The Association of Exercise Blood Glucose Levels and Post-Exercise Hypoglycemia in Adults with Type 1 Diabetes

by

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Abstract

Guidelines suggest that people with type 1 diabetes (T1D) start exercise with moderately high blood glucose (8-10 mmol/L) (BG) to reduce the risk of hypoglycemia; however, those fearing hypoglycemia often start higher. This study aimed to determine the impact of afternoon aerobic exercise with a higher BG on post-exercise glycemia, as measured by continuous glucose monitoring (CGM). Eleven active T1D participants [8 female, 3 male, 30 ± 8 years, A1C 7.7 ± 0.8%, VO_{2peak} 38.3 ± 7.8 ml/kg/min] completed two exercise sessions in random order: 1) with BG between 8.0-10.0 mmol/L (MOD) and 2) with BG between 12.0-14.0 mmol/L (HI). Participants were asked to keep meal timing/composition and insulin doses consistent between sessions. Participants cycled for 45 minutes at 60% VO_{2peak}. Exercise intensity (respiratory exchange ratio, heart rate) was identical between sessions ($p>0.05$). CGM data [mean ± standard deviation] were assessed between 6:00pm-12:00am (6hr), and 12:00am-6:00am (nocturnal) after exercise. ANOVA revealed a main effect of condition for mean CGM glucose [MOD vs. HI, 6hr: 8.8 ±1.0 mmol/L vs 10.5 ± 2.6 mmol/L; nocturnal: 8.6 ± 1.4 mmol/L vs 9.8 ± 2.8 mmol/L; $p=0.03$], percent time in range [MOD vs HI, 6hr: 76 ± 16% vs 48 ± 28%; nocturnal: 72 ± 33% vs 58 ± 33%, $p<0.01$] and percent time in hyperglycemia (MOD vs HI, 6hr: 24 ± 16% vs 49 ± 29%; nocturnal: 27 ± 31% vs 42 ± 33%, $p<0.01$). We were unable to evaluate hypoglycemia protection due to a low number of events. Overall, higher exercise BG was associated with increased time in hyperglycemia and decreased time in range, and therefore, we recommend exercisers with T1D complete moderate aerobic exercise in the MOD range.

Preface

This thesis is an original work by Heather Hinz. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Biomedical Research Ethics Board, “Electrolyte balance during exercise in type 1 diabetes” (Pro00075503) December 6, 2017. Table 2 and Table 4 are used with permission, as seen in Appendix A: Permission for the Use of Table 2 and Appendix B: Permission for the Use of Table 4, respectively.

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Chapter 1: Introduction

Type 1 diabetes (T1D) is an autoimmune condition characterized by the destruction of the β cells and the body's inability to maintain glucose homeostasis (1). People with T1D have an increased risk of cardiovascular disease (2), and are encouraged to exercise to reduce their risk; exercise is associated with decreased cardiovascular risk factors (3), improving lipid profiles (3), and improving aerobic endurance (4). The principal reason people with T1D are not physically active is the fear of hypoglycemia (5), including the risk of nocturnal hypoglycemia, which can be fatal.

Recommendations from the American Diabetes Association (6), and a consensus statement on exercise in T1D published by experts in the field, (7) suggest that individuals should begin aerobic exercise with blood glucose values between 5.0 and 13.9 mmol/L (6) or between 7.0 mmol/L and 10.0 mmol/L (7). While the expert committee (7) creating the consensus did not explicitly cite any specific works for the latter recommendation, other research studies completed in T1D and exercise have also used this range (8-11) in an attempt to keep participants from having hypoglycemia unrelated to the study goals; the combination of these studies and others is presumably how the committee arrived their recommendation. Many exercisers with T1D start exercising with blood glucose levels higher than this suggested concentration in order to avoid hypoglycemia during their exercise or after (12). Currently, there is limited research comparing starting glucose levels with the same exercise condition to determine if a higher starting blood glucose concentration is better at preventing post-exercise hypoglycemia. One observational study found that higher pre-exercise blood glucose levels had a greater rate of decline during exercise than moderately high blood glucose levels, and was only somewhat protective against hypoglycemia (13). However, this study was a secondary analysis, some participants were using

insulins that are less prescribed now than they once were, and there was a broad range of baseline blood glucose levels reported (13). Other research has demonstrated that aerobic exercise performed between 3.9 mmol/L and 16.7 mmol/L in the late afternoon can produce post-exercise hypoglycemia, with some occurring overnight (14-16). A greater understanding of how blood glucose levels are affected during and after exercise may lead to improved glucose management; therefore, it may remove a significant barrier to exercise for this population (5).

The data hereby analysed were a subset of a larger study looking primarily at the hydration of physically active people with T1D presenting with two different blood glucose ranges during a late afternoon aerobic exercise session: a moderate (MOD) session between 8.0 and 10.0 mmol/L, and a high (HI) session between 12.0 and 14.0 mmol/L. We measured blood glucose levels during and up to 12 hours post exercise, to determine if higher exercise blood glucose levels allowed a person with T1D to avoid post-exercise hypoglycemia. We hypothesized that the time spent in hypoglycemia after both the MOD and HI sessions would be the same in the 12 hours post-exercise.

Chapter 2: Literature Review

2.1 Relevant Anatomy and Physiology of Type 1 Diabetes

The human pancreas contains four major cell types that each produce different hormones. The two cell types most involved in T1D are the α and β cells found in the islets of Langerhans. The α cells produce glucagon, an essential hormone in glucose homeostasis that increases blood glucose concentration when necessary. The β cells produce insulin, which lowers blood glucose concentration. In the case of T1D, most of the β cell mass is destroyed by the immune system. The person is no longer able to secrete insulin, and the α cells are no longer as responsive. The islet cell types, hormones, and functions can be found in Table 1 (1).

Table 1: Cell Types Found in the Pancreatic Islets and Hormones Produced

Cell type	**Hormones produced**	**Function**
α cells	Glucagon	Raises blood glucose levels
β cells	Insulin	Lowers blood glucose levels
δ cells	Somatostatin	Inhibits insulin and glucagon release
PP cells	Pancreatic polypeptide	Inhibits pancreatic exocrine functions

Adapted from Robbins and Kumar, 2010 (1)

In people without diabetes, glucose homeostasis is tightly regulated between glucose production in the liver, glucose uptake in peripheral tissues (primarily skeletal muscle), and the actions of two opposing pancreatic hormones, insulin, and glucagon. Insulin promotes glucose uptake and utilization in the skeletal muscles (as well as other tissues to a lesser degree) as it prevents hyperglycemia after meals (1). During fasting, insulin levels decrease, and glucagon levels increase, which facilitates gluconeogenesis and glycogenolysis in the liver (1). This process, in turn, lowers glucose uptake for glycogen synthesis, thereby preventing hypoglycemia (1). After

a meal, insulin levels rise, and glucagon levels lower to allow for the uptake of glucose by tissues in the liver and skeletal muscle (1).

2.2 Diabetes Classifications

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia due to a lack of insulin secretion, action, or both (17). In addition, it has a hallmark of disturbances of carbohydrate, fat, and protein metabolism (18). Traditionally, the classification of diabetes depended on the age of diagnosis (juvenile diabetes vs. adult-onset diabetes), or therapy type (insulin-dependent diabetes vs. non-insulin-dependent diabetes). However, this nomenclature has been discarded, and its etiology and presentation now classify diabetes at the time of diagnosis. Diabetes Canada recognizes up to ten different classifications of diabetes, as seen in Table 2 (17).

Table 2: Diabetes Classifications

Type 1 diabetes encompasses diabetes that is primarily a result of pancreatic β cell destruction with consequent insulin deficiency, which is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta-cell destruction is unknown
Type 2 diabetes may range from predominant insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance. Ketosis is not as common
Gestational diabetes mellitus refers to glucose intolerance with onset or first recognition during pregnancy
Other specific types include a wide variety of relatively uncommon conditions, primarily specifically genetically defined forms of diabetes or diabetes associated with other diseases or drug use

Adapted from Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, Page S10, Copyright (2018) with permission from Elsevier(17)

Despite the stark increase in diabetes diagnoses in the world (19), TID is still considered rare and only affects up to 10% of the diabetes population, roughly 200,000 Canadians (19, 20).

Despite its rarity, it is still the most common chronic endocrine condition diagnosed in people younger than 20 years old (21) and can be diagnosed at any age (17).

2.3 Pathophysiology of Type 1 Diabetes

Type 1 diabetes is an autoimmune condition characterized by the destruction of the β cells in the islets of Langerhans. To be classified as an autoimmune condition, two out of four criteria must be fulfilled (1, 22), as seen in Table 3. In T1D, the first three criteria apply to humans, and all four are applicable in animal models (23).

Table 3: Criteria for Diagnosis of Autoimmune Conditions

1. The disease state can be transferred by the patients' antibodies or T cells
2. The disease course can be stopped or slowed by immunosuppressive therapy
3. The disease is associated with manifestations of humoral or cell-mediated autoimmunity directed against the target organ
4. The disease can be experimentally induced by sensitization against an autoantigen present in the target organ, which presupposes the knowledge of the target autoantigen

Adapted from Bach (1994)(22)

While the exact cause of T1D is unknown, it is multifactorial and likely a combination of environmental triggers and genetic predisposition (22). There is a small chance of concordance among first-degree relatives with T1D (roughly 6-7%), which is considerably higher in identical twins (24). However, twins are often exposed to the same environments, eat similar diets, and have the same genetic predisposition, which could inflate their risk (24). The antibodies seen can precede diagnosis and include glutamic acid decarboxylase (GAD) antibodies and insulin antibodies. Insulitis (where lymphocytes surround and infiltrate the β cells and consequently destroy them) is also present (25).

Although autoimmunity is the most common cause of T1D, there is a subtype that is considered idiopathic (Type 1b diabetes) (23). This type of diabetes is differentiated from autoimmune diabetes by the absence of insulitis, islet cell antibodies, GAD antibodies, or insulin

antibodies, which are indicative of the autoimmune attack on the β cells (23). Further, studies have supported that idiopathic diabetes is more commonly found in people of African or Asian descent (19). These people typically present with complete insulin deficiency and the rapid onset of β cell destruction. There are theories that this type of T1D could be viral, but that remains to be confirmed (17, 26).

2.4 Diagnostic Criteria

There are currently four tests available to diagnose diabetes, and clinicians are strongly encouraged to confirm results on two runs of the same test promptly to confirm the diagnosis (17). In suspected T1D, people often present as thin, young, and with symptomatic hyperglycemia (including extreme thirst, lethargy, frequent urination, and potentially ketones in the urine or blood). A random plasma glucose test resulting in ≥11.1 mmol/L and a fasting plasma glucose of ≥7.0 mmol/L are two options for an accurate diagnosis of T1D, as A1C is not recommended (17). However, the delay for results on a confirmatory test should not delay the treatment of hyperglycemia. This immediate treatment will decrease the risk of kidney, eye, or microvascular damage. If two different tests are used, and their results are not concurrent, the one above the diagnostic cut point should be repeated for confirmation (17, 27).

2.5 Insulin Therapy

Injectable subcutaneous insulin therapy is necessary for all people with T1D for the maintenance of blood glucose homeostasis, regardless of classification. The only exception to this is those who have received an islet cell transplant. Despite advances in transplant protocols, including post-transplant immunosuppression drug regimens, observational studies have found that most people eventually require subcutaneous insulin therapy to maintain homeostasis post-transplant (28, 29).

The two preferred methods of insulin delivery for adults with T1D are either multiple daily injections (MDI), or continuous subcutaneous insulin infusion (CSII, or pump therapy) as these regimens most closely resemble typical pancreatic function (27). MDI therapy consists of an injection of basal (long-acting) insulin (given once or twice per day) that keeps blood glucose concentration steady if a person were not to consume glucose and is considered background insulin. Basal insulin is complemented with bolus injections of rapid-acting insulin to account for carbohydrate intake or increases in blood glucose levels (27). This type of therapy can be advantageous as the latest delivery devices (insulin pens or syringes) are small and portable, and some of the new basal insulins only need to be injected once every 36 hours. The rapid-acting bolus insulin permits the person flexibility in their eating habits and daily activities and does not require being attached to a device (such as an insulin pump) (27). However, exercise must generally be planned days in advance to adjust basal insulin as necessary, which can be complicated and restrictive for people with T1D. Although the administration of insulin via insulin pens may be less expensive, the newer basal insulins can be quite costly and are rarely covered by provincial insurance (27). For a comparison of the insulins most commonly used in MDI and insulin pump therapy that are available in Canada as of April 2018, seen in Table 4.

The other recommended therapy type for people with T1D is continuous subcutaneous insulin infusion (CSII), or insulin pump therapy (27). Pager-sized devices are attached to people with T1D 24 hours per day either via external tubing and a small cannula or just a cannula inserted under the skin. Common infusion sites include the abdomen, buttocks, arm, thigh, or upper flank. A rapid-acting insulin is loaded into the pump, and dosages are developed by the person and their diabetes care team. The insulin then drips continuously over a 24-hour cycle. This constant infusion is known as the basal rate and provides enough insulin for the body to perform routine

functions when fasting. People using pump therapy also use bolus insulin doses, much like their MDI counterparts. People with T1D give an insulin bolus when consuming carbohydrates and may have different ratios for these carbohydrates during different periods of the day (27).

Table 4: Types of Insulin Available in Canada Most Commonly Used in Pump or MDI Therapy

Bolus insulins		
Rapid-acting insulin analogues	Peak	Duration
Insulin aspart (NovoRapid®)	1-1.5 hours	3-5 hours
Insulin glulisine (Apidra®)	1-1.5 hours	3.5-5 hours
Insulin lispro (Humalog®)	1-2 hours	3-4.75 hours
Faster-acting insulin aspart (Fiasp®)	0.5-1.5 hours	3-5 hours
Short-acting insulins		
Insulin regular (Humulin-R®, Novolin® ge Toronto)	2-3 hours	6.5 hours
Basal Insulins		
Intermediate-acting		
Insulin neutral protamine Hagedorn (Humulin N®, Novolin® NPH)	2-3 hours	6.5 hours
Long-acting		
Insulin detemir (Levemir®)	Not applicable	16-24 hours
Insulin glargine U-100 (Lantus®)		24 hours
Insulin glargine U-300 (Toujeo®)		> 30 hours
Insulin degludec (Tresiba®)		42 hours

Adapted from the Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Appendix 6 Types of Insulin, Copyright (2018), with permission from Elsevier MDI=multiple daily injections (30)

Benefits of pump therapy include the ability to make micro-adjustments to basal rates, and a smaller number of injections, as infusion sites are moved only approximately every three days. Disadvantages include the cost of the pump (approximately $8,000 in 2020) and supplies (approximately $500 per month in 2020), as well as the cumbersome nature of wearing a device full-time (Lara Soukeroff 2018, oral communication, April 3). However, an observational study conducted in 2013 demonstrated that people using pump therapy experienced less hyperglycemia and more stable interstitial glucose levels after exercise than those using MDI (31).

Despite there being additional insulin regimens available, most are not prescribed as much as they once were due to the advantages of insulins with lower or no peaks and shorter action time (as seen in Table 4). These insulins are now only used in certain circumstances, as determined by the person and their diabetes care team (27). As mentioned above, MDI and pump therapy most closely resemble typical pancreatic function and are the recommended therapy types for adults with T1D by Diabetes Canada (27).

2.6 Continuous Glucose Monitoring

To maintain euglycemia (more commonly referred to time in range [TIR]), patients with T1D must monitor blood glucose levels externally to inform treatment decisions. Glucose monitoring can be achieved using readily available, hand-held glucose monitors that require a finger prick of capillary blood and a test strip to administer. Unfortunately, these monitors only provide snapshots of blood glucose concentration, fail to provide glucose trends, and can be inconvenient. Continuous glucose monitors (CGMs) can provide uninterrupted data and are becoming smaller and more convenient for the people who wear them. They can provide immediate data without a finger prick, which allows for more immediate treatment decisions by patients in real-time.

2.6.1 Components of the CGM System

Commercially available CGM systems consist of a sensor, recorder or transmitter, and an insertion device. Sensor filaments are inserted under the skin into the interstitial fluid and remain there until expiry (generally six to ten days, depending on the manufacturer). The CGM sensor filament functions by monitoring an electrical current across two electrodes. Then the CGM sensor sends a signal to the transmitter or recording device, which is connected externally to the person (32). The sensor used in this study takes interstitial glucose values every ten seconds, averages

them every five minutes, and then sends them to the recorder, resulting in 288 readings per day. For research purposes, it is helpful to have a system that has a recorder, and therefore blinds the values to the person. Each system is different, and many still require calibration from two to four times daily with a capillary blood glucose test.

2.6.2 Limitations of CGM Technology in Research

As mentioned previously, CGMs can provide trending and pattern data to people with T1D. CGMs have acceptable accuracy during exercise (33-37) and can improve time in range (38, 39) and/or A1C (38-41) for those who use them continuously. However, the data have been mostly collected on physically active men with T1D, and studies are mostly completed with participants in euglycemia. Also, CGM systems rely on an oxygen-based reaction (42). Acetaminophen, a readily available over the counter analgesic, is electrically active and can interfere with accurate data collection if participants take it during sensor wear (42, 43).

2.7 Type 1 Diabetes and Exercise: Physiology

2.7.1 Exercise and Glycemia

During aerobic exercise, as part of an insulin-independent mechanism, skeletal muscle uses glucose up to five times faster than at rest in people without diabetes (44). During aerobic exercise in people with T1D, the rate of glucose production in the liver does not typically match the rate of glucose disposal from the blood to the working skeletal muscle (45, 46). In individuals with T1D, a hyperinsulinemic state can occur because injected (i.e., synthetic) insulin does not degrade at the same rate as endogenous insulin. This disparity can result in hypoglycemia if glucose uptake exceeds production (46), which can persist anywhere from the start of exercise up to 24 hours post-exercise (47). The timing of the hypoglycemia depends on many factors, such as exercise type (i.e., high-intensity interval training, aerobic, resistance) (10), time of day the exercise is completed

(48), and dietary adjustments around the exercise (if any) (49). Also, insulin sensitivity is increased with bouts of aerobic exercise, even if those bouts do not increase aerobic fitness as defined by VO_{2max} (50). This imbalance can be a burden for people with T1D as it is difficult to predict which methods of hypoglycemia prevention (insulin reduction or carbohydrate intake) to employ for the most significant effect.

In a recent consensus statement, experts suggest various strategies to help counteract hypoglycemia during exercise, including carbohydrate supplementation, starting at a moderate blood glucose level (between 8.0 mmol/L and 10.0 mmol/L) and decreasing insulin doses (7). However, carbohydrate supplementation can sometimes lead to overconsumption (inducing hyperglycemia) and can lead to potential weight gain. Even though many active individuals with T1D use insulin pump therapy, (which allows for minute adjustments at any time point), decreasing insulin before, during, or after exercise does not always prevent low blood glucose levels (15, 51, 52). Also, exercising in the evening could increase the risk of post-exercise hypoglycemia occurring when the individual is sleeping (53), which could be a popular time as it may accommodate work or school schedules.

Despite studies looking at T1D and exercise, recommendations for blood glucose management from diabetes and exercise experts tend to be broad, where they need to be specific and individual. One study found that people with T1D using different therapy modalities (i.e., pump only, MDI only, MDI with CGM, and pump with CGM) report differences in blood glucose management around exercise (54). This finding demonstrates that blood glucose management techniques should vary [e.g., sex (55), activity level, type of insulin, insulin therapy type (54), and among different types of exercise (7, 56)]. Current guidance from associations such as the American College of Sports Medicine (ACSM) are general and do not distinguish between therapy

(i.e., insulin pump vs. MDI) or technology types (i.e., CGM use vs. non-CGM use) (57). Following guidelines set out by organizations, such as Diabetes Canada, can be challenging for people with T1D when attempting to maintain glucose stability and incorporate exercise into their life (5), as some of the recommendations may sacrifice optimal blood glucose levels before, during, or after exercise sessions (5).

2.7.2 Fear of Exercise-Induced Hypoglycemia or Hyperglycemia

It has been noted that those with T1D are less active than those in the average population, with less than 40% considered physically active (58). As within the population at large without diabetes, people with T1D have various reasons for avoiding exercise, including time and work pressures, weather, and lack of energy (5). However, they also have an additional concern. The number one diabetes-related reason people with T1D do not exercise is the fear of hypoglycemia (5, 54). The risk of nocturnal hypoglycemia, which is particularly dangerous, has been demonstrated to be prevalent when exercise occurs in the evening (11, 53).

Also, after some forms of exercise, including a high-intensity aerobic workout (59) and fasted resistance exercise performed in the morning (48, 60, 61), post-exercise hyperglycemia can occur. For someone new to physical activity, this perturbation could increase barriers to activity as the management of diabetes could be difficult (5). A way to overcome these barriers is to continue to search for substantial evidence of glycemic response to exercise in the T1D population.

Chapter 3: Methods

3.1 Participant Recruitment

Adults between 18 and 50 years of age with T1D who were habitually active were recruited for the "Electrolyte balance during exercise in type 1 diabetes" study from January to June 2019. The primary study outcome was to determine and characterize the changes in hydration and electrolyte levels in response to exercise when glucose was moderately high (the MOD session) and during hyperglycemia (the HI session). In addition, the hydration and electrolyte outcomes from the MOD session would be compared to sex-, age-, height-, weight-, and fitness-matched control participants who did not have diabetes. Posters were printed and placed in prominent places on the University of Alberta campus. An email was sent out to participants of past studies who expressed interest and consented to be contacted for future research opportunities. The Alberta Diabetes Institute Clinical Research group posted our study on their clinical research website, and if participants expressed interest, a recruitment email was sent out to them. We also recruited through social media, including Facebook, Twitter, and LinkedIn. This experiment's protocol conformed to the standards set by the Declaration of Helsinki and was approved by the Biomedical Research Ethics Board of the University of Alberta Pro00075503. Exclusion criteria and the rationale behind the criteria are seen in Table 5**.**

Table 5: Criteria for Exclusion from Our Study

Exclusion Criterion	Rationale for exclusion
TID diagnosis <2 years ago	To avoid the "honeymoon phase, where insulin is still being secreted and therefore confounding glucose results and increasing the risk of hypoglycemia
A1C ≥9.9%	Suggests difficulty or inconsistency in managing blood glucose levels, which could also imply difficulty in adhering to study protocols
Frequent and unpredictable hypoglycemia or hypoglycemia unawareness	Increased risk of severe hypoglycemia during and after exercise sessions
Change in diabetes management strategy in the last two months	Increased risk of hypoglycemia during and after exercise sessions due to novel insulin regimen
Diagnosis of: • Uncontrolled hypertension (BP > 150 mmHg systolic or >95 mmHg diastolic) • Severe peripheral neuropathy • Proliferative retinopathy • Clinically significant gastroparesis • History of cardiovascular disease	For safety reasons, exercise is often contraindicated for individuals with these conditions
Use of medications that alter glucose metabolism (i.e., atypical antipsychotics, SLGT2 inhibitors, metformin)	Alter glucose metabolism and therefore, would confound glucose handling in the body
Over 50 years of age	Age-related changes in glucose metabolism that could confound results
Cognitive deficit	Participants would be unable to provide informed consent
Score <14 on Godin and Shepard Leisure-Time Physical Activity Questionnaire	Demonstrates a lack of habitual physical activity (62)

T1D= type 1 diabetes, BP= Blood pressure

3.2 Baseline Session and Peak Oxygen Uptake Test

Participants first visited the lab for a baseline session, where a detailed screening took place to determine eligibility and to ensure all inclusion criteria were met. All participants signed an

informed consent if they chose to participate at that time, as seen in Appendix C: Informed Consent Form. Anthropometric characteristics, including height (cm), weight (kg), and body mass index (k/m^2) were measured using the Tanita Bioelectrical Impedance Body Composition Analyzer balance scale (the protocol can be found in Appendix D: Body Composition Analyzer Protocol) and a fixed stadiometer (complete protocol can be found in Appendix E: Stadiometer Protocol). All information for the duration of the study was recorded in the case report form. A copy of the case report form can be found in Appendix F: Case Report Form.

Participants were given instructions on how to use the cycle ergometer (Monark Ergonomic 874E, Varberg, Sweden) and were encouraged to become familiar with the equipment. Participants were then asked to perform a graded exercise test to volitional exhaustion to determine their peak oxygen consumption (VO_{2peak}) using a Metabolic Measurement System (Parvo Medics TrueOne® 2400 Utah, USA). This test allowed us to determine the resistance required to provide the appropriate intensity in the subsequent exercise sessions (i.e., 60% of their VO_{2peak}). The participant maintained 80 revolutions per minute (RPM) for the entire test, and resistance was increased every minute. For females, resistance started at 0.5 kg and increased by 0.2 kg per minute, and male participants started at 1 kg and increased by 0.3 kg per minute. The complete protocol for both sexes can be found in Appendix G: VO2peak Cycle Ergometer Protocol**.**

The test was considered valid and complete when a participant met the following conditions: they reached their ventilatory threshold, achieved a stable (e.g., no longer increasing) heart rate near (within five beats per minute) their age determined maximum, reported a rating of perceived exertion on the 6-20 Borg Scale of 17 or higher (63), and could no longer maintain the 80 RPM pace. If participants met the previous conditions but could still maintain 80 RPM and stated that they could not continue, the test was also considered valid. Upon completion of the

baseline test, a coin was flipped to determine which exercise session would happen first (the MOD session: blood glucose levels between 8.0-10.0 mmol/L, or the HI session: 12.0-14.0 mmol/L). Participants were then provided a recovery period of at least 48 hours before the first session.

3.3 Testing Sessions

Twenty-four hours before the first session, participants visited the lab to have a Medtronic Enlite CGM sensor inserted subcutaneously in their abdominal region and attached to an iPro2 recorder that was blinded (Medtronic, Minneapolis, MIN). The CGM remained in place until the end of the study period (six days, and at least 24 hours after the last exercise session). Participants were given paper logbooks and access to a smartphone app synched to the provided capillary blood glucose monitor (OneTouch Reveal, LifeScan Canada, Burnaby, BC) to track food intake, capillary blood glucose, and insulin dosages. Participants were asked to keep their food intake and insulin regimen as consistent as possible (i.e., snacks/meals at the same time of day and with the same type of food). Capillary blood glucose was recorded in the logs or the app at least four times per day for calibration of the CGM. The Enlite sensor was found to be most accurate when calibrated three to four times daily (64, 65), and had acceptable, albeit lower, accuracy during exercise (34, 64). The food and blood glucose logs can be found in Appendix H: Food and Blood Glucose Logs. Participants were given recommendations to adjust basal insulin before and after the exercise sessions. The reductions were designed to reduce hypoglycemia during exercise and to keep the participants' blood glucose concentration in the desired range, based on an algorithm developed and implemented in previous T1D and exercise studies (9, 10, 66). Participants using MDI therapy were recommended to reduce basal insulin by 10% and not administer it in their leg. Pump therapy participants were given recommendations to reduce basal rates by 50% two hours

before arriving at the lab and, if requested, were sent a reminder by text message two hours before their exercise session time.

For the first exercise session, participants were asked to arrive at the lab at 4:00 pm (plus or minus one hour to accommodate their schedules) the day after the sensor insertion, having avoided exercise, alcohol, caffeine, insulin administration in the legs, and hypoglycemia (as much as possible) in the previous 24 hours. Their last meal before testing was eaten at least 90 minutes before arrival at the lab. Capillary blood glucose was tested, and if necessary, carbohydrates in the form of Dex4 tablets (AMG Medical, Montreal, Quebec) were provided to ensure blood glucose concentration was in the appropriate range for the testing condition (i.e., MOD or HI condition). The amount of Dex4 administered was determined by the participant's insulin to carbohydrate ratio and insulin sensitivity factor and was calculated as shown in Figure 1**.** If Dex4 was provided to raise blood glucose concentration, retesting took place every 10 minutes to determine if the appropriate capillary blood glucose level had been reached before starting. Both testing sessions occurred at 5:00 pm (plus or minus one hour), as one author surmised, this is a typical time for exercise for a large portion of the population and therefore mimics a real-life situation (67). Both tests took place in the same phase of the menstrual cycle for female participants (i.e., within the same week).

The exercise was performed at 60% of the participants' predetermined VO_{2peak} for 45 minutes. Cadence remained at 80 RPM for the entire session. After 10, 25, and 35 minutes, oxygen consumption was measured by indirect calorimetry for five minutes to ensure the resistance was correct. Caloric expenditure and non-protein fuel oxidation were estimated from indirect calorimetry (68) by the same software used in the maximal test. If VO_2 was too high, resistance weights were removed from the bike (to decrease workload) in the form of 100 g weights;

similarly, if VO_2 was too low, resistance was added to the bike to increase workload. The resistance that was used in the first session was used in the second session and adjusted if necessary (i.e., when VO_2 was over or under their 60% value by more than 5 mL/kg/min). Capillary blood glucose readings, heart rate, and ratings of perceived exertion (RPE) were recorded every five minutes during the exercise sessions.

Using a participant's insulin to carbohydrate ratio (ICR) and insulin sensitivity factor (ISF; how many mmol/L 1 unit of insulin decreases blood glucose concentration), we determined how many grams of carbohydrate would raise blood glucose levels by one mmol/L.

$$\frac{\text{Carbohydrates}}{\text{Insulin Unit}} \quad \frac{\text{Insulin Unit}}{\text{BG}} = \frac{\text{Carbohydrates (g)}}{\cancel{\text{1 unit}}} \quad \frac{\cancel{\text{1 unit}}}{\frac{\text{mmol}}{\text{L}}}$$

$$= \text{Carbohydrates to raise BG by 1 mmol/L}$$

For example:
Participant A has an ICR of 12 g/1 unit and an ISF of 1 unit/3 mmol/L

$$\frac{12\text{ g}}{1\text{ unit}} \quad \frac{1\text{ unit}}{3\text{ mmol/L}}$$

$$= \frac{12\text{ g}}{\cancel{1\text{ unit}}} \quad \frac{\cancel{1\text{ unit}}}{3\text{ mmol/L}}$$

$$= \frac{12\text{ g}}{3\text{ mmol/L}}$$

$$= \frac{4\text{ g}}{1\text{ mmol/L}}$$

Participant A will need 4 g of carbohydrate to raise their blood glucose level by one mmol/L.

Figure 1: Carbohydrates Required to Raise Blood Glucose Levels by 1 mmol/L BG=blood glucose

During the HI session, a ketone test was performed via a capillary blood sample using a handheld blood ketone monitor (Freestyle Precision Neo, Abbott Laboratories) if capillary blood glucose concentration was above 16.0 mmol/L. If ketones were measured at ≥1.5 mmol/L, the exercise was stopped.

If capillary blood glucose concentration dropped below 6.0 mmol/L during the MOD session, below 11.0 mmol/L in the HI session, were within one point of being out of the blood glucose range for the session, or were dropping after every two blood glucose checks (every 10 minutes), carbohydrates in the form of Dex4 tablets were supplied to maintain blood glucose

levels. Dex4 tablets were also administered if capillary blood glucose concentration was found to be decreasing after every two capillary blood glucose checks (i.e., every ten minutes). If capillary blood glucose concentration fell below 4.0 mmol/L in any session, the exercise was terminated, and the participant was provided with Dex4 tablets according to their specific ratio (calculated as seen in Figure 1). Capillary blood glucose was then checked after 10 minutes until it measured at or above 6.0 mmol/L. An exercise session that required termination due to low capillary glucose levels was considered valid if the participant completed more than two thirds (i.e., 30 minutes or more) of the session.

After exercise, participants recovered in the lab in a seated position for 60 minutes, with capillary blood glucose tests performed at 0, 15, 30 and 60 minutes post-exercise to determine if capillary glucose concentration was at a safe level to go home (i.e., at 5.0 mmol/L or above, following the clinical driving guidelines provided by Diabetes Canada) (69). If capillary glucose concentration was too low, Dex4 tablets were provided, and capillary blood glucose levels rechecked every ten minutes until they were at 5.0 mmol/L or above before leaving. Participants were reminded to keep the timing and type of meals and food as consistent as possible and to record all food and insulin dosages in the app or paper food log. The next exercise session was scheduled for later the same week, after 72 hours of recovery.

3.4 Outcomes of Interest

We investigated the amount of time spent in hypoglycemia in the 12 hours post exercise in two blocks, from 6:00 pm to 12:00 am, and 12:00 am to 6:00 am, as measured by CGM. Hypoglycemia was defined as a CGM glucose value <3.9 mmol/L that was sustained for 15 consecutive minutes (i.e., three CGM recordings) or more (70). We also looked at the time spent in range (3.9 mmol/L to ≤10.0 mmol/L) and hyperglycemia (≥10.1 mmol/L) (70) in the same 12

hours post exercise. We calculated the coefficient of variation to demonstrate the blood glucose variability, as higher values are related to an increased likelihood of hypoglycemia occurring (71). We also calculated differences in the 12-hour post-exercise kilocalorie (kcal) consumption (including total calories, as well as percent carbohydrate, protein, and fat).

3.5 Statistical Analysis

All analyses were completed with GraphPad Prism Software (version 8.4.2, GraphPad Software Inc., San Diego, CA, USA) and Microsoft Excel. The analysis of post-exercise CGM interstitial glucose concentrations were conducted according to a 2 X 2 repeated measures factorial ANOVA. This analysis considered the effects of the two glucose concentrations during exercise (MOD vs. HI), time (6 pm-12 am vs. 12 am-6 am), and their interactions. CGM variables included mean interstitial glucose and glucose variability (coefficient of variation). We also looked at the percentage of time (in minutes) spent in hyperglycemia (≥10.1 mmol/L), hypoglycemia (<3.9 mmol/L), and TIR (3.9 mmol/L to 10.0 mmol/L) post-exercise (70). Differences in post-exercise kilocalorie (kcal) consumption (including total calories, as well as percent carbohydrate, protein, and fat) were compared using a paired t-test when possible (e.g., when participants recorded food intake for that time). We compared the amount of time elapsed since the last meal before arriving at the lab, as well as the time elapsed since the last insulin bolus using a paired t-test as well as descriptive statistics.

Data were examined for normality using the Shapiro-Wilk test, and this was the case for all distributions except hypoglycemia ($p<0.0001$) and the MOD 12 am to 6 am timeslot for the time in hyperglycemia ($p=0.03$) and TIR ($p=0.02$). An ANOVA was completed on all normal data for the HI session. An ANOVA was completed on the MOD data as well, as ANOVA is robust to minor violations in normality (72). ANOVA was not completed time in hypoglycemia. Differences

between conditions or time points were considered statistically significant when $p<0.05$. Data were presented as mean ± standard deviation unless otherwise stated.

Chapter 4: Results

Fourteen participants completed the protocol; one participant was excluded for extreme bouts of hypoglycemia preceding exercise days and two others for failed CGM recordings. No participants dropped out of the study after starting the protocol. No session required the use of the ketone meter and associated protocol. Hypoglycemia during exercise requiring session termination occurred twice in two different participants during the study. One participant completed 38 minutes of exercise and was included in the analysis. Another participant completed 20 minutes of exercise; the visit was not included in the analysis, and the session was rescheduled for another day. Two participants required a lowering of resistance for their VO_2 to match 60% of their VO_{2peak} during the second exercise session.

Table 6: Participant Characteristics (n=11)

	Female (n=8)	Male (n=3)	(n=11)
Diabetes duration (years)	16 ± 7	8 ± 6	14 ± 7
A1C (%)	7.8 ± 0.8	7.7 ± 0.9	7.7 ± 0.8
VO_{2Peak} (mL/kg/min)	37.2 ± 7.0	41.2 ± 10.6	38.3 ± 7.8
Age (years)	31 ± 8	26 ± 8	30 ± 8
BMI (kg/m^2)	25.4 ± 2.0	26.2 ± 2.4	25.6 ± 2.1
Pump therapy	7	1	8
MDI therapy	1	2	3
Real time CGM (RT-CGM) use	4	0	4
Flash glucose monitor use	3	1	4

BMI=body mass index, MDI=multiple daily injections

Eleven participants (eight females, three males) with complete data were included in the analysis. All participants were using rapid acting insulin analogues either in their insulin pump for all their insulin, or for their insulin meal boluses or blood glucose corrections if using MDI. Two participants using MDI used insulin degludec for their basal insulin, and one used insulin glargine.

The mean age of participants was 30 ± 8 years, A1C 7.7 ± 0.8%, and diabetes duration 14 ± 7 years. Participant characteristics can be found in Table 6. Mean capillary glucose concentrations were statistically different between MOD and HI sessions pre-exercise, during exercise, and post exercise (as seen in Table 7). The mean respiratory exchange ratios (RER) were not different between sessions (p=0.78), and their mean values, as seen in Table 8, suggest participants were using mainly carbohydrates (67%) versus fats (33%) for fuel (68). Other intensity measures taken during exercise can be found in Table 8.

Table 7: Pre, During and Post-Exercise Capillary Blood Glucose Values

	MOD session	HI session	p value
Pre-exercise capillary blood glucose (mmol/L)	10.8 ± 1.7	14.5 ± 1.9	<0.001
Exercise capillary blood glucose (mmol/L)	8.5 ± 1.4	12.0 ± 1.8	<0.001
*Post-exercise capillary blood glucose (mmol/L)	9.9 ± 1.6	12.0 ± 1.6	0.006

MOD Session = Target blood glucose between 8-10 mmol/L, HI Session = Target blood glucose between 12-14 mmol/L. *Post-exercise capillary blood glucose values are the mean of four blood glucose tests taken over the hour of rest.

Table 8: Comparison of Exercise Intensities in Both Exercise Sessions

	MOD session	HI session	p value
RER	0.91 ± 0.04	0.91 ± 0.04	0.78
VO_2 (mL/kg/min)	23.5 ± 4.3	23.8 ± 4.7	0.48
VO_2 (% of VO_{2peak})	61.7 ± 4.3	62.1 ± 4.3	0.67
Heart Rate (BPM)	151 ± 13	152 ± 17	0.48
RPE	12 ± 1	13 ± 1	0.06

MOD Session = Target blood glucose concentration between 8-10 mmol/L, HI Session = Target blood glucose concentration between 12-14 mmol/L, RER = respiratory exchange ratio, VO_2 = oxygen consumption, BPM =beats per minute, RPE =ratings of perceived exertion

The amount of time in hypoglycemia in both conditions in the 12 hours post exercise was not normally distributed, and episodes were infrequent. In total, hypoglycemia occurred in two participants, with one participant experiencing hypoglycemia twice (once following each session). After the MOD session, there was one hypoglycemia episode (45 minutes in duration), and after the HI session, there were two episodes of hypoglycemia (35 and 65 minutes). One participant was missing seven glucose recordings from the CGM but had an appropriate signal from the sensor (i.e., ISIG values >15). EasyGV enabled workbook (Oxford University, 2010) was used to interpolate these missing data. A summary of CGM data can be found in Table 9. The CGM used in our study has a maximum recording value of 22.2 mmol/L. One participant had a 75-minute episode after the HI session that was recorded at 22.2 mmol/L and could have been higher. We

treated the data as 22.2 mmol/L, and it could have impacted mean glucose values if that were not precise.

Table 9: Statistical Analysis of CGM Interstitial Glucose Values 12 hours Post-Exercise

	MOD 6 pm TO 12 am	MOD 12 am TO 6 am	HI 6 pm TO 12 am	HI 12 am TO 6 am	Main effect of exercise BG	Main effect of time	Two-way interaction
Interstitial glucose (mmol/L)	8.6 [7.3-9.6]	8.6 [6.2-9.8]	10.3 [6.5-12.7]	9.3 [6.1-12.9]	p=0.03	p=0.48	p=0.67
Time in hypoglycemia (%)	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	n/a*	n/a*	n/a*
Time in range (%)	72 [64-92]	82 [53-100]	38 [31-60]	73 [32-85]	p<0.01	p=0.71	p=0.37
Time in hyperglycemia (%)	26 [8-36]	18 [0-47]	53 [22-69]	27 [15-68]	p<0.01	p=0.88	p=0.50
Coefficient of variation (%)	21 [13-25]	16 [12-24]	23 [17-43]	25 [17-31]	p<0.01	p=0.28	p=0.91

Data presented as median [interquartile range], hypoglycemia defined as <3.9 mmol/L, time in range defined as 3.9-10.0 mmol/L, hyperglycemia ≥10.1 mmol/L, MOD = blood glucose target 8.0-10.0 mmol/L, HI = blood glucose target 12.0-14.0 mmol/L, BG = blood glucose,*n/a= not analysed data were not normally distributed and episodes were very infrequent

4.1 Insulin Adjustments

Before the MOD session, only one of the three participants using MDI eliminated their lunchtime insulin bolus, and none decreased their basal insulin. Before the HI session, two of the MDI participants reduced their basal insulin by the recommended 10%. Participants used various approaches to reach either the MOD or HI blood glucose concentration. These approaches can be seen in Table 10. In the MOD session, two participants decreased their insulin bolus for their immediately pre-exercise food (i.e., their lunch or snack, roughly 90 minutes before exercise start time), nine participants decreased their basal rate or dose by various amounts and timings. Insulin adjustments were made 82% of the time before the MOD session and 91% of the time before the HI session.

Table 10: Pre-Exercise Food and Insulin Adjustment Strategies for all Participants (n=11)

MOD session (8.0-10.0 mmol/l)			HI session (12.0-14.0 mmol/l)		
Pre-exercise food increase (% of participants)	Insulin decrease (% of participants)	Both insulin & food adjustments (% of participants)	Pre-exercise food increase (% of participants)	Insulin decrease (% of participants)	Both insulin & food adjustments (% of participants)
27	82	27	36	91	36

Includes both MDI and pump therapy participants. Values calculated by evaluating pre-exercise session questionnaire participants answered upon arrival to the lab.

Insulin reduction strategies for participants using insulin pump therapy can be found in Table 11. On average, participants using insulin pumps reduced insulin by the same percentage ($p=0.09$) before each session, and the timing of basal rate reduction was the same ($p=0.82$). One participant reduced their basal rate on their pump according to their specific exercise insulin reduction protocol and removed their pump completely during exercise for both the MOD and HI sessions. Regarding insulin boluses, although records of units given were available, we do not know if this amount was lower, higher, or at the recommended dosage directly related to their

insulin to carbohydrate ratio at that given time (i.e., if participants adjusted their insulin bolus is unknown). The time elapsed since the last insulin bolus was not different between conditions (p=0.42), and ranged from [presented as median hours (minimum value, maximum value)] 3.7 hours (1.0, 7.5) before the MOD session and 4.3 hours (1.2, 12.5) before the HI session. The amount of insulin on board before exercise was not significantly different between conditions for insulin pump users (n=8, MOD: 2.8 hours ±1.4, HI: 2.6 hours ±1.4, p=0.54), nor was the time since the last insulin bolus for all of our participants (n=11, MOD: 4.1 hours ± 1.8, HI: 4.7 hours ± 3.2, p=0.42). One participant reduced their basal rate for their insulin pump from 8:00 pm to 12:00 am post-exercise after both sessions.

Table 11: Insulin Pump Users Insulin Adjustment Summary (n=8)

	MOD session (8.0-10.0 mmol/l)	HI session (12.0-14.0 mmol/l)	p value
Insulin adjustment timing (Hours before exercise)	2.1 ± 0.5	2.2 ± 1.0	0.82
Insulin adjustment amount (% change)	42.5 ± 14.0	51.3 ± 11.0	0.09

4.2 Dietary Adjustments

There was no significant difference between sessions concerning total calorie intake (p=0.36), as well as the percent of energy intake provided from protein (p=0.65), carbohydrate (p=0.14), or fat (p=0.26) for the 12 hours post-exercise. Values from this analysis can be found in Table 12. Diabetes Canada recommends people with T1D eat 45-65% carbohydrates, 10-35% protein and 20-35% fat in their diet (73). The number of people meeting the Diabetes Canada guidelines, are described in Table 13. There was no significant difference found between the MOD and HI sessions regarding the number of Dex4 tablets provided during exercise (p=0.75). Participants requiring carbohydrates during exercise included 10/11 people in the MOD session

and 9/11 in the HI session. Participants used additional food to achieve their pre-exercise blood glucose level for exercise 27% of the time for the MOD session, and 36% of the time for the HI session. The time elapsed since the last meal was not significantly different between conditions (p=0.54) and ranged from [presented as median hours (minimum value, maximum value)] 2.5 hours (1.3, 5.7) before the MOD session and 2.0 hours (1.2, 5.1) before the HI session.

Table 12: Macronutrient Intake 12 hours Post-Exercise (n=11)

	MOD session	HI session	p value
Carbohydrates (% of total kcal)	42 ± 19	45 ± 11	0.14
Protein (% of total kcal)	25 ± 12	23 ± 7	0.65
Fat (% of total kcal)	33 ± 19	31 ± 15	0.26
Total calories (kcal)	701 ± 508	522 ± 272	0.36

Table 13: Number of Participants Meeting Diabetes Canada Macronutrient Range (n=11)

	MOD session	HI session
Carbohydrate intake meeting guidelines	5	3
Protein intake meeting guidelines	7	7
Fat intake meeting guidelines	4	3

Chapter 5: Discussion

Our research has demonstrated that completing a moderate aerobic exercise in the HI blood glucose range increases the time spent in hyperglycemia and decreases the amount of TIR in the 12 hours post exercise for people with T1D. Unfortunately, we were unable to discern if exercising at a HI or MOD blood glucose concentration is more protective against post-exercise hypoglycemia due to a low frequency of hypoglycemia events in our participants. We did find significant differences in immediate post-exercise blood glucose, conflicting with Riddell et al. (74), which found higher blood glucose at the beginning of exercise corresponded to an increased rate of blood glucose fall (13). Our study is the first to compare blood glucose values 12 hours post exercise with the same exercise modality and intensity, but with different blood glucose ranges during the session.

5.1 Hypoglycemia

Our study found that hypoglycemic events were rare in the post-exercise period, with three episodes in two participants. One participant followed their own insulin adjustment pre-exercise protocol, which included complete removal of their pump for the duration of the exercise and had an episode of hypoglycemia in the 12 hours post exercise, in the 6:00 pm to 12:00 am time slot. This participant had a VO_{2peak} of 48.1 mL/kg/min, which is considered superior for their sex and age (57). We could speculate that this participant's high VO_{2peak} contributed to their hypoglycemia risk and episode. Al Khalifah et al. (75) found an increased aerobic fitness level also increased the risk of hypoglycemia during exercise, with 74% of participants in the "good fitness" group experiencing hypoglycemia compared to 38% of those in the "poor fitness" group. Although this may explain the hypoglycemia episodes of this participant, Al Khalifah et al. (75) only reported hypoglycemia during exercise, included teenagers in their sample, and only recruited people using

insulin pump therapy. Another participant in our study had two incidences of hypoglycemia in the 12 hours post-exercise. This participant reported a variable sleeping schedule, recorded only parts of their food intake, and was using MDI therapy. In their meta-analysis, Fatourechi et al. (76) reported no difference between therapy types (i.e., pump therapy or MDI) regarding nocturnal hypoglycemia (odds ratio 0.82, 95% confidence interval, 0.33, -2.03), and did not include any exercise studies in their analysis. This participant, therefore, was likely at no higher risk of hypoglycemia due to their insulin therapy type, independent of exercise.

A study by Zaharieva et al. (52) had participants complete two 40-minute exercise sessions, one a continuous moderate aerobic exercise session at 40-50% of their $VO_{2max,}$ and compared it with a resistance circuit workout. The authors found, as a secondary outcome, the mean time in hypoglycemia post continuous exercise was higher than what was observed in our study (10% of 12 hours post exercise) (52). However, they excluded participants using MDI, and insulin pumps were suspended entirely at the onset of exercise, not before, which likely increased the amount of hypoglycemia that participants experienced (52). Their exercise sessions either occurred in the late morning or late afternoon, and although they were consistent within participants, it is not stated how many were in each time frame (52). The time of day may be significant, as Gomez et al. (53) found significantly fewer hypoglycemia events when aerobic exercise occurred in the morning. However, when studying resistance exercise, Toghi-Eshghi et. al (48) found no differences with regards to post-exercise hypoglycemia when studying both morning and afternoon exercise sessions. Our protocol consistency of exercise timing (i.e., all sessions in the afternoon) eliminated this potential conflict.

The Gomez et al. (53) study differed from ours in protocol and participant inclusion criteria. Gomez et al. (53) only included those using pump therapy, had standardized pre-exercise

meals, and removed the pump immediately before exercise, keeping it off until 45 minutes post exercise. The structure of exercise sessions in this study was also different, with four 15-minute bouts, with five-minute breaks in between each bout, on a treadmill at a moderate pace (53). The participants' starting blood glucose range would be consistent with our MOD range (6.7 to 11.1 mmol/L), and exercise was stated as a moderate aerobic session, but how moderate intensity was determined was not described. Furthermore, if participants had glucose levels above their prescribed blood glucose range, they were given an insulin bolus as per their correction factor programmed in their pump (53). As insulin sensitivity increases after aerobic exercise (50), this insulin correction bolus likely increased the participant's hypoglycemia risk. In addition, the timing of insulin pump basal adjustment likely was not early enough, (53), because Roy-Fleming et al. (51) find that even an 80% reduction of basal rate 40 minutes prior to a 45-minute cycling exercise session at 60% of VO_2, is insufficient to reduce hypoglycemia during exercise (51). Our participants using insulin pumps were suggested to decrease basal insulin rates by 50% two hours before their exercise start time, and MDI participants to reduce basal insulin by 10% the day of exercise, to avoid hypoglycemia. Further, if participants in our study were above their prescribed range for that session, our protocol called for blood ketone testing. This ketone testing protocol would have allowed us to determine if the exercise was safe to proceed (77). Fortunately, we were not required to use the ketone testing protocol in our study.

Iscoe et al. (78), studied eleven recreationally active people with T1D on rest days, days with continuous moderate exercise (VO_{2peak} ~55%), and days with continuous moderate exercise interspersed with maximal sprints, using CGM monitoring throughout. The exercise sessions in this study were very similar to ours; exercise started at approximately 5:00 pm, used stationary cycling, and lasted for 45 minutes (78). Iscoe et al. (78) did not recommend participants adjust

insulin dose (including no recommendation to reduce basal rate) and found that CGM recordings at bedtime were higher on both types of exercise days; however, participants had episodes of hypoglycemia on sedentary (3/11 participants) and continuous exercise days (5/11 subjects) (78). The lack of basal rate reduction likely increased the amount of hypoglycemia found. Our study provided recommendations aligning with current guidelines (77) to protect participants from potentially fatal hypoglycemia in the overnight hours, while still evaluating common practices of people with T1D and exercise (i.e., starting at higher glucose than recommended, and a lower decrease in basal for MDI participants).

Our study was designed to have participants exercising, as one author suggested, at a time that could mimic a real-life situation (e.g., around 5:00 pm, perhaps after school or work plus or minus one hour) (67). Gomez et al. (53) found that participants experience hypoglycemia after both morning and afternoon treadmill exercise, albeit more (almost double) after the afternoon session. Most of the hypoglycemia they found occurred 15-21 hours post-exercise, so perhaps an increased period for monitoring and analysis in the present study would have increased the amount of hypoglycemia observed (53). However, the window of time our study analysed was chosen because hypoglycemia occurring overnight is dangerous, perhaps fatal, occurring when a participant is sleeping.

Maran et al. (16) compared the effects of afternoon high-intensity exercise versus moderate-intensity cycling on nocturnal hypoglycemia and, similar to the present study, found limited hypoglycemia (two episodes) in their eight male participants after the moderate session. It was not reported if the episodes were in different participants, how long the episodes were, or how hypoglycemia was defined (16). Their work rate (as defined by VO_{2peak}) was lower by 20% in comparison, and exercise time was 15 minutes shorter than ours (16). Our study determined

glycemic cut points according to the International Consensus on Continuous Glucose Monitoring (70) in order to report consistently with current recommendations and research, and our intensity is considered moderate according to the Canadian Society of Exercise Physiology definition of moderate aerobic exercise (79).

5.2 Hyperglycemia

Our study demonstrated a statistically significant difference in time spent in hyperglycemia between HI exercise blood glucose and MOD exercise blood glucose in the 12 hours post exercise. Concurrently, there is a significant difference in the TIR, as seen in Table 9, with less TIR found after the HI exercise session. The mean and standard deviations of blood glucose levels post-exercise show hyperglycemia was prevalent after both the MOD and HI sessions in our study, as seen in Table 9. Hyperglycemia post exercise has also been found in other studies, particularly when high-intensity interval exercise is incorporated (78). Increased time in hyperglycemia after HI exercise blood glucose is an essential discovery for people with T1D. Our study demonstrates that exercising at a higher capillary blood glucose concentration may increase the long-term risks associated with chronic hyperglycemia, such as nephropathy, retinopathy, and nerve damage (80).

The diabetes clinical community recognizes that A1C is an important metric (27), but there is also a shift away from it as a measure of diabetes management. A1C cannot show the range of blood glucose and can be misleading (81). Beck et al. (81) demonstrated in their review article that A1C fails to show the range of glucose and can make it challenging to interpret what adjustments to therapy would be most beneficial (i.e., basal rates, insulin-to-carbohydrate ratio, insulin sensitivity factor). In a different study, Beck et al. (82) demonstrated that an increase of TIR of 10% (just over two hours) could correlate to a decrease in A1C of 0.5%. Therefore, increasing TIR is likely correlated to a decreased risk of diabetes-related complications.

Our research found a significant difference in the coefficient of variation of the exercise sessions, with increased variation values in the HI session (as seen in Table 9). A lower coefficient of variation has been correlated with a lower risk of severe hypoglycemia (83). However, in our participants, we found very few hypoglycemic events (only three, two after the HI session), suggesting the larger variation we found attributing to more hyperglycemia. This finding may suggest to people with T1D, that exercising at MOD capillary blood glucose levels may increase their TIR and decrease their time in hyperglycemia. This discovery could remove a significant barrier (5) to exercise for this population.

5.3 Limitations and Considerations

CGMs are practical tools for use in research as glucose values can be observed without needing a capillary blood sample. They are continually decreasing in size, with recorders or transmitters the size of a thumb, depending on the manufacturer. Professional versions of CGMs can be blinded for research as not to impact therapy decisions by participants. Unfortunately, CGMs have limitations when blood glucose is not within range (34). The CGM used in our study records at a minimum value of 2.2 mmol/L and a maximum value of 22.2 mmol/L. This limit in range could have impacted blood glucose results (and, consequently, our calculations of means and standard deviations). In our study, no CGM values were recorded <2.6 mmol/L, and those recorded at 22.2 mmol/L were considered hyperglycemia.

Keenan et al. (84) found in their Enlite sensor accuracy study, a mean error of <14% with the sensor calibrated retrospectively, as it was in our study. However, this study did not test the system during an exercise condition (84). Taleb et al. (64) tested the Enlite sensor in 17 participants with T1D at rest and two different sessions of 60 minutes of stationary biking (one interval training and the other a continuous moderate session at 60% of $VO_{2peak,}$ with sessions matched for energy

expenditure). The sensors were placed on the abdomen or lower back and were matched to plasma glucose values taken during exercise (64). The authors found a lower accuracy during the exercise period (64); however, they did not look at the post-exercise period and only tested the sensor on day two and day three (64). We took data from days two, three, five, and six, therefore our data were recorded at perhaps a less accurate time of the sensor life (85) as Matuleviciene et al. (85) found the Enlite sensor to be less accurate on days four to six when compared to days one to three. However, the sensor in this study was not explicitly tested during or after exercise (participants were ambulatory, but it was not clear whether or not they were permitted to exercise during the study) (85). Participants in the Matuleviciene et al. (85) study were permitted to see their CGM readings, whereas Taleb et al. (64) did not state whether the CGM was blinded to participants or not. The blinded CGM used in our study was chosen to ensure consistency of behaviour of our participants during the observation period. The break between exercise sessions was selected to avoid the blunted counterregulatory response that occurs after people with T1D have a hypoglycemic episode (86) if one were to occur post-exercise.

It should be noted that over 70% of our participants used either RT-CGM (n=4) or flash glucose monitoring (n=4) as a part of their regular therapy regimen. Flash glucose monitors function like a CGM, with a filament inserted under the skin that stays in place for fourteen days. Flash monitoring systems require a reader (usually a smartphone application or blood glucose monitor), where glucose values and corresponding trending arrows are only displayed when the person "flashes" the reader past the sensor. A randomized control trial conducted in 2016 with 211 people with T1D (110 in the intervention arm) found that time in hypoglycemia was reduced by 38% for those using flash glucose monitoring when compared to capillary blood glucose monitoring (87). In the RT-CGM system, blood glucose values are shown continuously on a

receiver (e.g., smartphone, separate CGM receiver, or directly on the insulin pump screen). If a RT-CGM user's blood glucose drops below a pre-set value (can be chosen by the individual, although no lower than 3.9 mmol/L), the CGM will alarm every five minutes, until their blood glucose reads above their specific threshold. A meta-analysis in 2011 found that RT-CGM use corresponded to reduced median exposure to hypoglycemia by 23% (88). In 2011, Battelino et al. (39) studied 120 people with T1D and randomized them to a RT-CGM group or a blinded CGM group. Participants included ages 10 to 65, using MDI or pump therapy, and had an A1C under 7.5% (39). During the six months of observation, participants either wore a blinded CGM for five days every second week or a RT-CGM continuously for 26 weeks (changing the sensor every five days) (39). The authors counted glucose readings as hypoglycemia if they were ten minutes or more (i.e., they may have had more excursions than our study due to the new recommendations (89) for CGM reporting) (39). Battelino et al. (39) found that the RT-CGM group had a significantly lower amount of time spent in hypoglycemia (defined as <3.5 mmol/L) than the blinded CGM group. Further, the authors found a 41% reduction in time spent in hypoglycemia by the RT-CGM group (39).

Since participants in our study were encouraged and recommended to maintain their diabetes management as per usual, personal RT-CGM use may have increased the amount of TIR. Although there were no reports of hypoglycemia that were not recorded in our CGM tracing in the 12 hours post exercise, treatment due to the trending arrows (and potentially associated alarms) on their RT-CGM or flash monitoring system could have resulted in preventative feeding or insulin reductions; these treatments could have affected our results by reducing the amount of hypoglycemia measured. Since all CGM and flash glucose monitor algorithms are slightly different, a bout of hypoglycemia may have occurred and been caught by their personal CGM or

flash glucose system and missed on the CGM used in this study. This technology use by our participants could help explain why we found so little hypoglycemia post-exercise.

CGMs have also been shown to have higher variability from blood glucose values when acetaminophen is in the interstitial fluid, including the CGM used in our study (43). Basu et al. (43) found that despite keeping blood glucose at approximately 5.0 mmol/L, CGM readings varied from 5.0-22.0 mmol/L in the seven hours following acetaminophen administration. If participants in our study happened to take acetaminophen post exercise, Basu et al.'s (43) research demonstrated this could falsely elevate the CGM readings, therefore confounding our results. Although we did not specifically ask participants to refrain from taking acetaminophen, they were asked to record any additional medications, and we have no records of any being taken.

Our participants were asked to keep detailed records of their food intake and insulin adjustments via self-reported paper logs, in the app matched with the given blood glucose monitor, or some combination of the two. It has been shown that self-reported measures underestimate the amount of food eaten (90). In one study, participants were asked to recall food in the past 24 hours and given a blank paper (versus a questionnaire) and underestimated caloric intake by 30% (90). If our participants were consuming additional food that was not recorded and also inconsistent throughout the study period, it could have confounded our results (i.e., if they ate more on one exercise day compared to the other, the control measures would be invalid). Although standardized diets may have solved this problem, it was not feasible to provide them due to other medical conditions of our participants (e.g., celiac disease, food allergies); however, each participant served as their own control which increases our ability to detect differences between the MOD and HI exercise conditions. From this perspective, not standardizing the food is more likely to represent a

life-like situation and allow our participants to eat what works for them in the nutritional management of their diabetes (which may be different between participants).

Although the same recommendations were given to every participant, the techniques used to get blood glucose in range for the exercise sessions were highly variable. We did not specifically ask what participants did to get blood glucose in the desired range, and although they did fill in food and insulin records, these were largely inconsistent (e.g., the same meal was recorded, but 50% more insulin was given one day versus the next). The time elapsed since the last meal prior to exercise for our participants was variable, ranging from 1.3 to 5.7 hours before the MOD session and 1.2 to 5.1 hours before the HI session. Similarly, the time elapsed since the last insulin bolus was also variable between our participants (ranging from 1.0 to 7.5 hours before MOD and 1.2 to 12.5 hours before for HI). Despite asking participants to keep meal type and timing, as well as insulin dosing, consistent for the study duration, it would be impossible to do so and arrive at the lab with different blood glucose levels. There were no significant differences between HI and MOD sessions for the amount of insulin on board (for insulin pump users, values taken directly from their insulin pump), however without consistency and specifics in records (i.e., four units given; two for meal and two for correction) it is near impossible to ascertain what technique each participant used. Therefore, our study does not shed light on how different techniques to reach specific blood glucose profiles may affect post-exercise blood glucose concentrations. Future research should include very detailed insulin and food records, and ask specific information from participants personally (i.e., through a phone call or in person interview).

Our participant sample was very heterogeneous, including a wide range of activity levels, VO_{2peaks}, therapy regimens, and insulin types, among others. Although this might implicate broad spectrum generalizability, it can preclude us from making specific recommendations regarding

exercise blood glucose concentration and post-exercise glycemia. As Pinsker et al. (54) reported in their survey of 502 people with T1D regarding the management of their diabetes around exercise, people using different diabetes technology (i.e., using a CGM, insulin pump, both, or neither) are already employing different techniques. Participants using diabetes technologies (i.e., an insulin pump, both a CGM and an insulin pump, or a CGM with MDI) were more than twice as likely to report using basal adjustment as a strategy to avoid hypoglycemia when compared to those who use MDI alone (49% vs. 20%) (54).

Our study had more females than males (eight females vs. three males). A recent secondary analysis found that males were at a higher risk of hypoglycemia after resistance exercise (55). These findings regarding sex and resistance exercise may suggest that our results with aerobic exercise may be best when applied to females with T1D, and perhaps males with T1D would benefit from separate recommendations.

5.4 Future Directions

Diabetes technology, including the use of CGMs and flash glucose monitors, has been rapidly developing over the past 20 years. At the time of this study, the CGM used was the best choice as it was blinded to participants and was cost-effective. Since that time, flash glucose monitoring professional systems have become available. One study has shown greater accuracy of the flash glucose monitoring system during rest and exercise than the CGM we used (34), and this flash glucose monitor can still be blinded to participants in its professional format. Additional secondary analyses from other completed exercise studies using either CGM or flash glucose monitoring could also determine if there is an association between exercise blood glucose levels and protection against post-exercise hypoglycemia.

Future research should focus on how exercise blood glucose levels affect post-exercise hypoglycemia in a more specific T1D population (e.g., by sex or technology use). In addition, instead of using carbohydrate supplementation where a time delay must be accounted for, an intravenous glucose clamp could be used. This technique would allow for an exact amount of glucose into the participant's bloodstream and may be more comfortable for participants, as most of the participants anecdotally reported that ingesting dextrose tablets during exercise was unpalatable.

Unfortunately, our study was unable to evaluate if HI exercise blood glucose is more protective against post-exercise hypoglycemia than MOD exercise blood glucose. However, we did demonstrate that completing moderate aerobic exercise in the HI blood glucose range, compared to the MOD blood glucose range, increased the time spent in hyperglycemia and decreased TIR in the 12 hours post exercise. Clinical practitioners working with people with T1D can continue to encourage exercising at a MOD blood glucose range for afternoon aerobic sessions. This advice can help people with T1D that have dysglycemia and exercise concerns (5) feel comfortable, that by exercising at a moderate blood glucose level, they can positively impact their long term health by decreasing risks associated with chronic hyperglycemia.

References

1. Robbins SL, Kumar V. Pathologic basis of disease. 8th ed. / ed. Philadelphia, PA :: Saunders/Elsevier; 2010.
2. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet Diabetes Endocrinol. 2006;368(9529):29-36.
3. Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, et al. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: A cross-sectional multicenter study of 18,028 patients. Diabetes Care. 2015;38(8):1536-43.
4. D'Hooge R, Hellinckx T, Van Laethem C, Stegen S, De Schepper J, Van Aken S, et al. Influence of combined aerobic and resistance training on metabolic control, cardiovascular fitness and quality of life in adolescents with type 1 diabetes: a randomized controlled trial. Clin Rehabil. 2011;25(4):349-59.
5. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care. 2008;31(11):2108-9.
6. 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(11):2065-79.
7. 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(5):377-90.
8. Dube MC, Lavoie C, Weisnagel SJ. Glucose or intermittent high-intensity exercise in glargine/glulisine users with T1DM. Med Sci Sports Exerc. 2013;45(1):3-7.
9. 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(4):669-75.
10. 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(3):537-42.
11. Campbell MD, Walker M, Trenell MI, Stevenson EJ, Turner D, Bracken RM, et al. A low-glycemic index meal and bedtime snack prevents postprandial hyperglycemia and associated rises in inflammatory markers, providing protection from early but not late nocturnal hypoglycemia following evening exercise in type 1 diabetes. Diabetes Care. 2014;37(7):1845-53.
12. Buoite Stella A, Yardley J, Francescato MP, Morrison SA. Fluid intake habits in type 1 diabetes individuals during typical training bouts. Ann Nutr Metab. 2018;73(1):10-8.
13. Riddell MC, Zaharieva DP, Tansey M, Tsalikian E, Admon G, Li Z, et al. Individual glucose responses to prolonged moderate intensity aerobic exercise in adolescents with type 1 diabetes: The higher they start, the harder they fall. Pediatr Diabetes. 2019;20(1):99-106.
14. Reddy R, El Youssef J, Winters-Stone K, Branigan D, Leitschuh J, Castle J, et al. The effect of exercise on sleep in adults with type 1 diabetes. Diabetes Obes Metab. 2018;20(2):443-7.
15. Franc S, Daoudi A, Pochat A, Petit MH, Randazzo C, Petit C, et al. Insulin-based strategies to prevent hypoglycaemia during and after exercise in adult patients with type 1

diabetes on pump therapy: the DIABRASPORT randomized study. Diabetes Obes Metab. 2015;17(12):1150-7.
16. Maran A, Pavan P, Bonsembiante B, Brugin E, Ermolao A, Avogaro A, et al. Continuous glucose monitoring reveals delayed nocturnal hypoglycemia after intermittent high-intensity exercise in nontrained patients with type 1 diabetes. Diabetes Technol Ther. 2010;12(10):763-8.
17. Punthakee Z, Goldenberg R, Katz P. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can J Diabetes. 2018;42:S10-S5.
18. Alberti KGMM, Zimmet, P.F. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic Med. 1998;15(7):539-53.
19. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract.128:40-50.
20. Statistics Canada. Health fact sheets: diabetes, 2016. In: Canada S, editor. 2017. p. 3-6.
21. Wherrett DK, Ho J, Huot C, Legault L, Nakhla M, Rosolowsky E. Type 1 diabetes in children and adolescents. Can J Diabetes. 2018;42 Suppl 1:S234-S46.
22. Bach J. Insulin-dependent diabetes mellitus as an autoimmune disease. Endocr Rev. 1994;15(4).
23. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. N Engl J Med. 2000;342(5):301-7.
24. Olmos P, A'Hern R, Heaton DA, Millward BA, Risley D, Pyke DA, et al. The significance of the concordance rate for type 1 (insulin-dependent) diabetes in identical twins. Diabetologia. 1988;31(10):747-50.
25. Nishimoto H, Kikutani H, Yamamura K, Kishimoto T. Prevention of autoimmune insulitis by expression of I-E molecules in NOD mice. Nature. 1987;328(6129):432-4.
26. Rastogi Kalyani R. Diagnosis and classification of diabetes: Johns Hopkins Diabetes Guide; 2017 [Available from: https://www.unboundmedicine.com/medline/view/Johns_Hopkins_Diabetes_Guide/547038/all/Diagnosis_and_Classification_of_Diabetes.
27. McGibbon A, Adams L, Ingersoll K, Kader T, Tugwell B. Glycemic management in adults with type 1 diabetes. Can J Diabetes. 2018;42:S80-S7.
28. Al-Adra DP, Gill RS, Imes S, O'Gorman D, Kin T, Axford SJ, et al. Single-donor islet transplantation and long-term insulin independence in select patients with type 1 diabetes mellitus. Transplantation. 2014;98(9):1007-12.
29. Barton FB, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B, et al. Improvement in Outcomes of Clinical Islet Transplantation: 1999-2010. Diabetes Care. 2012;35(7):1436-45.
30. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325.
31. 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(1):84-8.

32. Rossetti P, Bondia J, Vehi J, Fanelli CG. Estimating plasma glucose from interstitial glucose: the issue of calibration algorithms in commercial continuous glucose monitoring devices. Sensors. 2010;10(12):10936-52.
33. Bally L, Zueger T, Pasi N, Carlos C, Paganini D, Stettler C. Accuracy of continuous glucose monitoring during differing exercise conditions. Diabetes Res Clin Pract. 2016;112:1-5.
34. Aberer F, Hajnsek M, Rumpler M, Zenz S, Baumann PM, Elsayed H, et al. Evaluation of subcutaneous glucose monitoring systems under routine environmental conditions in patients with type 1 diabetes. Diabetes Obes Metab. 2017;19(7):1051-5.
35. Yardley JE, Sigal RJ, Kenny GP, Riddell MC, Lovblom LE, Perkins BA. Point accuracy of interstitial continuous glucose monitoring during exercise in type 1 diabetes. Diabetes Technol Ther. 2013;15(1):46-9.
36. Radermecker RP, Fayolle C, Brun JF, Bringer J, Renard E. Accuracy assessment of online glucose monitoring by a subcutaneous enzymatic glucose sensor during exercise in patients with type 1 diabetes treated by continuous subcutaneous insulin infusion. Diabetes Metab. 2013;39(3):258-62.
37. Moser O, Mader JK, Tschakert G, Mueller A, Groeschl W, Pieber TR, et al. Accuracy of continuous glucose monitoring (CGM) during continuous and high-intensity interval exercise in patients with type 1 diabetes mellitus. Nutrients. 2016;8(8).
38. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections. JAMA. 2017;317(4):371.
39. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011;34(4):795-800.
40. Tamborlane WV, Beck, R. W., Bode, B. W., Buckingham, B., Chase, P., Clemons, R., et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008;359(14):1464-76.
41. DeSalvo DJ, Miller KM, Hermann JM, Maahs DM, Hofer SE, Clements MA, et al. Continuous glucose monitoring and glycemic control among youth with type 1 diabetes: International comparison from the T1D exchange and DPV initiative. Pediatr Diabetes. 2018;19(7):1271-5.
42. Wang J. Electrochemical glucose biosensors. Chem Rev. 2008;108(2):814-25.
43. Basu A, Veettil S, Dyer R, Peyser T, Basu R. Direct evidence of acetaminophen interference with subcutaneous glucose sensing in humans: A pilot study. Diabetes Technol Ther. 2016;18 Suppl 2:S243-7.
44. Krzentowski G, Pirnay F, Pallikarakis N, Luyckx AS, Lacroix M, Mosora F, et al. Glucose utilization during exercise in normal and diabetic subjects: The role of insulin. Diabetes. 1981;30(12):983-9.
45. Nordlie RC, Foster JD, Lange AJ. Regulation of glucose production by the liver. Annu Rev Nutr. 1999;19:379-406.
46. Zinman B, Murray FT, Vranic M, Albisser AM, Leibel BS, McClean P, et al. Glucoregulation during moderate exercise in insulin treated diabetics. J Clin Endocrinol Metab. 1977;45(4):641-52.
47. MacDonald MJ. Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. Diabetes care. 1987;10(5):584-8.

48. Toghi-Eshghi SR, Yardley JE. Morning (fasting) vs afternoon resistance exercise in individuals with type 1 diabetes: A randomized crossover study. J Clin Endocrinol Metab. 2019;104(11):5217-24.
49. West DJ, Stephens JW, Bain SC, Kilduff LP, Luzio S, Still R, et al. A combined insulin reduction and carbohydrate feeding strategy 30 min before running best preserves blood glucose concentration after exercise through improved fuel oxidation in type 1 diabetes mellitus. Journal of Sports Sciences. 2011;29(3):279-89.
50. Bird SR, Hawley JA. Update on the effects of physical activity on insulin sensitivity in humans. Br J Sports Med. 2017;2(1):e000143.
51. Roy-Fleming A, Taleb N, Messier V, Suppere C, Cameli C, Elbekri S, et al. Timing of insulin basal rate reduction to reduce hypoglycemia during late post-prandial exercise in adults with type 1 diabetes using insulin pump therapy: A randomized crossover trial. Diabetes Metab. 2019;45(3):294-300.
52. Zaharieva D, Yavelberg L, Jamnik V, Cinar A, Turksoy K, Riddell MC. The Effects of Basal Insulin Suspension at the Start of Exercise on Blood Glucose Levels During Continuous Versus Circuit-Based Exercise in Individuals with Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion. Diabetes Technol Ther. 2017;19(6):370-8.
53. Gomez AM, Gomez C, Aschner P, Veloza A, Muñoz O, Rubio C, et al. Effects of performing morning versus afternoon exercise on glycemic control and hypoglycemia frequency in type 1 diabetes patients on sensor-augmented insulin pump therapy. J Diabetes Sci Technol. 2015;9(3):619-24.
54. Pinsker JE, Kraus A, Gianferante D, Schoenberg BE, Singh SK, Ortiz H, et al. Techniques for exercise preparation and management in adults with type 1 diabetes. Can J Diabetes. 2016;40(6):503-8.
55. Brockman NK, Sigal RJ, Kenny GP, Riddell MC, Perkins BA, Yardley JE. Sex-related differences in blood glucose responses to resistance exercise in adults with type 1 diabetes: A secondary data analysis. Can J Diabetes. 2020;44(3):267-73.e1.
56. 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(3):537-42.
57. Exercise prescription for individuals with metabolic isease and cardiovascular disease risk factors. In: Riebe D, editor. ACSM guidelines for exercise testing and prescription. 10 ed. Philadelphia: Wolters Kluwer; 2018. p. 268-76.
58. Plotnikoff RC, Taylor LM, Wilson PM, Courneya KS, Sigal RJ, Birkett N, et al. Factors associated with physical activity in Canadian adults with diabetes. Med Sci Sports Exerc. 2006;38(8):1526-34.
59. Aronson R, Brown RE, Li A, Riddell MC. Optimal insulin correction factor in post-high-intensity exercise hyperglycemia in adults with type 1 diabetes: The FIT study. Diabetes Care. 2019;42(1):10-6.
60. Turner D, Gray BJ, Luzio S, Dunseath G, Bain SC, Hanley S, et al. Similar magnitude of post-exercise hyperglycemia despite manipulating resistance exercise intensity in type 1 diabetes individuals. Scand J Med Sci Sports. 2016;26(4):404-12.
61. Turner D, Luzio S, Kilduff LP, Gray BJ, Dunseath G, Bain SC, et al. Reductions in resistance exercise-induced hyperglycaemic episodes are associated with circulating interleukin-6 in Type 1 diabetes. Diabet Med. 2014;31(8):1009-13.

62. Godin G. The Godin-Shephard leisure-time physical activity questionnaire. Hlth Fitn J Can. 2011;4(1):18-22.
63. Ferguson B. ACSM's guidelines for exercise testing and prescription 9th Ed. 2014. The Journal of the Canadian Chiropractic Association. 2014;58(3):328.
64. Taleb N, Emami A, Suppere C, Messier V, Legault L, Chiasson JL, et al. Comparison of two continuous glucose monitoring systems, Dexcom G4 Platinum and Medtronic Paradigm Veo Enlite system, at rest and during exercise. Diabetes Technol Ther. 2016;18(9):561-7.
65. Bailey TS, Ahmann A, Brazg R, Christiansen M, Garg S, Watkins E, et al. Accuracy and acceptability of the 6-day Enlite continuous subcutaneous glucose sensor. Diabetes Technol Ther. 2014;16(5):277-83.
66. McAuley SA, Horsburgh JC, Ward GM, La Gerche A, Gooley JL, Jenkins AJ, et al. Insulin pump basal adjustment for exercise in type 1 diabetes: a randomised crossover study. Diabetologia. 2016;59(8):1636-44.
67. Lascar N, Kennedy A, Hancock B, Jenkins D, Andrews RC, Greenfield S, et al. Attitudes and barriers to exercise in adults with type 1 diabetes (T1DM) and how best to address them: a qualitative study. PLoS One. 2014;9(9):e108019.
68. Powers SK, Howley ET. Exercise physiology: Theory and application to fitness and performance: McGraw-Hill New York, NY; 2007.
69. Houlden RL, Berard L, Lakoff JM, Woo V, Yale JF. Diabetes and driving. Can J Diabetes. 2018;42 Suppl 1:S150-S3.
70. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, Devries JH, et al. International consensus on use of continuous glucose monitoring. Diabetes Care. 2017;40(12):1631-40.
71. DeVries JH. Glucose variability: where it is important and how to measure it. Diabetes. 2013;62(5):1405-8.
72. Lund Research Ltd. Laerd Statistics: Two-way ANOVA in SPSS statistics: Lund Research Ltd; 2018 [Available from: https://statistics.laerd.com/spss-tutorials/two-way-anova-using-spss-statistics.php.
73. Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. Nutrition therapy. Can J Diabetes. 2018;42 Suppl 1:S64-S79.
74. Riddell MC, Zaharieva, D.P., Tnasey, M., Tsalikian, E, Admon, G., Li, Z.,et al. Individual glucose responses to prolonged moderate intensity aerobic exercise in adolescents with type 1 diabetes: The higher they start, the harder they fall. Pediatr Diabetes. 2018:99-106.
75. Al Khalifah RA, Suppère C, Haidar A, Rabasa-Lhoret R, Ladouceur M, Legault L. Association of aerobic fitness level with exercise-induced hypoglycaemia in type 1 diabetes. Diabetic Med. 2016;33(12):1686-90.
76. Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Hypoglycemia with intensive insulin therapy: A systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab. 2009;94(3):729-40.
77. Sigal RJ, Armstrong MJ, Bacon SL, Boulé NG, Dasgupta K, Kenny GP, et al. Physical activity and diabetes. Can J Diabetes. 2018;42:S54-S63.
78. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. Diabet Med. 2011;28(7):824-32.

79. Canadian Society for Exercise Physiology. Canadian 24-hour movement guidelines: Glossary of terms Canada2017 [Available from: https://csep.ca/en/guidelines/glossary-2017.
80. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.
81. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA1c alone to assess glycemic control can be misleading. Diabetes Care. 2017;40(8):994-9.
82. Beck RW, Bergenstal RM, Cheng P, Kollman C, Carlson AL, Johnson ML, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. J Diabetes Sci Technol. 2019;13(4):614-26.
83. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial--revisited. Diabetes. 2008;57(4):995-1001.
84. Keenan DB, Mastrototaro JJ, Zisser H, Cooper KA, Raghavendhar G, Lee SW, et al. Accuracy of the Enlite 6-day glucose sensor with guardian and Veo calibration algorithms. Diabetes Technol Ther. 2012;14(3):225-31.
85. Matuleviciene V, Joseph JI, Andelin M, Hirsch IB, Attvall S, Pivodic A, et al. A clinical trial of the accuracy and treatment experience of the Dexcom G4 sensor (Dexcom G4 system) and Enlite sensor (guardian REAL-time system) tested simultaneously in ambulatory patients with type 1 diabetes. Diabetes Technol Ther. 2014;16(11):759-67.
86. Galassetti P, Tate D, Neill RA, Morrey S, Wasserman DH, Davis SN. Effect of antecedent hypoglycemia on counterregulatory responses to subsequent euglycemic exercise in type 1 diabetes. Diabetes. 2003;52(7):1761-9.
87. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet Diabetes Endocrinol. 2016;388(10057):2254-63.
88. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ. 2011;343:d3805.
89. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593-603.
90. Acheson KJ, Campbell IT, Edholm OG, Miller DS, Stock MJ. The measurement of food and energy intake in man—an evaluation of some techniques. Am J Clin Nutr. 1980;33(5):1147-54.

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Appendix C: Informed Consent Form

Information Sheet and Consent Form

Title of Research Study: **Electrolyte Balance during Exercise in Type 1 Diabetes**

Principal Investigator: **Jane Yardley, Ph.D. (jeyardle@ualberta.ca)**

Co-Investigator: **Normand Boulé, PhD (nboule@ualberta.ca)**

Heather Hinz, B. Kin (hscherer@ualberta.ca)

Background. You are being asked to take part in a research study on the effects of blood glucose levels during aerobic exercise (stationary biking) on the balance of water and electrolytes (minerals like sodium, potassium, and calcium) in your body. Exercise is recommended for people with type 1 diabetes, and we don't know much about how blood glucose levels affect the water and electrolyte levels of the exerciser. Since most type 1 diabetes patients who exercise do so at blood glucose levels of 12-14 mmol/L, and the current recommendation is 7.0-10.0 mmol/L, we want to see if your kidneys handle water and electrolytes differently at the higher blood glucose concentrations. Studies have been done on how people with T1D process these electrolytes in their kidneys; however, there are no studies done during exercise.

Purpose. This study is looking at how exercise affects the electrolytes in your body when exercising at two different blood glucose levels (between 8 and 10 mmol/L and between 12 and 14 mmol/L).

Procedures. The total time commitment for the duration of the study is expected to be about 2 weeks depending on your availability. During this time, we will ask you to come to the University of Alberta ~4 times, for about ~7 hours altogether.

Step 1. Determining if you are eligible (Baseline visits)

- **Initial Meeting.** You will come to the Physical Activity and Diabetes Laboratory (**PADL**) on the University of Alberta's main campus or the Exercise Physiology Laboratory at the

Augustana campus. We will address any questions/concerns you may have and ask you to fill out this consent form. You will also fill out questionnaires to check your eligibility. These include information about your health and medications, your ability to exercise, and your regular activities. A drop of blood will be taken to measure your A_{1c}, which reflects your average blood glucose over the past 3-4 months. Height, weight, and blood pressure will also be measured. This initial meeting will take ~ 1 hour.

- **Exercise Fitness Test.** If your blood pressure and A_{1c} are in the correct range, we will ask you to come to the lab (either **PADL** or Augustana**)** again for some exercise tests or to complete those exercise tests the same day. We will test your aerobic fitness, which involves cycling on a stationary bike with increasing speed and load. We will monitor your heart rate and measure the gases that you are breathing in and out to determine your aerobic capacity. You will probably perform ~20 minutes of exercise, but the visit may take ~1.5 hours with explanation, preparation, and some pre- and post-exercise measures, such as your blood pressure.

Step 2. Inserting the continuous glucose monitor (CGM).

On a day preceding the testing days (after the familiarization sessions), we will ask you to come to the lab for a CGM sensor insertion. A CGM is a small device (~ 2 x 3 cm) that measures your blood glucose every 5 minutes for up to 6 days. A small sensor (~1 cm long, ~0.1 cm wide) will be inserted under the skin of your abdomen by a person trained by the CGM manufacturer. The CGM will then be attached to the sensor. The tape will be placed over the CGM to hold it in place. You may feel a slight pinch with the sensor insertion, but most often, the only sensation is that of light pressure on the skin from the inserter. Inserting the sensor sometimes causes minor bleeding, and there is a small risk of infection. The risk of infection will be minimized with proper procedures, including the disinfection of the area by alcohol swabs. The CGM insertion will take no more than 5 minutes.

Step 3. Testing days.

We will ask you to take part in two different testing sessions which involve aerobic exercise. The first session will take place the day after the CGM sensor is inserted (day 2 of sensor wear). The second session will take place on day 4 of sensor wear. Alternately, days 3 and 5 may also be used. Each of these sessions will be testing aerobic exercise and differing glucose levels. The order in which the sessions are completed will be decided by flipping a coin.

- **Exercise testing session.** Upon arrival for the first session, we will check your blood glucose, and may give you some Dex4 tablets to eat. We will ask you to follow the Diabetes Canada guidelines for adjusting insulin dosage before exercise. If you are not familiar with these guidelines, we will either provide you with a copy of them or provide you with a link to where they are found on the Diabetes Canada website. You will wear a heart rate monitor throughout exercise. The aerobic exercise will take about 45 minutes, and you will be asked to stay for another hour after you have finished exercise. An appropriately trained person will take a blood sample from you before exercise. Samples will also be taken at the end of exercise, and

one hour after the end of exercise. We will also ask you to provide a urine sample before and after your session. This will allow us to measure the changes in your blood glucose, your hydration levels and some of your body's electrolytes. A catheter will be inserted into your arm or hand so we can draw blood during your exercise for glucose readings. This procedure will be followed on two separate days (separated by at least 48 hours) during the same week to test during both the 7.0-10.0 mmol/L state and the 12.0-14.0 mmol/L state.

After leaving the lab. On the first day of CGM wear, you will record your food intake. Then on subsequent days, you will repeat the same dietary intake. Glucerna bars will be provided to you so that this part of your daily food intake can be the same every day. In this way, we know that changes in blood glucose (if any) are due to exercise, not due to changes in your diet. Also, we would like you to match your insulin dosage as closely as possible each day of CGM sensor wear. We will request that you avoid exercise and wear a step counter while wearing the CGM. We will also ask you to measure your blood glucose before each meal and bed. These measurements are necessary to calibrate the CGM. The blood glucose meter provided to you for use during the study has an application ("app") that is convenient to record glucose, exercise and food data. Instead of writing data on paper, it can send the data from your meter to a website managed by OneTouch, if you choose. You can opt in to share your data with the Study Team for the duration. If you decide to use the app, we will email you a detailed User Manual for your convenience, or you can access it here: https://www.onetouch.ca/sites/onetouch_ca/files/onetouchrevealapp_ios_usermanual_en_ca.pdf (Apple Devices) or here: https://www.onetouch.ca/sites/onetouch_ca/files/onetouchrevealapp_android_usermanual_en_ca_0.pdf for Android devices. Using the app for the study is entirely optional.

Possible Benefit. We hope that this study will help us better understand how to hydrate during exercise when you have T1D.We will provide you with information on your current level of physical fitness and your CGM results. You are not otherwise expected to get benefits from participating in this research study.

Possible Risks. It is possible that you experience light headedness, muscle cramps, fatigue, nausea, joint pain, and in rare cases, heart attack from participating in exercise. Personnel certified in CPR will supervise every exercise session to minimize the risks. However, you are free to stop exercising if you feel any discomfort or do not wish to continue exercising.

The CGM sensor inserted in your abdomen may cause bruising and poses a small risk of infection. The risk will be minimized through alcohol cleaning of the insertion area. Adhesive tape that covers the CGM may also cause minor irritation.

Lastly, there is a small possibility that you will experience hypoglycemia during or after exercise. We will monitor your blood glucose levels closely. We will have a rapid-acting source of glucose (Dex-4 tablets) on hand in order to prevent hypoglycemia from occurring. Should you experience significant hypoglycemia during the session, exercise will be stopped. You will be provided with Dex-4 tablets and monitored until blood glucose has returned to a safe level.

Compensation for Injury. If you become ill or injured as a result of being in this study, you will receive necessary medical treatment, at no additional cost to you. By signing this consent form, you are not releasing the investigators, institution or sponsors from their legal and professional responsibilities.

Confidentiality. Any personal information relating to this study will be kept confidential. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your health information is kept private. Study data will be stored in a locked cabinet or in a password protected computer with your name excluded. Data will only be used for research purposes. The access to data is limited to study investigators. Data published as a result of this study will be presented as group data.

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The continuous glucose monitor data will be uploaded to a secure website. It uses a software application called CareLink iPro. This is centralized, web-based software from Medtronic used by health care professionals and researchers to upload, store and analyze glucose readings from patients who have worn a device. No identifying information will be uploaded to this site; only your study ID, blood glucose readings, and logbook information will be uploaded. Medtronic is responsible for hosting and maintaining the CareLink iPro servers, and therefore will have access to the non-identifying information uploaded to the website. Medtronic may also study the uploaded information for purposes of advancing or improving its products, therapies or services for the benefit of future patients.

If you decide to use the app, your data from the blood glucose monitor will be anonymized and only your Study ID, blood glucose readings and logbook data will be uploaded. This web-based software from OneTouch is used by health care professionals and researchers to upload, store and analyze logbook entries from blood glucose monitors. Once your participation in the study is complete, the meter will be disconnected to our system, and we will have no access to further logbook data (including blood glucose readings). OneTouch is responsible for hosting and maintaining the application servers, and therefore will have access to non-identifying information that could be used for population analysis. Once your participation in the study is complete, the meter will be disconnected to our system, and we will have no access to further logbook data (including blood glucose readings). Using the app for the study is entirely optional. If you wish to know more about the app, you can visit https://register.onetouchreveal.ca/privacy/?countryISO=CA&langISO=en_CA&step=0 .

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If you have any concerns or questions, please contact the principal investigator, Jane Yardley (780) 679-1688 (or jeyardle@ualberta.ca) at any time.

Title of Project: Electrolyte Balance during Exercise in Type 1 Diabetes

Principal Investigator	**Phone Number**
Dr. Jane Yardley, PhD	(780)679-1688
Co-Investigator	**Phone Number**
Dr. Normand Boulé, PhD	(780)492-4695

To be completed by the research subjects:

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks of taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your information?	☐	☐
Do you want the investigator(s) to inform your family doctor that you are participating in this research study? If so, give his/her name _____	☐	☐
I agree to take part in this study:	☐	☐

Who explained this study to you? _____

Signature of Research Participant _____

(Print Name) _____

Date: _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date_____

Appendix D: Body Composition Analyzer Protocol

TANITA TBF-300A Operating Instructions

1. Before you begin:
Ensure that individuals are in light clothing, with metal items removed.
Individuals with a pacemaker or other internal electrical medical devices, as well as women that are pregnant should not participate in this test.

2. Press the [ON/OFF] key to turn on the Power
After a momentary automatic display check, the ◄ mark and "0.0" will appear on the LCD. If measuring units need to be changed, do so at this time by pressing the [kg/lb] key. An arrow on the LCD will follow the selection of weighing units. Throughout data entry, mistakes may be corrected by pressing the [CE] key. Follow the flashing arrow on the LCD for proper sequence.

3. Enter Clothes Weight
This function will automatically subtract the chosen amount of clothes weight. Enter Clothes Weight to the first decimal place, or the flashing arrow will not advance.
Example: 2.0kg = Press the [2] [.] [0] keys
4.0lb = Press the [4] [.] [0] keys
Clothes weight can be entered by 0.1kg / 0.2lb increments (TBF-310: 0.2kg / 0.5lb increments). The flashing arrow will now appear next to the MALE Icon, FEMALE Icon, and ATHLETIC on the LCD.

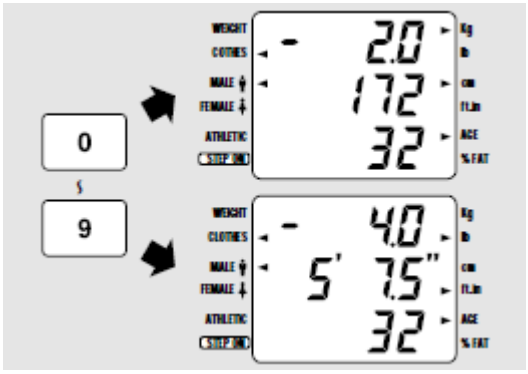
4. Enter Gender and Body Type
Select from one of four body types: Standard Male, Standard Female, Athletic Male, Athletic Female. Athletic consists of individuals aged 17 or more and under the following conditions:

- A person involved in intense physical activity of at least 10 hours/week and who has a resting heart rate of ~60 beats/minute or less.
- Individuals who have been fit for years but currently exercise less than 10 hours/week.
- Tanita's athlete definition does not include "enthusiastic beginners" who are making a real commitment to exercising at least 10 hours/week but whose bodies have not yet changed to require the Athlete mode.

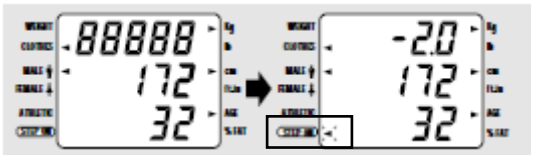
5. Enter Age
Enter age of the subject using two digits. For children under ten years old, first enter [0].

Example: 32 years old = Press the [3] [2] keys
9 years old = Press the [0] [9] keys
Age range is from 7 to 99 years old.
After age is entered, the arrow will automatically advance to [HEIGHT] on the LCD.

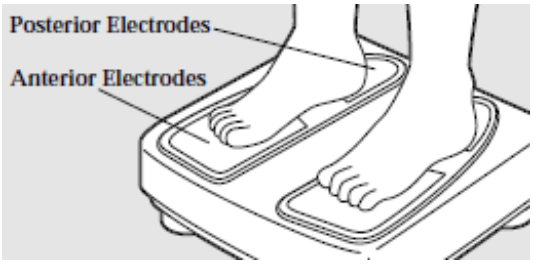
6. Enter Height
Using Centimeters, measurement is made to the First Whole Number.
Example: 172 cm = Press the [1] [7] [2] keys.
Using Feet and Inches, measurement is made to the First Decimal Place by 0.5 inch increments.
Example: 5 ft 7.5 in = Press the [5] [7] [.] [5] keys.
6 ft 0 in = Press the [6] [0] [.] [0] keys.
The range for height is from 90cm (3'0") to 249cm (7'11.5"). When using the lb. mode, height will automatically round up or down to the nearest 0.5 in or whole number.



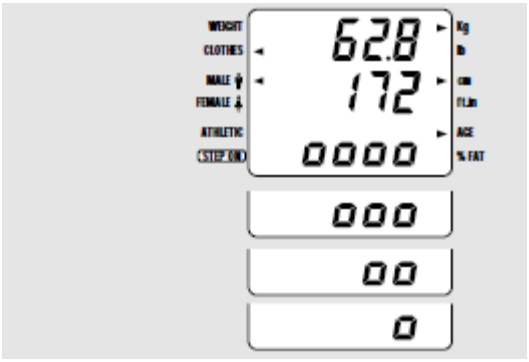
7. Step On
The flashing arrow will appear next to STEP ON after the LCD display "88888".



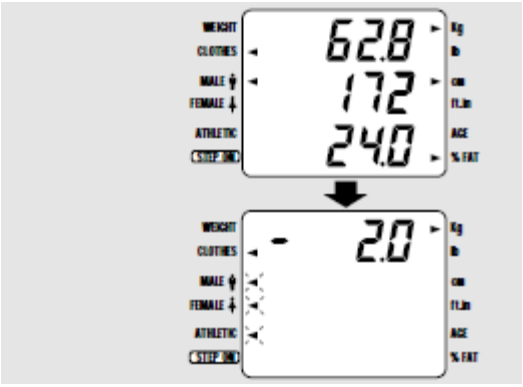
8. Taking Measurement
Step on the weighing platform in bare feet. Make sure heels are placed on the posterior electrodes, and the front part of the feet are in contact with the anterior electrodes.



9. Weight and Impedance Measurement
Weight is displayed on the upper portion of the LCD. After weight stabilizes, impedance measurement is taken. This is denoted by four "bubbles" which appear on the bottom half of the LCD. As the measurement is being taken, the bubbles will begin to disappear one by one.



10. Measurement is Now Complete
Weight and percent body fat will be displayed on the LCD, and detailed results will automatically print out. The LCD will return to the Gender and Body Type screen (Step 3) in about 10 seconds, which allows for convenient screening.



Appendix E: Stadiometer Protocol

Operation Instructions

For Consistent & Accurate Measurements:
Have the patient stand with their back against the Heightronic!". They should have bare feet, heels close together legs straight. Ask the patient to Stand tall, take a deep breath and look straight ahead. Lower the head beam to touch the crown of patient's head and note your measurement.

The Heightronic offers five measurement modes:
1/16: Measurements are displayed in sixteenths of an inch, and black bars just right of the fraction are used to indicate increments above the indicated value. Each bar represents one sixty-fourth of an inch.
1/32: Measurements are displayed in thirty-seconds of an inch, and black bars just right of the fraction are used to indicate increments above the indicated value. Each bar represents one sixty- fourth on an inch.
1/64: Measurements are displayed in sixty-fourths of an inch.
Decimal Inch: Measurements are displayed in inches to the closest one-thousandth inch.
Centimeter: Measurements are displayed in Centimeter to the closest one-hundredth Centimeter.

To convert between Metric (CM) and Inches & Fractions (IN):
Scales with no output capabilities Press the mode key, (IN) **will** be displayed to indicate inch mode and fractions. (CM) **will not** be displayed in centimeter mode. * Scales with output capabilities, Press the mode key, (IN) **will** be displayed for inches and fractions, (CM) **will** be displayed in the centimeter mode.

Digital Stadiometer

Digital Infantometer

Digital Display Unit

In

Appendix F: Case Report Form

ANTHROPOMETRICS
1. Sex: ☐M ☐F
2. Date of birth (dd/mm/yyyy): __ __ / __ __ / __ __ __ __
3. Age (years): ___ ___
4. Participant weight: ___ ___ ___ . ___ Kg Average: ___ ___ ___ ___ ___ . ___ Kg
5. Participant height: ___ ___ ___ . ___ cm Average: ___ ___ ___ ___ ___ ___ . ___ cm
6. Systolic BP (SBP): (1)___ ___ ___mm Hg (2)___ ___ ___mm Hg (3)___ ___ ___mm Hg (4)___ ___ ___mm Hg (5) ___ ___ ___mm Hg **Average SBP: ___mm Hg**
7. Diastolic BP (DBP): (1)___ ___ ___mm Hg (2)___ ___ ___mm Hg (3)___ ___ ___mm Hg (4)___ ___ ___mm Hg (5)___ ___ ___mm Hg **Average DBP: __mm Hg**
8. Resting Heart Rate (HR): (1) ___ ___ ___bpm (2)___ ___ ___bpm (3)___ ___ ___bpm (4)___ ___ ___bpm (5)___ ___ ___bpm **Average HR: ____ bpm**
9. Cuff size:
10. Allergies (list): _____ _____ _____ _____

11. **MEDICATIONS**			
NAME	TYPE	TABS (digits)	DOSAGE (mg)
	☐ Statin ☐ B-blocker ☐ Anti-platelet		

	□ Fibrate □ ARB □ Anti-obesity □ Lipid □ Ca chan. Block □ Birth control □ Ace inhibit □ Other antiHTN □ Daily multivitamin □ Diuretic □ Anti-depressant □ Other:_______________		
NAME	TYPE	TABS (digits)	DOSAGE (mg)
	□ Statin □ B-blocker □ Anti-platelet □ Fibrate □ ARB □ Anti-obesity □ Lipid □ Ca chan. Block □ Birth control □ Ace inhibit □ Other antiHTN □ Daily multivitamin □ Diuretic □ Anti-depressant □ Other:_______________		
NAME	TYPE	TABS (digits)	DOSAGE (mg)
	□ Statin □ B-blocker □ Anti-platelet □ Fibrate □ ARB □ Anti-obesity □ Lipid □ Ca chan. Block □ Birth control □ Ace inhibit □ Other antiHTN □ Daily multivitamin □ Diuretic □ Anti-depressant □ Other:_______________		
NAME	TYPE	TABS (digits)	DOSAGE (mg)
	□ Statin □ B-blocker □ Anti-platelet □ Fibrate □ ARB □ Anti-obesity □ Lipid □ Ca chan. Block □ Birth control □ Ace inhibit □ Other antiHTN □ Daily multivitamin □ Diuretic □ Anti-depressant □ Other:_______________		
NAME	TYPE	TABS (digits)	DOSAGE (mg)

	□ Statin □ B-blocker □ Anti-platelet □ Fibrate □ ARB □ Anti-obesity □ Lipid □ Ca chan. Block □ Birth control □ Ace inhibit □ Other antiHTN □ Daily multivitamin □ Diuretic □ Anti-depressant □ Other:_____		

DIABETES INFORMATION
12. Date of T1D diagnosis (dd/mm/yyyy): __ __ / __ __ / __ __ __ __
13. Insulin Administration: MDI or CSII Pump Brand: _____ 14. Insulin type used and dosage: _____ _____ _____
15. Length of Type 1 Diabetes: __ __ years Latest HbA1c results:_____
16. Diabetes complications Has a doctor ever told the participant they have: High blood pressure □Y □N Retinopathy □Y □N Nephropathy □Y □N Neuropathy □Y □N
17. Does the participant have a history of cardiovascular disease? □Y □N If yes, further details: _____
18. History of lows (blood glucose < 3.9 mmol/L) How many lows per week, on average, do they have? Are they random or do they happen after exercise? Meals? Do they usually feel (know) when they are low? □Y □N

When the participant feels low, do they test and record their blood glucose? □Y □N Do they treat with CHO? □Y □N If they treat, how many grams of CHO do they usually eat? __ __ . __ grams Does the low usually resolve itself within 15 minutes? □Y □N
19. Type of glucometer:

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week
a) **STRENUOUS EXERCISE** **(HEART BEATS RAPIDLY)** (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
b) **MODERATE EXERCISE** **(NOT EXHAUSTING)** (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
c) **MILD EXERCISE** **(MINIMAL EFFORT)** (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1. ☐	2. ☐	3. ☐

MAXIMAL OXYGEN UPTAKE TESTING

Emergency Contact Information

Name: _____

Email: _____

Phone number: (c)_____

Relationship to participant: _____

Name: _____

Email: _____

Phone number: (c)_____

Relationship to participant: _____

Note: Please place a * next to preferred method/number of contact

Time	Resistance	RPM	RPE	HR	Manual BP	Comments
-15MIN						Pre BG readings: Reading 1: __ _ _. __ mmol/L
IMMEDIATELY BEFORE TEST START						Reading 2: __ __ . __ mmol/L
0-1:00						
1:00-2:00						
2:00-3:00						
3:00-4:00						
4:00-5:00						
5:00-6:00						
6:00-7:00						
7:00-8:00						
8:00-9:00						
9:00-10:00						
10:00-11:00						
11:00-12:00						
12:00-13:00						
13:00-14:00						
14:00-15:00						
IMMEDIATELY POST-TEST						
5 MIN POST-TEST						
Before leaving						BG = __ __ . __ mmol/L

VO_2 Max=_____60% of VO_2Max=_____

Calibration: Pre O_2_____%; Pre CO_2:_____%. Post O_2___%; Post CO_2____%

EXERCISE TESTING SESSION: 7.0-10.0 mmol/L **Order:**

☐ First ☐ Second

PRIOR TO TESTING, ENSURE SUBJECT EMERGENCY CONTACT FORM IS IN THE ROOM

Time of Arrival_____ Date of first day of last menstrual period _____

Capillary glucose_____ Resting BP_____ HR _____

1. When did you last eat? _____
2. How big was the meal/snack? What did you eat? _____
3. Are you on an insulin pump? Yes/No
    a. Which brand? _____
    b. When was your last bolus? _____
    c. How much? _____
    d. For what? _____
    e. What is your insulin sensitivity factor for the next three hours?_____
    _____
4. Do you use MDI? Yes/No
    a. What type of long acting do you use? _____
    b. When is it administered? _____
    Where?_____
    c. What type of short acting do you use? _____
    d. When was your last bolus? _____
    e. How much? _____
    f. For what? _____
    g. What is your insulin sensitivity factor for the next three hours?_____
    _____
    h. What is your insulin to carb ratio for the next three hours? _____
    _____
    _____
5. What type of insulin do you use? _____
6. How much insulin do you have on board? _____
7. When did you reduce insulin? _____
8. By how much? _____

Target HR range: _____Target VO_2 (60% of max): _____ **Bike weights: _____Estimated Resistance: _____ Estimated RPM:_____**
Amount of Dex4 to raise BG by 1 mmol/L:_____

PRIOR TO TESTING, ENSURE SUBJECT EMERGENCY CONTACT FORM IS IN THE ROOM

Time	Blood & Urine	BP	HR	RPE	BG	Calorimetry	Dex4	Comments
-15MIN								
IMMEDIATELY BEFORE TEST START								
5:00 min								
10:00 min						Mask on		
15:00 min								
20:00 min								
25:00 min						Mask on		
30:00 min								
35:00 min								
40:00 min						Mask on		
45:00 min								
15 min post								
30 min post								
Before leaving, 60 min post								

Urine specific gravity: Exercise Start Time: _____

1st Sample Time _____ Reading_____

2nd Sample Time _____ Reading_____

3rd Sample Time _____ Reading_____

Additional Notes:

EXERCISE TESTING SESSION 2: 12.0-14.0 mmol/L **Order: ☐**

First ☐ Second

PRIOR TO TESTING, ENSURE SUBJECT EMERGENCY CONTACT FORM IS IN THE ROOM*

Time of Arrival_____ Date of first day of last menstrual period _____

Capillary glucose_____ Resting BP_____ HR _____

9. When did you last eat? _____
10. How big was the meal/snack? What did you eat? _____
11. Are you on an insulin pump? Yes/No
    a. Which brand? _____
    b. When was your last bolus? _____
    c. How much? _____
    d. For what? _____
    e. What is your insulin sensitivity factor for the next three hours?_____
       _____
12. Do you use MDI? Yes/No
    a. What type of long acting do you use? _____
    b. When is it administered? _____
       Where?_____
    c. What type of short acting do you use? _____
    d. When was your last bolus? _____
    e. How much? _____
    f. For what? _____
    g. What is your insulin sensitivity factor for the next three hours?_____
       _____
    h. What is your insulin to carb ratio for the next three hours? _____
       _____
       _____
13. What type of insulin do you use? _____
14. How much insulin do you have on board? _____
15. When did you reduce insulin? _____
16. By how much? _____

Target HR range: _____Target VO_2 (60% of max): _____ **Bike weights: _____Estimated Resistance: _____ Estimated RPM:_____ Amount of Dex4 to raise BG by 1 mmol/L:_____**

PRIOR TO TESTING, ENSURE SUBJECT EMERGENCY CONTACT FORM IS IN THE ROOM

Time	Blood & Urine	BP	HR	RPE	BG	Calorimetry	Dex4	Comments
-15MIN								
IMMEDIATELY BEFORE TEST START								
5:00 min								
10:00 min						Mask on		
15:00 min								
20:00 min								
25:00 min						Mask on		
30:00 min								
35:00 min								
40:00 min						Mask on		
45:00 min								
15 min post								
30 min post								
Before leaving, 60 min post								

Urine specific gravity: Exercise Start Time:

_____

1st Sample Time _____ Reading_____

2nd Sample Time _____ Reading_____

3rd Sample Time _____ Reading_____

Additional Notes

Appendix G: VO_{2peak} Cycle Ergometer Protocol

Male VO2 Max Protocol

80 RPM must be maintained	Basket resistance = 1 kg	
15 min before start	BG	
Immediately before start	BG	
		Total mass on the bike (kg)
0 min	Basket only	1
1 min	Add 300 g, RPM, RPE, HR	1.3
2 min	Add 300 g, RPM, RPE, HR, BP	1.6
3 min	Add 300 g, RPM, RPE, HR	1.9
4 min	Add 300 g, RPM, RPE, HR, BP	2.2
5 min	Add 300 g, RPM, RPE, HR	2.5
6 min	Add 300 g, RPM, RPE, HR, BP	2.8
7 min	Add 300 g, RPM, RPE, HR	3.1
8 min	Add 300 g, RPM, RPE, HR, BP	3.4
9 min	Add 300 g, RPM, RPE, HR	3.7
10 min	Add 300 g, RPM, RPE, HR, BP	4
11 min	Add 300 g, RPM, RPE, HR	4.3
12 min	Add 300 g, RPM, RPE, HR, BP	4.6
13 min	Add 300 g, RPM, RPE, HR	4.9
14 min	Add 300 g, RPM, RPE, HR	5.2
15 min	Add 300 g, RPM, RPE, HR	5.5
Immediately post test	HR, BP	
5 min post test	HR, BP	
Before leaving	HR, BP, BG	

Female VO2 Bike Protocol

80 RPM must be maintained Bike basket resistance = 1kg

15 min before start	BG		
Immediately before start	BG		
		Total mass on the bike (kg)	Counterweights
0 min		0.5	0.5
1 min	Add 200 g, RPM, RPE, HR	0.7	0.3
2 min	Add 200 g, RPM, RPE, HR, BP	0.9	0.1
3 min	Add 200 g, RPM, RPE, HR	1.1	
4 min	Add 200 g, RPM, RPE, HR, BP	1.3	
5 min	Add 200 g, RPM, RPE, HR	1.5	
6 min	Add 200 g, RPM, RPE, HR, BP	1.7	
7 min	Add 200 g, RPM, RPE, HR	1.9	
8 min	Add 200 g, RPM, RPE, HR, BP	2.1	
9 min	Add 200 g, RPM, RPE, HR	2.3	
10 min	Add 200 g, RPM, RPE, HR, BP	2.5	
11 min	Add 200 g, RPM, RPE, HR	2.7	
12 min	Add 200 g, RPM, RPE, HR, BP	2.9	
13 min	Add 200 g, RPM, RPE, HR	3.1	
14 min	Add 200 g, RPM, RPE, HR	3.3	
15 min	Add 200 g, RPM, RPE, HR	3.5	
Immediately post test	HR, BP		
5 min post test	HR, BP		
Before leaving	HR, BP, BG		

Appendix H: Food and Blood Glucose Logs

Food Record

Study ID: _____

Please record everything that you eat and drink on days where you are wearing a continuous glucose monitor (CGM). We would like you to eat the same food at the same time of day any time you are wearing a CGM. Please be as specific as you can.

The detailed instructions can be found on the next page.

INSTRUCTIONS FOR KEEPING FOOD RECORD

The purpose of this record is to discover everything you eat and drink on days where you are wearing a CGM. It is important to record ALL foods and beverages – whether it is a full course meal at home or a quick can of pop at school/work. Please read the following instructions and the sample recording before you start recording your intake.

It is a good idea to carry your Food Record book with you and record your entries as soon after eating as possible. Foods and beverages consumed away from home – at a friend's house, at the mall, at a restaurant- are just as important to record. Please include the following information on your food record:

1. **TIME OF DAY** Column**:** Enter the time of day you consumed foods and beverages.

2. **FOOD AND BEVERAGE ITEMS** Column: Enter all foods and beverages consumed at the meal or snack time. Please record the specific type of food (for example: *WHOLE WHEAT* bread, *FROSTED FLAKES* cereal). In the same column, record all toppings or items added at the time of eating (for example: sugar, syrup, jam, butter, mayonnaise, gravy, milk, salt, etc.). For combination foods, please include detailed information on each item. For example: If you had a tuna sandwich, you would list the following foods and include detailed information for each of them: white bread, mayonnaise, celery, solid white tuna, salt.

3. **DESCRIPTION OF ITEM** Column: For every food or beverage item listed, include the following (if applicable):
   - **Brand**: *MIRACLE WHIP* mayonnaise, *PIZZA HUT DEEP DISH* pizza, *OREO* cookie
   - **Type of flavour**: *BLUEBERRY* muffins, *STRAWBERRY* yogurt
   - **Method of cooking**: *FRIED, BAKED, BBQ'D, HOMEMADE*

All other relevant information included on food label: *LOW FAT* ranch salad dressing, *28% M.F. (MILK FAT*) cheddar cheese, *LEAN* Ground Beef

4. **Amount/Quantity** Column: In this area, record the number of units consumed, as well as the unit of measure you are using for this item. Include the amount of the food or beverage item and the amount of any topping or items added. For example: enter the word "cup", "grams", "piece", "ounce", "number", "teaspoon", or "tablespoon" followed by the number of unit. Enter a unit of measure not only for the menu item, but for toppings or items added as well. Each entry must have its own unit of measure. Use measuring cups and spoons whenever possible.

5. On the bottom of each recording sheet, please provide time and types of medications you have taken during the day.

All foods and beverages you consume should reflect the way you usually eat. Please do not change your normal eating habits for the 3 days you are recording your food intake. Your honesty is crucial to the success of this research study. We have provided a page at the back of your food record for you to include any additional information that will help us interpret your diet. Recipes and information from labels are particularly helpful. **If you have any questions please contact:** jeyardle@ualberta.ca.

PLEASE READ THIS SAMPLE MEAL

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments
1:00	Spaghetti with tomato/meat sauce:			BG = 5.5
	Pasta	Spaghetti, cooked	2 cups	
	Tomato sauce	Hunt's canned sauce, roasted garlic flavour	1 cup	
	Meat balls	Made with extra lean ground beef	5 oz	
	Parmesan cheese, grated	Kraft, 30% Milk Fat (M.F.)	1 tablespoon	Novorapid 6U
	Garlic Bread:			
	Italian Bread	Toasted	3 pieces (large slice)	
	Garlic Butter		3 teaspoons	
	Caesar salad:			
	Lettuce	Romaine	1 cup	
	Bacon bits	Simulated flavour, No Name Brand	2 tablespoons	
	Caesar salad dressing	Kraft, Fat free	2 tablespoons	Lantus 10U
3:30	Milk	1%	1 cup	BG = 4.1
	Tiramisu	Sarah Lee	1 slice	
	Coffee	Black	1 cup	

Time of medication: 1:30 pm **. Medication taken:** Ramipril (10mg) .

Test Day 1: (date) **BG 1 hour post insertion** **BG 3 hrs post insertion**

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of medication:_____ Medication taken:_____

Steps taken: _____ Time Pedometer on: _____ Time pedometer off: _____

Total daily insulin:_____

Test Day 2: _____

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of medication:_____ Medication taken:_____

Steps taken: _____ Time Pedometer on: _____ Time pedometer off: _____

Total daily insulin:_____

Test Day 3: _____

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of medication:_____ Medication taken:_____

Steps taken: _____ Time Pedometer on: _____ Time pedometer off: _____

Total daily insulin:_____

Test Day 4: _____

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of medication:_____ Medication taken:_____

Steps taken: _____ Time Pedometer on: _____ Time pedometer off: _____

Total daily insulin:_____

Test Day 5: _____

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of medication:_____ Medication taken:_____

Steps taken: _____ Time Pedometer on: _____ Time pedometer off: _____

Total daily insulin:_____

Test Day 6: **BG 15 min before CGM Removal:**

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of day	Food and Beverage Items	DESCRIPTION OF ITEM	AMOUNT/QUANTITY	INSULIN AND BLOOD GLUCOSE (BG)
	Enter all foods and beverages consumed. For combination foods, please include detailed information on each item.	Include a detailed description of each food and drink item consumed: - Brand name (flavor), method of cooking - All other relevant information on food/drink label	Enter unit of measure and number of units: for example: cup, grams, ounce, piece, teaspoon, tablespoon	Enter any measured BG levels, as well as insulin dosages (basal or bolus) and adjustments

Time of medication:_____ Medication taken:_____

Steps taken: _____ Time Pedometer on: _____ Time pedometer off: _____

Total daily insulin:_____

ADDITIONAL INFORMATION

(For example: recipes or food/drink label information)

Appendix I: Participant Information Booklet

Patient Information Booklet

Thank you for participating in our study! This booklet contains important study related information you should be familiar with.

Contact Information:

Phone: (587) 215-9480

Investigator email: hscherer@ualberta.ca

Introduction

This booklet is intended as a reference guide for you to use when you are not at the research lab. It has a few purposes:

1) Provides information about how to wear the continuous glucose monitor (CGM), and what information we ask that you write down while you are wearing it.
2) Provides information regarding the appropriate apps necessary to record your information in our database.
3) Provides some recommendations on how to adjust your carbohydrate intake and make insulin adjustments for exercise during the time of the study.

Continuous Glucose Monitor (CGM)

What it is: This is a device that records blood sugar levels throughout the day and night. In this study, an individual trained by the manufacturer will insert the small sensor that sits under the skin of your abdomen, attach a small recorder that stores the information from the sensor, and secure it with tape. The sensors last for up to six days, so the goal is for you to wear the device for six entire days, all day and night. You will be shown how to remove your device on your own and asked to return it to study staff at your drop off appointment.

How to wear it: The device will be inserted for you. It will be your job to check it a few times a day to make sure it is still secure, and the tape has not come loose.

On the **first day**:

- Take your first BG meter reading at least 1 hour after the recorder is attached. Record it in your food record logbook and sync your meter with the OneTouch Reveal app.
- Take a second BG meter reading at least 3 hours after the recorder is attached. Record it in the logbook and sync your meter with the OneTouch Reveal app.
- Collect at least one more meter reading before going to bed. Record in logbook nd sync your meter with the OneTouch Reveal app.

All other days

- Collect **at least 4 BG meter readings each day**, such as before breakfast, lunch, dinner, and bedtime. Record all in logbook and sync your meter with the OneTouch Reveal app.
    - These readings MUST be less than 12 hours apart (important for bedtime and wake-up BGs)
- We will provide you with a standardized BG meter to use for the study that is yours to keep
- Use the same blood glucose meter for all BG meter readings
- Do not let anyone else use your meter during the study
- Do not use control solution during the study

Care and Wearing

- Live your life with your normal behaviors

- Keep tape over the sensor and recorder to prevent accidental removal or sensor movement. If the sensor comes out even a small amount, it may stop working. If new tape is needed, just put it over the existing tape. If the sensor comes out, place the sensor and recorder into a plastic re-sealable bag and notify the Study Investigator
- Check the site 4 times a day to ensure that the sensor and recorder are firmly connected, the sensor is still fully inserted, and there is no bleeding or irritation
- If the sensor is partly pulled out, attempt to gently push it back into place
- Remove the sensor if you have redness, pain, tenderness, or swelling at the site, and notify the Study Investigator
- You may shower and swim while wearing the recorder and sensor. The recorder is watertight at a depth of up to 2.4 meters (8 feet) for 30 minutes. There is no time limit if you are swimming on the surface of a pool or showering
- Insulin should be injected at least 7.5 centimeters (3 inches) away from the sensor insertion site, and insulin pump infusion should be at least 5 centimeters (2 inches) from the sensor insertion site
- The recorder must be removed (but the sensor can be left in) prior to an x-ray, CT scan or MRI. Simply remove the recorder (the clamshell piece) by pinching and pulling parallel to the skin. After the x-ray, CT or MRI, reconnect the recorder and re-tape

Removing the CGM

- On the last day: record your last BG about 15 minutes before the device is removed.
- Gently peel off the whole device. Do not pull the recorder (grey seashell-shaped piece) off by itself. Leave it attached to the sensor.
- Place the device in a Ziplock bag, and hand it to a member of the research team at your drop off appointment.

Recording BG, Food and Insulin

How to record BG, food and exercise in the app

- You will need to download the OneTouch Reveal app on your cell phone. This will be done on your first visit to the clinic, along with a training session on how to record water intake, food and exercise in the app as well
- You will also be instructed on how to connect with our clinic, so your data will be shared with us for the duration of the study
- At the end of the study, we will show you how to disconnect from sharing with us
- Additional troubleshooting with your meter or app can be found in these documents:
    - **https://www.onetouch.ca/sites/onetouch_ca/files/onetouchrevealapp_ios_usermanual_en_ca.pdf (Apple Devices)**
    - **https://www.onetouch.ca/sites/onetouch_ca/files/onetouchrevealapp_android_usermanual_en_ca_0.pdf (Android Devices)**

How to fill out the Food Record

- Instructions on how to fill out the food record can be found on page one of the food record booklet

- We have provided you with two pages worth of space for each of the six days of sensor wear. An additional page is included at the back for any extra information
- Always keep the food record with you so you can write down the information immediately after each event
- Record the time and date within 5 minutes of each BG meter reading
- If you run out of room on the page, you may add extra pages at the end

Guidelines for Insulin Dosing and Carbohydrate Supplementation

The following recommendations for insulin adjustments and carbohydrate supplementation before, during and following exercise are based on the 2018 Diabetes Canada Clinical Practice Guidelines. We would like to emphasize that these are recommendations, and you are not required to follow them. Feel free to discuss them with your endocrinologist if you have any uncertainties. They are in place to act as a starting point if you are unsure of what to do. Please be as consistent as possible and make a note of any changes that you make in your Food Record book.

Pre-Exercise

- Avoid insulin injections/infusion sites in legs at least 12 hours before exercise
- **If you use multiple daily injections:**
    - Decrease your long-acting insulin dose by 10% (either night before or morning of exercise session) and adjust accordingly with fast acting insulin correction doses throughout the day to avoid excessive hyperglycemia
    - If you are eating before the study, you may want to reduce your bolus by half
    - Do not consume any food past **3:30 pm** on days you are coming to the lab
- **If you use an insulin pump:**
    - Decrease your basal rate by 50% two hours before exercise and maintain reduced basal rates until the end of exercise
    - If you are eating before the study, you may want to reduce your bolus by half
    - Do not consume any food past **3:30 pm** on days you are coming to the lab

Exercise Sessions

- You will be asked to do two finger stick tests prior to exercise: one upon arrival at the lab, and one immediately prior to exercise
- **If your blood glucose level is lower than 5.7 mmol/l prior to starting exercise you will be asked to consume glucose**
- **If your blood glucose level is higher than 15.0 mmol/l prior to starting exercise you will be asked to do a test for ketones**
- **If your blood glucose level is higher than 20.0 mmol/l prior to starting exercise the session will be re-scheduled**
- The Study Investigator will test blood glucose levels using your glucometer every 5 minutes during the session

Post-Exercise

- Reduce your insulin intake prior to bed to prevent nighttime lows:
    - **MDI users** (if you take insulin at night): decrease in long acting insulin injection by 20%
    - **Pump users:** lower basal rates by 20% between midnight and 3 am

After experiencing the exercise protocols involved in the study, if you wish to make changes to your insulin doses, please follow guidelines given to you by your diabetes care team.

MPORTANT INFORMATION

CGM: You may take out your continuous glucose monitor on _____

Your drop off appointment for the CGM is_____