

## STAIR CLIMBING AND GLYCEMIC CONTROL IN TYPE 2 DIABETICS

THE EFFECT OF BRIEF INTERMITTENT STAIR CLIMBING EXERCISE ON  
GLYCEMIC CONTROL IN PEOPLE WITH TYPE 2 DIABETES

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TITLE: The effect of brief intermittent stair climbing exercise on glycemic control in people with type 2 diabetes.

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## **LAY ABSTRACT**

Physical activity is important for the management of type 2 diabetes (T2D). Interval training, which involves alternating periods of relatively intense exercise and recovery, can improve blood sugar control in adults with T2D. This has largely been shown in laboratory settings using specialized equipment and protocols that may not be practical or time-efficient. This small, proof-of-concept study examined whether brief, intermittent stair climbing exercise could improve blood sugar control in people with T2D. Average blood sugar measured over 24 hours was unchanged after a single bout of stair climbing and after 18 sessions of training performed over 6 weeks. However, stair-climbing exercise reduced blood sugar fluctuations in response to specific meals. These preliminary findings suggest that interval stair climbing is a feasible exercise option for adults with T2D, but the precise effects on blood sugar control remain to be clarified.

## ABSTRACT

Physical activity is important for the management and treatment of type 2 diabetes (T2D). Interval exercise training has been shown to improve glycemic control in people with T2D; however, studies have generally utilized high volume protocols and/or specialized equipment that limit translation to a “real world” setting. The present proof-of-concept study examined the efficacy of brief, intermittent stair climbing exercise to improve indices of glycemic control in adults with T2D, using continuous glucose monitoring (CGM) under controlled dietary conditions. Each session involved 3 x 60-s bouts of vigorously ascending and slowly descending a single flight of stairs. This was set within a 10-min period, which otherwise involved walking for a warm-up, cool-down and recovery in between bouts. Data are reported for n=5 participants ( $52 \pm 18$  y, BMI:  $31 \pm 5$  kg/m<sup>2</sup>, HbA1c:  $6.6 \pm 0.7$  %; mean  $\pm$  SD) who performed 18 training sessions over 6 weeks. Mean 24-h glucose and time spent in hyperglycemia ( $> 10$  mmol/L) were unchanged after an acute session of stair climbing ( $p=0.38$  and  $p=0.42$ , respectively) or after 6 weeks of training ( $p=0.15$  and  $p=0.47$ , respectively). Measures of glycemic variability were improved in the 24-h period following a single session of stair climbing, based on reductions in the mean amplitude of glycemic excursions (MAGE) ( $4.4 \pm 1.5$  vs.  $3.5 \pm 1.0$  mmol/L,  $p=0.02$ ) and the standard deviation (SD) around the mean ( $1.7 \pm 0.5$  vs.  $1.4 \pm 0.5$  mmol/L,  $p=0.02$ ). There was a meal-specific improvement in postprandial hyperglycemia after training, with the incremental area under the curve (iAUC) of the lunchtime meal reduced by  $36 \pm 42$  % ( $p=0.01$ ). These preliminary results demonstrate the feasibility of stair climbing as a physical activity option for people with T2D,

although the acute and chronic effects of this training on indices of glycemic control remain equivocal.

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## LIST OF ABBREVIATIONS

1,5-AG	serum 1,5-anhydroglucitol
6MWT	six minute walk test
AMPK	5'- adenosine monophosphate-activated protein kinase
AUC	area under the curve
BMI	body mass index
CGM	continuous glucose monitoring
DOMS	delayed onset muscle soreness
EHC	euglycemic hyperinsulinemic clamp
FFM	fat free mass
GLUT4	glucose transporter 4
HbA1c	glycated hemoglobin
HIIT	high-intensity interval training
HR	heart rate
IGT	impaired glucose tolerance
IVGTT	intravenous glucose tolerance test
MAGE	mean amplitude of glycemic excursions
MET	metabolic equivalent
MICT	moderate-intensity continuous training
OGTT	oral glucose tolerance test
PACES	physical activity enjoyment scale
PPS	postprandial spike
QUICKI	quantitative insulin sensitivity check index
RPE	rating of perceived exertion
SD	standard deviation around the mean
SIT	sprint interval training
SMBG	self-monitored blood glucose
T2D	type 2 diabetes
VO <sub>2max</sub>	maximal oxygen consumption

## **DECLARATION OF ACADEMIC ACHEIVEMENT**

### **Format and Organization of Thesis**

This thesis is prepared in the standard format as outlined in the School of Graduate Studies' Guide for the Preparation of Master's Theses. The first chapter is a literature review and the second chapter is a draft of a manuscript for submission to a journal.

### **Contributions to Content of Thesis**

Godkin, F. E., Jenkins, E. M., Little, J. P., Nazarali, Z., Percival, M.E., Tarnopolsky, M.A., and Gibala, M. J.

### ***Contribution***

F.E. Godkin and M.J. Gibala conceptualized and designed the study with input from J.P. Little. F.E. Godkin and Z. Nazarali screened potential participants and facilitated participant recruitment with medical oversight from M.A. Tarnopolsky. F.E. Godkin and E.M. Jenkins facilitated data collection with assistance from M.E. Percival. F.E. Godkin and E.M. Jenkins completed data analyses. F.E. Godkin and M.J. Gibala interpreted the results, with input from J.P. Little. F.E. Godkin drafted the thesis version of the manuscript, with input from M.J. Gibala. All coauthors will be involved with subsequent revision of the manuscript prior to eventual submission.

## **CHAPTER 1: LITERATURE REVIEW**



## 1.1 INTRODUCTION

Diabetes is an umbrella term that encompasses a group of metabolic diseases characterized by elevated levels of blood glucose, as a result of insulin deficiency, resistance to insulin action, or both (American Diabetes Association, 2014; Goldenberg & Punthakee, 2013). Diabetes affects more than 400 million people worldwide, with a projected increase to over 600 million cases by the year 2040 (International Diabetes Federation, 2015). The prevalence of diabetes in Canada is estimated to reach 3.7 million by 2018-2019 (Public Health Agency of Canada, 2011), with about 90% of those affected by type 2 diabetes (T2D) (ADA, 2014). T2D is characterized by systemic perturbations to multiple tissues, but progressive insulin resistance primarily in skeletal muscle is recognized as a key initiating factor and hallmark of the disease (DeFronzo & Tripathy, 2009). Skeletal muscle insulin resistance can lead to chronic hyperglycemia and a reduced capacity of pancreatic beta cells to secrete insulin (Polonsky et al. 1988). Excess body mass, physical inactivity and poor nutrition are known modifiable risk factors implicated in the development of T2D, with the exact causes of T2D likely to be interrelated and difficult to fully elucidate (IDF, 2015).

Largely owing to chronic elevations in blood glucose levels, T2D is associated with premature mortality and the development of comorbidities such as blindness, cardiovascular, kidney and nerve diseases (Goldenberg & Punthakee, 2013). A diagnosis of T2D is typically made based on a glycated hemoglobin level (HbA1c)  $> 6.5\%$ , a fasting plasma glucose (FPG) level  $> 7.0$  mmol/L, or a 2 hour plasma glucose level  $> 11.1$  mmol/L during an oral glucose tolerance test (OGTT) (ADA, 2014). These benchmarks

have been selected because they reflect thresholds of glycemia that are associated with the development of diabetic complications (Goldenberg & Punthakee, 2013). Beyond these parameters, T2D is characterized by glycemic instability and post-meal hyperglycemia, as depicted by rapid and large increases in blood glucose levels following a meal (Ceriello, 2005; van Dijk et al. 2011). Accumulating evidence suggests that glycemic variability and postprandial hyperglycemia are each independent risk factors for the development of cardiovascular complications (Cavalot et al. 2011; Nalysnyk et al. 2010), with postulated mechanisms involving increased oxidative stress leading to micro- and macrovascular damage (Ceriello, 2005; Ceriello et al. 2008). Furthermore, postprandial hyperglycemia is hypothesized to be associated with insulin resistance at the level of skeletal muscle (Abdul-Ghani et al. 2006), which suggests that better control of post-meal glucose excursions may represent a valuable area for therapeutic intervention and a modifiable target when studying exercise-induced improvement in adults with T2D.

Exercise is considered a cornerstone treatment of T2D, with Diabetes Canada recommending 150 minutes per week of aerobic exercise performed at a moderate (40-60% of maximal oxygen uptake ( $VO_{2max}$ )) to vigorous (> 60%  $VO_{2max}$ ) intensity, spread across at least three days of the week (Sigal et al. 2013). Interval training involves alternating bouts of relatively intense exercise and recovery (Gillen & Gibala, 2014). Emerging research suggests that interval training can improve disease risk parameters in adults with lifestyle-induced cardiometabolic disease including T2D (Weston et al. 2014), with some evidence that improvements in insulin resistance may be superior to moderate intensity continuous training (MICT) (Jelleyman et al. 2015). With some exceptions

(Karstoft et al. 2013), most interval training studies have been conducted in a traditional laboratory environment that limits translation to a real world setting. In establishing the framework that led to the present thesis, the goals of this review are to: 1) summarize the key methods used to quantify changes in insulin sensitivity and subsequent glycemic control; 2) examine the exercise-induced changes in insulin sensitivity and glycemic control with traditional MICT; 3) determine the utility of interval training as a time-efficient option to improve insulin sensitivity and glycemic control in T2D; and 4) explore the suitability of stair climbing as an exercise alternative for people with T2D.

## **1.2 EXERCISE AND GLYCEMIC CONTROL**

In response to nutrient ingestion under healthy conditions, insulin maintains normal blood glucose homeostasis by suppressing hepatic glucose production and activating a signaling cascade in peripheral tissues, particularly skeletal muscle, that results in blood glucose uptake into those insulin sensitive tissues and clearance from the circulation (DeFronzo, 2004; Muniyappa et al. 2015). Insulin binds to and activates the insulin receptor on the cell surface of skeletal muscle, resulting in a cascade of reactions (via the PI-3 kinase (PI-3K)/Akt pathway) that leads to the translocation of an intracellular pool of glucose 4 transporters (GLUT4) to the muscle cell membrane, an influx of glucose into the muscle cell, and subsequent metabolism through glycolysis (oxidation) or glycogen synthesis (DeFronzo, 2004). During exercise, the activation of 5'-adenosine monophosphate-activated protein kinase (AMPK) has been shown to play a key role in regulating contraction-stimulated glucose uptake, which results in activation

of the GLUT4 transport system to the sarcolemma and an increased uptake of glucose to match the energy demands of exercise (Jensen & O’Rahilly, 2017; Kjøbsted et al. 2017).

### **1.2.1 Etiology of type 2 diabetes: skeletal muscle insulin resistance**

Although the contraction-mediated, insulin-independent pathway remains intact in the skeletal muscle of those with T2D, the ability of insulin to stimulate GLUT4 protein translocation within skeletal muscle is impaired due to selective defects within the insulin-signaling cascade (Henriksen, 2002; Krook et al. 2000). Proposed mediators of skeletal muscle insulin resistance include excessive fatty acid availability (Horowitz, 2007) and impaired mitochondrial oxidative capacity (Petersen et al. 2003; Petersen et al. 2004; Kelley et al. 2002), which are associated with increased accumulation of intramyocellular lipid metabolites (e.g., ceramides) that can disrupt insulin-stimulated glucose transport in skeletal muscle (Horowitz, 2007; Amati et al. 2011). In addition, these fatty acid intermediates can activate inflammation-related signaling pathways within skeletal muscle (Horowitz, 2007), leading to an elevated release of proinflammatory cytokines that also impair the insulin signaling cascade (Karstoft & Pedersen, 2016; Röhling et al. 2016). Although the primary mechanisms of skeletal muscle insulin resistance are complex, the diminished sensitivity of skeletal muscle to insulin results in increased levels of blood glucose, which, if left uncontrolled, can impair the insulin secretory response of the pancreatic beta-cell (Polonsky et al. 1988). A combination of reduced insulin sensitivity and impaired insulin secretion results in compromised glycemic control in those with T2D (Kearney & Thyfault, 2016). As such,

therapeutic intervention with exercise is warranted to try and improve insulin sensitivity and restore glycemic control.

### **1.2.2 Methods of assessing insulin sensitivity and glycemic control**

Various methods can be employed to quantify changes in insulin sensitivity and subsequent improvements in glycemic control, including the impact of lifestyle interventions and acute and chronic exercise in people with T2D. The euglycemic hyperinsulinemic clamp (EHC) is widely accepted as the “gold standard” method and is a direct measure of insulin sensitivity (DeFronzo et al. 1979). Performed in the fasted state, this procedure involves an elevated insulin infusion rate coupled with a variable rate of glucose infusion that reflects whole body glucose disposal under steady state conditions (DeFronzo et al. 1979). Although a reproducible and reliable measure of insulin sensitivity, the EHC does not mimic post-meal responses and may not be as feasible due to time, labor, and cost requirements (Patarrao et al. 2014). In an effort to circumvent some of these barriers, surrogate indexes for insulin sensitivity have been developed as tools that can be applied more readily in research settings (Muniyappa et al. 2008). Both the Homeostatic Model of Insulin Resistance (HOMA-IR) and the Quantitative Insulin Sensitivity Check Index (QUICKI) use fasting blood glucose and plasma insulin levels in different mathematical equations derived to provide an estimate of primarily hepatic insulin sensitivity (Bird & Hawley, 2017). Across the insulin sensitivity spectrum, the QUICKI has demonstrated a better linear correlation with EHC values than those derived using the HOMA-IR (Katz et al. 2000).

Although assessing insulin sensitivity during fasted conditions is of value, the association of postprandial hyperglycemia with increased cardiovascular disease risk allows for the evaluation of glycemic control in ways that more closely mimic physiological conditions (Roberts et al. 2013; Stratton et al. 2000). As an indirect measure of insulin sensitivity, the most commonly used method for assessing whole-body glucose tolerance and diagnosing T2D is the OGTT (Matsuda & DeFronzo, 1999; ADA, 2014). Following an overnight fast, a 75g standard oral glucose load is consumed and coupled with frequent blood sampling over a 2-h period to monitor blood glucose and insulin concentrations. The magnitude of the resultant rise in plasma glucose concentration is used to determine the level of insulin resistance (ADA, 2014).

Another common metric used in the diagnosis and management of T2D is glycated hemoglobin (HbA1c) (Kohnert et al. 2015). As a measure of long-term glycemic control, this universally accepted biomarker reflects average blood glucose concentrations during the previous 1-3 months (Kohnert et al. 2015). Based on the positive association of HbA1c with the development of diabetic complications, with evidence suggesting that each 1% reduction in HbA1c is associated with a 21% decrease in risk of death related to diabetes, management of T2D has traditionally been focused on lowering HbA1c values (Stratton et al. 2000). However, HbA1c is unable to provide insight into the effectiveness of day-to-day diabetes management on minimizing glycemic fluctuations or the differences in blood glucose profiles between people (MacLeod et al. 2013).

#### ***1.2.2.1 Continuous glucose monitoring (CGM)***

Adjunct measures such as continuous glucose monitoring (CGM) may be beneficial for those with T2D to capture short-term changes in glycemic variability that are not detectable when relying on HbA1c (MacLeod et al. 2013; Monnier et al. 2008). CGM consists of a minimally invasive, transcutaneous sensor inserted under the skin of the abdomen, which transmits an electrical charge (created from the reaction of interstitial glucose with the glucose oxidase enzyme) to a recorder every 5-min throughout the day (Castle & Jacobs, 2016; Kearney & Thyfault, 2016). A device-specific algorithm and calibration with regular finger-prick measurements are then used to provide an estimate of circulating blood glucose levels (Riddell & Perkins, 2009). Thus, CGM provides rapid feedback on the magnitude, frequency, and direction of blood glucose fluctuations and allows for the examination of glucose profiles over an entire free-living 24-h period (see Fig. 1) (Klonoff, 2005). CGM can be contrasted to self-monitored blood glucose (SMBG) with single finger stick measures, which only provides a snapshot of specific time points and cannot detect acute variations in glycemic control occurring between measurements (Kohnert et al. 2015; Monnier et al. 2008).

Used under conditions of controlled feeding where the timing of meal ingestion is recorded, CGM can also differentiate between the postabsorptive and the postprandial blood glucose response to mixed meals (Roberts et al. 2013). Post-meal glucose responses are influenced by both food consumption and level of physical activity (Monnier et al. 2008). With the deleterious impact of glycemic fluctuations and post-meal spikes predictive of the development of cardiovascular complications (Cavalot et al. 2011), and

with CGM technology continuing to improve (Schnell et al. 2017), blinded CGM may be a viable option to evaluate the impact of exercise interventions on postprandial hyperglycemia. A meta-analysis conducted by MacLeod et al. (2013) concluded that exercise training in adults with T2D (ranging from a single bout up to > 2 months of training) improved CGM-derived glycemic control parameters, without significantly impacting fasting blood glucose concentrations. This finding suggests that CGM may capture acute changes in glycemic control that would otherwise go undetected based on static, laboratory-based blood glucose measurements (van Dijk & van Loon, 2015)

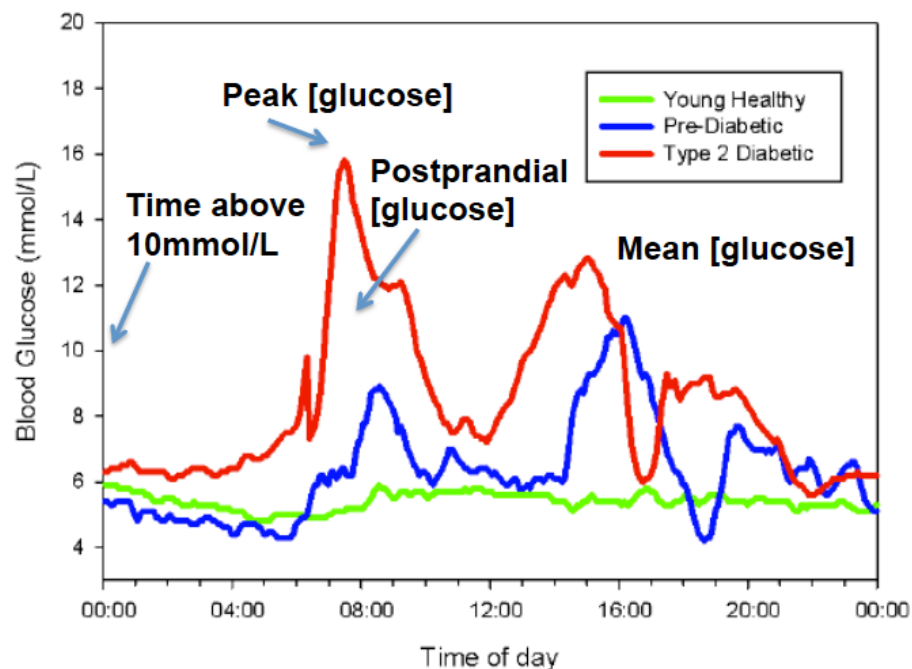


Figure 1. CGM trace from previous pilot testing depicting excursions in glycemic control in different populations (Figure courtesy of Dr. J. Little).

### 1.2.3 Exercise-induced changes in insulin sensitivity and glycemic control

Lifestyle modifications are at the forefront of improving glycemic regulation, with exercise considered a cornerstone of T2D prevention and management (Tuomilehto et al.



2001). Skeletal muscle can adapt to exercise training (reviewed by Egan & Zierath, 2013) and comprising 30-40% of an individual's body mass (Janssen et al. 2000), it is the primary sink for ingested glucose (DeFronzo, 2004; DeFronzo et al. 1981). Evidence from large-scale, randomized trials has demonstrated that diet and physical activity-altering lifestyle interventions resulted in a 58% reduction in the risk of diabetes compared to controls (Tuomilehto et al. 2001), were more effective than metformin (an anti-diabetic agent) at the end of a 4 year follow up (Knowler et al. 2002), and resulted in sustained improvements in weight loss, fitness and blood glucose control in older adults with T2D (n=5145) (Wing et al. 2013). Although these results exemplify the modifiable nature of the T2D disease trajectory, the independent effect of physical activity is confounded by an interaction with weight loss in each of these studies.

It is now widely accepted that adopting a physically active lifestyle is an important treatment in a range of cardiometabolic diseases (Pedersen & Saltin, 2006). Cardiorespiratory fitness has been identified as an independent predictor of mortality in people with T2D (Kohl et al. 1992; Wei et al. 2000). Additionally, exercise training has been shown to have a beneficial impact on glycemic control in adults with T2D, independent of weight loss (Boulé et al. 2001). In alignment with the physical activity guidelines for those with T2D, a meta-analysis conducted by Umpierre et al. (2011) looking at structured exercise interventions of at least 12 weeks in duration demonstrated the greatest improvements in glycemic control (based on reductions in HbA1c) when aerobic exercise was undertaken for at least 150 minutes per week (Umpierre et al. 2011). However, Liubaoerjijin et al. (2016) showed that the greatest reductions were seen with

higher-intensity exercise compared to lower intensity exercise (Liubaoerjijin et al. 2016). Notably, exercise training-induced reductions in HbA1c levels have been shown to be similar in magnitude (reductions of ~ 0.6-0.8%) to the effects elicited through interventions based exclusively on long-term drug or insulin therapy (Boulé et al. 2001; Snowling & Hopkins, 2006). Although it is clear that exercise is an effective treatment strategy to improve health in T2D, the optimal dose is unknown and additional work is warranted to examine the effect of varying intensities and durations on glycemic control.

#### ***1.2.3.1 Acute effect of endurance exercise***

Improved skeletal muscle insulin sensitivity is one of the primary mechanisms proposed to account for beneficial changes in glycemic control with exercise (Hawley & Gibala, 2009; Henriksen, 2002). Both acute periods and more chronic endurance exercise training have been shown to counteract some of the metabolic dysfunction associated with skeletal muscle insulin resistance (Röhling et al. 2016). Many of the major benefits of exercise on insulin sensitivity persist for 12-24 h, and sometimes 72-h following one session of aerobic exercise (Holloszy, 2005; Horowitz, 2007; Tjønnå et al. 2011; Bird & Hawley, 2017). An increase in skeletal muscle glucose uptake after a single session of exercise occurs in two phases, with contraction-mediated glucose transport persisting into the first couple of hours post-exercise, followed by improved insulin-mediated glucose uptake (Holloszy, 2005). For example, a reduction in blood glucose during and immediately following 45-min of MICT cycling (70% of  $W_{max}$ ) in adults with T2D most likely reflects increased contraction-mediated glucose uptake (Musi et al. 2001). In contrast, evidence of enhanced insulin-stimulated glucose disposal can be seen ~ 15-h

following a single session of endurance exercise (90-min at  $\sim 65\%$   $\text{VO}_{2\text{peak}}$ ) in a study in healthy women, shown by a reduction in fatty acid-induced insulin resistance measured by an intravenous glucose tolerance test (IVGTT) (Schenk & Horowitz, 2007). Moreover, in adults with T2D, 45-60 minutes of MICT cycling (35-50% of  $W_{\text{max}}$ ) improved CGM-derived glycemic control for 24 to 48-h compared to a non-exercise control group (van Dijk et al. 2012; van Dijk et al. 2013). This window of time for acute improvements in glycemic control is reflected in the current physical activity guidelines for those with T2D, which suggest that no more than two consecutive days occur between exercise bouts (Colberg et al. 2016).

One of the key mechanisms postulated to mediate the increase in skeletal muscle glucose uptake with acute exercise is through the activation of AMPK in response to changes in cellular energy state (Benziane et al. 2008). Indeed, a single session of endurance exercise has been shown to result in increased activation of AMPK within the skeletal muscle of those with T2D during and immediately following exercise (Musi et al. 2001). The activation of AMPK as a cellular energy sensor may regulate the contraction-induced transcription of GLUT4 (increased GLUT4 mRNA) and translocation of GLUT4 to the sarcolemma, both representing important mechanisms in insulin resistant individuals to facilitate skeletal muscle glucose uptake and improve post-exercise insulin action (Richter & Hargreaves, 2013). An exercise-induced decrease in muscle glycogen concentration has also been associated with the observed improvements in insulin sensitivity in response to an acute bout of endurance exercise (Horowitz, 2007). However,

the minimum effective exercise “dose” required to evoke acute improvements in insulin sensitivity has not been determined.

### ***1.2.3.2 Adaptation to endurance exercise training***

The beneficial effects of endurance exercise training on insulin sensitivity and glycemic control are related to skeletal muscle adaptations (Bird & Hawley, 2017). For example, an increase in skeletal muscle GLUT4 protein levels is a fundamental adaptation to exercise training, hypothesized to result from the repetitive, transient increases in GLUT4 transcription following successive exercise bouts (Richter & Hargreaves, 2013). An increase in skeletal muscle GLUT4 protein content has been demonstrated following 9 weeks of single-leg cycling (6 days/wk, 30-min/day, ~ 70% one-legged  $VO_{2max}$ ) in adults with T2D (Dela et al. 1994) and is also apparent in adults with the metabolic syndrome following an 8-wk period of intermittent cycling training (Stuart et al. 2013). Associated with improved skeletal muscle glucose disposal, the transport of more GLUT4 to the sarcolemma in response to a given insulin stimulus is an adaptation that has also been shown to contribute to enhanced muscle glycogen storage following endurance training (Greiwe et al. 1999). Another classic adaptation to endurance training is an increase in skeletal muscle mitochondrial content, accompanied by a shift in aerobic energy metabolism to be more reliant on oxidizing fats as opposed to carbohydrates (Egan & Zierath, 2013). These alterations in muscle lipid metabolism and increased flux through fatty acid oxidation following exercise training may play a role in moderating insulin sensitivity, by reducing the accumulation of fatty acid metabolites and the associated activation of proinflammatory pathways (Horowitz, 2007). Following a 12-

wk aerobic exercise training intervention (60-min/day, 5 days/wk, ~ 50-70%  $\text{VO}_{2\text{max}}$ ) in adults with T2D, improvements in peripheral insulin sensitivity (as measured by the euglycemic hyperinsulinemic clamp) were accompanied by reductions in the accumulation of plasma ceramide content (Kasumov et al. 2015).

It is also possible that chronic endurance exercise training may improve insulin sensitivity and glycemic control by targeting tissues outside of skeletal muscle. One such mechanism could involve the restoration of pancreatic beta-cell function, which is otherwise compromised in the T2D state (Polonsky et al. 1988). A study by Malin et al. (2013) showed that beta-cell function was increased with concomitant weight loss following 12 weeks of relatively high doses [5 days/wk, 60-min/day, 85% heart rate maximum ( $\text{HR}_{\text{max}}$ )] of endurance training in adults with prediabetes (Malin et al. 2013). The utility of exercise training interventions that involve a lower time-commitment and target the underlying pathology of T2D by preserving pancreatic beta-cell function warrants further attention. It is likely that a coordinated upregulation of these metabolic pathways may account for improved skeletal muscle glucose uptake following endurance exercise training, with further mechanistic work in humans required to elucidate the precise mechanisms.

### **1.3 INTERVAL EXERCISE AS AN ALTERNATIVE TO TRADITIONAL ENDURANCE TRAINING**

Despite the undisputed health benefits of regular physical activity, the majority of people with T2D do not meet these guidelines (Morrato et al. 2007; Thomas et al. 2004), with “lack of time” cited as one of the most common barriers to regular exercise participation (Korkiakangas et al. 2009). Proposed as a time-efficient alternative, interval

exercise generally refers to intermittent periods of higher intensity effort, separated by periods of recovery, within a single training session (Gillen & Gibala, 2014). It can be broadly separated into two categories, based on the classification scheme proposed by Weston et al. (2014) as a way to standardize terminology. Sprint interval training (SIT) involves ‘supra-maximal’ or ‘all-out’ efforts, in which the target intensity is  $> 100\%$  of  $\text{VO}_{2\text{max}}$  (Weston, et al. 2014). A classic approach utilizes the Wingate test and requires participants to perform four to six 30-sec ‘all out’ cycling sprints against a supra-maximal workload (7.5% of body weight), interspersed with 4 minutes of recovery (Gibala et al. 2012). In contrast, high-intensity interval training (HIIT) represents a more practical model and refers to protocols in which the target intensity of the efforts is ‘near maximal’ (80-100% of  $\text{HR}_{\text{max}}$ ), coupled with longer work bouts and shorter rest intervals (Weston et al. 2014). It should be noted, however, that the intensity of the bouts is based on the individual fitness level of the exerciser (Francois & Little, 2015). Studies employing both types of training have demonstrated physiological adaptations similar to traditional endurance training despite a reduced time commitment (Burgomaster et al. 2008; Gibala et al. 2006; Gillen et al. 2016; Little et al. 2010). Beyond these two categories, recent work has also shown that oscillating the intensity within a smaller range, reflecting more “moderate intensity” interval training, can elicit superior adaptations to exercise performed at a continuous moderate intensity (Karstoft et al. 2013). While much of the foundational work establishing the efficacy of interval training has been conducted in younger, healthy populations, the application of interval training has also been shown to improve disease risk parameters in adults with coronary artery disease, congestive heart

failure, T2D and the metabolic syndrome (Batacan Jr et al. 2016; Currie et al. 2013; Guiraud et al. 2012; Tjønnå et al. 2008; Weston et al. 2014). As such, an interval training approach may provide a suitable alternative to introduce higher intensity exercise in a range of populations that may otherwise be more averse to intense exercise.

### **1.3.1 Effect of interval exercise on insulin sensitivity and glycemic control**

Foundational work in young (~20-30 y), healthy populations has demonstrated the efficacy of interval training for improving insulin sensitivity and glycemic control (Babraj et al. 2009). Performing six sessions of Wingate-based SIT over a 2-wk period resulted in improvements in whole body insulin sensitivity and glucose homeostasis in sedentary and overweight adults (Richards et al. 2010; Whyte et al. 2010). In an effort to utilize a more practical model of interval training, Hood et al. (2011) demonstrated an increased capacity for skeletal muscle glucose transport, as reflected by a two-fold increase in GLUT4 protein content, following 6 sessions of HIIT cycling (10 x 1 min at 80-95% HR<sub>max</sub>) (Hood et al. 2011). Although there are fewer studies in T2D, there is evidence that interval-based training can elicit both acute and chronic improvements in glycemic control and health-related outcomes in people with T2D (Alvarez et al. 2016; Gillen et al. 2012; Jelleyman et al. 2015; Madsen et al. 2015; Terada et al. 2016).

#### ***1.3.1.1 Acute effect of interval exercise***

From an acute perspective, a single session of cycling HIIT (10 x 1-min at 90% HR<sub>max</sub>, separated by 1-min recovery) in 7 adults with T2D (mean age ~62 y, BMI >30 kg/m<sup>2</sup>) reduced postprandial hyperglycemia in the 24-h period immediately following exercise compared to a non-exercise control group (Gillen et al. 2012). Extending this

approach to include a non-interval comparison group, ‘exercise snacks’ (6 x 1-min walking intervals at 90%  $HR_{max}$ , interspersed with 1-min recovery) performed before breakfast, lunch, and dinner were found to be more effective at improving postprandial blood glucose control in the day following exercise than a single session of MICT (30-min walking at 60%  $HR_{max}$ ) in 9 adults with insulin resistance (mean age ~48 y, BMI > 35 kg/m<sup>2</sup>) (Francois et al. 2014). In an effort to better elucidate if the timing of exercise may be important for trying to reduce post-meal glucose spikes and improve acute glycemic control, a study was conducted by Terada et al. (2016) to directly compare the effects of HIIT (15 x 1-min at 100%  $VO_{2peak}$ , separated by 3-min at 40%  $VO_{2peak}$ ) and energy-matched MICT (60-min at 55%  $VO_{2peak}$ ) on glycemic control when performed in the fasted or post-breakfast state by 10 adults with T2D (mean age ~60 y, BMI ~ 31 kg/m<sup>2</sup>). HIIT was shown to acutely improve some CGM-derived glycemic parameters to a greater extent than MICT, with reductions in postprandial glycemia most apparent when performing exercise under fasted conditions (Terada et al. 2016). However, discrepancies in the time window of analysis for the blood glucose response to the breakfast meal between fasted and post-meal exercise conditions in this study suggests a need for further research to definitively discern if exercise before or after a meal is more advantageous. Taken together, the use of CGM to assess glycemic control in the above-mentioned studies provides evidence that HIIT in T2D may preferentially and acutely target specific glycemic parameters such as postprandial hyperglycemia, a finding that holds clinical relevance in staving off the development of diabetic complications associated with glycemic excursions (Ceriello, 2005). As most of these studies did not monitor glycemic



control beyond 24-h post-exercise and used different methods to analyze the CGM data, the duration and scope of the acute exercise effects require further characterization (Cassidy et al. 2017).

### ***1.3.1.2 Adaptation to interval exercise training***

Two recent meta-analyses assessing more chronic exercise training interventions concluded that HIIT is effective at improving measures of insulin sensitivity and glucose regulation in adults with T2D (Jelleyman et al. 2015; Liubaoerjijin et al. 2016). One of the first studies to assess HIIT in a T2D population demonstrated that as little as six sessions of interval cycling (same protocol as Gillen et al. 2012), over a 14 day period, improved indices of glycemic control and markers of mitochondrial biogenesis in 8 individuals with T2D who were previously inactive (mean age ~63 y, BMI > 30kg/m<sup>2</sup>) (Little et al. 2011a). Subsequently, Karstoft et al. (2013) examined a free-living exercise intervention that had 12 participants with T2D (mean age ~60 y, BMI ~30kg/m<sup>2</sup>) alternate between 3-min walking repetitions at a lower and higher intensity (70% of VO<sub>2peak</sub>) for 60 min/day, on 5 days/week over a 16-wk training period (Karstoft et al. 2013). When compared with a group who completed energy-matched walking exercise at a continuous moderate intensity (55% of VO<sub>2peak</sub>) (n=12), the interval walking elicited superior improvements in body composition, physical fitness, and CGM-derived glycemic control parameters (Karstoft et al. 2013). The improvement in CGM-derived glycemic control variables in this study, in the absence of alterations in more traditional measures of glycemia (i.e., HbA1c and fasting glucose) (Karstoft et al. 2013), highlights the potential utility of CGM in capturing changes in glucose control that may otherwise go undetected.

With these findings generated from a relatively large dose of exercise per week (i.e., 300 minutes/week), another study showed that 14 people with T2D who completed a less time-intensive HIIT protocol involving 6 x 1-min walking repeats at 80-85% of maximal aerobic capacity, with 4-min of recovery, on 3 days/week for 12 weeks, had greater improvements in fitness and HbA1c compared to an energy-matched continuous training group (30-40 min at 60-65%  $\text{VO}_{2\text{peak}}$ ) (n=14) (Mitranun et al. 2014). The ability of 12 weeks of HIIT to improve markers of glycemic control and cardiovascular risk factors to a greater extent than MICT in those with T2D has also been recapitulated using a protocol involving 4 x 4-min repeats of walking/running at 85-95% of  $\text{HR}_{\text{max}}$ , separated by 3-min of recovery, on 3 days/week (Hollekim-Strand et al. 2014; Støa et al. 2017). Although a study conducted by Revdal et al. (2016) produced conflicting results, concluding that 12 weeks of SIT and HIIT in 18 adults with T2D was not effective at improving glycemic control despite increased aerobic capacity, it could be argued that additional, more dynamic measures of glycemic control (beyond relying on HbA1c and fasting glucose) are required to substantiate this conclusion (Revdal et al. 2016). In light of the fact that a limited number of studies have assessed the potency of HIIT exercise interventions lasting less than 12 weeks in adults with T2D (Little et al. 2011a; Madsen et al. 2015), questions still remain surrounding the efficacy of short-term, low-volume HIIT exercise interventions to improve markers of glycemic control.

### **1.3.2 Potential mechanisms of interval training-induced improvements in insulin sensitivity and glycemic control**

Specific metabolic adaptations that characterize the interval training stimulus may contribute to improvements in insulin sensitivity and glycemic control. An acute session of interval training has been shown to result in AMPK activation (Gibala et al. 2009; Little et al. 2011b), with greater activation apparent when compared to a bout of continuous exercise matched for work and intensity (Combes et al. 2015). Coupled with evidence of a corresponding increase in nuclear peroxisome-proliferator activated receptor- $\gamma$  coactivator (PGC)-1 $\alpha$  protein content following SIT (Little et al. 2011b), these adaptations are indicative of an upregulation of the molecular signaling cascade regulating mitochondrial biogenesis (Gibala & Hawley, 2017). A summation of this transient signal with each successive exercise bout may be responsible for the increases in skeletal muscle mitochondrial content observed following interval training interventions (Gibala et al. 2006; Hood et al. 2011; Jacobs et al. 2013; Little et al. 2011a). This adaptation may mediate some of the mitochondrial dysfunction that has been associated with the pathogenesis of T2D (Petersen et al. 2004; Petersen et al. 2003) by providing an increased capacity for skeletal muscle lipid oxidation, thus improving insulin sensitivity by minimizing the accumulation of harmful lipid intermediates (Horowitz, 2007). Additionally, the association of AMPK with activating the skeletal muscle glucose transport system may contribute to the increases in membrane-bound GLUT4 (Karstoft et al. 2014) and GLUT4 protein content observed across interval training interventions in both young, healthy and T2D populations (Burgomaster et al. 2007; Gillen et al. 2014; Hood et al. 2011; Little et al. 2011a).

The ability of interval training to elicit improvements in glycemic control may also be related to the notion that high intensity exercise requires a greater degree of muscle fiber recruitment than MICT (Edgett et al. 2013; Vollestad & Blom, 1985), which may result in beneficial metabolic adaptations (i.e., increased GLUT4 and mitochondrial content) occurring in a larger proportion of muscle fibers (Roberts et al. 2013). The involvement of a larger proportion of muscle fibers with more intense exercise may also contribute to the rapid depletion in muscle glycogen that has been observed following a single session of brief, intense interval exercise (Gibala et al. 2009; MacDougall et al. 1977). A decrease in muscle glycogen stores and increased requirement for subsequent glycogen resynthesis has been hypothesized to result in a more potent and prolonged stimulation of post-exercise muscle glucose uptake than MICT, thus mediating some of the interval training induced improvements in peripheral insulin sensitivity (Little et al. 2014; Metcalfe et al. 2012). Additional adaptations have been observed following interval training and may be involved in improving skeletal muscle insulin sensitivity by targeting some of the underlying pathologies associated with T2D. These include improved beta cell function following 8 weeks of HIIT cycling (Madsen et al. 2015) and favourable body composition changes, such as decreases in visceral and hepatic fat mass following longer interval training interventions (Boutcher, 2011; Cassidy et al. 2016; Karstoft et al. 2013). Although a coordinated interplay between the above-mentioned mechanisms is likely to result in improved glycemia with interval training exercise, it is evident that the specific adaptations responsible still require further elucidation.

### **1.3.3 Feasibility and safety of interval training in T2D**

Despite the apparent efficacy of interval training to improve glycemic control, proposing high intensity exercise in a clinical population may be perceived as risk-inducing and associated with increased concern about tolerability and safety. With respect to safety, while there are no specific data on people with T2D, a major retrospective analysis of ~ 5000 patients with cardiovascular disease over 7 years of supervised cardiac rehabilitation exercise reported a low risk of acute cardiovascular events with HIIT (Rognmo et al. 2012). Other recent studies have confirmed this finding, showing that HIIT is safe and effective in a range of clinical populations, including those with coronary artery disease, peripheral artery disease, heart failure, and lifestyle-induced cardiometabolic disease (Batacan Jr et al. 2016; Currie et al. 2013; Gayda et al. 2016; Guiraud et al. 2012; Kessler et al. 2012; Weston et al. 2014). In alignment with these findings, a recent review concluded that HIIT should be considered a safe therapeutic option for the majority of individuals at elevated cardiometabolic risk (Cassidy et al. 2017).

From a tolerability perspective, studies conducted directly in adults at an increased risk of or with T2D have demonstrated the feasibility and high adherence to HIIT programs (Cassidy et al. 2016; Jung et al. 2015; Karstoft et al. 2013; Terada et al. 2013). For example, when looking at self-reported adherence rates to two different exercise programs outside of a supervised lab setting in adults with prediabetes, 89% of participants adhered to the prescribed HIIT program in comparison to a 71% adherence rate in the MICT condition (Jung et al. 2015). When looking at the psychological

response to a single session of differing exercise protocols in inactive adults, participants reported greater enjoyment and displayed a greater preference towards HIIT compared to MICT (Jung et al. 2014), and towards shorter (i.e., 30 and 60 s intervals) versus longer (i.e., 120 s) interval trials (Martinez et al. 2015). This demonstrates that the incorporation of vigorous exercise in an intermittent pattern may elicit more favourable outcomes than continuous vigorous exercise. Furthermore, a recent review by Stork et al. (2017) concluded that participants' experienced equal or greater enjoyment following interval compared to continuous exercise. Although further studies are warranted in those with T2D, these findings suggest that HIIT may be a safe and appealing alternative to more traditional exercise when trying to combat pervasive inactivity levels.

#### **1.4 STAIR CLIMBING AS A PRACTICAL APPLICATION OF INTERVAL TRAINING**

Interval training has primarily been studied in laboratory-based settings that may not be practical or scalable for the general population (Jelleyman et al. 2015). This is important when it has been reported that other barriers to physical activity for adults with T2D include lack of access to and affordability of exercise facilities (Thomas et al. 2004). In an effort to circumvent these environmental and financial barriers, the use of stair climbing may be proposed as a suitable exercise alternative. From an accessibility perspective, stairs exist frequently within everyday settings (i.e., homes, office buildings) and do not require specialized equipment. Stair climbing is also a necessary activity of daily living (ADL) to maintain functional independence (Unver et al. 2014), with mobility restrictions that impair stair climbing capacity resulting in approximately one

third of elderly individuals living sedentary lives (Mustafaoglu et al. 2015). Additionally, results from the Harvard Alumni Health study suggest that stair climbing is predictive of longevity, with evidence of declining mortality rates with more stairs climbed per week (Lee & Paffenbarger, 2000).

In light of these characteristics, early research into the utility of stair climbing as an exercise modality focused on the cardiorespiratory responses that occur acutely with stair climbing. A small study by Oldenburg et al. (1979) demonstrated similar HR and oxygen consumption ( $\text{VO}_2$ ) responses between a single session of stair climbing and cycling in healthy subjects, when matched for duration and power output (Oldenburg et al. 1979). In a larger scale study, 103 healthy participants were instructed to climb up 22 flights of stairs at a brisk and constant pace (spanning ~ 2 min) (Teh & Aziz, 2002). Based on continuous data collected during the climb (through a portable spirometry system), stair climbing elicited an average  $\text{VO}_2$  of 83% and an average HR of 89% of the corresponding maximal values (Teh & Aziz, 2002). When aligning these responses to the minimum intensity values previously recommended by the American College of Sports Medicine (ACSM) for attaining cardiorespiratory benefit (i.e., 40-50% of  $\text{VO}_{2R}$  and 55-65%  $\text{HR}_{\text{max}}$ ) (Pollock et al. 1998), it is evident that stair climbing can elicit a sufficient cardiorespiratory response. These findings suggest that stair climbing may provide an optimal modality for adapting lab-based exercise training protocols that would otherwise rely on specialized exercise equipment, without compromising physiological adaptation.

#### **1.4.1 Stair climbing training and cardiorespiratory fitness**

One approach to studying the physiological effects of long-term, stair climbing training interventions has been to embed programs into workplace settings as a pragmatic method of integrating physical activity into daily life (Fardy & Ilmarinen, 1975; Ilmarinen et al. 1978; Meyer et al. 2010). Following 10-12 weeks of climbing ~ 25 flights of stairs throughout the course of each workday, increases in predicted  $\text{VO}_{2\text{max}}$  of ~ 10-15% were elicited in untrained male office workers, compared to their elevator-taking counterparts (Fardy & Ilmarinen, 1975; Ilmarinen et al. 1978). Another approach has been to rely on the use of step machines to assess the impact of higher volume stair climbing protocols, more in alignment with the physical activity guidelines. After completing a 12-wk stair climbing intervention, involving 35-min (80-85%  $\text{HR}_{\text{max}}$ ) on a stair climbing machine on 4 days/week, a group of sedentary females increased their aerobic fitness and quadriceps muscle strength compared to non-active controls (Loy et al. 1994). Although this finding demonstrates the efficacy of a relatively high dose of stair climbing, more recent work has shifted to focus on the impact of accumulating multiple short bouts of vigorous, free-living stair climbing on variables related to cardiometabolic health (Boreham et al. 2005; Boreham et al. 2000). Following 8 weeks of a progressive stair climbing program, involving ~ 11 minutes of stair climbing spread across five bouts per day on five days of the week, sedentary women ( $n=8$ ) increased their  $\text{VO}_{2\text{max}}$  by ~ 17% and improved their lipid profile relative to controls (Boreham et al. 2005). Despite showing that a relatively inconspicuous stair climbing regime can improve cardiovascular disease risk factors, these studies were reliant on self-report training logs and were based



on small doses of exercise distributed throughout the day, as opposed to a single training session (Boreham et al. 2005; Boreham et al. 2000).

A recent study conducted by Allison et al. (2017) assessed the impact of a supervised 10-min SIT stair climbing protocol (3 x 20 sec ‘all out’ sprints up multiple flights of stairs, interspersed with 2-min walking recovery) in sedentary but otherwise healthy women (n=12). When performed on three days a week for 6 weeks, totaling a 30-min time commitment per week, stair climbing exercise elicited improvements in cardiorespiratory fitness of ~ 1 metabolic equivalent (MET) that were similar to changes induced by a previous cycling-based SIT protocol (Allison et al. 2017; Gillen et al. 2014). Even when adapted to be applicable to a home setting, completion of a more practical interval stair climbing protocol (3 x 1-min of ‘vigorous’ stair climbing up and down a single flight of stairs, interspersed with 1-min walking recovery) demonstrated that an ‘all out’ pace was not required to achieve improvements in cardiorespiratory fitness after 6 weeks (Allison et al. 2017). Epidemiological studies have shown that a 1 MET higher level of fitness is comparable to a 13% reduction in risk of all cause mortality, 15% reduction in risk of cardiovascular disease, and 1 mmol/L lower fasting blood glucose level (Kodama et al. 2009). With evidence to suggest improvements in cardiorespiratory fitness following a low-volume, interval stair climbing protocol in a healthy population, the application of a similar stair climbing strategy to directly assess changes in glycemic control parameters in at-risk or T2D populations is warranted.

#### **1.4.2 Stair climbing for those with impaired glycemic control and T2D**

The translation of time-efficient, laboratory-based interval regimes to “real world” settings remains largely unexplored, including in people with T2D. In light of the difficulties associated with implementing fully supervised training programs as a primary-care exercise strategy for adults with T2D, the utility of stair climbing as a therapeutic modality is worth investigating. Only a few preliminary studies have used stair climbing to examine changes in glycemic control in adults with impaired glucose tolerance (IGT) and T2D (Honda et al. 2016; Honda et al. 2017; Takaishi et al. 2012). Takaishi et al. (2012) concluded that a 6-min bout of MICT stair climbing up and down a single flight (21 steps) of stairs, when performed at 90 minutes after a meal, reduced the immediate postprandial blood glucose levels compared to a control and walking group in 8 men with IGT (mean age ~48 y, BMI ~ 23kg/m<sup>2</sup>) (Takaishi et al. 2012). Applying a similar protocol in 16 adults with T2D (mean age ~65 y, BMI ~ 24kg/m<sup>2</sup>), two ~ 3-min bouts of MICT stair climbing, performed at 60 and 120 minutes after a meal, were shown to reduce the remaining post-meal glucose response compared to a non-exercise control group (Honda et al. 2016). When using the same repeated 3-min stair climbing protocol, but performed following each meal in a home-based program completed over a 2-wk period, 7 adults with T2D (mean age ~68, BMI ~22kg/m<sup>2</sup>) improved their serum 1,5-anhydroglucitol (1,5-AG) levels despite no change in fasting blood glucose levels (Honda et al. 2017). As an alternative measure of glycemic control, 1,5-AG levels have been shown to negatively correlate with 2-h postprandial glucose values over the previous 2 weeks (Stettler et al. 2008). Therefore, the higher 1,5-AG levels measured following this

study may be indicative of improvements in postprandial hyperglycemia (Honda et al. 2017; Kohnert et al. 2015).

Despite highlighting the potential utility of low-volume stair climbing in targeting glycemia, Takaishi et al. (2012) and Honda et al. (2016) only monitored the very acute glycemic changes following a single MICT stair climbing session and relied on finger stick blood sampling to examine the post-meal glucose response. Used largely as a self-monitoring tool, capillary blood sampling only provides a snapshot of a specific point in time (Kohnert et al. 2015). The use of CGM may allow for a more detailed characterization of the glycemic response to both acute and more chronic stair climbing interventions. Furthermore, based on previous evidence to suggest that interval training can elicit improvements in glycemic control in adults with T2D when compared to MICT (Liubaoerjijin et al. 2016), an approach that oscillates the intensity and intersperses brief bursts of stair climbing with lower intensity periods may provide greater benefit.

## **1.5 PURPOSE AND HYPOTHESIS**

This thesis examined the effect of brief, intermittent stair climbing on indices of glycemic control using CGM in people with T2D. While previous studies have demonstrated the efficacy of interval training to improve glycemic control in those with T2D, most have been conducted in laboratory-based settings and the minimally effective “dose” remains to be elucidated. The present study aimed to assess whether (i) a single session of stair climbing exercise improved 24-h blood glucose in the period immediately following exercise; and (ii) if training three days per week for 6 weeks improved 24-h blood glucose when measured > 72-h following the final training bout. We hypothesized that (i) an

acute bout of brief intermittent stair climbing exercise would improve 24-h blood glucose; and (ii) 24-h blood glucose would be improved following 6 weeks of stair climbing training, as assessed by CGM under controlled dietary conditions in people with T2D. The primary indices of glycemic control examined were mean 24-h glucose, time spent in hyperglycemia ( $> 10$  mmol/L), and postprandial hyperglycemia.

## 1.6 REFERENCES

- Abdul-Ghani, M. A., Jenkinson, C. P., Richardson, D. K., Tripathy, D., & DeFronzo, R. A. (2006). Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the veterans administration genetic epidemiology study. *Diabetes*, 55(5), 1430–1435. <http://doi.org/10.2337/db05-1200>
- Allison, M. K., Baglole, J. H., Martin, B. J., MacInnis, M. J., Gurd, B. J., & Gibala, M. J. (2017). Brief intense stair climbing improves cardiorespiratory fitness. *Med. Sci. Sports. Exerc.*, 49(2), 298–307. <http://doi.org/10.1249/MSS.0000000000001188>
- Alvarez, C., Ramirez-Campillo, R., Martinez-Salazar, C., Mancilla, R., Flores-Opazo, M., Cano-Montoya, J., & Ciolac, E. G. (2016). Low-volume high-intensity interval training as therapy for type 2 diabetes. *Int. J. Sports. Med.*, 37, 723–729. <http://doi.org/10.1055/s-0042-104935>
- Amati, F., Dube, J. J., Alvarez-Carnero, E., Edreira, M. M., Chomentowski, P., Coen, P. M., ... Goodpaster, B. H. (2011). Skeletal muscle triglycerides, diacylglycerols, and ceramides in insulin resistance: Another paradox in endurance-trained athletes? *Diabetes*, 60(10), 2588–2597. <http://doi.org/10.2337/db10-1221>
- American Diabetes Association (ADA). (2014). *Diagnosis and classification of diabetes mellitus*. *Diabetes Care* (Vol. 37).
- Babraj, J. A., Volvaard, N. B., Keast, C., Guppy, F. M., Cottrell, G., & Timmons, J. A. (2009). Extremely short duration high intensity interval training substantially improves insulin action in young healthy males. *BMC. Endocr. Disord.*, 9(3), 1–8. <http://doi.org/10.1186/1472-6823-9-3>
- Batacan Jr, R. B., Duncan, M. J., Dalbo, V. J., Tucker, P. S., & Fenning, A. S. (2016). Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br. J. Sports. Med.*, 0, 1–12. <http://doi.org/10.1136/bjsports-2015-095841>
- Benziane, B., Burton, T. J., Scanlan, B., Galuska, D., Canny, B. J., Chibalin, A. V., ... Stepto, N. K. (2008). Divergent cell signaling after short-term intensified endurance training in human skeletal muscle. *Am. J. Physiol. Endocrinol. Metab*, 295, E1427–E1438. <http://doi.org/10.1152/ajpendo.90428.2008>.
- Bird, S. R., & Hawley, J. A. (2017). Update on the effects of physical activity on insulin sensitivity in humans. *BMJ. Open. Sport. Exerc. Med.*, 2, e000143. <http://doi.org/10.1136/bmjsem-2016-000143>
- Boreham, C. A. G., Kennedy, R. A., Murphy, M. H., Tully, M., Wallace, W. F. M., & Young, I. (2005). Training effects of short bouts of stair climbing on cardiorespiratory fitness, blood lipids, and homocysteine in sedentary young women. *Br. J. Sports. Med.*, 39(9), 590–593. <http://doi.org/10.1136/bjsm.2002.001131>
- Boreham, C. A. G., Wallace, W. F. M., & Nevill, A. (2000). Training effects of accumulated daily stair-climbing exercise in previously sedentary young women. *Prev. Med.*, 30(4), 277–281. <http://doi.org/10.1006/pmed.2000.0634>
- Boulé, N. G., Haddad, E., Kenny, G. P., Wells, G. A., & Sigal, R. J. (2001). Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA*, 286(10), 1218–1227.

- <http://doi.org/10.1001/jama.286.10.1218>
- Boutcher, S. H. (2011). Review article: high-intensity intermittent exercise and fat loss. *J. Obes.*, 2011, 868305. <http://doi.org/10.1155/2011/868305>
- Burgomaster, K. A., Cermak, N. M., Phillips, S. M., Benton, C. R., Bonen, A., & Gibala, M. J. (2007). Divergent response of metabolite transport proteins in human skeletal muscle after sprint interval training and detraining. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 292, R1970–R1976. <http://doi.org/10.1152/ajpregu.00503.2006>.
- Burgomaster, K. A., Howarth, K. R., Phillips, S. M., Rakobowchuk, M., MacDonald, M. J., McGee, S. L., & Gibala, M. J. (2008). Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *J. Physiol.*, 586.1, 151–160. <http://doi.org/10.1113/jphysiol.2007.142109>
- Cassidy, S., Thoma, C., Hallsworth, K., Parikh, J., Hollingsworth, K. G., Taylor, R., ... Trenell, M. I. (2016). High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia*, 59(1), 56–66. <http://doi.org/10.1007/s00125-015-3741-2>
- Cassidy, S., Thoma, C., Houghton, D., & Trenell, M. I. (2017). High-intensity interval training: a review of its impact on glucose control and cardiometabolic health. *Diabetologia*, 60(1), 7–23. <http://doi.org/10.1007/s00125-016-4106-1>
- Castle, J. R., & Jacobs, P. G. (2016). Nonadjunctive use of continuous glucose monitoring for diabetes treatment decisions. *J. Diabetes. Sci. Technol.*, 10(5), 1169–1173. <http://doi.org/10.1177/1932296816631569>
- Cavalot, F., Pagliarino, A., Valle, M., Di Martino, L., Bonomo, K., Massucco, P., ... Trovati, M. (2011). Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the san luigi gonzaga diabetes study. *Diabetes Care*, 34, 2237–2243. <http://doi.org/10.2337/dc10-2414>
- Ceriello, A. (2005). Postprandial hyperglycemia and diabetes complications. Is it time to treat? *Diabetes*, 54(1), 1–7. <http://doi.org/10.2337/diabetes.52.1.1>
- Ceriello, A., Esposito, K., Piconi, L., Ihnat, M. A., Thorpe, J. E., Testa, R., ... Giugliano, D. (2008). Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*, 57, 1349–1354. <http://doi.org/10.2337/db08-0063.FMD>
- Colberg, S. R., Sigal, R. J., Yardley, J. E., Riddell, M. C., Dunstan, D. W., Dempsey, P. C., ... Tate, D. F. (2016). Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. *Diabetes Care*, 39(11), 2065–2079. <http://doi.org/10.2337/dc16-1728>
- Combes, A., Dekerle, J., Webborn, N., Watt, P., Bougault, V., & Daussin, F. N. (2015). Exercise-induced metabolic fluctuations influence AMPK, p38-MAPK and CaMKII phosphorylation in human skeletal muscle. *Physiol. Rep.*, 3(9), e12462. <http://doi.org/10.14814/phy2.12462>
- Currie, K. D., Dubberley, J. B., McKelvie, R. S., & MacDonald, M. J. (2013). Low-volume, high-intensity interval training in patients with CAD. *Med. Sci. Sports. Exerc.*, 45(8), 1436–1442. <http://doi.org/10.1249/MSS.0b013e31828bbbd4>

- DeFronzo, R. A. (2004). Pathogenesis of type 2 diabetes mellitus. *Med. Clin. N. Am.*, 88, 787–835. <http://doi.org/10.1016/j.mcna.2004.04.013>
- DeFronzo, R. A., Jacot, E., Jequier, E., Maeder, E., Wahren, J., & Felber, J. . (1981). The effect of insulin on the disposal of intravenous glucose. *Diabetes*, 30, 1000–1007. <http://doi.org/10.1113/jphysiol.2012.235127>
- DeFronzo, R. A., Tobin, J. D., & Andres, R. (1979). Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am. J. Physiol.*, 237(3), E214–E223. <http://doi.org/10.1089/dia.2011.0278>
- DeFronzo, R. A., & Tripathy, D. (2009). Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care*, 32(Supplement 2), S157–S163. <http://doi.org/10.2337/dc09-S302>
- Dela, F., Ploug, T., Handberg, A., Petersen, L. N., Larsen, J. J., Mikines, K. J., & Galbo, H. (1994). Physical training increases muscle GLUT4 protein and mRNA in patients with NIDDM. *Diabetes*, 43, 862–865. <http://doi.org/10.2337/diabetes.43.7.862>
- Edgett, B. A., Foster, W. S., Hankinson, P. B., Simpson, C. A., Little, J. P., Graham, R. B., & Gurd, B. J. (2013). Dissociation of increases in PGC-1alpha and its regulators from exercise intensity and muscle activation following acute exercise. *PLoS ONE*, 8(8), e71623. <http://doi.org/10.1371/journal.pone.0071623>
- Egan, B., & Zierath, J. R. (2013). Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell. Metab.*, 17, 162–184. <http://doi.org/10.1016/j.cmet.2012.12.012>
- Fardy, P. S., & Ilmarinen, J. (1975). Evaluating the effects and feasibility of an at work stairclimbing intervention program for men. *Med. Sci. Sports. Exerc.*, 7(2), 91–93.
- Francois, M. E., Baldi, J. C., Manning, P. J., Lucas, S. J. E., Hawley, J. A., Williams, M. J. A., & Cotter, J. D. (2014). “Exercise snacks” before meals: a novel strategy to improve glycaemic control in individuals with insulin resistance. *Diabetologia*, 57(7), 1437–1445. <http://doi.org/10.1007/s00125-014-3244-6>
- Francois, M. E., & Little, J. P. (2015). Effectiveness and safety of high-intensity interval training in patients with type 2 diabetes. *Diabetes. Spectr.*, 28(1), 39–44. <http://doi.org/10.2337/diaspect.28.1.39>
- Gayda, M., Ribeiro, P. A. B., Juneau, M., & Nigam, A. (2016). Comparison of different forms of exercise training in patients with cardiac disease: where does high-intensity interval training fit? *Can. J. Cardiol.*, 32(4), 485–494. <http://doi.org/10.1016/j.cjca.2016.01.017>
- Gibala, M. J., & Hawley, J. A. (2017). Sprinting toward fitness. *Cell. Metab.*, 25(5), 988–990. <http://doi.org/10.1016/j.cmet.2017.04.030>
- Gibala, M. J., Little, J. P., MacDonald, M. J., & Hawley, J. A. (2012). Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J. Physiol.*, 590.5, 1077–1084. <http://doi.org/10.1113/jphysiol.2011.224725>
- Gibala, M. J., Little, J. P., van Essen, M., Wilkin, G. P., Burgomaster, K. A., Safdar, A., ... Tarnopolsky, M. A. (2006). Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *J. Physiol.*, 575.3, 901–911. <http://doi.org/10.1113/jphysiol.2006.112094>

- Gibala, M. J., McGee, S. L., Garnham, A. P., Howlett, K. F., Snow, R. J., & Hargreaves, M. (2009). Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1 $\alpha$  in human skeletal muscle. *J. Appl. Physiol.*, *106*, 929–934. <http://doi.org/10.1152/jappphysiol.90880.2008>
- Gillen, J. B., & Gibala, M. J. (2014). Is high-intensity interval training a time-efficient exercise strategy to improve health and fitness? *Appl. Physiol. Nutr. Metab.*, *39*, 409–412. <http://doi.org/10.1139/apnm-2013-0187>
- Gillen, J. B., Little, J. P., Punthakee, Z., Tarnopolsky, M. A., Riddell, M. C., & Gibala, M. J. (2012). Acute high-intensity interval exercise reduces the postprandial glucose response and prevalence of hyperglycaemia in patients with type 2 diabetes. *Diabetes. Obes. Metab.*, *14*(6), 575–577. <http://doi.org/10.1111/j.1463-1326.2012.01564.x>
- Gillen, J. B., Martin, B. J., MacInnis, M. J., Skelly, L. E., Tarnopolsky, M. A., & Gibala, M. J. (2016). Twelve weeks of sprint interval training improves indices of cardiometabolic health similar to traditional endurance training despite a five-fold lower exercise volume and time commitment. *PLoS ONE*, *11*(4), 1–14. <http://doi.org/10.1371/journal.pone.0154075>
- Gillen, J. B., Percival, M. E., Skelly, L. E., Martin, B. J., Tan, R. B., Tarnopolsky, M. A., & Gibala, M. J. (2014). Three minutes of all-out intermittent exercise per week increases skeletal muscle oxidative capacity and improves cardiometabolic health. *PLoS ONE*, *9*(11), e111489. <http://doi.org/10.1371/journal.pone.0111489>
- Goldenberg, R., & Punthakee, Z. (2013). Clinical practice guidelines: definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. *Can. J. Diabetes*, *37*, S8–S11. <http://doi.org/10.1016/j.jcjd.2013.01.011>
- Greiwe, J. S., Hickner, R. C., Hansen, P. A., Racette, S. B., Chen, M. M., & Holloszy, J. O. (1999). Effects of endurance exercise training on muscle glycogen accumulation in humans. *J. Appl. Physiol.*, *87*(1), 222–226.
- Guiraud, T., Nigam, A., Gremeaux, V., Meyer, P., Juneau, M., & Bosquet, L. (2012). High-intensity interval training in cardiac rehabilitation. *Sports. Med.*, *42*(7), 587–605. <http://doi.org/10.2165/11631910-000000000-00000>
- Hawley, J. A., & Gibala, M. J. (2009). Exercise intensity and insulin sensitivity: how low can you go? *Diabetologia*, *52*, 1709–1713. <http://doi.org/10.1007/s00125-009-1425-5>
- Henriksen, E. J. (2002). Invited review: effects of acute exercise and exercise training on insulin resistance. *J. Appl. Physiol.*, *93*, 788–796. <http://doi.org/10.1152/jappphysiol.01219.2001>
- Hollekim-Strand, S. M., Bjørgeas, M. R., Albrektsen, G., Tjønnå, A. E., Wisløff, U., & Ingul, C. B. (2014). High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction: a randomized controlled trial. *JACC*, *64*(16), 1758–1760. <http://doi.org/10.1016/j.jacc.2014.07.971>
- Holloszy, J. O. (2005). Exercise-induced increase in muscle insulin sensitivity. *J. Appl. Physiol.*, *99*(1), 338–343. <http://doi.org/10.1152/jappphysiol.00123.2005>
- Honda, H., Igaki, M., Hatanaka, Y., Komatsu, M., Tanaka, S.-I., Miki, T., ... Hayashi, T.



- (2017). Repeated 3-minute stair climbing-descending exercise after a meal over 2 weeks increases serum 1,5-anhydroglucitol levels in people with type 2 diabetes. *J. Phys. Ther. Sci.*, 29(1), 75–78. <http://doi.org/10.1589/jpts.29.75>
- Honda, H., Igaki, M., Hatanaka, Y., Komatsu, M., Tanaka, S., Miki, T., ... Hayashi, T. (2016). Stair climbing/descending exercise for a short time decreases blood glucose levels after a meal in participants with type 2 diabetes. *BMJ. Open. Diabetes. Res. Care*, 4(1), e000232. <http://doi.org/10.1136/bmjdr-2016-000232>
- Hood, M. S., Little, J. P., Tarnopolsky, M. A., Myslik, F., & Gibala, M. J. (2011). Low-volume interval training improves muscle oxidative capacity in sedentary adults. *Med. Sci. Sports. Exerc.*, 43(10), 1849–1856. <http://doi.org/10.1249/MSS.0b013e3182199834>
- Horowitz, J. F. (2007). Exercise-induced alterations in muscle lipid metabolism improve insulin sensitivity. *Exerc. Sport Sci. Rev.*, 35(4), 192–196. <http://doi.org/10.1097/jes.0b013e318156e084>
- Ilmarinen, J., Rutenfranz, J., Knauth, P., Ahrens, M., Kylian, H., Siuda, A., & Korallus, U. (1978). The effect of an on the job training program - stairclimbing - on the physical working capacity of employees. *Eur. J. Appl. Physiol.*, 38, 25–40.
- International Diabetes Federation (IDF). (2015). IDF Diabetes Atlas, 7th edn. *International Diabetes Federation, Brussels*. Retrieved from <http://www.diabetesatlas.org>
- Jacobs, R. A., Flück, D., Bonne, T. C., Bürgi, S., Christensen, P. M., Toigo, M., & Lundby, C. (2013). Improvements in exercise performance with high-intensity interval training coincide with an increase in skeletal muscle mitochondrial content and function. *J. Appl. Physiol.*, 115, 785–793. <http://doi.org/10.1152/japplphysiol.00445.2013>
- Janssen, I., Heymsfield, S. B., Wang, Z., & Ross, R. (2000). Skeletal muscle mass and distribution in 468 men and women aged 18 – 88 yr. *J. Appl Physiol*, 89, 81–88.
- Jelleyman, C., Yates, T., O'Donovan, G., Gray, L. J., King, J. A., Khunti, K., & Davies, M. J. (2015). The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. *Obes. Rev*, 16(11), 942–961. <http://doi.org/10.1111/obr.12317>
- Jensen, J., & O'Rahilly, S. (2017). AMPK is required for exercise to enhance insulin sensitivity in skeletal muscles. *Mol. Metab.*, 6, 315–316. <http://doi.org/10.1016/j.molmet.2017.01.012>
- Jung, M. E., Bourne, J. E., Beauchamp, M. R., Robinson, E., & Little, J. P. (2015). High-intensity interval training as an efficacious alternative to moderate-intensity continuous training for adults with prediabetes. *J. Diabetes. Res.*, 2015, 191595. <http://doi.org/10.1155/2015/191595>
- Jung, M. E., Bourne, J. E., & Little, J. P. (2014). Where does HIT fit? An examination of the affective response to high-intensity intervals in comparison to continuous moderate- and continuous vigorous-intensity exercise in the exercise intensity-affect continuum. *PLoS ONE*, 9(12), e114541. <http://doi.org/10.1371/journal.pone.0114541>
- Karstoft, K., & Pedersen, B. K. (2016). Exercise and type 2 diabetes: focus on

- metabolism and inflammation. *Immunol. Cell. Biol.*, 94, 146–150.  
<http://doi.org/10.1038/icb.2015.101>
- Karstoft, K., Winding, K., Knudsen, S. H., James, N. G., Scheel, M. M., Olesen, J., ... Solomon, T. P. J. (2014). Mechanisms behind the superior effects of interval vs continuous training on glycaemic control in individuals with type 2 diabetes: a randomised controlled trial. *Diabetologia*, 57(10), 2081–2093.  
<http://doi.org/10.1007/s00125-014-3334-5>
- Karstoft, K., Winding, K., Knudsen, S. H., Nielsen, J. S., Thomsen, C., Pedersen, B. K., & Solomon, T. P. (2013). The effects of free-living interval-walking training on glycemic control, body composition, and physical fitness in type 2 diabetic patients. *Diabetes Care*, 36, 228–236. <http://doi.org/10.2337/dc12-0658>.
- Kasumov, T., Solomon, T. P. J., Hwang, C., Huang, H., Haus, J. M., Zhang, R., & Kirwan, J. P. (2015). Improved insulin sensitivity after exercise training is linked to reduced plasma C14:0 ceramide in obesity and type 2 diabetes. *Obesity (Silver Spring)*, 23(7), 1414–1421. <http://doi.org/10.1007/978-1-4939-2914-6>
- Katz, A., Nambi, S. S., Mather, K., Baron, A. D., Follmann, D. A., Sullivan, G., & Quon, M. J. (2000). Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J. Clin. Endocrinol. Metab.*, 85(7), 2402–2410.
- Kearney, M., & Thyfault, J. P. (2016). Exercise and postprandial glycemic control in type 2 diabetes. *Curr. Diabetes. Rev.*, 12, 1–12.
- Kelley, D. E., He, J., Menshikova, E. V., & Ritov, V. B. (2002). Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes*, 51(10), 2944–2950.
- Kessler, H. S., Sisson, S. B., & Short, K. R. (2012). The potential for high-intensity interval training to reduce cardiometabolic disease risk. *Sports. Med.*, 42(6), 489–509.
- Kjøbsted, R., Munk-Hansen, N., Birk, J. B., Foretz, M., Viollet, B., Bjørnholm, M., ... Wojtaszewski, J. F. P. (2017). Enhanced muscle insulin sensitivity after contraction/exercise is mediated by AMPK. *Diabetes*, 66, 598–612.  
<http://doi.org/10.2337/db16-0530>
- Klonoff, D. C. (2005). Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care*, 28(5), 1231–1239. <http://doi.org/10.2337/diacare.28.5.1231>
- Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., & Nathan, D. M. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.*, 346(6), 393–403.
- Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., ... Sone, H. (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*, 301(19), 2024–2035.
- Kohl, H. W., Gordon, N. F., Villegas, J. A., & Blair, S. N. (1992). Cardiorespiratory fitness, glycemic status, and mortality risk in men. *Diabetes Care*, 15(2), 184–192.
- Kohnert, K. D., Heinke, P., Vogt, L., & Salzsieder, E. (2015). Utility of different glycemic control metrics for optimizing management of diabetes. *World. J.*

- Diabetes.*, 6(1), 17–29. <http://doi.org/10.4239/wjd.v6.i1.17>
- Korkiakangas, E. E., Alahuhta, M. A., & Laitinen, J. H. (2009). Barriers to regular exercise among adults at high risk or diagnosed with type 2 diabetes: a systematic review. *Health. Promot. Int.*, 24(4), 416–427. <http://doi.org/10.1093/heapro/dap031>
- Krook, A., Björnholm, M., Galuska, D., Jiang, X. J., Fahlman, R., Myers, M. G., ... Zierath, J. R. (2000). Characterization of signal transduction and glucose transport in skeletal muscle from type 2 diabetic patients. *Diabetes*, 49(2), 284–92. <http://doi.org/10.2337/diabetes.49.2.284>
- Lee, I. M., & Paffenbarger, R. S. (2000). Associations of light, moderate, and vigorous intensity physical activity with longevity: the Harvard Alumni Health Study. *Am. J. Epidemiol.*, 151(3), 293–299. <http://doi.org/10.1093/oxfordjournals.aje.a010205>
- Little, J. P., Gillen, J. B., Percival, M. E., Safdar, A., Tarnopolsky, M. A., Punthakee, Z., ... Gibala, M. J. (2011a). Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *J. Appl. Physiol.*, 111, 1554–1560. <http://doi.org/10.1152/jappphysiol.00921.2011>.
- Little, J. P., Jung, M. E., Wright, A. E., Wright, W., & Manders, R. J. F. (2014). Effects of high-intensity interval exercise versus continuous moderate-intensity exercise on postprandial glycemic control assessed by continuous glucose monitoring in obese adults. *Appl. Physiol. Nutr. Metab.*, 39(7), 835–841. <http://doi.org/10.1139/apnm-2013-0512>
- Little, J. P., Safdar, A., Bishop, D., Tarnopolsky, M. A., & Gibala, M. J. (2011b). An acute bout of high-intensity interval training increases the nuclear abundance of PGC-1 $\alpha$  and activates mitochondrial biogenesis in human skeletal muscle. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 300, R1303–R1310. <http://doi.org/10.1152/ajpregu.00538.2010>
- Little, J. P., Safdar, A., Wilkin, G. P., Tarnopolsky, M. A., & Gibala, M. J. (2010). A practical model of low-volume high-intensity interval training induces mitochondrial biogenesis in human skeletal muscle: potential mechanisms. *J. Physiol.*, 588.6, 1011–1022. <http://doi.org/10.1113/jphysiol.2009.181743>
- Liubaoerjijin, Y., Terada, T., Fletcher, K., & Boulé, N. G. (2016). Effect of aerobic exercise intensity on glycemic control in type 2 diabetes: a meta-analysis of head-to-head randomized trials. *Acta. Diabetol.*, 53(5), 769–781. <http://doi.org/10.1007/s00592-016-0870-0>
- Loy, S. F., Conley, L. M., Sacco, E. R., Vincent, W. J., Holland, G. J., Sletten, E. G., & Trueblood, P. R. (1994). Effects of stairclimbing on VO<sub>2</sub>max and quadriceps strength in middle-aged females. *Med. Sci. Sports. Exerc.*, 26(2), 241–247.
- MacDougall, J. D., Ward, G. R., Sale, D. G., & Sutton, J. R. (1977). Muscle glycogen repletion after high-intensity intermittent exercise. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.*, 42(2), 129–132.
- MacLeod, S. F., Terada, T., Chahal, B. S., & Boulé, N. G. (2013). Exercise lowers postprandial glucose but not fasting glucose in type 2 diabetes: a meta-analysis of studies using CGM. *Diabetes. Metab. Res. Rev.*, 29, 593–603. <http://doi.org/10.1002/dmrr>

- Madsen, S. M., Thorup, A. C., Overgaard, K., & Jeppesen, P. B. (2015). High intensity interval training improves glycaemic control and pancreatic B cell function of type 2 diabetes patients. *PLoS ONE*, 10(8), 1–24.  
<http://doi.org/10.1371/journal.pone.0133286>
- Malin, S. K., Solomon, T. P. J., Blaszcak, A., Finnegan, S., Filion, J., & Kirwan, J. P. (2013). Pancreatic beta-cell function increases in a linear dose-response manner following exercise training in adults with prediabetes. *Am. J. Physiol. Endocrinol. Metab.*, 305, E1248–E1254. <http://doi.org/10.1152/ajpendo.00260.2013>
- Martinez, N., Kilpatrick, M. W., Salomon, K., Jung, M. E., & Little, J. P. (2015). Affective and enjoyment responses to high-intensity interval training in overweight-to-obese and insufficiently active adults. *J. Sport. Exerc. Psychol.*, 37(2), 138–149.
- Matsuda, M., & DeFronzo, R. A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*, 22(9), 1462–1470. <http://doi.org/10.2337/diacare.22.9.1462>
- Metcalf, R. S., Babraj, J. A., Fawcner, S. G., & Volvaard, N. B. J. (2012). Towards the minimal amount of exercise for improving metabolic health: beneficial effects of reduced-exertion high-intensity interval training. *Eur. J. Appl. Physiol.*, 112(7), 2767–2775. <http://doi.org/10.1007/s00421-011-2254-z>
- Meyer, P., Kayser, B., Kossovsky, M. P., Sigaud, P., Carballo, D., Keller, P.-F., ... Mach, F. (2010). Stairs instead of elevators at workplace: cardioprotective effects of a pragmatic intervention. *Eur. J. Cardiovasc. Prev. Rehabil.*, 17(5), 569–575.  
<http://doi.org/10.1097/HJR.0b013e328338a4dd>
- Mitranun, W., Deerochanawong, C., Tanaka, H., & Suksom, D. (2014). Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. *Scand. J. Med. Sci. Sports.*, 24(2), e69–e76.  
<http://doi.org/10.1111/sms.12112>
- Monnier, L., Colette, C., & Owens, D. R. (2008). Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it? *J. Diabetes. Sci. Technol.*, 2(6), 1094–1100.  
<http://doi.org/10.1177/193229680800200618>
- Morrato, E. H., Hill, J. O., Wyatt, H. R., Ghushchyan, V., & Sullivan, P. W. (2007). Physical activity in U.S. adults with diabetes and at risk for developing diabetes, 2003. *Diabetes Care*, 30, 203–209. <http://doi.org/10.2337/dc06-1128>
- Muniyappa, R., Lee, S., Chen, H., & Quon, M. J. (2008). Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *Am. J. Physiol. Endocrinol. Metab.*, 294, E15–E26.  
<http://doi.org/10.1152/ajpendo.00645.2007>
- Muniyappa, R., Madan, R., & Quon, M. J. (2015). Assessing insulin sensitivity and resistance in humans. *NCBI Bookshelf*, 1–13.
- Musi, N., Fujii, N., Hirshman, M. F., Ekberg, I., Froberg, S., Ljungqvist, O., ... Goodyear, L. J. (2001). AMP-activated protein kinase (AMPK) is activated in muscle of subjects with type 2 diabetes during exercise. *Diabetes*, 50, 921–927.
- Mustafaoglu, R., Unver, B., & Karatosun, V. (2015). Evaluation of stair climbing in elderly people. *J. Back. Musculoskelet. Rehabil.*, 28(3), 509–516.

- <http://doi.org/10.3233/BMR-140549>
- Nalysnyk, L., Hernandez-Medina, M., & Krishnarajah, G. (2010). Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. *Diabetes. Obes. Metab.*, 12, 288–298.  
<http://doi.org/10.1111/j.1463-1326.2009.01160.x>
- Oldenburg, F. A., McCormack, D. W., Morse, J. L. C., & Jones, N. L. (1979). A comparison of exercise responses in stairclimbing and cycling. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.*, 46(3), 510–516.
- Patarrao, R. S., Lutt, W. W., & Macedo, M. P. (2014). Assessment of methods and indexes of insulin sensitivity. *Rev. Port. Endocrinol. Diabetes. Metab.*, 9(1), 65–73.  
<http://doi.org/10.1016/j.rpedm.2012.12.001>
- Pedersen, B. K., & Saltin, B. (2006). Evidence for prescribing exercise as therapy in chronic disease. *Scand. J. Med. Sci. Sports*, 16(Suppl. 1), 3–63.
- Petersen, K. F., Befroy, D., Dufour, S., Dziura, J., Ariyan, C., Rothman, D. L., ... Shulman, G. I. (2003). Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science*, 300(5622), 1140–1142.  
<http://doi.org/10.1126/science.1082889>
- Petersen, K. F., Dufour, S., Befroy, D., Garcia, R., & Shulman, G. I. (2004). Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N. Engl. J. Med.*, 350, 664–671.  
<http://doi.org/10.1056/NEJMoa031314>
- Pollock, M. L., Gaesser, G. A., Butcher, J. D., Despres, J. P., Dishman, R. K., Franklin, B. A., & Garber, C. E. (1998). ACSM position stand: the recommended quality and quantity of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med. Sci. Sports. Exerc.*, 30(6), 975–991.
- Polonsky, K. S., Given, B. D., Hirsch, L. J., Tillil, H., Shapiro, E. T., Beebe, C., ... Cauter, E. V. (1988). Abnormal patterns of insulin secretion in non-insulin dependent diabetes mellitus. *N. Engl. J. Med.*, 318(19), 1231–1239.
- Public Health Agency of Canada. (2011). *Diabetes in Canada: Facts and figures from a public health perspective*. Ottawa, ON. Retrieved from <http://www.phac-aspc.gc.ca/cd-mc/publications/diabetes-diabete/facts-figures-faits-chiffres-2011/index-eng.php>
- Revdal, A., Hollekim-Strand, S. M., & Ingul, C. B. (2016). Can time efficient exercise improve cardiometabolic risk factors in type 2 diabetes? A pilot study. *J. Sports. Sci. Med.*, 15(2), 308–313.
- Richards, J. C., Johnson, T. K., Kuzma, J. N., Lonac, M. C., Schweder, M. M., Voyles, W. F., & Bell, C. (2010). Short-term sprint interval training increases insulin sensitivity in healthy adults but does not affect the thermogenic response to  $\beta$ -adrenergic stimulation. *J. Physiol.*, 588.15, 2961–2972.  
<http://doi.org/10.1113/jphysiol.2010.189886>
- Richter, E. A., & Hargreaves, M. (2013). Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiol. Rev.*, 93, 993–1017. <http://doi.org/10.1152/physrev.00038.2012>
- Riddell, M., & Perkins, B. A. (2009). Exercise and glucose metabolism in persons with diabetes mellitus: perspectives on the role for continuous glucose monitoring. *J.*

- Diabetes. Sci. Technol*, 3(4), 914–923.
- Roberts, C. K., Little, J. P., & Thyfault, J. P. (2013). Modification of insulin sensitivity and glycemic control by activity and exercise. *Med. Sci. Sports. Exerc*, 45(10), 1868–1877. <http://doi.org/10.1249/MSS.0b013e318295cddb>
- Rognmo, O., Moholdt, T., Bakken, H., Hole, T., Mølsted, P., Myhr, N. E., ... Wisløff, U. (2012). Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. *Circulation*, 126, 1436–1440. <http://doi.org/10.1161/CIRCULATIONAHA.112.123117>
- Röhling, M., Herder, C., Stemper, T., & Müssig, K. (2016). Review article: influence of acute and chronic exercise on glucose uptake. *J. Diabetes. Res*, 2016, 2868652. <http://doi.org/10.1155/2016/2868652>
- Schenk, S., & Horowitz, J. F. (2007). Acute exercise increases triglyceride synthesis in skeletal muscle and prevents fatty acid – induced insulin resistance. *J. Clin. Invest.*, 117(6), 1690–1698. <http://doi.org/10.1172/JCI30566.1690>
- Schnell, O., Barnard, K., Bergenstal, R., Bosi, E., Garg, S., Guerci, B., ... Home, P. (2017). Role of continuous glucose monitoring in clinical trials: recommendations on reporting. *Diabetes. Technol. Ther*, 19(7), 1–9. <http://doi.org/10.1089/dia.2017.0054>
- Sigal, R. J., Armstrong, M. J., Colby, P., Kenny, G. P., Plotnikoff, R. C., Reichert, S. M., & Riddell, M. C. (2013). Clinical practice guidelines: physical activity and diabetes. *Can. J. Diabetes*, 37, S40–S44. <http://doi.org/10.1016/j.jcjd.2013.01.018>
- Snowling, N. J., & Hopkins, W. G. (2006). Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. *Diabetes Care*, 29(11), 2518–2527. <http://doi.org/10.2337/dc06-1317>
- Stettler, C., Stahl, M., Allemann, S., Diem, P., Schmidlin, K., Zwahlen, M., ... Christ, E. (2008). Association of 1,5-anhydroglucitol and 2-h postprandial blood glucose in type 2 diabetic patients. *Diabetes Care*, 31, 1534–1535. <http://doi.org/10.2337/dc08-0385>
- Støa, E. M., Meling, S., Nyhus, L.-K., Strømstad, G., Mangerud, K. M., Helgerud, J., ... Støren, Ø. (2017). High-intensity aerobic interval training improves aerobic fitness and HbA1c among persons diagnosed with type 2 diabetes. *Eur. J. Appl. Physiol.*, 117(3), 455–467. <http://doi.org/10.1007/s00421-017-3540-1>
- Stork, M. J., Banfield, L. E., Gibala, M. J., & Martin Ginis, K. A. (2017). A scoping review of the psychological responses to interval exercise: is interval exercise a viable alternative to traditional exercise? *Health. Psychol. Rev.*, 0(0), 1–47. <http://doi.org/10.1080/17437199.2017.1326011>
- Stratton, I. M., Adler, A. I., Neil, H. A. W., Matthews, D. R., Manley, S. E., Cull, C. A., ... Holman, R. R. (2000). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*, 321, 405–412. <http://doi.org/10.1136/bmj.321.7258.405>
- Stuart, C. A., South, M. A., Lee, M. L., McCurry, M. P., Howell, M. E. A., Ramsey, M. W., & Stone, M. H. (2013). Insulin responsiveness in metabolic syndrome after eight weeks of cycle training. *Med. Sci. Sports. Exerc*, 45(11), 2021–2029. <http://doi.org/10.1016/j.immuni.2010.12.017>. Two-stage

- Takaishi, T., Imaeda, K., Tanaka, T., Moritani, T., & Hayashi, T. (2012). A short bout of stair climbing–descending exercise attenuates postprandial hyperglycemia in middle-aged males with impaired glucose tolerance. *Appl. Physiol. Nutr. Metab*, 37(1), 193–196. <http://doi.org/10.1139/h11-140>
- Teh, K. C., & Aziz, A. R. (2002). Heart rate, oxygen uptake, and energy cost of ascending and descending the stairs. *Med. Sci. Sports. Exerc.*, 34(4), 695–699.
- Terada, T., Friesen, A., Chahal, B. S., Bell, G. J., McCargar, L. J., & Boulé, N. G. (2013). Feasibility and preliminary efficacy of high intensity interval training in type 2 diabetes. *Diabetes. Res. Clin. Pract*, 99(2), 120–129. <http://doi.org/10.1016/j.diabres.2012.10.019>
- Terada, T., Wilson, B. J., Myette-Côté, E., Kuzik, N., Bell, G. J., McCargar, L. J., & Boulé, N. G. (2016). Targeting specific interstitial glycemic parameters with high-intensity interval exercise and fasted-state exercise in type 2 diabetes. *Metab. Clin. Exp*, 65(5), 599–608. <http://doi.org/10.1016/j.metabol.2016.01.003>
- Thomas, N., Alder, E., & Leese, G. P. (2004). Barriers to physical activity in patients with diabetes. *Postgrad. Med. J*, 80, 287–291. <http://doi.org/10.1136/pgmj.2003.010553>
- Tjønnå, A. E., Lee, S. J., Rognmo, O., Stølen, T., Bye, A., Haram, P. M., ... Wisløff, U. (2008). Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation*, 118(4), 346–354. <http://doi.org/10.1161/CIRCULATIONAHA.108.772822.Aerobic>
- Tjønnå, A. E., Rognmo, Ø., Bye, A., Stølen, T. O., & Wisløff, U. (2011). Time course of endothelial adaptation after acute and chronic exercise in patients with metabolic syndrome. *J. Strength. Cond. Res*, 25(9), 2552–2558.
- Tuomilehto, J., Lindstrom, J., Eriksson, J. G., Valle, T. T., Hamalainen, H., & Ilanne-Parikka, P. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.*, 344(18), 1343–1350. <http://doi.org/10.1056/NEJM200105033441801>
- Umpierre, D., Ribeiro, P. A. B., Kramer, C. K., Leitao, C. B., Zucatti, A. T. N., Azevedo, M. J., ... Schaan, B. D. (2011). Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*, 305(17), 1790–1799. <http://doi.org/10.1001/jama.2011.576>
- Unver, B., Ertekin, Ö. A., & Karatosun, V. (2014). Pain, fear of falling and stair climbing ability in patients with knee osteoarthritis before and after knee replacement: 6 month follow-up study. *J. Back. Musculoskelet. Rehabil.*, 27, 77–84. <http://doi.org/10.3233/BMR-130422>
- van Dijk, J. W., Manders, R. J. F., Canfora, E. E., van Mechelen, W., Hartgens, F., Stehouwer, C. D. A., & van Loon, L. J. C. (2013). Exercise and 24-h glycemic control: equal effects for all type 2 diabetes patients? *Med. Sci. Sports. Exerc*, 45(4), 628–635. <http://doi.org/10.1249/MSS.0b013e31827ad8b4>
- van Dijk, J. W., Manders, R. J. F., Hartgens, F., Stehouwer, C. D., Praet, S. F. E., & van Loon, L. J. C. (2011). Postprandial hyperglycemia is highly prevalent throughout the day in type 2 diabetes patients. *Diabetes. Res. Clin. Pract*, 93(1), 31–37.

- <http://doi.org/10.1016/j.diabres.2011.03.021>
- van Dijk, J. W., Tummers, K., Stheouwer, C. D. A., Hartgens, F., & van Loon, L. J. C. (2012). Is daily exercise required to optimize glycemic control ? *Diabetes Care*, 35, 948–954. <http://doi.org/10.2337/dc11-2112>.
- van Dijk, J. W., & van Loon, L. J. C. (2015). Exercise strategies to optimize glycemic control in type 2 diabetes: a continuous glucose monitoring perspective. *Diabetes Spectr*, 28(1), 24–31. <http://doi.org/10.2337/diaspect.28.1.24>
- Vollestad, N. K., & Blom, P. C. S. (1985). Effect of varying exercise intensity on glycogen depletion in human muscle fibres. *Acta. Physiol. Scand.*, 125, 395–405.
- Wei, M., Gibbons, L. W., Kampert, J. B., Nichaman, M. Z., & Blair, S. N. (2000). Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with T2D. *Ann. Intern. Med*, 132(8), 605–611.
- Weston, K. S., Wisloff, U., & Coombes, J. S. (2014). High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br. J. Sports. Med*, 48, 1227–1234. <http://doi.org/10.1136/bjsports-2013-092576>
- Whyte, L. J., Gill, J. M. R., & Cathcart, A. J. (2010). Effect of 2 weeks of sprint interval training on health-related outcomes in sedentary overweight/obese men. *Metab. Clin. Exp.*, 59, 1421–1428. <http://doi.org/10.1016/j.metabol.2010.01.002>
- Wing, R. R., Bolin, P., Brancati, F. L., Bray, G. A., Clark, J., Coday, M., ... Yanovski, S. Z. (2013). Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N. Engl. J. Med.*, 369(2), 145–154. <http://doi.org/10.1056/NEJMoa1212914>



## **CHAPTER 2: MANUSCRIPT**

### **THE EFFECT OF BRIEF INTERMITTENT STAIR CLIMBING EXERCISE ON GLYCEMIC CONTROL IN PEOPLE WITH TYPE 2 DIABETES**

In preparation for:

Applied Physiology, Nutrition, and Metabolism

## 2.1 INTRODUCTION

Type 2 diabetes (T2D) is characterized by glycemic instability and heightened periods of postprandial hyperglycemia, which are both independent risk factors for the development of cardiovascular complications (Cavalot et al. 2011; Nalysnyk et al. 2010). Exercise is considered a cornerstone of T2D prevention and management (Tuomilehto et al. 2001). Regular exercise training has been shown to have a beneficial impact on glycemic control in adults with T2D, independent of weight loss (Boulé et al. 2001). Researchers investigating the effects of exercise on glycemic control have traditionally relied on metrics such as glycated hemoglobin (HbA1c), which reflects glycemic control over the previous 1-3 months but does not provide information on short-term changes in glycemic variability (Kohnert et al. 2015). Adjunct measures such as continuous glucose monitoring (CGM), which involves a wearable device that captures a more detailed picture of blood glucose profiles over an entire 24-h period, may provide an optimal method for evaluating the glycemic response to exercise under free-living conditions (Kearney & Thyfault, 2016; Monnier et al. 2008). A meta-analysis by MacLeod et al. (2013) concluded that exercise in adults with T2D improved CGM-derived glycemic control parameters, changes that may otherwise go undetected based on traditional, laboratory-based blood glucose measures (van Dijk & van Loon, 2015).

Diabetes Canada recommends at least 150 minutes of aerobic exercise performed at a moderate to vigorous intensity, spread across at least three days of the week (Sigal et al. 2013). The majority of people with T2D do not meet these guidelines (Morrato et al. 2007; Thomas et al. 2004), with perceived “lack of time” cited as one of the most

common barriers to regular exercise participation (Korkiakangas et al. 2009). Emerging research suggests that interval training, which involves alternating bouts of relatively intense exercise and recovery, can improve disease risk parameters in adults with T2D (Jelleyman et al. 2015; Liubaoerjijin et al. 2016). Karstoft et al. (2013) showed that 16 weeks of interval walking in people with T2D elicited superior improvements in CGM-derived glycemic control parameters as compared to an energy expenditure-matched period of continuous moderate intensity walking (Karstoft et al. 2013). While effective, the protocol involved a large exercise volume totaling 300 minutes of weekly exercise. High-intensity interval training (HIIT) involving a lower exercise volume and reduced time commitment has also been found to be effective in people with T2D. Gillen et al. (2012) showed that a protocol involving 10 x 1-min cycling repeats at ~90% of maximum heart rate ( $HR_{max}$ ), interspersed with 1-min of recovery, acutely improved 24-h postprandial hyperglycemia. A related study by the same authors showed that six sessions of the same protocol performed over two weeks reduced 24-h mean glucose in the same group of participants (Little et al. 2011). Although these findings suggest the potential utility of time-efficient HIIT for improving glycemic control, the use of specialized equipment within a traditional laboratory environment may limit translation to a real-world setting. This is especially important considering that another reported barrier to physical activity for adults with T2D is lack of access to and affordability of exercise facilities (Thomas et al. 2004). Additional research is warranted into potentially more practical exercise protocols and the potential minimum effective “dose” required for improving glycemic control in people with T2D.

Stair climbing may serve as an accessible modality for performing interval training outside of the laboratory. Previous literature has established the efficacy of higher volumes of moderate to vigorous stair climbing exercise for improving cardiorespiratory fitness when performed over 8-12 weeks in healthy adults (Boreham et al. 2005; Boreham et al. 2000; Loy et al. 1994). Recent evidence from our laboratory based on a low-volume HIIT stair climbing protocol in sedentary adults, involving three intermittent bouts of ‘vigorous’ stair climbing on three days a week for 6 weeks, resulted in a 1 MET improvement in cardiorespiratory fitness (Allison et al. 2017). According to epidemiological studies, a 1 MET higher level of fitness is comparable to a 1 mmol/L lower fasting blood glucose level (Kodama et al. 2009). However, the efficacy of translating time-efficient interval protocols to “real world” settings as a method of targeting glycemic control remains largely unexplored, including in people with T2D. As such, the purpose of the present study was to explore the effect of brief, intermittent stair climbing on indices of glycemic control using CGM in people with T2D. We assessed whether (i) a single session of stair climbing exercise improved 24-h blood glucose in the period immediately following exercise; and (ii) if training three days per week for 6 weeks improved 24-h blood glucose when measured > 72-h following the final training bout. We hypothesized that (i) an acute bout of brief intermittent stair climbing exercise would improve 24-h blood glucose; and (ii) 24-h blood glucose would be improved following 6 weeks of stair climbing training, as assessed by CGM under controlled dietary conditions.

## **2.2 METHODS**

### **Participants**

Individuals were recruited through poster and newspaper-based advertisement, as well as through collaboration with the Diabetes Care and Research Program at the McMaster University Medical Centre. Inclusion criteria included physician-diagnosed T2D for at least 6 months based on Canadian Diabetes Association (CDA) guidelines (i.e., HbA1c > 6.5%, FPG > 7.0 mmol/L, or 2hPG in a 75 g OGTT > 11.1 mmol/L) (Goldenberg & Punthakee, 2013), no treatment by insulin, no significant changes in body weight (> 5%) or diabetes medication in the last three months, HbA1c < 9.0%, and no previous myocardial infarction, stroke or diagnosed coronary artery disease. Prior to being enrolled in the study, potential participants completed a physician-directed 12-lead electrocardiogram (ECG) exercise stress test to confirm the absence of any cardiac abnormalities that might prevent participation in vigorous exercise (Colberg et al. 2010). This test was conducted using the Bruce Protocol on a treadmill at the Medical Diagnostics Unit of Hamilton General Hospital.

The required sample size was calculated a-priori based on changes in the average 24-h blood glucose concentration and standard deviations obtained pre- ( $7.6 \pm 1.0$  mmol/L) and post-training ( $6.6 \pm 0.7$  mmol/L) reported by Little et al. (2011). Based on these values (and assuming a moderate to high correlation of 0.6 between the two sets of data), 6 participants were needed to detect changes at an alpha level of 0.05 and with 80% power (G\*Power 3.1). To preserve power and account for possible attrition, the goal was to recruit and test 8 participants. A total of 33 individuals were identified for preliminary

screening; 17 completed a baseline assessment and 11 performed an exercise stress test (Fig. 1). Six individuals were excluded and referred for additional medical follow-up and data for five individuals who completed the study are described here (Table 1). All participants were taking blood glucose lowering medications, which included metformin, sitagliptin, canagliflozin, and gliclazide. Participants were instructed to follow their usual medication regime and continue with typical dietary and activity habits throughout the duration of the study. The study protocol was approved by the Hamilton Integrated Research Ethics Board (HiREB).

### **Experimental Design**

The study was a within-subject intervention design spanning across ~ a 9-wk period. The experimental design consisted of five phases: i) pre-screening; ii) familiarization; iii) baseline testing and assessment of the acute response to a single session of interval-based stair climbing; iv) a 6-wk interval-based stair climbing training intervention; and v) assessment of the post-training response (Fig. 2). The general procedures to assess the acute and post-training responses were similar and involved strict dietary and physical activity controls over ~ 72-h during which the CGM data was collected.

#### ***Pre-Screening***

On the first visit to the laboratory, participants who met the inclusion criteria and volunteered to participate provided written informed consent. Baseline data was collected including: anthropometry (e.g., height, mass), medical history (e.g., duration of diabetes, medications), as well as recent blood test results detailing HbA1c, blood lipids in the last

6 months and serum creatinine levels within the last year. Participants then completed the Physical Activity Readiness Questionnaire Plus (PAR-Q+), Godin Leisure-Time Exercise Questionnaire, Patient Health Questionnaire (PHQ-8), Pittsburgh Sleep Quality Index (PSQI), and a food preference checklist. Resting blood pressure and heart rate measurements were taken as a preliminary screening tool. Participants were then scheduled to complete the 12-lead ECG exercise stress test.

### ***Familiarization***

Once cleared to participate following the exercise stress test, participants completed two measures of functional fitness: the 6-minute walk test (6MWT) and the 30-sec chair stand test. Participants also became familiar with brief, intermittent stair climbing by completing a modified version of the training protocol. This involved two intervals of climbing up and down a single flight of stairs for one minute, with the ascents conducted at a “comfortable” and then “challenging” pace. One minute of walking recovery was completed between intervals, as well as a 3-min walking warm-up and cool-down. This allowed the participants to become familiar with elements of the stair climbing protocol and provided preliminary monitoring of the blood glucose, blood pressure, and heart rate response to interval exercise.

### ***Baseline Testing and Acute Response to Stair Climbing***

At least 48-h after the fitness and familiarization session, participants returned to the laboratory following an overnight fast for body composition analysis. Seated resting blood pressure and heart rate measurements were conducted and a fasting blood sample was obtained for the subsequent measurement of glucose, insulin, and fructosamine.

Participants were provided a breakfast meal and then the 6MWT was repeated, with the initial 6MWT treated as a practice trial (Rikli & Jones, 1998). The blinded CGM device was then inserted (day 1) and participants were given a glucose meter with instruction on obtaining finger stick blood samples. On day 2, participants were asked to refrain from purposeful exercise and this served as the non-exercise control day for 24-h CGM data collection. On the third day, participants returned to the laboratory ~ 1 hour after breakfast to perform the interval-based stair climbing protocol. The CGM was removed greater than 24-h following the cessation of this stair climbing session (day 4). This allowed for CGM assessment of the acute glycemic response under controlled dietary conditions in the 24-h period following a single bout of stair climbing versus a non-exercise control day (Fig. 2).

### ***Exercise Training***

Training occurred over a 6-wk period, with three sessions performed each week (aimed for Monday, Wednesday, and Friday), resulting in a total of 18 training sessions. All sessions took place at the northeast staircase in the Ivor Wynne Centre at McMaster University. This location was selected because of the low traffic volume, accessible railings, ground-foot traction and ample lighting. The stair climbing protocol was modeled after previous work in our laboratory that has shown to be effective for improving cardiorespiratory fitness in previously sedentary adults (Allison et al. 2017). Briefly, the protocol consisted of 3 x 1-min bouts of repeatedly ascending and descending a single flight of stairs. This was set within a 10-min period which otherwise involved walking for a 1-min recovery period in between bouts, 2-min warm-up, and 3-min cool-



down. For the stair-climbing bouts, participants were instructed to, “Climb up and down the stairs one step at a time for one minute. Ascend at a pace that you find challenging, and descend at a pace you find comfortable, such that you feel you can safely manage the three bouts of stair climbing. Use the railings for support if you wish.” Participants were asked to identify their rating of perceived exertion (RPE) at baseline, immediately following each interval, and at the end of each session. Heart rate was monitored continuously throughout and blood pressure was measured before and after each session. A finger prick blood glucose sample was also taken ~ 10-min before and 5-min post-exercise. All training sessions were supervised.

### ***Post-training Response***

At least 72-h following the final training session, participants returned to the laboratory in the fasted state to complete the same procedures conducted at baseline. This included resting blood pressure and heart rate measures, body composition, and a fasting blood sample. Participants then consumed a breakfast meal before completing the 6MWT and 30-sec chair stand test. Participants were fitted with a CGM, given a glucose meter and provided a controlled diet to match what was consumed during baseline testing (day 1). On day 2, participants were asked to avoid exercise and this served as the non-exercise control day for 24-h CGM data collection post-training. Participants then returned to the lab the following day ~ 1 hour after breakfast to perform their last stair climbing session (day 3). In the 5-10 minute period after the cessation of exercise, level of enjoyment of interval-based stair climbing was assessed using the Physical Activity Enjoyment Scale (PACES), an 18-item scale providing an overall score out of 126 related to the enjoyment

of the exercise just performed (Kendzierski & DeCarlo, 1991). At this time, task and scheduling self-efficacy were also assessed on a 10-point Likert scale ranging from 1 (not confident at all) to 10 (completely confident) and intentions to implement high intensity exercise were assessed based on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree), using an approach modeled after Boyd et al. (2013).

## **Measurements**

### ***Continuous Glucose Monitoring***

CGM involves inserting a flexible microneedle into the subcutaneous tissue of the abdomen, which transmits measurements of interstitial glucose levels every 5 minutes to a recording device (Castle & Jacobs, 2016). CGM allows for an estimate of circulating blood glucose levels within a free-living environment, based on calibration with frequent capillary blood glucose samples (Riddell & Perkins, 2009). As such, participants were provided a glucose meter (OneTouch Ultra2, Lifescan, Inc., Burnaby, BC) (DirecNet Study Group, 2003) and instructed to take capillary blood glucose samples at four time points during each day (before breakfast, lunch, dinner and bed) while wearing the CGM (CGMS iPro2, Medtronic, Northridge, CA). The capillary blood glucose values were used to retrospectively calculate blood glucose concentration when downloading the CGM data from the iPro2 using an algorithm within the CareLink software (CareLink Pro, Medtronic, Northridge, CA) (Rossetti et al. 2010). CGM data was then exported to Microsoft Excel for CGM analysis for each 24-h period. The CGM and sensors have previously been shown to provide measures within clinically accurate or acceptable ranges ~ 96-98% of the time (using Clarke error grid analysis), with a mean absolute

relative difference (MARD) of  $< 14\%$  when compared to laboratory YSI reference samples (Bailey et al. 2014; Keenan et al. 2012). Key outcomes of interest in the present study included mean 24-h glucose, time spent in hyperglycemia ( $> 10$  mmol/L), and postprandial hyperglycemia. Postprandial hyperglycemia was assessed via calculation of both the absolute and incremental post meal area under the glucose curve (AUC) over a 2-h period following each meal using the trapezoid method (Pruessner et al. 2003), as well as the postprandial spike (PPS) in glucose from pre-meal (average of 15-min prior to each meal) to the highest post-meal value (Little et al. 2014). Parameters of glycemic variability were also assessed in each of the 24-h periods using the EasyGV platform (<http://www.phc.ox.ac.uk/research/technology-outputs/easygv>) and included mean amplitude of glycemic excursions (MAGE) (Service et al. 1970) and standard deviation (SD) from mean glucose level (Rodbard, 2011). An acute comparison was made between the 24-h glycemic response to a single session of stair climbing (commencing at the start of the exercise session) versus a non-exercise control day. The training response compared the 24-h non-exercise control day pre-training to a non-exercise control day following 6 weeks of stair climbing. In four instances, aspects of post-training CGM monitoring were repeated owing to missing sensor data or to ensure compliance with nutritional or physical activity controls.

### ***Standardized Diet and Physical Activity Monitoring***

In order to assess CGM-derived glucose control measures under standard dietary conditions, participants were provided with all of their food (3 meals and 2 snacks) over each 3-day monitoring period. Macronutrient profile was based on Canadian Diabetes

Association guidelines, with each meal providing ~55% carbohydrate, ~30% fat, and ~15% protein (Dworatzek et al. 2013). Energy intake was estimated according to the calculation of resting metabolic rate using the Harris Benedict equation, multiplied by a physical activity level of 1.4 metabolic equivalents (Harris & Benedict, 1918). The timing, composition, and quantity of food consumption was matched between the pre and post-training monitoring periods. Participants were given a physical activity monitor watch (Polar A300, Polar Electro OY, Kempele, Finland) to wear during each monitoring period. A logbook was also provided to confirm compliance with diet and timing of food consumption, as well as to record daily steps and finger prick blood samples.

### ***Fasting Measures***

During the fasted visit in the baseline and post-testing monitoring period, an automated oscillometric device (Omron BP765CAN, Kyoto, Japan) was used to measure resting blood pressure. In accordance with the standardized technique proposed by the Canadian Hypertension Education Program, participants sat quietly in a room for ~ 10 minutes, before three measurements were taken with at least one minute between readings (Dasgupta et al. 2014). Resting blood pressure was determined by taking an average of the second two readings. At the same time, heart rate was monitored continuously and a resting heart rate measure was determined by averaging the values over the last five minutes of quiet sitting, before the blood pressure measure began.

Body composition was measured via air-displacement plethysmography (BOD POD, Life Measurement, Inc., Concord, CA) and a fasting blood sample was obtained by venipuncture of an antecubital vein. Blood plasma and serum samples were separated by

centrifugation (10 min at 1300g), aliquoted and stored at -20°C until analysis. Plasma and serum samples were sent to the Hamilton Regional Laboratory Medicine Program at McMaster University for subsequent analyses of glucose, insulin, and fructosamine. Glucose was analyzed using the Architect Hexokinase/G-6-PDH method (Abbott Diagnostics, Abbott Park, IL). Insulin was analyzed using an Architect Insulin Chemiluminescent Microparticle Immunoassay (Abbott Diagnostics, Abbott Park, IL). Fructosamine was analyzed using the Nitrotetrazolium Blue Method (Roche P800, Roche Diagnostics, Basel, Switzerland). Fructosamine was included in the analysis because it has been shown to reflect changes in overall glycemic control following relatively short-term training interventions (Moura et al. 2014). Insulin sensitivity was determined using the quantitative insulin sensitivity check index (QUICKI) method (Katz et al. 2000), a reproducible and valid estimate of insulin sensitivity values derived from the “gold standard” hyperinsulinemic euglycemic clamp technique in patients with T2D (Sarafidis et al. 2007).

### ***Exercise Measures***

During exercise, heart rate was monitored continuously using a chest strap and corresponding watch (Polar Team System, Polar Electro OY, Kempele, Finland). RPE was assessed after each interval and at the end of exercise using the Borg 0-10 Category-Ratio (CR-10) Scale (Borg, 1982). Capillary blood glucose was measured using a finger-prick glucose meter before and after each training session according to recommendations by Hortensius et al. (2011), to confirm the absence of hypo- or hyperglycemia and quantify the change in blood glucose immediately following stair climbing. Blood

pressure (manual sphygmomanometer) was also measured before exercise and into recovery. The number of stairs climbed per bout was recorded at each session and vertical work output ( $\text{Work [kJ]} = \text{body mass [kg]} \times 9.81 \text{ m/s}^2 \times \text{height [m]} / 1000$ ) was calculated for a representative session during weeks 1, 3 and 6.

### ***Physical Function Measures***

The 6MWT was used as a validated measure of physical endurance and functional capacity in older adults and people with physical impairment (Rikli & Jones, 1998; Enright, 2003). Participants received standardized instructions to walk as far as possible around a track in a 6-min period at a self-selected pace, with heart rate monitored continuously and RPE measured before and after the test. The second task was a 30-sec chair stand test, requiring participants to rise to a full stand from a chair with their arms across their chest as many times as possible in 30 seconds, as an indicator of lower body strength in older adults (Jones et al. 1999).

### **Statistical Analysis**

Data are presented as mean  $\pm$  SD. All data are based on  $n=5$  except for mean HR analyses ( $n=4$ ) owing to difficulties in continuous HR collection for one participant. One-tailed paired t-tests were used to analyze the acute differences between the 24-h non-exercise and 24-h post-stair climbing CGM parameters, and all data collected pre- and post-training. Effect sizes (Cohen's  $d_z$  for repeated measures) were calculated for all t-tests (Lakens, 2013). A two-tailed Pearson's correlation coefficient was used to determine the relationship between variables of interest. Data collected within the first training session (i.e., mean HR, RPE, and stairs climbed) and during selected training sessions

across weeks were analyzed using a one-way repeated measures analysis of variance (ANOVA) with time as the within factor. The Greenhouse-Geisser correction was used when data did not meet the assumption of sphericity, and post-hoc analyses were completed using t-tests with a Bonferroni correction. The level of significance for all analyses was set at  $p \leq 0.05$ . Data analyses were performed with Microsoft Excel 2011 (version 14.7.1) and IBM SPSS (version 22). Figures were produced in Prism GraphPad (version 6).

## **2.3 RESULTS**

### **Acute Response to a Single Session of Exercise**

#### ***Exercise Characterization***

Mean HR over the entire 10-min exercise session was  $73 \pm 4\%$  of age-predicted maximum. Mean HR over the three climbing bouts was  $77 \pm 4\%$  and peak HR was  $86 \pm 4\%$  of age-predicted maximum (ranging from  $80 \pm 7\%$  to  $90 \pm 9\%$  across participants) (Fig. 3; Table 2). There was a main effect of time across bouts for stairs climbed, vertical work output, peak HR, and RPE per bout ( $p < 0.05$ ; Table 3), with RPE and peak HR increasing across the session.

#### ***Glycemic Parameters***

Capillary blood glucose decreased from  $11.6 \pm 2.9$  to  $8.7 \pm 1.8$  mmol/L when measured ~ 5 minutes following the acute session of stair climbing exercise ( $\Delta = -2.9 \pm 2.2$  mmol/L;  $p = 0.02$ ,  $d_z = 1.36$ ; Fig. 4). Mean blood glucose concentration over 24-h was not different following a single session of stair climbing compared to the non-exercise control day ( $7.9 \pm 0.6$  mmol/L vs.  $7.8 \pm 1.4$  mmol/L,  $p = 0.38$ ,  $d_z = 0.15$ ; Fig. 5)

and there was no difference in the total time spent in hyperglycemia ( $163 \pm 211$  vs.  $152 \pm 159$  min,  $p=0.42$ ,  $d_z=0.10$ ; Table 4). Acute stair climbing improved metrics of glycemic variability in the 24-h period following exercise versus control, as measured by reductions in the SD around the mean ( $1.7 \pm 0.5$  vs.  $1.4 \pm 0.5$  mmol/L,  $p=0.02$ ,  $d_z=1.3$ ; Table 4) and MAGE ( $4.4 \pm 1.5$  vs.  $3.5 \pm 1.0$  mmol/L,  $p=0.02$ ,  $d_z=1.5$ ; Fig. 6). There were no differences in the absolute or incremental glycemic responses to any of the meals between conditions (all  $p$  values  $> 0.05$ ; Table 4), although 4 out of 5 participants exhibited a lower iAUC in response to the standardized lunch meal following stair climbing (i.e., the first meal eaten after the morning exercise session). Individual acute glycemic responses for the primary outcomes are shown in Figure 7.

## **Exercise Training Response**

### ***Exercise Characterization***

All participants completed all prescribed training sessions. Participants spent  $24 \pm 2$  s ascending and  $36 \pm 1$  s descending during each 60-s bout (Table 5). Total stairs climbed averaged  $167 \pm 29$  stairs per session and mean RPE over the 3 bouts was  $4.3 \pm 1.6$  (“somewhat hard”), with no main effect of time across the six weeks ( $p=0.20$  for stairs climbed and  $p=0.11$  for RPE). Mean HR for the entire 10-min session, averaged over each training session, was  $73 \pm 3\%$  of age-predicted maximum ( $n=4$ ). Mean peak HR per session was  $90 \pm 6\%$  of age-predicted maximum. Mean HR over the three climbing bouts was  $76 \pm 1\%$  when measured across a representative session in weeks 1, 3, and 6.

### ***Glycemic Parameters***



Capillary blood glucose decreased immediately following stair climbing exercise across the training period from  $9.2 \pm 1.8$  to  $8.0 \pm 1.8$  mmol/L ( $\Delta = -1.2 \pm 0.7$  mmol/L;  $p=0.01$ ,  $d_z=1.78$ ; Fig. 8). Mean 24-h glucose was not different after 6 weeks of stair climbing exercise ( $7.9 \pm 0.6$  mmol/L vs.  $8.1 \pm 0.9$  mmol/L,  $p=0.15$ ,  $d_z=0.53$ ; Fig. 9) and there was no change in time spent in hyperglycemia ( $163 \pm 211$  vs.  $165 \pm 211$  min,  $p=0.47$ ,  $d_z=0.04$ ; Table 6). Training-induced reductions in glycemic variability neared statistical significance when assessed using MAGE ( $4.4 \pm 1.5$  vs.  $3.4 \pm 0.7$  mmol/L,  $p=0.059$ ,  $d_z=0.89$ ; Table 6), but were not apparent when using the SD around the mean ( $1.7 \pm 0.5$  vs.  $1.4 \pm 0.5$  mmol/L,  $p=0.12$ ,  $d_z=0.61$ ; Table 6). There were no differences in the absolute or incremental glycemic responses to the breakfast and dinner meals following 6 weeks of training (all  $p$  values  $> 0.05$ ; Table 6), however, a reduction in the lunch postprandial spike (PPS) ( $p=0.01$ ), absolute AUC ( $p=0.03$ ), and incremental AUC ( $p=0.01$ ) were evident post-training (Table 6). More specifically, the incremental AUC of the lunchtime meal was reduced by  $36 \pm 42$  % ( $p=0.01$ ,  $d_z=2.11$ ), with all 5 participants experiencing a decrease in this meal-specific postprandial response (Fig. 10). There were no training-induced changes in fasting blood glucose parameters measured, including glucose ( $p=0.43$ ), fructosamine ( $p=0.38$ ), insulin ( $p=0.10$ ), and the QUICKI ( $p=0.09$ ; Table 6).

### ***Cardiometabolic, Performance and Psychological Measures***

Total distance walked ( $575 \pm 80$  vs.  $566 \pm 78$  m,  $p=0.25$ ,  $d_z=0.33$ ) and 30-sec chair stand performances ( $15 \pm 4$  vs.  $14 \pm 2$  stands,  $p=0.35$ ,  $d_z=0.19$ ; Table 7) were unchanged following training. There were no training-induced changes in resting

cardiovascular measures, including systolic blood pressure ( $p=0.23$ ,  $d_z=0.36$ ), diastolic blood pressure ( $p=0.29$ ,  $d_z=0.27$ ), or resting heart rate ( $p=0.38$ ,  $d_z=0.14$ ; Table 7). Fat free mass (FFM) ( $54.1 \pm 6.2$  vs.  $54.1 \pm 7.2$  kg,  $p=0.50$ ,  $d_z=0.01$ ) and body fat percentage ( $37.1 \pm 11.6$  vs.  $36.4 \pm 13.4$  %,  $p=0.27$ ,  $d_z=0.30$ ; Table 7) were also unchanged following training. The change in FFM was negatively correlated with the change in 24-h mean glucose ( $r = -0.88$ ,  $p = 0.049$ ), with an increase in FFM related to a reduction in average glucose (Fig. 11). The overall enjoyment score determined by the PACES was  $89 \pm 19.2$ . Participants reported scores of  $5.2 \pm 1.9$ ,  $6.8 \pm 3.1$ , and  $5.3 \pm 0.8$  when assessing task self-efficacy, scheduling self-efficacy, and intentions to implement high intensity exercise, respectively.

## 2.4 DISCUSSION

The major novel finding of this study was that most indices of 24-h glycemic control determined by CGM were unchanged after a single session of brief, intermittent stair climbing exercise and after 6 weeks of stair climbing training in people with T2D. There was no change in the primary outcomes of interest, including mean glucose, time spent in hyperglycemia and the overall postprandial hyperglycemic response in the 24-h period following a single session or following 6 weeks of low-volume stair climbing exercise. These results are contrary to our primary hypotheses, although the small sample size may have impacted on our ability to detect a potential effect of exercise. We did detect improvements in overall glycemic variability, as measured by MAGE and SD, in the 24-h period following a single session of stair climbing and an isolated, meal-specific effect of improvement in the postprandial glycemic response to lunch following 6 weeks

of training. To our knowledge, this is the first study to assess 24-h glycemic control using CGM in response to interval-based stair climbing in adults with T2D. The training was generally well tolerated as evidenced by high adherence rates and no adverse events, which highlights the potential feasibility of this type of activity in people with T2D.

### **Acute Effects of Stair Climbing on Glycemic Control**

Current physical activity guidelines for individuals with T2D recommend bouts at least 10 minutes in duration (Colberg et al. 2016). With respect to glycemic control, plasma glucose concentrations have been shown to peak approximately 60-90 minutes after the start of a meal in people with T2D and remain elevated for several hours (ADA, 2001). The midmorning period also represents a critical time point as the post-meal response to breakfast is typically the highest glycemic excursion experienced across the day (Monnier et al. 2007). As such, participants in the present study performed the 10-min session of stair climbing exercise ~ 1 hour ( $81 \pm 15$  min) after consumption of a standardized breakfast for the acute analyses. The decrease in capillary blood glucose levels we detected in the 5-min period following stair climbing (Fig. 4) is consistent with the work of Takaishi et al. (2012). These authors observed a reduction in capillary blood glucose of ~ 3.2 mmol/L when stair climbing was performed 90-min after lunch in adults with impaired glucose tolerance (Takaishi et al. 2012). An immediate decrease in blood glucose post-exercise may be the result of contraction-mediated glucose uptake (Holloszy, 2005). It is possible that the acute session of stair climbing in the present study may have been performed in the period when postprandial glucose was already decreasing. The non-significant change in CGM values at the same time points on the

non-exercise control day seemingly supports a role of the stair climbing exercise *per se* in hastening the decrease.

There are a number of possible parameters that can be used to assess glycemic variability, or the deviation of glucose concentrations from mean levels over a specified time period, and thus, using different tools concomitantly is recommended (Monnier et al. 2008). Two well-established markers of within-day glycemic variability are the SD around the mean glucose value and the MAGE (Monnier et al. 2008; Monnier & Colette, 2011). In the present study, acute improvements in glycemic variability were demonstrated by reductions in both the SD and MAGE in the 24-h period following a single session of stair climbing (Table 4; Fig. 6). Although the contributions of glycemic variability to the risk of diabetic complications remains controversial (Rodbard, 2011), glycemic variability as assessed by the MAGE was positively correlated with the activation of oxidative stress (increased free radical production) in non-insulin treated adults with T2D (Monnier et al. 2006). With the generation of oxidative stress considered a key player in the pathogenesis of macrovascular diabetic complications (Brownlee & Hirsch, 2006), therapeutic options that minimize glucose oscillations may be of value.

Despite the immediate decrease in blood glucose and acute improvement in glycemic variability, we did not observe changes in mean 24-h glucose, time spent in hyperglycemia, or postprandial hyperglycemia following 3 x 1-min bouts of stair climbing exercise (Table 4; Fig. 5). These results conflict with previous work demonstrating that HIIT is an effective option for acutely improving some of these CGM-derived 24-h glycemic control parameters in adults with T2D (Gillen et al. 2012; Francois

et al. 2014; Terada et al. 2016). For example, a single session of cycling HIIT performed ~ 90 minutes after breakfast, involving 10 x 1 min bouts at 90% HR<sub>max</sub> interspersed with 1-min of recovery, reduced post-meal glucose and time spent in hyperglycemia over 24-h in 7 adults with T2D (Gillen et al. 2012). In another study conducted by Terada et al. (2016), a higher volume of HIIT performed in the fasted state on a treadmill, based on 15 x 1-min intervals (workload corresponding to ~ 100% of VO<sub>2peak</sub>) separated by 3-min recovery, reduced postprandial hyperglycemia and improved average 24-h glucose in 10 adults with T2D (Terada et al. 2016). It is possible that the protocol used in the present study did not elicit a high enough intensity, with HR per 1-min bout averaging ~ 77% of age-predicted maximum and RPE ratings corresponding to “somewhat hard” on the Borg CR-10 scale. Furthermore, in support of the importance of exercise intensity, preliminary results from an ongoing study assessing the acute glycemic response to moderate intensity exercise of longer duration demonstrated that 24-h mean glucose level was unaffected following 50 minutes of walking exercise (~ 3.5 METS) in 40 adults with T2D (The Canadian E-PARA DiGM Protocol, clinicaltrials.gov #NCT02834689). The discrepancies in these findings suggest that there may be a “threshold” dose, as a function of intensity and volume, required to elicit improvements in 24-h glycemic control and that exercise timing may influence the effect. Based on the low number of intervals employed and with participants instructed to climb at a self-selected “challenging” pace, the current exercise regime may have been an insufficient stimulus to acutely evoke purported classical HIIT mechanisms of improved insulin sensitivity (Roberts et al. 2013).

Although an insufficient dose of exercise may have been a key reason for the lack of change in glycemic responses, it is also possible that an acute bout of repetitive stair climbing exercise induced some eccentric muscle damage during the descending phase of the exercise protocol. We did not attempt to assess blood indices of muscle damage (i.e., creatine kinase) following stair climbing; however, anecdotal reports of delayed onset muscle soreness (DOMS) by participants following the first stair climbing session may be indicative of skeletal muscle disruption (Paschalis et al. 2013). It is well established that the insulin-sensitizing effect of a single bout of exercise is markedly impaired 48-h following unaccustomed eccentric exercise that induces transient muscle damage and trauma (Green et al. 2010; Kirwan et al. 1992). Previous work in young, healthy men has shown that a higher volume of stair climbing descending exercise (5 x 5-min descending, separated by 3-min recovery) resulted in increased DOMS, elevated levels of creatine kinase, and impaired indices of insulin sensitivity when measured two days following the exercise bout (Paschalis et al. 2013). Despite the absence of mechanistic insight into muscle damage in the current investigation, it is possible that the time spent descending during stair climbing exercise may have induced some eccentric muscle damage and acutely disrupted skeletal muscle glucose uptake in the subsequent 24-h period. Future studies are warranted to quantify muscle soreness and address the time course of skeletal muscle damage with this type of stair climbing exercise.

### **Training Effects**

#### ***Glycemic Control***

Current physical activity guidelines for adults with T2D also suggest that exercise should be spread over three times per week, with no more than two consecutive days without exercise (Colberg et al. 2016). In alignment with this recommendation, we investigated the impact of 6 weeks of low-volume stair climbing exercise training on glycemic control, performed over three days per week. The decrease in capillary blood glucose immediately following stair climbing exercise across the training intervention (Fig. 8) is consistent with that of Terada et al. (2013a). These authors found that HIIT resulted in acute reductions in capillary blood glucose when measured post-exercise during a 12-wk training program in adults with T2D (Terada et al. 2013a). The acute reduction in blood glucose immediately following stair climbing across the training period in the current study may reflect a preservation of contraction-mediated glucose uptake in skeletal muscle, a pathway that is active during and in the first few hours post-exercise (Henriksen, 2002; Holloszy, 2005). This speculation may be supported by recent work showing that the 5'-adenosine monophosphate-activated protein kinase (AMPK) signaling network, known to play a role in regulating contraction-stimulated glucose transport, remains intact in the skeletal muscle of men with T2D in response to exercise (Kjøbsted et al. 2017).

When comparing a diet-matched, non-exercise control day completed before training to a replicated control day post-training, we did not observe changes in mean 24-h glucose (Fig. 9), time spent in hyperglycemia, and metrics of glycemic variability (i.e., SD and MAGE) with training (Table 6). These findings are in contrast to some previous interval training interventions where improvements in CGM-derived measures of

glycemic control were observed in adults with T2D (Francois et al. 2017; Karstoft et al. 2013; Karstoft et al. 2017; Little et al. 2011). For example, MAGE was lower following two weeks of interval walking (10 x 3 min at  $\sim 70\%$   $\text{VO}_{2\text{max}}$ , 3 min recovery, 5 times/week) (Karstoft et al. 2017) and 12 weeks of combined aerobic and resistance HIIT (Francois et al. 2017). Moreover, improvements in average 24-h glucose were observed after 2 weeks of HIIT cycling (Little et al. 2011) and 16 weeks of interval walking (Karstoft et al. 2013). Although it is difficult to discern the independent effect of exercise on glycemic control in the Karstoft et al. (2013) study due to concomitant changes in fitness and body composition, these studies support the idea that a minimum “threshold” dose may be needed to elicit measurable changes in glycemic control over a 24-h period. Additionally, between study inconsistency exists in the timing of post-training CGM monitoring relative to the last training session, with some studies commencing the CGM measurements within 24-h (Karstoft et al. 2017) or after 48-h (Karstoft et al. 2013; Little et al. 2011) following the final exercise bout. Starting monitoring this close to the last training session may confound the interpretation based on evidence to suggest that the blood-glucose lowering and insulin sensitizing effect of a single session of exercise can persist for 24-72-h (Newsom et al. 2013; Tjønnå et al. 2011). In an effort to isolate training-induced changes in glycemic control in the present study, CGM monitoring was conducted  $> 72\text{-h}$  ( $110 \pm 41$  hr) following the last training session. Although justified, it is possible that we actually missed the time window of capturing an effect, with evidence from long-term endurance training studies suggesting that improvements in insulin sensitivity are lost within 3-6 days of the last training bout (Boulé et al. 2005; Dela et al.



1992). More work is needed to determine a time-course of post-training adaptation in glycemic control and to establish greater inter-study consistency.

There are equivocal data regarding the change in insulin sensitivity and subsequent glycemic control in response to interval training interventions in adults with T2D (Shaban et al. 2014). Two studies involving 12-wk of either treadmill HIIT (Revdal et al. 2016) or mixed treadmill/cycling HIIT (7-14 x 1 min at 100%  $\text{VO}_2\text{R}$ , 3-min recovery, 4 times/week) (Terada et al. 2013b) found no change in HbA1c and fasting blood glucose. Despite the reliance on more traditional measures that cannot detect dynamic changes in glycemic control, these conflicting results lend support to the idea that other variables such as baseline HbA1c level may explain some of the heterogeneity between studies (Jelleyman et al. 2015). With evidence to suggest a greater magnitude of physical activity effects when baseline HbA1c levels are high ( $> 7\%$ ) (Umpierre et al. 2011), the relatively low HbA1c at baseline across participants in this study ( $6.6 \pm 0.7 \%$ ) may have contributed to the lack of change observed. Furthermore, although stair climbing is an accessible exercise modality that can elicit improvements in cardiorespiratory fitness, the utility of this method for improving glycemia in populations who are at an increased risk or who have T2D requires further investigation (Takaishi et al. 2012; Honda et al. 2016). In a recent study by Allison et al. (2017), the authors did not observe improvements in measures of fasting insulin sensitivity following 6 weeks of low volume stair climbing in sedentary but otherwise healthy adults, despite a 1 MET improvement in fitness. Coupled with the lack of change in most parameters of CGM-derived glycemic control and fasting glycemia in the present study (Table 6), it is possible

that the current prescription of 10 minutes of interval stair climbing involving only three minutes of intense exercise may not enable participants to perform enough work to elicit marked improvements in glycemic control. Considering participants spent more than half of each 60-s bout descending the stairs and were unable to increase the number of flights climbed per session across the training intervention, a prescription based instead on volume of stair climbing repetitions with built in progression across weeks may be a more effective stair climbing strategy in an overweight and clinical population.

#### Postprandial Hyperglycemia

As one of the earliest abnormalities in glucose homeostasis in adults with T2D (ADA, 2001), postprandial hyperglycemia is a major contributor to glycemic variability and an independent risk factor for cardiovascular disease (Ceriello, 2005; Cavalot et al. 2011). The development of CGM technology has enabled researchers to examine the impact of physical activity on the postprandial response to mixed meals under free-living conditions (Kearney & Thyfault, 2016). By calculating the incremental area under the curve (iAUC) above the pre-meal glucose concentration for each meal, information about the magnitude of the postprandial glucose excursion can be determined (Le Floch et al. 1990; Monnier et al. 2008). Despite no change in overall postprandial hyperglycemia (i.e., the sum of iAUC) following 6 weeks of training in the present study (Table 6), the post-meal iAUC response to lunch was lower across all 5 participants (Fig. 10). This finding partially aligns with a meta-analysis conducted by MacLeod et al. (2013) in adults with T2D, which concluded that exercise might preferentially target particular glycemic control parameters, including postprandial hyperglycemia (MacLeod et al. 2013).

With skeletal muscle considered the major sink for ingested glucose (DeFronzo, 2004), postprandial hyperglycemia is likely associated with skeletal muscle insulin resistance (Abdul-Ghani et al. 2006). Although there were no training-induced changes in the measure of insulin sensitivity at the group level in the present study (Table 6), it is possible that any small improvements in skeletal muscle insulin resistance with 6 weeks of stair climbing may be most apparent when measuring the post-meal response. However, if we postulate that the capacity of skeletal muscle to take up glucose in the postprandial state has been impacted post-training, one would reason that the response to each meal would be improved. Only a few chronic (Little et al. 2011; Karstoft et al. 2013) and acute (Gillen et al. 2012) interval-training studies in adults with T2D have measured and found improvements in postprandial hyperglycemia across a 24-h period, with two acute studies reporting evidence of a divergent, meal-specific response based on absolute (Francois et al. 2014) and incremental AUC measures (Little et al. 2014). With the largest post-meal glucose excursion occurring following the breakfast meal in the present study (Table 6), and consumption of a morning snack in close proximity to the start of lunch, it is possible that a delayed insulin secretory response in those with T2D (ADA, 2001) may have resulted in elevated levels of insulin at the start of the lunch meal. As insulin plays a critical role in controlling the postprandial glucose response, by blunting hepatic glucose output (Rizza, 2010), greater suppression of endogenous glucose production around lunch may have resulted in an imbalance between glucose production and utilization. Other slight discrepancies inherent to a free-living monitoring period, such as medication timing and pattern of activity throughout the day, may have also contributed to a lower post-meal

glucose response to lunch. Although the mechanisms behind the meal-specific improvement are unclear, and clinically relevant iAUC changes have yet to be defined, the reduction of even one postprandial glucose excursion may have value in minimizing the deleterious effect of glucose oscillations.

### ***Body Composition and Performance Outcomes***

Although at the group level, metrics of body composition (Table 7) and mean 24-h glucose were unchanged with training (Fig. 9), a negative correlation was found between change in FFM and change in 24-h mean glucose (Fig. 11). This suggests that those who gained the most FFM had the greatest reduction in 24-h mean glucose. An association between the change in body composition and glycemic control is consistent with previous data from our laboratory, which demonstrated a positive correlation ( $r=0.54$ ,  $p < 0.05$ ) between the change in insulin AUC and the change in abdominal percent fat following 6 weeks of HIIT in overweight and obese women, despite no change in insulin sensitivity at the group level (Gillen et al. 2013).

Low cardiorespiratory fitness has been identified as an independent predictor of mortality in people with T2D (Kohl et al. 1992; Wei et al. 2000). A meta-analysis looking at aerobic exercise interventions of at least 8 weeks in adults with T2D concluded that there was a ~12% increase in  $VO_{2max}$  following exercise training, with studies involving higher exercise intensities tending to elicit greater improvements in fitness (Boulé et al. 2003). More recently, employing a similar interval-based stair climbing protocol in sedentary but healthy adults resulted in comparable fitness improvements to a low-volume cycling-based SIT intervention after 6 weeks (Allison et al. 2017; Gillen et al.

2014). However, the validity of directly measuring  $\text{VO}_{2\text{max}}$  in exercise-naïve and patient populations has recently been questioned, due to difficulties in differentiating the efficacy of the training intervention from a practice effect that may occur with repeated testing (Poole & Jones, 2017). Instead, the 6MWT was used in the present study as a surrogate measure of fitness (Higgs et al. 2016), based on the validity of this test to assess physical endurance in older adults (60-87 y) (Rikli & Jones, 1998) and the reliability of this test in older adults (> 65 y) with T2D (Alfonso-Rosa et al. 2014). No clinically significant change in total distance walked, as defined by an increase of ~ 50 m (Higgs et al. 2016), was detected following training in the present study (Table 7). With participants sitting at a lower average age (~ 52 y) and experiencing less physical impairment compared to some of the populations in which the 6MWT has been validated, this test may not have been sensitive to measure training-induced changes in fitness in the present study. Some participants may have been limited by a “ceiling effect” (Frost et al. 2005), with 3 out of 5 participants exceeding predicted distance walked at baseline using reference equations developed for “healthy” adults (Enright & Sherrill, 1998).

Lower body strength is an important factor contributing to the maintenance of functional ability and independence with age (Hicks et al. 2012). The 30-sec chair stand test was used as a reliable and valid way to assess lower body strength in generally active, older adults (> 60 y) (Jones et al. 1999). Total number of chair stands was unchanged following 6 weeks of stair climbing training in the present study (Table 7). A lack of change in number of chair stands was somewhat surprising as most participants were not regularly performing exercise of this intensity, with only two participants engaging in

vigorous activity (~ 9 METS) on a weekly basis and the remaining 3 participants classified as “insufficiently active” (scores of < 23) based on responses to the Godin Leisure-Time Exercise Questionnaire (Amireault & Godin, 2015). The nature of the exercise stimulus was also novel across participants, as they were not habitually completing stair-climbing exercise. An improvement in 30-sec chair stand performance (a strength outcome) in adults with T2D has been observed following a 9 month combined exercise program, incorporating aerobic, resistance, flexibility, and balance training (Mendes et al. 2016). However, no change in 30-sec chair stand performance was noted following a 3 month intervention in adults with T2D that utilized only aerobic exercise training (Lambers et al. 2008). The absence of improvement in lower-body strength following aerobic exercise interventions suggests that exercise mode may impact adaptation. Future work may benefit from increasing the dose or length of the stair climbing intervention to determine if this modality is able to elicit measurable improvements in lower body strength, or if a combined approach may be required.

### ***Psychological Responses***

In briefly looking at the psychological response to exercise assessed 5-10 minutes following the final stair climbing session, the overall enjoyment score determined using the PACES ( $89 \pm 19.2$ ) was similar to that reported following an acute bout of cycling HIIT ( $87.4 \pm 13.8$ ) in adults at an increased risk of diabetes (Little et al. 2014). This finding is consistent with previous work showing that shorter interval length (30-60 sec) and total exercise time elicited higher enjoyment scores in an overweight population (Martinez et al. 2015). When compared to the response following three weeks of HIIT

cycling (10 x 1-min protocol) in an overweight, sedentary population (Boyd et al. 2013), participants in the present study reported lower task self efficacy ( $5.2 \pm 1.9$  vs.  $8.4 \pm 2.3$ ) and scheduling self-efficacy ( $6.8 \pm 3.1$  vs.  $7.9 \pm 1.4$ ), but similar intention to implement high intensity exercise ( $5.3 \pm 0.8$  vs.  $5.4 \pm 1.2$ ).

### **Limitations and Future Directions**

It is difficult to extrapolate the results of this study due to the relatively short duration of training and a small sample size, which was due in part to individuals not being cleared following the exercise stress test (Fig. 1). In the absence of a maximal exercise test at the start of the study, we were reliant on age-predicted  $HR_{max}$  and unable to interpret heart rate values based on true  $HR_{max}$ . Although a free living environment affords the ability to monitor glycemic control in physiologically relevant ways, slight discrepancies in food consumption, activity level or pattern, and medication timing may have confounded the independent contribution of stair climbing exercise to changes in glycemic control. Future work may benefit from increasing the volume of stair climbing exercise and duration of training in order to determine the efficacy of this modality to induce changes in insulin sensitivity and other clinically established endpoints of glycemic control (i.e., HbA1c). Incorporating a moderate intensity control group and using a more sensitive method to quantify changes in cardiorespiratory fitness are also warranted. Despite the accessibility of stair climbing and preliminary assessment of psychological responses in the present investigation, further research is needed to more comprehensively address the enjoyment and adherence of adults with T2D to stair climbing exercise in a free-living environment. Ongoing data collection may enable more

robust conclusions to be made about the potency of interval-based stair climbing exercise to improve glycemic control.

## **Conclusion**

In summary, we report that indices of CGM-derived 24-h glycemic control were largely unchanged in people with T2D after a single session or following 6 weeks of performing a 10-min exercise protocol involving three minutes of intermittent stair climbing. However, acute stair climbing exercise improved glycemic variability and 6 weeks of stair climbing training resulted in a lunch-specific improvement in postprandial hyperglycemia. These preliminary findings are noteworthy given glycemic variability and postprandial hyperglycemia have emerged as independent risk factors for the development of diabetic complications. Although longer, more comprehensive examinations with larger sample sizes are warranted, the results from this study highlight the feasibility of brief, vigorous stair climbing as a physical activity option for people with T2D.



## 2.5 REFERENCES

- Abdul-Ghani, M. A., Jenkinson, C. P., Richardson, D. K., Tripathy, D., & DeFronzo, R. A. (2006). Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the veterans administration genetic epidemiology study. *Diabetes*, 55(5), 1430–1435. <http://doi.org/10.2337/db05-1200>
- Alfonso-Rosa, R. M., del Pozo-Cruz, B., del Pozo-Cruz, J., Sanudo, B., & Rogers, M. E. (2014). Test – retest reliability and minimal detectable change scores for fitness assessment in older adults with type 2 diabetes. *Rehabil. Nurs*, 39, 260–268. <http://doi.org/10.1002/rnj.111>
- Allison, M. K., Baglione, J. H., Martin, B. J., MacInnis, M. J., Gurd, B. J., & Gibala, M. J. (2017). Brief intense stair climbing improves cardiorespiratory fitness. *Med. Sci. Sports. Exerc*, 49(2), 298–307. <http://doi.org/10.1249/MSS.0000000000001188>
- American Diabetes Association. (2001). Postprandial blood glucose. *Diabetes Care*, 24, 775–778.
- Amireault, S., & Godin, G. (2015). The godin-shephard leisure-time physical activity questionnaire: validity evidence supporting its use for classifying healthy adults into active and insufficiently active categories. *Percept. Mot. Skills*, 120(2), 604–622. <http://doi.org/10.2466/03.27.PMS.120v19x7>
- Bailey, T. S., Ahmann, A., Brazg, R., Christiansen, M., Garg, S., Watkins, E., ... Lee, S. W. (2014). Accuracy and acceptability of the 6-day enlite continuous subcutaneous glucose sensor. *Diabetes. Technol. Ther*, 16(5), 277–283. <http://doi.org/10.1089/dia.2013.0222>
- Boreham, C. A. G., Kennedy, R. A., Murphy, M. H., Tully, M., Wallace, W. F. M., & Young, I. (2005). Training effects of short bouts of stair climbing on cardiorespiratory fitness, blood lipids, and homocysteine in sedentary young women. *Br. J. Sports. Med*, 39(9), 590–593. <http://doi.org/10.1136/bjsm.2002.001131>
- Boreham, C. A. G., Wallace, W. F. M., & Nevill, A. (2000). Training effects of accumulated daily stair-climbing exercise in previously sedentary young women. *Prev. Med.*, 30(4), 277–281. <http://doi.org/10.1006/pmed.2000.0634>
- Borg, G. A. V. (1982). Psychophysical bases of perceived exertion. *Med. Sci. Sports. Exerc*, 14(5), 377–381.
- Boulé, N. G., Haddad, E., Kenny, G. P., Wells, G. A., & Sigal, R. J. (2001). Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA*, 286(10), 1218–1227. <http://doi.org/10.1001/jama.286.10.1218>
- Boulé, N. G., Kenny, G. P., Haddad, E., Wells, G. A., & Sigal, R. J. (2003). Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in Type 2 diabetes mellitus. *Diabetologia*, 46, 1071–1081. <http://doi.org/10.1007/s00125-003-1160-2>
- Boulé, N. G., Weisnagel, S. J., Lakka, T. A., Tremblay, A., Bergman, R. N., Rankinen, T., ... Bouchard, C. (2005). Effects of exercise training on glucose homeostasis: the HERITAGE family study. *Diabetes Care*, 28(1), 108–114.
- Boyd, J. C., Simpson, C. A., Jung, M. E., & Gurd, B. J. (2013). Reducing the intensity

- and volume of interval training diminishes the cardiovascular adaptation but not mitochondrial biogenesis in overweight/obese men. *PLoS ONE*, 8(7), e68091. <http://doi.org/10.1371/journal.pone.0068091>
- Brownlee, M., & Hirsch, I. B. (2006). Glycemic variability: a hemoglobin A1c – independent risk factor for diabetic complications. *JAMA*, 295(14), 1707–1708.
- Castle, J. R., & Jacobs, P. G. (2016). Nonadjunctive use of continuous glucose monitoring for diabetes treatment decisions. *J. Diabetes. Sci. Technol.*, 10(5), 1169–1173. <http://doi.org/10.1177/1932296816631569>
- Cavalot, F., Pagliarino, A., Valle, M., Di Martino, L., Bonomo, K., Massucco, P., ... Trovati, M. (2011). Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the san luigi gonzaga diabetes study. *Diabetes Care*, 34, 2237–2243. <http://doi.org/10.2337/dc10-2414>
- Ceriello, A. (2005). Postprandial hyperglycemia and diabetes complications. Is it time to treat? *Diabetes*, 54(1), 1–7. <http://doi.org/10.2337/diabetes.52.1.1>
- Colberg, S. R., Sigal, R. J., Fernhall, B., Regensteiner, J. G., Blissmer, B. J., Rubin, R. R., ... Braun, B. (2010). Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association joint position statement. *Diabetes Care*, 33, e147–e167. <http://doi.org/10.2337/dc10-9990>
- Colberg, S. R., Sigal, R. J., Yardley, J. E., Riddell, M. C., Dunstan, D. W., Dempsey, P. C., ... Tate, D. F. (2016). Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. *Diabetes Care*, 39(11), 2065–2079. <http://doi.org/10.2337/dc16-1728>
- Dasgupta, K., Quinn, R. R., Zarnke, K. B., Rabi, D. M., Ravani, P., Daskalopoulou, S. S., ... Reid, D. J. (2014). The 2014 Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can. J. Cardiol.*, 30, 485–501. <http://doi.org/10.1016/j.cjca.2014.02.002>
- DeFronzo, R. A. (2004). Pathogenesis of type 2 diabetes mellitus. *Med. Clin. N. Am.*, 88, 787–835. <http://doi.org/10.1016/j.mcna.2004.04.013>
- Dela, F., Mikines, K. J., von Linstow, M., Secher, N. H., & Galbo, H. (1992). Effect of training on insulin-mediated glucose uptake in human muscle. *Am. J. Physiol. Endocrinol. Metab.*, 263, E1134–E1143.
- Dworatzek, P. D., Arcudi, K., Gougeon, R., Husein, N., Sievenpiper, J. L., & Williams, S. L. (2013). Clinical practice guidelines: Nutrition therapy. *Can. J. Diabetes*, 37, S45–S55. <http://doi.org/10.1016/j.jcjd.2013.01.019>
- Enright, P. L. (2003). The Six-Minute Walk Test. *Respir. Care*, 48(8), 783–785.
- Enright, P. L., & Sherrill, D. L. (1998). Reference equations for the six-minute walk in healthy adults. *Am. J. Respir. Crit. Care. Med.*, 158, 1384–1387.
- Francois, M. E., Baldi, J. C., Manning, P. J., Lucas, S. J. E., Hawley, J. A., Williams, M. J. A., & Cotter, J. D. (2014). “Exercise snacks” before meals: a novel strategy to improve glycaemic control in individuals with insulin resistance. *Diabetologia*, 57(7), 1437–1445. <http://doi.org/10.1007/s00125-014-3244-6>
- Francois, M. E., Durrer, C., Pistawka, K. J., Halperin, F. A., Chang, C., & Little, J. P.

- (2017). Combined interval training and post-exercise nutrition in type 2 diabetes: a randomized control trial. *Front. Physiol*, 8(528), 1–11. <http://doi.org/10.3389/fphys.2017.00528>
- Frost, A. E., Langleben, D., Oudiz, R., Hill, N., Horn, E., McLaughlin, V., ... Barst, R. J. (2005). The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. *Vascul. Pharmacol*, 43, 36–39. <http://doi.org/10.1016/j.vph.2005.03.003>
- Gillen, J. B., Little, J. P., Punthakee, Z., Tarnopolsky, M. A., Riddell, M. C., & Gibala, M. J. (2012). Acute high-intensity interval exercise reduces the postprandial glucose response and prevalence of hyperglycaemia in patients with type 2 diabetes. *Diabetes. Obes. Metab*, 14(6), 575–577. <http://doi.org/10.1111/j.1463-1326.2012.01564.x>
- Gillen, J. B., Percival, M. E., Ludzki, A., Tarnopolsky, M. A., & Gibala, M. J. (2013). Interval training in the fed or fasted state improves body composition and muscle oxidative capacity in overweight women. *Obesity (Silver Spring)*, 21(11), 2249–2255. <http://doi.org/10.1002/oby.20379>
- Gillen, J. B., Percival, M. E., Skelly, L. E., Martin, B. J., Tan, R. B., Tarnopolsky, M. A., & Gibala, M. J. (2014). Three minutes of all-out intermittent exercise per week increases skeletal muscle oxidative capacity and improves cardiometabolic health. *PLoS ONE*, 9(11), e111489. <http://doi.org/10.1371/journal.pone.0111489>
- Goldenberg, R., & Punthakee, Z. (2013). Clinical practice guidelines: definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. *Can. J. Diabetes*, 37, S8–S11. <http://doi.org/10.1016/j.jcjd.2013.01.011>
- Green, M. S., Doyle, J. A., Ingalls, C. P., Benardot, D., Rupp, J. C., & Corona, B. T. (2010). Adaptation of insulin-resistance indicators to a repeated bout of eccentric exercise in human skeletal muscle. *Int. J. Sport. Nutr. Exerc. Metab*, 20, 181–190.
- Harris, J. A., & Benedict, F. G. (1918). A biometric study of human basal metabolism. *Proc. Natl. Acad. Sci. U S A*, 4(12), 370–373.
- Henriksen, E. J. (2002). Invited review: effects of acute exercise and exercise training on insulin resistance. *J. Appl. Physiol*, 93, 788–796. <http://doi.org/10.1152/japplphysiol.01219.2001>
- Hicks, G. E., Shardell, M., Alley, D. E., Miller, R. R., Bandinelli, S., Guralnik, J., ... Ferrucci, L. (2012). Absolute strength and loss of strength as predictors of mobility decline in older adults: The InCHIANTI Study. *J. Gerontol. A. Biol. Sci. Med. Sci.*, 67A(1), 66–73. <http://doi.org/10.1093/gerona/glr055>
- Higgs, C., Skinner, M., & Hale, L. (2016). Outcomes of a community-based lifestyle programme for adults with diabetes or pre-diabetes. *J. Prim. Health. Care*, 8(2), 130–139. <http://doi.org/10.1071/HC15038>
- Holloszy, J. O. (2005). Exercise-induced increase in muscle insulin sensitivity. *J. Appl. Physiol*, 99(1), 338–343. <http://doi.org/10.1152/japplphysiol.00123.2005>
- Honda, H., Igaki, M., Hatanaka, Y., Komatsu, M., Tanaka, S., Miki, T., ... Hayashi, T. (2016). Stair climbing/descending exercise for a short time decreases blood glucose levels after a meal in participants with type 2 diabetes. *BMJ. Open. Diabetes. Res. Care*, 4(1), e000232. <http://doi.org/10.1136/bmjdr-2016-000232>

- Hortensius, J., Slingerland, R. J., Kleefstra, N., Logtenberg, S. J. J., Groenier, K. H., Houweling, S. T., & Bilo, H. J. G. (2011). Self-monitoring of blood glucose: the use of the first or the second drop of blood. *Diabetes Care*, *34*(3), 556–560. <http://doi.org/10.2337/dc10-1694>
- Jelleyman, C., Yates, T., O'Donovan, G., Gray, L. J., King, J. A., Khunti, K., & Davies, M. J. (2015). The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. *Obes. Rev*, *16*(11), 942–961. <http://doi.org/10.1111/obr.12317>
- Jones, C. J., Rikli, R. E., & Beam, W. C. (1999). A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res. Q. Exerc. Sport*, *70*(2), 113–119. <http://doi.org/10.1080/02701367.1999.10608028>
- Karstoft, K., Clark, M. A., Jakobsen, I., Müller, I. A., Pedersen, B. K., Solomon, T. P. J., & Ried-Larsen, M. (2017). The effects of 2 weeks of interval vs continuous walking training on glycaemic control and whole-body oxidative stress in individuals with type 2 diabetes: a controlled, randomised, crossover trial. *Diabetologia*, *60*(3), 508–517. <http://doi.org/10.1007/s00125-016-4170-6>
- Karstoft, K., Winding, K., Knudsen, S. H., Nielsen, J. S., Thomsen, C., Pedersen, B. K., & Solomon, T. P. (2013). The effects of free-living interval-walking training on glycemic control, body composition, and physical fitness in type 2 diabetic patients. *Diabetes Care*, *36*, 228–236. <http://doi.org/10.2337/dc12-0658>
- Katz, A., Nambi, S. S., Mather, K., Baron, A. D., Follmann, D. A., Sullivan, G., & Quon, M. J. (2000). Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J. Clin. Endocrinol. Metab*, *85*(7), 2402–2410.
- Kearney, M., & Thyfault, J. P. (2016). Exercise and postprandial glycemic control in type 2 diabetes. *Curr. Diabetes. Rev.*, *12*, 1–12.
- Keenan, D. B., Mastrototaro, J. J., Zisser, H., Cooper, K. A., Raghavendhar, G., Lee, S. W., ... Shah, R. V. (2012). Accuracy of the enlite 6-day glucose sensor with guardian and veo calibration algorithms. *Diabetes. Technol. Ther*, *14*(3), 225–231. <http://doi.org/10.1089/dia.2011.0199>
- Kendzierski, D., & DeCarlo, K. J. (1991). Physical activity enjoyment scale: two validation studies. *J. Sport. Exerc. Psychol*, *13*, 50–64.
- Kirwan, J. P., Hickner, R. C., Yarasheski, K. E., Kohrt, W. M., Wiethop, B. V., & Holloszy, J. O. (1992). Eccentric exercise induces transient insulin resistance in healthy individuals. *J. Appl. Physiol*, *72*(6), 2197–2202.
- Kjøbsted, R., Munk-Hansen, N., Birk, J. B., Foretz, M., Viollet, B., Bjørnholm, M., ... Wojtaszewski, J. F. P. (2017). Enhanced muscle insulin sensitivity after contraction/exercise is mediated by AMPK. *Diabetes*, *66*, 598–612. <http://doi.org/10.2337/db16-0530>
- Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., ... Sone, H. (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*, *301*(19), 2024–2035.
- Kohl, H. W., Gordon, N. F., Villegas, J. A., & Blair, S. N. (1992). Cardiorespiratory

- fitness, glycemic status, and mortality risk in men. *Diabetes Care*, 15(2), 184–192.
- Kohnert, K. D., Heinke, P., Vogt, L., & Salzsieder, E. (2015). Utility of different glycemic control metrics for optimizing management of diabetes. *World. J. Diabetes*, 6(1), 17–29. <http://doi.org/10.4239/wjd.v6.i1.17>
- Korkiakangas, E. E., Alahuhta, M. A., & Laitinen, J. H. (2009). Barriers to regular exercise among adults at high risk or diagnosed with type 2 diabetes: a systematic review. *Health. Promot. Int*, 24(4), 416–427. <http://doi.org/10.1093/heapro/dap031>
- Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t -tests and ANOVAs. *Front. Psychol*, 4, 1–12. <http://doi.org/10.3389/fpsyg.2013.00863>
- Lambers, S., Van Laethem, C., Van Acker, K., & Calders, P. (2008). Influence of combined exercise training on indices of obesity, diabetes and cardiovascular risk in type 2 diabetes patients. *Clin. Rehabil*, 22, 483–492.
- Little, J. P., Gillen, J. B., Percival, M. E., Safdar, A., Tarnopolsky, M. A., Punthakee, Z., ... Gibala, M. J. (2011). Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *J. Appl. Physiol*, 111, 1554–1560. <http://doi.org/10.1152/japplphysiol.00921.2011>.
- Little, J. P., Jung, M. E., Wright, A. E., Wright, W., & Manders, R. J. F. (2014). Effects of high-intensity interval exercise versus continuous moderate-intensity exercise on postprandial glycemic control assessed by continuous glucose monitoring in obese adults. *Appl. Physiol. Nutr. Metab*, 39(7), 835–841. <http://doi.org/10.1139/apnm-2013-0512>
- Liubaoerjijin, Y., Terada, T., Fletcher, K., & Boulé, N. G. (2016). Effect of aerobic exercise intensity on glycemic control in type 2 diabetes: a meta-analysis of head-to-head randomized trials. *Acta. Diabetol*, 53(5), 769–781. <http://doi.org/10.1007/s00592-016-0870-0>
- Loy, S. F., Conley, L. M., Sacco, E. R., Vincent, W. J., Holland, G. J., Sletten, E. G., & Trueblood, P. R. (1994). Effects of stairclimbing on VO<sub>2</sub>max and quadriceps strength in middle-aged females. *Med. Sci. Sports. Exerc*, 26(2), 241–247.
- MacLeod, S. F., Terada, T., Chahal, B. S., & Boulé, N. G. (2013). Exercise lowers postprandial glucose but not fasting glucose in type 2 diabetes: a meta-analysis of studies using CGM. *Diabetes. Metab. Res. Rev*, 29, 593–603. <http://doi.org/10.1002/dmrr>
- Martinez, N., Kilpatrick, M. W., Salomon, K., Jung, M. E., & Little, J. P. (2015). Affective and enjoyment responses to high-intensity interval training in overweight-to-obese and insufficiently active adults. *J. Sport. Exerc. Psychol*, 37(2), 138–149.
- Mendes, R., Sousa, N., Themudo-Barata, J., & Reis, V. (2016). Impact of a community-based exercise programme on physical fitness in middle-aged and older patients with type 2 diabetes. *Gac. Sanit*, 30(3), 215–220.
- Monnier, L., & Colette, C. (2011). Glycemic variability: Can we bridge the divide between controversies? *Diabetes Care*, 34, 1058–1059. <http://doi.org/10.2337/dc11-0071>
- Monnier, L., Colette, C., Dunseath, G. J., & Owens, D. R. (2007). The loss of

- postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care*, 30(2), 263–269. <http://doi.org/10.2337/dc06-1612>
- Monnier, L., Colette, C., & Owens, D. R. (2008). Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it? *J. Diabetes. Sci. Technol*, 2(6), 1094–1100. <http://doi.org/10.1177/193229680800200618>
- Monnier, L., Mas, E., Ginet, C., Michel, F., Villon, L., Cristol, J. P., & Colette, C. (2006). Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*, 295(14), 1681–1687.
- Morrato, E. H., Hill, J. O., Wyatt, H. R., Ghushchyan, V., & Sullivan, P. W. (2007). Physical activity in U.S. adults with diabetes and at risk for developing diabetes, 2003. *Diabetes Care*, 30, 203–209. <http://doi.org/10.2337/dc06-1128>
- Moura, B. P., Amorim, P. R., Silva, B. P., Franceschini, S. C., Reis, J. S., & Marins, J. C. (2014). Effect of a short-term exercise program on glycemic control measured by fructosamine test in type 2 diabetes patients. *Diabetol. Metab. Syndr*, 6, 1–6. <http://doi.org/10.1186/1758-5996-6-16>
- Nalysnyk, L., Hernandez-Medina, M., & Krishnarajah, G. (2010). Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. *Diabetes. Obes. Metab*, 12, 288–298. <http://doi.org/10.1111/j.1463-1326.2009.01160.x>
- Newsom, S. A., Everett, A. C., Hinko, A., & Horowitz, J. F. (2013). A single session of low-intensity exercise is sufficient to enhance insulin sensitivity into the next day in obese adults. *Diabetes Care*, 36, 2516–2522. <http://doi.org/10.2337/dc12-2606>
- Paschalis, V., Theodorou, A. A., Panayiotou, G., Kyparos, A., Patikas, D., Grivas, G. V., ... Vrabas, I. S. (2013). Stair descending exercise using a novel automatic escalator: effects on muscle performance and health-related parameters. *PLoS ONE*, 8(2), 1–10. <http://doi.org/10.1371/journal.pone.0056218>
- Poole, D. C., & Jones, A. M. (2017). Measurement of the maximum oxygen uptake VO<sub>2</sub>max: VO<sub>2</sub>peak is no longer acceptable. *J. Appl. Physiol*, 122, 997–1002. <http://doi.org/10.1152/japplphysiol.01063.2016>
- Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*, 28, 916–931. [http://doi.org/10.1016/S0306-4530\(02\)00108-7](http://doi.org/10.1016/S0306-4530(02)00108-7)
- Revdal, A., Hollekim-Strand, S. M., & Ingul, C. B. (2016). Can time efficient exercise improve cardiometabolic risk factors in type 2 diabetes? A pilot study. *J. Sports. Sci. Med*, 15(2), 308–313.
- Riddell, M., & Perkins, B. A. (2009). Exercise and glucose metabolism in persons with diabetes mellitus: perspectives on the role for continuous glucose monitoring. *J. Diabetes. Sci. Technol*, 3(4), 914–923.
- Rikli, R. E., & Jones, C. J. (1998). The reliability and validity of a 6-Minute Walk Test as a measure of physical endurance in older adults. *J. Aging. Phys. Act*, 6, 363–375.
- Rizza, R. A. (2010). Pathogenesis of fasting and postprandial hyperglycemia in type 2

- diabetes: implications for therapy. *Diabetes*, 59, 2697–2707.  
<http://doi.org/10.2337/db10-1032>
- Roberts, C. K., Little, J. P., & Thyfault, J. P. (2013). Modification of insulin sensitivity and glycemic control by activity and exercise. *Med. Sci. Sports. Exerc*, 45(10), 1868–1877. <http://doi.org/10.1249/MSS.0b013e318295cddb>
- Rodbard, D. (2011). Glycemic variability: measurement and utility in clinical medicine and research — one viewpoint. *Diabetes. Technol. Ther*, 13(11), 1–4.  
<http://doi.org/10.1089/dia.2011.0104>
- Rossetti, P., Bondia, J., Vehi, J., & Fanelli, C. G. (2010). Estimating plasma glucose from interstitial glucose: the issue of calibration algorithms in commercial continuous glucose monitoring devices. *Sensors*, 10, 10936–10952.  
<http://doi.org/10.3390/s101210936>
- Sarafidis, P. A., Lasaridis, A. N., Nilsson, P. M., Pikilidou, M. I., Stafilas, P. C., Kanaki, A., ... Bakris, G. L. (2007). Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes. *J. Hum. Hypertens*, 21, 709–716. <http://doi.org/10.1038/sj.jhh.1002201>
- Service, F. J., Molnar, G. D., Rosevear, J. W., Ackerman, E., Gatewood, L. C., & Taylor, W. F. (1970). Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes*, 19(9), 644–655.
- Shaban, N., Kenno, K. A., & Milne, K. J. (2014). The effects of a 2 week modified high intensity interval training program on the homeostatic model of insulin resistance (HOMA-IR) in adults with type 2 diabetes. *J. Sports. Med. Phys. Fitness*, 54(2), 203–209.
- Sigal, R. J., Armstrong, M. J., Colby, P., Kenny, G. P., Plotnikoff, R. C., Reichert, S. M., & Riddell, M. C. (2013). Clinical practice guidelines: physical activity and diabetes. *Can. J. Diabetes*, 37, S40–S44. <http://doi.org/10.1016/j.jcjd.2013.01.018>
- Takaishi, T., Imaeda, K., Tanaka, T., Moritani, T., & Hayashi, T. (2012). A short bout of stair climbing–descending exercise attenuates postprandial hyperglycemia in middle-aged males with impaired glucose tolerance. *Appl. Physiol. Nutr. Metab*, 37(1), 193–196. <http://doi.org/10.1139/h11-140>
- Terada, T., Friesen, A., Chahal, B. S., Bell, G. J., McCargar, L. J., & Boulé, N. G. (2013a). Exploring the variability in acute glycemic responses to exercise in type 2 diabetes. *J. Diabetes. Res*, 2013, 591574.
- Terada, T., Friesen, A., Chahal, B. S., Bell, G. J., McCargar, L. J., & Boulé, N. G. (2013b). Feasibility and preliminary efficacy of high intensity interval training in type 2 diabetes. *Diabetes. Res. Clin. Pract*, 99(2), 120–129.  
<http://doi.org/10.1016/j.diabres.2012.10.019>
- Terada, T., Wilson, B. J., Myette-Côté, E., Kuzik, N., Bell, G. J., McCargar, L. J., & Boulé, N. G. (2016). Targeting specific interstitial glycemic parameters with high-intensity interval exercise and fasted-state exercise in type 2 diabetes. *Metab. Clin. Exp*, 65(5), 599–608. <http://doi.org/10.1016/j.metabol.2016.01.003>
- The Diabetes Research in Children Network (DIRECNET) Study Group. (2003). A multicenter study of the accuracy of the one touch® ultra® home glucose meter in children with type 1 diabetes. *Diabetes. Technol. Ther*, 5(6), 933–941.

- Thomas, N., Alder, E., & Leese, G. P. (2004). Barriers to physical activity in patients with diabetes. *Postgrad. Med. J*, 80, 287–291.  
<http://doi.org/10.1136/pgmj.2003.010553>
- Tjønnå, A. E., Rognmo, Ø., Bye, A., Stølen, T. O., & Wisløff, U. (2011). Time course of endothelial adaptation after acute and chronic exercise in patients with metabolic syndrome. *J. Strength. Cond. Res*, 25(9), 2552–2558.
- Tuomilehto, J., Lindstrom, J., Eriksson, J. G., Valle, T. T., Hamalainen, H., & Ilanne-Parikka, P. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.*, 344(18), 1343–1350. <http://doi.org/10.1056/NEJM200105033441801>
- Umpierre, D., Ribeiro, P. A. B., Kramer, C. K., Leitao, C. B., Zucatti, A. T. N., Azevedo, M. J., ... Schaan, B. D. (2011). Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*, 305(17), 1790–1799.  
<http://doi.org/10.1001/jama.2011.576>
- van Dijk, J. W., & van Loon, L. J. C. (2015). Exercise strategies to optimize glycemic control in type 2 diabetes: a continuous glucose monitoring perspective. *Diabetes. Spectr*, 28(1), 24–31. <http://doi.org/10.2337/diaspect.28.1.24>
- Wei, M., Gibbons, L. W., Kampert, J. B., Nichaman, M. Z., & Blair, S. N. (2000). Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with T2D. *Ann. Intern. Med*, 132(8), 605–611.



## 2.6 TABLES

TABLE 1. Participant characteristics.

Variable	S01	S02	S03	S04	S05	Mean
Sex	F	M	F	M	M	
Age (y)	21	53	56	70	60	52 ± 18
Body Mass (kg)	91	83	102	74	90	88 ± 11
BMI (kg/m <sup>2</sup> )	37	26	36	25	30	31 ± 5
HbA1c (%)	6.8	7.8	6.3	6.1	6.2	6.6 ± 0.7
Fasting blood glucose (mmol/L)	6.5	10.1	6.4	8.3	6.6	7.6 ± 1.6
Duration of T2D (y)	0.7	24	0.6	4	10	7.9 ± 9.8
Medications:						
Metformin	Y	Y	Y	Y	Y	
SGLT2 Inhibitor (Canagliflozin)		Y				
Gliclazide (Diamicron)				Y		
DPP-4 Inhibitor (Sitagliptin)		Y			Y	
ACE Inhibitor		Y			Y	
Statin		Y			Y	
Analgesic (Pregabalin)			Y			
Proton Pump Inhibitor			Y		Y	

Values are means ± SD. BMI, body mass index. HbA1c, glycated hemoglobin level.

TABLE 2. Characterizing the acute HR response to a single session of brief, intermittent stair climbing exercise.

<b>Parameter</b>	<b>BPM</b>	<b>% of age predicted max</b>
Bout 1	124 ± 13	72 ± 4
Bout 2	135 ± 17	78 ± 4
Bout 3	137 ± 15	80 ± 5
Bout <sub>mean</sub>	132 ± 7	77 ± 4
Peak <sub>mean</sub>	148 ± 18	86 ± 4
Total 10 min	125 ± 12	73 ± 4

Values are means ± SD; n=4.

TABLE 3. Acute exercise responses during a single session of brief, intermittent stair climbing exercise.

<b>Bout</b>	<b>Stairs Climbed*</b>	<b>Work Output* (kJ)</b>	<b>Peak HR* (bpm)</b>	<b>RPE*</b>
1	59 ± 14	10.1 ± 1.7	139 ± 18	3.4 ± 1.5
2	50 ± 10	8.7 ± 0.8	144 ± 19	4.4 ± 1.5 <sup>#</sup>
3	52 ± 8	9.0 ± 0.6	147 ± 19 <sup>#</sup>	5.2 ± 1.6 <sup>#</sup>

Values are means ± SD; n=5 for all measures except peak HR, where n=4. \* Main effect for time across bouts ( $p < 0.05$ ). <sup>#</sup> Significantly different than previous bouts ( $p < 0.05$ ).

TABLE 4. Acute assessment of glycemic control parameters measured by CGM at baseline over a 24-h non-exercise control day versus the 24-h period following brief, intermittent stair climbing exercise.

Variable	Control	Exercise	P value	d <sub>z</sub>
Mean 24-h glucose (mmol/L)	7.8 ± 1.4	7.9 ± 0.6	0.38	0.15
Time spent > 10 mmol/L (min)	163 ± 211	152 ± 159	0.42	0.10
SD (mmol/L)	1.7 ± 0.5	1.4 ± 0.5*	0.02	1.31
MAGE (mmol/L)	4.4 ± 1.5	3.5 ± 1.0*	0.02	1.46
Abs AUC <sub>Breakfast</sub>	1135 ± 173	1243 ± 112	0.18	0.46
Abs AUC <sub>Lunch</sub>	1115 ± 279	992 ± 179	0.08	0.77
Abs AUC <sub>Dinner</sub>	1027 ± 157	1052 ± 211	0.28	0.28
Sum of Abs AUC	3277 ± 538	3287 ± 459	0.48	0.03
iAUC <sub>Breakfast</sub>	117 ± 106	132 ± 50	0.41	0.11
iAUC <sub>Lunch</sub>	102 ± 84	80 ± 88	0.17	0.48
iAUC <sub>Dinner</sub>	54 ± 29	62 ± 59	0.39	0.14
Sum of iAUC	274 ± 154	273 ± 139	0.49	0.01
PPS <sub>Breakfast</sub> (mmol/L)	3.1 ± 0.7	3.8 ± 1.5	0.22	0.38
PPS <sub>Lunch</sub> (mmol/L)	3.0 ± 2.0	2.6 ± 1.9	0.22	0.38
PPS <sub>Dinner</sub> (mmol/L)	2.0 ± 0.3	2.4 ± 0.9	0.18	0.46

**Note:** Values are mean ± SD (n=5). All per-meal values are measured in mmol/L x 120 min while the sum of post-meal values are reported as mmol/L x 6 hr. \*p < 0.05 vs. control. (d<sub>z</sub>, Cohen's d for repeated measures; MAGE, mean amplitude of glycemic excursions; Abs, absolute; AUC, area under the curve; iAUC, incremental area under the curve; PPS, postprandial spike.)

TABLE 5. Weekly stair climbing characteristics.

Variable	Week 1	Week 3	Week 6
Time spent ascending (s)	26 ± 4	22 ± 4	24 ± 3
Time spent descending (s)	34 ± 4	37 ± 3	37 ± 3
Stairs climbed (stairs/bout)*	54 ± 9	54 ± 10	58 ± 10
Height climbed (m/bout)*	11.1 ± 1.8	11.1 ± 2.1	11.9 ± 2.1
Climbing rate (m/s)	0.435 ± 0.03	0.496 ± 0.03	0.504 ± 0.05
Work output (kJ)*	9.36 ± 0.6	9.31 ± 0.8	9.98 ± 1.1
Mean power (W)	394 ± 52	445 ± 59	447 ± 52
Relative power (W/kg)	4.53 ± 0.31	5.15 ± 0.63	5.16 ± 0.38
Fatigue index per bout (%)	11.6 ± 16.3	15.5 ± 4.4	7.8 ± 10.4

**Note:** Values are means ± SD (n=5) and based on a single session during weeks 1, 3 and 6. Stair height = 0.205m; 10 stairs per flight. Mean power is an average of the power generated during the first and last ascent. Power = F (body mass (kg) x 9.81m/s<sup>2</sup>) x d (height of stair x number of stairs)/(time of ascent (s)). \* Main effect for time across a representative session in weeks 1, 3, and 6 ( $p \leq 0.05$ ).

TABLE 6. Training-induced changes in glycemic control parameters following 6-wk of brief, intermittent stair climbing exercise.

Variable	PRE	POST	P value	d <sub>z</sub>
<b>Continuous Glucose Monitoring</b>				
Mean 24-h glucose (mmol/L)	7.8 ± 1.4	8.1 ± 0.9	0.15	0.53
Time spent > 10 mmol/L (min)	163 ± 211	165 ± 211	0.47	0.04
SD (mmol/L)	1.7 ± 0.5	1.4 ± 0.5	0.12	0.61
MAGE (mmol/L)	4.4 ± 1.5	3.4 ± 0.7	0.06	0.89
Abs AUC <sub>Breakfast</sub>	1135 ± 173	1223 ± 239	0.24	0.34
Abs AUC <sub>Lunch</sub>	1115 ± 279	1000 ± 365*	0.03	1.24
Abs AUC <sub>Dinner</sub>	1027 ± 157	1067 ± 198	0.18	0.46
Sum of Abs AUC	3277 ± 538	3290 ± 704	0.46	0.05
iAUC <sub>Breakfast</sub>	117 ± 106	102 ± 83	0.37	0.16
iAUC <sub>Lunch</sub>	102 ± 84	65 ± 78*	0.01	2.11
iAUC <sub>Dinner</sub>	54 ± 29	77 ± 39	0.18	0.46
Sum of iAUC	274 ± 154	244 ± 134	0.33	0.21
PPS <sub>Breakfast</sub> (mmol/L)	3.1 ± 0.7	3.4 ± 2.0	0.39	0.14
PPS <sub>Lunch</sub> (mmol/L)	3.0 ± 2.0	1.8 ± 1.7*	0.01	1.83
PPS <sub>Dinner</sub> (mmol/L)	2.0 ± 0.3	2.1 ± 0.7	0.33	0.22
<b>Fasting Blood Results</b>				
Glucose (mmol/L)	7.6 ± 1.6	7.5 ± 1.2	0.43	0.08
Fructosamine (µmol/L)	253 ± 70	259 ± 36	0.38	0.14
Insulin (pmol/L)	110 ± 66	93 ± 46	0.10	0.69
QUICKI	0.307 ± 0.02	0.312 ± 0.02	0.09	0.74

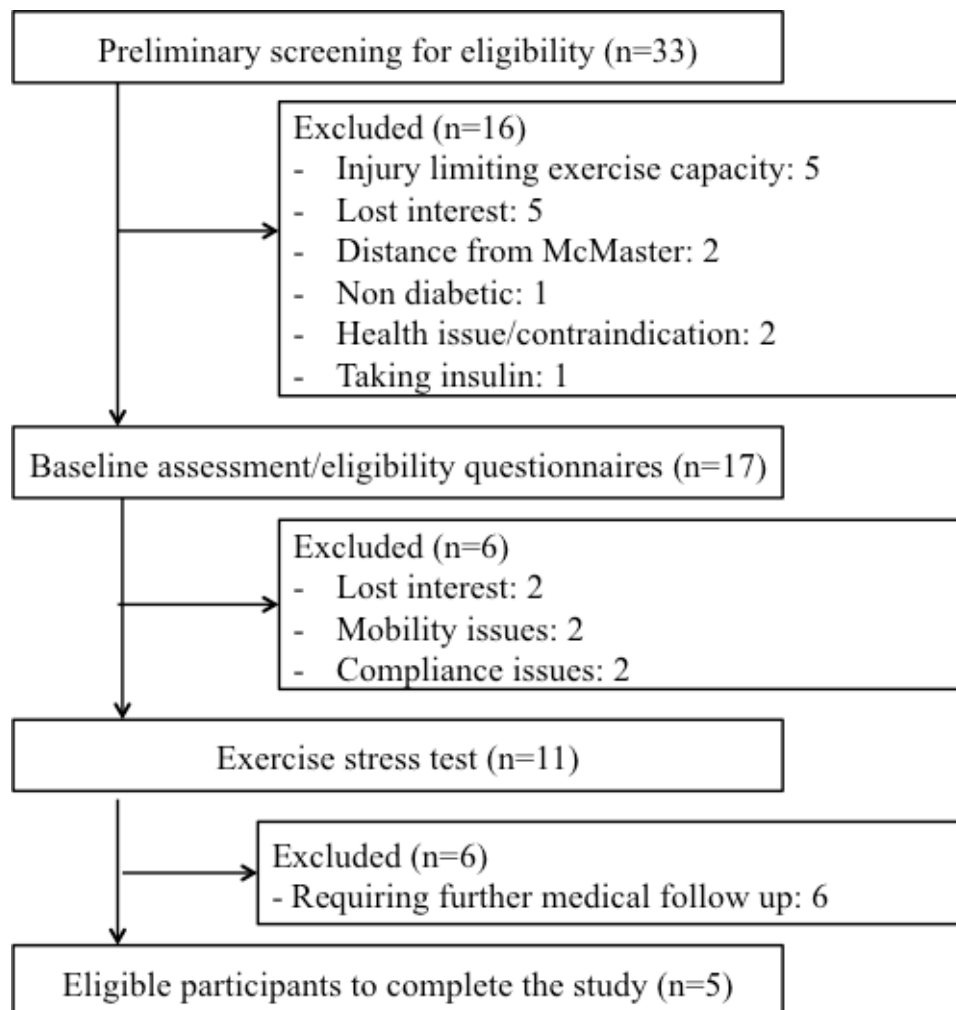
**Note:** Values are mean ± SD (n=5). CGM parameters reflect a 24-h non-exercise control day before training (PRE) versus a diet-matched non-exercise control day following 6-wk of stair climbing (POST). The per-meal values are measured in mmol/L x 120 min while the sum of post-meal values are reported as mmol/L x 6 hr. \*p < 0.05 vs. PRE. (d<sub>z</sub>, Cohen's d for repeated measures; MAGE, mean amplitude of glycemic excursions; Abs, absolute; AUC, area under the curve; iAUC, incremental area under the curve; PPS, postprandial spike; QUICKI, quantitative insulin sensitivity check index).

TABLE 7. Cardiometabolic and performance outcomes following 6-wk of brief, intermittent stair climbing exercise.

Variable	PRE	POST	P value	d <sub>z</sub>
<b>Performance Outcomes</b>				
6MWT (m)	575 ± 80	566 ± 78	0.25	0.33
30 sec chair stand (stands)	15 ± 4	14 ± 2	0.35	0.19
<b>Resting Cardiovascular Measures</b>				
SBP (mmHg)	115 ± 12	111 ± 8	0.23	0.36
DBP (mmHg)	77 ± 8	79 ± 5	0.29	0.27
HR (bpm)	77 ± 8	78 ± 6	0.38	0.14
<b>Body Composition</b>				
Fat Free Mass (kg)	54.1 ± 6.2	54.1 ± 7.2	0.50	0.01
Body Fat (%)	37.1 ± 11.6	36.4 ± 13.4	0.27	0.30

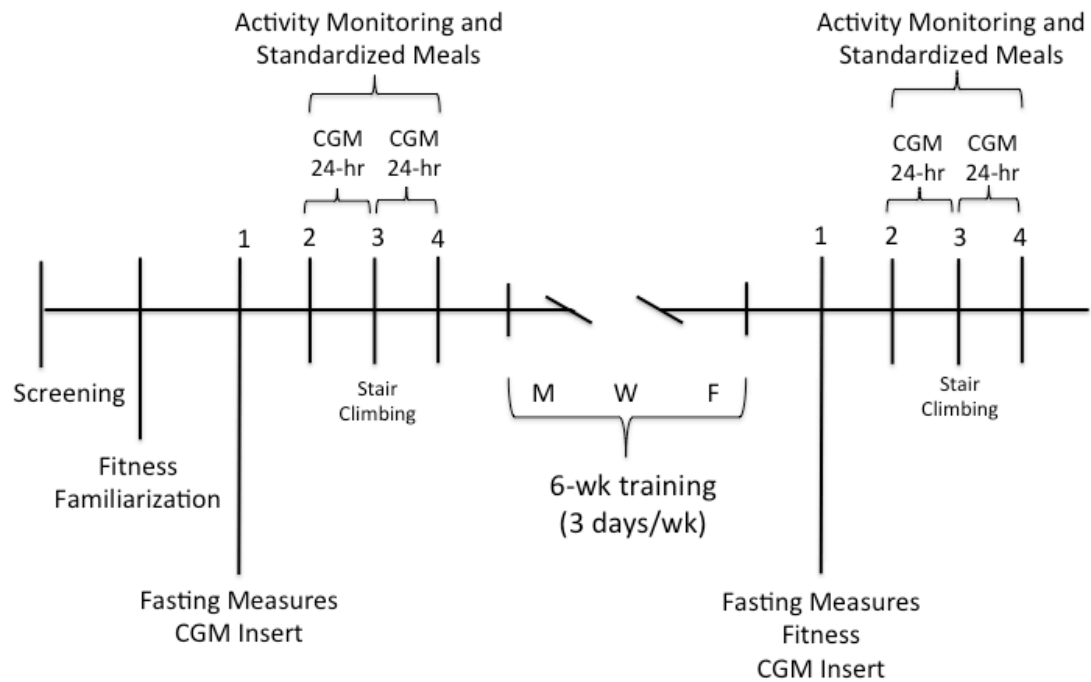
**Note:** Values are mean ± SD (n=5). (d<sub>z</sub>, Cohen's d for repeated measures; 6MWT, 6-minute walk test; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.)

## 2.7 FIGURES

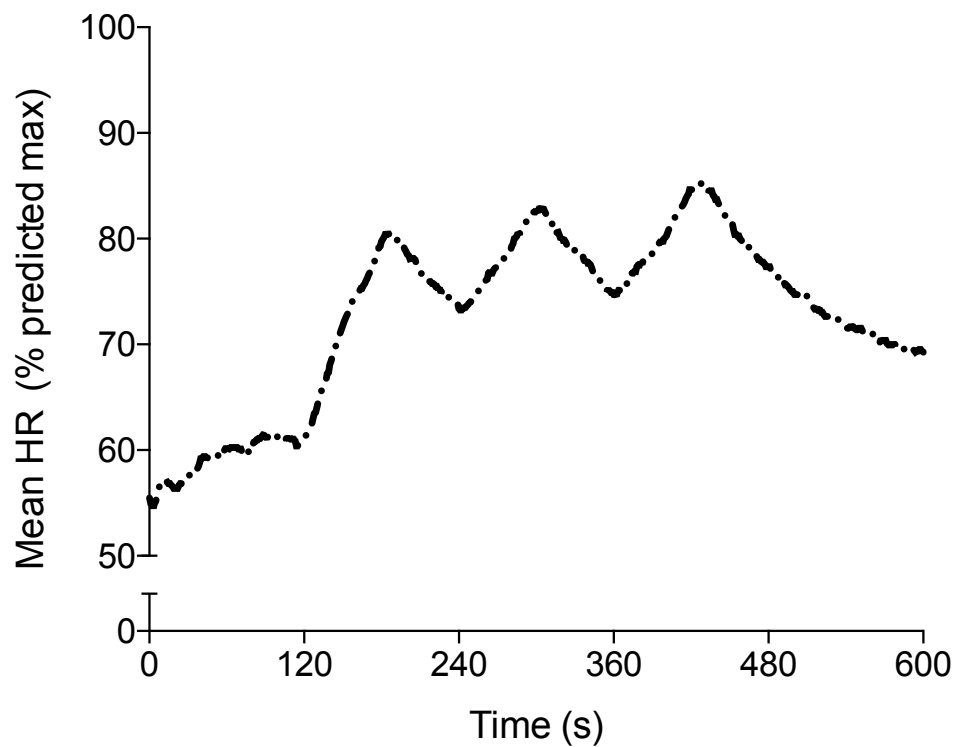


**Figure 1. Study flow diagram detailing participant recruitment.**

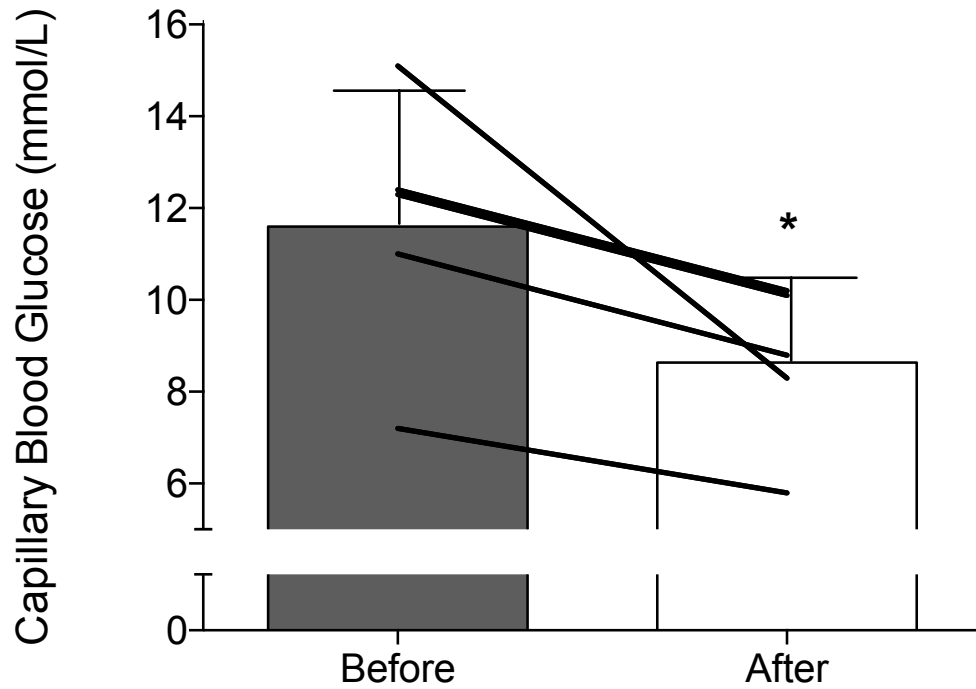




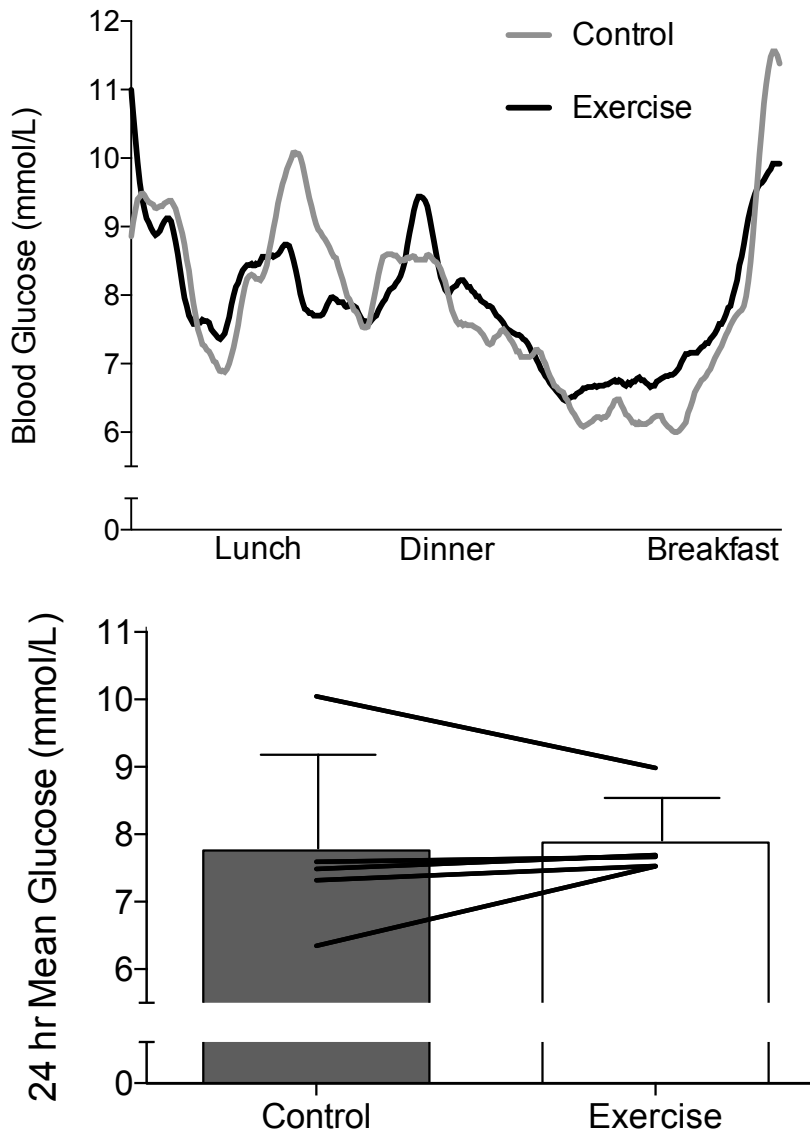
**Figure 2. Overview of the experimental design spanning across ~ a 9-wk period.** (CGM, continuous glucose monitoring).



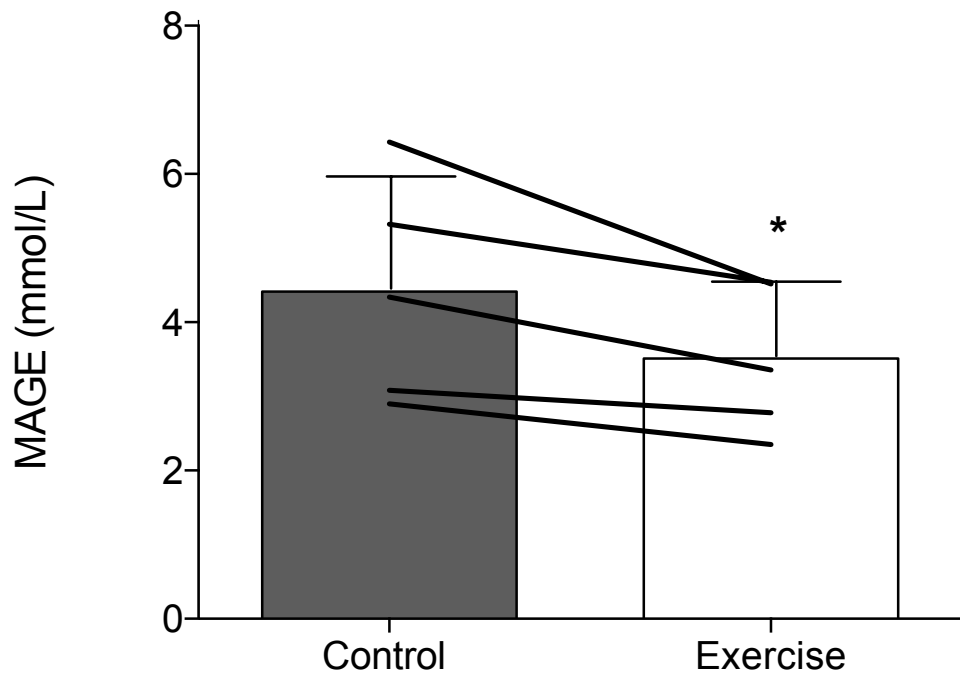
**Figure 3. Relative mean HR response to the acute 3 x 1-min stair climbing protocol.** Values are from the acute session of stair climbing exercise, anchored to age-predicted heart rate maximum values (n=4).



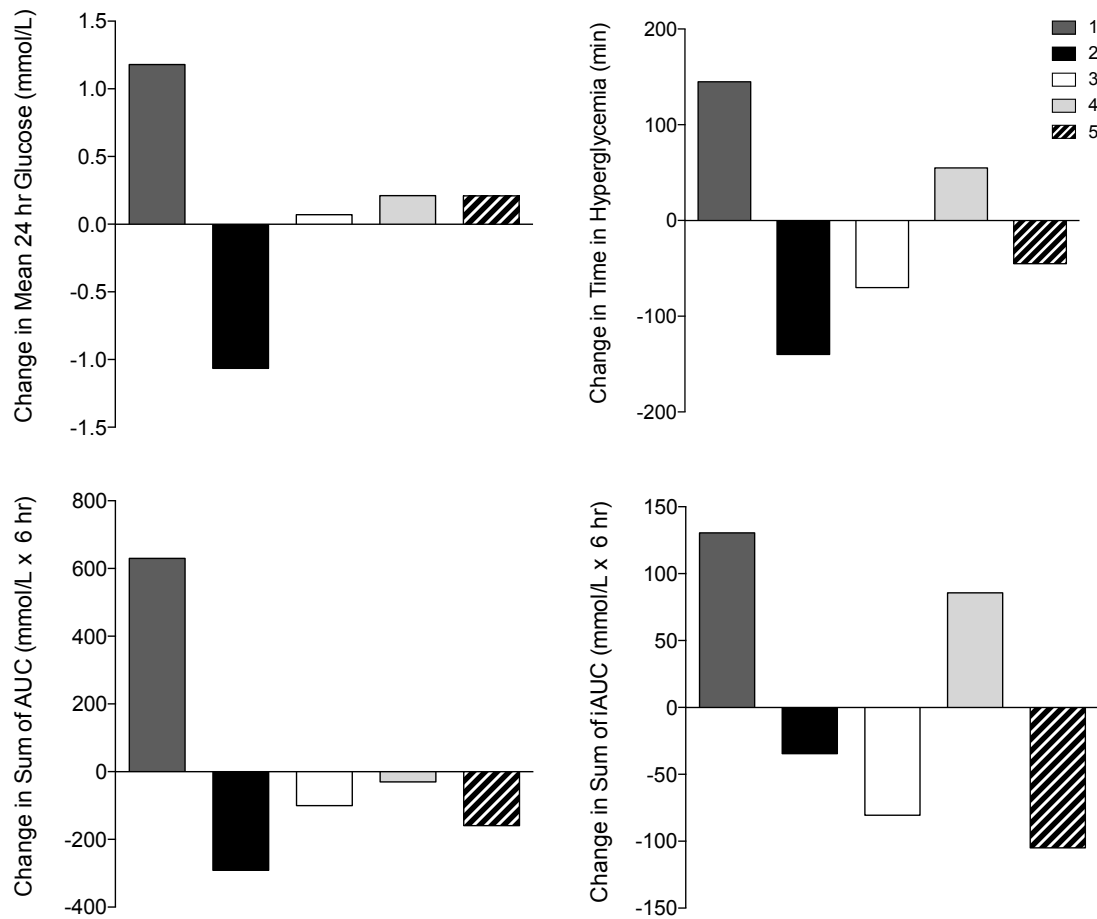
**Figure 4. Capillary blood glucose in the 5-min period following a single session of brief, intermittent stair climbing exercise.** Measured ~ 10-min prior to (Before) and in the 5-min period following exercise (After). Each line represents an individual participant. Values are mean  $\pm$  SD. \* $p < 0.05$  vs. Before.



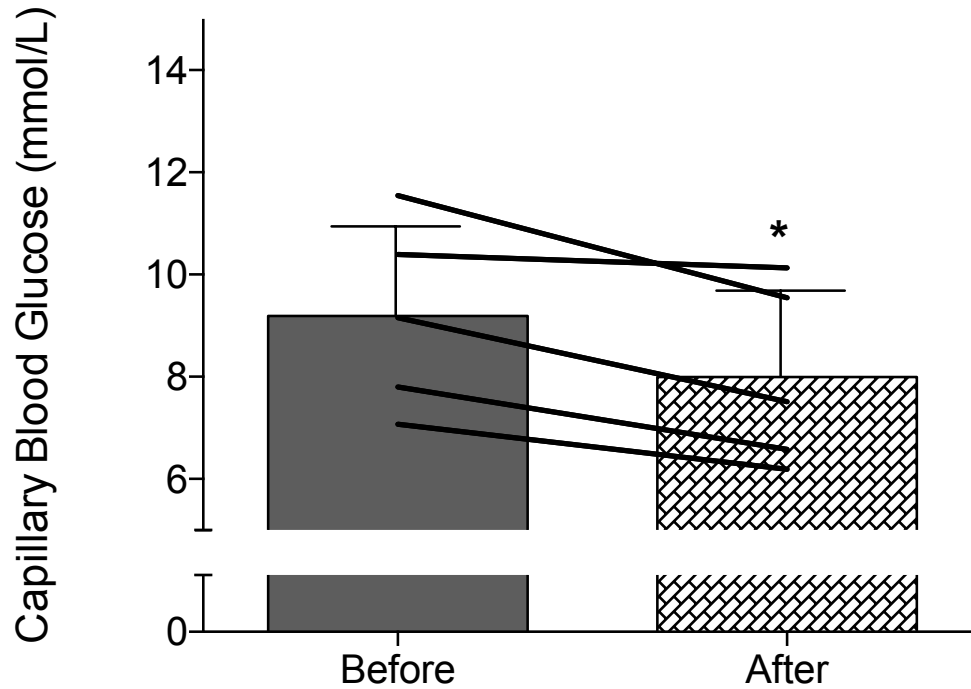
**Figure 5. 24-h mean glucose following a single session of brief, intermittent stair climbing exercise.** Average CGM data (upper panel) across a diet-matched 24-h non-exercise day (Control) and in the 24-h period following a single session of stair climbing (Exercise). Each line represents an individual participant (lower panel). Values are mean  $\pm$  SD.



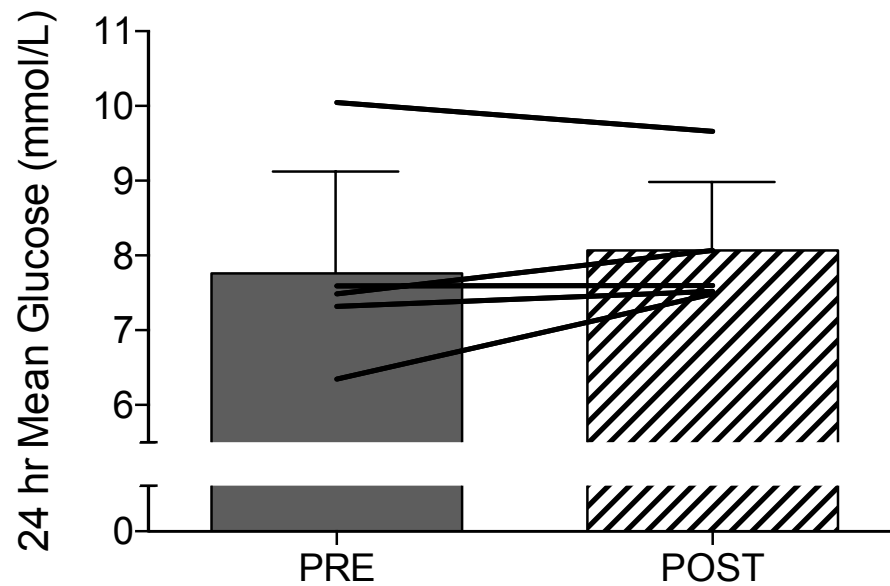
**Figure 6. Glycemic variability as measured by mean amplitude of glycemic excursions (MAGE) in the 24-h period following a single session of brief, intermittent stair climbing exercise.** Measured across a diet-matched 24-h non-exercise day (Control) and in the 24-h period following a single session of stair climbing (Exercise) using CGM. Each line represents an individual participant. Values are mean  $\pm$  SD. \* $p < 0.05$  vs. Control.



**Figure 7. Individual 24-h glycemic response across primary outcomes following a single session of brief, intermittent stair climbing exercise.** Each bar represents an individual participant, presented in participant order for each panel (see legend). The acute change in primary glycemic control outcomes measured by CGM during a diet-matched 24-h non-exercise day compared to the 24-h period following a single session of stair climbing. The post-meal responses to breakfast, lunch, and dinner were added together to calculate the sum of the absolute and incremental area under the curve (AUC) (lower panels).

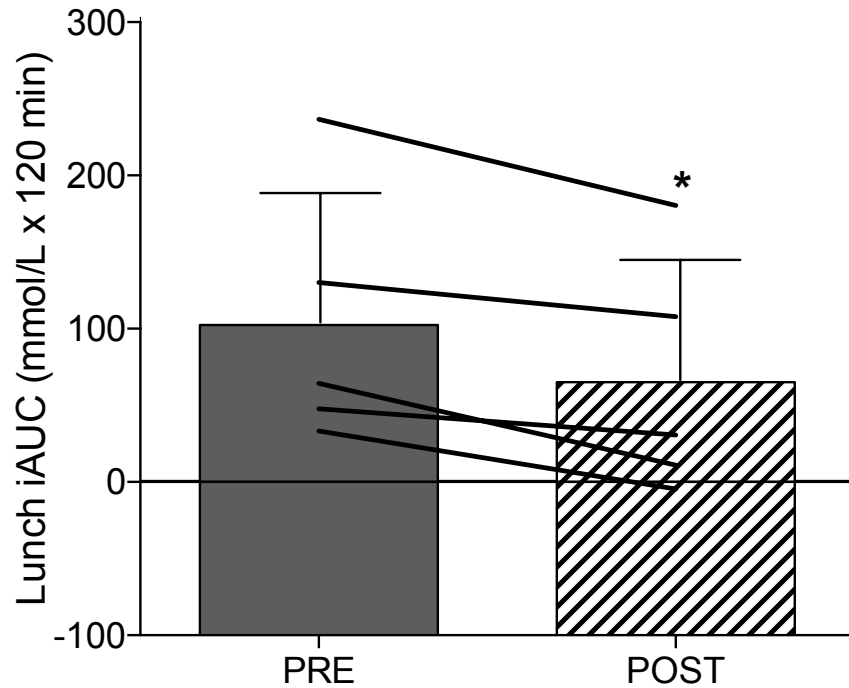


**Figure 8. Capillary blood glucose in the 5-min period following brief, intermittent stair climbing exercise across the training period.** Measured ~ 10-min prior to (Before) and in the 5-min period following each exercise session (After) across 6 weeks of training. Each line represents the mean values across 18 training sessions for an individual participant. Values are mean  $\pm$  SD. \* $p < 0.05$  vs. Avg Before.

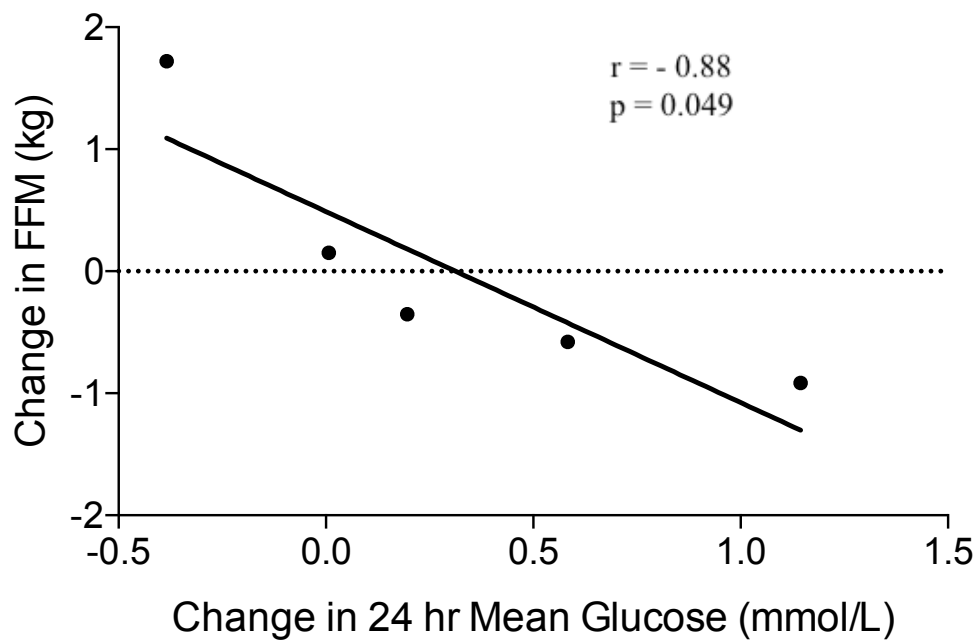


**Figure 9. 24-h mean glucose following 6-wk of brief, intermittent stair climbing training.** Measured across a 24-h non-exercise day before (PRE) and a diet-matched non-exercise day after 6 weeks of stair climbing training (POST). Each line represents an individual participant. Values are mean  $\pm$  SD.





**Figure 10. Post-meal glucose response to lunch following 6-wk of brief, intermittent stair climbing training.** Presented as the lunch incremental area under the curve (iAUC). Measured across a 24-h non-exercise day before (PRE) and a diet-matched non-exercise day after 6 weeks of stair climbing training (POST). Each line represents an individual participant. Values are mean  $\pm$  SD. \* $p < 0.05$  vs. PRE.



**Figure 11. Relationship between change in fat free mass (FFM) and change in 24-h mean glucose following 6-wk of brief, intermittent stair climbing training.**

## **APPENDICES**

## **APPENDIX A: PARTICIPANT INFORMED CONSENT**

### **Title of Study**

Does brief intermittent stair climbing exercise improve blood glucose control in individuals with type 2 diabetes?

### **Locally Responsible Investigator and Principal Investigator**

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### **Funding Source**

McMaster Internally Sponsored Research Grant

### **OVERVIEW**

You are being invited to participate in a research project because you are an adult with type 2 diabetes who is not being treated with insulin. Other reasons that might make you suited, or not suited, to take part in the study are described in this document. In order to decide whether or not you want to be part of this research study, you should understand what is involved and the potential risks and benefits. This form gives you detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate. Please

take your time to make your decision. Feel free to discuss it with your friends and family and/or your family physician.

### **WHY IS THIS RESEARCH BEING DONE?**

Individuals with type 2 diabetes have high blood glucose and may develop health complications including heart disease, kidney disease, and nerve damage. Exercise is beneficial for people with type 2 diabetes and may help to improve blood glucose control. Despite this benefit, the majority of people, including those with type 2 diabetes, do not engage in regular physical activity. The most frequent cited barrier to regular exercise participation is “lack of time”. Growing evidence suggests that a type of exercise called interval training may be a time-efficient way to improve health and fitness, including in people with type 2 diabetes. Much of this research has been conducted in a laboratory setting, which required specialized equipment that may not be accessible for the general population. There is a need to try and translate these findings to the “real world”, and as such, a goal of the present study is to examine the effect of stair climbing exercise on blood sugar control in people with type 2 diabetes.

Researchers rely on single measures to describe the effects of exercise on blood glucose (sugar) control. For example, they measure glucose from a finger stick blood sample before and after exercise. The development of continuous glucose monitoring (CGM) technology has provided researchers with a better tool to examine different aspects of glucose control. Small portable CGM devices can be worn for several days at a time, which provide blood sugar readings every 5 minutes. A small CGM sensor is placed on the skin of the abdomen, with a small and flexible filament that is inserted under the skin and held in place by a piece of tape. Any slight discomfort that may be felt when the device is initially placed typically subsides shortly after insertion, allowing individuals to go about their daily activities without any noticeable interference. CGM will be used in the current study to monitor changes in blood glucose following exercise.

### **WHAT IS THE PURPOSE OF THE STUDY?**

The main purpose is to examine the effect of brief intermittent stair climbing exercise on blood sugar control in people with type 2 diabetes. We will examine the effects of an acute (single) session of exercise and also potential changes that occur after a 6-week training intervention.

### **WHO CAN PARTICIPATE IN THIS STUDY?**

You may be eligible to participate in this study if:

- You are an adult who has been diagnosed with type 2 diabetes for at least 6 months
- You have an A1C less than 9%

- You have never been diagnosed with heart disease, stroke, kidney disease (or any other chronic condition that may impact your ability to exercise)
- You are able to understand and comply with study requirements (e.g., attend visits during the day and eat the meals that will be provided to you)

### **WHO SHOULD NOT PARTICIPATE IN THIS STUDY?**

You will not be eligible to participate in this study if:

- If your doctor has informed you that you have a heart condition and should only do physical activity recommended by a doctor.
- If you feel pain in your chest when you perform any physical activity.
- If you have had chest pain while resting (no physical activity) in the past month.
- If you lose your balance or consciousness because of dizziness.
- If you have a bone or joint problem (for example, back, knee, or hip) that could be made worse by a change in your physical activity.
- If you are currently pregnant or planning on becoming pregnant in the next 3 months
- If you have a history of hypoglycemia (low blood glucose) during activity or sleep
- You are currently taking exogenous insulin
- If your most recent hemoglobin A1C result was over 9.0%
- You have previously had a heart attack or stroke
- You have been diagnosed with peripheral neuropathy
- If you know of any other reason why you should not do physical activity

### **WHAT DOES THE STUDY INVOLVE?**

This study involves repeated visits to several different locations on the McMaster University campus. Initially, you will visit a laboratory in the Ivor Wynne Centre (IWC) and a clinic in the Diabetes Care and Research Program. During the 6-week training period, you will report to the laboratory in IWC 3 times per week to complete the stair climbing interval exercise, for a total of 18 training visits. Your total time commitment, including all pre- and post- testing measurements, will be about 18-20 hours over a 9-week period.

#### **VISIT 1: PARTICIPANT SCREENING AND ANTHROPOMETRIC MEASURES**

You will come to room AB101 in IWC to have details of the study fully explained, including potential risks, benefits, and any questions you may have. You will be asked to read and sign the consent form, provided you wish to participate in the study. You will complete a couple of questionnaires to assess medical and exercise history, and we will take some anthropometric measures such as height, weight, and waist/hip circumference. We will also take a resting blood pressure and heart rate measurement. At this visit, the details of the 12-lead ECG exercise test will be explained as a quick and relatively simple way to ensure that you are suitable to participate in vigorous exercise. You will be given

instructions on where and when the procedure will take place. After being cleared by a physician to participate in vigorous exercise based on the results from this test, the actual study will involve the following series of visits.

### Baseline Testing

#### **VISIT 2: FUNCTIONAL FITNESS AND EXERCISE FAMILIARIZATION**

You will return to IWC AB101 to complete two measures of functional fitness as a part of a short physical performance battery. This first 6-minute walk test (6MWT) will serve as a practice session, allowing you to become more comfortable with covering as much distance as possible while walking in 6 minutes. The second task will require you to rise to a full stand from a chair with your arms across your chest as many times as possible in 30 seconds (see more details below). We will then teach you how to complete the stair climbing protocol and how to use the rating of perceived exertion (RPE) scale to assess how hard you are working during the exercise. You will wear a heart rate monitor strap around your chest in order to monitor your exercise intensity. Blood glucose will be monitored before and after exercise using a finger-stick measurement. This visit will last approximately 45 minutes.

#### **VISIT 3: BODY COMPOSITION AND CONTINUOUS GLUCOSE MONITORING**

Following an overnight fast, you will return to the laboratory so that we can take a fasting blood sample and measure your body composition using the BOD POD<sup>TM</sup> chamber. We will provide a breakfast meal to be consumed in the lab and have you complete the 6MWT one more time as a measure of baseline fitness. We will then attach the continuous glucose monitor (CGM) to be worn for the next 3 days. CGM is a small device that measures your blood glucose every 5 minutes. The small CGM sensor will be placed on the skin of your abdomen by a person trained by the CGM manufacturer. The CGM sensor has a small filament that is inserted under your skin with a small needle (less than 1 cm long). The needle is then removed and only the flexible filament remains under your skin. Tape will be placed over the CGM to hold it in place. A picture of the CGM is shown in the figure below. The CGM insertion should take *no more than 5 minutes*. You will be given a small booklet containing important information about the CGM, a glucose meter to take finger stick measures, meals for the next 3 days, and a food log. You will also be given a physical activity-monitoring device to wear for the next 3 days. This device is about the size of a pager and you wear it on your waistband during all waking hours of the day. This visit should last about 90 minutes.

**Figure: A continuous glucose monitor.**

**Note:** Only the flexible filament is inserted under the skin.



#### **VISIT 4: INTERVAL STAIR CLIMBING SESSION (ACUTE ASSESSMENT)**

You will first report to the laboratory and then we will proceed to the northeast stairwell of the Ivor Wynne Centre to complete the stair climbing exercise session. This stairwell has railings that can be used when necessary for support. Including warm up and cool down, the entire exercise session will last no more than 10 minutes. Heart rate and rating of perceived exertion will be recorded during this exercise session. We will monitor your blood pressure and finger stick blood glucose levels before and after exercise, as well as into recovery. You will be instructed on how to remove your CGM (similar to pulling off a Band-Aid) to be returned at the first training session. This visit will last about 45 minutes.

#### *6-week Training Intervention*

#### **VISIT 5-22: INTERVAL STAIR CLIMBING INTERVENTION**

All training sessions will be completed in the northeast stairwell of the Ivor Wynne Centre, supervised by a study investigator. You will complete the 18 training sessions over 6 weeks (3 each week). Training will begin with a 2-minute warm-up of easy walking. You will then be asked to climb up and down the stairs for 1 minute, repeated 3 times with 1 minute of rest in between each interval. Each session will conclude with a 2 minute cool down of easy walking, resulting in a total exercise session that is 10 minutes in duration. We will measure your heart rate, rating of perceived exertion (or RPE), blood pressure, and finger stick blood glucose during each session. All sessions will be about 30 minutes.

#### *Post-training Testing*

#### **VISIT 23: FUNCTIONAL FITNESS AND HEALTH MEASURES (~45 min).**

At least 72 hours following the last training session, you will return to the laboratory and we will take the same anthropometric measures taken before training. We will also take a resting blood pressure measurement. You will then complete the same two measures of functional fitness from the baseline assessment (i.e., 6MWT and 30-s chair stand). Blood glucose will be monitored before and after exercise using a finger-stick measurement. This visit will last approximately 30-45 minutes.

#### **VISIT 24: BODY COMPOSITION AND CONTINUOUS GLUCOSE MONITORING**

Following an overnight fast, you will return to the laboratory so that we can take a fasting blood sample and measure your body composition using the BOD POD™ chamber. We will then attach the continuous glucose monitor (CGM) and give you a physical activity monitor to be worn for the next 3 days. Similar to pre-training, you will be given a glucose meter, meals for the next 3 days, and a food log. This visit should last about 1 hour.

#### **VISIT 25: POST-TRAINING INTERVAL STAIR CLIMBING SESSION**

You will first report to the laboratory and then we will proceed to the northeast stairwell of the Ivor Wynne Centre to complete the stair climbing exercise session. You will



complete the same exercise protocol as completed during the training sessions for the last time. Heart rate and RPE will be recorded during this exercise session. We will monitor your finger stick blood glucose levels before and after exercise, as well as into recovery. A drop-off time will be scheduled for you to return your CGM at least 48 hours following this exercise session. This visit will last about 30 minutes.

### **WHAT ARE MY RESPONSIBILITIES IF I PARTICIPATE IN THE STUDY?**

- 1) Complete a 12-lead ECG stress test under physician supervision to determine eligibility for the study.
- 2) Attend baseline testing and post-training testing sessions to determine any changes in measures of body composition, fitness and health.
- 3) Wear a continuous glucose monitor for 3-4 days before and after training.
- 4) Consume all standardized meals to the best of your ability and record any changes that you make to your provided food plan while wearing the continuous glucose monitor.
- 5) Check your capillary glucose 4 times per day (i.e., finger prick glucose; supplies provided) while wearing the continuous glucose monitor.
- 6) Please show up to all training sessions across the 6-week period.
- 7) Report any noticeable changes in your health status (e.g., sickness, cold).

### **DETAILED DESCRIPTION OF TESTS AND PROCEDURES.**

**BOD POD™ (Body Composition):** This non-invasive procedure requires you to sit comfortably in a chamber while the amount of fat mass and fat-free mass is measured. You will not feel anything different while the test is being conducted and it lasts about 3-5 minutes.

**Venous Blood Sampling:** A small needle will be inserted into a forearm vein to collect your blood, similar to donating blood. The discomfort of this procedure is temporary and is very similar to having an injection by a needle, or when donating blood. We will remove approximately 6 ml of blood on each sample (i.e. before and after training). Pressure will be placed on the site in order to minimize bleeding and facilitate healing once the needle is withdrawn.

**Continuous Glucose Monitoring (CGM):** This procedure involves inserting a small micro dialysis tube under your skin on your stomach beside your belly button with the assistance of a small needle. The discomfort of this procedure is temporary and is very similar to having an injection by a needle, or when donating blood. Once the needle is removed there should be minimal sensation from the micro dialysis tube. The tube is connected to a small device (approximately the size of a loonie), which continuously measures glucose concentration. Both the tube and device will be attached to the skin of your stomach with sterile tape. You may feel some discomfort when the device is inserted but this should subside shortly after insertion. You will be able to go about your daily life

with the monitor on but sometimes you may feel some irritation. To minimize irritation, you should be careful when doing anything that could irritate the skin on your stomach, such as putting on your clothes, when showering, and when putting on your seatbelt.

**Functional Fitness Measures:** You will complete 2 short fitness tasks in order to assess your overall physical capacity before and after the training intervention. The 6-minute walk test (6MWT) will require you to walk repetitively out and back (on a section of the indoor track in the David Braley Athletic Centre), covering as much distance as possible in 6 minutes. This will serve as indicator of your functional capacity and physical endurance. The second task will require you to rise to a full stand from a chair with your arms across your chest as many times as possible in 30 seconds. This 30-second chair stand test will give us a better indication of your lower body strength.

**12-lead ECG Stress Test:** Current guidelines recommend 12-lead electrocardiogram (ECG) exercise screening for people with T2D before engaging in any vigorous exercise. The details of the test will be explained to you before beginning and you will be encouraged to ask questions. This test involves exercising at progressively higher workloads, starting with a warm up and increasing the intensity with each work stage. Your heart rhythm will be monitored during the test using an ECG machine by connecting electrodes to the skin of your chest. This test will help to ensure that you are suitable for participating in more strenuous exercise. Additionally, this test will help to determine your maximal heart rate and exercise capacity, which we can use throughout the exercise training program to gauge how hard you are working at each training session.

## **DESCRIPTION OF POTENTIAL RISKS AND DISCOMFORTS**

**Body composition testing:** The risks associated with body composition testing using BodPod are minimal. You will be asked to sit inside a small chamber and will be able to breathe comfortably. This testing requires that you wear only fitted shorts/sports bra as well as bathing cap within the chamber to get as accurate a measurement as possible. Some discomfort may arise over this required attire as well as if you have any problems with claustrophobia, as the chamber is somewhat small.

**Continuous glucose monitoring:** There is a theoretical risk of infection and an extremely low risk of bruising/skin discoloration from the insertion of the micro needle that could last for up to a few days. The insertion of the CGM is done under sterile conditions by a trained individual and we have never experienced any complications in our laboratory. There is also a small risk of bleeding at the site of insertion. The skin of some individuals is sensitive to adhesive used in tape or Band-Aids and can get red or itchy when the CGM is attached with the medical tape used. There may be redness, irritation, soreness, rash, or tenderness in the area where the tape was applied after removal of the CGM but this will usually disappear after a few days. If you experience pain or discomfort related to the CGM, you can remove it at anytime, consult the study staff to have it removed, or contact your healthcare provider for assistance. Removal involves taking off the adhesive, similar

to removing a Band-Aid. The CGM is approved for continual wear for up to 6 days. You should not go into a hot tub (sauna, whirlpool) while wearing the CGM nor should you undergo an MRI scan while wearing the CGM.

**Exercise testing:** Exercise has many health benefits but there is also a small risk of an adverse cardiovascular event during exercise. The potential risks and discomforts associated with the exercise testing procedures are similar to those associated with any form of strenuous physical activity. These include fatigue, fainting, abnormal blood pressure, irregular heart rhythm, and in very rare instances, heart attack, stroke, or death. Every effort will be made to minimize these potential risks by evaluation of preliminary information relating to your health and fitness and by careful observations during testing, including monitoring blood glucose levels. Ensuring that all exercise is supervised will also minimize the risks.

- **Stair Climbing:** As with any form of exercise training, or even climbing up and down stairs as a part of activities of daily living, there is always a risk of tripping or falling. This could lead to strains, sprains, fractures, or a concussion. As a safeguard, railings will always be available to use at any point if necessary for support while completing the exercise training.
- **Low blood sugar (“hypoglycemia”):** There may be a small risk of low blood sugar after exercise. This risk is significantly reduced since you are currently not on insulin, which carries a risk of causing hypoglycemia. Measuring your blood glucose before and after exercise using a finger stick blood glucose meter reduces this risk.

**Venous blood sampling procedure:** The insertion of a needle for blood sampling is a common medical practice and involves minimal risk provided proper precautions are taken. The needle is inserted under completely sterile conditions, however there is a theoretical risk of infection. There is also chance of bleeding if adequate pressure is not maintained upon removal of the needle. This may cause some minor discomfort and could result in bruising/skin discoloration that could last up to a few weeks. There is also the remote risk that trauma to the vessel wall could result in the formation of a small blood clot, which could travel through the bloodstream and become lodged in a smaller vessel. However, we have never experience such a complication in our laboratory after several thousand venous blood sampling procedures.

No pharmacological agents will be given in this study, so there is no risk of drug interactions with your current medications. It is not possible to know all of the risks that may happen in a study. The researchers have taken all reasonable safeguards to minimize any known risks to a study participant.

### **HOW MANY PEOPLE WILL BE IN THIS STUDY?**

We plan to recruit and test 10 participants.

### **WHAT ARE THE POSSIBLE BENEFITS FOR ME AND/OR FOR SOCIETY?**

You may not benefit directly from participating in this study. However, exercise does have widespread health benefits, which include improved muscle health and aerobic fitness. We hope this study will help us better understand how exercise affects glucose levels, both immediately following an exercise session as well as after a more prolonged period of training. You will receive information on how your blood glucose responds to exercise. You are not expected to receive any other benefits from participating in this study.

If there are findings that may be of interest or importance to you or your primary care physician (e.g., low or high blood glucose values during the day or night) you will be provided with this data and encouraged to discuss with your primary care physician.

### **WHAT INFORMATION WILL BE KEPT PRIVATE?**

All data obtained in connection with this study will remain confidential. Appropriate measures, consistent with Research Ethics Board guidelines, will be taken to ensure privacy. The results from this study will be used for educational purposes and shared with the scientific community. However, all personal information will be removed from the data and subjects will only be identified by a code number. If the results of the study are published, your name will not be used and no information that discloses your identity will be released. Upon completion of the study, you will have access to your own data and the group data for your own interest. The data, with identifying information removed will be securely stored in a locked office for a period of 10 years.

For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of the Hamilton Integrated Research Ethics Board may consult your research data. However, no records that identify you by name or initials will be allowed to leave the institution/university/hospital. By signing this consent form, you authorize such access.

### **CAN PARTICIPATION IN THE STUDY END EARLY?**

If you volunteer to be in this study, you may withdraw at any time without giving reasons. You also have the option of removing your data from the study. You may also refuse to answer any questions you don't want to answer and still remain in the study. The investigators may also withdraw you from the study if you are not able to follow the requirements of the study or if any other circumstances arise which warrant doing so.

### **WILL I BE PAID TO PARTICIPATE IN THE STUDY?**

If you agree to take part, you will receive an honorarium of \$200.00 in order to compensate you for your time and effort. In the event that you do not complete the study,

you will receive a pro-rated amount based on the proportion of the study completed. You will also receive free meals while wearing the continuous glucose monitor.

### **WILL THERE BE ANY COSTS?**

Your participation in the study will not involve any costs to you. If you need to park on campus for visits that are exclusively related to the study, please discuss this in advance with one of the study investigators. An appropriate plan can be put in place (e.g., parking vouchers) to offset any costs that you might incur in this regard. Any costs associated with transport to and from McMaster University (e.g., gasoline, bus or taxi fare) are not covered.

### **WHAT HAPPENS IF I HAVE A RESEARCH-RELATED INJURY?**

If you are injured as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost. Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not routinely available. However, if you sign this consent form it does not mean that you waive any legal rights you may have under the law, nor does it mean that you are releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

### **IF I HAVE ANY QUESTIONS OR PROBLEMS, WHOM CAN I CALL?**

In the event of an emergency please contact Dr. Martin Gibala at 905-525-9140 ext 23591 (office) or 905-912-2060 (24 hr) or Beth Godkin at 519-897-7614. As with any medical emergency, you should proceed to the urgent care/emergency department of the closest hospital if an emergency situation should arise during the course of the study.

If you have questions regarding your rights as a research participant, you may contact the office of the Chair of the Hamilton Integrated Research Ethics Board at 905-521-2100, ext. 42013.

The REB Project Number for this study is #2402.

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**CONSENT STATEMENT**

**SIGNATURE OF RESEARCH PARTICIPANT**

I have read the preceding information thoroughly. I have had the opportunity to ask questions, and all of my questions have been answered to my satisfaction. I agree to participate in this study. I understand that I will receive a signed copy of this form.

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Name of Participant

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Signature of Participant

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Date

**Consent form administered and explained in person by:**

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Name and title

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Signature

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Date

**SIGNATURE OF INVESTIGATOR**

In my judgment, the participant is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent to participate in this study.

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Signature of Investigator

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Date

## APPENDIX B: HiREB APPROVAL LETTER



18 November 2016

**Project Number:** 2402

**Project Title:** Effect of brief intermittent stair climbing exercise on glycaemic control in individuals with type 2 diabetes.

**Principal Investigator:** Dr. Martin Gibala

This will acknowledge receipt of your letter dated November 08-2016 which enclosed revised copies of the Application and the Consent Form along with a response to the additional queries of the Board for the above-named study. These issues were raised by the Hamilton Integrated Research Ethics Board at their meeting held on October 18-2016. Based on this additional information, we wish to advise your study had been given *final* approval from the full HiREB.

The following documents have been approved on both ethical and scientific grounds:

Document Name	Document Date	Document Version
1. Phone Screening 09-16	27/Sep/2016	1
2a. Screening form 09-16	27/Sep/2016	1
2B PARQ+ 09-16	27/Sep/2016	1
2C Godin PA 09-16	27/Sep/2016	1
2D Patient Health Questionnaire (PHQ-8)	27/Sep/2016	1
2E Pittsburgh Sleep Quality Index (PSQI) 09-16	27/Sep/2016	1
2F Food Preference Checklist 09-16	27/Sep/2016	1
2G Anthropometric Assessment 09-16	27/Sep/2016	1
Godkin Recruitment Poster 09-16	27/Sep/2016	1
Informed Consent V2 Clean	08/Nov/2016	2
MSc Thesis Proposal V2 Clean 11-16	08/Nov/2016	2

The following documents have been acknowledged:

Document Name	Document Date	Document Version
Gibala TCPS2 Core Certificate Mar2013	27/Sep/2016	1

**Please Note:** All consent forms and recruitment materials used in this study must be copies of the above referenced documents.

We are pleased to issue final approval for the above-named study for a period of 12 months from the date of the HiREB meeting on October 18-2016. Continuation beyond that date will require further review and renewal of HiREB approval. Any changes or revisions to the original submission must be submitted on a HiREB amendment form for review and approval by the Hamilton Integrated Research Ethics Board.

**PLEASE QUOTE THE ABOVE REFERENCED PROJECT NUMBER ON ALL FUTURE CORRESPONDENCE**

Sincerely,

Dr. Mark Inman, MD, PhD  
Chair, Hamilton Integrated Research Ethics Board

The Hamilton Integrated Research Ethics Board operates in compliance with and is constituted in accordance with the requirements of: The Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans; The International Conference on Harmonization of Good Clinical Practices; Part C Division 5 of the Food and Drug Regulations of Health Canada, and the provisions of the Ontario Personal Health Information Protection Act 2004 and its applicable Regulations; for studies conducted at St. Joseph's Hospital, HiREB complies with the health ethics guide of the Catholic Alliance of Canada.