Comparing the Effects of Three Exercise Intensities on the Prevention of Hypoglycemia in People with Type 1 Diabetes

By

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ABSTRACT

Statement of the Problem: The appropriate intensity of exercise needed to reduce the risk of hypoglycemia (≤3.9 mmol/L) in persons with type 1 diabetes (T1D) is not known.

Methods: Ten participants with T1D performed four exercise sessions on a treadmill lasting 45 minutes: a control condition at 45-55% of heart rate reserve and three high intensity sessions at 70, 80, and 90% of heart rate reserve. A blinded continuous glucose monitor was used to measure time spent ≤3.9 mmol/L and glucose variability in the 12 hours following exercise.

Results: There were no significant changes in the percentage of time spent ≤3.9 mmol/L (p=0.58) and glucose variability as measured by mean absolute glucose change (p=0.53) and continuous overall net glycemic action (CONGA1: p=0.95; CONGA2: p=0.90; CONGA4: p=0.72) between the sessions.

Conclusions: High intensity exercise at 70, 80, and 90% of HRR does not significantly reduce the amount of time spent ≤3.9 mmol/L or glucose variability compared to the 45-55% session alone.

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INTRODUCTION

Statement of the Problem

Physical inactivity is a significant public health concern as over two thirds of the Canadian population are considered physically inactive [1]. The World Health Organization has identified physical inactivity as the fourth leading risk factor for global mortality at approximately 6% of global deaths per year [2]. This is an issue for all citizens, but individuals with type 1 diabetes (T1D) tend to be less active than their peers without diabetes [3] which is largely due to fear associated with exercise induced hypoglycemia [4]. Recent studies have indicated that the addition of high intensity intervals to a standard bout of moderate intensity physical activity can be used to reduce the risk of falls in glycemia after exercise and/or nocturnal hypoglycemia [5-11], however the intensity required to elicit this protective effect remains unclear. Knowing this information could help establish physical activity guidelines for the prevention of hypoglycemia after exercise in persons with T1D.

Purpose and Hypothesis

The purpose of this study was to address the gap in our understanding of the prevention of post-exercise hypoglycemia and determine the appropriate intensity of exercise required to reduce the time spent in hypoglycemia and glucose variability in individuals with T1D.

We hypothesized that adding six, one minute bouts of exercise at 80-90% of heart rate reserve (HRR) during a session at 45-55% of HRR would significantly reduce the time spent in hypoglycemia (≤3.9 mmol/L) and glucose variability in the 12 hours following exercise compared to a session at 45-55% of HRR in inactive persons with T1D. We further hypothesized that adding bouts at 70% of HRR would not be sufficiently intense to reduce the time spent in hypoglycemia, however it was included as this intensity is currently untested.

REVIEW OF LITERATURE

What is Diabetes?

Diabetes mellitus is a metabolic disorder that is marked by high blood glucose (hyperglycemia) which can be the result of absolute insulin deficiency, ineffective insulin action, incomplete insulin secretion, or a combination of the latter two [12]. Although there are several forms of diabetes mellitus, the most commonly recognized forms are type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes. Individuals with T1D require exogenous insulin for survival and to prevent complications associated with hyperglycemia. They are therefore at a greater risk for exercise-induced hypoglycemia as they have no internal mechanism to reduce exogenous insulin. Accordingly, the remainder of this thesis will focus on the metabolic responses to exercise in persons with T1D.

The causes of T1D are discussed in detail in subsequent sections, however the primary cause of hyperglycemia in persons with T1D is an inappropriate autoimmune-based destruction of beta cells in the pancreas resulting in complete insulin deficiency [12] and is not considered a disease based on lifestyle choices.

Prevalence of Type 1 Diabetes

Canada faces a significant burden to the health care system as the number of people living with diabetes increases [13]. Currently, over 3 million people in Canada live with diabetes, and approximately 10% of this population (~300,000) live with T1D [14]. T1D is the most common form of diabetes in children and young adults [15]. The Public Health Agency of Canada reported that prevalence rates of diabetes in 2008 for youth aged 1-19 were 0.3% (cases=24,136) and incidence rates were 0.4 per 1000 people (cases=3,258) [16].

Causes of Type 1 Diabetes

To fully understand the pathophysiology of T1D an in-depth look at the role and function of the pancreas is pertinent. Under normal fasting conditions in persons without diabetes, blood glucose is tightly regulated to remain <5.6 mmol/L [17] which is a result of the intricate role the pancreas plays in controlling blood glucose [18]. The pancreas has both exocrine (secretes substances into ducts then directly to the external environment of the gastrointestinal tract) and endocrine (secretes hormones into the bloodstream which then travel to different tissues) functions that contribute to this tight regulation of blood glucose. Within the pancreas, clusters of cells known as "islets of Langerhans," house hormones that contribute to this regulation [19]: (1) β-cells that produce and secrete insulin and (2) α-cells that produce and secrete glucagon [18]. Insulin is the primary hormone for reducing blood glucose by promoting uptake of glucose from the circulation into myocytes, hepatocytes, and adipocytes [20] while glucagon promotes the breakdown of glycogen into glucose within hepatocytes, to increase blood glucose levels [21]. Tight blood glucose regulation is thus a result of harmonized and coordinated actions of both β-cells and α-cells.

When an individual develops T1D the β-cells undergo a cell-mediated attack brought forth by T-lymphocytes of the immune system. T-lymphocytes are white blood cells of the adaptive immune system that help rid the body of foreign invaders like viruses and infections [22], however in the setting of T1D β-cells are interpreted as a foreign invader by the T-lymphocytes and are therefore destroyed. As a result the pancreas can no longer regulate the production of insulin. Individuals with T1D therefore require exogenous insulin to maintain blood glucose control [23]. Interestingly, α-cells are still intact however their ability to respond to falling levels of glucose is impaired [24]. It is currently unknown why the body produces an

autoimmune response towards β-cell destruction, however genetic research may assist in answering this question.

Genetic factors appear to play a major role in the immune system's destruction of β-cells. The main gene responsible is the major histocompatibility complex class II (MHC class II) on chromosome six which is encoded by the human leucocyte antigen (HLA) [25]. In other words, HLA is responsible for producing certain substances or behaviours in MHC. HLA are surface proteins that are located on antigen-presenting cells like MHC, which allow the immune system to differentiate between self-cells or host-cells, and foreign invaders. When HLA expresses antigens such as DR3 and DR4 the body will not recognize these as self-cells and will therefore produce T-lymphocytes to mediate their destruction [25]. Transmembrane glycoprotein co-receptor 8 (CD8) is the dominant T-lymphocyte type involved in the pathogenesis of T1D [25]. Simply expressing these genes does not cause T1D. Rather, the presence of HLA-DR3 and HLA-DR4 antigens (as well as numerous other variations) with an environmental stimulus, leads to immune targeting of pancreatic β-cells [26]. Proposed environmental triggers include viruses such as enteroviruses [27], environmental toxins such as nitrosamines [28], and early exposure to cow's milk proteins, cereal or gluten [29].

The cause and effect relationship between environmental triggers and T1D has not yet been established, however there is a strong association between environmental triggers and predisposition to autoimmune diseases [26]. Currently, conventional wisdom suggests that T1D results from an autoimmune destruction of pancreatic β-cells potentially triggered by an environmental stimulus in a genetically susceptible individual.

Diagnosis of Diabetes

Diabetes is officially diagnosed using the guidelines established by the Canadian [12] and/or American Diabetes Association [30]:

- Fasting blood glucose ≥7.0 mmol/L or
- HbA_{1c} ≥6.5% in adults or
- 2 hour plasma glucose in a 75g oral glucose tolerance test (OGTT) ≥11.1 mmol/L or
- Random plasma glucose ≥11.1 mmol/L

The criteria for diagnosing diabetes is the same for T1D and T2D, therefore other characteristics can be used to distinguish T1D from T2D. Individuals with T1D tend to be: (1) younger at diagnosis (children or adolescence) although it can present at any age [26, 31, 32], (2) a lean phenotype at diagnosis, (3) symptomatic for hyperglycemia at diagnosis (polyuria, polydipsia, and polyphagia), and (3) presenting with ketonuria (ketone bodies present in the urine) or ketonemia (detectable levels of ketones in the plasma), however this can also present in T2D) [12]. In addition, those with T1D may express specific biomarkers for autoimmunity such as anti-glutamic acid decarboxylase or anti-insulin antibodies [12]. Measuring circulating levels of c-peptide (a polypeptide chain that is cleaved off from proinsulin when insulin is formed) can be measured as well to confirm β-cell destruction. A c-peptide ≤0.16 nmol/L indicates near absolute beta cell destruction, and the requirement for exogenous insulin that characterizes T1D [33]. Once an individual has officially been diagnosed with T1D, monitoring blood glucose becomes a requirement to control the disease as the β-cells and α-cells no longer intrinsically control blood glucose.

Treatment for T1D

The sole treatment for T1D is exogenous insulin administered through daily injections or an insulin pump (small catheter inserted into subcutaneous tissue that supplies continual insulin) [12]. Individuals on multiple daily injection (MDI) can be on a basal-bolus regimen. Basal insulin is long acting, injected at least once per day and is designed to simulate the basal release of insulin from the pancreas [12, 34]. Bolus insulin is rapid or short acting, and is injected with meals or as a correction when blood glucose is too high; it is designed to simulate the surge of insulin released upon meal consumption [12, 34]. Individuals using continuous subcutaneous insulin infusion (CSII) will have a reservoir of insulin (~300 units) of rapid or short acting insulin that is constantly infused all day and all night to mimic basal insulin secretion [35]. Upon meal consumption, an individual can deliver a bolus of insulin [35]. Refer to Table 1 [12] for an outline of different types of insulin.

Table 1: Insulin Treatment

Insulin	Onset of Action (hours)	Peak Action (hours)	Duration of Action (hours)	Use in MDI or CSII
Rapid Acting Insulin				
Lispro (Humalog)	0.2-0.5	0.5-2	3-4	Both
Aspart (Novorapid)	0.2-0.5	0.5-2	3-4	Both
Glulisine (Apidra)	0.2-0.5	0.5-2	3-4	Both
Intermediate-Acting Insulin				
NPH (Humulin N, Novolin N)	1.5-4	4-10	Up to 20	MDI
Long-Acting Insulin				
Glargine (Lantus)	1-3	No peak	Up to 24	MDI
Detemir (Levemir)	1-3	No peak	Up to 24	MDI

Adapted from CDA Clinical Practice Guidelines 2013 [12]

Blood Glucose Monitoring and Control

Blood glucose control can be determined: (1) acutely with self-monitoring of blood glucose using finger-stick measures of capillary blood glucose [36] and (2) chronically using hemoglobin A1c (HbA_{1c}) to assess glucose regulation over a period of approximately 3 months [37]. These two methods provide different information. Capillary blood glucose gives an instantaneous representation of blood glucose, while HbA_{1c} is a reflection of the average blood glucose over the past eight to twelve weeks and is measured as a percentage or in mmol/mol [38, 39]. In the general population without diabetes, HbA_{1c} values can range from 4% (20.2 mmol/mol) to 6% (42.1 mmol/mol) [26, 40]. Individuals with T1D have specific targets for HbA_{1c}, fasting capillary blood glucose, and post-prandial capillary blood glucose based on age (Table 2) in order to reduce the risk of microvascular and macrovascular complications in the future [12].

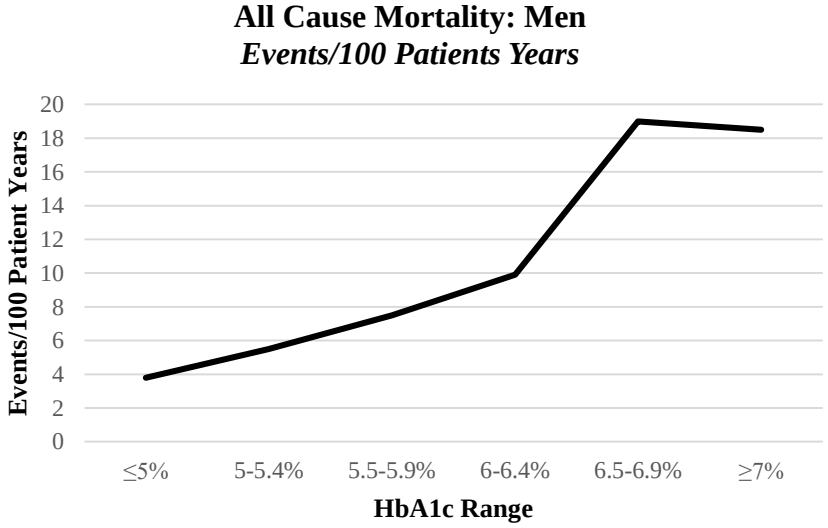
Table 2: Blood Glucose Targets Based on Age

Age (years)	HbA_{1c} (%) HbA_{1c} (mmol/mol)	Fasting/preprandial plasma glucose (mmol/L)	Two-Hour Postprandial Plasma Glucose (mmol/L)
<6	<8.0 <63.9	6.0-10.0	–
6-12	≤7.5 ≤58.5	4.0-10.0	–
13-18	≤7.0 ≤53.0	4.0-7.0	5.0-10.0
>18	≤7.0 ≤53.0	4.0-7.0	5.0-10.0

Adapted from CDA Clinical Practice Guidelines 2013 [12]

The Diabetes Control and Complications Trial [41] established that for individuals with diabetes, a target HbA_{1c} level of <7% (<53.0 mmol/mol) significantly reduces the risk of all diabetes-related complications including retinopathy (-50%), nephropathy (-34%), neuropathy (-69%), and cumulated macrovascular events (-41%) [41]. However for individuals who could achieve a target HbA_{1c} of 6.05% (42.6 mmol/mol) rates of retinopathy decreased even more (0.52 per 100 patient-years), which suggests that there is a dose response decrease in diabetes complications and HbA_{1c} levels [42]. A prospective population study conducted in Europe found that for every 1% increase in HbA_{1c} above normal range the risk of mortality and cardiovascular events increased by 20-30% [43]. Figure 1 illustrates the relationship between HbA_{1c} and risk of mortality according to HbA_{1c} category ranges [43].

Figure 1: Relationship between Hb_{A1c} and Mortality



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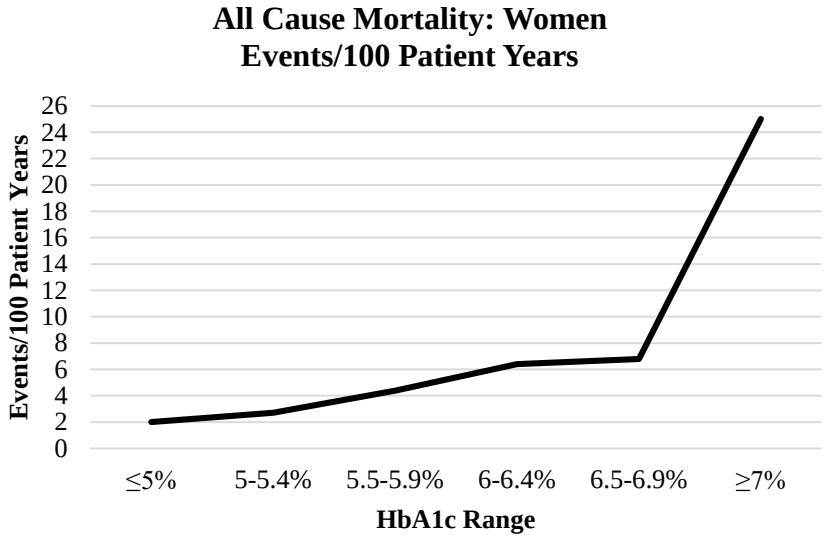


Adapted from Khaw, 2004 [43]

Although the reduction in diabetic complications decreases significantly with lower HbA_{1c}, tight blood glucose control increases the incidence of hypoglycemic events by three-fold as established by the DCCT [44].

Hypoglycemia

Hypoglycemia is a frequent and potentially life threatening complication of T1D. It is defined [12] as: plasma blood glucose ≤3.9 mmol/L, with or without the development of neurogenic (autonomic) and neuroglycopenic symptoms (Table 3), that resolve with the administration of carbohydrates. The severity (i.e., mild, moderate, and severe) of hypoglycemia is defined by clinical manifestations (Table 4). Neurogenic symptoms are a result of the perception of physiological changes triggered by the autonomic nervous system to hypoglycemia and neuroglycopenic symptoms are a result of glucose deprivation to the brain [24].

Table 3: Neurogenic and Neuroglycopenic Symptoms of Hypoglycemia

Neurogenic (Autonomic)	Neuroglycopenic
Trembling	Difficulty concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision changes
Nausea	Difficulty speaking
Tingling	Headache
	Dizziness

Table 4: Clinical Manifestations of Hypoglycemia based on Severity

Mild	Moderate	Severe
Neurogenic (autonomic) symptoms are present and individual is able to self-treat	Both neurogenic and neuroglycopenic symptoms are present and individual is able to self-treat	Individuals require assistance from another person, unconsciousness may occur and plasma glucose is typically <2.8 mmol/L

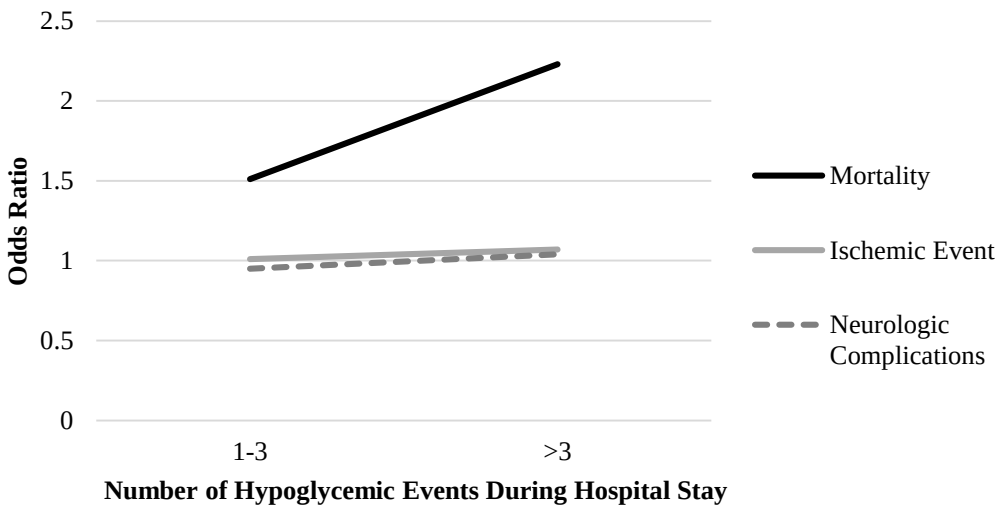
Hypoglycemia is life-threatening as glucose is the primary energy source for the central nervous system [45]. The brain uses glucose to make adenosine triphosphate (ATP), the principal energy currency in the body [46] as it is involved in regulating metabolism, the release of neurotransmitters, and opening sodium channels for the development of an action potential [45]. The reliance on blood glucose as a primary fuel source explains why the primary symptoms of hypoglycemia are neurologic in nature. Unlike other organs, such as the heart where lactate and fat can readily be used for fuel [47], the brain relies almost solely on glucose to maintain proper functioning [48].

According to one study, a person with T1D can experience on average two episodes of symptomatic hypoglycemia per week, numerous asymptomatic hypoglycemic episodes daily

where blood glucose is between 2.8-3.3 mmol/L, and one disabling hypoglycemic event per year [24, 49].

Hypoglycemia is a major limiting factor for blood glucose control in individuals with T1D. In an effort to prevent hypoglycemia, patients will often maintain a degree of hyperglycemia, particularly during nocturnal hours [50]. Reasons for fearing hypoglycemia are the numerous neurogenic and neuroglycopenic manifestations [51] and its association with mortality (defined as death that occurred during hospitalization), increased hospital stay time, neurologic complications (defined as seizure, comma, or alterations in mental status), and ischemic events (defined as acute myocardial infarction, acute/subacute ischemic heart disease, unstable angina, stroke, transient ischemic attack, or cerebrovascular disease that occurred during the hospitalization) (Figure 2) [52].

Figure 2: Relationship between Hypoglycemia, Mortality, and Complications



This figure describes the relationship between hypoglycemia (defined as blood glucose ≤3.9 mmol/L) and the risk of having an adverse event. Participants had a median hospital stay time of 9.0 days (5.2, 14.8) for patients with at least one severe hypoglycemic event (blood glucose <2.8 mmol/L) and 7.9 days (4.8, 13.2) with a non-severe event (blood glucose >2.8 mmol/L but ≤3.9 mmol/L)

Adapated from Brodovicz, 2013 [52]

Unfortunately, frequent hypoglycemia affects the nervous system and leads to an unawareness of subsequent hypoglycemic episodes [53]. Under normal conditions, a decline in blood glucose ≤3.9 mmol/L is counteracted by a decrease in insulin secretion, an increase in glucagon secretion, and hepatic glucose secretion mediated by an increase in circulating epinephrine [54]. In the setting of T1D, insulin is supplied exogenously and therefore cannot be reduced rapidly, glucagon secretion and the counterregulatory response to hypoglycemia is dampened, creating a perfect storm for hypoglycemia [54]. Because persons living with T1D supply insulin exogenously, insulin is not reduced with changes in insulin sensitivity [49]. The elevated circulating level of insulin dampens the release of glucagon and blunts the catecholamine effect on the liver in response to hypoglycemia [55]. Taken together, when a person has hypoglycemia, he or she may not experience the signs and symptoms often coupled with low blood glucose with each episode if left unchecked. As hypoglycemia is common and can lead to severe neurologic defects, including the loss of consciousness, strategies are needed to prevent it.

Risk Factors for Hypoglycemia

Tight blood glucose control is the primary risk factor for hypoglycemia in persons with T1D [41]. The landmark Diabetes Control and Complications Trial (DCCT) reported this phenomenon when individuals in the treatment arm were instructed to achieve near normal blood glucose control [41]. Although the trial successfully achieved significantly lower HbA_{1c} through intensive insulin therapy (defined as: preprandial blood glucose target between 3.9-6.7 mmol/L and postprandial blood glucose target <10.0 mmol/L), the rate of severe hypoglycemia and hypoglycemic coma were three times greater in the intensive treatment group compared to the standardized treatment group (defined as: no specific glycemic target) with 62 vs. 19 events/100

person-years) [41]. As tight glycemic control is associated with a reduced risk of complications, strategies are needed to achieve tighter glycemic control while simultaneously mitigating the risk for hypoglycemia in persons with T1D.

In addition to tight blood glucose control, several other risk factors for hypoglycemia exist: (1) exogenous insulin administration that is excessive or ill-timed, (2) dampened exogenous glucose delivery due to missed meals or fasting, (3) increases in insulin sensitivity during and after exercise, (4) diminished endogenous glucose production such as after alcohol consumption, (5) increase in glucose utilization such as during exercise, (6) decrease in insulin clearance due to renal failure [24, 49], and (7) high glucose variability [56-58].

Frequent blood glucose monitoring can reduce the risk of hypoglycemia as it allows for careful titration of blood glucose, preventing sporadic or profound deviations in glucose from desired values. However self-monitoring of blood glucose (SMBG) is limited in the information it provides as it cannot give a clear indication of continuous glucose values. Additionally, avoiding big swings in blood glucose is recommended to avoid excessive corrections and increased risk of hyperinsulinemia. Measuring glucose variability is often seen as the solution to compliment sporadic measures of blood glucose. The high level of "glucose variability" that can occur among individuals with T1D is one of the primary predictors of hypoglycemic events [56-58].

Glucose Variability

Glucose variability is defined as fluctuations or the spread of glucose values where higher numbers indicate higher variability (Figure 3) [59]. Figure 3 is a graphic representation of glucose variability. The solid black line at 8.0 mmol/L indicates the mean blood glucose for two individuals and the sporadic curve is representative of glucose fluctuations throughout the day. It

is interesting to note that two individuals with the same mean blood glucose can have such drastic differences in glucose variability [59]. This phenomenon is also represented in Figure 4 [60].

Figure 3: Glucose Variability

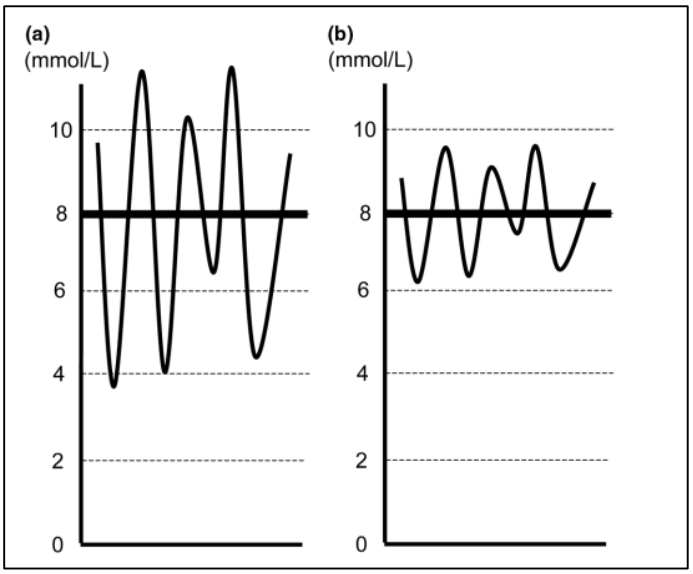


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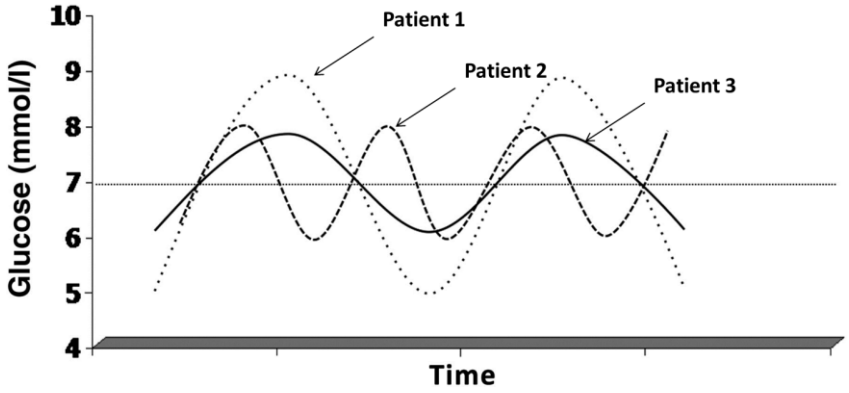
Figure 4: Example of Glucose Variability



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Glucose variability can be measured using several different methods such as mean absolute glucose change (MAG) [61] continuous overall net glycemic action (CONGA) [62], mean, standard deviation (SD), mean amplitude of glycemic excursions (MAGE), and mean of daily differences [63]. Some methods for measuring glucose variability are described in detail in Table 6. The focus of this thesis will be on MAG and CONGA.

No gold standard for measuring glucose variability exists as each measurement has its own limitations (Table 6) [61]. MAG is unique as it takes into account all glycemic variations over time, including the glucose values in a normal physiological range and is measured in mmol/L/h [61]. However, MAG is sensitive to sampling frequency as fewer blood glucose samples correlate to smaller glucose variability. A retrospective study looked at MAG and its correlations to other values of glucose variability such as CONGA, MAGE, and SD. They concluded that when glucose values are obtained from continuous glucose monitoring (CGM), MAG correlates very well with the above measures (Table 5) [61].

Table 5: Correlation Between Measures of Glucose Variability in Patients with T1D and T2D

	MAG5	**MAG60**	**MAG7pt**	**SD**	**MAGE**	**CONGA1**	**CONGA3**	**CONGA 6**
MAG5	1	0.818	0.542	0.699	0.587	0.809	0.719	0.686
MAG60	0.818	1	0.542	0.889	0.822	0.979	0.935	0.882
MAG7pt	0.542	0.745	1	0.759	0.749	0.754	0.793	0.758

This table indicates Pearson correlations and all have p-values <0.001 [61]. MAG5 represents blood glucose taken every 5 minutes. MAG60 represents blood glucose measures taken every hour. MAG7pt represents blood glucose taken 7 times/day [61].

Table 6: Glucose Variability Measures

	How is it Measured	Equation	Advantages	Limitations
Mean [63, 64]	The average of all glucose values recorded	$\frac{\sum_{t=t1}^{t_n} BG_t}{n}$	Very easy to calculate	Greatly affected by extreme values
Standard Deviation [63-65]	The standard deviation or the variance of blood glucose measures around the mean	$\sqrt{\frac{\sum_{t=t_1}^{t_n}(BG_{ti}-\overline{BG})^2}{n-1}}$	Easy to calculate	Glucose values are not normally distributed and two widely different glucose curves can have the same standard deviation
Mean Amplitude of Glycemic Excursions (MAGE) [62-64]	The arithmetic average of absolute value differences between adjacent glucose peaks and nadirs that exceed 1 SD from the mean	$\sum \frac{\lambda}{\chi}\ if\ \lambda > v$	Well validated and widely used measure	Determination of nadirs and peaks are arbitrary and subjective
Mean of Daily Differences (MODD) [63, 64]	Inter-day measure of the mean of all valid absolute value differences between glucose concentrations	$\frac{\sum_{t=t_1}^{k}\lvert BG_t - BG_{t-1440}\rvert}{k}$	Allows comparison between two consecutive days	Dependent on adherence between regular meals and insulin due to the comparison of glucose values on two consecutive days
Mean Absolute Glucose Change (MAG) [61, 63, 64, 66]	Takes into account all glycemic variations over time	$\frac{\sum_{n=1}^{N-1}\ (G_n - G_n + 1)}{T}$	Takes into account glucose measures in a physiological range	Very sensitive to sampling frequency. Fewer BG samples corresponds to lower glycemic variability
Continuous Overall Net Glycemic Action (CONGA) [62-64, 67]	Represents the standard deviation of all valid differences between a current observation and an observation *n* hours earlier	$\sqrt{\frac{\sum_{t=t_1}^{t_k}(D_t - \overline{D})^2}{k-1}}$	Allows for determination of intra-day variability and can assess variation in increments less than 24 hours	CONGA values can range from 1-8 hours post observation and it is not known which one is preferable

In addition, Hermanides et al. [66] performed a retrospective cohort study and found that glucose variability as measured by MAG was strongly correlated with death in the intensive care unit in patients with and without diabetes (12.2% patients with diabetes: 699/5782) [66]. MAG is an appropriate measure of glucose variability and is comparable to other methods such as MAGE; some have even suggested it could become the gold standard [61]. According to Kohnert [61], standard MAG values for people with T1D are 2.91 ± 0.14 mmol/L/h, this is compared to individuals without diabetes who have an average MAG value of 1.3 ± 0.4 mmol/L/h [64].

CONGA is the difference in glucose values after the first *n* observations and is measured in mmol/L. It is the difference in the blood glucose taken at the current time and *n* hours before and calculates the standard deviation [62]. CONGA1, 2, 3…8 refers to blood glucose measurements one hour previous, two hours previous, and three hours previous from the current time. McDonnell [62] was the first to establish this method of measuring glucose variability as it measures intra-day variability in comparison to MAGE, MAG, and MODD which measure inter-day variability [62]. Refer to Table 7 for average CONGA values for individuals with and without T1D.

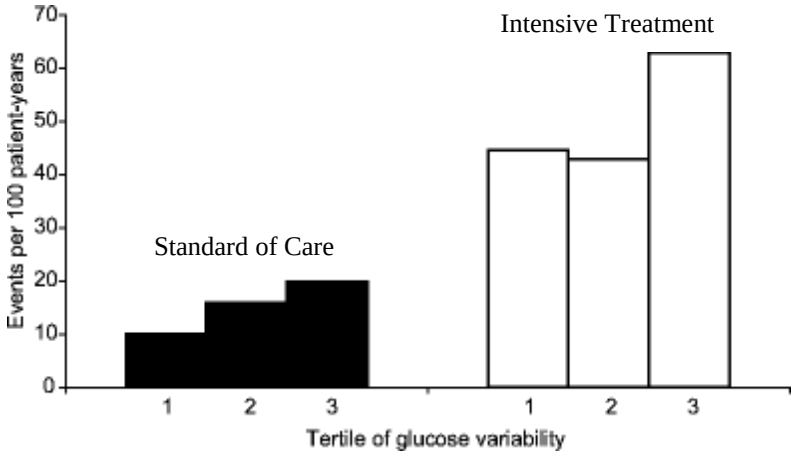
Table 7: Average CONGA Values (mmol/L)

	Rawlings-2011 [63]		**McDonnell-2005 [62]**		**Kohnert-2013 [61]**		**Service-2013 [65]**	
	T1D	***Healthy Adults***	***Youth T1D***	***Healthy Adults***	***T1D***	***T2D***	***T1D***	***T2D***
CONGA1	2.7 ± 0.61	0.72	2.5 ± 0.8	0.7 ± 0.3	2.16 ± 0.04	1.59 ± 0.04	-	-
CONGA2	4.0 ± 0.83	0.88	3.56	0.81	-	-	3.8 ± 1.59	2.3 ± 0.88
CONGA4	5.3 ± 1.11	1.01	4.6	1.0	-	-	-	-

CONGA values for individuals with T1D, T2D, and healthy controls.

Glucose variability is an important aspect of diabetes management as higher values are linked with greater rates of hypoglycemia [57]. A retrospective study of the DCCT examined the relationship between rates of severe hypoglycemia and glucose variability as measured by standard deviation (Figure 5). A dose-response relationship was found between the standard deviation measure of glucose variation and the number of severe hypoglycemic episodes in a year [57]. The rate of severe hypoglycemia in the intensive treatment group was ~50% higher in individuals within the upper tertile of glucose variability compared to those in the lowest tertile of glucose variability (43.5% vs 64.0%) (Figure 5) [57].

Figure 5: Glucose Variability is Predictive of Hypoglycemic Events



This figure shows the relationship between glucose variability as measured by standard deviation and hypoglycemic episodes. Despite the treatment group (standard of care: black bars or intensive treatment: white bars) as glucose variability increased (moving from 1 to 3 standard deviations away from the mean) so did hypoglycemic events [57]. Figure reprinted with permission from Kilpatrick, E.S., et al., Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes Diabetologia, 2007. 50: p. 2553-2561. Copyright 2007, with permission Copyright Clearance Centre. Permission obtained September 24, 2014 [57].

For a given change in the glucose variability (assessed from SMBG) the risk of hypoglycemia increased in a dose-response manner in patients from the DCCT. Regardless of the target glucose control, the greater the variability the higher the risk of hypoglycemia [57].

These results suggest that rates of severe hypoglycemia increase as the standard deviation of glucose values (glucose variability) increases. A study conducted in T2D patients treated with insulin also found that rates of hypoglycemia increased with increasing glucose variability, measured by standard deviation [58].

With the association between glucose variability and hypoglycemia, novel approaches to limiting glucose variability should be explored. Previous studies have documented that exercise can reduce glucose variability in patients with both non-insulin and insulin treated T2D [68, 69]. A randomized crossover trial in 60 men with T2D (insulin and non-insulin treated) examined the effect of moderate intensity exercise for 45-60 minutes on a cycle ergometer at 35-50% maximum wattage. Glucose variability was measured using a CGM for 24 hours and calculated using $CONGA_1$, $CONGA_2$, $CONGA_4$, and SD. Over the 24 hours after exercise a significant reduction in glucose variability as measured by all CONGA values was observed as compared to no exercise [69]; $CONGA_1$: ~2.3 mmol/L vs ~2.5 mmol/L; $CONGA_2$: ~2.9 mmol/L vs. ~3.2 mmol/L; and $CONGA_4$: ~3.3 mmol/L vs. ~3.5 mmol/L for exercise vs. non-exercise days. Another randomized crossover trial examined the influence of aerobic exercise or aerobic exercise plus resistance training on glucose variability in 14 participants with non-insulin treated T2D [68]. Glucose variability was measured using a CGM for three days and calculated using MAGE and SD. The aerobic exercise protocol consisted of 45 minutes of continuous cycling at 70% of peak heart rate. Combined exercise consisted of the aerobic exercise protocol plus four resistance exercises (leg press, leg extension, bench press, and bicep curl) at 3 sets of 12

repetitions at 65% of 1-RM. Both forms of exercise induced similar reductions in glucose variability [68]. ***To date there are no studies examining the influence of exercise on glucose variability in persons with T1D, nor is the effect of vigorous intensity exercise on glucose variability understood.***

Physical Activity and T1D

Although no established physical activity guidelines exist for individuals with T1D in terms of the frequency, intensity, time or type of exercise [70], exercise in general offers numerous health benefits for everyone [71]. The current Canadian Physical Activity guidelines for youth aged 12-17 years are 60 minutes of moderate-to-vigorous-intensity physical activity (MVPA) daily. Additionally, youth are recommended to achieve at least 10 minutes of vigorous intensity activity and activities that strengthen muscle and bone at least three days per week [72]. Achieving these guidelines is associated with improved cholesterol levels, body composition, blood pressure, cardiorespiratory fitness, musculoskeletal fitness, and bone density [73]. For adults, the guidelines are slightly different as it is recommended that adults aged 18-64 participate in 150 minutes of MVPA every week accumulated in ten minute bouts or more [74]. These guidelines in adults were established as a means to reduce the incidence of premature death, stroke, coronary artery disease, hypertension, breast cancer, colon cancer, T2D, and osteoporosis [73].

Regular physical activity offers significant health benefits for people with T1D such as: improved fitness, endothelial function, lipid profile, insulin sensitivity [70], decrease in fasting blood glucose and HbA_{1c} [75, 76], decrease insulin dosage [77], lower LDL cholesterol values [78], improved body composition [79], the potential for reduced glucose variability [68, 69] and improved quality of life [80]. Despite the numerous health benefits, individuals with T1D are

often less active then their healthy peers [3] and remain physically inactive.

Factors Influencing Physical Activity Participation

Only 15% of the adult Canadian population aged 20-79 years and 7% of youth aged 6-19 achieve the Canadian Physical Activity Guidelines [72, 74, 81, 82]. Primary barriers to achieving the recommended levels of PA include lack of enjoyment of structured PA, lack of time, lack of motivation, cost, environmental factors, and other commitments such as work or family all contribute to low involvement in PA [83, 84]. While these barriers are common among the general population, individuals with T1D have an added obstacle to physical activity participation, fear of hypoglycemia [4]. Exercise leads to acute and rapid reductions in blood glucose. The insulin sensitizing effects of exercise can last up to 72 hours following exercise [85]. The combined effects of exercise-mediated glucose uptake and exogenous insulin, significantly increase the risk for hypoglycemia in persons living with T1D. This is further discussed in the section entitled: *Physiological Effects of Varying Intensities of Exercise*.

Several strategies exist to prevent exercise-induced hypoglycemia. They include consumption of extra carbohydrates prior to exercise or altering basal insulin rate for insulin pump users or to limit pre-prandial bolus insulin or basal insulin injection [12]. The downside of these strategies are that individuals will often over compensate with carbohydrates and/or reduce insulin rates such that their blood glucose values are higher on exercise days as compared to non-exercise days. This will negate the beneficial effects of exercise on glycemic control for these individuals [86].

An emerging, yet understudied approach for preventing hypoglycemia involves the addition of vigorous intensity intervals during moderate intensity exercise as a method of reducing the risk of hypoglycemia without increasing caloric intake [5-11].

Exercise Intensity

Exercise intensity is the level of exertion experienced during an activity [87] and can be measured in a variety of different ways. There are two primary classifications of intensity according to energy demand, absolute and relative energy expenditure [88]. Absolute energy expenditure includes work rate (watts), caloric/energy expenditure (kCal/min), absolute oxygen uptake (mL/min or L/min), and metabolic equivalents (METS); these measurements do not take into account body weight, sex, and fitness level [88]. Relative measurements that control for differences in body weight and fitness level include oxygen consumption (VO_2) reserve, heart rate reserve (HRR), percent of maximum heart rate (%HRmax), %VO_2max, and %MET_{max}. Other measurements of intensity rely on self-perception which include rate of perceived exertion (RPE) [88] and the talk test [89]. Refer to Table 8 for a list of definitions of the above terms.

The gold standard method for prescribing exercise is to express exercise relative to maximal oxygen uptake (VO_2max). VO_2max is measured during a graded exercise test to exhaustion on a cycle ergometer or treadmill with direct gas analysis [90]. Criteria for achieving VO_2max include: (1) a plateau in oxygen uptake despite an increased workload (VO_2 differs by no more than 2.1 ml/kg/min) [91], (2) heart rate within five beats of age-predicted maximum, (3) venous lactate concentration >8 mmol/L, (4) respiratory exchange ratio >1.15, and (5) RPE >17 [92, 93].

Table 8: Definitions for Measuring Intensity

Term	Definition
Caloric/Energy Expenditure	The total amount energy (gross) during exercise, including the resting energy expenditure; (resting energy expenditure + exercise energy expenditure). [88]
Maximal Oxygen Consumption (VO_2max)	Highest rate at which the body can transport and utilize oxygen during exercise. [94]
Respiratory Exchange Ratio (RER)	Ratio between $\dot{V}CO_2$ and $\dot{V}O_2$obtained exclusively from ventilator expired gas analysis. [95]
Metabolic Equivalents (METS)	The ratio of the rate of energy expended during an activity to the rate of energy expended at rest. 1 MET is the rate of energy expenditure while sitting and is equal to = 3.5 mL/kg/min. [88]
Oxygen Consumption Reserve (VO_2R)	Percentage difference between maximal and resting values of VO_2.[96]
Heart Rate Reserve (HRR)	Percentage difference between maximal heart and resting heart rate.$[(HR_{max} - HR_{resting}) \times percent\ of\ workload] + HR_{resting}$ [96]
%HRmax	Percentage of heart rate maximum. [97]
%VO_2max	Percentage of maximum oxygen uptake. [96]
%MET_{max}	Percentage of maximal metabolic equivalent. [88]
Rate of Perceived Exertion (RPE)	A commonly used indirect measure of intensity where individuals rate how hard they think they are working on a scale from 6-20 or 1-10. These scales are known as the Borg Scale. [98]
Talk Test	An indirect simplistic method to determine exercise intensity. If an individual "can just respond to conversation," then the exercise intensity is "just about right." [89]

Exercise intensity can also be classified as very light, light, moderate, vigorous, near maximal and maximal [88] (Table 9). Both moderate and vigorous intensity exercise are associated with numerous health benefits (discussed in previous sections) [88] and is the intensity of exercise recommended in the Canadian Physical Activity Guidelines [72, 74]. In the subsequent section, physiological differences between moderate and vigorous intensity will be discussed.

Table 9: Classification of Exercise Intensity

	Relative Intensity				Absolute Intensity	Absolute Intensity (METS) by Age		
Intensity	**%HRR or %VO_2R**	**%HR_{max}**	**%VO_{2max}**	**RPE (6-20 Scale)**	**METS (x3.5 mL/kg/min)**	**Young (20-39 yr)**	**Middle Aged (40-64 yr)**	**Older (>65 yr)**
Very light	<30	<57	<37	<9	<2	<2.4	<2.0	<1.6
Light	30-39	57-63	37-45	9-11	2.0-2.9	2.4-4.7	2.0-3.9	1.6-3.1
Moderate	40-59	64-76	46-63	12-13	3.0-5.9	4.8-7.1	4.0-5.9	3.2-4.7
Vigorous	60-89	77-95	64-90	14-17	6.0-8.7	7.2-10.1	6.0-8.4	4.8-6.7
Near max to max	≥90	≥96	≥91	≥18	≥8.8	≥10.2	≥8.5	≥6.8

Table reprinted with permission from Garber, C.E., et al., American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc, 2011. **43**(7): p. 1334-59. Copyright 2011, with permission Copyright Clearance Centre. Permission Obtained September 24, 2014 [88].

Physiological Effects of Varying Intensities of Exercise

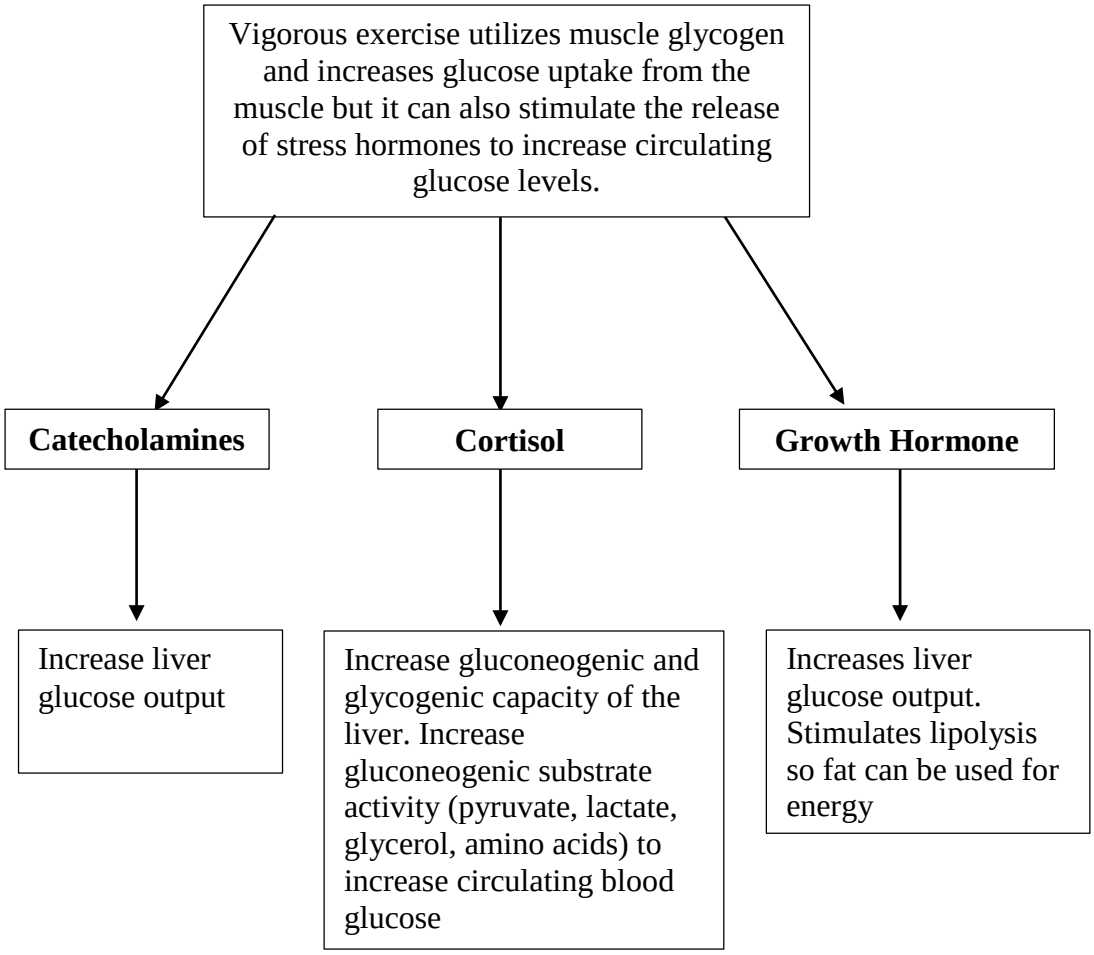
The energy required for muscular contraction can be obtained from amino acids, free fatty acids and glucose. For moderate intensity physical activity, myocytes rely primarily on glucose which come from three different sources: muscle glycogen, plasma glucose, and liver glycogen which is utilized as the intensity of exercise increases [20, 71, 99-103]. Muscle glycogen tends to be the first form of glucose utilization upon initiation of exercise as the stored glycogen can be converted into glucose via glucose-6-phosphate within the myocyte. Once these stores become depleted the body will use plasma glucose to fuel exercise [104]. Exercise-mediated glucose uptake is achieved through the translocation of GLUT-4 (glucose transport protein-4) to the plasma membrane independent of insulin concentration [20]. Muscular contraction activates a separate intra-cellular pathway for the translocation of GLUT-4 as compared to insulin [20]. Although not fully understood, contraction of myocytes induces calcium release from the sarcoplasmic reticulum, production of 5'AMP-activated protein kinase (AMPK); a homeostatic enzyme energy modulator of the cell, and nitric oxide (NO) [100]. These three separate signalling molecules act to release GLUT-4 from GLUT-4 containing vesicles within the cell allowing glucose uptake to occur [20, 100]. As plasma glucose utilization increases, the body will increase glucagon release and decrease insulin release as a way to maintain plasma glucose levels during exercise. [103, 104].

This mechanism of maintaining plasma glucose during moderate intensity exercise is absent in individuals with T1D. Because insulin is supplied exogenously, the insulin administered is maintained in the blood stream and substantially increases the risk of hypoglycemia [71]. The presence of insulin and the inability to decrease the circulating levels of

exogenous insulin can exaggerate glucose uptake into skeletal muscle and down-regulate glucose production from other sources such as the liver thereby inducing hypoglycemia [71].

Vigorous intensity exercise may be a way to reduce the risk of hypoglycemia for individuals with T1D. Although intense exercise increases glucose uptake, it also signals the body to release catecholamine's (epinephrine and norepinephrine) [103], cortisol [105], and growth hormone [101, 102]. Catecholamine's and growth hormone act directly on the liver to induce hepatic glucose output to endogenously increase plasma glucose during activity [71, 101-103]. Growth hormone also stimulates lipolysis so fat can be readily utilized for energy [106]. Cortisol acts to increase the gluconeogenic and glycogenic capacity of the liver and increase gluconeogenic substrate (pyruvate, lactate, glycerol, amino acids) activity in order to increase endogenous glucose production [105]. Refer to Figure 6 for a theoretical model of the processes involved for increasing blood glucose with high intensity exercise. One study found that the hyperglycemic effect of vigorous intensity exercise was so potent that persons living with T1D experienced an increase by 7.8 mmol/L to as much as 22.2 mmol/L in blood glucose following very intense exercise [71]. Several acute studies have capitalized on this phenomenon to reduce hypoglycemia in patients with T1D [5-11].

Figure 6: Theoretical Model for Reducing Risk of Hypoglycemia with High Intensity Intervals



Inflammation, Exercise, and Type 1 Diabetes

T1D is an autoimmune disease and it is marked by a degree of inflammation (a biologic response that is triggered by an infection or tissue damage, stress, or malfunction) [107]. A cascade of events is triggered that leads to inflammation in response to injury or stress, marked by a transient elevation in cytokines (polypeptide inflammatory mediator) in the circulation. The inflammatory response to exercise is marked by an elevation in myocyte-derived cytokines including tumor necrosis factor alpha (TNF-α) and interleukins 2 and 6 (IL-2, IL-6) [108]. Increased levels of TNF-α are associated with increases in insulin resistance which can perpetuate hyperglycemia [108]. Additionally, there can be a dose dependent relationship in acute inflammatory markers with increasing exercise intensity [109]. Although these responses to exercise can produce acute pro-inflammatory responses, chronic exercise training has an anti-inflammatory effect [110]. The anti-inflammatory effect of chronic exercise may contribute to the reduction in the risk of developing micro and macrovascular disease for people with T1D who are regularly physically active [111]. The anti-inflammatory effects of exercise however are not sufficient to blunt or prevent that autoimmune destruction of beta cells and prevent T1D. It is not known whether the inflammatory response plays a role in reducing the risk of hypoglycemia in persons with T1D, through the modulation of insulin sensitivity.

Acute Exercise Studies Comparing Moderate Exercise to High Intensity Training on Hypoglycemia

We recently conducted a systematic review and meta-analysis (waiting to be published) of acute exercise studies comparing moderate intensity exercise to high intensity exercise on post-exercise hypoglycemia. The initial search strategy found 3497 articles related to "exercise," "high intensity," and "diabetes." Twelve met our inclusion criteria which were as follows: (1) individuals with T1D, (2) acute high intensity or vigorous exercise training (aerobic or resistance), (3) comparisons to moderate exercise alone, and (4) post-exercise glucose measurements. Of the 12 studies included, 7 found high intensity exercise to be protective against early post-exercise hypoglycemia [5-11]. Unfortunately the studies suffered from several drawbacks, and they include: (1) only five studies utilized CGM technology [7, 11, 112-114], one was an observational study [114] and one utilized the CGM as a means to detect hypoglycemia before exercise not after [112], (2) only one study utilized a treadmill and it was for the moderate condition only [7], as running is a common form of exercise and requires minimal equipment, (3) only a single intensity for the high intensity intervals was used, (4) seven studies used maximal sprint effort which is unlikely to be self-selected by an inactive population [5, 6, 8-11, 112], (5) the duration of the high intensity burst was short lasting 4-15 seconds, (6) only three studies measured glucose values at night [7, 11, 113], and most studies recruited active participants with T1D [5-11, 113]. These limitations make it difficult to translate the results to an inactive population living with T1D; which forms a basis for addressing them in the present study. Refer to Appendix 4 for a complete breakdown of the acute studies.

Summary

T1D is an autoimmune disease in which beta cells of the pancreas are destroyed requiring exogenous insulin to maintain blood glucose. Hypoglycemia is a major limiting factor for blood glucose management and is greatly influenced by glucose variability. Risk of hypoglycemia is considered the primary barrier to physical activity participation because of the increased risk of low blood glucose particularly after moderate intensity exercise. Many acute exercise studies have capitalized on a physiological phenomenon where high intensity intervals trigger the release of catecholamine's, cortisol, and growth hormone thereby increasing hepatic glucose output and reducing the risk of post-exercise hypoglycemia.

The present study took advantage of this effect and compared three exercise intensities (70%, 80%, and 90% of HRR as measured by a maximal treadmill test) on time spent in hypoglycemia (≤3.9 mmol/L) and glucose variability in the 12 hours following exercise. It utilized sophisticated CGM technology (previously utilized by only five acute studies) and treadmill exercise in an inactive population with T1D which no acute studies have made use of for high intensity intervals.

METHODS

Aims and Hypotheses

This project was designed to address the limitations of past acute studies to determine the appropriate intensity of exercise needed to reduce the risk of post-exercise hypoglycemia. We hypothesized that adding intermittent bouts of high intensity exercise at 80-90% of HRR to an exercise session at 45-55% of HRR would significantly reduce the time spent in hypoglycemia (≤3.9 mmol/L) and glucose variability in the 12 hours following exercise compared to 45-55% alone. We further hypothesized that exercising at 70% of HRR would not be sufficient to reduce hypoglycemia, however it was included because it is a formally untested intensity.

Study Design

To test these hypotheses, we performed a 4-arm randomized cross-over exercise trial (Appendix 5). The Biomedical Research Ethics Board from the University of Manitoba approved this study in accordance with the Declaration of Helsinki (see attached documents – Appendix 10).

Study Population

Recruitment

Participants were recruited through posters placed at The Children's Hospital Research Institute of Manitoba, University of Manitoba, Walmart, Shoppers DrugMart, Diabetes Education Resource for Children and Adolescents, and Winnipeg Clinic. Pediatric and adult endocrinologists screened and referred patients to the study coordinator. Social media was also utilized through Facebook and Twitter to advertise the trial.

Inclusion Criteria

We recruited 10 participants between the ages of 15-35 years old living with T1D with an Hb_{A1c} <9.9% and were not considered sufficiently active to meet the national guidelines (<150 minutes of MVPA per week). Inactive participants were chosen as a means to assist people in weight loss goals in the hopes that glucose supplementation would not be necessary.

Exclusion Criteria

Individuals were excluded based on the additional criteria: (1) frequent and unpredictable hypoglycemia, defined as either a severe low requiring assistance within the last three months or hypoglycemia unawareness, (2) unable to exercise due injury or other restriction, (3) participate in structured physical activity (>150 minutes MVPA/week), (4) insulin management that changed in the past three months, (5) conditions that would make vigorous exercise unsafe such as high blood pressure, evidence of neuropathy, or a family history of heart disease, (6) cognitive impairment resulting in an inability to provide informed consent, (7) taking atypical antipsychotics or corticosteroids, (8) taking beta blockers, (9) are a woman who is currently pregnant, breastfeeding, or planning on becoming pregnant, and (10) shift workers who are awake at night.

Intervention

Each participant completed three intervention arms consisting of 45 minutes of moderate intensity exercise (45-55% HRR) with the addition of six, one minute high intensity bouts at 70, 80, and 90% of HRR every 4 minutes. A duration of 45 minutes and intervals dispersed every four minutes was selected as this procedure was similar to a study we were modelling our protocol after [11]. High intensity intervals of one minute were used as this protocol is well tolerated by inactive populations living with and without chronic disease [115-118]. In addition it

is a similar approach used by the Running Room in their "Learn to Run Program" [119]. HRR was used to measure intensity as it is a common way of prescribing exercise. A minimum intensity of 70% was selected as it has been shown to activate AMPK [120]. AMPK can be activated by muscle contraction and initiates the translocation of GLUT-4 thereby increasing glucose uptake into the muscle [121]. In addition, the ACSM position stand in 2011 defined vigorous intensity exercise as 70-89% of HRR, and 90% of HRR as near maximal activity [88]. A maximum intensity of 90% was chosen because it was unlikely that inactive individuals would self-select maximal effort. We believe that an inactive population is more apt to self-select intensities ranging from 70-90% compared to maximal effort.

Comparator (Control Condition)

The control arm consisted of 45 minutes of moderate intensity exercise at 45-55% of HRR and was selected to approximate the Canadian Physical Activity Guidelines [72, 74].

Outcome Measures

Primary Outcome

Time spent in hypoglycemia (≤3.9 mmol/L) in the 12 hours following each exercise session as measured by CGM.

Secondary Outcome

Glucose variability measured by mean absolute glucose change (MAG) and continuous overall net glycemic action (CONGA) in the 12 hours following exercise as measured by CGM.

Exploratory Outcome

Cortisol measured by competitive immunoassay before, during, and after exercise at 0 minutes (baseline-before exercise), 10 minutes (end of warm up), 35 minutes (end of intervals), 45 minutes (end of exercise), 75 minutes (mid recovery), and 105 minutes (end of recovery).

Timeframe

Primary and secondary outcome measures were assessed for a total of six days as the sensor used for the CGM must be removed after six days. Two exercise sessions were recorded on each sensor (sensor 1: moderate + vigorous #1; sensor 2: vigorous #2 + vigorous #3) in addition to days without exercise. This is unique compared to other studies, as the CGM was worn for a maximum of three days [7, 11, 112-114]. Exploratory outcome measure was assessed for a total of 105 minutes.

Data Collection

All participants were screened by an endocrinologist and study staff using the above eligibility criteria and had a resting electrocardiogram (ECG) to test for left ventricular hypertrophy, arrhythmias, or signs of coronary artery disease that may have been exacerbated with vigorous physical activity. Once a cardiologist confirmed their eligibility from the ECG, participants had a baseline appointment scheduled at the Children's Hospital Research Institute of Manitoba.

Baseline Appointment: Determination of Maximal Oxygen Uptake

All 10 participants completed a total of six visits to the exercise lab. On their first visit, all participants arrived at the lab for 9:00 AM on a Monday, Thursday, or Saturday for baseline measurements, a maximal exercise test, and a CGM insert. Upon arrival participants had the following measurements taken: (1) automated resting blood pressure (mmHg) averaged over five measurements, the final three measurements were used to estimate resting blood pressure [122] (2) resting heart rate (bpm) averaged over five measurements, (3) height (cm) averaged over two measurements, (4) weight (kg) averaged over two measurements, and (5) capillary blood glucose (mmol/L) checked via a finger poke upon arrival. Prior to starting the maximal exercise test to

predict maximal aerobic capacity, participants were given a Polar heart rate monitor to wear for the duration of the test. Immediately before participants started exercising blood glucose was checked via finger poke. If blood glucose was between 5.7-15.0 mmol/L, the exercise session started. If blood glucose was <5.7 mmol/L, glucose was administered in the form of Dex4 tablets (four grams of carbohydrates per tablet) until blood glucose rose ≥5.7 mmol/L (tested 10-15 minutes after carbohydrate administration). In the event of a severe hypoglycemic emergency (i.e. loss of conscious) the exercise lab was equipped with glucagon (no participant experienced a severe hypoglycemic emergency). If blood glucose was >15.0 mmol/L ketones were checked on a urine ketone strip, if the test was negative the max test began and if ketones were present the max test was rescheduled. No participant had to reschedule as ketones were always negative.

The graded maximal aerobic exercise test utilized direct gas analysis from the ParvoMedics TrueOne Metabolic System – OUSW 4.2cx (20061010) to quantify maximal oxygen uptake. Due to the constraints of the treadmill and the inability to go above 14% grade, we devised our own graded maximal aerobic exercise protocol see Table 10. Three, three minute submaximal stages were used as a comparison to other maximal exercise tests such as Bruce, Modified Bruce, Naughton, Wilson, and Kattus [93]. Submaximal stages below the anaerobic threshold (the point at which lactic acid begins to accumulate in the blood) were utilized because it allows oxygen to steady state and increase in a linear fashion as work rate increases which allows for a predictable response [123]. Incremental stages lasting at least three minutes below the anaerobic threshold are necessary for lactate to plateau allowing for precise measurements and reduces the risk of stopping exercise as a result of lactate accumulation as opposed to aerobic exhaustion [124, 125].

Before leaving the exercise lab a nurse inserted a CGM (CGMS®iPro2^{TM}; Medtronic MiniMed, Northbridge, CA, USA) into the subcutaneous tissue on the back just above the belt line or the abdomen. This device recorded interstitial glucose values every five minutes over the six day period. The output from the CGM was uploaded to a computer where the percentage of time spent ≤3.9 mmol/L (primary outcome) and glucose variability as measured by MAG and CONGA (secondary outcome) were calculated. Each participant was equipped with a logbook for recording food intake (to ensure participants were keeping meals consistent), glucose measurements (used as calibration points for uploading the CGM data), and insulin dosage (to estimate total daily insulin dose), as well as Glucerna shakes to consume at night, and Glucerna bars to be consumed at 4:00 PM; this is similar to another acute study allowing for our results to compare with theirs [11].

Table 10: Maximal Aerobic Power Exercise Protocol

Time	Speed (mph)	Grade (%)
0:00 – 3:00	2.0	0
3:00 – 6:00	3.5	0
6:00 – 9:00	5.0	0
9:00 – 10:00	5.0	2
10:00 – 11:00	5.0	4
11:00 – 12:00	5.0	6
12:00 – 13:00	5.0	8
13:00 – 14:00	5.0	10
14:00 – 15:00	5.0	12

All participants were asked to consume the same foods at the same time of day while wearing the CGM and record that information in the logbook during the days of data collection. This method was used in a previous study [126] and helped to reveal how consistent participants kept to the meal regimen. Each participant followed the schedule outlined in Appendix 1.

Exercise Sessions

Each participant arrived at 4:00 PM at the Children's Hospital Research Institute of Manitoba to ensure peaks and nadirs of an influential hormone on glucose metabolism (cortisol) was kept consistent. Upon arrival the participants consumed a Glucerna bar, if they had not done so already, as this guideline for reducing rapid onset exercise induced hypoglycemia has been established previously [127]. A nurse then inserted an IV into the antecubital space on the arm preferred by the participant. If an IV could not be inserted into the antecubital space, a hand vein was utilized for blood sampling as this is a viable alternative used in previous acute studies [10, 112, 113]. The IV was inserted approximately one hour prior to exercise to ensure stress hormones came closer to resting values prior to exercise as individuals may experience stress anticipating the IV insertion which can raise blood glucose [128]. Blood was sampled at (baseline-before exercise), 10 minutes (end of warm up), 35 minutes (end of intervals), 45 minutes (end of exercise), 75 minutes (mid recovery), and 105 minutes (end recovery) from the start of exercise as a means to compare changes in glucose and cortisol throughout exercise and recovery. Glucose was measured using a two-point end enzymatic assay with hexokinase and cortisol was measured using a competitive immunoassay with biotinylated polyclonal antibody against cortisol. Streptavidin was added and the chemiluminescent emission was measured by a photomultiplier and results were determined from a point calibration curve. Cortisol was

measured because changes in this hormone may help explain why high intensity exercise might be protective against hypoglycemia.

All exercise sessions began between 4:45 PM and 5:00 PM and lasted for 45 minutes as a means to keep hormone levels consistent. A duration of 45 minutes was chosen to keep our results comparable to a previous acute exercise study [11]; refer to Table 11 for an outline of the exercise sessions. To monitor blood glucose throughout exercise, a small amount of blood from the IV was taken with a syringe and tested on a glucometer at baseline, 15, 30, 75, and 105 minutes from the start of exercise to ensure the safety of the participant.

Table 11: Timeline for all Exercise Sessions

4:00 PM	Participant arrived and consumed a Glucerna Bar
4:15-4:45 PM	IV inserted by nurse
4:45 PM	Baseline blood draw
4:45-5:00 PM	Exercise session begins
5:00-5:45 PM	Exercise session ends
5:45-6:45 PM	Passive recovery

Control Condition: Moderate Exercise

The control condition consisted of 45 minutes of continuous exercise at 45-55% of HRR based on the maximum heart rate derived from the maximal exercise test. Refer to Appendix 2 for an outline of the session. HRR was used as a means to monitor exercise because it is a common method used to prescribe exercise [129]. Measurements of heart rate were based on the average heart rate from the baseline test (this is an estimation of resting heart rate) and the

maximum heart rate achieved during the maximal exercise test. The following formula [130] was used to calculate HRR for the moderate and high intensity sessions:

$$[(HR_{max} - HR_{rest}) \times \%HRR] + HR_{rest}$$

$$\boldsymbol{Example}: [(198 - 72) \times 0.45] + 72 = 129\ bpm$$

Intervention: Vigorous Intensity Exercise

The vigorous exercise sessions were allocated in a random order from www.randomnumbers.org where 1=70%, 2=80%, and 3=90% in order to minimize the potential confounding effects of utilizing a non-random order. The session began with a 10 minute warm-up at 45-55% of HRR to prepare the body for exercise [131]. The first high intensity interval occurred after the warm-up and lasted for one minute. There was a total of six high intensity intervals each lasting one minute and four minutes of recovery at 45-55% HRR between each interval. This protocol was used because of its success in previous studies using high intensity interval training in both healthy and unhealthy subjects [115-117] and it is a similar method used at the Running Room in their Learn to Run Program [119]. The first 2-3 intervals were used to determine the appropriate intensity for the session; this was determined based on predicted HRR. Once target heart rate was achieved for the intervals, the workload was kept as consistent as possible. In the event that a participant could not recover during the rest period, workload was adjusted. Each exercise session had six intervals at 70% HRR, six intervals at 80% HRR, or six intervals at 90% HRR depending on the sequence produced by the number generator. The speed and percent grade used for the 45-55% HRR session was used for the warm-up and recovery period between each interval, unless the workload needed to be adjusted due to an inability for heart rate to recover. Refer to Appendix 3 for a detailed outline of the session.

Equipment

Treadmill: Super Tread ST4600 HRT

The treadmill used for the study (Super Tread ST4600 HRT, Glendora California) had a maximum incline of 14% and speed of 12.0 miles/hour. It used a force multiplier motor system and two stage shock absorption systems on pivoting deck mounts [132].

Daily Physical Activity: Accelerometer: Respironics Actical®

A GT3X accelerometer (Actical, Montreal Canada) was used to measure daily physical activity. It utilized vector magnitude data from all three axis and assigned a number to distinguish whether a person was not wearing the monitor (number 0), standing (number 1), lying down (number 2), or sitting (number 3) [133].

Continuous Glucose Monitoring: CGM: iPro™ 2 Medtronic MiniMed

These devices (iProTM 2 Medtronic MiniMed, Brampton Ontario) use a flexible electrode that is inserted underneath the skin. This electrode measures interstitial glucose through a reaction with glucose oxidase. Glucose oxidase catalyses the oxidation reaction of glucose into hydrogen peroxide. Hydrogen peroxide can then be used to activate the sensors in the electrode. From this information glucose measurements can be quantified from the levels of hydrogen peroxide produced; therefore the more hydrogen peroxide produced the more glucose in circulation [134, 135]. CGM data was downloaded onto a secure website (http://ipro.medtronic.com) with only study ID and birthdate used as verifiers.

Heart Rate During Exercise: Polar RS800CX N Heart Rate Monitor

Polar RS800CX N heart rate monitors were used during the exercise sessions to monitor heart rate. After each exercise session the heart rate data was uploaded to *Polar Trainer 5* software.

Statistical Analysis

All statistical analysis were conducted using SPSS software version 22. Data are presented as median and interquartile range (IQR) unless otherwise stated. A friedman test (non-parametric) and repeated measures ANOVA (parametric) were used for primary and secondary outcome measures, while all other analysis utilized a friedman test only. Parametric and non-parametric tests were utilized to ensure lack of differences (if present) were not a result of an overly conservative approach to analysis (i.e. non-parametric test). We needed to recruit and test 10 individuals to detect a 50% difference in the time spent in hypoglycemia between the sessions that include high intensity intervals and the 45-55% session assuming a β=0.2 and α = 0.017 (adjusted for 3 comparisons). The projected 50% reduction in the time spent in hypoglycemia was derived from a previous acute study using a similar protocol and is considered clinically relevant [11]. Our projected sample size was also based on the other acute studies that had similar sample sizes ranging from seven to eleven participants [5-10, 112, 113, 136].

RESULTS

Demographics

A total of 54 people were initially screened for the study: 5 people declined participation, 19 were contacted but did not follow up with additional screening, 20 people were determined ineligible as they did not meet one or more inclusion criteria: (HbA_{1c} n=4, physical activity level n=12, medication n=1, possible neuropathy n=1, hypertension n=1, and age n=1). Finally, 10 participants met inclusion criteria, passed all stages of screening and completed all four arms of the experimental trial (Figure 7). Participants had a median age of 30 years (IQR (interquartile range): 25-32 yrs), with a median duration of diabetes of 9.5 years (IQR: 5.3-5.8 yrs). The majority of participants were male (60%) with a median VO_2max of 40.5 ml/kg/min (IQR: 39.0-42.5 ml/kg/min), females had a median VO_2max of 32.2 ml/kg/min (IQR: 26.8-35.7 ml/kg/min). Median HbA_{1c} was 8.0% (7.0-8.6) for the cohort. All but one participant was on multiple daily injections (MDI). Refer to Table 12 for baseline characteristics.

Figure 7: Enrollment Flow Diagram

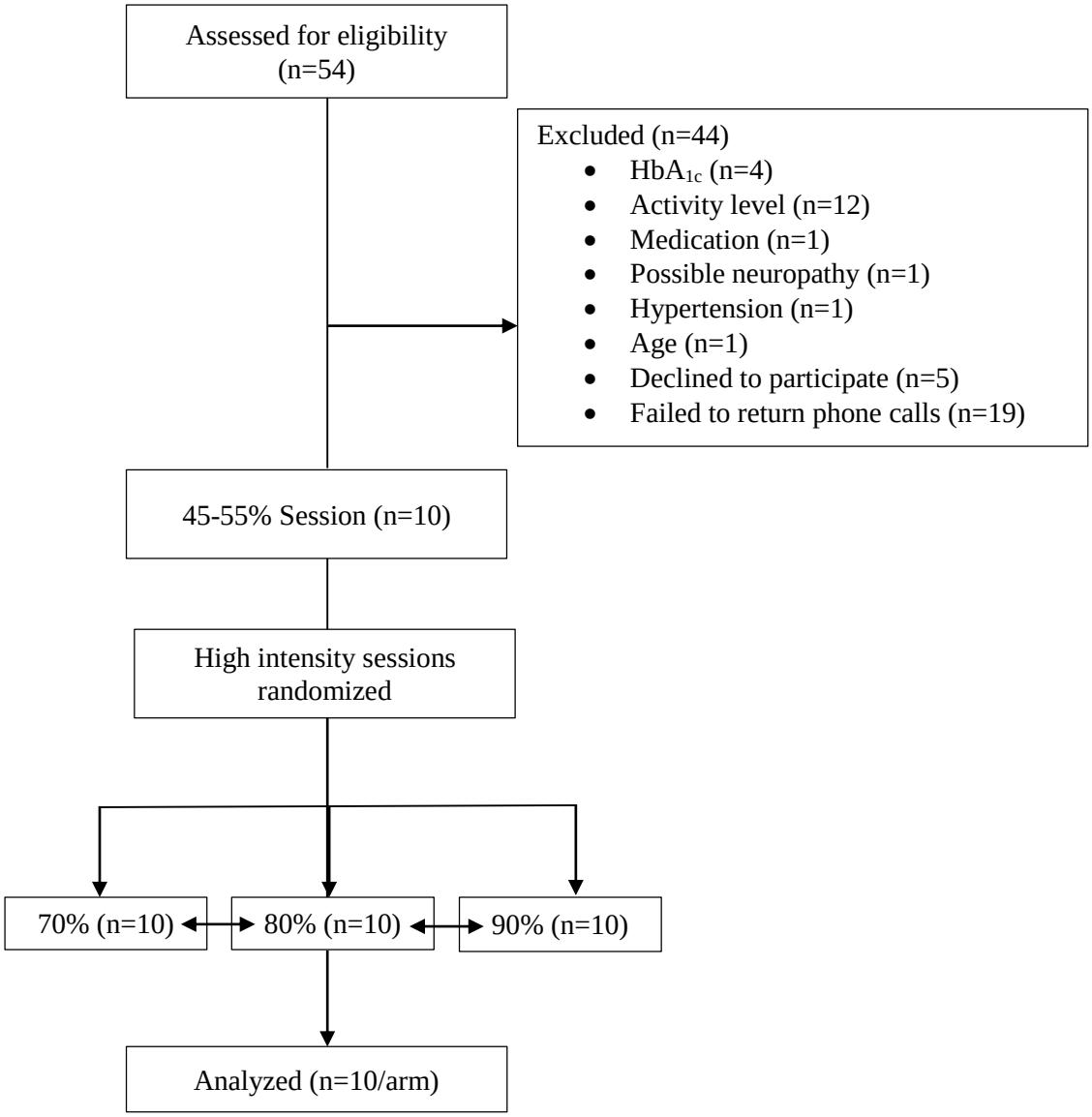


Table 12: Baseline Characteristics

Variable	Median (IQR)
Age (yrs)	30 (25-32)
Sex (male)	6 (60)
Height (cm)	178.2 (167.9-183.5)
Weight (kg)	88.4 (76.6-95.1)
Resting HR (bpm)	87 (81-96)
Systolic BP (mmHg)	127 (120-131)
Diastolic BP (mmHg)	79 (76-82)
VO_2 (ml/kg/min)	37.6 (30.8-41.0)
Diabetes Duration (yrs)	9.5 (5.3-15.8)
Insulin Regimen (MDI)	9 (90)
Total Daily Insulin Dose (IU)	52.3 (42.9-57.6)
HbA_{1c} (%)	8.0 (7.0-8.6)
HbA_{1c} (mmol/mol)	63.9 (53-70.5)
Total MVPA Minutes for Week 1	50.3 (33.3-76.1)
Total MVPA Minutes for Week 2	33.3 (5.4-54.0)

Results are presented as median and interquartile range (25^{th}-75^{th}) or N (%). Acronyms: bpm (beats per minute), MDI (multiple daily injections), IU (international units), MVPA (moderate to vigorous physical activity). Insulin regimen for other participant was continuous subcutaneous insulin injection. Total MVPA accumulated in 10 minute bouts or more retrieved from accelerometer using Kinesoft Program. Each participant wore an accelerometer on two separate occasions.

Training Data

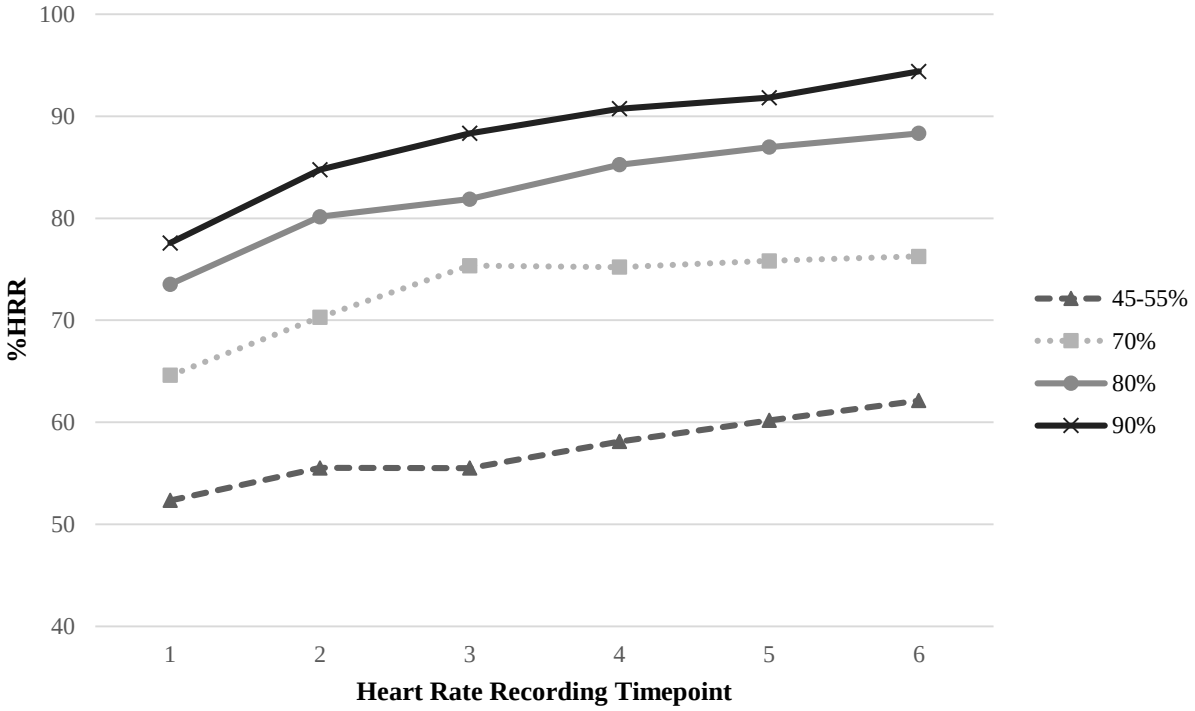
During each session, intensity was assessed using heart rate reserve (HRR) and rate of perceived exertion (RPE). All participants reached the desired intensity as measured by %HRR by the end of each session. Median %HRR increased with each incremental session: 45-55%: 58.1% of HRR, 70%: 73.7% of HRR, 80%: 84.4% of HRR, and 90%: 88.9% of HRR (Table 13, Figure 8). Some individuals struggled with the RPE scale and ranked themselves above 13 for the 45-55% session because of calf soreness. The median RPE for the 45-55% session and the 80% reflected the intensities predicted (12-13 and 14-17) [88], however the median RPE for the 70% and 90% session were lower than predicted (14-17 and ≥18) [88]. However, the overall median RPE increased with each session: 45-55%: 12, 70%: 13, 80%: 14, and 90%: 16 (Table 13, Figure 9).

Table 13: Heart Rate Reserve and RPE During Exercise

Study Arm*	Median %HRR	Median RPE
45-55%	58.1 (53.6-62.3)	12 (11-12)
70%	73.7 (70.2-79.0)	13 (13-13)
80%	84.4 (78.9-87.0)	14 (13-14)
90%	88.9 (83.0-92.2)	16 (15-16)

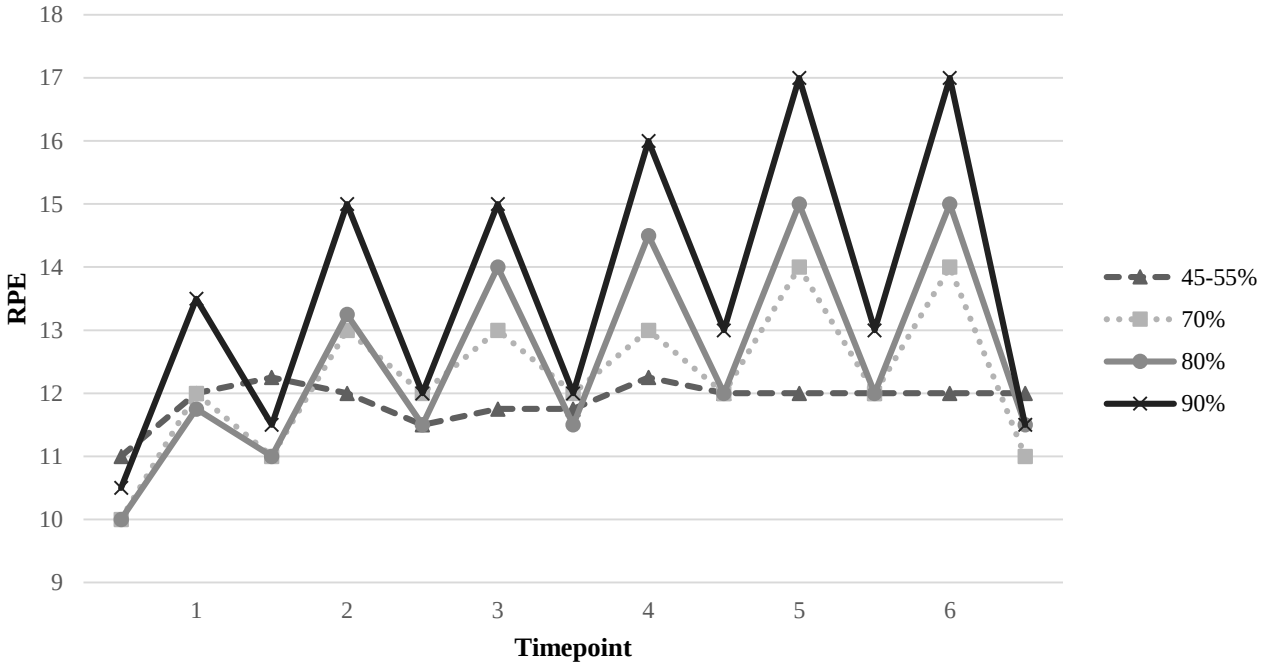
*of HRR. Data are presented as median and IQR (25^{th}-75^{th}). Acronyms: heart rate reserve (HRR) and rate of perceived exertion (RPE). Median RPE and median HRR for the interval sessions (70, 80, and 90%) are for the intervals only.

Figure 8: Median Heart Rate per Session



Acronyms: percentage of heart rate reserve (%HRR). Data are represented as the median percent heart rate reserve during each exercise session. Heart rate recording timepoint was recorded at the end of every interval. For the moderate session heart rate was recorded every five minutes expect during the warm up (10 minutes) and cool down (10 minutes). Timepoints are indicative as follows: (1) baseline, (2) end of warm up, (3) end of intervals, (4) end of exercise, (5) mid recovery, (6) end recovery.

Figure 9: Median RPE per Session



Acronyms: rate of perceived exertion (RPE). Data are represented as median RPE values throughout exercise. Heart rate recording timepoint was recorded at the end of every recovery period and interval. The six timepoints above represent heart rate recording at the end of each interval. For the moderate session heart rate was recorded every five minutes expect during the warm up (10 minutes) and cool down (10 minutes). Timepoints are indicative as follows: (1) baseline, (2) end of warm up, (3) end of intervals, (4) end of exercise, (5) mid recovery, (6) end recovery.

Baseline Blood Glucose, CHO, and Insulin

A Friedman test was used to determine differences in baseline glucose, CHO intake, and insulin between the four study arms. No significant difference in baseline blood glucose values were present (p=0.22). The majority of participants did not require CHO supplementation during exercise, although there was variation in the amount of CHO required by the participants, it was not significant (p=0.56). There was also no significant difference in insulin (IU/kg) on board prior to exercise (p=0.07). Refer to Table 14.

Table 14: Blood Glucose, Insulin, and Carbohydrates

Study Arm*	Baseline Glucose (mmol/L)	Insulin Prior to Exercise (U/kg)	CHO prior to Exercise (g)	CHO during Exercise (g)	Number of Participants Requiring CHO During Exercise
45-55%	5.8 (4.9-7.0)	0.27 (0.21-0.43)	0 (66)	0 (44)	3
70%	8.7 (6.2-9.4)	0.22 (0.16-0.26)	0 (24)	0 (12)	2
80%	7.3 (6.2-8.6)	0.24 (0.19-0.33)	0 (8)	0 (44)	1
90%	6.4 (5.5-7.3)	0.29 (0.14-0.30)	0 (20)	0 (36)	2

*of HRR. Data are presented as medians and interquartile range: median (IQR: 25^{th}-75^{th}). CHO prior to exercise and during exercise are presented as median and (total grams). Insulin prior to exercise was calculated from patient logbooks. Dex4 tablets were given as CHO supplementation. No significant groupwise differences for all values (p>0.05).

Serum Blood Glucose During Exercise

A Friedman test was used to determine differences in blood glucose values during exercise between sessions. Blood glucose was measured during exercise on a glucometer and blood samples were sent to Health Science Centre Clinical Chemistry Department for analysis. There was no significant difference in median serum blood glucose during exercise in all conditions (p=0.39). In addition there was no significant change in blood glucose during exercise (p=0.66) or change in blood glucose one hour post exercise (p=0.46), refer to Table 15 for these values and Appendix 6 for individual serum blood glucose values for all participants.

Table 15: Serum Blood Glucose During and After Exercise

Study Arm*	Blood Glucose During Exercise (mmol/L)	Change in Blood Glucose During Exercise (mmol/L)	Change in Blood Glucose 1 Hour Post Exercise (mmol/L)
45-55%	5.8 (4.4-6.8)	0.9 (0.0-2.7)	-0.2 (-0.6-(-0.1))
70%	7.6 (5.8-9.3)	1.1 (0.2-1.6)	-0.2 (-0.9-0.2)
80%	6.9 (5.4-7.8)	0.7 (-0.4-3.0)	-0.1 (-0.6-0.3)
90%	5.6 (4.2-7.3)	1.0 (0.0-2.0)	-0.4 (-0.9-(-0.2))

*of HRR. Data are represented as median values and (IQR: 25^{th}-75^{th}) in mmol/L. Blood glucose during exercise = median blood glucose value between baseline, end of warm up (10 mins), end of intervals (35 mins), and end of exercise (45 mins). Change in blood glucose during exercise is equal to baseline minus end of exercise. Change in blood glucose 1 hour post exercise is equal to 30 minute recovery time minus 60 minute recovery time. See Appendix 6 for raw data of each participant.

Primary Outcome: Percent Time Spent ≤3.9 mmol/L

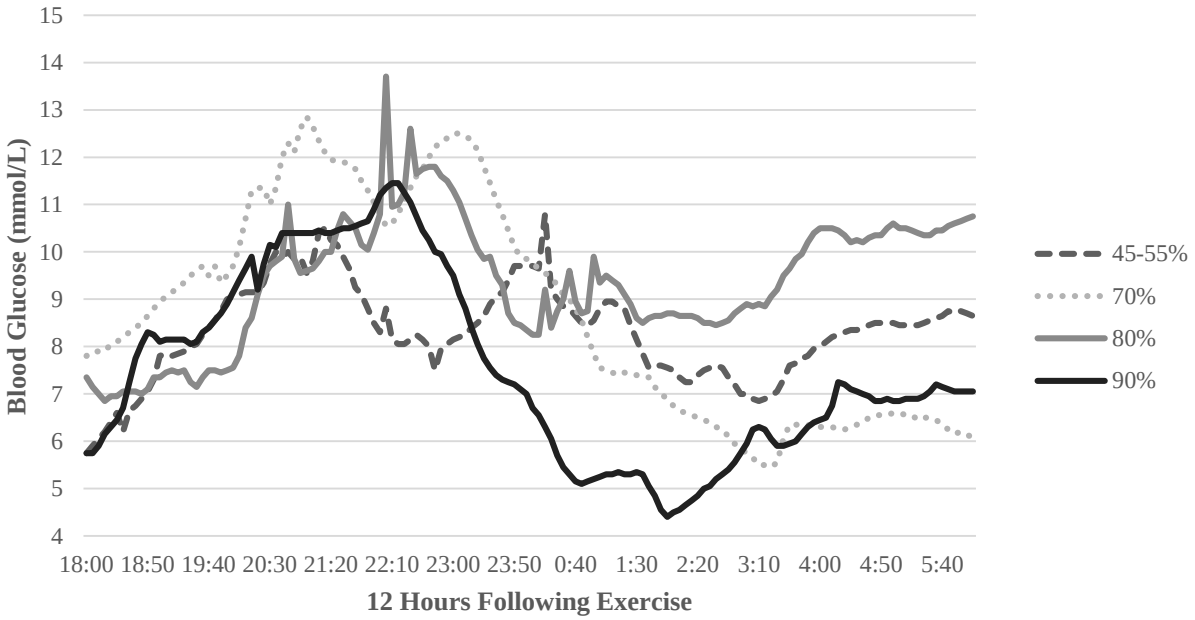
A Friedman test was used to determine if there were differences in the percentage of time spent ≤3.9 mmol/L between the exercise conditions, without adjusting for potential confounders. There was no statistical difference between the median (IQR) percentage of time spent ≤3.9 mmol/L between the conditions; 45-55% [0.0 (0.0-3.1)%], 70% [2.8 (0-6.7)%], 80% [0.0 (0-3.9)%], and 90% [4.1 (0.0-11.6)%], $\chi^2(2)=2.0$, $p=0.58$. Analyses were repeated using a repeated measures ANOVA, controlling for differences in baseline glucose levels and results remained unchanged F (1.4, 11.4) = 1.1, $p=0.33$. There was no trend in the median percentage of time spent ≤3.9 mmol/L between the conditions. Expected results would have been a decreasing trend in the percentage of time spent ≤3.9 mmol/L moving from 45-55% to 90% of HRR. Table 16 describes the percentage of time spent ≤3.9 mmol/L for each participant as measured CGM. A graphical CGM output is displayed in Figure 10 represents the median interstitial glucose values of all participants based on session.

Table 16: Individual Percent Time Spent ≤3.9 mmol/L in the 12 Hours Following Exercise

Study Arm*	1	2	3	4	5	6	7	8	9	10	Median
45-55%	54.5	0	28.3	4.1	0	0	0	0	0	0	0
70%	6.9	1.4	17.9	6.2	8.3	0	0	4.1	0	0	2.8
80%	0	0	13.1	3.4	0	4.1	17.2	0	0	0	0
90%	23.4	0	26.9	0	0	4.1	13.1	6.9	0	4.1	4.1

*of HRR. Data represents the percentage of time spent in ≤3.9 mmol/L in the 12 hours following exercise for each participant (1-10) as well as the median value for each session as measured by CGM.

Figure 10: Median Interstitial Glucose Values in the 12 Hours Following Exercise



Data is presented as median values for all participants over the four exercise sessions in the 12 hours following exercise as measured by CGM.

Secondary Outcome: Glucose Variability

Mean Absolute Glucose Change (MAG)

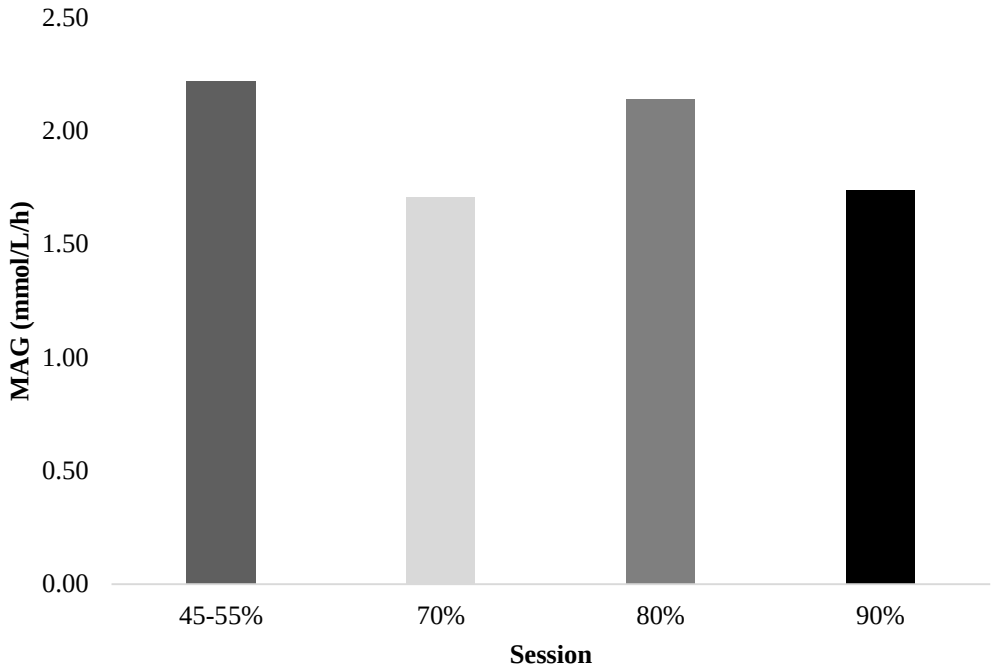
A Friedman test was used to determine if there were differences in glucose variability as assessed by MAG between the exercise conditions. MAG is measured in mmol/L/h and is an assessment of glucose variability between exercise days. MAG was not significantly different between conditions; 45-55% [2.2 (1.3-2.6) mmol/L/h], 70% [1.7 (1.5-2.2) mmol/L/h], 80% [2.1(1.5-3.1) mmol/L/h], and 90% [1.7 (1.3-2.4) mmol/L/h], $\chi^2(2)=2.2$, $p=0.53$. The analysis was repeated using a repeated measures ANOVA controlling for blood glucose levels prior to exercise, and results remained unchanged $F(1.5, 12.0) = 0.2$, $p=0.74$. There does a appear to be a minor trend of decreasing MAG values with high intensity exercise compared to the 45-55% session albeit not significant as all high intensity sessions had lower MAG values compared to the 45-55% session. This may indicate a beneficial effect of glucose variability as measured by MAG with high intensity intervals compared to exercise at 45-55% of HRR. Table 17 illustrates individual MAG values for each participant divided by session and Figure 11 depicts the median values.

Table 17: Individual Mean Absolute Glucose Change in the 12 Hours Following Exercise

Study Arm*	1	2	3	4	5	6	7	8	9	10	Median
45-55%	0.6	2.4	4.0	2.7	1.3	2.6	1.3	0.9	2.1	2.6	2.2
70%	0.6	2.4	2.1	1.7	1.1	2.2	1.5	1.7	2.8	1.6	1.7
80%	0.9	2.7	4.3	3.2	0.9	1.4	2.5	1.5	7.9	1.7	2.1
90%	0.7	1.8	2.7	1.7	1.7	2.2	3.3	2.5	1.2	1.2	1.7

*of HRR. Data represents the MAG value (mmol/L/h) in the 12 hours following exercise for each participant (1-10) as well as the median value for each session as measured by CGM.

Figure 11: Median MAG Values in the 12 Hours Following Exercise



Data is presented as median MAG values (mmol/L/h) for all participants over the four exercise sessions in the 12 hours following exercise as measured by CGM.

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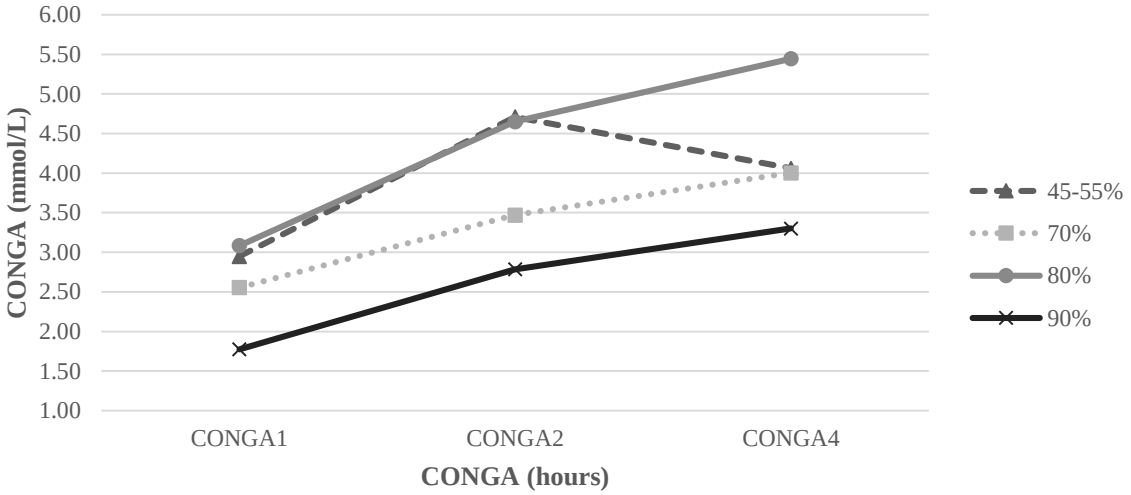
Continuous Overall Net Glycemic Action (mmol/L/h)

A Friedman test was used to determine if there were differences in glucose variability as assessed by CONGA between the exercise conditions which is measured in mmol/L and assesses glucose variability within the same day. CONGA values one, two, and four are presented as these are common among other studies [62, 63, 137, 138]. Median CONGA values are depicted in Figure 12. There were no significant differences in CONGA1 values between the sessions; 45-55% [3.0 (1.8-3.5) mmol/L], 70% [2.6 (2.1-3.1) mmol/L], 80% [3.1 (1.8-4.3) mmol/L], and 90% [1.8 (1.5-4.0) mmol/L], $\chi^2(2)=0.4$, $p=0.95$. There were no significant differences in CONGA2 values between the session; 45-55% [4.7 (2.6-5.5)mmol/L], 70% [3.5 (2.7-4.8) mmol/L], 80% [4.7 (2.4-6.9) mmol/L], and 90% [2.8 (2.0-5.8) mmol/L], $\chi^2(2)=0.6$, $p=0.90$. Finally, there were no significant differences in CONGA4 values between the session; 45-55% [4.1 (2.8-6.4) mmol/L], 70% [4.0 (2.8-6.4) mmol/L], 80% [5.4 (2.7-6.7) mmol/L], and 90% [3.3 (2.5-5.6) mmol/L], $\chi^2(2)=1.3$, $p=0.72$. Analysis was repeated using a repeated measures ANOVA controlling for blood glucose prior to exercise and results remained unchanged for all CONGA values; CONGA1: $F(1.6, 12.6) = 0.2$ $p=0.80$; CONGA2: $F(1.7, 13.9) = 0.4$ $p=0.68$ and CONGA4: $F(2.0, 16.2) = 2.1$ $p=0.16$. Although not significant, there does seem to be a trend for decreasing CONGA values with the 90% session compared to the 45-55% session. Table 18 illustrates individual CONGA values for participants based on session and Figure 12 represents median CONGA values for each session.

Figure 12: Median CONGA Values (1, 2, and 4) in the 12 Hours Following Exercise



Data are represented as median values for CONGA1, 2 and 4 (mmol/L) in the 12 hours following exercise for each exercise session as measured by CGM.

Table 18: Individual Continuous Overall Net Glycemic Action Values in the 12 Hours Following Exercise

Study Arm*	CONGA	1	2	3	4	5	6	7	8	9	10	Median
	CONGA1	0.9	2.9	5.4	3.7	1.5	2.4	3.5	1.6	3.0	3.5	3.0
45-55%	CONGA2	1.5	4.5	8.3	5.9	2.0	3.2	5.7	2.4	4.9	4.9	4.7
	CONGA4	2.0	6.6	7.9	4.8	2.4	3.3	5.7	2.7	7.5	3.1	4.1
	CONGA1	1.3	2.5	3.6	3.3	1.5	2.6	2.9	3.2	2.3	2.0	2.6
70%	CONGA2	1.8	3.4	4.2	5.8	2.4	3.6	5.0	5.4	2.6	3.1	3.5
	CONGA4	1.9	3.8	4.2	8.7	2.6	4.2	7.6	7.1	2.2	3.3	4.0
	CONGA1	1.6	4.2	3.0	4.4	1.0	2.5	4.5	1.2	4.8	3.2	3.1
80%	CONGA2	2.1	7.5	4.4	7.0	1.4	3.4	7.5	1.7	6.7	4.9	4.7
	CONGA4	2.1	10.5	6.3	5.7	1.9	4.7	10.4	1.7	6.8	5.2	5.5
	CONGA1	1.7	1.0	4.4	1.8	1.2	2.7	5.0	5.0	1.5	1.8	1.8
90%	CONGA2	2.8	1.1	6.6	2.8	1.8	3.5	9.2	7.0	1.7	2.6	2.8
	CONGA4	3.6	1.4	6.2	3.1	1.9	3.2	13.9	8.1	2.2	3.4	3.3

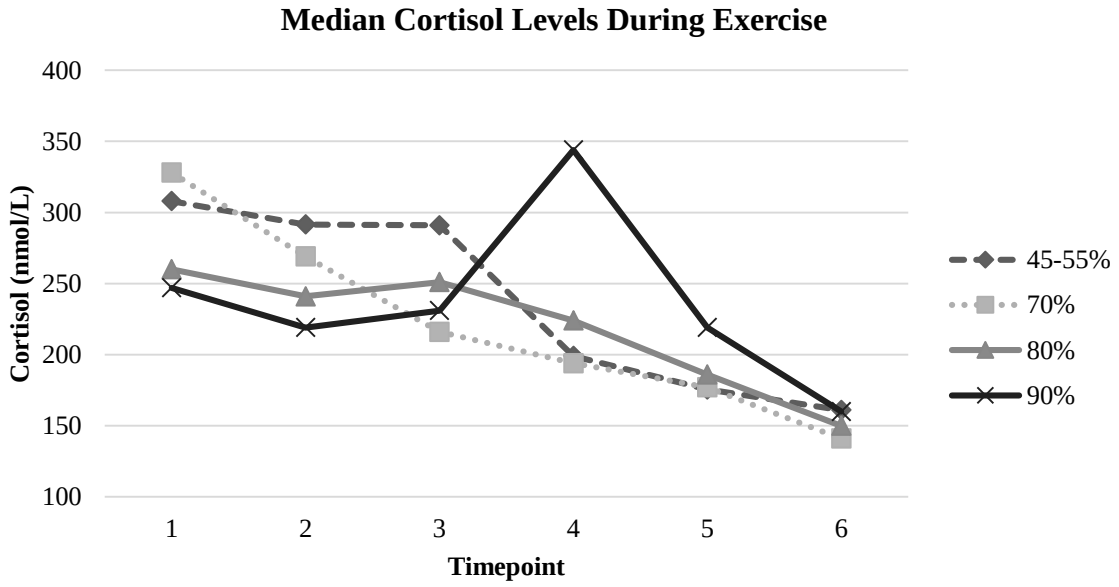
*of HRR. Data represents the CONGA values (mmol/L) in the 12 hours following exercise for each participant (1-10) as well as the median value for each session as measured by CGM.

Exploratory Outcomes

Cortisol

A Friedman test was used for all analyses. Cortisol levels were similar prior to starting exercise as no significant difference was found in baseline cortisol levels (p=0.86). There was a general decline in cortisol levels throughout exercise at every intensity in contrast to the theoretical framework proposed in Figure 6 which would suggest an increase in cortisol levels with increasing intensity. There was a significant pairwise comparison in the cortisol levels measured during the 90% at the end of exercise (timepoint 4) and the end of recovery (timepoint 6) (p=.004), however there was no significant difference in cortisol levels measured at the end of exercise between the conditions (p=0.62). Median cortisol levels during and after exercise are depicted in Figure 13 and Appendix 7 gives individual cortisol levels at each timepoint for every session.

Figure 13: Median Cortisol Levels During and After Exercise



Data are represented as median cortisol levels for each timepoint as measured by competitive immunoassay. Timepoints are indicative as follows: (1) baseline (p=0.86), (2) end of warm up (p=0.80), (3) end of intervals (p=0.98), (4) end of exercise (p=0.62), (5) mid recovery (p=0.32), (6) end recovery (p=0.54).

DISCUSSION

General Conclusion

We hypothesized that adding one minute bursts of high intensity exercise at 80-90% of HRR every 4 minutes into a 45-55% of HRR session would significantly reduce the amount of time spent in hypoglycemia and glucose variability in the 12 hours following exercise compared to session at 45-55% of HRR in an inactive population with T1D. We further hypothesized that adding bouts at 70% of HRR would not be sufficient to reduce the time spent in hypoglycemia, however it was still included because this intensity was untested. The results of this multi-arm cross over experiment in inactive persons with T1D do not confirm these hypotheses. Because there was no statistical significance when comparing exercise conditions, it is not possible to conclude that the 70% session was not sufficient in reducing the time spent in hypoglycemia. Although the 70% session had a higher median value of percent time spent in hypoglycemia (2.8%) compared to the 80% session (0.0%), it had a lower percent time compared to the 90% session (4.1%). An observed benefit during the 80% session was found in three participants who had the following declines in hypoglycemia compared to the session at 45-55%: -54.5%, -15.2%, and -0.7%. We also found that the 80% and 90% sessions did not offer a significant reduction in glucose variability as measured by MAG or CONGA compared to the control condition, however there were minor non-significant trends observed particularly with the 90% session. Several factors in the design of this study compared to other studies may explain these findings which are discussed in the following sections. Based on these observations the current study does not support previous acute trials demonstrating that high intensity intervals reduce the risk of hypoglycemia in persons with T1D

Hypoglycemia

Hypoglycemia is a common barrier to physical activity participation among people living with T1D [4]. To date, three acute studies have examined the effects of adding high intensity intervals to a continuous exercise session at a moderate intensity as a means to protect against post-exercise hypoglycemia [7, 11, 113]. In the present study, three different high intensity interval sessions (70%, 80%, and 90% of HRR) were compared to a moderate session at 45-55% of HRR on the percentage of time spent in hypoglycemia in the 12 hours following exercise. No added benefit of high intensity intervals was found to protect against hypoglycemia; this is similar to the findings of a cross-over study conducted by Campbell et al. [7]. They recruited nine physically active volunteers with T1D with interstitial glucose measures recorded for 24 hours following exercise using a CGM. Each participant completed a 45 minute continuous treadmill run at 77 ± 2.5% VO_2peak (~8.3 ± 0.6 km/h) and an intermittent protocol designed to simulate game-play activities separated by at least 48 hours at 8:00 AM. The intermittent protocol consisted of 45 minutes of the following rotation of activities: 3×20 meter walking, 1×20 meter sprinting with 4 seconds of recovery, 3×20 meter running at 55% VO_2peak, and 3×20 meter running at 95% VO_2peak. There was no significant difference in the total time spent in hypoglycemia (≤3.5 mmol/L) between the continuous protocol (157 ± 59 minutes) versus the intermittent protocol (223 ± 55 minutes, p=0.808). Also the total number of participants experiencing nocturnal hypoglycemia was the same for both conditions (n=6). Our study was similar to that of Campbell [7] and different from others that found that high intensity exercise elicited protection against hypoglycemia in that we used intensities less than 100% of peak workload and did not control pre-exercise meals/glucose levels as rigorously. These differences may explain the lack of protection against hypoglycemia in the current study.

In addition to the study conducted by Campbell et al. [7], one other study did not find high intensity exercise to be protective against nocturnal hypoglycemia compared to moderate exercise alone [113]. Maran et al. [113] conducted a cross-over study comparing moderate intensity activity at 40% of VO_2max to submaximal sprint effort at 85% VO_2max performed on a cycle ergometer for five seconds every two minutes in eight active males with T1D. They found that high intensity exercise performed at ~2:00 PM produced significantly (p=0.04) more time in hypoglycemia (23.3 ± 3.0 mg/dL/420 minutes) compared to moderate exercise (16.0 ± 3 mg/dL/420 minutes) in the nighttime hours. Based on the studies of Maran et al. [113], Campbell et al. [7] and the results of the present study, it is possible to hypothesize that submaximal sprint effort is not intense enough to produce a protective response and that maximal sprint effort may be required to reduce the risk of nocturnal hypoglycemia in people with T1D. However this likely does not apply to this study as we did not observe the near universal post-exercise hypoglycemia following moderate intensity activity. The failure to observe an effect was not related to a failure to prevent hypoglycemia, it was a failure to observe it during the control condition. It is possible that inactive individuals are less likely to experience hypoglycemia with exercise as they overcorrect with glucose or insulin adjustments prior to falling asleep.

The above studies and those observed in the present study contradict those found by Iscoe and Riddell [11] whose findings support the notion that high intensity exercise protects against nocturnal hypoglycemia. They recruited 11 physically active individuals with T1D (mean age 35 years) for a randomized cross-over trial with 12 hours of interstitial glucose monitoring following exercise. The participants performed two different exercise trials at 5:00 PM on two separate occasions separated by 1-4 weeks: (1) 45 minutes of moderate intensity exercise on a bike at 55% work rate peak and (2) a 45 minute intermittent high intensity protocol with nine 15-

second bouts at 100% work rate peak every five minutes. After the moderate session 5/11 people had a blood glucose ≤3.9 mmol/L during the nighttime hours while 3/11 subjects experienced hypoglycemia after high intensity exercise. Furthermore the percentage of time spent in hypoglycemia was 5.2% vs. 1.5% $p<0.05$. Iscoe and Riddell [11] concluded that in athletes with T1D the addition of high intensity bursts of activity into a moderate session is associated with less risk of nocturnal hypoglycemia.

Another major difference between the present study and those that observed reductions in hypoglycemia with high intensity exercise is the methods used to feed participants prior to the trial. For example, Iscoe and Riddell used standardized meals and snacks for all days under investigation whereas participants in the present study were asked to keep their meals as consistent as possible which is similar to a protocol used by a Yardley et al. [126]. The use of standardized meals eliminates the confounding effects of variable carbohydrate consumption before exercise. Participants in the present study did not keep their meals consistent as some missed meals, changed what they ate from day to day, and did not eat at the same time. This inconsistency may explain why there were numerous participants who experienced no hypoglycemia.

In addition, the present study enrolled inactive participants as compared to other studies who recruited physically active participants [11]. Some individuals are considered "non-responders" and can have an impaired activation of counterregulatory hormones with exercise [71]. Trained individuals are known to have higher norepinephrine, epinephrine, growth hormone, and cortisol responses to exercise (even at moderate intensities) [139] compared to non-trained individuals in persons without T1D. Additionally, trained individuals are known to be more sensitive to insulin and to counterregulatory hormones [140]. This could pose a possible

explanation for why studies in active individuals with T1D found significant responses to high intensity exercise [11], and more importantly, why we did not observe a significantly higher time spent in hypoglycemia during the control condition (45-55% of HRR). An observational study conducted in sedentary and physically active youth aged 16 ± 1.6 years with T1D concluded that physically fit individuals had an increased risk of developing hypoglycemia if exercise was performed in the afternoon/evening hours compared to sedentary individuals (p=0.03). This observation may pose a rationale why studies in active participants were able to detect an effect of high intensity exercise on hypoglycemia [11] while the present observed high rates of no hypoglycemia.

The lack of protection from hypoglycemia could also be explained by how the data was analysed. We relied on the more conservative median values and non-parametric tests for groupwise comparisons as data had significant outliers and median values are less resistant to extreme values [141]. However, the present study ran two different analysis, a Friedman test and repeated measures ANOVA. Both non-parametric and parametric tests produced non-significant results. When comparing the median and mean percentage time spent in hypoglycemia (Figure 14) it is apparent the use of mean values reveal a modest trend towards protection against hypoglycemia with increasing intensity of exercise.

Figure 14: Median vs. Mean Percent Time ≤3.9 mmol/L

Study Arm*	Median (IQR_1-IQR_3)	Mean ± SD
45-55%	0.0 (0.0-3.1)	8.7 ± 18.4
70%	2.8 (0.0-6.7)	5.0 ± 6.1
80%	0.0 (0.0-3.9)	3.8 ± 6.3
90%	4.1 (0.0-11.6)	7.9 ± 10.0

*of HRR. Data represents both median and mean values of the percentage of time spent ≤3.9 mmol/L in the 12 hours following exercise as measured by CGM.

Glucose Variability

To the best of our knowledge, one study examined the impact of high intensity interval training on glucose variability in people with T1D [11] (demographics of this study are described in the previous section). In persons with T1D, glucose variability has been associated with hypoglycemia [57] which is a common fear for these individuals [4]. Iscoe and Riddell [11] found a decrease in glucose variability as measured by standard deviation during the sedentary day (2.0 ± 0.31 mmol/L) compared to the moderate session (2.6 ± 0.51 mmol/L) and the high intensity exercise (2.8 ± 0.44 mmol/L) (p<0.05). No significant differences in glucose variability were found between the moderate or high intensity sessions in the above study. We found an improved response in glucose variability as measured by MAG and CONGA, albeit not significant, in the 90% session compared to the 45-55% session. The lack of consistency between our findings could be related to the measures used to quantify glucose variability. Using different measures of glucose variability make it difficult to compare from study to study. In the present study CONGA and MAG were used to quantify glucose variability, and in the above study standard deviation was used; a measure not best suited for non-normal glucose profiles [65]. CONGA and MAG are highly correlated with each other (r=0.809, p<0.001) [61], while standard deviation has weak correlation with CONGA (r=0.3, p=0.05) and no significant correlation with MAG values [64]. These differences in measurement make it hard to compare results considering the weak and lack of association between the measures of glucose variability utilized by Iscoe and Riddell and those of the present study.

A few studies have examined the association between exercise and glucose variability in patients with T2D [68, 69]. Van Dijk et al. [69] conducted a randomized cross-over trial and recruited 60 men with insulin and non-insulin treated T2D. In the 24 hours post exercise, there was a significant reduction in glucose variability as measured by CONGA1, CONGA2, and

CONGA4 compared to a non-exercise day. T2D is marked by insulin resistance and incomplete insulin secretion [12] and the primary goal of exercise is to reduce blood glucose and improve insulin sensitivity [142, 143], whereas T1D is marked by absolute insulin deficiency and caution is taken with exercise as it can lead to hypoglycemia [12]. Exercise has been shown to improve glucose variability in people with T2D [68, 69], however this relationship has not yet been found in people with T1D. The results of the present study are one of the first to analyze glucose variability after high intensity interval exercise (as measured by MAG and CONGA). Although the results were not significant, the 90% session had the lowest MAG and CONGA values compared to the 45-55% session. More research is needed on this topic, and future studies should examine the effect of exercise, and in particular high intensity exercise, on glucose variability in people with T1D.

Change in Blood Glucose

It is well established that continuous moderate intensity exercise reduces blood glucose and increases the risk for hypoglycemia during and immediately after exercise [71]. Several cross-over studies have found that adding maximal sprint effort into a moderate intensity exercise session attenuated the decline in blood glucose during the immediate recovery period (~2 hours post exercise) and in some cases reduced the risk of hypoglycemia [5, 6, 8-10]. For example Guelfi, Jones, and Fournier [8] conducted a cross-over study in seven physically active male and female volunteers with T1D. The purpose of the study was to establish whether or not high intensity exercise could reduce the risk of hypoglycemia after aerobic exercise. Exercise was randomized to either moderate intensity which consisted of 30 minutes of continuous cycling at 40% VO_2peak or high intensity which involved 30 minutes of continuous cycling at 40% VO_2peak interspersed with 4-second maximal sprint efforts every two minutes for a total of

16 sprints. The decline in blood glucose in the two hours following exercise was significantly (p=0.006) greater with moderate intensity exercise (-4.4 ± 1.2 mmol/L) compared with high intensity exercise (-2.9 ± 0.8 mmol/L). Blood glucose continued to decline into recovery with moderate intensity exercise but remained stable after high intensity exercise. These findings have been replicated in other studies in active participants with T1D [5, 6, 8-10]

Similar results were found in a cross-over study conducted by the same lab but with a single 10 second sprint added at the end of exercise [5]. Seven physically active men with T1D between the ages of 18 and 24 participated in the study and were randomized to one of two exercise conditions: 20 minutes of continuous moderate intensity exercise at 40% VO_2peak on a cycle ergometer and 20 minutes of moderate exercise at the same intensity but with an added 10 second maximal sprint at the end of exercise. Both exercise conditions had significant rapid declines in blood glucose during exercise, moderate: -3.1 ± 0.5 mmol/L and sprint: -3.6 ± 0.5 mmol/L, however blood glucose continued to drop into recovery after the moderate session (3.6 ± 1.2 mmol/L) but the maximal sprint effort prevented this additional decline in glucose during the recovery period.

In contrast to these observations the present study found that the change in blood glucose during exercise or immediately after exercise was not different between the conditions. For example blood glucose values after one hour of recovery were nearly identical across all four conditions (with a trend toward lower glucose with higher intensity): 45-55%: 6.4 (5.6-7.6) mmol/L, 70%: 7.3 (6.2-9.6) mmol/L, 80%: 6.0 (5.2-7.7) mmol/L and, 90%: 4.9 (4.1-9.5) mmol/L; p= 0.31.

Possible differences between the present study and those of the Fourneir lab likely explain the disparate results including: (1) a wider range of starting blood glucose values in the present study, (2) the time of day of exercise, (3) the intensity of the intervals, and (4) the inter-subject variability. For example serum blood glucose prior to exercise ranged from a median of 5.8-8.7 mmol/L (p=0.22) in the present study but was ~11.0 mmol/L in the majority of Fournier's studies [5, 6, 8, 10]. Other studies had a range of 7.0-12.0 mmol/L [7], and two studies had unspecified ranges [11, 113]. Starting blood glucose at a lower value increases the risk of dropping into a hypoglycemic range requiring carbohydrate supplementation to increase blood glucose [12], therefore in theory we should have been able to detect changes in hypoglycemia. However, we did not observe significant declines in blood glucose during or after exercise in the control (45-55%) condition. It is possible that the carbohydrate supplementation strategy negated the hypoglycemic effects of exercise, although the majority of people did not require CHO supplementation. In the absence of data from other studies, we are not able to compare CHO supplementation rates between trials.

In addition to differences in starting glucose levels, the differences in the time of day that the exercise sessions were held could also play a role in the blood glucose response. Blood glucose can be higher in the morning as a result of the Dawn Phenomenon [144]; in addition morning exercise is associated with less risk of post-exercise hypoglycemia as compared to afternoon exercise [145]. The above studies [5, 6, 8-10] started exercise in the morning ~8:00 AM and a strict morning schedule in terms of meal time, insulin dose, and blood glucose prior to exercise. This is contrasted to our study where exercise began at ~5:00 PM with less regimented protocols prior to exercise. One possible explanation for a lower risk of hypoglycemia in the evening exercise with the present study, compared to morning exercise is an increased

susceptibility to stress as stress increases blood glucose levels [146, 147]. A cross-over study where participants performed their exercise experiment at ~5:00 PM found similar non-significant falls in glycemia during the moderate and high intensity sessions [11]. Taken together high intensity intervals in the morning appear to negate the fall in glycemia that normally occurs with moderate exercise, however high intensity intervals performed in the evening does not oppose the fall in glycemia immediately after exercise.

Another major difference between previous cross over trials of acute exercise is the range of intensities used during the high intensity sessions. Previous studies have used single or repeated bouts of exercise at a workload equivalent to 100% of maximal fitness [5, 6, 8-11]. In contrast to other studies, the high intensity intervals in the present study were delivered at sub-maximal intensities for longer periods of time (60s vs 4-10s). While it is enticing to theorize that the intensities used to prevent hypoglycemia in the current study were sub-optimal to prevent hypoglycemia that is not the case. A primary limitation of the current study was the failure to observe post-exercise hypoglycemia or reductions in blood glucose during exercise in the control condition. In the absence of post-exercise reductions in blood glucose it is not possible to detect a protective effect of higher intensity intervals. This line of evidence supports the theory that strategies used to prevent hypoglycemia during and following exercise may have been too conservative and washed out the effects of exercise.

Finally, several key differences existed in the patient populations of previous studies and the one presented here. First the participants studied here were older (30 vs 21 yrs), displayed lower fitness levels (37.6 vs 44.5 ml/kg/min) and did not receive standardized meals prior to exercise. The failure to replicate the findings of others with a more heterogeneous sample,

suggests this approach to prevent falls in glycemia during and after exercise may not be ideal for broad translation into the general population of individuals living with T1D.

Cortisol

According to the theoretical model proposed by Hill et al. [148] an intensity threshold of ≥60% VO_2max is required for significant elevations in circulating cortisol levels to occur with exercise. The present studied proposed a mechanistic model in Figure 6 of hormonal release during high intensity intervals and its effects on blood glucose levels in people with T1D. Cortisol was measured because it has been shown to enhance the glycolytic and gluconeogenic capacity of the liver thereby increasing circulating blood glucose levels [105]. Therefore, high cortisol levels during exercise could be associated with less time spent in hypoglycemia in the 12 hours following exercise. When examining the effects of cortisol on other acute studies, only one found a significant increase in cortisol with a single maximal sprint effort [5] compared to moderate exercise alone. All other studies that measured cortisol found no significant difference in cortisol levels between conditions [6, 8-11, 113, 136]. Our results are comparable to the other acute studies who had negative results with no significant difference in cortisol levels between the exercise conditions [6, 8, 10, 11, 113, 136]. We also found no significant associations between the median cortisol levels and percent time spent in hypoglycemia as shown, 45-55%: -0.2 p=0.69; 70%: -0.3 p=0.44; 80%: -0.6 p=0.08, and 90%: -0.6 p=0.09. It is possible that cortisol does not play a significant role in maintaining blood glucose following high intensity intervals, as other studies have proposed that catecholamine's play a more important role [149]. The majority of acute studies that found high intensity exercise to be protective against falls in glycemia found a significant increase in epinephrine and/or norepinephrine in the high intensity

session compared to moderate exercise [5, 6, 8-10] as these hormones can be regulators of glucose production [150].

Strengths and Limitations

The following study had several strengths that should be discussed. First, our study used CGM technology to measure post-exercise interstitial glucose, which was only used in five other studies analysing the glucose response to acute exercise in persons with T1D [7, 11, 112-114]. CGM technology takes blood glucose measurements every five minutes over a six day period which gives a better picture of blood glucose measurements as opposed to self-monitoring alone [134, 135]. Second, our study utilized a treadmill, formally used in only one study [7]. This is a strength as walking and running are common forms of exercise that require minimal equipment. Third, our study utilized three different exercise intensities below maximal effort as we felt that maximal effort would not be self-selected by an inactive population. Fourth, the high intensity intervals used in the current study were similar to conventional programs designed to gradually introduce inactive individuals to higher intensity activities like running (i.e. the Learn to Run program at the Running Room) [119]. Fifth, we studied an inactive population which is unique as most studies recruited active participants [5-11, 113]. Finally we employed the use of CGM technology during the night time hours, formally used in only three studies [7, 11, 113]. This is a strength as little information exists describing the impact of higher intensity exercise on nocturnal glycemia, which is a critical time period for experiencing hypoglycemia [151].

Although we had several strengths that addressed the drawbacks of other studies, we also had several limitations. First, the small sample size coupled with the high degree of variability in the post-exercise glucose levels provided insufficient power to test for an effect of the intervention on hypoglycemia. Additionally we did not standardize the pre-exercise meal,

particularly CHO intake or the timing/dose of insulin prior to each session. We simply instructed participants to keep meals as consistent as possible, which is similar to a previous study [126]. When looking at the food diaries submitted by each participant it was evident that almost all participants did not keep their meals consistent. Most participants were able to keep breakfast the same from day to day but changes in lunch and dinner were apparent. It is possible that these meal inconsistences masked the effect that high intensity intervals could have played on post-exercise hypoglycemia.

For safety purposes we administered a Glucerna bar prior to exercise, CHO in the form of Dex4 tablets before, during, and after exercise if blood glucose dropped ≤3.9 mmol/L, and Glucnera shakes before bed. Previous studies did not report the strategy used to prevent severe hypoglycemia therefore it is difficult to compare the current strategy to others, however the liberal use of CHO administration during and following exercise to protect participants from a severe hypoglycemic event, likely contributed to the low rates of time spent below 3.9 mmol/L in the current study.

Future Directions

Although acute studies have detected a beneficial effect of high intensity intervals on glycemia in the short term [5, 6, 8-11] a quality randomized controlled trial has not been conducted to see if this effect on glycemia can be sustained over a longer period of time (~3 months). Therefore, a large randomized controlled trial could be conducted to see if high intensity intervals can protect against nocturnal hypoglycemia over a long period of time; this is already in progress in our lab. While Glucerna bars and shakes were used to protect against drastic falls in glycemia [11, 126], their use may have masked the effect of higher intensity exercise. It is possible that consuming Glucerna shakes before bed protected against some

nocturnal hypoglycemia [152] and may be a confounding factor in detecting protection from high intensity exercise. While this is a positive outcome for patients, it limited the ability to detect the effect of higher intensity exercise however, Iscoe and Riddell [11] found high intensity intervals to be protective against hypoglycemia in the nighttime hours even with Glucerna shake consumption before bed and a standardized snack before exercise.

It has been hypothesized that protection from hypoglycemia may be a result of increased levels of catecholamine's [71, 103] and cortisol [105], however the half-life of these hormones is only ~2-3 minutes [153] and ~66 minutes [154] respectively. It would be interesting to examine these hormone levels during the nighttime hours on three separate occasions: rest, moderate exercise, and high intensity exercise in people with T1D to see if there would be differences that might explain why Iscoe and Riddell found high intensity exercise to be protective despite the short half-life of those hormones. Future studies could also compare differences between maximal/supramaximal exercise and submaximal exercise on nocturnal hypoglycemia. As the results of the current study were negative, the "dose" or intensity of activity needed to elicit the response remains unclear. Finally, it is unclear if the beneficial effects of this approach are restricted to or heighted among physically active individuals, studies comparing the effects of this model between individuals with T1D across a range of activity levels, would provide greater insight into the generalizability of this model across patient populations.

Lessons Learned

Throughout this project I have learned that the response to exercise and CHO supplementation is quite variable among people with T1D. Some participants responded exactly as you would predict to high intensity intervals while others did not. According to the Clinical practice guidelines 15 grams of glucose should increase blood glucose by ~2.1 mmol/L, however

this was not the case for all individuals. Although my hypotheses were not confirmed, I would still recommend high intensity interval training to people with T1D because of the numerous health benefits associated with such training and our study found no increased risk of hypoglycemia when doing so [155]. I would recommend that precautions before, during, and after exercise be taken such as: avoiding insulin injection in the legs, avoid insulin injection two hours prior to exercise, and testing blood glucose throughout exercise to ensure it is in a safe range.

CONCLUSIONS

In conclusion, exercise is beneficial for individuals living with T1D for reasons such as improved cholesterol levels, body composition, blood pressure, cardiorespiratory fitness, musculoskeletal fitness, and bone density [73]. However, based on these study findings, there does not seem to be a diabetes specific benefit of high intensity intervals on hypoglycemia or glucose variability in inactive people living with T1D.

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APPENDICES

Appendix 1: Schedule of Appointments

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	
						Baseline or *CGM re-insert*	**Option 1**
No exercise	Moderate session or *Vigorous session #2*	No exercise	Vigorous session #1 or *Vigorous session #3*	No exercise	CGM removed in the morning	Accel removed in the morning	
	Baseline or *CGM re-insert*	No exercise	Moderate session or *Vigorous session #2*	No exercise	Vigorous session #1 or *Vigorous session #3*	No exercise	**Option 2**
CGM removed in the morning	Accel removed in the morning						
				Baseline or *CGM Re-insert*	No exercise	Moderate session or *Vigorous session #2*	**Option 3**
No exercise	Vigorous session #1 or *Vigorous session #3*	No exercise	CGM removed in the morning	Accel removed in the morning			

Appendix 2: Moderate Session

Stage	Time	Speed	Incline	HR	RPE	Blood Draw	Blood Glucose
Baseline	0					0	
Moderate Exercise 45-55% HRR	0-**10** (Warm up)					10	
	10-**15**						15
	15-**20**						
	20-**25**						
	25-**30**						30
	30-**35**					35	
	35-**40**						
	40-**45**					45	
						75	75
						105	105

Appendix 3: Vigorous Intensity Sessions

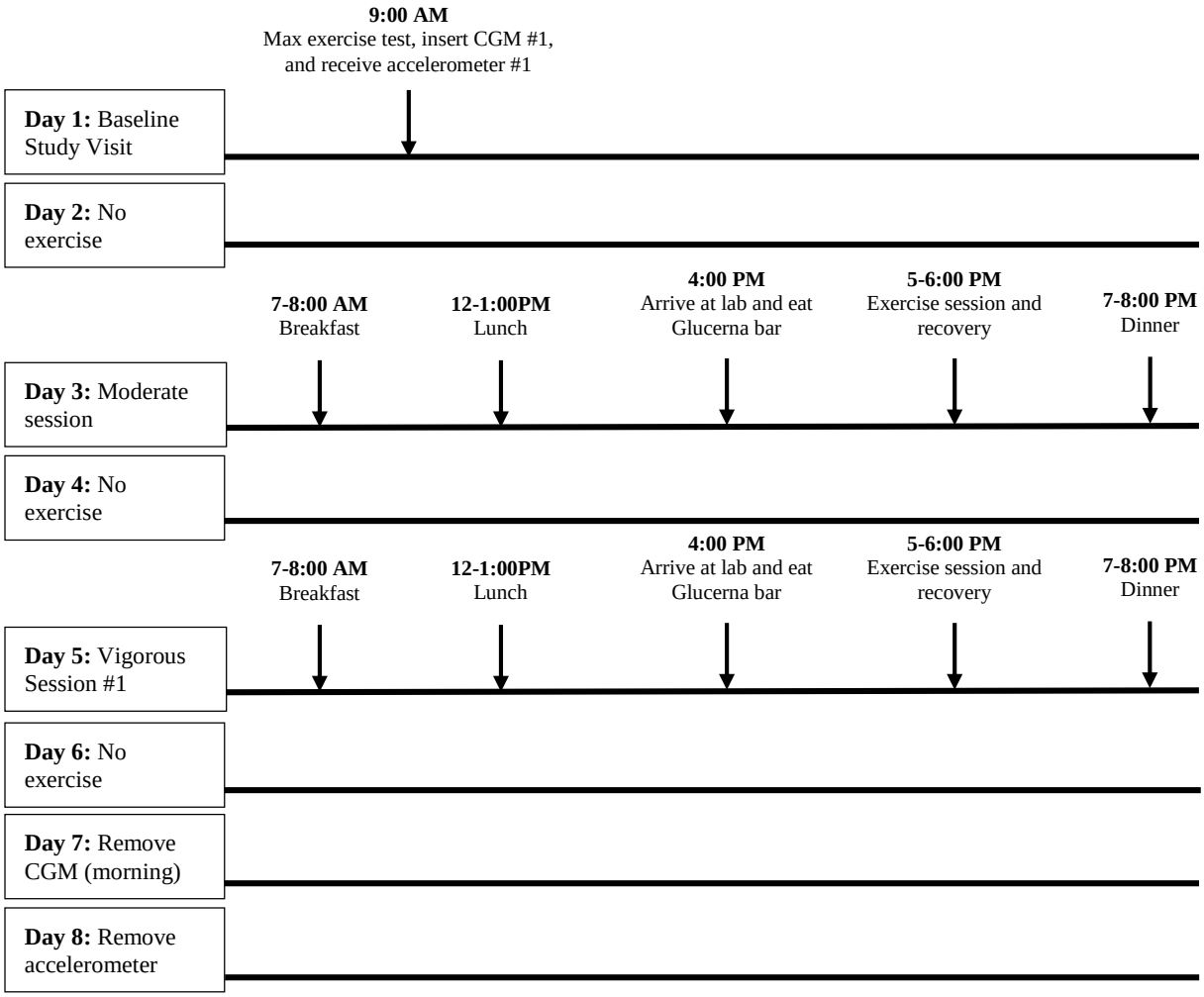
Stage	Time	Speed	Incline	HR	RPE	Blood Draw	Blood Glucose
Baseline	0					0	
Warm-up	0-10					10	
Interval 1	**10-11**						
Recovery	11-15						
Interval 2	**15-16**						
Recovery	16-20						
Interval 3	**20-21**						21
Recovery	21-25						
Interval 4	**25-26**						
Recovery	26-30						
Interval 5	**30-31**						31
Recovery	31-35						
Interval 6	**35-36**					35	
Cool down	36-45					45	
Recovery 1	45-75					75	60, 75
Recovery 2	75-105					105	90, 105
				Overall RPE			

Appendix 4: Summary of Acute Studies

Study	Age (years)	N (males/females)	Activity Level of Participants	Moderate Session	High Intensity Session	Time of Day of Exercise	Conclusion
Metcalf et al. (2014) **[114]**	16 ± 1.6	9/10	Habitually active and sedentary	Observational habitual exercise		Active at any time of day	Moderate to vigorous physical activity in the afternoon/evening increases risk of hypoglycemia
Silveira et al. (2014) **[156]**	24 ± 6.4	6/6	Not specified	40% of 1 RM	60-80% of 1 RM	2:00-6:00 PM	Resistance training lowers blood glucose regardless of the intensity
Campbell et al. (2014) [7]	35 ± 4	7/2	Habitually active	45 minutes 77 ± 2.5% of VO_2peak	45 minutes 55-95% of VO_2peak (Loughborough Intermittent Shuttle Test)	8:00 AM	High intensity exercise protective in early recovery but does not protect against nocturnal hypoglycemia
Davey et al. (2013) **[112]**	21.3 ± 2.6	6/2	Not specified	Morning hypoglycemia clamp or morning euglycemia clamp	10 s sprint at 100% VO_2peak	3:00 PM	A 10 s sprint increases blood glucose even after morning hypoglycemia
Iscoe, Riddell (2011) [11]	35.1 ± 3.5	5/6	Habitually active	45 minutes 55% Work Rate peak	45 minutes 9×15s sprints at 100% work rate peak	5:00 PM	High intensity sprints are associated with less nocturnal hypoglycemia
Maran et al. (2010) **[113]**	34 ± 7	8/0	Habitually active	30 minutes 40% VO_2peak	45 minutes 5 s sprints at 85% VO_2peak every 2 minutes	2:00PM	High intensity exercise is associated with delayed risk of hypoglycemia in the nighttime hours
Bussau et al. (2007) [6]	21.6 3.6	7/0	Not specified	20 minutes 40% VO_2peak	10 s sprint at 100% VO_2peak before 20 minutes of moderate exercise	8:00 AM	10 s sprint prior to moderate exercise delays the fall in glycemia up to 45 minutes after exercise
Guelfi et al. (2007) [10]	22.6 ± 5.7	5/4	Habitually active	30 minutes 40% VO_2peak Blood glucose maintained at 5.5 mmol/L	20 minutes 4 s sprints at 100% VO_2peak every 2 minutes	7:30 AM	Glucose production is greater with high intensity sprints to compared to moderate exercise alone

Study	Age (years)	N (males/females)	Activity Level of Participants	Moderate Session	High Intensity Session	Time of Day of Exercise	Conclusion
Bussau et al. (2006) [5]	21 ± 3.5	7/0	Active	20 minutes 40% VO_2peak	20 minutes 40% VO_2peak with a 10 s sprint at 100% VO_2peak at the end of exercise	8:00 AM	A 10 second maximal sprints opposes the fall in glycemia that naturally occurs with moderate exercise for up to 2 hours post exercise
Guelfi et al. (2005) [9]	18.6 ± 2.1	8	Active	20 minutes No exercise	20 minutes 11×4 s sprints at 100% VO_2peak every 2 minutes	8:00 AM	High intensity intervals does not increase the risk of post-exercise hypoglycemia
Guelfi et al. (2005) [8]	17.6-25.6	4/3	Physically active	30 minutes 40% VO_2peak	30 minutes 16×4 s sprints at 100% VO_2peak every 2 minutes	8:00 AM	The decline in blood glucose was less with high intensity exercise during and after exercise
Hubinger et al. (1985) **[136]**	20-47	4/5	Untrained	30 minutes 75-125 watts	3 × 10 minute bouts at 75-125 watts with 2 minutes of passive rest between each bout	9:00 AM	There were similar declines in blood glucose in both conditions

Appendix 5: Randomized Cross-Over Trial



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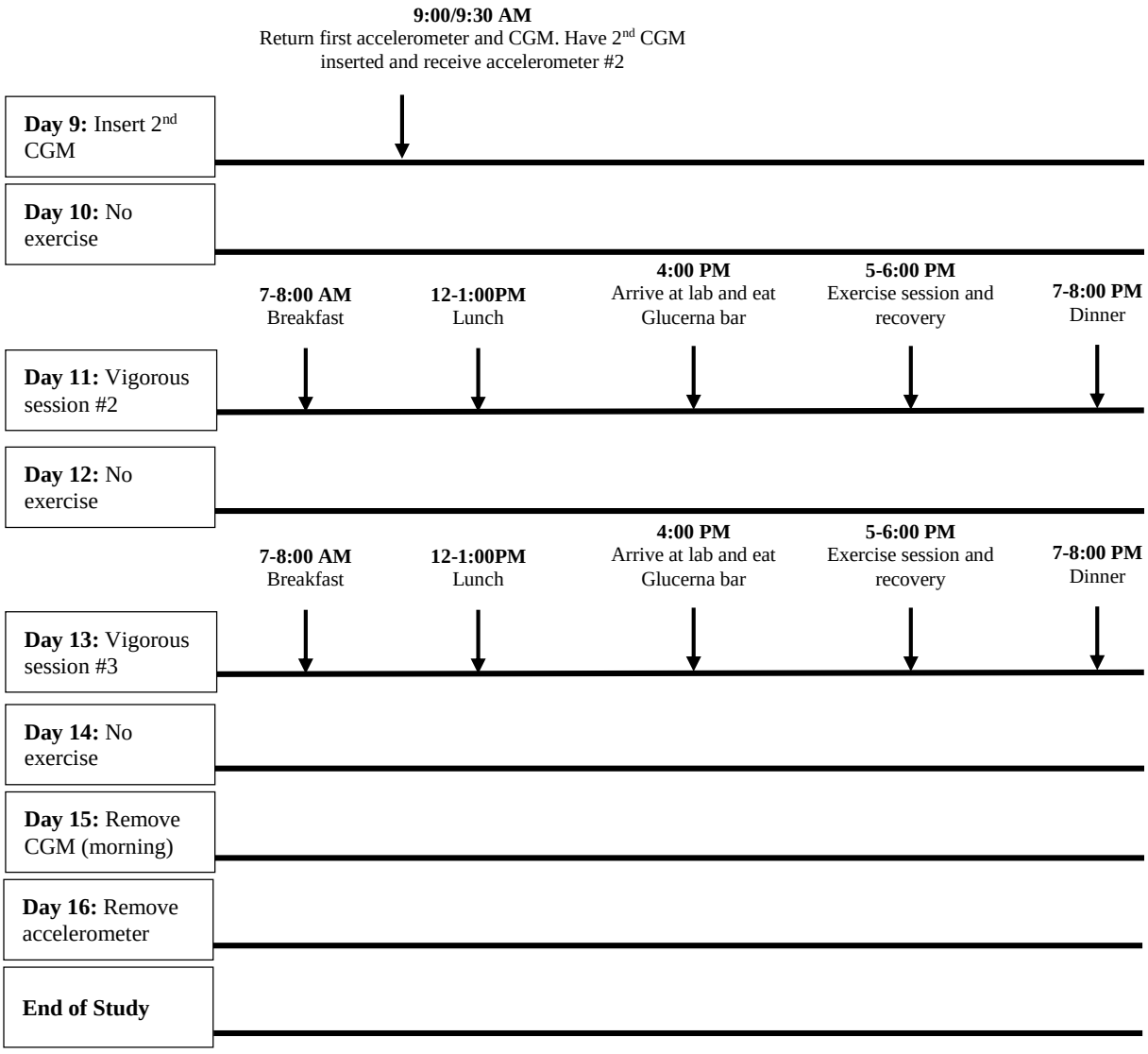

9:00/9:30 AM
Return first accelerometer and CGM. Have 2nd CGM inserted and receive accelerometer #2
Day 9: Insert 2nd CGM
Day 10: No exercise
7-8:00 AM Breakfast
12-1:00PM Lunch
4:00 PM Arrive at lab and eat Glucerna bar
5-6:00 PM Exercise session and recovery
7-8:00 PM Dinner
Day 11: Vigorous session #2
Day 12: No exercise
7-8:00 AM Breakfast
12-1:00PM Lunch
4:00 PM Arrive at lab and eat Glucerna bar
5-6:00 PM Exercise session and recovery
7-8:00 PM Dinner
Day 13: Vigorous session #3
Day 14: No exercise
Day 15: Remove CGM (morning)
Day 16: Remove accelerometer
End of Study

Appendix 6*:* Serum Blood Glucose Measures During and After Exercise

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
					45-55%					
Mean BG During Exercise	6.2	8.5	5.0	6.4	7.2	3.9	4.8	5.2	4.5	5.7
Change in BG During Exercise	-0.1	3.6	0.4	-2.0	1.3	0.8	3.3	3.1	1.0	-1.3
Change in BG 1 Hour Post Exercise	-0.2	-0.1	0.3	-0.1	-1.1	-0.3	-0.2	-1.0	0.1	-0.7
					70%					
Mean BG During Exercise	8.9	6.2	8.0	6.2	10.4	6.2	5.7	3.4	12.4	8.6
Change in BG During Exercise	-0.7	6.1	1.6	-0.1	0.5	1.2	0.1	0.9	6.8	1.5
Change in BG 1 Hour Post Exercise	0.0	0.3	-0.3	0.3	-1.9	-1.1	0.3	-0.3	-0.1	-1.6
					80%					
Mean BG During Exercise	12.4	6.4	6.1	6.5	7.5	7.8	4.8	7.0	6.1	5.2
Change in BG During Exercise	-1.6	1.1	3.2	-2.3	0.3	4.4	2.4	-0.5	5.6	0.1
Change in BG 1 Hour Post Exercise	-0.7	-0.1	0.1	-0.6	-1.3	0.4	-0.5	-0.1	0.3	1.6
					90%					
Mean BG During Exercise	7.3	4.4	11.1	4.2	5.7	4.7	3.6	5.6	5.1	9.6
Change in BG During Exercise	-1.0	3.6	0.0	0.3	1.7	2.1	0.0	3.1	1.7	-0.7
Change in BG 1 Hour Post Exercise	-0.2	-0.7	-1.0	-0.2	-2.3	-0.5	1.5	0.1	-0.3	-2.9

Data are represented as raw values for each participant in mmol/L. Mean BG is calculated from timepoint one through four, change in BG during exercise = baseline minus end of exercise. Change in BG 1 hour post = mid recovery minus end recovery.

Appendix 7: Cortisol Levels During and After Exercise

	1	2	3	4	5	6	7	8	9	10
					45-55%					
Baseline	370	848	-	306	-	308	159	-	532	209
10 mins	-	911	-	387	-	101	125	-	538	196
35 mins	-	840	-	446	-	85	95	-	618	136
45 mins	199	800	-	351	-	84	87	-	579	134
75 mins	-	665	-	244	-	68	80	-	518	107
105 mins	161	525	-	206	-	62	69	-	404	91
					70%					
Baseline	-	593	250	191	273	85	328	647	383	346
10 mins	-	536	243	185	269	77	252	567	360	310
35 mins	-	329	151	114	327	151	216	564	454	216
45 mins	-	295	142	97	277	116	191	466	425	194
75 mins	-	274	132	82	197	90	139	348	403	177
105 mins	-	223	126	67	176	79	112	267	337	141
					80%					
Baseline	-	593	161	350	260	367	232	562	241	241
10 mins	-	566	241	286	225	318	200	495	229	231
35 mins	-	326	185	523	621	213	128	251	464	162
45 mins	-	319	207	522	678	184	117	224	437	146
75 mins	-	277	186	244	510	136	92	178	370	123
105 mins	-	228	150	206	381	105	79	136	293	108
					90%					
Baseline	-	512	102	266	238	94	170	293	516	247
10 mins	-	498	139	288	215	86	158	252	517	219
35 mins	-	322	113	231	544	79	287	201	641	172
45 mins	-	362	127	480	635	81	344	184	679	171
75 mins	-	419	108	380	428	76	219	136	582	157
105 mins	-	312	93	264	307	58	160	101	471	128

Data are represented as raw values for each participant in nmol/L. Participant 1 did not want blood taken as the nurse could not find appropriate veins for an IV. Blanks (-) are indicative of a nurse not being available.

Appendix 8: Consent Form

Participant #:_____

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

Title of Study: Determining the Appropriate Intensity of Vigorous Intensity Exercise to Prevent Post-exercise Hypoglycemia in Persons Living with type 1 diabetes - A Pilot Study

Protocol #: B2014:095

Date of Approval: October 8th, 2014

Date of Expiration: August 25th, 2015

Principal Investigator: Jonathan McGavock, PhD

Co-Investigators:

Name	Address	Phone
Lori Berard, RN	[redacted]	
Dan Chateau, PhD		
Heather Dean, MD		
Carmen Hurd, MD		
Pamela Katz, MD		
Terry Klassen, MD		
Seth Marks, MD		
Colleen Rand, RD		
Elizabeth Sellers, MD		
Brandy Wicklow, MD		

Sponsor: The Lawson Foundation

Why Are You Being Given this Document?

You are being asked to participate in a human research study. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this pilot trial and you may discuss it with your regular doctor, friends and family before you make your decision. This consent form may contain words that you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not clearly understand. The study is voluntary and if you decide not to participate or withdraw, your normal medical care will not be affected in any way.

What Is the Research About?

The safest and most effective type of physical activity for individuals with type 1 diabetes (T1D) is unknown. In fact, no guidelines exist for the appropriate amount and type of physical activity for reducing the risk of having exercise-related low blood sugar (hypoglycemia – during or following exercise). Currently, it is believed that participating in physical activity results in a drop in your blood sugars both during and after exercise. Some studies have shown that doing vigorous intensity exercise (exercising at a level where you have trouble talking) can help slow the decrease in your blood sugar both during and after exercising, which would mean that there is less of a risk of low blood sugar. This pilot study is being done to address the gaps in previously published studies in order to determine the most appropriate intensity of exercise to prevent low blood sugars and potentially provide physical activity guidelines for individuals with T1D in the future. This pilot study is focused on the acute blood sugar response to exercise over a 16 day period.

Am I Eligible to Participate?

We plan to enroll approximately 10 people in this study. You are being asked to take part in this study because you are 15-35 years old, have had T1D for at least two years, and have an HbA1C <9.9%.

Exclusion Criteria: If any of the following applies to you, you may not participate in the study:

1. You have frequent and unpredictable hypoglycemia
2. You are unable to exercise on a regular basis due to an injury or other restriction
3. You participate in structured physical activity (i.e. more than 150 min/week)
4. Your insulin management has changed or you have started an insulin pump in the last three months
5. You have conditions that would make vigorous exercise unsafe: high blood pressure, problems with your nerves, or a family history of heart disease
6. You have a cognitive impairment resulting in an inability to provide informed consent
7. You take medications in the class of drugs called atypical antiphyschotics or corticosteroids
8. You take medications in the class of drugs called beta-blockers
9. You are a woman who is pregnant, planning pregnancy, or breastfeeding
10. Have a job or profession that involves shift work (working during the night time, and being asleep during the daytime, as this alters glucose levels

Screening Test

If you are eligible based on the above criteria, we will ask that you complete a test called a resting electrocardiogram or ECG. The test is very short, and involves having electrodes placed on your abdomen and chest while you are still for a few minutes. The test will produce a tracing of the electrical activity in your heart that will be read by a cardiologist. This is done to ensure you do not have any unknown heart problems before starting this study. You will be given a requisition form by study staff to have the ECG done on a drop-in basis at St Boniface Hospital (no appointment required). You may not proceed with the rest of the study until the results of the test are in, and there are no positive findings. If there is a positive finding, you will be withdrawn from the study and referred for further testing.

Study Design:

We are asking you to participate in a study that will involve 6 visits to our exercise physiology laboratory over a period of approximately 16 days (There is a 2 part option to this study which will be explained on page 6). You will be asked to perform a test of your fitness followed by four exercise sessions lasting ~45 minutes at different exercise intensities. The first exercise session will consist of walking at a moderate pace for 45 minutes. The next 3 sessions will involve walking at a moderate intensity for 45 minutes but will include 1 minute of running every 4 minutes. The one minute of running will be done at speeds equivalent to 70%, 80% and 90% of your maximal fitness. The order of the sessions will be random and separated by 2 days without any exercise.

We will ask you to wear a continuous glucose monitoring system (CGM) on two separate occasions for 6 days to see how the exercise sessions affect your blood sugar. The monitors record data for a period of up to two weeks, but the sensors need to be replaced after 6 days.

Procedures and Measurements

Blood Work: We would like to study your body's hormones during exercise. To do this, a nurse will place an IV in a vein in your arm for each of the four exercise sessions, and it will remain in your arm for the 45 minute period you are exercising, and one hour after each session. A total of six blood samples (approximately 1/3 of a cup (72 mL) will be drawn from the IV per session (at baseline, end of warm-up, end of intervals, end of exercise, mid-recovery, and end-recovery) and they will be analyzed for glucose, cortisol, lactate, and growth hormone levels. There are changes in these levels during exercise that help explain how your blood sugars change after exercise. The baseline blood sample from the first exercise session will also be used to measure your HbA1c (a measure of your blood sugars over the last 3 months).

Blood Pressure: While you sit comfortably, five resting blood pressure measurements will be taken using a digital machine prior to the exercise test (and once for each exercise session). A blood pressure cuff will be placed on your arm. The cuff will be inflated and then the air will be released allowing a meter to measure your blood pressure.

Anthropometrics: We will measure your height and weight.

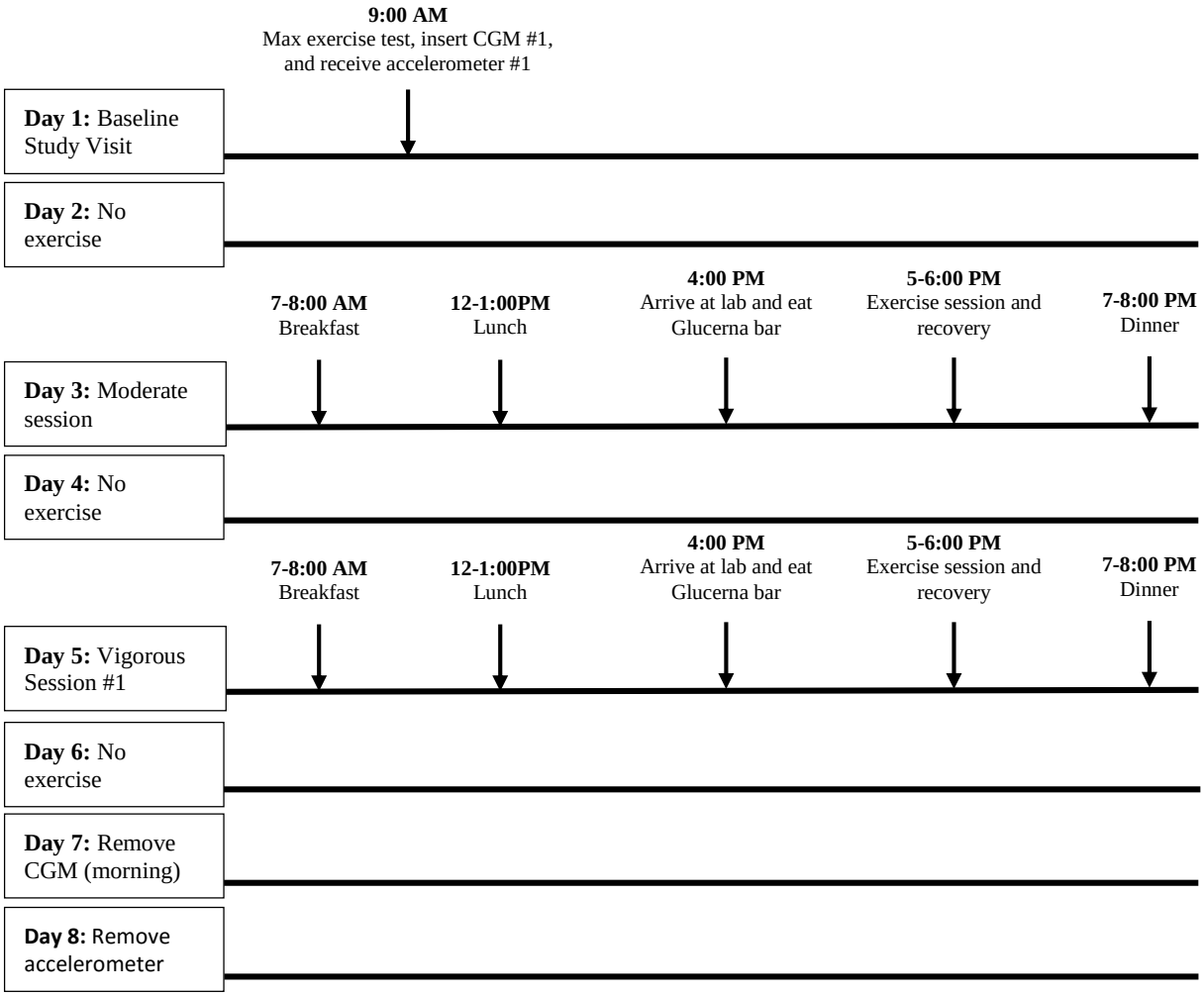
Exercise (Fitness) Test: The exercise test will be performed on a treadmill. We will measure your heart rate and blood pressure throughout the test. Heart rate is measured with a small black band around your chest and blood pressure is measured with a cuff on your arm. We will also measure the air you exhale (breath out) during the exercise test. The test starts by walking at an easy pace and we will increase the speed and or incline every few minutes. As the exercise becomes more difficult we will encourage you to continue until you are no longer able to. When you can no longer keep going we will stop the exercise test. You will be the one who decides when to stop exercising, the study staff will only encourage you to continue as long as you can. The amount of oxygen in your breath at the end of the test will give us an estimate of your current fitness level.

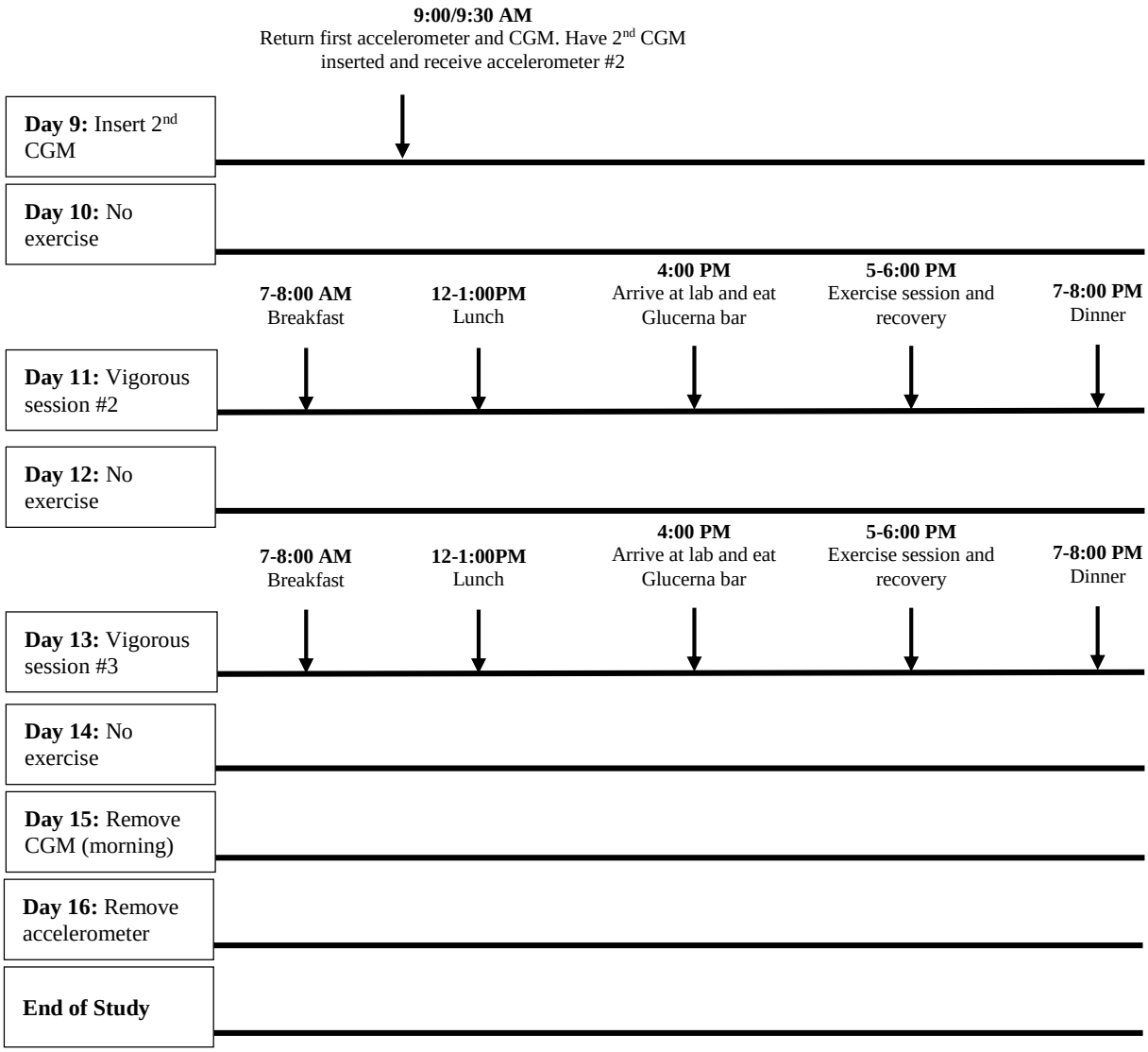
Continuous Glucose Monitoring System (CGMS): This is a device that records blood sugar levels continuously throughout the day and night. First, a tiny sugar-sensing device called a "sensor" is inserted just under the skin of your hip above the buttocks. This is quick, and doesn't usually hurt too badly. Tape is used to hold it in place. A small recorder, called an iPro™2, which is the shape of a seashell and the size of a toonie, is connected to the sensor. The sensor sends information about your blood sugar to the recorder. The system automatically records an average sugar value every five minutes for up to two weeks. Results of at least four finger stick blood sugar readings taken with a standard sugar meter at different times each day are entered into the monitor for calibration. A study nurse will replace the sensor midway through the study because it is recommended that sensors be changed after 6 days. Each sensor will then be downloaded onto a computer.

Accelerometer: An accelerometer is a small device that can accurately measure a person's activity energy expenditure and step count. Lightweight, small, waterproof, and durable, accelerometers are practical for all activities, and can be used indoors or outdoors. The accelerometer is safe, non-invasive and is only attached to the body by a belt around the waist. It is recommended that the accelerometers be worn underneath clothing against the skin, however this can be uncomfortable for some so weaving the accelerometer strap through belt loops is an acceptable alternative. The most important feature to consider is the accelerometer should fit snugly above the right hip to prevent flopping and extra motion. The words written on the accelerometer should be right-side-up for someone looking at you (upside-down for you). We ask that you wear the accelerometer for one week during your waking day. Please refrain from vigorous physical activity while participating in the study.

Food Intake: What you eat and when you eat will affect your blood sugars, and we would like to keep this as consistent as possible for all study days. This means, to the best of your ability, eat the same meals (particularly lunch and supper) at the same time on every day of the study including days without exercise. We will provide you with a mid-afternoon snack and a bedtime snack.

Summary of Study Protocol





2 Part Option:

You have the option to complete this study in two separate bouts; each bout will require that you visit the lab 3 times. During the first bout you will complete the baseline study visit, the moderate exercise session and one of the vigorous exercise sessions. During the second bout you will come into the lab to replace the CGM and receive a new accelerometer, and will finish the remaining vigorous exercise sessions. There can be a few days of lag time between bout one and bout two and when bout two starts the CGM will be replaced. This option is given to individuals who feel they cannot complete the study in 16 consecutive days as outlined in the above schematic.

What Will I Have to Do?

Before doing any study measurement visits, we will schedule an appointment to explain the study in detail and for you to ask any questions you may have. After you have had a chance to ask questions, you (and your parent/guardian if applicable) will sign the consent and receive instructions on how to complete the ECG test. If the ECG is normal, we will schedule the study measurement visits. At the baseline measurement visit, Day 1, study staff will measure your blood pressure, height and weight. You will then change into clothes appropriate for exercising. Once you are changed, you will then complete the exercise test.

Continuous Glucose Monitoring and Exercise Sessions

Following the initial fitness test a study nurse will place a continuous glucose monitor under your skin (on your lower back just above the buttocks). We will ask you to wear the continuous glucose monitor for 6 days (this means you will wear the CGM for 2 exercise session days) after this the sensor can be removed and brought to the lab. Whether you choose to complete the study in 16 days or 2 bouts, the CGM must be removed after 6 full days and returned to the lab (reminders of when the CGM can be removed will be on the front cover of your patient manual). You will come to the laboratory at the Children's Hospital Research Institute of Manitoba to perform 45 minutes of walking and running every 2 days (refer to the above schematic) Members of the study team will supervise exercise visits and all sessions will be performed in the afternoon to standardize meals and the hormonal response to exercise. The first session will involve 45 minutes of walking at a pace considered moderate for you. The next 3 sessions will be provided in a random order and involve walking for 45 minutes with 1 minute of running every 4 minutes at different exercise intensities. The intensities will be based on your fitness from the fitness test and target intensities of 70, 80 and 90% of maximal fitness. The running will only last 1 minute and you will be provided with 4 minutes of easy walking in between to catch your breath. The continuous glucose monitor will monitor your blood sugar levels to determine how your body responds to the higher intensity exercise. We will study your body's hormones during exercise by taking blood samples during each of the four exercise sessions.

What Are the Possible Risks or Discomforts of the Study?

Blood sampling: Some people experience slight discomfort, bleeding and/or bruising during the collection of blood samples. Sometimes people feel dizzy or faint. An infection in your arm can develop if the testing site is not clean, so we will clean your arm with alcohol before taking blood. Every effort will be made to reduce any risks and discomfort. We have trained nurses that will do all the blood collection.

Continuous glucose monitoring: There is a risk of bruising and bleeding at the injection site. A nurse will help with the placement of the sensor. If the site is not kept clean, there is also a small risk that it may become infected. If so, we will remove the device, clean the site, seek medical care if needed, and postpone study data collection until the infection is resolved.

Cardiopulmonary Exercise Testing: There is a possibility of certain changes occurring during the exercise test. Serious complications of exercise testing occur in approximately 1 in 10,000 tests in adults. These may include abnormal blood pressure, fainting, disorders of heart rate and, in rare instances heart attack, stroke and death. Exercise testing may also cause slight injury to muscles and joints that will go away within a few days after the test. Every effort will be made to minimize these risks by reviewing information about your health and fitness before the test and by closely monitoring how your body responds to the exercise. We will reduce these risks by closely monitoring your condition throughout the exercise test. If you experience an abnormal response to exercise, the test will be stopped. Emergency equipment and trained personnel are available to deal with any situations that may arise.

Risks of exercise: When individuals with T1D exercise there is an increased risk of hypoglycemia (low blood sugar). To prevent this, you will be asked to frequently monitor your blood sugar levels and adjust your carbohydrate intake and insulin dosage accordingly. All exercise will be performed in the presence of a trainer who will know what to do in case of low blood sugar. At each session, the supervising team will have a hypoglycemia rescue kit, consisting of sugar tablets, juice and glucagon. The team will also have equipment for glucose monitoring which include disposable single use lancet devices to measure your blood glucose. If you experience a severe hypoglycemic episode following exercise, you will be asked to meet with your doctor or diabetes educator to assess the situation before continuing to exercise. For your safety, we will ask that you wake up once during the night on exercise days of the study to monitor your glucose. In addition to hypoglycemia, there is also an increased risk of injury while running on a treadmill such as losing balance. However to minimize this risk, qualified personal will always be present during the exercise sessions and will show you how get on and get off the treadmill safely.

What Are the Possible Benefits of the Study?

Benefit to you: As this is a research study, there may not be any direct benefit from participation in this study. By participating in the study, you will receive information about your health and physical activity. You will also receive your tests results so that you can give them to your doctor.

Benefit to other people: Regular physical activity has substantial health benefits in persons with T1D. Despite these benefits, individuals with T1D generally fail to meet physical activity requirements. The information collected from this study will provide information for a larger study that will help to determine the best exercise to prevent low blood sugar after exercise and improve blood sugar control. It will also support future guidelines and instructions (a toolkit) for individuals with T1D who are starting an exercise program.

What Are the Costs of the Study?

All clinic and professional fees, diagnostic and laboratory tests which will be performed as part of this study are provided at no cost to you. There will be no cost for the study intervention that you will receive.

Payment for Participation

You will be given $20 per completed study visit (baseline visit plus 4 exercise session visits) to a maximum of $100 upon termination of your participation in this research study.

Is the Study Confidential?

Information gathered in this research study may be published or presented in public fora, however your name and other identifying information will not be used or revealed. Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

All study documents related to your exercise chart will bear only your assigned ID number. These records will be kept in a locked secure area and only those identified will have access to those records. No information revealing any personal information, such as your name, phone number or address will leave the Children's Hospital Research Institute of Manitoba. All data collected will be entered into computers, however all data will be password protected and data files will not include any identifying information, only the subject ID number.

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 log book 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.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- The University of Manitoba Research Ethics Board, who approved this project.
- Any of the agencies that fund the project may ask to see the data.

Do I Have the Right to Change My Mind?

Your decision to take part in this study is totally up to you. You may refuse to participate or you may quit at any time. Your decision to participate or withdraw from the study will not affect your normal medical care. The investigators reserve the right to end your participation in the study for any reason.

Medical Care for Injury Related to the Study

In the case of injury or illness resulting from this study, necessary medical treatment will be available at no additional cost to you.

Questions:

You are free to ask any questions that you may have about your rights as a research participant. If any questions come up during or after the study, contact the research team/staff, Dr. Jonathan McGavock, Primary Investigator, [redacted] and/or Andrea MacIntosh or Meaghan Rempel, Research Assistant, [redacted]

For questions about your rights as a research participant, you may contact the University of Manitoba Bannatyne Campus Research Ethics Board at [redacted].

Only sign this form if you have had a chance to ask questions and have been given satisfactory answers to all of your questions.

Statement Of Consent:

Participant:

I have read and understand this form. I have had the opportunity to discuss this research with Dr. Jonathan McGavock or a member of the research study team. I have had all of my questions answered by them in a language I understand. I believe I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship I may have with the research team has not influenced my decision to participate. The risks and benefits have been explained to me. I understand I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my records that relate to this study by the University of Manitoba Research Ethics Board for quality assurance purposes.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

I consent to participate in the research study "Determining the Appropriate Intensity of Vigorous Intensity Exercise to Prevent Post-exercise Hypoglycemia in Persons Living with Type 1 Diabetes - A Pilot Study." I consent □ to providing the name, address, and phone number of a contact person for the study team to contact in the event I change my phone number or address (please circle one).

YES □ NO□

If YES,

Name of contact person:_____

Address:_____

Phone number: _____

By signing this consent form, I agree that I have read, understood, and agree to the above information.

Participant signature: _____ Date: _____

(day/month/year)

Participant printed name: _____

Parent/legal guardian's signature: _____

Date: _____
(day/month/year)
Parent/legal guardian's printed name: _____

Research Staff

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that participant has understood and has knowingly given their consent.

Printed name: _____ Date: _____
(day/month/year)

Signature: _____

Role in Study: _____

If you want to make an appointment to participate in the study call:

Andrea MacIntosh [redacted]
Meaghan Rempel

To receive additional information from the researchers:

Jonathan McGavock, PhD [redacted]
Andrea MacIntosh,BSc, BA
Seth Marks, MD
Heather Dean, MD
Elizabeth Sellers, MD
Brandy Wicklow, MD

For questions about your rights as a research subject, you may contact:
The University of Manitoba, Bannatyne Campus Research Ethics Board Office at [redacted]

Appendix 9: Patient Manual

VIGOR Trial

PARTICIPANT INFORMATION BOOK: Acute

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

Accelerometer: the last full day you will wear your accelerometer is_____

Your drop off appointment for the accelerometer and CGM is_____

Research Lab Contact Information:

[redacted]

Study Coordinator email: *Andrea* [redacted] or
Meaghan [redacted]

Table of Contents

Preliminary Instructions

VIGOR Trial Baseline Study Visit Information

Your baseline VIGOR Trial study visit involves a maximal exercise test and a medical history. Please follow the instructions below to ensure we can complete your study visit:

1. Bring a list of all medications you take, or bring the medication bottles themselves
2. Bring comfortable clothes to perform exercise in and a water bottle
3. Refrain from consuming a large meal 2 hours prior to exercise testing
4. Refrain from consuming caffeinated beverages 2 hours prior to testing
5. Refrain from consuming alcoholic beverages 6 hours prior to testing
6. Refrain from exercising 6 hours prior to the exercise test

Basic Information

Log Book Instructions

1. For each day please record all of the information asked in the Log Book
    a. Write down your blood glucose (BG) meter readings, food, drink, number of carbohydrates, physical activity and duration (how long you exercised for and what did you do), medications and dosages, and other events (such as feeling hypoglycemic, stress, or illness).
    b. Keep the log sheet with you at all times so you can write down the information immediately after each event
    c. Record the time and date within 5 minutes of each BG meter reading

2. Throughout the evaluation your blood glucose should be tested at least **four** times each day (please refer to **CGM Instructions on page 8-9**), for example: before breakfast, lunch, dinner, and bedtime.

3. On the last day test your blood glucose at least **three** times

4. Record if you made any adjustments or changes to your insulin dose, whether that be an injection or from the pump.

Accelerometer Instructions

1. The belt should be fitted snugly on the waistline, with the sensor positioned at the **RIGHT** hip and slightly to the front of the body. The words on the accelerometer should be upside down to the user (right-side up to an on-looker).

2. The accelerometer should be worn at **ALL** times except for when sleeping, showering/bathing. The monitor will be worn at the same time you wear the CGM. The CGM will be worn for a total of 6 days, and the accelerometer will be worn for a total of 7 days.

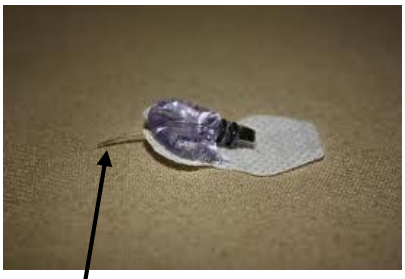
3. Please note that it is important to wear the monitor while performing **ALL** daily activities. It is durable, and therefore **CAN** be worn while playing contact sports. You **MAY** wish to take the belt and monitor off if you are swimming because the belt becomes wet and uncomfortable to wear once you are out of the pool. The monitor is sweat-proof and waterproof.

4. The accelerometers are a very smart and expensive tool; made for measuring physical activity. It is important that all monitors are returned to the researcher. Please **RETURN** the **ACCELEROMTER** & the **LOG BOOK** on the assigned **END DATE!**

CGM Instructions

What is a CGM

This is a device that records blood sugar levels throughout the day and night. In this study, a nurse will insert the small sensor that sits under the skin of your butt/hip, attach a small piece 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 the research lab.



Sensor – the little flexible "needle" is what sits in the skin

iPro2 – this is what records glucose information

This is what it looks like on someone (yours will be on your butt/hip)

Blood Glucose Testing while Wearing the CGM

- **On the <u>First Day:</u>**
  - Take your <u>first</u> BG meter reading at least <u>1 hour after</u> the iPro2 is connected
  - Take a <u>second</u> BG meter reading at least <u>3 hours after</u> the iPro2 is connected
  - Collect at least one more meter reading before going to bed.
- **Every Other Day:**
  - Collect at least 4 BG meter readings each day, such as before breakfast, lunch, dinner, and bedtime.
    - Please be sure to test when BG levels are stable ie. <u>before</u> meals
  - Do not change any settings on your meter during the study, even if a daylight savings time change occurs.
  - 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 behaviours.
- Keep tape over the sensor and iPro2 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 iPro2 into a plastic reusable bag and notify your research coordinator.
- Check the site 4 times a day to ensure that the sensor and iPro2 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 your physician's office.
- You may shower and swim while wearing the iPro2 and sensor. The iPro2 is watertight at a depth of up to 2.4 metres (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 cm (3 inches) away from the sensor insertion site, and insulin pump infusion should be at least 5 cm (2 inches) from the sensor insertion site.
- The iPro2 MUST be removed (but the sensor can be left in) prior to an X-ray, CT scan, or MRI. Simply reconnect the iPro2 afterward.

Removing the Device

- **On Day 7:** 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 with the letter "I" on it) off by itself. Leave it attached to the sensor.
    - Place the device in the Ziploc bag provided to you.
- **On Day 8:** Remove the accelerometer and place in the Ziploc bag with the CGM. Please return both of these devices to lab on the date specified at the front of your manual in addition the log book sheets.
- ***Clarification:**
    - You will wear the CGM alone on Day 1, together with the accelerometer from Day 2 – 7, and the accelerometer alone on Day 8.

Exercise Session Information

What to Bring

- Comfortable clothes and shoes to exercise in
- Water bottle
- Glucometer and test strips
- Log book
- Some form of entertainment (iPod, movies on iPad, book, etc.)

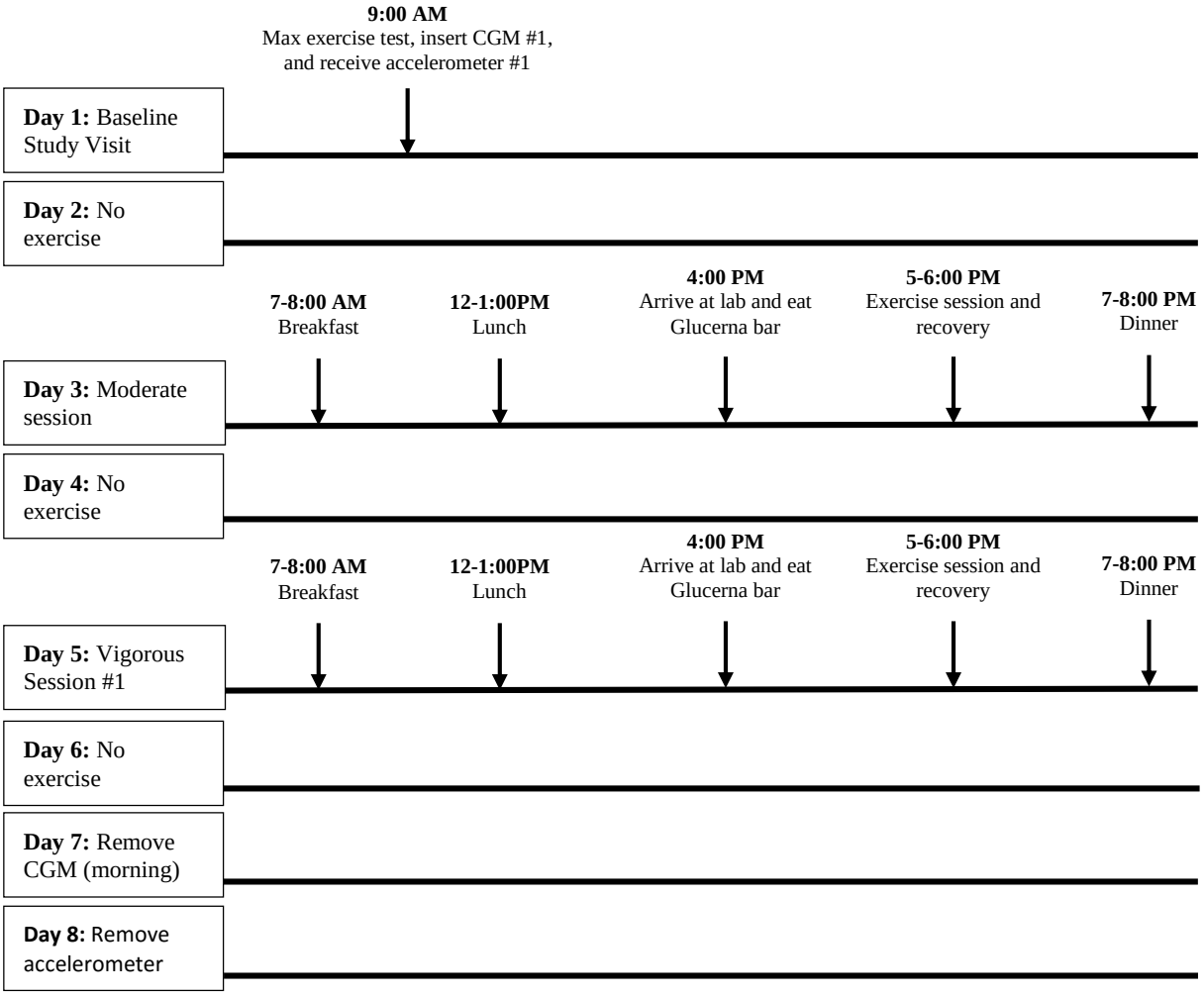
****Prior to the Exercise Sessions:****

- Refrain from consuming large meals 2 hours prior to exercise session
- Refrain from consuming caffeine 2 hours prior to exercise session
- Refrain from participating in exercise 6 hours prior exercise session
- Refrain from consuming alcohol 6 hours prior to exercise session

Exercise Session Breakdown (refer to the chart below for a general breakdown of the study)

1. Moderate Intensity:
2. Vigorous Intensity: 70%, 80%, or 90% bouts
3. Vigorous Intensity: 70%, 80%, or 90% bouts
4. Vigorous Intensity: 70%, 80%, or 90% bouts

The intensities will be assigned in a random order



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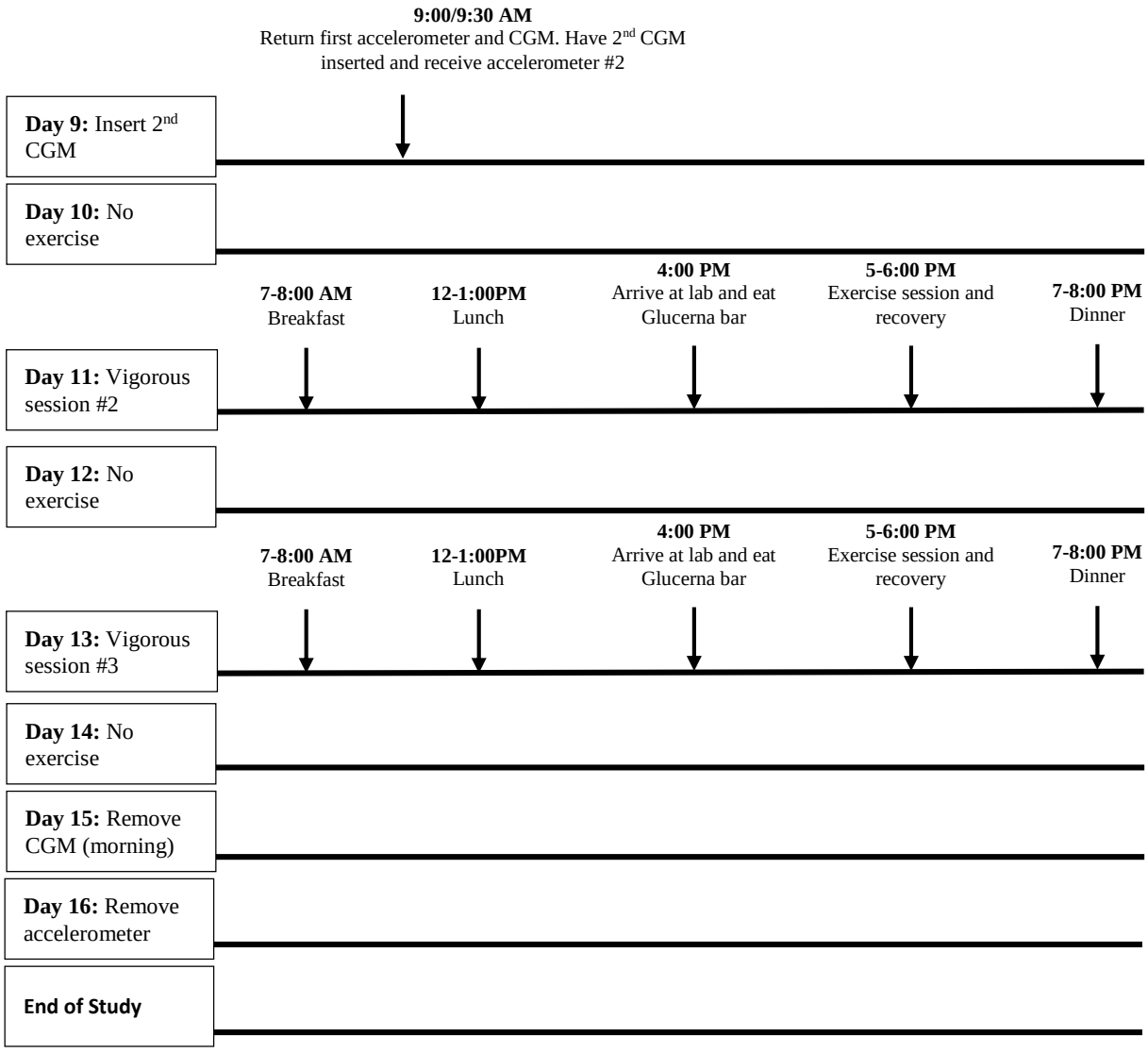

9:00/9:30 AM
Return first accelerometer and CGM. Have 2nd CGM inserted and receive accelerometer #2
Day 9: Insert 2nd CGM
Day 10: No exercise
7-8:00 AM Breakfast
12-1:00PM Lunch
4:00 PM Arrive at lab and eat Glucerna bar
5-6:00 PM Exercise session and recovery
7-8:00 PM Dinner
Day 11: Vigorous session #2
Day 12: No exercise
7-8:00 AM Breakfast
12-1:00PM Lunch
4:00 PM Arrive at lab and eat Glucerna bar
5-6:00 PM Exercise session and recovery
7-8:00 PM Dinner
Day 13: Vigorous session #3
Day 14: No exercise
Day 15: Remove CGM (morning)
Day 16: Remove accelerometer
End of Study

Diabetes Information

Insulin and Glucose Guidelines for Exercise

The study doctors have put together a list of recommendations for you to follow regarding insulin adjustments and carbohydrate supplementation before, during, and after exercise. We would like to emphasize that these are recommendations, and you are not required to follow them. They are in place to act as a starting point if you are unsure of what to do.

Pre-Exercise Insulin Recommendations

- Avoid the following 12 hours before exercise:
    - Insulin injections in the legs. Ideally it is recommended that you avoid insulin in the legs for the duration of the study.
- Avoid the following 2 hours before exercise:
    - Alcohol
    - Caffeine
    - Insulin (for example, if you take carbohydrates within 2 hours of exercise, avoid a correction dose)
- **If you are an MDI patient:** decrease long-acting insulin dose by 10% (either the night before or the morning of the exercise session) and adjust accordingly with fast acting insulin correction doses throughout the day to avoid excessive hyperglycemia
- **If you are using an insulin pump:** decrease your basal rate by 50% two hours before exercise, and maintain reduced basal rates until the end of exercise
- Please record any adjustments you have made in the log book

Exercise/Testing Session Recommendations

- Do your best to have a blood glucose between 5.7-11.0 mmol/L prior to starting each exercise session
- Please eat the *Glucerna* bar upon arrival at the exercise lab (this will be around 4:00 PM)
- You will be asked to do a minimum of one finger stick blood glucose test upon arrival at the lab (4:00 PM)
    - 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 urine test for ketones and we will wait 30 minutes to see if your glucose falls below 11.0 mmol/L. if it does not, we will reschedule the exercise session.
    - If your blood glucose level is **higher than 20.0 mmol/l** prior to starting exercise the session will be re-scheduled
- You will be asked to preform one finger stick upon arrival at the lab

During Exercise

- Your blood glucose will be tested every time there is a blood draw (0, 10, 35, 45, 75, and 105 minutes). This does not require any finger pokes, the blood used from the blood draw will be tested on a hand held glucometer.
- If your blood glucose drops to 3.9 mmol/L or less, you will be asked to consume glucose
- If your blood glucose drops to 2.9 mmol/L OR 3.9 mmol/L and you have symptoms of hypoglycemia, you will be asked to stop exercising and consume glucose.

Post Exercise

- It is recommended that you reduce your insulin dose prior to bedtime in order to prevent nighttime lows (lower basal rates by 20% between midnight and 3 am if you are a pump user, or decrease long acting insulin injection if you are an MDI user if you are taking it at night with boluses of fast acting insulin to correct when necessary).
- To the best of your ability, get up once a night on the night following each exercise session to test BG to the best of your ability.

Guidelines for Ketone Management

- If your exercise session is cancelled because you have moderate to heavy ketones, make corrections as previously instructed by your diabetes educator. If you are vomiting, **seek immediate medical attention!**
- If you are an adolescent participant who is seen at the DER-CA, your doctors have provided this information for you:
    - **If on insulin injections:** You should have a "ketone" correction dose – individualised in the same way that your correction dose is. For example, a child whose correction dose is one unit of rapid acting insulin every 3 mmol/L greater than 7.0, they might do that and add an extra 2 units of rapid acting insulin if moderate to large ketones are present.
    - **If on insulin pump:** Correct the first time through your pump site but if BG and ketones don't' decrease in 1-2 hours then correct using a needle injection and change your pump site.

Timeline Checklist

This checklist can be used for you to make sure you have completed what is asked for in the study. It is up to you whether or not you would like to use this. To the best of your ability, please try to eat the same meals around the same time. Try to keep all days as consistent as possible but always treat your diabetes first.

Baseline Study Visit

- ☐ Arrive at the agreed upon time for you baseline study visit at the Children's Hospital Research Institute of Manitoba
- ☐ Complete max test and have CGM inserted
- ☐ Take blood glucose 1 hour after iPro2 has been connected and record value in log book
- ☐ Take blood glucose 3 hours after iPro2 has been connected and record value in log book
- ☐ Have dinner and record blood glucose in log book
- ☐ Take blood glucose and record in log book

Day 2: No Exercise

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch and record blood glucose in log book
- ☐ *Eat Glucerna Bar* (around 4:00 PM)
- ☐ If you are an MDI patient it is recommended to decrease long-acting insulin dose by 10% either the night before or the morning of the exercise session.
- ☐ Have dinner and record blood glucose in log book (consider timing to keep it consistent).
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

Day 3: Moderate Session

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same lunch as *Day 2*) and record blood glucose in log book
- ☐ Come in to the lab for 4:00 and eat *Glucerna Bar*
- ☐ If on MDI it is recommended to reduce long acting insulin by 10% after exercise
- ☐ Have dinner (same dinner as *Day 2*)
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

Day 4: No Exercise

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ *Eat Glucerna Bar* (around 4:00 PM)
- ☐ If you are an MDI patient it is recommended to decrease long-acting insulin dose by 10% either the night before or the morning of the exercise session.
- ☐ Have dinner (same as above) and record blood glucose in log book
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

Day 5: Vigorous Session One

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ Come in to the lab for 4:00 and eat Glucerna Bar
- ☐ If on MDI it is recommended to reduce long acting insulin by 10% after exercise
- ☐ Have dinner (same as above)
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

Day 6: No Exercise

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ *Eat Glucerna Bar* (around 4:00 PM)
- ☐ Have dinner (same as above) and record blood glucose in log book
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

Day 7: No Exercise-Remove CGM

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ Eat Glucerna Bar around 4:00 before CGM is removed
- ☐ *Remove CGM and place in a plastic bag around the same time of day it was inserted. Be sure to record one more blood glucose before the CGM is removed.*

Day 8: Accelerometer Only

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ Take off accelerometer at the end of the day
- ☐ Arrange to drop off the CGM and accelerometer with a study staff member

You have now completed the first bout of this study. You may choose to finish the study as it was originally designed (16 straight days), or you may now take a break and finish the second bout at a later agreed upon time.

Day 9: Second CGM Inserted

- ☐ Arrive at the agreed upon time to have second CGM inserted at the Children's Hospital Research Institute of Manitoba
- ☐ Take blood glucose 1 hour after iPro2 has been connected and record value in log book
- ☐ Take blood glucose 3 hours after iPro2 has been connected and record value in log book
- ☐ Have dinner and record blood glucose in log book
- ☐ Take blood glucose and record in log book

Day 10: No Exercise

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch and record blood glucose in log book
- ☐ *Eat Glucerna Bar* (around 4:00 PM)
- ☐ If you are an MDI patient it is recommended to decrease long-acting insulin dose by 10% either the night before or the morning of the exercise session.
- ☐ Have dinner and record blood glucose in log book (consider timing to keep it consistent).
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

Day 11: Vigorous Session Two

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same lunch as *Day 2*) and record blood glucose in log book
- ☐ Come in to the lab for 4:00 and eat *Glucerna Bar*
- ☐ If on MDI it is recommended to reduce long acting insulin by 10% after exercise
- ☐ Have dinner (same dinner as *Day 2*)
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

Day 12: No Exercise

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ *Eat Glucerna Bar* (around 4:00 PM)
- ☐ If you are an MDI patient it is recommended to decrease long-acting insulin dose by 10% either the night before or the morning of the exercise session.
- ☐ Have dinner (same as above) and record blood glucose in log book
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

Day 13: Vigorous Session Three

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ Come in to the lab for 4:00 and eat Glucerna Bar
- ☐ If on MDI it is recommended to reduce long acting insulin by 10% after exercise
- ☐ Have dinner (same as above)
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

Day 14: No Exercise

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ *Eat Glucerna Bar* (around 4:00 PM)
- ☐ Have dinner (same as above) and record blood glucose in log book
- ☐ Drink *Glucerna Shake* before bed; take blood glucose and record in log book
- ☐ Remove accelerometer and indicate time of day in logbook

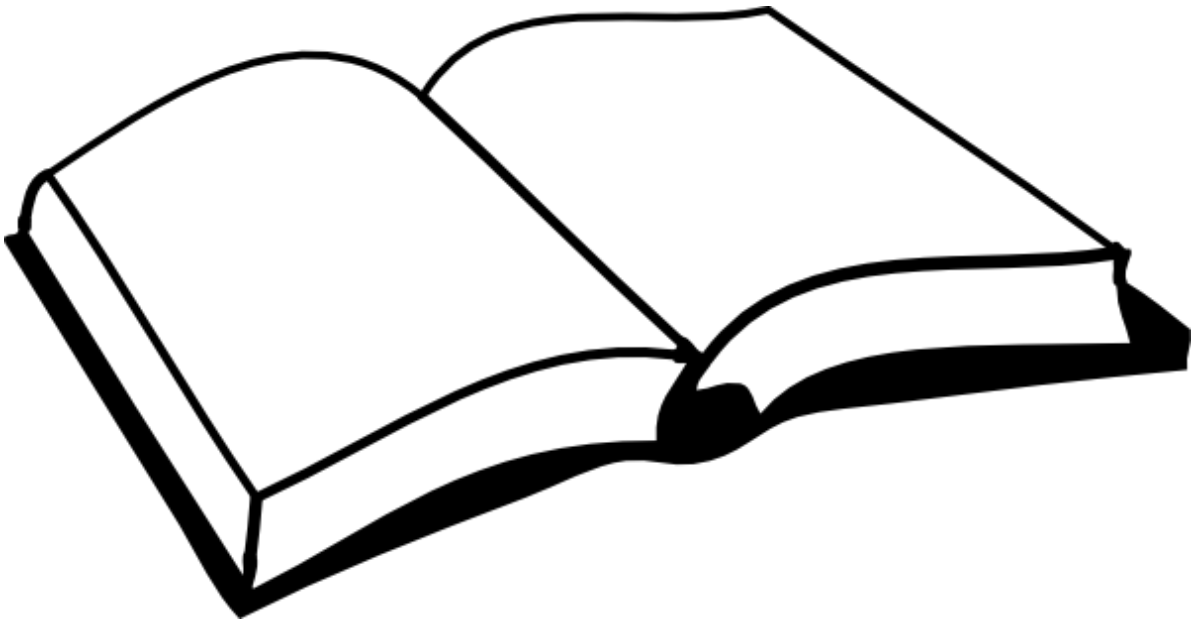
Day 15: No Exercise-Remove CGM

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ Eat Glucerna Bar around 4:00 before removing CGM
- ☐ Record BG before removing CGM (wait 10 minutes to remove)
- ☐ *Remove CGM and place in a plastic bag around the same time of day it was inserted.

Day 16: Accelerometer Only – End of Study ☺

- ☐ Put on accelerometer and indicate time of day in logbook
- ☐ Have breakfast and record blood glucose in log book
- ☐ Have lunch (same as above) and record blood glucose in log book
- ☐ Take off accelerometer at the end of the day
- ☐ Arrange to drop off the CGM and accelerometer with a study staff member. Thank you very much for participating in this study!

Log Book Sheets



Please record your **first blood glucose level **1 hour AFTER** your iPro2 is connected**

**Please record AM or PM when logging time of day **

****At the end of day 7:** record last BG **15 minutes** before you remove your sensor**

Please keep insulin as consistent as possible: Avoid insulin injections 2 hours prior to exercise sessions.

Please **avoid** consuming caffeine 2 hours prior, alcohol 6 hours prior, smoking 2 hours prior, and large meals 2 hours prior to exercise**

Other Information

Copy of Consent Form

Appendix 10: Ethics Certificate of Final Approval

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS Research Ethics Board

[redacted]

BIOMEDICAL RESEARCH ETHICS BOARD (BREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Full Board Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Dr. J. McGavock	U of M/Pediatric and Child Health-Faculty of Medicine	B2014:095
BREB MEETING DATE:	**APPROVAL DATE:**	**EXPIRY DATE:**
August 25, 2014	October 8, 2014	August 25, 2015
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		

PROTOCOL NUMBER:

PROJECT OR PROTOCOL TITLE:
Determining the Appropriate Intensity of Vigorous Intensity Exercise to Prevent Post-Exercise Hypoglycemia in Persons Living with Type 1 Diabetes

SPONSORING AGENCIES AND/OR COORDINATING GROUPS:
The Lawson Foundation

Submission Date(s) of Investigator Documents:	REB Receipt Date(s) of Documents:
August 5, September 23 and October 8, 2014	August 5, September 23 and October 8, 2014

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol:		
Protocol	2	September 23, 2014
Consent and Assent Form(s):		
Research Participant Information and Consent Form(Trained Individuals)	2	September 23, 2014
Research Participant Information and Consent Form (Sedentary Individuals)	2	September 23, 2014
Other:		
Participant Information Book: Acute	2	September 23, 2014
Participant Information Book: Trained Individuals	2	September 23, 2014
Screening Check List	3	October 8, 2014
Vigor Acute Studies Logbook	1	Submitted August 5, 2014
Advertisement		Submitted August 5, 2014
Payment Receipt	1	August 4, 2014

CERTIFICATION
The University of Manitoba (UM) Biomedical Research Board (BREB) has reviewed the research study/project named on this ***Certificate of Final Approval*** at the ***full board meeting*** date noted above and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM BREB.

BREB ATTESTATION
The University of Manitoba (UM) Biomedical Research Board (BREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba.

In respect to clinical trials, the BREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the BREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures
7. The UM BREB must be notified regarding discontinuation of study/project closure on the **Bannatyne Campus Final Study Status Report.**

Sincerely,

[redacted]

Lindsay Nicolle, MD, FRCPC
Chair, Biomedical Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary Telephone: (204) 789-3255/ Fax: (204) 789-3414