1.8	2.6	3.4	4.3
145		2.4	3.4	4.5	5.6					

Modified from nomogram in I. Astrand, *Acta Physiologica Scandinavica*, 49, suppl. 169, 1960, by P. O. Astrand in *Work Test with Bicycle Ergometer*, Varberg, Sweden, Monark, 1988.

Prediction of Maximal Oxygen Consumption from Heart Rate (HR) and Cycling Power (WOMEN)

Maximal Oxygen Consumption ($L \cdot min^{-1}$)						Maximal Oxygen Consumption ($L \cdot min^{-1}$)					
Women's HR ($b \cdot mn^{-1}$)	Power ($kgm \cdot min^{-1}$)					Women's HR ($b \cdot min^{-1}$)	Power ($kgm \cdot min^{-1}$)				
	300	450	600	750	900		300	450	600	750	900
120	2.6	3.4	4.1	4.8		146	1.6	2.2	2.6	3.2	3.7
121	2.5	3.3	4.0	4.8		147	1.6	2.1	2.6	3.1	3.6
122	2.5	3.2	3.9	4.7		148	1.6	2.1	2.6	3.1	3.6
123	2.4	3.1	3.9	4.6		149		2.1	2.6	3.0	3.5
124	2.4	3.1	3.8	4.5		150		2.0	2.5	3.0	3.5
125	2.3	3.0	3.7	4.4		151		2.0	2.5	3.0	3.4
126	2.3	3.0	3.7	4.4		152		2.0	2.5	2.9	3.4
127	2.2	2.9	3.5	4.2		153		2.0	2.4	2.9	3.3
128	2.2	2.8	3.5	4.2		154		2.0	2.4	2.8	3.3
129	2.2	2.8	3.4	4.1		155		1.9	2.4	2.8	3.2
130	2.1	2.7	3.4	4.0	4.7	156		1.9	2.3	2.8	3.2
131	2.1	2.7	3.4	4.0	4.6	157		1.9	2.3	2.7	3.2
132	2.0	2.7	3.3	4.0	4.5	158		1.8	2.3	2.7	3.1
133	2.0	2.6	3.2	3.8	4.4	159		1.8	2.2	2.7	3.1
134	2.0	2.6	3.2	3.8	4.4	160		1.8	2.2	2.6	3.0
135	2.0	2.6	3.1	3.7	4.3	161		1.8	2.2	2.6	3.0
136	1.9	2.5	3.1	3.6	4.2	162		1.8	2.2	2.6	3.0
137	1.9	2.5	3.0	3.6	4.2	163		1.7	2.2	2.6	2.9
138	1.8	2.4	3.0	3.5	4.1	164		1.7	2.1	2.5	2.9
139	1.8	2.4	2.9	3.5	4.0	165		1.7	2.1	2.5	2.9
140	1.8	2.4	2.8	3.4	4.0	166		1.7	2.1	2.5	2.8
141	1.8	2.3	2.8	3.4	3.9	167		1.6	2.1	2.4	2.8
142	1.7	2.3	2.8	3.3	3.9	168		1.6	2.0	2.4	2.8
143	1.7	2.2	2.7	3.3	3.8	169		1.6	2.0	2.4	2.8
144	1.7	2.2	2.7	3.2	3.8	170		1.6	2.0	2.4	2.7
145	1.6	2.2	2.7	3.2	3.7						

Modified from nomogram in I. Astrand, *Acta Physiologica Scandinavica*, 49, suppl. 169, 1960, by P. O. Astrand in *Work Test with Bicycle Ergometer*, Varberg, Sweden, Monark, 1988.

Table II-11
Age Correction Factors
for Åstrand-Ryhming Submaximal Cycle Test

Age	Factor	Age	Factor	Age	Factor
15	1.10	34	0.88	53	0.73
16	1.09	35	0.87	54	0.72
17	1.08	36	0.86	55	0.71
18	1.07	37	0.85	56	0.70
19	1.06	38	0.85	57	0.70
20	1.05	39	0.84	58	0.69
21	1.04	40	0.83	59	0.68
22	1.03	41	0.82	60	0.68
23	1.02	42	0.81	61	0.67
24	1.01	43	0.80	62	0.67
25	1.00	44	0.79	63	0.67
26	0.99	45	0.78	64	0.66
27	0.97	46	0.77	65	0.65
28	0.96	47	0.77	66	0.65
29	0.94	48	0.76	67	0.64
30	0.93	49	0.75	68	0.64
31	0.92	50	0.75	69	0.64
32	0.90	51	0.74	70	0.63
33	0.89	52	0.73	71	0.63

Astrand-Rhyming Submaximal Exercise Test

Time (min)	RPM	KP	HR (bpm)	SBP/DBP (mmHg)
1				
2				
3				
4				
5				
6				
7				
8				

Average HR @ 7^{th} and 8^{th} minute = _____

Final Workrate kp.m/min = ____(kp) x_____(rpm) X 6 (m) =_____(kp*m/min)

Predicted VO_2max = _____(L/min)*_____ (Age Correction Factor)= _____(L/min)

Relative VO_{2max}=_____(L/min)* 1000 (ml/L) / _____(mass kg) = _____(ml/kg/min)

Recovery Intensity = (((0.3 *_____(ml/kg/min)) – 2.1)/1.8)*_____ (mass kg)

APPENDIX II

Overnight CGM Glucose

Characteristic	**Cooldown**, N = 16[1]	**No cooldown**, N = 16[1]	**p-value**[2]
Total time analysed (mins)	360 (360, 360)	360 (360, 360)	
Average sensor glucose (mmol/l)	9.2 (8.41, 11.41)	8.0 (6.48, 9.54)	0.2
Standard deviation (mmol/l)	1.9 (0.87, 2.48)	1.20 (0.73, 1.81)	0.10
Coefficient of variation (%)	0.18 (0.10, 0.30)	0.19 (0.09, 0.21)	0.2
Percentage time 3.9-10 mmol/l	71 (31, 80)	92 (58, 100)	0.2
Percentage time level 1 hypoglycemia (3-3.9 mmol/l)	0.00 (0.00, 0.00)	0.00 (0.00, 1.74)	0.6
Percentage time level 2 hypoglycemia (<3 mmol/l)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.4
Percentage time level 1 hyperglycemia (>10 mmol/l)	27 (2, 69)	0 (0, 42)	0.2
Percentage time level 2 hyperglycemia (>13.9 mmol/l)	0 (0, 7)	0 (0, 0)	0.8
LBGI	0.00 (0.00, 1.77)	0.04 (0.00, 3.20)	>0.9
HBGI	7 (6, 13)	3 (1, 7)	0.2
AUC	3,275 (2,988, 4,061)	2,830 (2,304, 3,387)	0.2

[1]Median (IQR)

[2]Wilcoxon signed rank test with continuity correction; Wilcoxon signed rank exact test

24 hour Post Exercise CGM Results

Characteristic	**Cooldown**, N = 16[1]	**No Cooldown**, N = 16[1]	**p-value**[2]
Total time analysed (mins)	1,440 (1,440, 1,440)	1,440 (1,440, 1,440)	0.8
Average sensor glucose (mmol/l)	9.2 (8.21, 10.68)	8.7 (7.46, 9.36)	0.12
Standard deviation (mmol/l)	2.7 (2.20, 3.50)	3.1 (2.15, 3.51)	0.4
Coefficient of variation (%)	0.30 (0.24, 0.34)	0.35 (0.26, 0.41)	0.2
Percentage time 3.9-10 mmol/l	64 (46, 82)	79 (53, 85)	0.3
Percentage time level 1 hypoglycemia (3-3.9 mmol/l)	0.70 (0.00, 1.90)	0.87 (0.00, 3.40)	0.2
Percentage time level 2 hypoglycemia (<3 mmol/l)	0.00 (0.00, 1.13)	0.00 (0.00, 0.00)	0.07
Percentage time level 1 hyperglycemia (>10 mmol/l)	34 (17, 52)	20 (13, 42)	0.09
Percentage time level 2 hyperglycemia (>13.9 mmol/)	6 (0, 16)	9 (0, 12)	0.9
LBGI	3.47 (0.66, 5.08)	2.50 (0.96, 3.40)	0.09
HBGI	8.2 (5.6, 13.0)	7.7 (5.7, 11.4)	0.9
AUC	13,207 (11,748, 15,310)	12,415 (10,712, 13,416)	0.02

[1]Median (IQR)

[2]Wilcoxon signed rank test with continuity correction; Wilcoxon signed rank exact test