The Effect of Adding Vigorous Intensity Physical Activity to Moderate Intensity Physical Activity in Self-Reported Active Persons Living with Type 1 Diabetes

by

Andrea MacIntosh

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ABSTRACT

Background: Physical activity (PA) poses an additional burden on people living with type 1 diabetes (T1D) as it increases the risk of hypoglycemia, if performed at a moderate intensity. It is hypothesized that adding vigorous PA (VPA) into moderate PA (MPA) may help attenuate exercise-related hypoglycemia.

Methods: Seventeen participants with T1D (23.7±6.6 years) completed an observational study of six days with continuous glucose monitoring and accelerometer-derived measures of PA to determine the association between PA intensity and both hypoglycemia risk and glucose variability (GV).

Results: Higher evening moderate-to-vigorous PA (MVPA) increased the risk of overnight hypoglycemia (OR 1.03; 95% CI 1.002-1.047, p=0.031). Increased evening VPA was not associated with reduced hypoglycemia, but decreased overnight GV (3.20±0.25 for low vs 2.27±0.29 for high; p=0.022).

Conclusions: Performing evening MVPA increases hypoglycemia risk overnight, but incorporating VPA did not prove to be protective. However, VPA reduced GV, which is a predictor of hypoglycemia.

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INTRODUCTION

Physical activity (PA) confers many positive benefits to the health of individuals living with type 1 diabetes (T1D)[1], and collectively these benefits translate into a lower risk of complications and an increased life expectancy[2]. However, participating in PA, at least at a moderate intensity increases hypoglycemia risk[3]. Hypoglycemia is an acute complication that, if not recognized and treated is quite serious and can result in risk of death[4]. It is characterized by the presence of negative symptoms such as dizziness, confusion, and nausea[4], and can affect willingness to participate in PA[5] and impact overall quality of life[4]. A series of small experiments have shown that adding short bursts of vigorous PA (VPA) to a session of moderate PA (MPA) may help prevent exercise-related hypoglycemia[6-12], thus offering a potential strategy beyond making carbohydrate and insulin adjustments to protect individuals against it. Studies also support the concept that the degree of variability in one's glucose profile, or glucose variability (GV) is a predictor of hypoglycemia risk[13,14].

The overall purpose of this study was firstly, to determine if increasing moderate-to-vigorous intensity PA (MVPA) was associated with an increased risk of hypoglycemia. Secondly, we sought to determine if higher amounts of VPA would be associated with a reduction in hypoglycemia, in the context of a minimum amount of MPA. Thirdly, since GV has been reported to be a predictor of hypoglycemia, it was important to determine the association between higher amounts of VPA and GV, also in the context of a minimum amount of MPA. All of this was important to study in both 1)

self-reported active individuals, as this is lacking in the literature, and 2) free-living conditions in order to add to the very sparse literature in this area in the absence of an experiment, and to attempt to translate the findings of experiments into a real-life setting.

DIABETES MELLITUS AND ITS DIAGNOSIS

Diabetes mellitus is the most common endocrine condition[15], and one of the leading chronic conditions in children and young adults[16,17]. It is a metabolic disorder characterized by hyperglycemia due to either defective insulin secretion, defective insulin action, or both[15]. When sustained over time, a hyperglycemic state accelerates the progression of macrovascular and microvascular complications. As such, the diagnostic criteria for diabetes are based on glycemia levels that correspond to the development of complications, including nephropathy, neuropathy, and especially retinopathy[15]. Diabetes can be classified into four main types: T1D, type 2 diabetes (T2D), gestational diabetes (GDM) and other less common forms of diabetes, however the diagnostic criteria for diabetes are the same and rely on fasting, random, post-prandial glucose or HbA_{1c}. HbA_{1c}, or glycosylated hemoglobin, is a measurement of average blood glucose over a two to three month period[18]. The test used to make a diagnosis of diabetes is left to clinical judgement, however if an individual does not display symptoms of diabetes such as frequent urination (polyuria), excessive thirst (polydipsia), and increased appetite (polyphagia), a repeat test of those listed below, except a random glucose, is recommended on a separate day[15]. A summary of diagnostic criteria can be found in Table 1.

GDM is hyperglycemia first diagnosed during pregnancy, where transient insulin resistance uncovers beta cell defects in women. GDM is estimated to occur in 3-5% of all

Canadian women who give birth in Canada[19,20]. While hyperglycemia during pregnancy is typically restored after giving birth, women who had GDM are at increased risk of developing T2D[21].

TABLE 1. DIAGNOSTIC CRITERION FOR DIABETES MELLITUS

Test name	Normal value/range	Prediabetes	Diabetes
Fasting plasma glucose	4.0-6.0 mmol/L	6.1-6.9 mmol/L	≥7.0 mmol/L
2-hour oral glucose tolerance test plasma glucose	<7.0 mmol/L	7.0-11.0 mmol/L	≥11.1mmol/L
HbA_{1c}	<5.9%	6.0-6.4%	≥6.5%
Random glucose	-	-	≥11.1mmol/L

Adapted from the Canadian Diabetes Association Clinical Practice Guidelines[15]
HbA_{1c}=glycosylated haemoglobin

In T2D, insulin resistance is coupled with insulin secretory defects causing hyperglycemia[22]. Since insulin secretion is only partially reduced in T2D, the progression to dysglycemia is much longer than in T1D. In fact, individuals with T2D may live with the disease symptom-free for a prolonged period of time and start to develop complications before they are diagnosed. This underscores the importance of screening and early detection of T2D, which has not been proven important in T1D[15].

T1D is characterized by complete insulin deficiency resulting in most cases from autoimmune pancreatic beta cell destruction. When diagnosing T1D it is important to test for markers of beta cell destruction, such as islet cell antibodies, insulin autoantibodies, glutamic acid decarboxylase antibodies, and antibodies against tyrosine phosphatase[23]. These markers of beta cell destruction are an important feature of T1D that would help distinguish it from T2D. Since the autoimmune process leaves individuals with little to no insulin, the onset of T1D is relatively quick, and the presence of ketoacidosis is common[15]. Ketoacidosis is considered a medical emergency. It is a

condition where insulin deficiency and resulting hyperglycemia cause the body to begin breaking down fatty acids, and the acidic ketone bodies produced lead to symptoms such as nausea, vomiting, changes in breathing, and confusion[24]. A summary of the clinical characteristics distinguishing T1D from T2D is provided below.

TABLE 2. TYPE 1 VERSUS TYPE 2 DIABETES

	T1D	T2D	GDM
Symptoms	Polyuria, polydipsia, polyphagia	Polyuria, polydipsia, polyphagia	Largely asymptomatic
Age of onset	Usually <40 years	Usually >40 years	During pregnancy
Body weight	Typically lean	Typically overweight	Risk increases if BMI ≥30 kg/m^2
Ketoacidosis	Yes	No	Unlikely
Prevalence	5-10%	90%	3-5% of pregnant women in Canada
Circulating ICA	50-85%	No	No
Treatment	Insulin required to survive	Lifestyle modification, insulin, antihyperglycemic drugs	Lifestyle modification, insulin, antihyperglycemic drugs

T1D=type 1 diabetes; T2D=type 2 diabetes; GDM=gestational diabetes mellitus; ICA = islet cell antibodies

The pathophysiology of T1D and T2D are significantly different[25], resulting in different management approaches and complication patterns[15]. The risk of T2D is increased in individuals who are overweight or obese and physically inactive[15], and in people of certain ethnicities[26,27]. The treatment of T2D thus often focuses on changing modifiable risk factors that improve insulin sensitivity namely diet and PA. If lifestyle modifications such as nutritional therapy and increasing PA do not ameliorate dysglycemia, pharmacological treatment may be necessary and can include a large number of antihyperglycemic agents in nine different drug classes, including insulin[15]. Insulin may be prescribed alone, or in combination with other oral glucose-lowering

medications. In contrast, T1D is an autoimmune disease, resulting in the destruction of pancreatic beta cells and therefore, the only treatment strategy for T1D is with insulin therapy, which is necessary for survival[15].

The 'other forms of diabetes' category includes monogenic diabetes, and diabetes associated with other diseases or drugs[18], but they are less common. For example, monogenic diabetes, which is a category of several different single-gene defects that usually presents in adolescence and young adulthood, accounts for 1% of all diabetes cases[28]. Regardless of the type of diabetes however, the one thing they all classes of diabetes share in common are the treatment targets for blood glucose control (reviewed below).

INCIDENCE, PREVALENCE AND CAUSES OF TYPE 1 DIABETES

Globally, the incidence of T1D has been increasing over the past few decades[29] and rates vary greatly worldwide[30,31]. For example, a large population-based study measuring incidence of T1D in and children showed variations in cumulative incidence ranging from 0.1/100,000 per year in China to 36.5/100,000 in Finland[30]. The prevalence of T1D in the United States is approximately 1 in 300 among youth 18 years and under[32]. In Canada, the prevalence of diabetes is 6.8%, and in Manitoba it is 5.9%[21], and of all those living with diabetes, 5-10% of Canadians with diabetes have T1D[21]. Interestingly, some data suggest between 5-15% of adults diagnosed with T2D may actually have autoantibodies suggestive of T1D[33], which means the number of cases of T1D may be greatly underestimated.

T1D is a very heterogeneous or variable disease whereby pancreatic beta cell destruction leads to an absolute insulin deficiency. Most cases are a result of

autoimmune-mediated beta cell destruction, but others are due to beta cell destruction or failure of unknown cause[32]. According to the current known etiology, the trigger for beta cell destruction is environmental, but genetic susceptibility also plays a role[34]. With both genetic and environmental influences at play, it is understandable that there would be some heterogeneity in disease characteristics.

There are known risk factors for the development of T1D, which encompass age, gender, race/ethnicity, genotype, seasonality of onset, birth month, and other environmental and nutritional risk factors[32]. Presentation of T1D can occur at virtually any age[35], although the incidence is lower in adults than children[36]. Peaks in presentation of the disease occur in children around puberty[30,37,38] and the increasing incidence in children is reported to be especially high in very early childhood (0-4 years of age)[38]. The influence of gender is interesting, with some studies reporting increased risk among girls in non-European populations, while males appear to be at higher risk in populations of European decent[39,40]. Worldwide data on race/ethnic differences is limited, however in the United States data show in general, that the incidence and prevalence of T1D is highest in the non-Hispanic white population, compared to African American and Hispanic youth, followed by Asian and Pacific Islander youth, and lastly Navajo youth[41]. There are multiple genes involved in susceptibility to T1D, but the most important are within the human leukocyte antigen (HLA) complex, which is located on chromosome six[32]. In terms of familial risk, having a first degree relative with T1D[42] is a marker of increased risk. Additionally, siblings of a child diagnosed before the age of five years are at higher risk of developing diabetes by the age of 20, when compared to children with a sibling diagnosed with T1D between age five and 15[43]. It has been observed that more

cases are diagnosed in youth born during the spring and summer months compared to the fall and winter months in more Northern climates[44,45] and could be related to mothers vitamin D levels[46,47]. There are also seasonal differences in the month of diagnosis for T1D, with more incident cases in the fall, winter, and early spring, compared to summer months[48]. This is suspected to be related to seasonal variation in infections. There have been investigations into the environmental and nutritional factors in the etiology of T1D, but they remain largely undefined[32]. In the absence of a cure for T1D, it is critical to find ways to address the various clinical issues faced by patients on a daily basis in order to reduce the significant burden that diabetes imposes.

BLOOD GLUCOSE CONTROL

Maintaining adequate blood glucose control is a cornerstone to diabetes management[49]. Long-term exposure to hyperglycemia results in microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular disease) complications and is associated with significant morbidity and mortality[50,51]. Current clinical practice guidelines contain blood glucose targets for individuals living with diabetes that are based on experimental evidence showing increased risk for complications above the chosen thresholds (see Table 3).

The landmark study in T1D that helped define these recommendations was the Diabetes Control and Complications Trial, or DCCT[52]. Before the DCCT, there was not consistent clinical evidence of the benefits of intensive diabetes therapy on the development and progression of complications[52]. The study was a multi-centre randomized controlled trial conducted in the United States and Canada from 1983-1993

TABLE 3. BLOOD GLUCOSE RECOMMENDATIONS FOR PEOPLE LIVING WITH DIABETES

Parameter	Recommendation
HbA_{1c}	≤7%
Fasting or pre-prandial PG	4.0-7.0 mmol/L
2-hour post prandial PG	5.0-10.0 mmol/L

Adapted from the Canadian Diabetes Association Clinical Practice Guidelines[49]
HbA_{1c} = glycosylated hemoglobin; PG= plasma glucose

including 1441 patients with T1D aged 13-39 years. This study showed that intensive insulin therapy (pre-prandial and post-prandial blood glucose targets of 3.9-6.7 mmol/L and <10.0 mmol/L, respectively) substantially slowed or delayed the progression of retinopathy, nephropathy, and neuropathy. This was the first convincing evidence that demonstrated compared to conventional therapy, which consisted of 1-2 insulin injections per day, that intensive insulin therapy significantly reduced the development or progression to complications, and it changed the way T1D was managed, such that glycemic targets were lowered. A consequence of this new approach however was an increased risk of hypoglycemia, especially among people with T1D who exercise or adopt a physically active lifestyle.

In order to control blood glucose levels, the daily management of diabetes includes careful control of 1) insulin administration and 2) carbohydrate intake, and being able to match insulin to carbohydrate quantity[53]. While there have certainly been advances in insulin therapy since it was discovered in 1923[54] effective management of diabetes still represents an endless challenge, as insulin therapy is an "imperfect science"[55]. A third strategy for reducing blood glucose is increasing daily PA, although there is far less experimental evidence for the role of PA than the first two strategies[56].

Besides glycosylated hemoglobin (HbA_{1c}) as a measure of glycemic control, since the publication of the DCCT, GV is a measure that is more widely discussed. Glucose variability is a measure of variance or spread in a given set of blood glucose values[57]. It can also be described further in terms of frequency and magnitude of dispersions in glucose. For example, for two individuals with the same HbA_{1C}, they may have a very different frequency and magnitude of dispersions in blood glucose from fasting levels[58]. There are several measures of GV that have been developed. Although there is no gold standard, they are broadly categorized into methods that 1) involve using standard deviation; 2) are related to glucose excursions; 3) are based on day-to-day variability; or 4) are based on variability over shorter periods of time (hours)[59,60]. GV was related to mortality in a study of non-diabetic individuals in the intensive care unit[61], which emphasizes the possible negative health consequences of having high GV. With respect to diabetes, the importance of GV stems from the fact that it is a daily issue faced by all people with diabetes[62], and it is thought to 1) be involved in contributing to complications and 2) be a predictor of hypoglycemia risk. While in vitro and animal studies show a relationship between GV and mechanisms for development of complications[62], the results in humans are mixed[63-66], and there is a lack of experimental evidence[58]. Over time, the development of technologies such as continuous glucose monitors (CGM) has been important, as studies using finger stick blood glucose values have failed to demonstrate a relationship between GV and complications[63,67], whereas studies using CGM data have shown a relationship[63]. In terms of hypoglycemia risk, GV has been shown in both T1D[13,14] and T2D[68-70] to be a predictor of hypoglycemia. In addition to preceding episodes of hypoglycemia, increased GV plus a high HbA_{1C} are associated with increased

frequency and severity of hypoglycemia in persons with T1D and T2D[71-73]. Reassuringly, other studies have shown less frequent occurrences of hypoglycemia with lower GV[74-76]. This reinforces the idea that more studies targeting ways to decrease GV and thus hypoglycemia are needed, as hypoglycemia causes considerable morbidity[77] and mortality[78] in people with T1D, and will be reviewed in more detail below. One such strategy involves PA. There is evidence showing an inverse relationship between maximal oxygen uptake (VO_2 max) and GV[79], suggesting that increasing ones fitness level could be associated with better GV.

DIABETES-RELATED COMPLICATIONS

Complications associated with diabetes are often categorized as either microvascular, or macrovascular. Microvascular complications refer to disease of small blood vessels, such as retinopathy, neuropathy, and nephropathy, while macrovascular disease refers to cardiovascular disease[15]. The risk for micro-and macrovascular disease increases exponentially with increasing HbA_{1c}, therefore over the past 10 years, the development of strategies to reduce blood glucose levels has increased substantially.

There are a few mechanisms for how chronically high blood glucose levels result in diabetes complications: 1) the glucose in blood gets converted into non-metabolizable sugars in non-insulin requiring tissues, which causes disruptions in the osmotic balance in the cell[80]; 2) the glycosylation of proteins, which damages the proteins as a result of their tertiary structure being disrupted[81]; 3) the formation of advanced glycosylated end-products[82]. All of these can activate other pathways that induce oxidative stress[83] or other inflammatory pathways which in turn lead to vascular, immunological, and end-organ tissue damage[84].

Encouragingly, diabetes complications are preventable if blood glucose is controlled, and the result of these interventions can be quite impressive. For example, the landmark DCCT demonstrated that an absolute 2% reduction in HbA_{1c} in the intensive treatment study arm (pre-prandial and post-prandial blood glucose targets of 3.9-6.7 mmol/L and <10.0 mmol/L, respectively) resulted in a 50% reduced cumulative incidence of retinopathy in people aged 27±7 years living with T1D for 2.6±1.4 years between year five and year nine (the second half) of the study. Intensive therapy also reduced the risk of albuminuria (kidney injury), by 56%, and reduced the appearance of neuropathy at five years by 69%[52]. The risk-reduction in retinopathy and nephropathy was maintained in the intensive group at a four-year follow-up after the trial ended, despite an increase in HbA_{1c} during that time[85]. Also, after a mean 27 years follow-up, the initial mean period of 6.5 years of intensive treatment translated into a modestly lower all-cause mortality rate compared to the conventional group[86]. While the long-term vascular consequences are significant, the most immediate and life threatening risk for persons with diabetes is hypoglycemia.

HYPOGLYCEMIA AND TYPE 1 DIABETES

Hypoglycemia is defined as having a blood glucose ≤3.9 mmol/L, the presence of symptoms (autonomic or neuroglycopenic) which can be restored when carbohydrate is ingested[4]. It is perhaps the most dangerous acute complication for people living with T1D. The symptoms are variable for each individual, and are listed in Table 4.

Hypoglycemia can be classified as mild, moderate, or severe. In mild hypoglycemia, only autonomic symptoms are present, for example trembling, palpitations, and sweating. In mild and moderate hypoglycemia the individual can self-

TABLE 4. SYMPTOMS OF HYPOGLYCEMIA

Neurogenic (autonomic)	Neuroglycopenic (glucose shortage in the brain)
Trembling	Difficulty concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision changes
Nausea	Difficulty speaking
Tingling	Headache
	Dizziness

Adapted from the Canadian Diabetes Association Clinical Practice Guidelines[4]

treat and symptoms are present. Severe hypoglycemia arises when an individual cannot self-treat and requires assistance from another person[4]. Severe hypoglycemia was the main adverse event during the DCCT, with a two-to-three fold increase in the intensive treatment group - treatment that consisted of more insulin injections to target near-normal blood glucose values - which is now standard of care[87].

There are several risk factors for severe hypoglycemia in people with T1D, which include: 1) having a prior episode of severe hypoglycemia; 2) tighter glucose control (i.e. lower HbA_{1c}); 3) hypoglycemia unawareness; 4) longer duration of diabetes; 5) autonomic neuropathy; 6) adolescence; and 7) pre-school age; 8) and regular PA[4].

In the short term, consequences of hypoglycemia can range from being unrecognized by the patient, to having a drastic impact on a person's life through physical and psychological morbidity, and even risk of death[88]. The potential long-term complications of severe hypoglycemia include mild intellectual impairment, and although rare, permanent neurologic problems[4]. Furthermore, frequent episodes of hypoglycemia prevent patients from maintaining near-normal blood glucose control [88].

In general, the primary goal of treating hypoglycemia (blood glucose ≤3.9) is to relieve the patient symptoms quickly. In adults, it is recommended to ingest 15g of carbohydrate, which will produce an increase in blood glucose of about 2.1 mmol/L after 20 minutes time[4]. The evidence that supports re-testing blood glucose after 15 minutes and re-treating if it is <4.0 mmol/L is less robust[4]. The preferable type of glucose to be ingested is a glucose tab, but examples of other sources of sugar include juice, soft drinks, or candy[4]. If the patient is unconscious, glucagon should be administered subcutaneously, depending on if intravenous access is available to administer glucose[4]. Treatment of hypoglycemia is different in children and adolescents 18 years or younger compared to adults, especially dosages[89]. As hypoglycemia is intimately linked with PA, novel strategies are needed to prevent it and the associated complications.

PHYSICAL ACTIVITY AND TYPE 1 DIABETES

PA has many health benefits for people living with T1D that include improved fitness, vascular health, quality of life, and lower cholesterol[1]. These benefits translate to lower risk of complications and increased life expectancy[2]. Despite these benefits, in a study of adults with T1D, 63.9% did not meet PA guidelines[90], which are the same as for people without diabetes. Children with T1D are also reported to achieve significantly fewer (18%) accelerometer counts per minute than their non-diabetic peers[91].

Participation in regular PA is linked to hypoglycemia, and has been cited as a barrier[5] and a challenge[92] to exercise participation. At the onset of exercise, there is an increase in muscle glucose uptake and insulin sensitivity[93-95], which coupled with the fact that people with T1D cannot auto-regulate insulin levels, can result in hypoglycemia[88]. A study in children aged 11-17 years involving a day with a 75-minute exercise session at

55% of their maximal heart rate, compared to a sedentary day showed significantly lower blood glucose consistently throughout the night on the exercise day compared to the sedentary day. This resulted in an increase in hypoglycemia by 3-fold on the exercise night compared to the sedentary night[96]. Even increasing MVPA by 30 minutes in 14-20 year-olds can result in an increased risk of overnight and next-day hypoglycemia[97]. In contrast, a study in men with T1D comparing a rest condition to 11, four-second sprints spaced out over 20 minutes did not find differences in the change in glucose at 1 hour after exercise[98]. Therefore, although PA is recommended for overall long-term health in persons with T1D, participating in PA, at least at moderate intensity, can represent an additional burden and safety concern acutely for persons living with T1D. Future studies are needed to investigate novel approaches, such as sprinting, to reduce hypoglycemia risk in people living with T1D.

PHYSICAL ACTIVITY INTENSITY

Physical activity can be based either on absolute work rates or relative intensities. Absolute refers to the total amount of energy demand of a PA[99], and methods of absolute measurement include caloric expenditure, absolute oxygen uptake, and METs[100]. For population-based studies, intensity of physical activity is usually expressed in absolute terms, using the metabolic equivalent of task (MET). A MET is the ratio of a person's working metabolic rate to the resting metabolic rate, and is a way of measuring the energy cost of physical activities, and therefore intensity[101]. One MET is by convention, equivalent to consuming 3.5 ml/kg/min of oxygen[101]. Absolute methods are not considered optimal for individual exercise prescription because they do not take into account factors such as a person's body weight, sex, and fitness level[102-104]. Relative

measures on the other hand, express PA intensity relative to a person's maximal capacity, and are recommended for prescribing exercise to individuals.

Heart rate (HR) is a reflection of the number of heart beats per minute, and can be measured by auscultation with a stethoscope, by palpation with one's own index and middle fingers, by electrocardiogram (ECG) or with a HR monitor[101]. Given that HR is relatively easy to measure makes it a practical way to monitor PA intensity for the general public[101]. Directly measuring HR using a HR monitor, as opposed to predicting it with published equations is more accurate. To make a prescription, a clinician will usually measure or estimate maximal capacity and recommend to workout at a % of that maximum based on goals.

HR reserve (HRR) is one way used to prescribe PA intensity. It is calculated as the difference of maximal HR and resting HR[101]. Using HRR is an advantage because it is approximately equivalent to objective measures such as VO_2 reserve (VO_2R), described in more detail below[105]. A person's maximal rate of oxygen utilization, or VO_2 max is a reflection of the functional capacity of the cardiorespiratory system[101]. Usually, this can be defined as having no increase in oxygen consumption despite an increase in workload. This is different from VO_2 peak, which is the highest oxygen consumption recorded during an incremental exercise test, regardless of if a plateau is recorded[101]. However, it has been reported that VO_2 peak is a valid index of VO_2 max[106-108]. VO_2R is the difference between VO_2 max, and resting VO_2. It is preferable to use this method over $\%VO_2$, as $\%VO_2$ does not correlate well with %HRR [109], whereas $\%VO_2R$ and %HRR are approximately equal and could therefore be used interchangeably.

Rating of perceived exertion (RPE) measures the perceived level of exertion during aerobic exercise, and is a valid and reliable method of prescribing and monitoring exercise intensity[110]. Ranges of the RPE scale are related to percentages of HRR[111], which would make it an easy method to use alone or in combination with HR methods of monitoring exercise intensity.

PA can be stratified into light, moderate, and vigorous intensities. Light PA is equivalent to 2.0-2.9 METs[100]. This would be similar to walking at a pace of <3.2 km/h, and does not represent much more effort over resting, which is equivalent to 1 MET. MPA is equivalent to 3.0-5.9 METS[100], and would correspond to walking at >3.2 km/hour. This is the intensity currently recommended for adults to achieve health benefits. The Canadian Physical Activity guidelines call for adults aged 18-64 years to perform 150 minutes of MVPA per week, in bouts of at least ten minutes[112]. VPA is equivalent to 6.0-8.7 METS[100], and would equate to jogging for most people. A summary of moderate and vigorous-intensities using different methods can be found in Table 5.

PHYSIOLOGICAL EFFECTS OF VARYING INTENSITIES OF EXERCISE

When a person without diabetes performs moderate PA, the body is using primarily aerobic energy systems, and fuel for exercise is being drawn from muscle glycogen and free fatty acids under sympathetic nervous system control[55]. There is an increase in glucose uptake into the muscle, however several homeostatic mechanisms exist to maintain blood glucose levels and avoid hypoglycemia. These include a reduction in circulating insulin, and an increase in glucagon levels[55], which collectively increase glucose output from the liver to help maintain blood glucose. The matching of

TABLE 5. SUMMARY OF MODERATE AND VIGOROUS INTENSITIES USING DIFFERENT METHODS

Method	Moderate Intensity	Vigorous Intensity	Reference
MET	3 – 5.9	≥6	[100]
Heart Rate	64 - 76% HR max 40 - 59% HRR	≥77% HR max ≥60% HRR	[100]
Oxygen Consumption	46 - 63%VO_2 max 40 - 59% VO_2R	≥64% VO_2 max ≥60% VO_2R	[100]
Actical Accelerometer (counts per minute)	≥ 1535*	>3962	[113]
Borg Scale (RPE)	12 - 13 on scale of 20	>13	[114]

*Ages 20-59 years
MET=metabolic equivalent of task; HR=heart rate; HRR=heart rate reserve; VO_2=volume of oxygen; VO_2R= volume of oxygen reserve; VO_2 max=maximal oxygen consumption

glucose output to glucose utilization results in normoglycemia in persons without T1D[115].

In individuals living with T1D, it is well recognized that PA of moderate intensity increases the risk of hypoglycemia during and after exercise[116-119]. Since insulin is supplied exogenously, circulating insulin levels will depend on how much insulin was injected and when, relative to the start of exercise[120]. Consequently, during MPA, the increase in glucose uptake into skeletal muscles combined with the lack of control over circulating insulin levels creates a potentially dangerous situation[5] that can lead to hypoglycemia[116,118]. This makes moderate intensity much less desirable for individuals living with T1D[5], despite it being recommended for overall health benefits.

VPA uses anaerobic energy systems and is also dependant on glucose as a primary fuel source[55]. In contrast to MPA, VPA causes a significantly higher release of catecholamines (epinephrine and norepinephrine)[115]. These counter regulatory hormones stimulate the release of glucose from the liver, and a partial reduction in glucose uptake into skeletal muscle resulting in mild hyperglycemia[55], and potentially a reduction of

hypoglycemia associated with PA. This important process has been suggested to protect individuals with T1D from exercise-related hypoglycemia in the short-term[6-12].

STUDIES COMPARING MODERATE TO VIGOROUS INTENSITY PHYSICAL ACTIVITY

A series of acute studies have capitalized on the potential blood glucose stabilizing effects of adding VPA to MPA as an approach to preventing hypoglycemia associated with MPA[6-12,121]. All studies relied on a cross over design with a small number of subjects with T1D (n= between six and 12; ages 17-47 years; 47 males and 22 females) who performed one session of moderate intensity, and on a separate occasion a moderate intensity PA session with the addition of VPA burst(s). All studies recruited participants that were otherwise healthy, with fair to good glycemic control and the primary outcomes of interest were measures of blood glucose, or the change in glucose during and following exercise.

Two of the original studies were performed by Busseau (2006, 2007) and relied on a ten second (10s) maximal sprint (i.e. a workload substantially higher than that associated with VO_2 peak) performed before[7], or immediately after[6] 20 minutes of MPA. The addition of this maximal sprint helped prevent further declines in blood glucose when measured for 120 minutes after exercise compared to a moderate intensity session alone, and thus reduced risk of early post-exercise hypoglycemia. Alternatively, performing intermittent-high-intensity exercise (IHE) at a workload ~100% of VO_2 peak throughout a moderate intensity session as done by Guelfi showed a smaller change in blood glucose during and one hour after exercise, when compared to only MPA[10]. This is despite the fact that in the trial that used IHE, more total work was performed (~1750 j/kg

vs ~2100 j/kg, $p<0.05$ for moderate and IHE, respectively). Taken together, these studies suggest that adding VPA at a high intensity to a session of MPA may be a novel tool for reducing the occurrence of exercise-related hypoglycemia in the short-term period following exercise.

In contrast to the above-mentioned studies, a similar IHE protocol to the Guelfi[10] study was performed by participants with T1D in a study by Maran (2010) and found conflicting results[121]. The Guelfi study had subjects perform a four second sprint every two minutes in a 30 minute experiment, whereas in the Maran study it was a five second effort at 85% VO_2 peak every two minutes for a total of 30 minutes. When the follow-up period of glucose levels was extended into the overnight period following exercise, Maran observed an increase in delayed hypoglycemia with the IHE protocol, compared to moderate intensity alone. Specifically, interstitial glucose levels were significantly lower between midnight and 6:00 am, and the number of episodes of hypoglycemia was significantly higher with IHE compared to moderate intensity alone. It is unclear why the results conflicted with previous trials, however, the authors hypothesized differences in circulating FFAs or differences in glucose production and use. It is also important to note that while many aspects of the Maran study were similar to the study performed by Guelfi, the intensity of vigorous exercise was significantly lower (85% vs 100% of VO_2 peak) compared to previous studies. All of the other seven acute studies that saw positive effects of VPA were using intensities >85%[6-12]. This would suggest that VPA performed at the higher end of the VPA spectrum potentially leads to a different response in terms of glucose levels than at the lower end of the VPA spectrum as in the Maran study.

The majority of these acute studies also measure counter-regulatory hormones such as epinephrine and norepinephrine, as this is the generally accepted mechanism for the increase in glucose levels with VPA exercise[115]. In the seven studies that measured counter-regulatory hormones, all of them show either significantly higher lactate[8,12] or catecholamine levels[6,11], or lactate and catecholamine levels[7,10,121] with VPA.

While carefully controlled experiments are efficacious and lend themselves well to having high internal validity, the experimental scenarios above may not capture what individuals who participate in a variety of activities and organized sports do. Unfortunately, to our knowledge there is only one study in free-living conditions that investigates the association between PA intensity and hypoglycemia in individuals with T1D[97]. In that study, participating in (accelerometer-measured) MVPA increased the risk of hypoglycemia (assessed with a CGM) that night and the next day. When the day was segmented into morning/afternoon and afternoon/evening, the risk of overnight hypoglycemia was ~43% higher with afternoon/evening MVPA. This supports the concept that PA can lead to increased risk of hypoglycemia, and also provides further information on the following temporal associations: 1) the risk of hypoglycemia can be in the immediate overnight period or 2) extend into the following day; and 3) that the risk is higher if PA is performed later in the day. One of the advantages of this design of study and the use of tools that frequently sample glucose and PA over a period of days is that it provides a high volume of simultaneous continuous data over an extended period of time and is done under free-living conditions. It would thus be important to replicate this type of study as there are currently very few or no others like it and may be more relevant to patients than the experimental studies that have been published to date. In addition, it

would be important to extend the study to investigate the role of MPA versus MPA with added VPA in a real life scenario.

GAPS IN THE LITERATURE

There are several gaps in the current literature that should be addressed in future studies. Firstly, very few studies extend the follow-up period of glucose levels into the overnight period following exercise. It may be due to the fact that the majority of the exercise sessions in these studies occurred in the morning or midday, whereas only two studies[12,121] had subjects perform exercise in the late afternoon or early evening. This is a common time for performing PA[97] (after school or work hours), and this may increase the risk of hypoglycemia occurring in the early morning hours when individuals are asleep, which could be quite dangerous if individuals do not wake up to treat themselves. There is a need for more studies that test an IHE protocol in the late afternoon/evening hours and follow glucose levels overnight to test the potential of this strategy to reduce hypoglycemia in the overnight period following exercise. Secondly, there is only one study where the authors conducted the experiment on a treadmill or track[8]. All other studies use a cycle ergometer. Although it may be easier to prescribe a workload on a cycle ergometer, the muscle actions involved in cycling fail to represent the physiological atmosphere of games-type activities, which usually involve running[8]. Thus, a study involving running would be more widely transferrable to more activities/sports than cycling. Thirdly, very few studies measure, define, and report on hypoglycemia as a main outcome. This seems odd given that the clinical problem under investigation is exercise-related hypoglycemia. The majority of the experiments measure absolute glucose, or change in glucose levels as an indicator of hypoglycemia risk[6,7,10,11]. Fourth,

to our knowledge only one study measured and reported GV[12]. In that study, it was reported that GV was significantly lower on sedentary days compared to exercise days. Unfortunately, it was not reported if GV was different between days when moderate intensity exercise sessions were done compared to days when the IHE protocol was done. As discussed previously, GV is a predictor of hypoglycemia risk and there is a lack of data in the current studies regarding this measure. Fifth, the populations studied were largely sedentary, ranging in fitness level from poor to average, with very few studies describing the effect of VPA exercise on post-exercise hypoglycemia in in active individuals. It is unclear if fit individuals with T1D would show similar glucose and hormone responses to VPA. However, some evidence shows an association between higher fitness and the risk of hypoglycemia[97], indicating that evidence for strategies to counter exercise-related hypoglycemia are especially important in individuals with high fitness levels. Lastly, there is a lack of studies which explore the role of VPA in hypoglycemia risk in free-living conditions.

EXERCISE, FITNESS LEVEL, AND TYPE 1 DIABETES

Knowing that exercise can lead to hypoglycemia and hyperglycemia, the challenge for active individuals with T1D becomes maintaining adequate glycemic control despite the potential for these large dispersions in glucose concentrations during and after exercise sessions. This requires constant work to balance food intake, insulin, and the particular demands of the sport or activity depending on its intensity and duration[55]. In addition, active individuals must deal with the stress of competition and the environmental conditions they are competing in[122].

There remains little information on the effect that diabetes has on athletic performance[122]. Compared to healthy individuals, the additional problems that active individuals with T1D face include fatigability and poor performance[123], and there are a number of diabetes-related factors that help to explain why, namely hypoglycemia and hyperglycemia. Active individuals with T1D who experience hypoglycemia after exercise may experience a blunting of the counter regulatory hormone response to subsequent exercise, which affects their performance because it lowers endogenous glucose production and thus increases risk of hypoglycemia[124]. If the hypoglycemia is severe enough, it would be worth considering whether or not even participating in exercise is healthy[123]. Hypoglycemia has also been shown to increase RPE and therefore lead to early fatigue, which diminishes performance[122]. Similarly, hyperglycemia can also be related to dehydration[122] and impact performance. Higher RPE and lower fitness level have also been documented in studies in adolescents with T1D when compared to controls which may help explain reduced athletic performance in adolescents with T1D[54]. Finally, the hyperglycemia could likely be a result of increases in counter regulatory hormones in response to competition stress[122].

Strategies that currently exist to help individuals maintain glycemic control with exercise are 1) a reduction in insulin dose[15,54,125]; 2) consumption of extra carbohydrate before or during exercise[54,126]; and 3) the addition of IHE to a moderate intensity exercise session. Reductions in insulin dose can reduce the amount of carbohydrate intake necessary and importantly help reduce hypoglycemia related to exercise, but is not useful for unplanned activity[123]. Conversely, consumption of extra carbohydrate with exercise is useful for unplanned activity, but if too much is consumed can lead to hyperglycemia,

potentially increased weight[123], and potentially compromised glycemic control[125,127]. It is important to note that consumption of extra carbohydrate is hypothesized to be an explanation for why some studies do not show a positive effect of exercise on glycemic control. Consuming extra carbohydrate may mask the positive effects of exercise on glycemic control. Some recent cross sectional studies show that athletes consumed a larger proportion of energy from carbohydrate than lipid sources, and had significantly higher HbA_{1c}[128]. Taken together, this information highlights the need for strategies that do not compromise glycemic control. The small group of acute studies using VPA to help counter the decline in blood glucose after exercise are a promising alternative for reducing exercise-related hypoglycemia. However, there are very few studies that have explored adding VPA bursts to a moderate intensity exercise session in active individuals, and in people's usual lives.

Active individuals, and perhaps especially people who train for a specific sport or activity, are, generally speaking, a highly motivated group and would be willing to test different strategies to help them perform at their maximal capability. Active individuals with T1D are likely a group of people who would be highly motivated to participate in studies and receive new information on exercise strategies to help reduce exercise-related hyper and hypoglycemia. If the proposed strategy, described below, could reduce hypoglycemia after exercise, it would potentially allow for fewer disruptions in training, less fatigability, and improved performance in active people living with T1D. It may also have more broad applications for less active people with T1D who perform PA.

METHODS

AIMS AND HYPOTHESES

Aim 1: Replicate the observation of Metcalf et al[97] that there is an association between daytime MVPA and both overnight and next-day hypoglycemia (% time spent ≤3.9mmol/L) among persons living with T1D when measured under free-living conditions.

Hypothesis 1: Individuals living with T1D who spend more time in MVPA, regardless of the time frame it is measured, will experience more time in hypoglycemia overnight, and the following day.

Aim 2: To determine if, for a given amount of MPA, the addition of VPA will reduce the time spent in hypoglycemia (≤3.9mmol/L) overnight.

Hypothesis 2: Higher amounts of VPA will be associated with a reduction in overnight hypoglycemia on days with at least 20 minutes of MVPA.

Aim 3: To determine the association between VPA and GV as measured by MAG and CONGA.

Hypothesis 3: During days with a minimum amount of moderate activity, those with more VPA will have less GV when than days with less VPA.

STUDY DESIGN

To test the study hypotheses, an observational study was designed that involved six days of continuously measured physical activity and glucose values collected under free-living conditions in youth and young adults living with T1D. All study visits for the current study occurred at the Children's Hospital Research Institute of Manitoba in

Winnipeg. The study received approval from the University of Manitoba Biomedical Research Ethics Board (Appendix A).

STUDY POPULATION

Recruitment

Participants were recruited through endocrinologists and other diabetes care team members approached by study staff during clinical visits who were willing to refer potential participants. Poster advertisements (see Appendix B) were also placed at the research centre on notice boards, at pharmacies, and in the community. Additionally, advertisements appeared in online newsletters of organizations who work with people living with T1D. A business card was developed with the contact the research staff and link to a social media page explaining the study (see Appendix C).

Inclusion Criteria

The inclusion criteria for Aims 1-3 were: 1) Age between 15-35 years old; 2) had lived with T1D for at least two years prior to enrolment so as to avoid the honeymoon period when insulin production is still occurring; 3) an HbA_{1c} <9.9%. For Aims 2 and 3, analyses were restricted to active individuals. This referred to participants who reported regular performance of vigorous endurance exercise ≥3 times weekly for the past year. This definition is taken from two meta-analysis studies that describe the relationship between VO_2 and age across physical activity categories[129,130]. We restricted enrolment to people 15-35 years of age because the adrenergic response to VPA is greater in younger individuals[131,132] and therefore, they are more likely to respond to this approach. We restricted recruitment to those with an HbA1c < 9.9% as they would be less likely to

experience profound GV that would add variation to the study outcomes. Participants who met all criteria qualified to meet the research staff for the study visit.

Exclusion Criteria

We excluded individuals that:1) were diagnosed with T1D within two years of enrolment as they may experience a honeymoon phase, where little insulin is required to maintain glycemia[133-136]; 2) had an HbA_{1c} ≥9.9% as the lack of compliance with insulin suggests they may not be able to comply with the prescribed exercise requirements; 3) had frequent and unpredictable hypoglycemia as they would been at a greater risk of serious hypoglycemic events[72,137]; this included either a severe low requiring assistance within the last three months or hypoglycemia unawareness; 4) had a change in insulin management strategy, including adoption of a pump within two months of enrolment or switching back to multiple daily injections in the last two months, as they may have been at risk for a hypoglycemic event due to the novel insulin management approach; 5) currently did not participate in vigorous endurance exercise ≥3 times weekly for > 1 year (Aims 2&3); 6) had conditions that would render VPA activity contraindicated including: uncontrolled hypertension: blood pressure >150 mm Hg systolic or >95 mm Hg diastolic in a sitting position; severe peripheral neuropathy; 7) cognitive deficit resulting in an inability to provide informed consent; 8) were taking beta-blockers as this could affect particinant's heart rates during exercise; 9) were being treated with medications (other than insulin) that alter glucose metabolism (i.e. atypical antipsychotics, corticosteroids) ; 10) women who were pregnant, breastfeeding, or who may become pregnant during their participation; 11) had a job or profession that involved shift work (working during the night time, and being asleep during the daytime).

DATA COLLECTION

Procedure

Participants underwent one study visit to sign the informed consent (see Appendix D) have a medical history, anthropometric measurements, glycosylated hemoglobin testing, fill out questionnaires, and perform a VO_2 peak test. At the end of the visit, participants left wearing a CGM and accelerometer during six days of their usual training. After the six day recording period, the devices were removed and returned to the research lab.

PRIMARY OUTCOME MEASURE

The primary outcome for Aims 1 and 2 of this study was hypoglycemia. This was defined as the percent time spent ≤3.9mmol/L (≤3.9mmol/L being the standard definition of hypoglycemia[4]), and was sub-divided into overnight and next day hypoglycemia. Overnight hypoglycemia referred to hypoglycemia during the time period between bedtime and wake time, and next-day hypoglycemia referred to hypoglycemia experienced between wake time and sleep time. Wake and sleep times were collected in log sheets filled out by participants. Hypoglycemia was measured by CGM (Medtronic, Northridge, CA, USA). First, an Enlite sensor was inserted subcutaneously into the abdomen using an insertion device called a serter. The sensor contains an electrode with enzymes that react to glucose in the interstitial fluid. The interstitial glucose level is recorded at five minute intervals and stored on a recording device called the iPro™2; attached to the sensor. CGM systems require repeated calibrations with capillary glucose values throughout the day, ideally when glucose levels are relatively stable before exercise or before meals. Participants were therefore asked to check and record their

capillary glucose a minimum of four times each day. Participants were also asked to record their sleep and wake times in order to separate days of data collection into overnight and next-day periods. At the end of the six-day recording period, which is what Health Canada has approved, data from the iPro™2 was uploaded to a secure website for analysis. The CGM model that was chosen blinded participants to the interstitial glucose readings, which ensured that the values did not alter their behaviour towards managing their blood glucose levels.

SECONDARY OUTCOME MEASURE

The secondary outcome, glucose variability, was examined in Aim 3. It was quantified from the CGM using the mean absolute glucose change (MAG) and continuous overall net glycemic action (CONGA-n). MAG calculates the sum of the differences between successive glucose values collected every 5 minutes and divided by the total time measured in hours, and is advantageous because it takes into account the duration of an excursion[58,138]. CONGA-n is a novel method that assesses intra-day glycemic variability[138]. It is the standard deviation (SD) of the summed differences between one glucose observation and an observation n hours previously, and is considered more objective than some other measures[62].

EXPOSURE VARIABLE

Physical Activity

PA was monitored using an Actical® accelerometer (Bend, Oregon, USA) during the same six-day time period participants were wearing the CGM. Raw acceleration data was recorded in counts-per-minute every 15 seconds (i.e. 15 sec. epochs), and was converted to minutes of PA using KineSoft software[139,140]. Intensity cut points from

Colley et al were selected[141] as they were the same cut points used in a national survey of PA and health in Canada[113]. Non-wear time was considered any consecutive 60 minutes with no movement. The decision was made to analyze the adolescent participants (aged 15-17 years) using the adult cut points for a few reasons. Firstly, most of the pediatric studies identifying cut points had populations of children much younger than 15[142,143], very small numbers[141], or no vigorous cut point identified[144]. Secondly, the moderate cut point for moderate PA used in the current study was very similar to the two pediatric studies with comparable age participants[141,145] and would not have changed significantly. Thirdly, the vigorous cut point in pediatric studies is quite variable and there does not seem to be a consensus on what constitutes VPA. It was therefore decided to also run all participants data according to another vigorous cut point higher than the one used as part of Aim 2 to explore the relationship between VPA cut points and hypoglycemia. The cut point of 7000 counts-per-minute was chosen because it is similar to the highest VPA cut point for the Actical device we are aware of, and there were a number of days in which participants were achieving this intensity. The valid day criteria used was minimum three days of wear and eight hours per day[146]. This criterion was chosen over four days and ten hours because due to the limitations in the CGM, participants only wore both devices for six days. Using the lower threshold for valid day criteria also minimized the data that would be excluded. Overall time spent at different intensities over the six days for each individual participant were calculated and used to describe the study population. For the main aims, minutes of PA for each individual day of data collection were calculated for 1) all day, meaning 6am-bedtime (6-BT); 2) daytime, meaning 6am-3pm (6-15); and 3)

afternoon/evening, meaning 3pm-bedtime (15-BT). Bedtimes were based on self-reported sleep times written down by participants.

EXPLORATORY AND CONFOUNDING VARIABLES

Description of physical activity

Participants were asked to list physical activities they participated in, and the time of day they performed PA. Given that after work/school is a common time for PA, participants were asked if they usually perform PA at 5pm (± an hour). Possible responses were never, sometimes, and often. This measure was only assessed in active individuals.

Maximal Oxygen Uptake

A graded maximal exercise test to exhaustion was performed on a treadmill (Super Tread ST4600, Glendora, California) to determine VO_2 peak. Expired gas was measured using a ParvoMedics True One Metabolic System (Sandy, Utah). Participants performed three, three–minute stages at a self-selected speed with 1% incline, followed by an increase in incline by 2% every minute until volitional exhaustion, without any further increases in speed.

The inactive individuals included in Aim 1 had maximal oxygen uptake measured on the same equipment, but a protocol that differed slightly. Briefly, three three-minute stages were performed similar to other maximal protocols such as Bruce, modified Bruce, Naughton, Wilson, and Kattus. Incline was initially at 0% and at minute nine went up 2% every minute until volitional exhaustion, without any further increases in speed. The speeds used for the first three stages were pre-determined speeds that were modified due to the inability of the laboratory treadmill to go above 12 mph and 14% grade.

The main adverse event of concern during the course of exercise testing in the laboratory was exercise-related hypoglycemia. Safety measures were developed based on publications by Perkins and Riddell[122] which include minimal and maximal capillary glucose ranges appropriate for exercise (see Appendix E).

Body composition

Body composition, including lean muscle mass (kg) and body fat (%) was measured by a trained technician using dual energy x-ray absorptiometry (DXA). Body composition was assessed in 3 of the 5 inactive individuals and 11 of the 12 active individuals.

Insulin Regimen and Intake

Insulin regimen (pump or MDI (multiple daily injection)) was assessed by self-report. Total daily insulin dose was calculated based on the information provided in the CGM log sheets. Participants were asked to record all insulin given during each day (long and short acting). Total average daily units of insulin were calculated across all full days of data collection and also expressed as total units/kg body weight. Data was obtained for this measure in 3 of the 5 inactive individuals and 7 of the 12 active individuals.

Glycemic control

$HbA1_c$ was measured with a venous blood sample taken by a nurse and sent to the central laboratory. Data was obtained for this measure in 3 of the 5 inactive individuals and 11 of the 12 active individuals.

Anthropometrics

Height was measured using a stadiometer. Participants were asked to stand tall with their feet together, arms by their side, and looking straight ahead. The measurement was recorded twice, to the nearest 0.1cm and averaged. Weight was recorded twice using a mechanical scale (Health O Meter, Inc. Bridgeview, Illinois) in light clothing and no footwear to the nearest 0.1 kg and averaged. Resting heart rate, systolic and diastolic blood pressure was measured in triplicate in a sitting position with an automatic machine (Spacelabs Healthcare, Issaquah Washington) and averaged. Blood pressure and heart rate were measured after at least five minutes of sitting quietly and as far apart from the start of the maximal oxygen uptake test to avoid increases in these variables due to anticipation of the test.

Medications

Participants were asked to list all medications they were taking, including dosage, frequency and time of day.

Quality of life

In order to gain insight into the quality of life of the participants, they were asked to fill out the Diabetes Quality of Life questionnaire. Quality of life was scored on a 5 point Likert scale, with 1 being the highest quality of life and 5 being the lowest quality of life. This measure was assessed in all inactive individuals but only in 11 of the 12 active individuals.

STATISTICAL ANALYSIS

Power calculation

To test for association between MVPA and the risk of hypoglycemia in Aim 1, we categorized nights (rather than participants) into a binary outcome according to the presence of at least one episode of hypoglycemia (CGM reading ≤ 3.9mmol/L), similar to Metcalf and colleagues. Based on their observation that the odds of a hypoglycemic event increased 1.43-fold for every 30 minutes of MVPA, we estimated that we would require a minimum of 60 nights to replicate this observation assuming a base rate of 60% for the control nights, an OR of 1.36, a β=0.2 and α=0.05. We reduced the effect size from 1.43 to 1.36 to be conservative as this reflected the mean OR for all 8 multiple regression analyses performed by Metcalf et al. to detect an association between MVPA during the day and hypoglycemia that evening or the following day (Table 2 Met calf et al. OR range: 1.26-1.48). The base rate of hypoglycemia (60%) was obtained from pilot data collected in our lab (Rempel MSc Thesis 2015) and data from Metcalf et al where they observed that 70% of participants experienced at least one hypoglycemic event nightly during 82 nights of data collection.

In Aim 2, we used data from experimental studies to inform the calculation of sample size. In a cross over experiment, the effect of adding VPA to a moderate intensity session was an absolute reduction in time spent in hypoglycemia of 3.7% (from 5% to 1.1%). Overall, this represents a reduction in hypoglycemia of 71%. Using unpublished meta-analysis data from our group that pools the effect sizes of this study and other similar studies comparing moderate versus moderate + VPA as a guide[6,7,10,11,121], the result is a 32% reduction in hypoglycemia. This pooled effect size is a more conservative estimate. Using this, and an estimated SD of 2.1%, along with aβ=0.2 and α=0.05, we

needed to analyze 28 nights of data for each "arm" (56 nights in total), i.e. between nights that include VPA versus just MPA.

All aims

All analyses except descriptive statistics used individual days of data collection rather than participants to maximize sample size and fit with the aim to look at acute associations. Only days with minimum eight hours of accelerometer wear time were considered. The restrictions with a minimum number of minutes of MPA performed in Aims 2 and 3 also eliminated days with less than 8 hours of accelerometer wear time. A p-value of <0.05 was considered statically significant. All statistical analyses were performed using IBM SPSS Version 22.

Aim 1

The data for this aim was pooled with data from five individuals with T1D recruited for another study with the same outcomes and data collection procedures. The only difference was that participants were inactive, defined as not meeting Canadian Physical Activity Guidelines[112]. Data were pooled in order to have a group that spans the physical activity spectrum, and to have a comparable sample size as Metcalf et al.[97] Descriptive statistics, including mean and SD were calculated to describe participant characteristics. Medians and interquartile ranges were used to describe non-normally distributed data, and non-parametric tests were used to test for differences in these variables between active and inactive individuals. Hypoglycemia variables were not normally distributed and log transformation was attempted but was not possible due to a large number of zeroes. Independent t-tests were used to test for differences between the active and inactive individuals for all normally distributed variables. Initially, linear

regressions were performed to examine the relationship between MVPA and both overnight and next-day hypoglycemia. The number of days with zero hypoglycemia was large and thus logistic regressions were then performed. Adjustments were made for VO_2 peak and age. Adjustment for body fat was planned, however due to missing data in three participants, which translated into 18 nights of data collection lost, this was not done. OR's and 95% CI's are reported.

Aim 2

A series of logistic regressions were run to describe associations between overnight and next-day hypoglycemia and VPA. OR's and 95% CI's are reported. The relationship was also examined between overnight and next-day mean glucose and VPA with a series of general linear models. To test the theory that higher amount of VPA would attenuate the risk of hypoglycemia we stratified nights into those with low vs high VPA by the median number of minutes in the time window of interest. Means with SE's and p-values are reported. Given that accelerometer-measured VPA likely does not equate to the exercise intensity used in cross over experiments (i.e. a workload associated with 100% of VO_2 max or higher), the relationship between hypoglycemia and mean glucose was also examined using a higher cut point for VPA of 7000 counts per minute. In order to fit with the experimental theory that given a base amount of MPA, adding VPA could potentially attenuate exercise-related hypoglycemia, analyses were run restricting to days when at least 20 minutes of $MPA_{6\text{-}BT}$ was present. Other analyses were run restricting to days with at least ten minutes of $MPA_{15\text{-}BT}$, which was of interest based on the results in Aim 1.

Aim 3

Since GV is reported in the literature to be a predictor of hypoglycemia risk, a series of logistic regressions were first performed between overnight and next-day hypoglycemia and all of the GV variables (overnight MAG, overnight CONGA 1, 2, 3, 4, next-day MAG, next-day CONGA 1, 2, 3, 4). OR's and 95% CI's are reported. Any GV variables that were not normally distributed were log transformed. Adjustments were made for age and VO_2 peak. Secondly, a series of general linear models were performed with GV variables and VPA, with adjustments made for VO_2 peak, age, and HbA_{1c}. Means ± SE's are presented.

RESULTS

Demographics

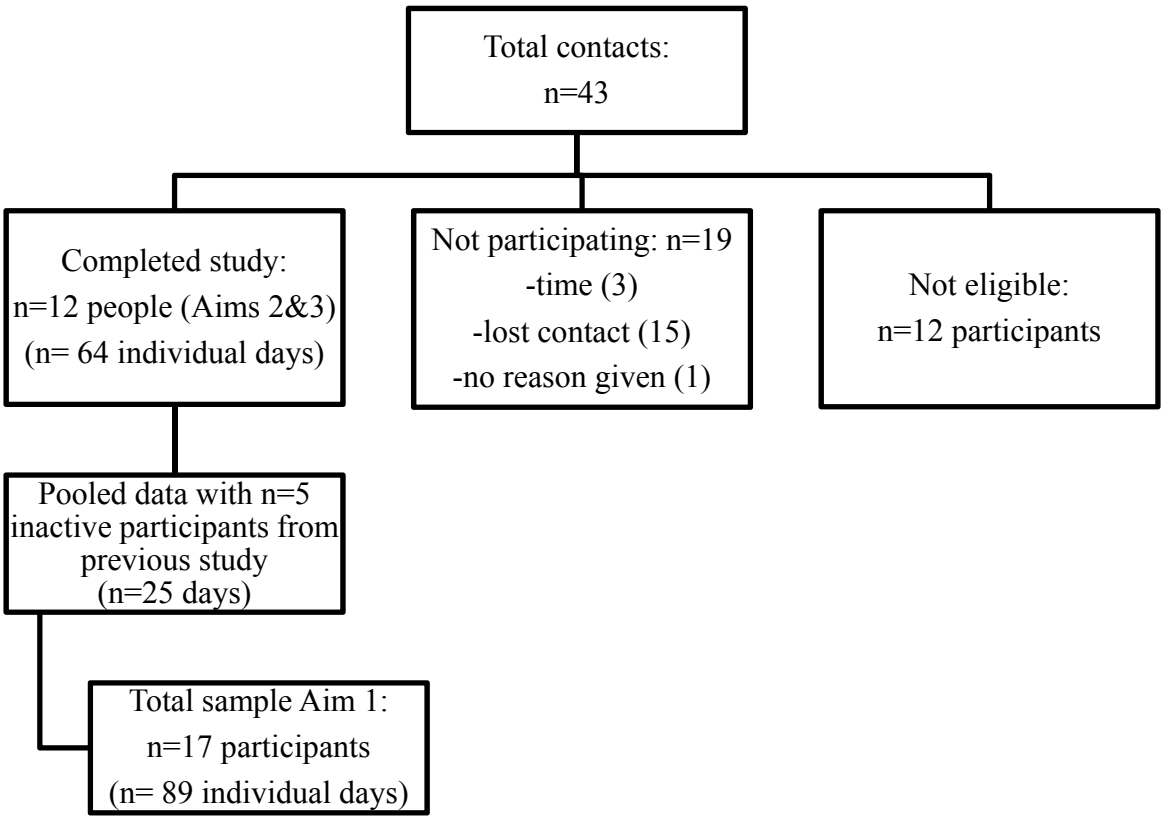
Between March and November 2015, 43 active people expressed interest in the study (Figure 1). Twelve were enrolled and completed the study, 12 were not eligible, and 19 did not participate or chose not to enroll. Between November 2013 and May 2015, seven inactive individuals were enrolled in a randomized trial of vigorous vs moderate PA for which the inclusion/exclusion criteria were the same, except self-reported PA level. The data for one inactive person was incomplete (accelerometer and CGM data not collected simultaneously), and the data for another was unreliable (had a significant number of spurious accelerometer readings and minutes per day at all intensities were statistical outliers) and thus the data were used for five individuals. The data for both groups (n=17) is pooled for Aim 1 only.

AIM 1

Data for 89 days and nights of accelerometer-derived PA and CGM-derived glucose values that were obtained from 17 individuals (5 inactive and 12 active) are included in this section. The average bedtime across all nights was 11:02pm. Participant characteristics are presented in Table 6. Participants were 23.7±6.6 years old, and 47.1% were female. They had lived with T1D for 9.3±6.9 years, and had a mean HbA_{1c} of 7.9±1.2 mmol/L (n=14).

Compared to the inactive individuals, active individuals had significantly lower resting heart rates (67±8 vs 82±7 bpm, p=0.002), body fat (23.0±5.3 vs 34.7±5.4%, p=0.002), and significantly higher peak fitness (44.2±5.5 vs 32.9±6.5 ml/kg/min, p=0.001) and quality of life (1.8±0.3 vs 2.8±0.4, p=0.000). Physical activity was not

FIGURE 1. RECRUITMENT FLOW



different between groups when reported as $MVPA_{6\text{-}BT}$ (41.3±30.9 vs 43.2±23.8 min, p=0.891); $MVPA_{6\text{-}15}$ (21.9±15.9 vs 22.2±10.2 min, p=0.962), and $MVPA_{15\text{-}BT}$ (8.6(34.8) vs 15.5(22.3) min, p=0.646). Analyses were also run for each participant across the six-day wear period and no differences were found between groups at any intensity (minutes valid days total, total per day, total per weekday day, total per weekend day, total per weekend, total per weekday). Due to limitations in the wear time of the CGM, accelerometers were only worn for six periods of 24 hours, which spanned seven dates. The median number of valid days of wear was thus five. There were no differences in number of valid days between groups (p=0.160). Across all participants, mean overnight

and next-day glucose were 8.3±2.2mmol/L and 9.9±2.1mmol/L. Of the 17 people studied, there were two individuals who did not have any readings ≤3.9mmol/L during the entire wear of the CGM. Median overnight and next-day hypoglycemia were 10.0(24.8) % and 3.6(9.4) %. There was a large difference in median overnight hypoglycemia between groups (9.0 vs 23.8 %), but the result was not statistically significant (p=0.314).

Overnight hypoglycemia

Logistic regression analyses were adjusted for VO_2 peak and age. For every additional 10 minutes of $MVPA_{15\text{-}BT}$ (n=77) the risk of overnight hypoglycemia was increased by 25% (adjusted OR 1.025 (95% CI 1.002-1.047), p=0.031). The relationship was not significant for $MVPA_{6\text{-}BT}$ (n=66) with an OR of 1.015 (95% CI 0.996-1.034, p=0.127), or $MVPA_{6\text{-}15}$ (n=66) (OR 0.991 (95% CI 0.964-1.017), p=0.486). VO_2 peak and age were both associated with overnight hypoglycemia. Specifically, higher VO_2 peak was associated with a decreased odds of overnight hypoglycemia when unadjusted (OR 0.928 (95% CI 0.865-0.996); p=0.038) and in the adjusted model with $MVPA_{6\text{-}BT}$ (OR 0.892 (95% CI 0.808-0.985); p=0.024) as well as with $MVPA_{15\text{-}BT}$ (OR 0.881 (95% CI 0.803-0.966); p=0.007).

Older age was positively associated with overnight hypoglycemia in the adjusted model with $MVPA_{15\text{-}BT}$ (OR 1.103 (95% CI 1.016-1.198); p=0.020). Results are presented in Table 7.

Next-day hypoglycemia

There were no significant relationships between previous-day MVPA and next-day hypoglycemia (Table 7).

TABLE 6. PARTICIPANT CHARACTERISTICS AIM 1

Variable	
Total number of participants (n)	17
Total number of individual days (n)	89
Number of days provided per participant	5.2±1.3
Sex (Male /Female)	9/8
Age (years)	23.7 ± 6.6
Weight (kg)	83.4 ± 18.1
Height (cm)	173.2 ± 9.9
SBP (mmHg)	118 ± 11
DBP (mmHg)	65 ± 11
RHR (BPM)	71 ± 10
Lean mass (kg)	58.3 ± 12.6
Body Fat (%)	25.2 ± 6.6
VO_2 peak (ml/kg/min)	41.3 ± 7.1
HbA_{1c} (%)	7.9 ± 1.2
Duration of T1D (years)	9.3 ± 6.9
Insulin regimen (pump/MDI)	6/11
Insulin (total daily units)	45.2 ± 20.7
Quality of life (DQOL total score)	2.1 ± 0.6
$MVPA_{6\text{-}BT}$ (minutes)*	42.6 ± 25.1
$MVPA_{6\text{-}15}$ (minutes)	22.1±11.6
$MVPA_{15\text{-}BT}$ (minutes)[§]*	13.6(27.1)
Overnight hypoglycemia (% time ≤3.9mmol/l) [§]	10(24.8)
Next-day hypoglycemia (% time ≤3.9mmol/l) [§]	3.6(9.4)

Data are presented as mean ± SD
*Group mean bedtime was 11:02pm
[§]Presented as median (interquartile range)
SBP=systolic blood pressure; DBP=diastolic blood pressure; RHR=resting heart rate; BPM=beats per minute; VO_2 peak=peak oxygen consumption; HbA_{1c} = glycosylated hemoglobin; MDI=multiple daily injections; DQOL=diabetes quality of life; $MVPA_{6\text{-}BT}$ =moderate-to-vigorous physical activity from 6am to bedtime; $MVPA_{6\text{-}15}$ =moderate-to-vigorous physical activity from 6am to 3pm; $MVPA_{15\text{-}BT}$ =moderate-to-vigorous physical activity from 3pm to bedtime

Mean glucose

A series of linear regressions were also run to investigate the association between mean overnight and next-day glucose and PA with similar adjustments as the previous analysis. A similar relationship was observed with $MVPA_{15\text{-}BT}$ and mean overnight

TABLE 7. ASSOCIATIONS BETWEEN MVPA AND HYPOGLYCEMIA

Variable	OR(95% CI)
Overnight hypoglycemia:	
$MVPA_{6\text{-}BT}$	1.015(0.996-1.034)
$MVPA_{6\text{-}15}$	0.991(0.964-1.017)
$MVPA_{15\text{-}BT}$	1.025(1.002-1.047)
Next-day hypoglycemia:	
$MVPA_{6\text{-}BT}$	1.011(0.992-1.029)
$MVPA_{6\text{-}15}$	1.013(0.986-1.040)
$MVPA_{15\text{-}BT}$	1.007(0.985-1.030)

Adjustments were made for VO_2 peak and age
$MVPA_{6\text{-}BT}$ =moderate-to-vigorous physical activity from 6am to bedtime; $MVPA_{6\text{-}15}$ =moderate-to-vigorous physical activity from 6am to 3pm; $MVPA_{15\text{-}BT}$ =moderate-to-vigorous physical activity from 3pm to bedtime

glucose. For every minute increase in $MVPA_{15\text{-}BT}$ in the adjusted model, mean glucose was lower by 2.5% (β=0.025, p=0.036) (Table 8).

AIM 2

The 12 active individuals (7 males and 5 females) included in this section contributed 64 individual days of data collection with an average bedtime of 11:06pm. They were on average 23.3±7.3 years old, weighed 78.6±12.5kg, and had a peak fitness level of 44.2±5.5 ml/kg/min. These individuals had lived with T1D for 9.7±6.5 years, and had a mean HbA_{1c} of 7.9±1.2 (see Table 9). All participants reported either participating in organized sports, running or used cardio equipment on their own. The time of day participants usually performed PA varied. Responses (n=10) for usually performing PA at 5pm± an hour were n=4 ‘never’, n=2 ‘sometimes’, and n=4 ‘often’. Besides vitamins, allergy medication, and birth control, no one was taking medications besides insulin.

In order to characterize the relationship between VPA and the outcome of hypoglycemia, we performed a series of logistic regressions treating hypoglycemia as a

TABLE 8. ASSOCIATIONS BETWEEN MVPA AND MEAN GLUCOSE

Variable	Mean±SD	p-value
Overnight mean glucose:		
$MVPA_{6\text{-}BT}$	8.3 ± 2.9	0.164
$MVPA_{6\text{-}15}$	8.3 ± 2.9	0.763
$MVPA_{15\text{-}BT}$	8.2 ± 2.8	0.036
Next-day mean glucose:		
$MVPA_{6\text{-}BT}$	10.2 ± 2.7	0.646
$MVPA_{6\text{-}15}$	10.2 ± 2.7	0.424
$MVPA_{15\text{-}BT}$	10.0 ± 2.6	0.780

Adjustments were made for VO_2 peak and age
$MVPA_{6\text{-}BT}$ =moderate-to-vigorous physical activity from 6am to bedtime; $MVPA_{6\text{-}15}$ =moderate-to-vigorous physical activity from 6am to 3pm; $MVPA_{15\text{-}BT}$ =moderate-to-vigorous physical activity from 3pm to bedtime

binary outcome (0=zero hypoglycemia; 1=any hypoglycemia), as well as a series of general linear models using mean glucose and treating it as a continuous outcome. Days with less VPA tended to have significantly less MVPA (either 6-BT or 15-BT depending on the stratification), and less VPA in all windows of time. MPA was not different between VPA low vs high days when restricting to days with $MPA_{6\text{-}BT}$ ≥20 minutes (47.1±24.3 vs 55.3±22.4 min for $MPA_{6\text{-}BT}$; 22.9±18.1 vs 24.0±15.2 min $MPA_{15\text{-}BT}$) or when restricting to days with $MPA_{15\text{-}BT}$ ≥10 minutes (47.0±28.6 vs 54.0±26.0 min for $MPA_{6\text{-}BT}$; 24.0±15.8 vs 30.4±15.7 min for $MPA_{15\text{-}BT}$). No significant relationships were seen when the cut point of 7000 counts-per-minute was used (49.4±23.1 vs 53.1±24.4 min for $MPA_{6\text{-}BT}$; 24.1±20.2 vs 22.7±11.2 min for $MPA_{15\text{-}BT}$ when restricted to $MPA_{6\text{-}BT}$ ≥20 minutes; 46.5±27.7 vs 55.3±26.8 min for $MPA_{6\text{-}BT}$ and 23.4±15.1 vs 32.0±15.9 min for $MPA_{15\text{-}BT}$ when restricted to $MPA_{15\text{-}BT}$ ≥10 minutes). VO_2 peak was significantly lower in participants with low vs high VPA days but only when restricting to days with $MPA_{6\text{-}BT}$ ≥20 minutes.

TABLE 9. PARTICIPANT CHARACTERISTICS AIM 2

Variable	
Total number of participants (n)	12
Total number of individual days (n)	64
Number of days provided per participant	5.3±1.2
Sex (Male /Female)	7/5
Age (years)	23.3 ± 7.3
Weight (kg)	78.6 ± 12.5
Height (cm)	173.8 ± 7.8
SBP (mmHg)	117 ± 13
DBP (mmHg)	63 ± 12
RHR (BPM)	67 ± 8
Lean mass (kg)	58.4 ± 11.1
Body Fat (%)	23.0 ± 5.3
VO_2 peak (ml/kg/min)	44.2±5.5
HbA_{1c} (%)	7.9 ± 1.2
Duration of T1D (years)	9.7 ± 6.5
Insulin regimen (pump/MDI)	5/7
Insulin (total daily units)	41.7 ± 14.6
Quality of life (DQOL total score)	1.8 ± 0.3
$MVPA_{6\text{-}BT}$ (minutes)*	43.2 ± 23.8
$MVPA_{6\text{-}15}$ (minutes)	22.2 ± 10.2
$MVPA_{15\text{-}BT}$ (minutes)[§]*	15.5(22.3)
Overnight hypoglycemia (% time ≤3.9mmol/l) [§]	9.0(17.3)
Next-day hypoglycemia (% time ≤3.9mmol/l) [§]	3.8(11.0)

Data are presented as mean ± SD
*Group mean bedtime was 11:06pm
[§]Presented as median (interquartile range)
SBP=systolic blood pressure; DBP=diastolic blood pressure; RHR=resting heart rate; BPM=beats per minute; VO_2 peak=peak oxygen consumption; HbA_{1c} = glycosylated hemoglobin; MDI=multiple daily injections; DQOL=diabetes quality of life; $MVPA_{6\text{-}BT}$ =moderate-to-vigorous physical activity from 6am to bedtime; $MVPA_{6\text{-}15}$ =moderate-to-vigorous physical activity from 6am to 3pm; $MVPA_{15\text{-}BT}$ =moderate-to-vigorous physical activity from 3pm to bedtime

Overnight hypoglycemia and mean glucose

There were no significant differences in overnight hypoglycemia or mean glucose in the nights with low vs high VPA, whether restricted to days with at least 20 minutes of MPA or evenings with at least 10 minutes (Table 10). On days with $MPA_{6\text{-}BT}$ ≥20 minutes however, we observed a significant increased odds of overnight hypoglycemia

(OR 9.15(95% CI 1.02-82.28); p=0.048) with low vs high VPA at > 7000 counts-per-minute (Table 11). This association was maintained after adjusting for sex, fitness and age.

TABLE 10. ASSOCIATIONS BETWEEN OVERNIGHT HYPOGLYCEMIA, OVERNIGHT MEAN GLUCOSE AND VPA

	Overnight hypoglycemia			Overnight mean glucose		
Restrict analysis to:	VPA low (N)	VPA high (N)	OR (95% CI)	VPA low mean±SE	VPA high mean±SE	p-value
$MPA_{6\text{-}BT}$ ≥20*	16/31	15/31	5.38(0.61-47.10)	9.06±0.57	8.29±0.59	0.387
$MPA_{15\text{-}BT}$ ≥10**	17/34	17/34	1.66(0.29-9.47)	9.18±0.57	8.49±0.57	0.404

*VPA low=≤7.8 minutes; VPA high=>7.8 minutes
** VPA low=≤3.4 minutes; VPA high=>3.4 minutes
Adjustments were made for sex, VO_2 peak, and age
$MVPA_{6\text{-}BT}$ =moderate-to-vigorous physical activity from 6am to bedtime; $MVPA_{15\text{-}BT}$ =moderate-to-vigorous physical activity from 3pm to bedtime

Next-day hypoglycemia and mean glucose

There were also no associations between VPA and next-day hypoglycemia or next-day mean glucose, regardless of how VPA was defined (Tables 12 and 13).

TABLE 11. ASSOCIATIONS BETWEEN OVERNIGHT HYPOGLYCEMIA, OVERNIGHT MEAN GLUCOSE AND VPA7000

	Overnight hypoglycemia			Overnight mean glucose		
Restrict analysis to:	VPA7000 low (N)	VPA7000 high (N)	OR (95% CI)	VPA7000 low mean±SE	VPA7000 high mean±SE	p-value
$MPA_{6\text{-}BT}$ ≥20*	17/31	14/31	9.15(1.02-82.28)	9.04±0.54	8.26±0.60	0.359
$MPA_{15\text{-}BT}$ ≥10**	19/34	15/34	2.75(0.37-20.31)	9.33±0.53	8.21±0.61	0.190

*VPA7000 low=≤2.0 minutes; VPA7000 high=>2.0 minutes
** VPA7000 low=≤0.5 minutes; VPA7000 high=>0.5 minutes
Adjustments were made for sex, VO_2 peak and age
$MVPA_{6\text{-}BT}$ =moderate-to-vigorous physical activity from 6am to bedtime; $MVPA_{15\text{-}BT}$ =moderate-to-vigorous physical activity from 3pm to bedtime

TABLE 12. ASSOCIATIONS BETWEEN NEXT-DAY HYPOGLYCEMIA, NEXT-DAY MEAN GLUCOSE AND VPA

	Next-day hypoglycemia			Next-day mean glucose		
Restrict analysis to:	VPA low (N)	VPA high (N)	OR (95% CI)	VPA low mean±SE	VPA high mean±SE	p-value
$MPA_{6\text{-}BT}$ ≥20*	13/24	11/24	7.35(0.71-76.07)	10.57±0.57	9.03±0.63	0.117
$MPA_{15\text{-}BT}$ ≥10**	15/29	14/29	0.66(0.09-4.53)	9.55±0.52	9.80±0.54	0.755

*VPA low=≤7.8 minutes; VPA high=>7.8 minutes.
** VPA low=≤3.4 minutes; VPA high=>3.4 minutes.
Adjustments were made for sex, VO_2 peak, and age
$MVPA_{6\text{-}BT}$ =moderate-to-vigorous physical activity from 6am to bedtime; $MVPA_{15\text{-}BT}$ =moderate-to-vigorous physical activity from 3pm to bedtime

AIM 3

The data in this section are from the same 64 days contributed by the active individuals in Aim 2. In support of previous work, we found that more GV was associated with a greater risk of hypoglycemia. Next-day CONGA 2, 3, and 4 were significantly related to next-day hypoglycemia (OR 1.68 (95% CI 1.05-2.68), p=0.031 for CONGA2); (OR 102.96 (95% CI 2.59-4086.60), p=0.014 for log10CONGA3); and (OR 55.70 (95% CI 2.15-1442.27), p=0.015 for log10CONGA4). To confirm some of the large OR's in the significant relationships, an independent sample t-test was performed between next-day CONGA 3 and 4 and none vs any hypoglycemia, and the relationship was significant (p=0.009 for CONGA3 and 0.011 for CONGA4). Data are presented in Table 14.

VPA and overnight glucose variability

On days with a minimum of 20 minutes of MPA, $VPA_{15\text{-}BT}$ was significantly associated with a lower MAG overnight (3.20±0.25 for VPA low vs 2.27±0.29 for VPA high; p=0.022).

TABLE 13. ASSOCIATIONS BETWEEN NEXT-DAY HYPOGLYCEMIA, NEXT-DAY MEAN GLUCOSE AND VPA7000

	Next-day hypoglycemia			Next-day mean glucose		
Restrict analysis to:	VPA7000 low (N)	VPA7000 high (N)	OR (95% CI)	VPA7000 low mean±SE	VPA7000 high mean±SE	p-value
$MPA_{6\text{-}BT}$ ≥20*	13/24	11/24	5.31(0.61-46.00)	10.02±0.57	9.67±0.62	0.696
$MPA_{15\text{-}BT}$ ≥10**	16/29	13/29	0.69 (0.11-4.29)	9.34±0.49	10.09±0.54	0.334

*VPA7000 low=≤2.0 minutes; VPA7000 high=>2.0 minutes
** VPA7000 low=≤0.5 minutes; VPA7000 high=>0.5 minutes
Adjustments were made for sex, VO_2 peak, and age
$MVPA_{6\text{-}BT}$ =moderate-to-vigorous physical activity from 6am to bedtime; $MVPA_{15\text{-}BT}$ =moderate-to-vigorous physical activity from 3pm to bedtime

As an exploratory section of this aim, VPA at 7000 counts-per-minute was also used, and the same association was also present (3.24±0.24 for VPA7000 low vs 2.20±0.31 for VPA high; p=0.016). There were no significant associations between VPA, no matter how it was expressed, and any of the CONGA measures.

Data are presented in Tables 15 and 16.

VPA and next-day glucose variability

There were no significant associations with VPA and next-day GV. Performing more VPA, no matter what section of the day, does not appear to influence any measures of GV the day following exercise.

TABLE 14. ASSOCIATIONS BETWEEN GLUCOSE VARIABILITY AND HYPOGLYCEMIA

Variable	OR(95% CI)
Overnight hypoglycemia:	
Overnight MAG	0.80(0.43-1.50)
Overnight log10CONGA1	5.08(0.36-71.97)
Overnight log10CONGA2	6.03(0.59-61.69)
Overnight log10CONGA3	8.68(0.80-93.60)
Overnight log10CONGA4	5.14(0.63-42.01)
Next-day MAG	1.39(0.49-3.91)
Next-day CONGA1	1.23(0.61-2.48)
Next-day CONGA2	1.22(0.81-1.85)
Next-day log10CONGA3	3.31(0.11-101.33)
Next-day log10CONGA4	3.07(0.15-63.60)
Next-day hypoglycemia:	
Overnight MAG	1.01(0.54-1.90)
Overnight log10CONGA1	4.21(0.31-57.39)
Overnight log10CONGA2	3.58(0.39-32.45)
Overnight log10CONGA3	2.59(0.30-22.39)
Overnight log10CONGA4	1.88(0.30-12.20)
Next-day MAG	1.18(0.44-3.15)
Next-day CONGA1	1.87(0.91-3.84)
Next-day CONGA2	1.68(1.05-2.68)
Next-day log10CONGA3	102.96(2.59-4086.60)
Next-day log10CONGA4	55.70(2.15-1442.27)

Adjustments were made for age and VO_2 peak
MAG=mean absolute glucose change; CONGA=continuous overall net glycemic action

TABLE 15. ASSOCIATIONS BETWEEN VPA AND OVERNIGHT GLUCOSE VARIABILITY

Variable	VPA low Mean±SE	VPA high Mean±SE	p-value
Overnight MAG:			
$VPA_{6\text{-}BT*}$	3.00±0.30	2.65±0.31	0.458
$VPA_{15\text{-}BT**}$	3.23±0.25	2.27±0.29	0.022
Overnight log10CONGA1:			
$VPA_{6\text{-}BT}$	0.09±0.06	0.08±0.07	0.944
$VPA_{15\text{-}BT}$	0.07±0.06	0.12±0.07	0.630
Overnight log10CONGA2:			
$VPA_{6\text{-}BT}$	0.25±0.07	0.22±0.07	0.785
$VPA_{15\text{-}BT}$	0.24±0.06	0.24±0.07	0.994
Overnight log10CONGA3:			
$VPA_{6\text{-}BT}$	0.30±0.08	0.25±0.08	0.657
$VPA_{15\text{-}BT}$	0.29±0.07	0.27±0.08	0.876
Overnight log10CONGA4:			
$VPA_{6\text{-}BT}$	0.32±0.08	0.26±0.08	0.656
$VPA_{15\text{-}BT}$	0.30±0.07	0.28±0.08	0.899

*VPA low=≤7.8 minutes; VPA high=>7.8 minutes

** VPA low=≤3.4 minutes; VPA high=>3.4 minutes

All analyses are restricted to days with a minimum of 20 minutes of $MPA_{6\text{-}BT}$ and are adjusted for VO_2 peak, age and HbA_{1c}

MAG=mean absolute glucose change; CONGA=continuous overall net glycemic action; $VPA_{6\text{-}BT}$= vigorous physical activity from 6am to bedtime; $VPA_{15\text{-}BT}$= vigorous physical activity from 3pm to bedtime

TABLE 16. ASSOCIATIONS BETWEEN VPA7000 AND OVERNIGHT GLUCOSE VARIABILITY

Variable	VPA7000 low Mean±SE	VPA7000 high Mean±SE	p-value
Overnight MAG:			
$VPA7000_{6\text{-}BT}$	2.99±0.28	2.64±0.31	0.428
$VPA7000_{15\text{-}BT}$	3.24±0.24	2.20±0.31	0.016
Overnight log10CONGA1:			
$VPA7000_{6\text{-}BT}$	0.07±0.06	0.11±0.07	0.679
$VPA7000_{15\text{-}BT}$	0.08±0.06	0.10±0.07	0.841
Overnight log10CONGA2:			
$VPA7000_{6\text{-}BT}$	0.22±0.06	0.26±0.07	0.745
$VPA7000_{15\text{-}BT}$	0.24±0.06	0.23±0.08	0.931
Overnight log10CONGA3:			
$VPA7000_{6\text{-}BT}$	0.27±0.07	0.29±0.08	0.876
$VPA7000_{15\text{-}BT}$	0.28±0.07	0.27±0.09	0.921
Overnight log10CONGA4:			
$VPA7000_{6\text{-}BT}$	0.28±0.07	0.30±0.08	0.809
$VPA7000_{15\text{-}BT}$	0.29±0.07	0.28±0.09	0.906

*VPA7000 low=≤2.0 minutes; VPA7000 high=>2.0 minutes

** VPA7000 low=≤0.5 minutes; VPA7000 high=>0.5

All analyses are restricted to days with a minimum of 20 minutes of $MPA_{6\text{-}BT}$ and are adjusted for VO_2 peak, age and HbA_{1c}

MAG=mean absolute glucose change; CONGA=continuous overall net glycemic action; $VPA_{6\text{-}BT}$= vigorous physical activity from 6am to bedtime; $VPA_{15\text{-}BT}$= vigorous physical activity from 3pm to bedtime

DISCUSSION

The purpose of this observational study was to determine 1) if MVPA was associated with overnight and next-day hypoglycemia, 2) if time spent in VPA attenuated the risk for overnight and next-day hypoglycemia during days with MPA, and 3) whether time spent in VPA was associated with less GV during the overnight period or the following day. Similar to previous studies, we found that increasing MVPA in the afternoon/evening increases risk of overnight hypoglycemia. In contrast to a series of experimental studies we observed an increased risk of overnight hypoglycemia with higher amounts of VPA (when using a more intense threshold for VPA than the standard cut point). Finally, we provide some novel observations that GV is associated with the risk of hypoglycemia and that reduced GV is also negatively associated with higher VPA.

AIM 1

The purpose of the first aim of this study was to attempt to replicate a previous study whose main finding was that increasing MVPA, particularly in the afternoon/evening, increases hypoglycemia risk overnight and into the next-day[97]. Our objective was to conduct a very similar analysis to build on this previous work as very little information has emerged concerning PA and hypoglycemia risk in a natural setting without an experiment. It is important to have studies with similar measurements and outcomes in order to more accurately compare results. In this case, it was also important to investigate whether or not the association between PA and the risk for hypoglycemia is seen in free-living conditions. This is important as observations in natural settings are quite different than controlled experiments and may be more generalizable to persons living with diabetes.

It is fairly well established that PA increases the risk for hypoglycemia among persons living with T1D[3]. More recently, studies have relied on accelerometry and CGM to study this association under free-living conditions. Using data for 82 nights collected from 19 adolescents (age = 16.6±1.6 years) of average fitness (VO_2 max 49.8±6.8 ml/kg/min for males and 43.9±6.4 ml/kg/min for females), Metcalf et al found that for every additional 10 minutes of $MVPA_{15\text{-}BT}$, the risk of overnight and next-day hypoglycemia increased ~12%[97]. Similar to Metcalf and colleagues we found that for every additional 10 minutes of MVPA performed in the afternoon/evening period the risk for hypoglycemia in the following overnight period was increased by ~25%. In contrast to Metcalf et al., daytime and afternoon/evening MVPA were not associated with hypoglycemia risk the following day in this study. We also observed a similar association between PA during the afternoon/evening and overnight mean glucose, such that for every additional 10 minutes of MVPA in the afternoon, night-time glucose was lower by ~25 %. These data support the concept that MVPA, particularly when performed during the afternoon/evening is associated with an increased risk for hypoglycemia.

There were a few interesting findings with respect to PA levels in this study, that make the findings generalizable to patients living with T1D. Firstly, PA levels were relatively comparable to other Canadians, suggesting this group living with a chronic disease are about as active as other Canadians. This is in contrast to some evidence suggesting youth[91] with T1D may be less active than age matched non-diabetic individuals. However, this study had an older sample. In the Canadian Health Measures Survey, youth 15-19 years old achieved an average of 53 minutes (boys) and 39 minutes

(girls) of MVPA per day[147]. Canadian men and women 20-39 years achieved an average of 33 minutes and 24 minutes of MVPA per day respectively[113]. The adolescents who participated in the Metcalf study spent more than 100 minutes in MVPA per day, which is considerably more than the current study; however, that study was comprised of much younger participants and the tool used to assess PA was different, which may have yielded different results. Secondly, despite the observation that participants who were active displayed a higher VO_2 peak compared to the inactive group, the daily PA levels were not much different than participants who were inactive. There are a few possible explanations for why MVPA levels were not different between active and inactive participants. Firstly, the definition of inactive was not meeting the current Canadian Physical Activity Guidelines (by self-report). If a person reported participating in less than 150 minutes of MVPA across a week they qualified as inactive. The definition of active was participating in regular, vigorous endurance activities at least three days a week for the past year. In contrast to the inactive definition, there was a minimum frequency, not absolute number of minutes of participation. It is possible that these definitions made for less of a separation in the groups than expected. Secondly, it is possible that seasonality played a role in PA levels with the active group. The active group were recruited over the spring, summer, and fall of 2015. Four of the five adolescents in the group were studied in the summer months, outside of their competitive season, and they reported to study staff they were not participating in as many competitive sports as during the school year. This could have lowered the daily amount of PA accumulated by the adolescents, who were likely the participants who would help to drive up MVPA numbers of the group.

It is difficult to find data to compare overnight hypoglycemia rates in free-living conditions in the absence of an experiment using CGM. In the relatively few studies that measure hypoglycemia rates during sleep using CGM, between 60-68% of hypoglycemic episodes occur during sleep[148,149], and approximately 11% of the night is spent below 4.0 mmol/L[150]. The mean percentage of time spent in hypoglycemia among persons in the Metcalf study (7% and 4% during the day for males and females, respectively and 5.4% vs 3.4 % for males and females during the night respectively) was less than this previous report, but similar to one experiment reporting between 1.5-5.2% of the time subjects experiencing post exercise hypoglycemia[12]. Despite a similar sample size and a sample of patients with less daily MVPA, we observed higher rates of overnight hypoglycemia than Metcalf et al (median overnight hypoglycemia was 10.0(24.8%)), but similar next-day hypoglycemia (median next-day hypoglycemia was 3.6(9.4%)). The rates in our study may be skewed by a small number of patients with very high rates (i.e. 31.1%) as the variation in hypoglycemia rates was substantially higher in our patient cohort as well. While common causes of hypoglycemia are related to timing of meals in relation to insulin administration and performing PA[151,152], information is sparse on who specifically may be at increased risk of delayed exercise-related hypoglycemia. Of the hypoglycemia reported here, it would appear that more of it is coming from a smaller group of individuals. Other factors that may influence hypoglycemia rates include a lack of control over diet and differences in using an insulin pump or MDI.

The main findings of Aim 1 were that afternoon/evening MVPA leads to an increased odds of both overnight hypoglycemia, and lower overnight mean glucose. The hypoglycemia finding is supported by Metcalf et al who also segmented the day in a

similar fashion and performed measurements in a non-experiment setting. Other studies in children have found similar results with increased hypoglycemia risk after performing MPA during the middle of the day. A study with adolescents (n=10) performing mid-day moderate exercise showed an increased glucose infusion rate to maintain euglycemia in the exercise condition from 9.8±1.4 to 30.6±4.7 g/h vs no change in the rest condition[153]. Another study in adolescents (n=50) also showed a significant increase in hypoglycemia (≤3.3mmol/l) on a moderate exercise night vs a sedentary night (26 vs 6%; p=0.009) as well as our observation of lower mean glucose (131±58 for moderate exercise vs 154±69 mg/dl for sedentary night; p=0.003)[96]. There is little data in cross over experiments using late-day PA, but one study using CGMs in physically active adults found that 45 minutes of MPA performed around 5pm led to significantly lower glucose values overnight (approximately midnight to 6am) compared to a sedentary night[12]. Collectively, these findings support the concept that timing of exercise is important, and given the popularity of after school/work evening exercise, it would be important to inform individuals of the potential increased risk with late day PA. At the very least, this would give individuals options when planning PA. Either re-scheduling late-day PA if possible, and if not, making adjustments to insulin, carbohydrate intake, and or blood glucose testing during the night. In the Metcalf study, the increased risk extended into the next day, whereas in the current study, the risk of hypoglycemia was restricted to the overnight period. It has been reported previously that hypoglycemia risk is increased due to an increase in insulin sensitivity immediately after exercise, and again 7-11 hours later[154]. The data presented here support these recommendations and calls to monitor glucose in the middle of night on days when a person exercises in the afternoon/evening (3pm to bedtime).

The current study found that VO_2 peak was negatively associated with overnight hypoglycemia in the adjusted model with $MVPA_{6\text{-}BT}$ (OR 0.892 (95% CI 0.808-0.985); p=0.024) as well as with $MVPA_{15\text{-}BT}$ (OR 0.881 (95% CI 0.803-0.966); p=0.007). This is in contrast to Metcalf and others who found increasing VO_2 max was associated with a higher risk of next-day hypoglycemia (OR 1.50 (95%CI 1.05-2.16); p=0.030). There is also another previous report indicating that increasing fitness level is associated with an increased risk of hypoglycemia during exercise[155]. The latter study was done in a group of 44 adults and adolescents with T1D all on insulin pumps who underwent a standardized moderate exercise session either on a treadmill or bike for 60 minutes or 30 minutes, respectively. When the sample was divided into poor and good fitness groups based on published norms, plasma glucose data revealed more hypoglycemia in the good fitness (n= 23) group compared to those with poor fitness (n=21). Authors speculate that the positive association between fitness and hypoglycemia risk could have been related to individuals in the good fitness group being less likely to having reduced their insulin dose before exercise compared to the poor fitness group. They also discuss that this doesn't seem logical as more fit individuals likely experienced exercise-related hypoglycemia previously, and thus might be more likely to make insulin reductions or supplement with carbohydrate in anticipation of exercise. In another previous study, fit individuals were more likely to consume a larger portion of total calories from carbohydrate, which negatively affected their glycemic control[128]. It is possible that the negative association we observed between fitness and hypoglycemia risk reflects more adjustments to diet or insulin than a function of higher cardiopulmonary function. While logs of total daily insulin administration were collected in the present study, specific information about

whether or not participants reduced their insulin dose in anticipation of exercise was not collected and cannot be compared between active and inactive individuals.

AIM 2

A growing body of small experimental studies reveal that adding brief bursts of VPA to an exercise session reduces exercise-related hypoglycemia[6-10,12]. To the best of our knowledge this is the first study to examine this association in individuals with T1D under free-living conditions. We sought to extend the findings of Metcalf et al and use the theoretical framework from experimental studies to determine if individuals that added vigorous intensity exercise to their training or practice were less likely to experience hypoglycemia compared to days when they did not add vigorous PA. In contrast to previous experimental studies we did not find any associations between VPA and either overnight or next-day hypoglycemia, or overnight or next day mean glucose. When we attempted to more closely mimic the intensity of VPA prescribed in experiments and used VPA at 7000 counts-per-minute, however, we found an association that was in contrary to our hypothesis. Specifically, when we stratified to days when at least 20 minutes of MPA was performed, having high vs low VPA was significantly associated with an increased odds of overnight hypoglycemia (OR 9.15; 95% CI 1.02-82.3).

The rationale for stratifying all these analyses to days on which a minimum number of minutes of MPA is present is to fit with the physiological framework of previous experimental studies that VPA has the potential to reduce hypoglycemia, within the context of a minimum amount of MPA[3]. The minimum amount of MPA that needs to be present to elicit an increased risk for hypoglycemia is unknown and thus it is difficult

to define. The rationale for stratifying days based on the threshold of $MPA_{6\text{-}BT} \geq 20$ minutes was; 1) 20 minutes was the number of minutes of MPA in two of the cross-over studies that found protection from hypoglycemia with VPA[6,7] and it was the minimum value used in all experimental trials; 2) all the participants in this analysis have self-reported that they are physically active and perform endurance exercise, which makes it likely that they would be meeting Canadian Physical Activity Guidelines. In order to meet the guidelines, about 21 minutes of MVPA should be performed daily to accumulate 150 minutes across a week. This fits roughly with the daily requirement to meet PA guidelines (but does not take into account the additional requirement that MVPA be performed in 10-minute bouts). The rationale to stratify to MPA in the evening was based on the observation in Aim 1 that every additional 10 minutes of MVPA increased odds of overnight hypoglycemia by 25%. Since the time period being considered is much shorter for the afternoon/evening period (3pm to bedtime), ten minutes was chosen as it gave approximately the same number of nights under consideration (n=31 for all day MPA ≥20 minutes vs n=34 for afternoon/evening MPA ≥10 minutes) for the two groups and the observation that an additional 10 minutes would increase the risk of hypoglycemia. Using this approach we were able to compare nights with high and low VPA, among similar individuals with a minimum amount of MPA. The strength of this approach was it allowed us to more closely mimic the conditions of the experimental studies and thus compare results. It also allowed a larger sample size when considering individual days of data collection compared to any of the experiments. The drawback was that by restricting in this manner resulted in about half the sample of nights to be excluded. Regardless of the stratification strategy and the use of nights in which VPA

levels were high, it did not protect against hypoglycemia risk nor was it associated with a higher nocturnal glucose. These data do not support experimental studies suggesting that the addition of higher intensity exercise protects against hypoglycemia.

One possible explanation for the disparate results with the experimental studies is related to differences in exercise intensity. In this study VPA was defined as exercise ≥ 3962 counts-per-minute. This is likely remarkably lower that the workloads used in the experimental trials and may not have been sufficient to elicit a release of the counter regulatory hormones that would in theory trigger hepatic glucose output. There is evidence to support this theory. The only experimental cross over study, that added bursts of VPA less than 100% among adult males (mean age 34±7 years) with T1D observed an increased risk of nocturnal hypoglycemia (between midnight and 6am) compared to a moderate exercise session alone (16±3 vs 23.3±3 mg/dL/420 minutes; p=0.04)[121]. This was the study with the lowest intensity (85% of VO_2 max) of VPA incorporated into MPA compared to other experimental trials that used doses ~100% of VO_2 peak. It could be hypothesized that the threshold used in this observational study was insufficient to detect the intensity of VPA needed to elicit the protective effects observed in experimental trials. Furthermore, in may be unlikely that physically active persons with T1D self-select training at intensities needed to elicit a counter-regulatory response. Since it is simply not known what intensity of accelerometer-derived VPA may attenuate the risk of hypoglycemia, it is plausible that the intensity cut points in the present study were not high enough to yield protection from hypoglycemia associated with MPA.

AIM 3

The rationale for studying VPA and GV is that previous studies suggest increased GV is associated with an increased risk of hypoglycemia[13,14,68-70]. The data presented here confirm previous studies that demonstrated these associations using CGM. The current study also extends by demonstrating that PA intensity, specifically VPA, is positively associated with MAG, which to our knowledge has never been documented using an accelerometer-CGM combination under free-living conditions.

Data collected in the landmark DCCT trial revealed that some patients experienced a higher risk of severe hypoglycemia that was thought to be related in part to GV. Specifically, severe hypoglycemia was tracked quarterly over a two year period in 817 people aged 13-39 years with T1D, and patients in the intensively treated group experienced a three-fold higher risk of severe hypoglycemia (glucose ≤2.8 mmol/l requiring assistance to treat or quick recovery after a source of glucose was administered) compared to that of the conventional treatment group, and the increased risk could not be explained by HbA_{1c} alone[87]. Additionally, of all hypoglycemia in both groups, 43% was experienced between midnight and 8am, and 55% during sleep, which highlights the importance of quantifying hypoglycemia during the overnight period. In a re-analysis of publicly available DCCT blood glucose data, it was found that in addition to HbA_{1c} and mean blood glucose, measures of GV (SD and MAGE (mean amplitude of glycemic excursions)) also contribute to determining hypoglycemia risk[14]. Interestingly, it has been found that severe hypoglycemia can also be predicted by variability in self-monitored capillary glucose readings[13]. These findings have been replicated in smaller settings, however, to the best of our knowledge, no studies in T1D have documented this association using CGM to quantify GV. The fact that our study was able to demonstrate

an association between hypoglycemia and GV, and in this case CONGAs 2, 3, and 4, lends further support to the notion that having larger dispersions in glucose values increases the likelihood of experiencing hypoglycemia. CONGA was specifically developed for use with CGM data and we found that higher daytime CONGA 2, 3, and 4 (i.e. a high degree of glucose dispersions over brief periods of time) was associated with a higher degree of same-day hypoglycemia. Taken together with the data presented in this thesis, this information highlights the observation that different measures of GV using different measurement methods (capillary glucose, blood glucose, CGM) can predict hypoglycemia risk in individuals with T1D. This is important clinically, because although having a lower HbA_{1c} lowers a person's risk of micro and macro-vascular disease, it increases their risk for hypoglycemia. The observation that GV is associated with hypoglycemia risk independent is key as it represents another method to screen individuals who are at increased risk of hypoglycemia beyond HbA_{1c}[14].

Once individuals who are at increased risk of hypoglycemia have been identified, it becomes important to find methods to reduce their GV and thus prevent or reduce hypoglycemia. Switching from an insulin pump to MDI[74] and taking specific kinds of long-acting insulin[75] reduces measures of GV in individuals with T1D and lowers risk for hypoglycemia. A study in T1D and T2D patients also showed reductions of 1.3 and 6.2% in glucose excursions (hypo and hyperglycemia respectively) with the use of a non-blinded CGM[156]. A non-blinded CGM is the type of CGM that provides sensor glucose values in real-time to participants so they can react and change their diabetes management immediately when the data is provided to them. The data presented here suggest that GV could also potentially be reduced through a change in exercise training

regimen, specifically by adding higher amounts of VPA, to an existing regime that includes MPA. Despite there being a small developing body of literature describing the potential for VPA to attenuate exercise-related hypoglycemia, there is little evidence, however, for the potential role of VPA in reducing glucose variability. To our knowledge, no studies have examined this concept in T1D, and this study is the first to describe a relationship between higher VPA and reducing GV. Specifically, we found that compared to days with low $VPA_{15\text{-}BT}$, days with high $VPA_{15\text{-}BT}$ were associated with a 25% lower overnight MAG value (3.23±0.25 vs 2.27±0.29; p=0.022). This was also true for VPA at 7000 counts-per-minute (3.24±0.24 vs 2.20±0.31; p=0.016). MAG values were first used to describe GV in hospital patients, with worsening MAG values being associated with hospital mortality and ICU death[157,158], highlighting the potential importance of having a low MAG. There were no significant associations between VPA and any of the CONGA measures. CONGA assesses intra-day variability and was designed specifically for use with CGM data, and is thus appropriate for this analysis as it offers a measure of variability over short periods of time[138]. This is in contrast to MAG, which is a measure of overall variability. Given the observations that hypoglycemia risk increased overnight with afternoon/evening MVPA (i.e. several hours between PA exposure and hypoglycemia occurring), it is possible that high VPA was not associated with any measures of CONGA because the measurement periods reported for CONGA (1,2,3,4) were not long enough for PA to have had any effect, whereas MAG was measuring overall variability over a longer window of time. Our finding that high VPA is associated with lower MAG, particularly at night, is interesting given the link established here and in the literature between hypoglycemia and GV. If GV and

hypoglycemia are positively associated, it would suggest that if higher VPA in the afternoon/evening reduces GV, that it could also potentially reduce risk of hypoglycemia in these individuals. However, there were no inverse relationships found in Aim 2 of this study between VPA and hypoglycemia. There was however, an inverse relationship between fitness and GV as reported by Singhvi et al[79]. In a group of adolescents with T1D, the correlation between VO_2 max and mean amplitude of glycemic excursions (MAGE) was -0.46 (p=0.048). Regardless of the measure of GV used, the fact that some evidence suggests higher fitness is inversely related to GV and other evidence suggests fitness is directly proportional to hypoglycemia is confusing given the reports that reducing GV may reduce hypoglycemia. More studies measuring the relationships between these variables are needed in order to clarify how they relate to one another. Interventions are also needed that attempt to reduce GV in order to prove whether or not this could reduce hypoglycemia, and to an extent that could be meaningful to patients.

If further data confirms an inverse relationship between VO_2 and GV this is important clinically because a study that attempts to increase VO_2 and in theory then reduce GV and could then potentially reduce hypoglycemia. Reducing GV and thus hypoglycemia would lessen negative symptoms of hypoglycemia, and reduce stress on patients and their families. Not only could reducing GV help ease the burden of hypoglycemia, but it would also theoretically reduce some of the burden of hyperglycemia, which in the long-term may ease the burden of complications.

LIMITATIONS

While an attempt to maximize the sample size was made by analyzing individual days of data collection, a limitation of this study was still a relatively small sample size. In Aim 2 we were likely underpowered to detect associations between VPA and hypoglycemia after making restrictions to days on which a minimum amount of MPA was accumulated. This strategy reduced the effective sample by about half (n = 64 vs 31 days). Although this resulted in a sample size that was still larger than any of the cross over experiments, it was likely too small to detect any differences in hypoglycemia risk between days that consisted of very similar physical activity patterns. Sample size also played a role when adjusting for confounders. Percent body fat was measured and was to be included as a confounder in Aim 1, but due to missing data on three participants, which in fact corresponded to approximately 18 nights, it was not kept in the analysis.

Some aspects of the CGM were also a limitation of the study. Although they provide continuous data and are much more practical for measuring glucose in free-living conditions, the CGM provides a measure of interstitial glucose, not blood glucose. These two measures are related, but a time lag (~4-10 minutes) exists between the reading obtained from an interstitial glucose monitor and the actual blood glucose[159]. In addition, the measurement accuracy declines at very low and very high glucose levels[160]. While CGM devices are indicated for use when performing PA, we experienced problems initially with keeping the devices attached to participants, especially those who played contact sports and outdoor activities in the heat of the summer. This did result in lost data as the CGM came off four of the 12 active individuals before the full six day recording period was done. CGMs do provide a considerable amount of data in a day (288 measurements), but as the readings are taken every five minutes this would be a

limitation if the desire was to match the CGM data to accelerometer readings, which were taken every 30 seconds. With readings every 5 minutes, we may have missed some brief periods of hypoglycemia.

While accelerometers are excellent tools for quantifying PA levels, especially in free-living conditions, they have a number of limitations. Firstly, there are relatively few studies with small numbers of participants validating the Actical accelerometer. Children and adult studies have been performed[141-145,161], however there are not specific cut points for physically active individuals, which makes results harder to generalize. Secondly, it is difficult to compare accelerometer results from studies using different brands of accelerometer, and different mounting locations. The results obtained from the wrist-mounted Genea accelerometer used in the Metcalf study, for example, may not be comparable to the waist-mounted Actical units used in the current study. Thirdly, the threshold for VPA as defined by the cut points used in this study are likely not equivalent to the intensity hypothesized to elicit protection from hypoglycemia. As mentioned above, there are different methods of measuring and defining VPA. The intensity hypothesized to lead to protection from exercise-related hypoglycemia in the small group of cross over experiments was close to 100% of peak fitness (close to a near sprint), whereas the minimum threshold used to define VPA with oxygen consumption is ≥64%. The minimum threshold for VPA used was >3960 counts-per-minute, but it is not known what threshold may correspond to a sprint. Finally, the accelerometer is unable to record activities that do not involve walking or running. Therefore, we may have missed cycling or resistance exercises that could contribute to both hypoglycemia risk and/or GV[162]. In future studies, participants should be asked to wear an accelerometer while performing a

maximal oxygen uptake test in order to quantify the count-per-minute threshold corresponding to maximal effort.

Diet is an important variable when measuring outcomes related to blood glucose, but it was not addressed in this study. In controlled experiments it is important to measure and account for factors such as timing and composition of meals, and carbohydrate supplementation before, during and after exercise. Another way to account for this would be to measure and adjust for blood glucose immediately prior to exercise. As this was an observational study, participants were asked to assume their usual lives and schedules, and were not asked to alter their diet. Participants were however, asked to keep a log of their diet, carbohydrate content of food, as well as medications and physical activity as part of the CGM data collection which required capillary glucose checks and a written log. While some individuals did track and log diet and PA variables, some only provided the capillary glucose data along with their wake and sleep times and it was therefore not possible to adjust for diet-related factors.

CONCLUSION

This study was novel because it used the physiological framework of a series of experimental studies and applied it to free-living conditions to investigate the role of MPA with added VPA on hypoglycemia risk and GV, which to the best of our knowledge has never been done. We found that increasing $MVPA_{15\text{-}BT}$ increased risk for overnight hypoglycemia and resulted in lower mean overnight glucose. This adds to the current evidence and strengthens the notion that timing of exercise is important to consider with regards to hypoglycemia risk. Educating patients about performing afternoon/evening exercise of moderate to vigorous intensity and the increased risk of hypoglycemia, and

the possible ways to avoid this could help reduce the burden of hypoglycemia for individuals with T1D. In Aim 1 we also found that higher fitness was associated with lower risk of overnight hypoglycemia, which is contrary to current evidence. This is an important finding and needs to be investigated further. If higher fitness is in fact associated with lower risk of overnight hypoglycemia, interventions designed to increase a person's fitness level may confer protection against hypoglycemia.

In Aim 2 we found there was a significant increased odds of overnight hypoglycemia with low vs high VPA at > 7000 counts-per-minute. The experimental studies adding VPA to MPA still suggest that VPA, at an intensity close to 100% effort, is protective against hypoglycemia, and this study was not able to support this. In the future, studies should be designed to measure accelerometer count-per-minute thresholds that would be equivalent to the ones used in cross over experiments. If an equivalent accelerometer intensity can be pinpointed that yields a counter regulatory response that elicits additional glucose release from the liver to reduce hypoglycemia, then accelerometers could be used to study individuals usual PA. Recommendations could then be made about how to reduce hypoglycemia that are more generalizable to people's usual activities. This is important because in addition to strategies to reduce exercise-related hypoglycemia that include adjustments to insulin and carbohydrate intake, very little is known that has been put into practice regarding PA strategies. PA strategies are important because they represent a cheap, easy way to potentially reduce hypoglycemia that could be used in conjunction with current strategies, or may not require additional carbohydrate or insulin adjustments.

In Aim 3 we confirmed that GV is positively associated with hypoglycemia risk and discovered that $VPA_{15\text{-}BT}$ was associated with a lower overnight MAG using traditional and more intense cut points. The next steps regarding these findings would be to design an experiment comparing moderate vs the combination of moderate and vigorous PA on different CGM-derived measures of GV to investigate if added VPA reduces GV. If this association is present, encouraging VPA may be a new novel strategy to reduce high and low dispersions in glucose, which could have both positive short and long-term benefits for glucose control in individuals with T1D.

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APPENDIX A - ETHICS APPROVAL FORM

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS Research Ethics Board

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

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: August 25, 2014	**APPROVAL DATE:** October 8, 2014	**EXPIRY DATE:** 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	Submited August 5, 2014
Advertisement		Submited 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 or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

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

APPENDIX B- STUDY ADVERTISEMENT

Do you Live & Train with Type 1 Diabetes?

If you have Type 1 Diabetes, and are:

- **15-35 years old**
- **Currently active**

...you may qualify for a study looking at the effect of exercise on preventing low blood sugars.

Interested, or know someone who would qualify?

Call 204-789-3591

University of Manitoba

The Lawson Foundation

The Children's Hospital Research Institute of Manitoba

Active T1D Study **789-3591**	Active T1D Study **789-3591**	Active T1D Study **789-3591**	Active T1D Study **789-3591**	Active T1D Study **789-3591**	Active T1D Study **789-3591**	Active T1D Study **789-3591**	Active T1D Study **789-3591**	Active T1D Study **789-3591**	Active T1D Study **789-3591**
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APPENDIX C- BUSINESS CARD

VIGORTrial

https://www.facebook.com/pages/VIGOR-Trial/619421154821319

Dr. Jonathan McGavock's Research Lab
University of Manitoba
Children's Hospital Research Institute of Manitoba

Phone: (204) 789-3591
Email: amacintosh@chrim.ca

APPENDIX D - CONSENT FORM

Participant #:_____

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

Title of Study: The effect of adding vigorous intensity activity to moderate intensity exercise in ENDURANCE-TRAINED persons living with T1D

Protocol #: B2014:095
Date of Approval: October 8th, 2014
Date of Expiration: August 25th, 2016

Principal Investigator: Jonathan McGavock, PhD
Address: 511D – 715 McDermot Avenue, Winnipeg, Manitoba
Phone: 204-480-1359

Co-Investigators:

Name	Address	Phone number
Lori Berard, RN	838 – 715 McDermot Avenue Winnipeg, Manitoba	204-789-3228
Dan Chateau, PhD	408 – 727 McDermot Avenue Winnipeg, Manitoba	204-975-7767
Heather Dean, MD	307 – 685 William Avenue Winnipeg, Manitoba	204-787-7435
Carmen Hurd, MD	804 - 715 McDermot Avenue Winnipeg, Manitoba	204-789-3228
Pamela Katz, MD	C5113 - 409 Tache Avenue Winnipeg, Manitoba	204-237 2908
Terry Klassen, MD	513 – 715 McDermot Avenue Winnipeg, Manitoba	204 -789-3754
Seth Marks, MD	307 – 685 William Avenue Winnipeg, Manitoba	204-787-7435
Elizabeth Sellers, MD	307 – 685 William Avenue Winnipeg, Manitoba	204-787-7435
Brandy Wicklow, MD	307 – 685 William Avenue Winnipeg, Manitoba	204-787-7435
Jane Yardley, PhD	4901 46 Avenue Camrose, Alberta	780-679-1688
Normand Boulé, PhD	8602 112 Street Edmonton, Alberta	780-492-4695
Michael Riddell, PhD	4700 Keele St Toronto, Ontario	416-736-2100, Ext. 40493

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 study 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 moderate intensity physical activity (for example, walking or light bicycling) 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. Most of the studies to date have studied people who are sedentary, or who do some physical activity, but very few look at endurance-trained people with T1D.

The aims of this study are to (1) measure the time you spend doing vigorous physical activity in your usual training to see if it is related to how variable your blood sugars are, and how often you experience hypoglycemia; and (2) determine if you have hypoglycemia less often when you do interval style exercise (moderate intensity with a burst of vigorous exercise every few minutes), compared to just doing moderate intensity exercise.

Am I Eligible to Participate?

We plan to enroll approximately 16 people in this study. You are being asked to take part in this study because you:

1. Are 15-35 years old
2. Have had T1D for at least two years
3. Have an H_bA_{1C} <9.9%.
4. Regularly perform vigorous endurance exercise ≥3 times weekly for > 1 year for an endurance sport
5. Have a fitness level that is at least 40.9 ml/kg/min if you are female, or 49.3 ml/kg/min if you are male

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 use an insulin pump and switch to injections (or vice versa) in the last two months
4. You have conditions that would make vigorous exercise unsafe: high blood pressure, problems with your nerves
5. You have a cognitive impairment resulting in an inability to provide informed consent
6. You take medications in the class of drugs called atypical antipsychotics or corticosteroids
7. You take medications in the class of drugs called beta-blockers
8. You are a woman who is pregnant, planning pregnancy, or breastfeeding
9. You have a job that involves shift work (being up at nighttime and asleep during the daytime)

Study Design:

We are asking you to participate in a study that will possibly involve 4 visits to our exercise physiology laboratory. In the first part, you will be asked to perform a test of your fitness at the research lab (visit 1), and when you leave, to wear a continuous glucose monitor (CGM) to record your blood sugar levels, and an accelerometer to record your physical activity during six days of your usual activities. After performing the fitness test at this visit, we will be able to tell you if you are eligible to complete part two (visits 2, 3 and 4). It will depend on if your fitness level meets the inclusion criterion (number five on the previous page). If you are not eligible for part two, you will complete part one only.

In the second part, you will be asked to wear a CGM and accelerometer while performing two exercise sessions lasting ~45 minutes at different exercise intensities. One visit will be to insert the CGM (visit 2) and give you an accelerometer, and on two other separate visits (visits 3 and 4) you will perform the two exercise sessions. One exercise session will consist of walking at a moderate pace for 45 minutes. The other session will involve walking at a moderate intensity for 45 minutes but will include short bouts of running every few minutes. The short bouts of running will be done at speeds equivalent to 90% of your maximal fitness. The two exercise sessions will be separated by one day in between without any exercise.

Procedures and Measurements

During your visits to the research lab, the following procedures and measurements will be done:

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.

Dual-energy X-ray absorptiometry (DEXA): We will perform a scan of your body called a DEXA scan that measures the amount of muscle, fat and bone inside your body. This test takes approximately 10 minutes to perform and all you have to do is lie still while the scan happens. The machine takes an x-ray (picture) of your body.

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 Monitor (CGM): 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 iPro™2. The system automatically records an average sugar value every five minutes for up to two weeks, but the sensor needs to be replaced after six days. 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. The information stored on the iPro™2 is then downloaded onto a computer, and the sensor is discarded.

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 two times throughout the study.

Blood Work: There will be one blood sample taken by a nurse during visit 1 to measure your H_bA_{1C} (average blood sugars over a three month period).

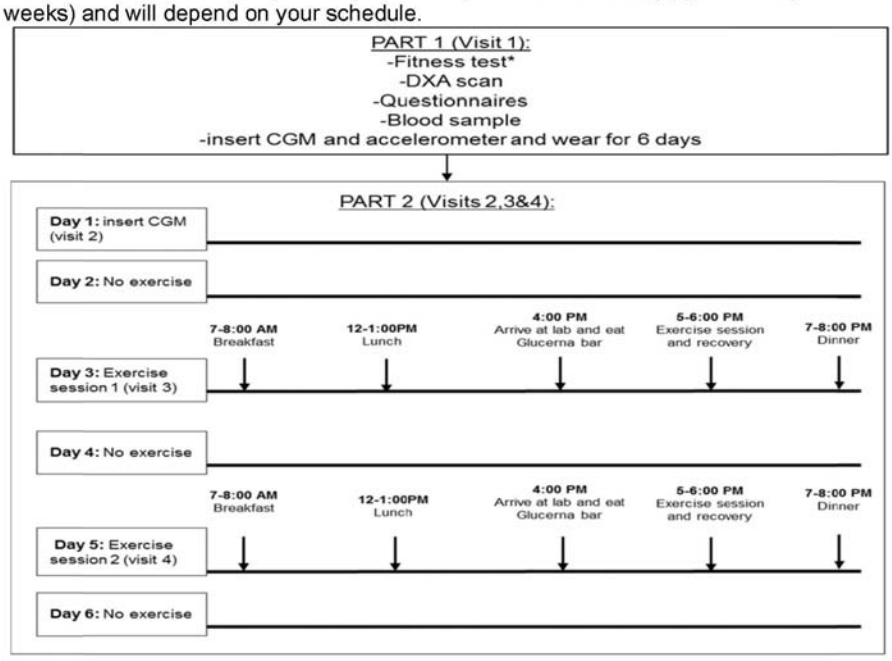
Food Intake: What you eat and when you eat will affect your blood sugars, and we would like to keep this as consistent as possible for all study days. This means, to the best of your ability, that we would like you to eat the same meals (particularly lunch and supper) at the same time on every day of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

Questionnaires: you will be asked to complete questionnaires measuring:

- Quality of life
- Barriers to physical activity

Summary of Study Protocol

The amount of time that separates part 1 and part 2 will be short (approximately 1-2 weeks) and will depend on your schedule.



*You will only complete part 2 if your fitness level meets the criteria listed in the inclusion criteria (#5)

What Will I Have to Do?

In part one, this will consist of one visit to the research lab 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 form. Then, study staff will measure your blood pressure, height and weight, you will complete questionnaires, and have the blood sample taken for the H_bA_{1C} test. You will then change into clothes appropriate for exercising. Once you are changed, you will then complete the DXA scan, and exercise test. After the exercise test, a nurse will insert the CGM, you will be given the accelerometer, and before you leave you will be given a manual with instructions on how to wear the devices and what information to record during the time you are wearing them. You will wear the CGM for six days, and the accelerometer for six days and assume your usual activities. This means that you should avoid scheduling this part of the study when you have a competition or race. While you are wearing these devices, the aim is to have you doing your usual activities.

In part two, you should be prepared to schedule this part of the study when you are able to commit to performing the two exercise sessions being asked of you, and not do your usual training. The study design asks that you perform exercise in our lab, and not exercise on the days before and after the sessions. If it is not possible for you to refrain from doing your usual training, we will ask that you try to do the same type and duration of exercise on the days before and after the sessions. Part two will consist of three more visits to the research lab. One will be a very short visit for a nurse to insert a new CGM sensor and give you an accelerometer to wear. This will be followed by a day without exercise. You will then come to the research lab for two, 45-minute exercise sessions with a day in between without exercise. The order of which exercise session you will do will be randomly assigned. During the moderate session, you will perform 45 minutes of walking at a pace considered moderate for you. During the interval session, you will perform 45 minutes of moderate exercise with 1-2 minutes of running every few minutes at 90% of maximal fitness. The continuous glucose monitor will monitor your blood sugar levels throughout all of part two to determine how your body responds to vigorous intensity exercise.

What Are the Possible Risks or Discomforts of the Study?

Dual-energy X-ray absorptiometry (DEXA): The amount of x-ray used in this test amounts to less than a regular chest x-ray and is similar to the amount of radiation a person is exposed to on a daily basis. Some researchers equate this to one commercial flight across Canada or living for one day in the city.

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 insertion 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 staff who will know what to do in case of low blood sugar. At each session, the staff will have a hypoglycemia rescue kit, consisting of sugar tablets 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 hypoglycemic episode following exercise, you will be asked to meet with your doctor or diabetes educator to assess the situation before continuing to exercise. 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 a treadmill safely.

Questionnaires: There are no risks associated with filling out the questionnaires. It is possible that some of the questions may make you feel uncomfortable. You do not have to answer any questions if they make you feel uncomfortable.

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 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 that will be performed as part of this study are provided at no cost to you.

Payment for Participation

You will be given $20 for each of the three study visits that involve testing (visits 1, 3 and 4), $60 total.

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 you 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 logbook information will be uploaded. Medtronic is responsible for hosting and maintaining the CareLink iPro servers, and therefore will have access to the non-identifying information uploaded to the website. Medtronic may also study the uploaded information for purposes of advancing or improving its products, therapies or services for the benefit of future patients.

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 completely 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:

- Dr. Jonathan McGavock, Primary Investigator, University of Manitoba (204) 480-1359
- Andrea MacIntosh, Research Assistant, University of Manitoba (204) 789-3591
- For questions about your rights as a research participant, you may contact the University of Manitoba Bannatyne Campus Research Ethics Board at (204)-789-3389.

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 "The effect of adding vigorous intensity activity to moderate intensity exercise in ENDURANCE-TRAINED persons living with T1D"

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/guardian signature: _____**Date:** _____
(day/month/year)

Parent/legal guardian's printed name: _____

As a participant in this study you will receive a summary of the health information collected about you during the study period. Would you like to receive a summary of the study findings once they become available? Please check the appropriate box:

☐YES ☐NO

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.

Signature: _____ **Date:** _____
(day/month/year)

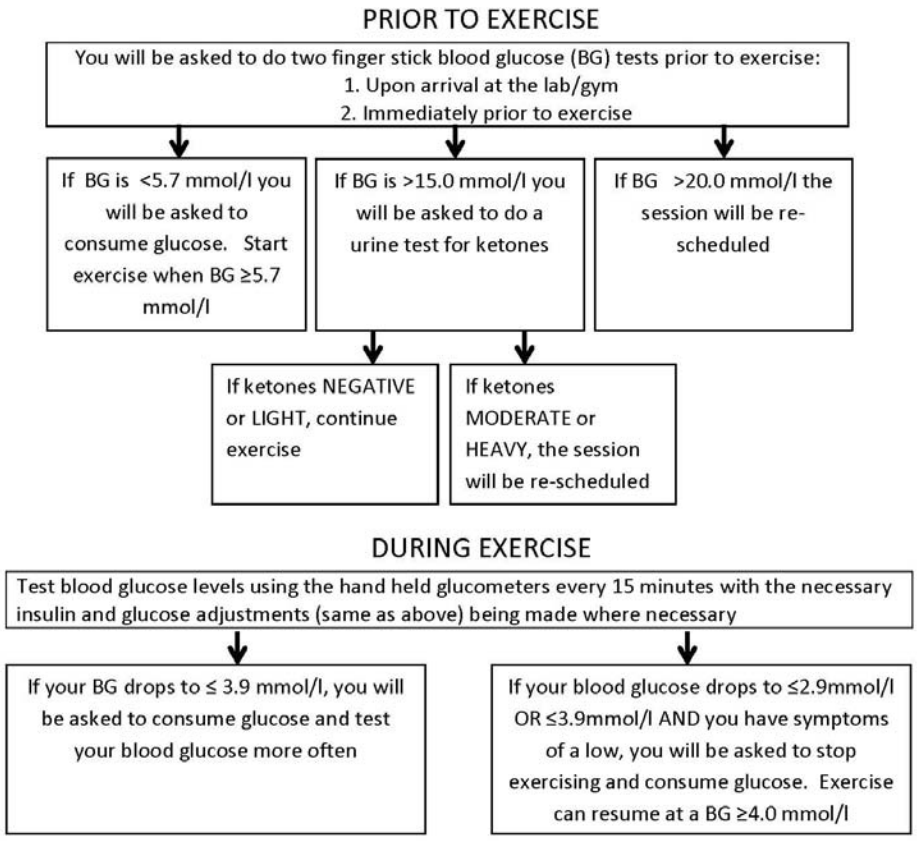
Printed name: _____

Role in Study:_____

APPENDIX E – GLUCOSE GUIDELINES FOR EXERCISE TESTING

Exercise Sessions

These are guidelines that have been put in place for your safety that you will be asked to follow when with staff:



Post-Exercise:

- Reduce your insulin intake prior to bed in order to prevent nighttime lows:
  - **Pump users:** lower basal rates by 20% between midnight and 3 am
  - **MDI users** (if you take insulin at night): decrease in long acting insulin injection by 10%
- Get up once a night during the night to check your blood glucose on exercise nights.