Effects of High Intensity Interval Exercise versus Moderate Intensity Continuous Exercise on Blood Glucose Profiles of Individuals with Type 2 Diabetes

By

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ABSTRACT

Achieving good control over glucose concentrations is the fundamental therapeutic goal for individuals with type 2 diabetes (T2D). The effects of exercise on individuals with T2D have been well received and contributed extensively to recent evidence-based exercise guidelines in several countries. However, knowledge regarding the therapeutic benefits of high intensity interval exercise (HIIE) in individuals with T2D was limited. While accumulating evidence suggested the potential benefits of HIIE, it was unknown if it confers additional benefits over traditionally recommended moderate intensity continuous exercise (MICE) in improving the glycemia of T2D. In addition, it was unknown if timing to perform such exercise impacts glycemic responses. Accordingly, a series of studies were performed to: 1) examine the feasibility and long-term efficacy of HIIE; 2) to compare the glycemic responses to HIIE and MICE during exercise; and 3) to compare the acute glycemic responses to HIIE and MICE. Results suggested that HIIE is as feasible as MICE, and, compared to MICE, lowers glucose concentrations to a greater extent during exercise, and induces greater reductions in nocturnal and fasting glucose concentrations on the day subsequent to exercise. While performing HIIE in the fasted-state attenuated the reduction of glucose concentration during exercise, it improved most aspects of dysglycemia measured over hours following the exercise bouts. Postprandial HIIE, on the other hand, resulted in the greatest reduction in glycemia during exercise; however, no glucose profiles were improved hours after exercise as compared to a sedentary day. These results suggest that HIIE has some potential

advantage over MICE in improving specific aspects of glycemia, and performing HIIE during a fasted-state may be more beneficial in lowering additional measures of glycemic profiles. In conclusions, HIIE is well tolerated by individuals with relatively well-controlled T2D and effectively improves various aspects of glycemia. The effects of HIIE may be magnified by performing it under fasted-state.

PREFACES

This thesis is an original work by Tasuku Terada. The research projects, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project names: "Exercise intensity, glycemic control and abdominal fat in people with type 2 diabetes: A pilot study", No. 11782, May 27th, 2012; and "Exercise intensity and meal timing in type 2 diabetes", No 31930, Mar. 18th, 2013.

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Contents

LIST OF ABBREVIATIONS:

The following is the list of abbreviations used in this dissertation.

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACSM	American College of Sports Medicine
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ACC2	acetyl-CoA carboxylase 2
A1c	glycosylated hemoglobin
CAD	coronary artery disease
CapBG	capillary blood glucose concentration
CDA	Canadian Diabetes Association
CG-EGA	continuous error-grid analysis
CGMS	continuous glucose monitor system
CONGA	continuous overlapping net glycemic action
CV	coefficient of variation
CVD	cardiovascular disease
DECODE	Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe
DXA	dual-energy X-ray absorptiometry
FBG	fasting blood glucose
GLU_{mean}	22-hour mean glucose concentration
GLUT4	glucose transporter 4
GV	glycemic variability
HIIE	high intensity interval exercise
HR	heart rate
HRR	heart rate reserve
IDF	International Diabetes Federation
MAGE	mean absolute glucose excursion
$MAGE_{ave}$	MAGE with the average of both upward and downward swings that exceeds 1 SD
$MAGE_{abs.gos}$	MAGE absolute group of signs method using both upstroke and downstroke excursions exceeding 1 SD.

MICE	moderate intensity continuous exercise
OGTT	oral glucose tolerance test
P-EGA	point accuracy error-grid analysis
PGC-1α	peroxisome proliferator-activated receptor-γ coactivator
PPG	postprandial glucose
SD_w	within-day glucose concentration standard deviation
SMBG	self-measured blood glucose
T2D	type 2 diabetes
UKPDS	United Kingdom Prospective Diabetes Study
VO_{2max}	maximum oxygen consumption
VO_{2peak}	peak oxygen consumption
VO_2R	oxygen consumption reserve
VT	ventilator threshold
$\%cv_w$	Within-day percentage coefficient of variation

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CHAPTER 1

1.1 Introduction

As more individuals adapt to the environment that promotes sedentary behaviour and allows easy access to energy-dense foods, the prevalence of overweight and obesity increases. One of the major health consequences of obesity is impaired insulin action, leading to the development of a progressive metabolic disorder involving defects in skeletal muscle, adipose tissue, liver, and β-cell dysfunction, namely Type 2 diabetes (T2D) (1). With the development of T2D, regulation of blood glucose concentrations to the narrow range otherwise seen in healthy individuals is disturbed. As a result, blood glucose concentrations are elevated and contribute to the development of diabetic complications (2,3). Thus, achieving better control over glucose concentrations is the fundamental therapeutic goal for better management of T2D (4,5).

It is well known that muscular contraction augments the rate of glucose oxidation and improves insulin action and because of this, exercise has been considered a cornerstone of diabetes management along with pharmacological and dietary interventions (4). To date, research has documented several benefits of exercise and many national agencies have endorsed exercise in their physical activity or exercise guidelines for T2D (5-9). These guidelines provide an important starting-point for healthcare practitioners and individuals aiming to obtain better education or control over T2D.

Despite the widely acknowledged importance of exercise in the management of T2D, glycemic responses to exercise can be highly heterogeneous (10). Because exercise can be performed in various ways, the heterogeneous responses may be attributable to the type of exercise interventions. In addition, given that glucose concentration differs markedly within a day in individuals with unstable glycemia (predominantly due to nutrient intake), the same exercise performed at different times of the day may induce different glycemic responses.

In these respects, the exercise guidelines still lack detailed information on the preferred exercise interventions and/or timing to maximize the benefits of exercise.

With concerns over the risk of injury (11), poor adherence (12), and low self-efficacy regarding the ability to implement high intensity exercise (13), low-to-moderate intensity [≤60% of maximum oxygen consumption ($\dot{V}O_{2max}$) (5-9) or ≤70% of maximal heart rate (8)] exercise has traditionally been favoured and the efficacy of high intensity [>60 of $\dot{V}O_{2max}$ (5-9), 60-84 % of oxygen consumption reserve ($\dot{V}O_2R$) (6), or >70% of maximal heart rate (8)] exercise on T2D has been less documented. Moreover, while one systematic review and meta-regression analysis suggested that higher intensity exercise training leads to better glycemic control, others have suggested no additional benefits compared to lower intensity exercise (10,14).

One approach to minimizing some of the barriers that exist in clinical populations to high intensity exercise may be the use of interval exercise training which alternates between high intensity exercise and lower intensity recovery periods. A series of recent studies have indicated that high intensity interval exercise (HIIE) can be safely implemented and well tolerated by elderly individuals with various heart conditions (15-23). Consequently, there is an increasing interest in the application of HIIE for people with comorbidity, including T2D. HIIE was shown to improve glycemia to a greater extent than energy-matched traditionally recommended moderate intensity continuous exercise (MICE) in patients with metabolic syndrome (24), and it has been suggested as a potent therapeutic intervention to improve blood glucose of individuals with T2D (25).

Regardless of the seminal studies showing the important role HIIE may play in the control of glucose (26-29), studies investigating the effects of HIIE on individuals with T2D are limited (30-36) and no study has compared the effects of HIIE to traditionally used moderate intensity continuous exercise (MICE) adjusted for both exercise duration and volume on glycemia. Furthermore, no

studies have considered the impact of the timing of exercise in relation to meals when investigating the efficacy of HIIE.

1.2 Blood Glucose Profiles of T2D

In healthy non-diabetic individuals, the blood glucose homeostasis is the result of the finely tuned balance between glucose production and glucose disposal. In contrast, in individuals with T2D present with an impaired autoregulation, blood glucose concentrations are less stable and often promptly influenced by external stimulus and/or internal circadian fluctuations in hormonal concentrations. As a consequence, individuals with T2D manifest either chronically elevated blood glucose concentrations or higher and longer glucose excursions in response to meal consumption.

Establishing a clear pathogenic link between hyperglycemia and diabetes-related complications is difficult with coexistent pathophysiological factors such as dyslipidemia, hyperinsulinemia, and hypertension. However, poor glycemic control remains as a key risk factor associated with diabetic complications (4). Abnormal glycemia accelerates the incidence of micro (37) and possibly macrovascular complications (38-41), both of which constitute the major causes of premature morbidity and mortality in T2D. With hyperglycemia recognized as the culprit for many diabetic complications, better control of glucose concentrations is of pivotal importance in managing the conditions of T2D. In addition, because not all glycemic profiles [i.e., fasting glucose, postprandial glucose, glycemic variability, glycosylated hemoglobin (A1c)] contribute the same risk, it may be important to target specific aspects of dysglycemia for better management of T2D (see “Glucose profiles of T2D and associated risks” in Appendix for more details).

1.3 The effect of exercise on blood glucose profiles

In addition to its long-term positive effects on body mass and many cardiovascular risk factors, exercise benefits individuals with T2D by acutely

lowering blood glucose concentration. During exercise, an increase in glucose disposal is normally counterbalanced by an increase in hepatic glucose output in healthy individuals (42). However, exercise typically lowers blood glucose concentrations in individuals with T2D. A greater reliance on plasma glucose rather than muscle glycogen (43,44) and/or an inadequate increase in hepatic glucose output (45) are likely to be responsible for this blood glucose reduction. The oxidation of blood glucose during exercise is followed by better insulin sensitivity, which can improve the control of blood glucose for up to 48 hours after exercise (46). The combination of a rapid fall in blood glucose concentration and improved insulin sensitivity following exercise constitutes the basis for recommending exercise to individuals with T2D.

With an increase in the number of different exercise studies on individuals with T2D, the acute glycemic responses to more varied exercise interventions have become available. Among the different factors affecting glycemic control, exercise intensity has been of particular interest as research has indicated that high intensity exercise stimulates intermediaries that may result in greater glucose uptake compared to lower intensity exercise interventions (47-50). See "Effects of exercise on glucose profiles of T2D" in Appendix for further details.

1.4 High intensity interval exercise in type 2 diabetes

HIIE alternates between high intensity exercise bouts and lower intensity recovery periods. During high intensity interval bouts, exercise intensity exceeds the intensity that can be maintained during continuous exercise albeit for shorter periods of time. Available evidence now suggests that the brief bursts of intense efforts induce intracellular perturbation that results in rapid activation of several intermediaries in the pathways leading to enhanced blood glucose uptake of individuals with various pathophysiological conditions (27,28,31,52-56). Consequently, HIIE is receiving considerable attention as a potent therapeutic intervention for individuals with T2D.

A systematic review by Boulé et al. (51) reported a study that incorporated HIIE elicited the greatest improvement in glycemia (-1.8 percentage points in

A1c) compared to other forms of high intensity exercise despite a relatively low frequency and duration of training (30). Unfortunately, such improvements have not been replicated and the study did not include a comparison group of different exercise intensities. Therefore, it is still unclear if individuals with T2D benefit more from participating in HIIE in comparison to MICE.

Finally, previous studies have demonstrated that only six sessions of low volume HIIE may improve glucose transport capacity of both young (52) and middle aged individuals (27). When compared to MICE adjusted for exercise volume and caloric expenditure, HIIE was superior in improving blood glucose and insulin sensitivity in participants characterized by the metabolic syndrome (28). Despite consistent evidence suggesting the positive impact of HIIE, studies investigating the effects of HIIE in individuals with T2D are still limited.

1.5 Timing of Exercise

Blood glucose concentration of an individual with T2D fluctuates throughout the day and one of the most important contributing stimuli is nutrient intake. Meal consumption prior to exercise elevates glucose and insulin concentrations, which accentuate the reduction in glucose concentrations elicited by exercise. Thus, time elapsed from last meal intake is a strong predictor of acute glycemic responses to exercise (57,58). When exercise is performed after a meal, high glucose and insulin concentrations induced by the meal blunt hepatic glucose output despite increased glucose demands by working muscles (45). This imbalance between glucose production and utilization results in lower glucose concentrations. In the fasted conditions, however, glucose responses differ depending on the intensity of exercise performed. A short bout (five minutes) of high intensity exercise in the fasted-state results in elevated glucose concentrations in individuals with T2D (59), whereas moderate intensity exercise results in little change (57,58,60). This inconsistency is primarily due to different degrees of hepatic glucose output. Hepatic glucose production exceeds glucose utilization during high intensity exercise if performed in the fasted condition (59), whereas a smaller degree of hepatic glucose output rarely elevates glucose

concentrations during fasted-state moderate intensity exercise. Interestingly, although high intensity exercise performed in the fasted state has been shown to acutely elevate glucose concentrations, studies have shown increased insulin sensitivity 12 to 24 hours after the exercise bout (34,59).

The most recent physical activity or exercise guidelines for patients with T2D recommend both moderate intensity and high intensity exercise, but the optimal timing of a daily exercise routine has been overlooked (61). Given the possible interactive effects of exercise intensity and food intake, the effect of exercise and meal timing requires further investigation. To date, there has not yet been a study assessing how HIIE performed under different meal states influences the blood glucose of individuals with T2D.

1.6 Summary and rationale

Regardless of accumulating evidence suggesting the potential advantages of HIIE over traditionally used MICE, only a limited number of studies have examined the impact of HIIE on glycemic control in individuals with T2D. In addition, whether HIIE is more effective in controlling glycemia than MICE remains unclear because 1) the effect of exercise intensity is frequently confounded by factors such as exercise volume and/or duration, 2) possible interactive effects between exercise intensity and meal timing, and 3) examining glycemic responses in detail has been technically limited. Further research is warranted to clarify the effects of HIIE on individuals with T2D.

1.7 Purpose of the dissertation

1.7.1 Overall purpose

This dissertation consists of four studies. The first two studies are based on a randomized research trial. **Study 1** investigated the feasibility of, and long-term glycemic responses (A1c) to HIIE (Chapter 2). **Study 2** examined glycemic responses to HIIE and MICE using a conventional hand-held glucose monitor while concomitantly considering potential factors that modulate exercise-induced

glucose concentrations changes, such as anti-hyperglycemic medication and timing of meal intake (Chapter 3).

Study 3 and **Study 4** were designed to provide better insight into unanswered questions raised by the first two studies. One of the limitations of using A1c as a variable in **Study 1** was that it did not reflect short-term glycemic changes. Additionally, the limitation of the hand-held glucose monitor used in **Study 2** was that, while its use is recommended for behavioral adjustment, it is a point measure and provides little information regarding the direction, duration, or magnitude of glucose concentration changes. Monitoring of glycemia over an extended period was considered necessary to fully investigate the effectiveness of different exercise interventions.

Recently, a continuous glucose monitor system (CGMS) has been developed and it has made sequential measurement of glycemia possible. **Study 3** and **Study 4** used this relatively new technology. **Study 3** examined test-retest reliability of CGMS-estimated glucose profiles of individuals with T2D under highly standardized environmental conditions (Chapter 4). The investigation of CGMS in **Study 3** was deemed important as **Study 4** used a repeated measure design to compare the effects of HIIE and MICE performed under different timing with respect to meals (Chapter 5). Thus, **Study 4** was designed to extend the results from **Study 1** and **Study 2** by examining acute glycemic responses (~24 hours following exercise bouts) using CGMS. Together, this dissertation aimed to clarify the efficacy of HIIE on glycemia of individuals with T2D. A schematic summary of the subsequent chapters and the associated main outcomes are introduced in **Figure 1**.

1.7.2 Specific purpose and hypothesis of each study

Study 1

Purpose: To examine the feasibility of HIIE in individuals with T2D. A secondary purpose was to assess the longer-term efficacy of HIIE on glycemic control as determined by A1c.

Hypotheses: HIIE was hypothesized to be as feasible as MICE in individuals with T2D. Additionally, HIIE was hypothesized to lower A1c than MICE.

Study 2

Purpose: To investigate the glycemic responses to HIIE and MICE during exercise while simultaneously considering external factors that may modulate exercise-induced glucose concentration changes.

Hypotheses: HIIE was hypothesized to reduce blood glucose concentrations to a greater extent than MICE during exercise. It was also hypothesized that meal and medication intake prior to exercise would accentuate the reduction in blood glucose concentrations during exercise.

Study 3

Purpose: To determine the test-retest reliability of CGMS.

Study 4

Purpose: To compare the effects of HIIE and MICE performed under fasted and postprandial states on subsequent 24-hour glycemic profiles in individuals with T2D.

Hypothesis: It was hypothesized that HIIE and exercise under fasted condition would lower glycemic profiles to a greater extent than MICE or postprandial exercise.

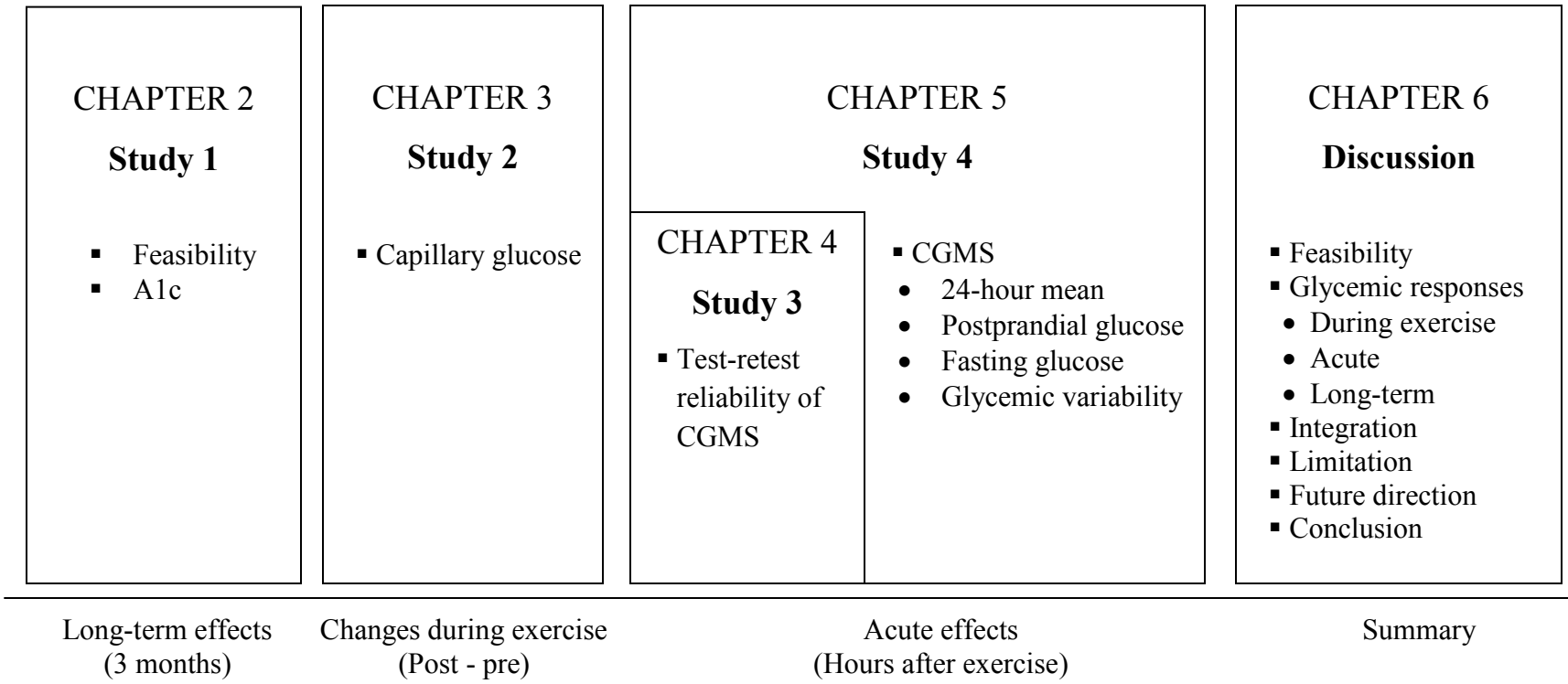

Figure 1.1 Schematic presentation of the dissertation. Each study compares the effects of high intensity interval exercise and moderate intensity continuous exercise on different aspects of glycemia except for **Study 3** which investigated the reliability of CGMS. The findings are integrated and summarized in Chapter 6. Bulleted points are the primary measures of each study (**Study 1-4**) and the points discussed (**Discussion**). A1c: glycosylated hemoglobin A1c; CGMS: continuous glucose monitoring system.

1.8 Delimitations and limitations

This dissertation focused on the effects of HIIE and MICE on blood glucose concentrations of individuals with T2D who were not on exogenous insulin and had relatively well controlled glycemia (A1c ≤10%). Glucose concentrations were examined in response to HIIE and MICE; however, the factors associated with the regulation of glycemia (i.e., hormonal changes) in response to these interventions were beyond the scope of this dissertation. This is one of the limitations of this dissertation as the same glucose concentration does not necessarily reflect the same degree of glucose regulation. For example, despite the same glucose concentration, insulin concentrations may differ. Lowering the concentrations of insulin required to induce the same glycemia could be an important outcome of future exercise interventions but were not captured in the present dissertation.

All four studies did not include a control group of individuals without T2D as the primary purposes of the dissertation were to elucidate how the blood glucose profiles of individuals with T2D were affected by the interventions. Because the efficacy of MICE in individuals with T2D was well established, MICE served as a control condition to investigate the efficacy of HIIE.

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CHAPTER 2

[1]Feasibility and preliminary efficacy of high intensity interval training in type 2 diabetes

2.1 Introduction

Current physical activity or exercise recommendations for patients with T2D suggest a minimum of 150 minutes per week of moderate to vigorous aerobic exercise (1). However, data are conflicting as to whether or not individuals with T2D benefit more from participating in high intensity exercise. Recent meta-analyses have highlighted the variability in the response to various exercise protocols and have suggested that a greater exercise dose predicts greater decreases in A1c (2). Conversely, greater exercise intensity per se has been shown to lead to greater improvements in A1c in some meta-analyses (3) but not others (2,4).

Similarly, while high intensity exercise has been indicated to improve insulin sensitivity (5-7), the mechanisms by which exercise intensity affects insulin sensitivity are not well understood. Acute increases in non-oxidative glucose disposal (8-10) or chronic preferential reduction in intra abdominal adipose tissue (IAAT) (11), just to name a few, may be more prominent following high intensity exercise and contribute to enhanced insulin sensitivity. Recently, more attention has been directed toward the effect of high intensity exercise on IAAT due to its role in the pathogenesis of insulin resistance and T2D. Nonetheless, studies have shown conflicting results with some studies showing preferential reductions in IAAT with higher intensity exercise irrespective of energy expenditure (12-14) while others report no differences (15,16). Thus, whether exercise intensity can be tailored to favour preferential reductions in IAAT and A1c remains inconclusive.

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While the benefits of high intensity exercise requires further research, there are several concerns regarding the feasibility of implementing high intensity exercise, particularly in older, sedentary or overweight participants with comorbidities such as T2D. Primary perceived barriers include concerns over the risk of injury (17), poor adherence (18), and low self-efficacy in the ability to implement exercise (19). One approach to minimizing the barriers to high intensity exercise may be the use of interval exercise training which alternates between high intensity exercise bouts and lower intensity recovery periods. Interestingly, while only a few previous studies (20-22) have prescribed interval training in people with T2D, all demonstrated preferable effects with one study (20) reporting greater reductions in A1c and IAAT than other studies identified in a meta-analysis (2). Unfortunately, this latter study did not have a moderate intensity exercise comparison group and it is unknown whether the greater than expected benefits were due to the intervention itself or to some characteristics of the participants.

As recently suggested by Hawley et al., high intensity interval training may be a potent therapeutic intervention to improve blood glucose concentrations and body composition (23). Nonetheless, to our knowledge there has not yet been a randomized trial that compares the feasibility and chronic effects of high intensity interval exercise (HIIE) and moderate intensity continuous exercise (MICE) interventions in T2D. The objective of this pilot study was to compare the feasibility (recruitment, adherence and retention) of HIIE versus MICE in patients with T2D. Secondary outcomes of interest included investigation of the preliminary efficacy of HIIE and MICE in improving A1c and estimates of IAAT. Compensatory changes in daily steps and energy intake throughout the study were also investigated.

2.2 Methods

Design. This was a 12-week, single center, parallel-group randomized trial (ClinicalTrials.gov registration number: NCT01144078) conducted in Edmonton,

Alberta, Canada. Ethical approval was obtained from the University of Alberta Health Research Ethics Board.

Participants. Initial recruitment was conducted through newspaper advertisement and websites. These recruitment strategies briefly outlined the inclusion criteria: 1) men and women between 55-75 years of age; 2) diagnosed with T2D; 3) able to exercise 5 days per week; and 4) non-smokers. Other recruitment procedures were conducted through word of mouth and by contacting the individuals with T2D who expressed interest in participating in research studies.

The study coordinator conducted a brief telephone interview to confirm the potential eligibility of participants, answered questions regarding the study, and scheduled a first meeting. In the first meeting participants responded to questionnaires to further screen for the following criteria: 1) post-menopausal for more than 5 years; 2) <150 minutes of structured exercise per week; 3) less than 3 kg body weight change within the last 6 months; 4) absence of diabetes-related complications and limitations to regular exercise; and 5) self-reported absence of alcohol or substance abuse within last 12 months. Blood pressure (BP) was measured at rest to ensure the participants were safe to perform exercise intervention (cutoff criteria < 140/90). The use of prescription medications that might affect body fat distribution (i.e. insulin and Thiazolidinedione) was considered a contraindication to participation. Participants meeting the inclusion criteria provided a baseline fasting blood sample measured at a local accredited diagnostic laboratory (DynaLIFE$_{DX}$, Edmonton, AB). Individuals with A1c >9 %, LDL >3.5 millimoles per liter (mmol·L^{-1}) or total cholesterol to HDL ratio >5.0 were excluded. The fasting blood sample was used to determine baseline lipids, lipoproteins, fasting blood glucose and A1c concentrations. All participants provided written informed consent.

Initial Assessment. Participants performed a graded exercise stress test on a treadmill (stress test) under the supervision of a trained physician, and reported to

the University of Alberta on a separate day to assess baseline anthropometric characteristics, body fat, peak oxygen consumption ($\dot{V}O_{2peak}$) and ventilatory threshold (VT). Height was measured with a wall-mounted stadiometer. Waist and hip circumferences and sagittal diameter were measured as previously described (24). Briefly, waist and hip circumferences were measured with a flexible tape measure (Almedic, Saint-Laurent, QC) in standing with feet together at the end of a normal expiration (end-tidal). Waist circumference was measured midway between the costal arch and the iliac crest and hip circumference was measured as the maximal circumference over the buttocks at the level of the trochanters. For sagittal diameter, while participants were lying supine on the floor, a sliding-beam caliper was used to measure the vertical distance between the floor and the abdomen at the level of umbilicus. All measures were performed in duplicate to the nearest 0.1 cm. Where the difference exceeded 0.5 cm, measurements were repeated and the average of the closest two was calculated.

Body fat, i.e., percent total body fat, trunk fat, arm and leg fat, was analyzed with dual-X-ray absorptiometry (DXA) scan (LUNAR Prodigy High Speed Digital Fan Beam X-Ray-Based Densitometry with encore 9.20 software; General Electric, Madison, WI). The detailed mechanism of DXA has been described elsewhere (25). Also, accuracy and reliability of DXA to determine abdominal adiposity has previously been demonstrated (26). A trained radiographer determined subcutaneous fat width from the DXA measures (24). IAAT was subsequently estimated based on the subcutaneous fat width and anthropometric measures, as described by Bertin et al (24).

$\dot{V}O_{2peak}$ and VT were determined using a cycle ergometer (Monark 818; Monark, Varberg, Sweden) and a TrueMax® (ParvoMedics, Sandy, UT) metabolic measurement system that was calibrated for air volume and gas concentrations as per the manufacturer's instruction. The exercise began pedaling at 60-65 revolution per minute (rpm) with no resistance. Power output was increased by approximately ~30 watts (W) for the first 2 minutes and then by 15 W per minute thereafter. The data were acquired every 15 seconds and the highest $\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$) observed before reaching volitional exhaustion determined $\dot{V}O_{2peak}$ (27).

VT was determined using a v-slope method (28). Participants were instructed to maintain the cadence between 60-65 rpm and the test was terminated when participant failed to keep up with the cadence. The highest resistance completed during the last min while maintaining 60-65 rpm was used to determine peak power output (PO).

Run-in Phase. Before randomization to the HIIE and MICE interventions, participants were required to participate in a 2-week run-in period. The purpose of the run-in period was two-fold: to favor the randomization of initially compliant participants; and to gradually habituate participants to the exercise interventions. During the run-in period, participants reported to the University of Alberta for 30-minutes exercise sessions on Monday, Wednesday and Friday for 2 weeks. The exercise intensity was set at workload corresponding to 40 % oxygen consumption reserve ($\dot{V}O_2R$), the ratio of the net oxygen costs to net maximal oxygen consumption (29). All exercise sessions were supervised by a member of the investigative team. The prerequisite for randomization was attendance at 5 out of the 6 run-in visits.

Randomization. Participants were randomly allocated to HIIE and MICE intervention groups. Randomization was stratified by sex and completed by a computer program. While blinding of the participants was not feasible, blood samples and body fat assessments were completed by individuals who were unaware of group allocation.

Intervention. Both groups exercised at the time of participants' convenience 5 days per week (Monday – Friday) for 12 consecutive weeks in a fitness center. Exercise duration, frequency, and average relative intensity ($\dot{V}O_2R$) of HIIE and MICE groups were matched. The MICE group performed continuous exercise at 40 % $\dot{V}O_2R$, whereas the HIIE protocol involved alternating between 1-minute intervals at 100 % $\dot{V}O_2R$ followed by 3-minute recovery intervals at 20 % $\dot{V}O_2R$ (average = 40 %) except for one day (Wednesday), when they performed MICE

protocol. As many complete intervals as possible were completed during HIIE training session (e.g., 7 intervals in a 30 minutes period (7 × 4 minutes = 28 minutes)), with the remaining time spent at 40 % $\dot{V}O_2R$ to ensure that the average work output for both groups corresponded to 40 % of the $\dot{V}O_2R$. To obtain appropriate workload for each individual, peak oxygen consumption was first determined from the baseline progressive maximal walking and stationary cycling exercise tests, followed by the calculation of the workload that yielded the oxygen cost equivalent to the $\dot{V}O_2R$ of interest (i.e., 20, 40 and 100 %). Briefly, American College of Sport Medicine (ACSM) equations were used to estimate oxygen consumption equivalent corresponding to the stage at which the $\dot{V}O_{2peak}$ was measured during the graded treadmill and stationary bike tests to exhaustion (29). The ACSM equations were used to estimate oxygen consumption equivalents as $\dot{V}O_{2peak}$ measured by metabolic cart was not expected to capture the anaerobic contribution of energy and thus would underestimate the true energy expenditure at very high intensity. Speed and slope, as well as cadence and resistance corresponding to 20% and 40% $\dot{V}O_2R$ of the calculated oxygen consumption equivalent were subsequently determined using the same formula (29). See Appendix II for more detailed calculation for exercise intensity calculation.

Participants were progressed from 30 min per session for weeks 1-4 to 45 min per session for weeks 5-8, and then to 60 min per session for weeks 9-12 post randomization. Stationary cycling and treadmill walking were performed alternately for exercise variety. All exercise sessions were supervised and delivered at a University of Alberta exercise facility.

Questionnaires. Participants completed the Subjective Exercise Experiences Scale (30), a 12-item, 7-point Likert scale to assess positive and negative feeling states: positive well-being, psychological distress, and fatigue. In addition, 3 types of self-efficacy: task-efficacy for elemental aspects of the behavior; coping-efficacy for exercising under challenging circumstances; and scheduling-efficacy

for arranging one's time commitments to exercise regularly were assessed by a 10-item, 10-point Likert scale questionnaire (31). Both questionnaires have been demonstrated to be sensitive to exercise interventions (30,31). Questionnaires were first provided during the run-in phase and were repeated in weeks 6 and 12 of the intervention. Consequently, questionnaires were completed during weeks of different exercise duration (i.e., 30, 45, and 60 min). Participants' satisfactions with the exercise training program were measured with another questionnaire provided at the completion of the 12-week exercise training. Participants were instructed to rate on a 7-point Likert scale anchored with 1='not beneficial at all' and 7='very beneficial'.

Outcomes and Measurement. The primary outcome of this study was the feasibility of conducting the planned study in terms of recruitment, retention and adherence. In regards to recruitment, we identified the number of potential participants who responded to our initial recruitment strategies, the proportion who remained interested after being informed of the requirements of the study, as well as the proportion being randomized. From the retention perspective, we were interested in identifying the attrition rate which was established as discontinuation of the intervention and loss to follow-up measurement for both conditions following randomization and by the end of 12 weeks of training. Finally, adherence was measured through attendance to the exercise sessions and compliance to the prescribed intensities. All exercise sessions were monitored by study personnel who noted attendance in a log and ensured each participant completed each exercise bout at the individually prescribed intensity and duration. For the Subjective Exercise Experiences Scale and self-efficacy questionnaires, means of positive well being, psychological distress, fatigue, and self-efficacies were calculated (31).

Important secondary outcomes were the preliminary efficacy of HIIE at reducing IAAT and improving A1c. Within a week of the last exercise session, $\dot{V}O_{2peak}$, VT, anthropometric analyses, DXA, and blood profile measurements were repeated. Our original intention was to estimate the amount of IAAT by

using a previously validated technique which combines DXA and anthropometric measurements to calculate IAAT (24). However, it became apparent that this indirect measurement was unsuitable for examining longitudinal changes as the calculation was confounded by changes in other parameters. Accordingly, raw anthropometric and DXA data were analyzed to determine changes in body composition. VT was visually determined using the graphically display generated by the software on the metabolic measurement system by a single researcher who was blinded to the participants and to the order of testing.

To assess compensatory behavior changes, participants used a provided pedometer (Walk4Life Inc, Plainfield IL). The pedometer was provided a week before the initiation of exercise training and was worn on a daily basis throughout the study period. Participants also completed 3-day dietary record during the run-in phase, the 6^{th} week of the training intervention, and within 1 week of the last day of the training session. Participants were encouraged to continue to consume their regular diet.

Data analysis. Data were tested for normality using histogram and normal probability plots. Where skewness was visually identified, the normality was further tested using Kolmogorov-Smirnov test. Treatment group differences in baseline characteristics were tested using independent t-tests. We used descriptive statistics to examine recruitment, retention and adherence rates, as well as quantitative analyses to investigate the differences between HIIE and MICE. Friedman ANOVA by ranks and Mann-Whitney U tests with Bonferroni adjusted p-value of 0.01 were undertaken for positive well being, psychological distress, fatigue, self-efficacy measures and training program satisfaction.

For the secondary outcomes measured before and after the intervention period (i.e., anthropometric measures, body fat and A1c) one-way ANCOVA (HIIE vs. MICE) was performed on post training outcomes with baseline values serving as covariates to compare the treatment effects. Paired sample t-tests were also performed to investigate within group changes from baseline. Intention-to-treat analysis was performed for all variables unless otherwise stated.

For step counts and dietary intake analyses, two-way (intervention by time) repeated-ANOVA was used. Step counts were stratified into before exercise training, 30 min per session, 45 min per session, and 60 min per session. Dietary records were analyzed using Fitday dietary analysis program (http://www.fitday.com) by two investigators and, where discrepancies in caloric intake exceeded 300 kilocalories (kcal) per day, the data were reanalyzed. The average of the two caloric intakes was used for the statistical analyses. Quantitative data was analyzed using Minitab 15 statistical software (Minitab Inc., State College, PA, US). All data are presented as means ± SD. P-values < 0.05 were considered significant unless otherwise stated.

2. 3 Results

Recruitment. Between June 2010 and February 2011, 126 participants were screened. The intervention was delivered between September 2010 and June 2011. **Figure 2.1** shows the flow of the participants from recruitment to follow-up. Of the 126 individuals screened, 59 did not meet the initial inclusion criteria and were excluded. The most common reasons for exclusion were time constraint to exercise 5 days per week (n=18) and loss of interest (n=17). Subsequently, another 49 were excluded after briefly meeting with the study coordinator. The most common reasons for exclusion were medication (n=15) and being too active (n=11). The remaining 18 participants provided a blood sample. Three did not meet our inclusion criteria and were excluded. Fifteen participants (12 %) entered the run-in phase. All completed the minimum of 5 exercise sessions during the run-in phase and were randomly allocated to HIIE and MICE intervention groups.

Participants. Descriptive characteristics of the 15 participants (8 males and 7 females) are summarized in **Table 2.1**. Of the 7 participants allocated to HIIE: 4 were treated with metformin alone; 1 with metformin and sitagliptin, and 2 with diet intervention alone. Of the 8 participants in MICE: 4 were treated with metformin alone, 1 with metformin and sitagliptin, 2 with metformin and sulfonylurea, 1 with sulfonylurea and sitagliptin. One participant in MICE group

discontinued anti-hyperglycemic medication 9 weeks into the 12-week intervention period. The discontinuation was not related to our exercise program but due to a delay in renewing a prescription. As a direct result of this, a large increase in blood glucose concentration was observed, and it was decided to repeat the fasting blood glucose and A1c analyses while excluding the participant. All the other data obtained from the participants were included in the analyses.

At baseline, sagittal diameter and waist circumference were lower in HIIE than MICE ($p < 0.05$). There were no significant baseline differences in body fat, fitness, or blood profiles between groups.

Retention. Once enrolled in the study, all 15 participants completed all phases of the study. No one dropped out from the exercise intervention after randomization.

Adherence. Through the 12 weeks of exercise training intervention, both HIIE and MICE groups had similar exercise adherence, with the mean attendance of 56 sessions for HIIE and 57 for MICE (97.2 ± 2.7 and 97.3 ± 3.7 % of the eligible exercise sessions completed within each exercise condition, respectively). Reasons for not attending sessions included: health issues, automobile troubles, and business trips.

Secondary outcomes. Contrary to our expectation, although it did not reach statistical significance, IAAT increased from 110.3 ± 20.0 to 116.8 ± 22.80 and from 141.6 ± 40.7 to 154.6 ± 43.1 cm^2 in HIIE and MICE, respectively. Because we suspected the increase was associated with the formula used to compute IAAT, raw-DXA data were analyzed and presented. **Table 2.1** summarizes changes from baseline. The decreases in percent trunk fat was significant in HIIE ($p = 0.007$) and showed tendency to decrease in MICE ($p = 0.075$). Total percent body fat, percent leg fat, and subcutaneous fat width were significantly reduced in both groups ($p < 0.05$). Conversely, in both exercise intervention groups fasting blood glucose, A1c, cholesterol, HDL, LDL, ratio of cholesterol to HDL, triglycerides concentration, body weight, sagittal diameter, waist circumference

and percent arm fat did not change from baseline to post intervention. One-way ANCOVA showed no significant differences between the interventions, indicating the similar effectiveness of both types of exercise after accounting for the baseline differences. For fasting blood glucose and A1c, neither intention-to-treat nor per-protocol analysis resulted in any significant differences. $\dot{V}O_{2peak}$ did not change in either group but oxygen consumption at VT increased significantly (p=0.025 for both groups). Maximal PO attained during $\dot{V}O_{2peak}$ test increased significantly only in HIIE (p=0.029).

Step counts tended to be higher when mean steps during the 60 minutes exercise bout were compared to the pre-training mean (p = 0.053), probably due to a longer time spent on the treadmill. The step counts differed significantly between HIIE and MICE, with HIIE consistently showing higher number of steps throughout the study ($p < 0.001$). After discarding the days on the treadmill, time did not affect step counts (p = 0.469), but between-group difference remained significant ($p<0.001$). Dietary intake of participants did not change over time (p=0.96) and was consistently higher in HIIE group ($p<0.01$). The result did not change when the same analysis was performed on caloric intake relative to body mass ($kcal \cdot kg^{-1}$). There were no group by time interaction effects.

Questionnaires. Overall results are summarized in **Table 2.2**. Changes in positive well being, psychological distress, fatigue, task-efficacy, scheduling-efficacy and coping-efficacy over time were not significant. There were no differences between HIIE and MICE. Equal satisfaction with the interventions was confirmed by the end-of-training questionnaire.

2.4 Discussion

To our knowledge, this is the first randomized trial to compare the feasibility of high intensity interval and moderate intensity continuous exercise training in individuals with T2D. The results suggest that both interventions are feasible and provide high satisfaction to participants. While the recruitment rate for this study (12 %) is similar to a larger study investigating the effects of

different exercise interventions on glycemic control (32,33), the key finding is that, for the subset of participants who were randomized into the exercise training program in the present study, HIIE training did not negatively impact exercise adherence and retention compared to more traditionally used MICE. Adherence and attrition rates observed in HIIE are superior to most of the studies reporting the rates of individuals with T2D enrolled in structured exercise (2). These findings are important in light of recent studies showing that interval training can possibly lead to substantial improvements in glucoregulation (21) or metabolic health (22) within a shorter timeframe than other forms of training (23).

A number of contributing factors, including positive feeling states, low psychological distress and fatigue, and high self-efficacy, explain the high adherence and retention rates. A relationship between positive feeling states and exercise participation in aging individuals has previously been reported (34). In our study psychological responses to exercise stimulus measured via Subjective Exercise Experiences Scale were positive throughout the exercise training regardless of exercise intensity and duration, and were highly comparable to those of younger and more fit individuals (35,36). Moderate intensity exercise has generally believed to be an optimum stimulus to induce positive psychological outcomes, while positive sense of achievement in the completion of a difficult task may also have resulted in the positive feeling states in HIIE (37). To date, a few studies have reported an association between high intensity continuous exercise and high psychological distress/fatigue (35,38,39). However, by performing high intensity exercise in interval fashion, HIIE showed similar levels of psychological distress and fatigue to MICE.

Self-efficacy is another important determinant of adherence. Task-efficacy, coping-efficacy, and scheduling-efficacy observed in this study were high in both groups and were comparable to avid exercisers (31). The reason for the positive psychological states and high self-efficacy is not clear but may be attributable to high motivation due to voluntary participation, easy accessibility of the training facility, and supervision of each exercise session (19). In any case, it was speculated that the same average relative intensity and the same exercise

duration and frequency explained the absence of differences in feeling states and self-efficacy between HIIE and MICE, and hence the similar adherence rates.

With regard to the secondary outcomes, compensatory increases in energy intake and/or decreases in non-exercise energy expenditure have been regarded as factors that, at least partially, negate exercise-induced weight loss (40). Consequently, we measured energy intake and step counts to exclude the possibility that the secondary outcomes were confounded by compensatory behavioral changes. When two-way ANOVA was performed on food intake and step counts, our results showed that there were no time effects or group by time interaction effects, indicating that caloric intake and physical activity outside the study remained relatively constant for both HIIE and MICE intervention groups. This allowed us to attribute the changes in body composition to the effects of the interventions.

While the secondary objective of the present study was to investigate the effects of different exercise modalities on IAAT and A1c, it became apparent that the experimental method chosen for estimating IAAT was inappropriate for detecting longitudinal changes. For example, in some cases where a large reduction in subcutaneous fat width was estimated, we observed an increase in IAAT despite meaningful losses of body mass or the amount of total body fat. This is contrary to what would be expected in studies that have utilized computed tomography or magnetic resonance imaging estimates of IAAT, which have shown that reductions in total body fat or subcutaneous fat width are strongly associated with reductions in IAAT (12,13,41-43). Accordingly, we analyzed raw anthropometric and DXA data and demonstrated favorable body composition changes in the abdominal area and in lower exercising limbs in both HIIE and MICE. This is an important benefit as excess body fat has long been recognized as an important modifiable risk factor for T2D.

Conversely, while HIIE resulted in a significant increase in PO, it showed no additional benefits on body composition over MICE after accounting for the baseline differences, suggesting the possibility that, when adjusted for relative intensity and volume, HIIE and MICE have equal effectiveness on body

composition. This finding is in line with the study by Cho et al., who reported similar impact on body composition changes when continuous high and moderate intensity exercise with duration adjusted for energy expenditure were compared (16). Since there were no significant changes in food intake and physical activity patterns outside the intervention throughout the study period, similar energy expenditure associated with HIIE and MICE may explain similar changes in body composition.

Our findings, however, need to be interpreted with caution given the small sample size, the presence of significant baseline differences in some characteristics despite random assignment, and large individual variability in certain changes. An investigation with more participants is warranted to elucidate the impact of different exercise interventions. Another potential factor that could have affected the outcome was the presence of a run-in phase. The run-in phase required the attendance of 5 out of 6 sessions to be eligible for the study and this could have resulted in a selection bias by favoring participants who were more likely to be compliant to the intervention. This selection of more compliant individuals strengthens internal validity but may weaken external validity. However, because all participants were able to complete the run-in phase and were randomized, the impact of the run-in phase on selection bias was minimized.

It is also important to note that there are many different forms of high-intensity interval training. A unique strength of our study is that both exercise groups were matched in regards to prescribed exercise duration, frequency, mean relative intensity and volume. While this allows us to control for confounding variables in a research, it may not represent some practical forms of interval training that may have less recovery and/or shorter total exercise durations. With regard to A1c, fasting glucose, cholesterols, lipoproteins, and triglycerides, there was minimal to no improvement observed in the present study. As indicated by a recent systematic review, relatively low A1c at baseline (2), as well as lack of statistical power to detect meaningful differences may be responsible for the lack of change. Lastly, while changes in $\dot{V}O_{2peak}$ did not achieve significant improvement, VT increased significantly, suggesting that both interventions were

effective in improving aerobic fitness. While $\dot{V}O_{2peak}$ is a valid surrogate of $\dot{V}O_{2max}$ (27), it was expected to be influenced by many factors especially in those who are not accustomed to exercising at a high intensity. Therefore, we regarded VT as more robust assessment of the intervention effects in this population.

2.5 Conclusion:

In conclusion, high adherence and retention rates indicated that, in individuals with T2D, implementing a 12-week structured high intensity interval exercise training can be as feasible as moderate intensity continuous exercise training. This information is essential for planning more definitive trials, which would require a relatively large sample size and more sensitive measures of glycemic control and intra-abdominal fat. Our results also demonstrated that 12-week HIIE and MICE interventions are equally effective in lowering total body fat but have little impact on A1c in relatively well controlled participants with type 2 diabetes.

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Table 2.1 Baseline blood profiles, anthropometric measures, body fat, and exercise performance changes over 12-week exercise training.

Variable	Intervention	Baseline	12 weeks	Changes from baseline	[a]P-value
n (M/F)	HIIE	4/4	4/4		
	MICE	4/3	4/3		
Age (year)	HIIE	62 (3)			
	MICE	63 (5)			
T2DM duration (year)	HIIE	6 (4)			
	MICE	8 (4)			
Body weight (kg)	HIIE	80.5 (9.9)	79.7 (10.2)	-0.8 (2.4)	NS
	MICE	93.9 (18.3)	92.6 (18.8)	-1.3 (0.9)	NS
BMI ($kg \cdot m^{-2}$)	HIIE	28.4 (4.1)	28.1 (4.0)	-0.3 (0.9)	NS
	MICE	33.1 (4.5)	32.6 (4.3)	-0.5 (0.9)	NS
Total body fat (%)	HIIE	36.1 (10.9)	34.2 (10.4)	-1.9 (1.4)	0.009
	MICE	41.6 (6.3)	40.1 (5.6)	-1.5 (1.5)	0.028
Trunk fat (%)	HIIE	41.7 (8.9)	39.2 (8.8)	-2.5 (1.6)	0.007
	MICE	46.1 (6.3)	44.3 (5.5)	-1.8 (2.4)	0.075
Arm fat (%)	HIIE	33.3 (15.8)	33.2 (15.5)	-0.1 (1.3)	NS
	MICE	40.0 (8.1)	39.6 (7.1)	-0.4 (2.1)	NS
Leg fat (%)	HIIE	30.0 (13.8)	28.4 (12.9)	-1.6 (1.6)	0.032
	MICE	36.7 (7.5)	35.4 (7.1)	-1.3 (1.5)	0.049
Sagittal diameter (cm)	HIIE	*24.2 (1.8)	24.3 (2.1)	0.2 (0.9)	NS
	MICE	27.7 (3.7)	28.2 (3.3)	0.5 (1.3)	NS
Waist circumference (cm)	HIIE	*102.6 (7.2)	102.2 (6.9)	-0.5 (2.6)	NS
	MICE	116.3 (11.0)	115.1 (11.5)	-1.2 (3.5)	NS
Hip circumference (cm)	HIIE	107.1 (10.3)	105.4 (9.4)	-1.7 (2.4)	NS
	MICE	116.0 (6.7)	114.3 (8.9)	1.7 (4.9)	NS
Subcutaneous fat width (cm)	HIIE	4.4 (1.6)	4.1 (1.6)	-0.3 (0.2)	0.029
	MICE	5.8 (1.9)	5.3 (1.9)	-0.5 (0.6)	0.042
Fasting glucose (mmol/L)	HIIE	6.8 (0.8)	6.7 (0.8)	-0.1 (0.8)	NS
	MICE	7.3 (1.7)	7.6 (3.0)	0.3 (2.9)	NS
	[b]MICE	7.3 (1.8)	6.7 (1.3)	-0.6 (0.9)	NS
A1c (%)	HIIE	6.6 (0.6)	6.5 (0.5)	-0.1 (0.3)	NS
	MICE	6.7 (0.9)	7.0 (1.1)	0.3 (0.5)	NS
	[b]MICE	6.6 (0.9)	6.7 (0.8)	0.1 (0.3)	NS
HDL ($mmol \cdot L^{-1}$)	HIIE	1.2 (0.2)	1.2 (0.2)	0.0 (0.1)	NS
	MICE	1.3 (0.4)	1.3 (0.4)	0.0 (0.1)	NS
LDL ($mmol \cdot L^{-1}$)	HIIE	2.0 (0.2)	2.2 (0.6)	0.2 (0.6)	NS
	MICE	1.8 (0.7)	1.8 (0.7)	0.0 (0.4)	NS
Cholesterol ($mmol \cdot L^{-1}$)	HIIE	3.9 (0.4)	4.0 (1.0)	0.2 (0.9)	NS
	MICE	3.9 (0.5)	3.8 (0.8)	-0.1 (0.3)	NS
Cholesterol to HDL ratio	HIIE	3.2 (0.3)	3.5 (0.7)	0.2 (0.7)	NS
	MICE	3.3 (1.1)	3.2 (1.3)	-0.1 (0.4)	NS
Triglyceride ($mmol \cdot L^{-1}$)	HIIE	1.5 (0.4)	1.6 (0.9)	0.1 (0.7)	NS
	MICE	2.1 (0.8)	1.6 (0.9)	-0.5 (1.2)	NS
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	HIIE	22.8 (5.4)	24.3 (7.4)	1.5 (3.2)	NS
	MICE	18.1 (2.7)	18.9 (4.1)	0.8 (2.5)	NS
$\dot{V}O_2$ at VT ($ml \cdot kg^{-1} \cdot min^{-1}$)	HIIE	10.5 (4.8)	12.2 (5.9)	1.7 (1.5)	0.025
	MICE	10.5 (1.3)	12.2 (1.5)	1.7 (1.7)	0.025
Peak power output (watts)	HIIE	145 (46)	162 (57)	17 (16)	0.029
	MICE	118 (34)	128 (35)	11 (18)	NS

HIIE, high intensity interval exercise; MICE, moderate intensity continuous exercise; A1c, glycosylated hemoglobin A_{1c}; $\dot{V}O_{2peak}$, peak oxygen consumption; VT, ventilator threshold; NS, not significant.

Values are presented as mean (SD)

[a]changes from the baseline values determined by paired sample t-tests; [b] n= 7, per-protocol analysis (one participant was excluded due to discontinuation of oral anti-hyperglycemic medication).

*significantly lower than MICE ($p<0.05$)

ANCOVA on changes from baseline showed no differences between HIIE and MICE among all parameters listed between HIIE and MICE ($p>0.05$)

Table 2.2 Means and standard deviations for psychological health, fatigue, and efficacy in response to exercise

	Exercise duration (min)	**HIIE** Mean (SD)	**MICE** Mean (SD)
PWB	30	5.5 (1.0)	5.4 (1.2)
	45	5.6 (1.0)	6.2 (0.6)
	60	5.6 (1.0)	6.5 (0.5)
PD	30	1.9 (0.9)	2.1 (1.3)
	45	1.9 (1.2)	1.3 (0.7)
	60	1.2 (0.2)	1.1 (0.2)
Fatigue	30	2.5 (0.9)	3.2 (1.7)
	45	2.5 (0.9)	2.3 (1.1)
	60	2.6 (1.6)	1.9 (1.0)
Task self-efficacy	30	8.4 (1.3)	8.8 (0.6)
	45	8.6 (0.7)	9.2 (0.8)
	60	9.2 (0.8)	9.6 (0.8)
Scheduling self-efficacy	30	7.5 (1.5)	8.0 (0.6)
	45	7.8 (0.9)	8.7 (1.4)
	60	8.3 (1.2)	9.0 (1.2)
Coping self-efficacy	30	8.0 (0.7)	8.7 (1.0)
	45	8.3 (0.9)	9.0 (0.8)
	60	8.1 (0.8)	9.1 (1.0)
Satisfaction (End of study)		6.8 (0.5)	6.8 (0.4)

PWB: Positive well-being; PD: Psychological Distress
There were no significant differences in the magnitude of changes among all parameters listed between HIIE and MICE ($p > 0.05$)

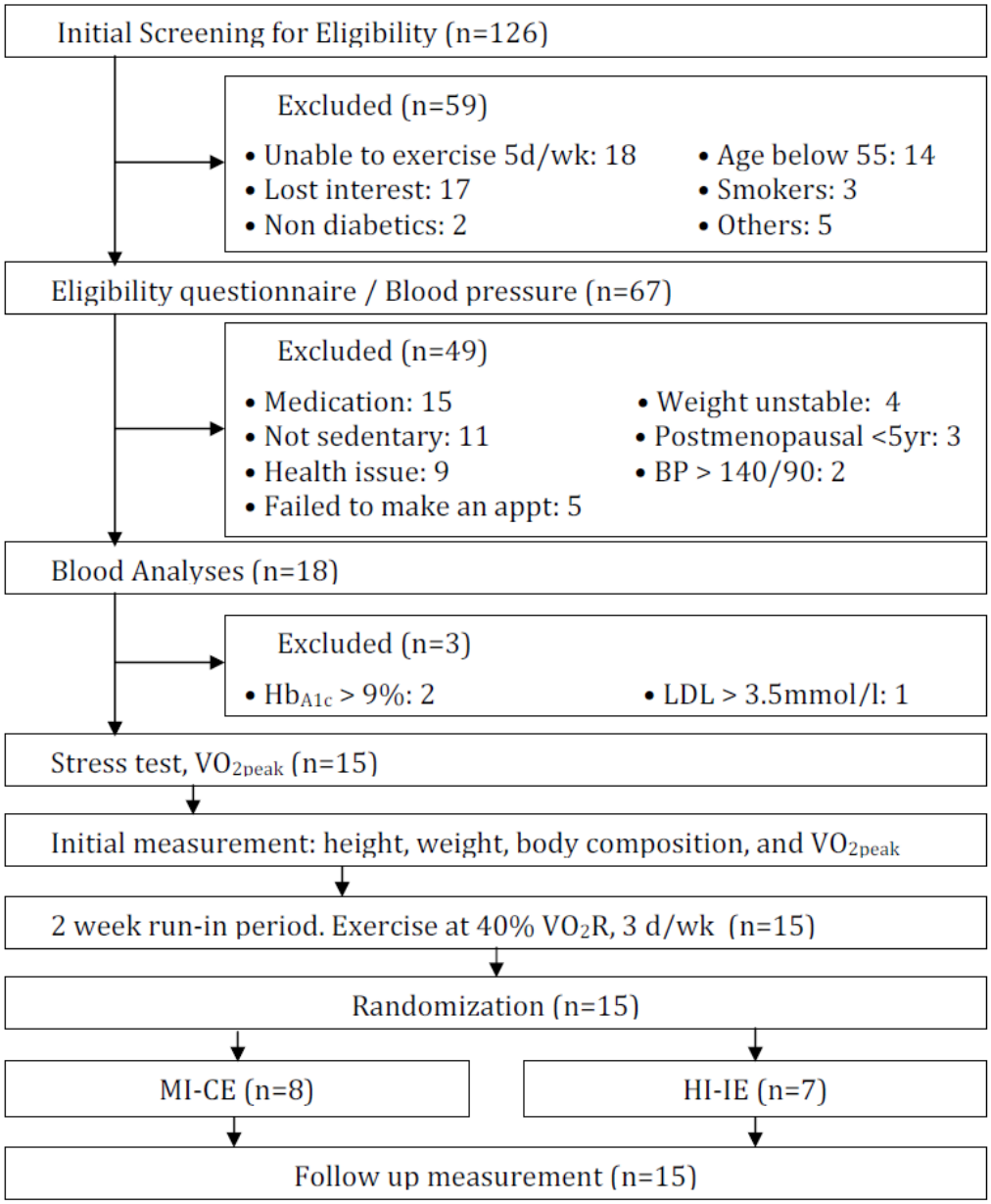

Figure 2.1 Study flow diagram

Questionnaires and 3-day dietary records were completed during the run-in phase, 6th week after randomization, and within one week of the last exercise session.

CHAPTER 3

[2]Exploring the variability in acute glycemic responses to interval and continuous exercise training in type 2 diabetes

3.1 Introduction

One of the major goals of prescribing exercise for individuals with T2D is to reduce hyperglycemia, a risk factor for long-term complications. There have been several meta-analyses demonstrating that, on average, exercise has a clinically meaningful impact on glycemic control in individuals with T2D (1-3). However, while the overall glucose-lowering effect of exercise is well recognized, large glycemic heterogeniety among studies and within individuals is often under appreciated. Indeed, there are divergent findings as to which characteristics best predict long-term improvements in glycemic control. One systematic review showed that exercise volume was the major determinant of glycemic changes in response to exercise training (4) while another showed exercise intensity is more closely associated (5).

The long-term glycemic benefit of exercise training is considered as the sum of the effects of each successive bout of exercise (6). Accordingly, an enhanced understanding of the heterogeneous acute responses to exercise may elucidate the varied degree of training effects. To date, a number of studies have examined the acute effects of different exercise interventions on blood glucose and, on the basis of these results, it is generally agreed that moderate intensity exercise reduces blood glucose (7,8). Glycemic responses to high intensity exercise, on the other hand, are inconsistent with some studies showing a greater reduction than moderate intensity exercise (8,9) while another showing markedly increased glucose concentration (10). Some researchers also argued that total exercise volume independent of exercise intensity determines the degree of glycemic reduction (11,12). Consequently, although exercise is an important

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factor for better glucoregulation, it is not clear how different exercise interventions acutely influence blood glucose.

While the contribution of different exercise interventions to the heterogeneity of glycemic responses remains to be clarified, available evidence suggests that the timing of exercise in relation to meals and medications also need to be considered. For example, Poirier et al. showed that moderate intensity exercise performed after a meal elicits a meaningful decrease in blood glucose but results in little change if performed under the fasting condition (13). Furthermore, the interactive effects of oral anti-hyperglycemic medication and exercise on blood glucose reduction have been suggested (14). Collectively, it can be speculated that glycemic responses to exercise are the result of a complex interplay between external factors that influence blood glucose concentrations and the effects of different exercise interventions.

Given that exercise is often performed at different times of the day when the influence of medication and food intake can vary, it is of importance to investigate the effect of the exercise intervention in conjunction with the timing of exercise. Elucidating the factors associated with varied glycemic responses may help explain heterogeneity in effect sizes and, thereby, lead to the development of more effective implementation of exercise interventions. The purpose of this study was to simultaneously investigate the effects of different exercise interventions and external factors known to influence exercise-induced changes in glucose concentration.

3.2 Methods

Participants: Posthoc analysis of a study examining the effects of high intensity interval exercise (HIIE) and moderate intensity continuous exercise (MICE) on A1c and abdominal fat (15) was conducted. In brief, participants were required to be diagnosed with T2D, 55–75 years of age, non-smokers, relatively sedentary (<150 minutes of structured exercise per week), and able to exercise 5 days per week (see (15) for complete details). Participants meeting the criteria had their

blood pressure (BP) measured, and those with BP < 140/90 mmHg performed a graded exercise stress test under the supervision of a physician to confirm the absence of any underlying contraindications to performing high intensity exercise. All participants provided written informed consent. Ethical approval was obtained from the University of Alberta Health Research Ethics Board.

Baseline measurement: Detailed baseline assessment was described elsewhere (15). Briefly, eligible participants reported to laboratories at the University of Alberta to assess baseline anthropometric characteristics and peak oxygen consumption ($\dot{V}O_{2peak}$). $\dot{V}O_{2peak}$ was determined using a cycle ergometer (Monark 818; Monark, Varberg, Sweden) and a TrueMax® (ParvoMedics) metabolic measurement system that was calibrated for air volume and gas concentration according to the manufacturer's instruction.

Study Protocol: The exercise intervention was comprised of a 2-week run-in period followed by a 12-week training period. The run-in period was to habituate the participants to the exercise intervention protocols and to assess their compliance. A total of 6 exercise sessions (3 sessions per week) were held during the run-in period and participants were instructed to complete a minimum of 5 sessions to be eligible for the study. The sessions alternated daily between stationary cycling and treadmill walking for 30 minutes at an exercise intensity corresponding to 40% of individually determined oxygen consumption reserve ($\dot{V}O_2R$) (16). Appropriate intensity was prescribed by adjusting the speed and slope on the treadmill, or power output on the stationary cycle (see "Intervention" in **Chapter 2** for more detail).

After the 2-week run-in period, the participants were randomly assigned (stratified by sex) to the HIIE and MICE training interventions, which were matched for exercise duration, frequency, and average relative intensity. Stationary cycling and treadmill walking were alternated daily for exercise variety. Participants were required to complete an entire exercise session on either bike or treadmill and could not alternate on a given day. The MICE group

performed continuous exercise at 40% $\dot{V}O_2R$, whereas the HIIE group repetitively performed a 1 minute interval at 100% $\dot{V}O_2R$ followed by 3 minutes at 20% $\dot{V}O_2R$ on Monday through Friday with the exception of Wednesday, when they performed MICE protocol. The duration of exercise was 30, 45, and 60 minutes per session for weeks 1-4, weeks 5-8, and weeks 9-12, respectively. Both groups exercised at the time of participants' convenience 5 days per week for 12 consecutive weeks. All training sessions were supervised.

Daily Measurement: Upon arrival to the fitness center for their exercise session, participants reported the timing of their most recent food intake and oral anti-hyperglycemic medication intake. The timing of events was chosen by the participants and not influenced by the investigators. A single capillary glucose (CapBG) was measured immediately (<10 minutes) before and after each exercise bout with a validated (17) One Touch Ultra® 2 (LifeScan Milpitas, CA. USA) handheld glucose monitor. Briefly, a finger was cleaned with an alcohol pad, allowed to dry and then was pricked with a disposable lancet. The first drop of blood was wiped off with gauze and the second drop was applied to the strip.

Data Analyses: Due to interdependent nature of the data, raw CapBG data from each participant were stratified according to exercise modality (bike vs. treadmill), exercise intensity, exercise duration, medication, and food intake. Mean blood glucose concentrations from each stratum were used for analysis.

The interval between the individual exercise bout and the most recent meal intake was stratified into <2 hours, 2-6 hours, and >6 hours prior to exercise while the time interval from the most recent oral anti-hyperglycemic medication was stratified into ≤6 hours and >6 hours. The cutoffs for food intake and medication were determined, respectively, from previous observations which revealed that hyperglycemia was most prominent for the first 2 hours subsequent to meal intake and remained elevated for the next 4 hours (18,19) and from the plasma elimination half-life of metformin (20), the most commonly used medication in these participants.

Treatment group differences in baseline characteristics were tested using independent t-test. Dependent t-test was used to compare pre- and post-exercise CapBG concentrations. To determine the independent association of exercise modality, exercise intensity, exercise duration, food intake, medication, and pre-exercise CapBG concentrations on exercise-induced CapBG changes, multiple regression analysis was performed. Categorical data were dummy coded for the analysis. Analysis of covariance (ANCOVA) with pre-exercise CapBG used as a covariate was also performed to assess if there were any interaction effects between external factors and exercise interventions.

Data are presented as mean ± standard deviation unless otherwise stated. All statistical tests were two-tailed and p values of <0.05 were considered significant. Normality of the data and lack of multicollinearity were examined by investigating the distributions of residuals and by variance inflation factor, respectively. Statistical analyses were performed with Minitab 15 statistical software (Minitab Inc., State College, PA, US).

3.3 Results

Participants: Seven participants in HIIE group and 8 in MICE completed all phases of the study. No severe adverse effect of exercise was observed and no participants dropped out from the training program once they were randomized. Adherence rates for the group mean attendance was 61 sessions for HIIE and 62 for MICE, respectively (>97 % of eligible exercise sessions for both groups). Descriptive characteristics of the 15 participants (8 males and 7 females) are summarized in **Table 3.1**.

Glycemic Responses to Acute Exercise: In total, 730 pre and 730 post exercise CapBG measures were obtained. Pre-exercise CapBG did not change over the course of either training intervention and was consistently higher in MICE ($p<0.001$). Overall changes in CapBG induced by exercise was significant (-1.9 ± 1.7 mmol; $p<0.001$). However, despite the overall glucose-lowering effect of exercise, the degree of changes was highly heterogeneous, ranging from an 8.9

mmol·L^{-1} reduction to a 2.7 mmol·L^{-1} increase. Multiple regression analysis revealed that higher pre-exercise CapBG (44%; $p<0.001$), anti-hyperglycemic medication within 6 hours of exercise (5%; $p<0.001$), food intake within 2 hours of exercise (4%, $p=0.043$), longer exercise duration (5%; $p=0.010$), and high exercise intensity (1%; $p=0.007$) were all associated with greater CapBG reduction, explaining 59% of the total variability ($p<0.001$: **Figure 3.1**). Mean pre-exercise CapBG and changes in CapBG obtained for each participant under different conditions were plotted to schematically present the effects of pre-exercise CapBG on glucose concentration changes (**Figure 3.2**). Variance inflation factors among the independent variables were low (<2.3), indicating small degree of multicollinearity among the variables. Repeated ANCOVA consistently indicated significant effects of above variables on CapBG changes induced by exercise; however, no significant interaction effects existed between exercise and food or medication.

3.4 Discussion

This study examined the factors associated with heterogeneous CapBG responses to exercise and their individual contribution to the exercise-induced CapBG reduction in individuals with T2D. The primary finding of this study is that variability in the acute glycemic response to exercise can in large part be explained by easily acquired variables such as pre-exercise glucose concentrations. In addition, while higher pre-exercise CapBG was the strongest determinant of exercise-induced CapBG changes, our results also showed that longer exercise duration and higher exercise intensity, as well as anti-hyperglycemic medication and food intake prior to exercise, magnify the reduction in CapBG.

The correlation between pre-exercise CapBG and CapBG change observed in the present study is in line with the finding of Jeng et al. in which higher pre-exercise CapBG was most strongly associated with a greater reduction in CapBG after exercise followed by exercise duration and intensity, explaining 37% of the variance (8). By including the external factors such as timing of medication and

food intake; however, we showed that our model explains more variance (59%) associated with exercise. Furthermore, because the previous study (8) did not take exercise volume into account, it was not clear whether the effect was due to exercise intensity *per se* or due to greater total exercise volume that accompanies higher exercise intensity. The setting in our study where the exercise volume was equated between 2 exercise intervention groups allowed us to investigate the effect of exercise intensity independent of exercise volume.

Our results demonstrated that, although its contribution to overall change in CapBG is small, higher exercise intensity results in greater reduction in CapBG than moderate intensity exercise matched for exercise volume. The MICE group had higher BMI at the baseline, which may explain higher fasting blood glucose and pre-exercise CapBG. After adjusting for the pre-exercise CapBG, however, our study demonstrated that high intensity exercise lowers CapBG significantly more than MICE. This finding contradicts with previous studies showing that the effect of exercise on blood glucose reduction is related to exercise volume but not to exercise intensity (11,12). Because, unlike these previous studies where energy demand was matched by altering exercise duration, we matched exercise volume and also exercise duration between the two interventions, different exercise interventions may explain the divergent glycemic responses reported. Our finding builds on previous studies indicating potential superior benefits of HIIE on body composition and insulin sensitivity (21) to isocaloric moderate intensity exercise and suggests that HIIE may also confer an additional benefit in terms of acute glycemic regulation.

The association between longer exercise duration and a greater CapBG decline observed in this study is in accordance with previous studies (7,8). Enhanced direct oxidation of excessive blood glucose associated with greater exercise volume is likely to be responsible for greater reduction in CapBG. Likewise, small difference in calculated exercise volume (0.7 $KJ \cdot min^{-1}$ difference) may explain the lack of difference in CapBG responses between bike and treadmill. Collectively, our results suggest that both greater exercise intensity and volume may contribute to greater reduction in CapBG.

Another important finding from the present study was that the timing of exercise can influence the exercise-induced CapBG reduction. Multiple regression analysis revealed that in addition to pre-exercise CapBG and exercise intervention, medication within 6 hours and food intake within 2 hours of exercise significantly increased the glucose-lowering effect of exercise. ANCOVA with pre-exercise CapBG as a covariate also confirmed significant effects of food intake and medication after accounting for pre-exercise CapBG differences ($p<0.05$). These results suggest that exercise after meal intake can enhance the glucose-lowering effect of exercise and that medication and exercise have an additive effect on CapBG reduction.

The finding that food intake accentuates exercise-induced CapBG reduction seen in our study was similar to that of Poirier et al., who reported little changes in plasma glucose when individuals with T2D performed moderate intensity aerobic exercise under fasting conditions while reported significant decreases in plasma glucose under fed conditions (13). In addition to these findings, however, we propose that the effect of prior meal intake persists during HIIE. When meals are consumed before exercise, meal-induced hyperglycemia and hyperinsulinemia blunt hepatic glucose output (22), which may have led to a greater imbalance between glucose production and utilization and thereby accentuated the reduction in CapBG. It is also possible that exercise was performed during the period when postprandial glucose was declining, producing synergistic effect with exercise. It can be postulated that exercise performed >6 hours after a meal, on the other hand, lacked the suppressive effect of meal-induced hyperglycemia and hyperinsulinemia on endogenous glucose production and resulted in smaller changes in CapBG. Given the possible pathogenic role postprandial hyperglycemia plays on the risk of diabetic complications (23,24), performing exercise within 2 hours of meal intake may be a good strategy to attenuate meal-induced hyperglycemia.

A magnified CapBG reduction after administration of anti-hyperglycemic medications may not be surprising as they often increase insulin secretion and/or insulin sensitivity in individuals with T2D. Nonetheless, an additive effect of

exercise and medication has only been shown with sulfonylurea (25-27) but not consistently with metformin (14,28), which was taken by the majority of our participants. Studies investigating the effect of exercise plus metformin are limited and the effect is somewhat equivocal. Since some of our participants were taking a combination of different types of medication, it is difficult to compare our results to existing studies separately investigating the combined effects of exercise and metformin (14,28) or exercise and sulfonylurea (25-27). However, when we repeated the same multiple regression analysis after separating the group according to the medication types, i.e., metformin only versus other types such as sulfonylurea and sitagliptin, the effect of medication was no longer significant in metformin group ($p=0.085$), whereas it remained significant in the combined group ($p=0.009$). Therefore, although lack of the significant effect of metformin may be simply due to low power, it is also possible that in the present study the effect of medication was mostly attributable to sulfonylurea and sitagliptin, or these medications combined with metformin. No severe hypoglycemia (CapBG <3.0 mmol$\cdot L^{-1}$) was observed in our exercise groups and this may indicate that medication combined with exercise poses a relatively small risk of hypoglycemia in individuals with relatively well controlled T2D (mean A1c = 6.7%), and the risk is likely to be smaller when only metformin is administered.

An important limitation of the study is that we only evaluated CapBG responses using a single-point measure and we were unable to determine how blood glucose responded during exercise as well as hours after exercise. Given that improved insulin sensitivity may last 24 hours after a bout of exercise without acute reduction of blood glucose (10), it is possible that exercise bouts resulting in small changes in CapBG observed in the present study led to improved glucoregulation hours following the bout. Nonetheless, because there were no changes in pre-exercise CapBG over the 12 weeks, the effects of exercise performed on the preceding days on CapBG are considered relatively small. The use of a device such as a continuous glucose monitor may provide more complete view of glycemic responses.

3.5 Conclusion

In conclusion, changes in glucose following exercise bouts can be highly variable. Our results showed that pre-exercise CapBG is the strongest predictor of changes in CapBG induced by exercise accounting for more than 40% of the variability. Furthermore, the glucose-lowering effects of exercise can be accentuated by increasing exercise intensity *per se* without altering exercise volume and/or by increasing exercise duration (volume), as well as by exercising after consuming meals and/or anti-hyperglycemic medications. These results suggest that individuals with less well controlled blood glucose, or those who manifest elevated glycemia prior to exercise may benefit more from participating in exercise at least in terms of acute glucose control. Lower blood glucose can be achieved with moderate intensity exercise but including brief bouts of intense exercise and/or prolonging exercise duration can result in a greater glucose reduction if the individual is cable of doing so. These effects of exercise on glycemia can further be enhanced by performing exercise within 2 hours of meal intake, and by combining sulfonylurea and sitagliptin. Adding metformin to exercise did not result in significant greater reduction in glucose concentration. However, this result needs to be interpreted with caution given the small sample size used in the present study. Above variables could be considered by people with T2D and their health care providers to plan exercise intervention and exercise timing to favor greater glycemic improvements. It remains to be seen if the strategy to produce greater acute blood glucose reduction can produce greater longer term improvements in glycemic control as reflected by A1c.

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Table 3.1 Baseline Characteristics

	MICE	HIIE	Total	P-value
n (M/F)	4/4	4/3	8/7	
T2D duration (year)	8 ± 4	6 ± 4	7 ± 5	0.41
Body Weight (kg)	93.9 ±	80.5 ± 9.9	87.7 ± 16.0	0.10
BMI ($kg \cdot m^{-2}$)	33.1 ±	28.4 ± 4.1	30.9 ± 4.8	0.06
anti-hyperglycemic medication				
Metformin alone, n	4	4	8	
Metformin & Sitagliptin, n	1	1	2	
Sulfonylurea & Metformin, n	2	0	2	
Sulfonylurea & Sitagliptin, n	1	0	1	
Fasting blood glucose ($mmol \cdot L^{-1}$)	7.3 ± 1.7	6.8 ± 0.8	7.1 ± 1.3	0.48
A1c (%)	6.7 ± 0.9	6.6 ± 0.6	6.7 ± 0.7	0.76
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	18.1 ± 2.7	22.8 ± 5.4 [a]	20.1 ± 4.5	0.10

MICE, moderate intensity continuous exercise; HIIE, high intensity interval exercise; $\dot{V}O_{2peak}$, peak oxygen consumption; A1c, glycosylated hemoglobin.
P-value refers to comparisons between HIIE and MICE by independent t-test.
Values are presented as mean ± standard deviation. There was no significant difference between HIIE and MICE.
[a] n=6, $\dot{V}O_{2peak}$ was not available for one participant.

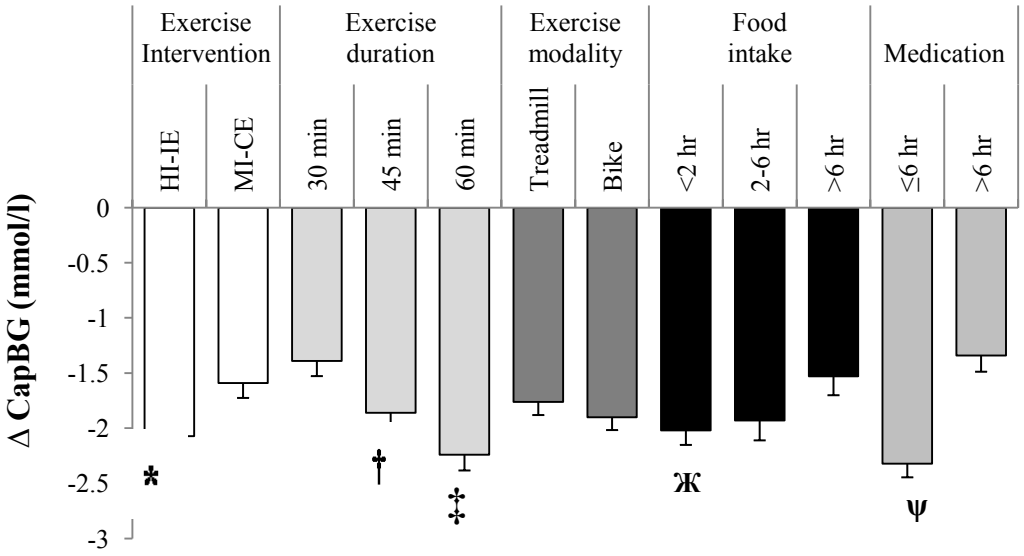

Figure 3.1 Effects of exercise intervention, exercise duration, exercise modality, food intake, and medication on exercise-induced CapBG reduction.

Values are least square mean ± SE.
***** HIIE (p=0.007), † 45-min exercise (p=0.015), ‡ 60-min exercise (p<0.001), **Ж** food intake <2 hours (p=0.043), and **Ψ** medication ≤6 hours of exercise (p<0.001) were all associated with greater CapBG reduction.
HIIE: high intensity interval exercise; MICE: moderate intensity continuous exercise; CapBG: capillary blood glucose

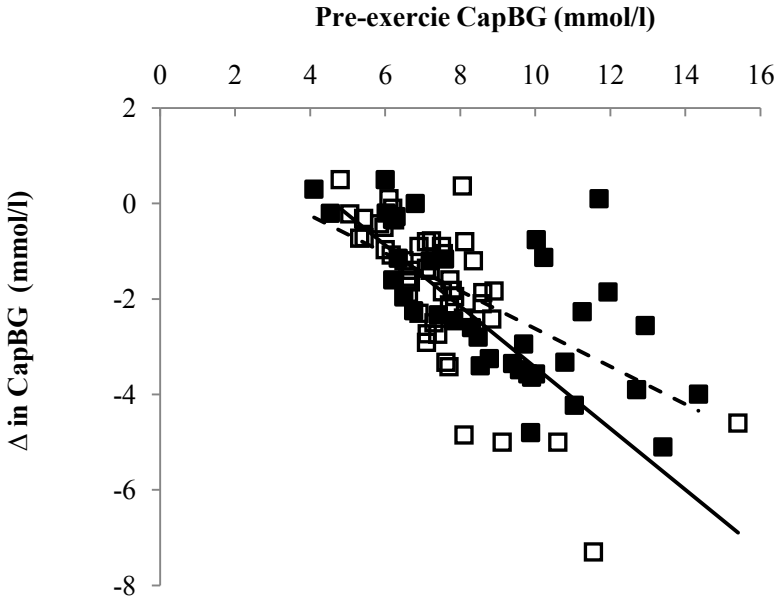

Figure 3.2 Correlations between pre-exercise CapBG and exercise-induced CapBG changes for both HIIE and MICE.

Filled and open squares represent MICE and HIIE, respectively.
Dotted and straight lines are regression lines of MICE and HIIE, respectively.
Glucose data obtained from each participant are categorized based on exercise intensity, duration, and modality, as well as food and medication status. Each box in the figure represents the mean glucose value obtained from each participant under different conditions.
HIIE: high intensity interval exercise; MICE: moderate intensity continuous exercise; CapBG: capillary blood glucose

CHAPTER 4

[3]Test-retest reliability of a continuous glucose monitoring system in individuals with type 2 diabetes

4.1 Introduction

The importance of controlling glycemia to avoid microvascular complications has been established (1–4). However, the assessment of glycemia under free-living conditions in a minimally invasive manner still remains a challenge. Self-monitored blood glucose and glycosylated hemoglobin (A1c) measurements have provided patients with diabetes and their healthcare professionals with the information necessary for planning the most appropriate antidiabetes treatment to optimize blood glucose. However, self-monitored blood glucose is invasive, cumbersome, and predominantly episodic in nature, making it difficult to capture rapid and overall changes in glucose concentrations in response to various stimuli. Similarly, A1c does not reflect short-term glycemic changes, such as postprandial glucose spikes and daily glycemic variability.

Recently, the advent of continuous glucose monitoring systems (CGMSs) has made it possible to measure a continuous temporal line of glucose concentrations. This continuous stream of data captures glucose concentrations in the context of its direction, periodicity, and amplitude in relation to food, exercise, and medication, providing an important overview of glycemic profiles. Furthermore, the continuous glucose data allow the documentation of glycemic variability, a strong stimulus that increases cellular oxidative stress (5), which can exacerbate endothelial cellular function (6). Detection of abnormalities in these variables can lead to tighter glycemic control and facilitate adjustments in therapy to improve glycemic control (7). The iPro2 CGMS (Medtronic, Northridge, CA) has been approved by the U.S. Food and Drug Administration and Health Canada, and its use has increasingly been investigated in individuals with T2D. Although

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the accuracy of the Medtronic sensors has been examined under various conditions (8–10) the test–retest reliability of the device has not been published. Consequently, to validate the measures of the device, it is important to evaluate its test–retest reliability. The purpose of this study was to determine test-retest reliability of various glucose profiles estimated based on iPro2 CGMS measures in individuals with T2D. In the current study, all CGMS measures were considered equally import, and none was specified as primary or secondary outcomes.

4.2 Methodology

Participants: Fifteen individuals with a clinical diagnosis of T2D treated with or without oral hypoglycemic agents were recruited. Inclusion criteria were as follows: between 40–75 years of age; not on exogenous insulin; non-smokers; comfortable staying in the isolated room over two 24-h periods; no dietary restrictions (i.e., celiac disease or severe food allergies); not on medication with known effects on energy expenditure; blood pressure <140/90 mmHg; stable body weight for the previous 6 months (<2.3 kg change); and no history of cardiovascular disease.

Pre tests: During the first visit, the nature of the study was explained, and anthropometric measures were obtained. Weight and height were measured with a stand-on scale (Health o meter; Pelstar LLC, McCook, IL) and wall-mounted stadiometer. Each participant was also introduced to the calorimetry unit. During the second visit, participants performed a modified Bruce graded exercise test (11). Expiratory gases were analyzed by a calibrated TrueOne® 2400 (ParvoMedics, Sandy, UT) metabolic measurement system, and ventilatory threshold was determined using the v-slope method (12). An oxygen consumption–carbon dioxide production curve was graphically monitored during the incremental exercise test. Exercise was terminated once a change in the slope of the curve caused by excess carbon dioxide production was visually determined.

The ventilatory threshold was used to establish the intensity of exercise to be performed within the calorimetry unit.

Standardized condition: Each participant spent two nonconsecutive days (1 day in between at home) in the whole-body indirect calorimetry unit, a self-contained airtight unit comprising a bed, chair, sink, toilet, television, personal computer, and treadmill. Participants were instructed to avoid intense physical activity the day before the test and to report to the unit by car or public transportation after at least 10 hours of fasting. On the first testing day (Day 1), participants reported to the laboratory at 07:00 hour. When the subject arrived, a Sof-sensor® (Medtronic) was subcutaneously inserted to the anterior abdominal area with the help of a designated device (Sen-serter; Medtronic). After enough time (>15 minutes) was allowed to wet the sensor, the iPro2 CGMS (Medtronic, Northridge, CA) was connected. At 08:00 h, the participant entered the calorimetry unit and remained supine on the bed for 1 hour. Meals standardized to meet individual energy requirement and a specific macronutrients distribution (50% carbohydrate, 30% fat, and 20% protein) were provided at 09:05, 12:00, and 18:00 hour. Standardized snacks were also provided at 15:00 and 21:00 hour. Participants were instructed to eat all the food and beverages provided within 30 minutes. Participants consumed their prescribed oral anti-hyperglycemic medication at their usual time as instructed by their physicians.

Capillary blood glucose was measured 5 minutes before each meal and 15 minutes before bed with a OneTouch® Ultra® 2 (LifeScan, Milpitas, CA) handheld glucose monitor, which has previously been validated(13). At 14:00 hour, each participant performed a 30-minute individualized treadmill walking protocol followed by 5 minutes of cool-down. The walking intensity was determined as the intensity corresponding to the stage below ventilatory threshold in the graded exercise test. Lights were turned off at 22:30 hour, and participants were instructed to sleep until 06:30 hour the following day. At 07:15 hour, participants left the calorimetry unit. During the hours of no assigned tasks,

participants were instructed to stay awake and perform their preferred sedentary activities, such as reading or watching television. On completion of 23 hours 15 minutes in the unit, participants spent 1 day outside of the calorimetry unit and returned on the following day at 07:00 hour to repeat the protocol (Day 2). At 07:15 hour on the final experimental day, participants exited the calorimetry unit, and the CGMS was removed. The temperature and relative humidity of the unit were maintained at approximately 22 °C and 55%, respectively, and the unit was continuously monitored by research assistants on both testing days. Energy expenditure was recorded every minute during the participants' stay.

Dietary intake: Meal portion size was individualized to target energy balance based on caloric expenditure measured in the calorimetry unit. ESHA food processing software (ESHA Research, Salem, OR) was used to standardize macronutrients proportions (i.e., 50% carbohydrate, 30% fat, and 20% protein) despite different meal portion sizes among participants. Participants were provided with the same food on Day 2. In rare cases where participants were unable to consume all food provided, caloric contents of leftovers were determined and subtracted from total daily caloric intake.

CGMS measures: Stored CGMS data were exported to an online program (CareLink iPro; Medtronic). The glucose data from a handheld glucose monitor were also entered to convert measured signals into glucose values as per the manufacturer's instruction. Because CGMS glucose values are only available after the entry of the first handheld glucose monitor measurement, CGMS data from 09:00 to 07:00 hour the following day obtained from Day 1 and Day 2 in the calorimetry unit were used for analysis. Several outcomes variables were calculated from CGMS data, including daily mean glucose over the entire 22-hour period (GLU_{mean}), glycemic variability, mean glucose concentrations in response to breakfast, lunch, and supper (2-hour mean since each meal was provided), mean glucose during exercise and 2-hour post-exercise, mean nocturnal

glucose (24:00–05:00 hour), and time spent in hyperglycemia (glucose concentrations >10.0 mmol·L^{-1} [$t_{>10.0mmol·L^{-1}}$]) for both testing days. Within-day glycemic variability was assessed by glucose SD_w (14), within-day percentage coefficient of variation (%cv_w) (14), mean amplitude of glycemic excursions (MAGE) (15), and continuous overlapping net glycemic action ($CONGA_n$) (16). SD_w was the SD of all of the measurements over the 22-hour period. %cv_w was calculated as ([SD_w/mean]·100). MAGE was estimated using three different protocols: the classical protocol as developed by Service et al. (15), which is the mean of single direction glucose excursions (either nadir to peak or peak to nadir) that exceeded 1 SD ($MAGE_c$); the average of both upward and downward excursions that exceeded 1 SD ($MAGE_{ave}$) (17); and an absolute group of signs method using both upstroke and downstroke excursions introduced by Zaccardi et al. ($MAGE_{abs.gos}$) (18). Graphical approaches were used for $MAGE_c$ and $MAGE_{ave}$. The value of 1 SD calculated for each testing day for each participant was used to calculate MAGE on each testing day. All calculation was completed by a single researcher. $CONGA_n$ was calculated as the SD of the glycemic differences between a specific point on the CGMS measure and another measure ‘‘n’’ hour(s) previous to the observation (19). $CONGA_1$, $CONGA_2$, $CONGA_4$, $CONGA_6$, $CONGA_8$, $CONGA_{10}$, and $CONGA_{12}$ were examined for their reliability. Lastly, the mean of daily differences (MODD) over 2 days ($MODD_2$) (14) was also examined for between-days glycemic variability. $MODD_2$ was calculated as the mean of absolute differences between glucose values at the same time of the two testing days.

Statistical analysis: Paired t test was initially performed for each variable to assess if there was a significant systematic difference between the testing days. Subsequently, both absolute and relative reliabilities were assessed to determine test-retest reliability of CGMS-estimated variables. The relative reliability was assessed using intraclass correlation coefficients (ICCs) based on a two-factor mixed-effects model and type consistency using average measures ($ICC_{3,k}$): (MS_S – MS_E)/(MS_S), where MS_S and MS_E represented the subject’s mean square and an

error mean square, respectively (20,21). The absolute reliability was assessed by coefficient of variation (CV) ([SD/mean]·100). All data are presented as mean ± SD values. The α level was set at 0.05 for statistical significance. Statistical analyses were performed with SPSS statistical software (SPSS Inc., Chicago, IL).

4.3 Results

Participants: Fourteen participants completed both testing days. One participant only completed the first day because of a minor allergic response in the calorimetry unit and was excluded from analysis. Of the 14 participants, one participant did not consume anti-hyperglycemic medication consistently on both days and was excluded. In addition, sporadic data were obtained from one participant on the second day, probably because of a loose sensor. Consequently, the data from 12 participants were included for analyses. No participant reported discomfort or negative effects for CGMS use except for minor bruising and irritation caused by adhesive tapes.

Descriptive characteristics of the 12 participants (6 males and 6 females) are summarized in **Table 4.1**. Of the 12 participants, three were not on any oral anti-hyperglycemic medication, three were on metformin alone, and the rest consumed various combinations of oral anti-hyperglycemic medication (e.g., metformin, sitagliptin/metformin, gliclazide, and repaglinide). Glycemic responses over two 22-hour periods are presented in **Figure 4.1**.

Dietary intake and energy expenditure: The participants' daily average energy expenditures for Day 1 and Day 2 were 2,273 ± 367 and 2,224 ± 353 kcal, respectively (mean difference of 49 ± 39 kcal; P = 0.001). Mean caloric intakes for Day 1 and Day 2 were 2,367 ± 330 and 2,337 ± 348 kcal, respectively (mean difference of 30 ± 97 kcal; P = 0.300). Of the 12 participants, one experienced low glucose concentration (<4.0 $mmol \cdot L^{-1}$) on the first day, and glucose tablets and juice were provided as prescribed by our safety protocol, making energy intake on the first day greater than the second day (+150 kcal). In another case, one participant showed markedly higher energy intake than energy expenditure on

the first day (+250 kcal), and thus the food portion was made smaller on the second day (–230 kcal). Lastly, one participant showed lower caloric intake on the second day after subtracting calories from leftover food (–130 kcal).

Daily glycemic responses: **Table 4.2** presents the reliability of various CGMS-related outcome measures. One participant was excluded from daily glucose analysis because of an unexpected large glucose spike in the morning immediately after the beginning of CGMS measurement on Day 1. Four individuals were not included in the analysis for $t_{>10.0mmol \cdot L}^{-1}$ as they spent no time in glucose concentration >10.0 $mmol \cdot L^{-1}$. Relative reliability as examined by $ICC_{3,k}$ was significant for GLU_{mean} ($P < 0.001$) and $t_{>10.0mmol \cdot L}^{-1}$ ($P < 0.01$). Absolute reliabilities for GLU_{mean} and $t_{>10.0mmol \cdot L}^{-1}$ were 3.9% and 59.4%, respectively. Among the various measures of glycemic variability, paired t test showed a systematic difference between the testing days in $MAGE_c$, $MAGE_{ave}$, $CONGA_6$, and $CONGA_{12}$. SD_w, $\%cv_w$, and $MAGE_{abs.gos}$ showed significant intraclass correlation ($P < 0.05$) and similar absolute reliability with CV ranging from 13.2% to 17.4%. Among different CONGA values, those with smaller "n," such as $CONGA_1$, $CONGA_2$, and $CONGA_4$, showed significant relative reliability ($R \geq 0.86$; $P < 0.01$). However, both absolute and relative reliabilities deteriorated as "n" or the distance between the two measures increased. For daily glucose profiles, heteroscedasticity was evident in Bland–Altman plots (22) (data not shown), indicating the tendency for larger measurement differences with higher mean values. The overall results were unaffected when statistical analyses were repeated after excluding the participants who showed large day-to-day differences in energy intake. Between-day variability as determined by $MODD_2$ was 0.9 ± 0.2 $mmol \cdot L^{-1}$.

Post-meals, exercise, and nocturnal glycemia: Reliability statistics for CGMS-measured glucose responses to meals and exercise and for nocturnal glycemia are also shown in **Table 4.2**. All but one participant had a treadmill exercise speed of 1.7 mph and slope of either 5% or 10%; one participant walked with the speed of

2.5 mph and 12% because of better performance during the baseline fitness test. All 12 participants completed the prescribed exercise protocol. There was no difference in energy expenditure during exercise between Day 1 and Day 2 (5.3 ± 1.2 and 5.2 ± 1.0 kcal/min, P=0.173). Paired t tests showed no between-day differences in glucose profiles in responses to meal intake or exercise, or in nocturnal glycemia. Relative reliability was significant for mean post-meal glucose concentrations ($0.77 \leq R \leq 0.88$; $P<0.01$ for post-breakfast and post-lunch, $P<0.05$ for post-supper), mean glucose concentrations during and post-exercise ($0.91 \leq R \leq 0.95$; both $P<0.001$), and mean nocturnal glycemia ($R=0.92$; $P<0.001$). Absolute reliability as determined by CV ranged from 6.5% to 11.7%.

4.4 Discussion

To our knowledge, this is the first test–retest reliability study of CGMS. Under standardized 22-hour periods, the Medtronic iPro2 system displayed high relative reliability for outcomes in both long-term and short-term measures such as GLU_{mean}, glycemic responses to meals and exercise, and nocturnal glycemia. Furthermore, compared with a previous study showing a test-retest intra-T2D-individual biological CV of 7.0% and 12.7% for fasting blood glucose and 2-hour post–oral glucose tolerance test, respectively (23), we found the absolute reliability of these CGMS variables also high. Among different measures for glycemic variability, our results indicated that SD_w, $\%cv_w$, and $MAGE_{abs.gos}$ had no systematic differences between the testing days and showed significant relative reliability. Absolute reliability was similar among these measures. Relative and absolute reliabilities of $CONGA_n$ measures were also high when small n was used ($n \leq 4$). These results support the applicability of CGMS to estimate daily glycemic profiles, as well as various short-term treatment effects.

Although Molnar et al. (24) measured this value only in one participant, the previously reported MODD under a standardized near-normal conditions in an individual with stable diabetes was reported to be 1.94 $mmol \cdot L^{-1}$. Our lower $MODD_2$ value of 0.9 ± 0.2 showed very small interday variability, which reflected the more standardized and consistent condition we created for both testing days.

Under this standardized condition, among measured daily glycemia, the relative reliability of $t_{>10.0mmol\cdot L^{-1}}$ was comparable to GLU_{mean} and was high. However, the absolute reliability of this variable was poor. This is likely because statistical tests, such as paired t test and ICC, can largely be influenced by sample heterogeneity and random variations between the tests (25). Considering that slight differences in glucose concentrations between days (i.e., 9.9 vs. 10.1 $mmol\cdot L^{-1}$) can contribute to large inconsistency, low absolute reliability may not be surprising. Nonetheless, highly heterogeneous results (our mean $t_{>10.0mmol\cdot L^{-1}}$ of Day 1 and Day 2 ranged from 48 to 1,083 minutes) seem to have contributed to high relative reliability. As absolute reliability represents the degree to which repeated measures vary for individuals (25), one must be cautious when investigating glycemia using $t_{>10.0mmol\cdot L^{-1}}$ at an individual level.

Within-day glycemic variables measured in the present study were similar to previously reported values. SD_w, $CONGA_1$, and $MAGE_c$ were similar to the previously reported values from individuals with T2D treated with diet only (1.17±0.56, 1.08±0.48, and 3.17±1.53, respectively) (26) Although our other CONGA values ($CONGA_2$-$CONGA_6$) were lower than previously reported values from a group with T2D(27), this is probably owing to better overall glycemia in our participants (mean glucose concentration, 7.0±1.2 vs. 10.6±3.3 $mmol\cdot L^{-1}$). These comparisons showed that our results were comparable to previously reported CGMS variables. Because many variables were estimated for glycemic variability, we also performed correlation analysis among measures (data not shown). The results were also very similar to those of previous reports (28,29). There were significant and high linear correlations among most of the measures, indicating these measures are conveying largely the same information. In addition, our ratio of $MAGE_c$ to SD_w was 2.43, which was in close agreement with previously reported values of 2.62 (26) and 2.54 (29), further indicating the relationships among our measured glycemic variability parameters were similar to previously reported ones. Despite the high correlations among measured variables, we observed no between-day systematic differences and relatively high reliability for SD_w, $\%cv_w$, $MAGE_{abs.gos}$, and $CONGA_n$ with $n\leq 4$, versus either

significant systematic difference or nonsignificant ICC for $MAGE_c$, $MAGE_{ave}$, and CONGA with n≥6. Our results showing that only the $MAGE_{abs.gos}$ computation method was reproducible (significant ICC with no systematic difference) among different MAGE methods are interesting given that $MAGE_c$ has previously been reported as the gold standard metric for measuring glycemic variability (6). Although $MAGE_c$ has frequently been used in literature, its ambiguity has been indicated (30). Because $MAGE_c$ only includes the glycemic excursions that correspond to the direction of the first major glucose swing, direction of the glycemic excursions was expected to play a major role in determining $MAGE_c$. However, 10 out of 11 participants in our study consistently showed an upward glycemic swing for their first major glycemic excursion on both testing days. Also, excluding the one participant who indicated inconsistent directions in glycemic excursion did not have a major impact on the results. Therefore, the direction of the excursions cannot explain the low reliability. Instead, it is speculated that less arbitrary determination of peaks and nadirs in $MAGE_{abs.gos}$ (18) resulted in higher reliability.

For SD_w, its application to CGMS-measured glucose values has been criticized for the lack of normal distribution in glucose concentrations (glucose concentrations of individuals with T2D are often skewed towards hyperglycemia), a mathematical condition for the use of SD (31). Consequently, we repeated SD_w calculation using log-transformed glucose values (14). The results remained robust ($R= 0.74$; $P< 0.05$). As previously indicated, given the high correlation between $MAGE_c$ and SD_w ($r = 0.85$ and 0.87 in the present and previous study (14), respectively), it is probable that SD_w and $MAGE_c$ convey primarily the same information. Because SD_w is easy to calculate and interpret (30), with its high reliability, SD_w may be a practical method that could be appreciated by clinicians and care practitioners in determination of glycemic variability. A recent study has also shown that SD is a significant predictor of coronary artery calcification in men with type 1 diabetes (32), suggesting its application for diabetes complications research. The $\%cv_w$ also indicated absolute and relative reliabilities to similar to those of SD_w, probably because mean glucose concentrations from

Day 1 and Day 2 were very similar (note that $\%cv_w$ was calculated as [SD_w /mean]·100).

Lastly, among the different "n" for CONGA calculations, $CONGA_1$ and $CONGA_2$ showed particularly high absolute and relative reliability. Nonetheless, reliability of $CONGA_n$ was lowered as n increased. Because $CONGA_n$ is calculated as the SD of the difference between an observation and observation n hour(s) before, our results suggest prolonging the duration between measurements increases test-retest variability. The lower reliability in proportion to an increase in n observed for different CONGA values is likely due to increased variability. As described by Rodbard (14), glycemic variability increases as the duration of the time frame increases. Thus, increased variability with the use of larger n may have contributed to lower reliability.

It is of importance to note that this also suggests that lower reliability of MAGE and SD_w compared with $CONGA_1$ and $CONGA_2$ may be due to the difference that MAGE and SD_w are based on the whole 22-hour period, whereas $CONGA_1$ and $CONGA_2$ are based on the glycemic variability only 1 or 2 hours apart. Because the period of 22 hours involves more factors that can affect variability than the shorter time frames, the longer time frame used for MAGE and SD_w calculation may have resulted in lower ICC and higher CV than the short-term criteria such as $CONGA_1$ and $CONGA_2$. Additionally, whether $CONGA_n$ measures with small n provide better and sensitive measure of changes or are equally informative in predicting clinical events or complications has yet to be investigated. In fact, although the $MAGE_c$ predicts total free radical production (5) and oxidative stress (27), in our study, the correlation between $MAGE_c$ and $CONGA_1$ was relatively small ($r= 0.46$, $P= 0.155$ for Day 1). It is also of importance to note that the intent of our study was to report the test-retest reliability of variables obtained from CGMS, not to suggest that certain measures are better than the others. Reliability of a measure is one aspect to predict clinical outcome, and high reliability does not necessarily translate into clinical or epidemiological importance. Given that $CONGA_n$ with small n measures high-frequency variability (hour to hour), whereas that with large n measures medium-

frequency variability (the circadian changes during the course of the day) (31), from reliability perspective, our results simply indicated that $CONGA_n$ may be useful if high-frequency glycemic variance is of interest but not for lower-frequency measures. Other methods, such as SD_w, $\%cv_w$, or $MAGE_{abs.gos}$, are more reliable for the longer-term estimation of glycemic variability.

One of the limitations to the present study was the significantly different energy expenditure regardless of the sedentary environment we provided. Nonetheless, given the small difference in energy expenditure between the days (< 50 kcal), the significant difference was likely attributable to a small random error and consistently lower energy expenditure on Day 2, possibly because of accustomization to the environment (10 out of 12 participants had smaller energy expenditure on the second day). Of the 10 participants, half of them showed a higher mean glucose concentration on Day 1, whereas the other half showed higher values on Day 2, suggesting a relatively small impact of energy expenditure despite the significant difference.

Another limitation was that we were unable to identify to what degree random errors were stemming from sensor errors or from biological fluctuations. The variability estimates reported here consists of the sum of biological fluctuation and possible within-sensor variability. However, a previous report showed that sensor performance was not affected by sensor life (33). Moreover, based on the fact that the CGMS devices were calibrated on both testing days using the same handheld glucose monitor, we speculate that the CGMS performance was similar on both days. Consequently, the values reported here are expected to be more closely associated with day-to-day biological fluctuations under minimal external stimuli. A less standardized environment, as well as allowing more time between testing sessions, will increase the biological fluctuations.

Lastly, the relatively small sample size used in the present study, especially in examining the reliability of $t_{>10.0 mmol \cdot L^{-1}}$, was another limitation. Because four of our 12 participants had glucose concentrations that remained below 10.0 $mmol \cdot L^{-1}$ on both testing days and one showed an unexplainable large

glucose spike in the morning, the result was based on seven participants. We cannot exclude the possibility that insufficient sample size is contributing to the large absolute variability for $t_{>10.0 mmol \cdot L^{-1}}$. A study with a larger sample size is warranted to elucidate the absolute reliability of $t_{>10.0 mmol \cdot L^{-1}}$.

4.5 Conclusion:

In conclusion, under the condition where glycemia was measured repeatedly within individuals with T2D who are not treated with exogenous insulin, we demonstrated that CGMS measurements are reliable when estimating GLU_{mean}, short-term glycemic responses to meals and exercise, and nocturnal glycemia. Caution is needed when using $t_{>10.0\ mmol \cdot L^{-1}}$ as it indicated high relative but poor absolute reliability. With regard to glycemic variability measurements, we demonstrated that $CONGA_n$ measurements with $n \leq 4$ are reliable in measuring high-frequency variability, whereas SD_w, $\%cv_w$, and $MAGE_{abs.gos}$ are reliable methods for longer-term glycemic variability. Although it remains to be seen which of the different glycemic parameters will be embraced by the investigators and clinical practitioners, our study examining the test–retest reliability of various CGMS measures provided one important aspect to consider.

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Table 4.1 Participants characteristics

Variables	All (n=12)	Women (n=6)	Men (n=6)
Age (year)	57 ± 10	51 ± 8	62 ± 9
Duration of T2D (year)	11 ± 9	15 ± 12	8 ± 4
Height (cm)	168.4 ± 7.8	165.8 ± 9.4	171.0 ± 5.4
Weight (kg)	80.2 ± 19.3	71.6 ± 21.6	88.9 ± 13.1
BMI ($kg \cdot m^{-2}$)	28.1 ± 5.5	25.8 ± 6.3	30.4 ± 3.8

BMI: body mass index. Data are mean ± SD

Table 4 2 Absolute and relative reliability of daily and short-term glucose profiles.

	Day 1	Day 2	T	[a]Average CV (%)	Intraclass correlation (R)	95% CI
Glucose (mmol·L^{-1})						
[b]22-hour mean	7.0 ± 1.2	7.1 ± 1.1	-0.81	3.9	0.95***	0.81-0.99
Post-breakfast mean glucose	8.4 ± 2.2	8.6 ± 1.6	-0.59	9.3	0.88**	0.57-0.97
Post-lunch mean glucose	7.8 ± 1.8	7.8 ± 1.5	-0.05	6.5	0.86**	0.50-0.96
Post-supper mean glucose	7.2 ± 1.7	7.2 ± 1.8	0.08	11.7	0.77*	0.20-0.93
Exercise mean glucose	7.0 ± 1.9	7.4 ± 1.6	-2.02	7.3	0.95***	0.83-0.99
Post-exercise mean glucose	7.3 ± 2.0	7.9 ± 1.5	-2.15	8.9	0.91***	0.70-0.98
Nocturnal mean glucose	6.7 ± 1.5	6.7 ± 1.7	0.03	7.9	0.92***	0.71-0.98
[c]$t_{>10.0mmil/L}$ (min)	250 ± 311	249 ± 451	0.02	59.4	0.93**	0.58-0.99
[b]SD_w (mmol·L^{-1})	1.16 ± 0.37	1.02 ± 0.35	1.59	16.3	0.80*	0.24-0.95
[b]$\%cv_w$ (mmol·L^{-1})	16.8 ± 5.2	14.4 ± 4.7	1.80	17.4	0.74*	0.05-0.93
[b]$MAGE_c$ (mmol·L^{-1})	2.83 ± 1.17	2.08 ± 0.66	2.38*	20.7	0.56	-0.62 to 0.88
[b]$MAGE_{ave}$ (mmol·L^{-1})	2.81 ± 0.93	2.31 ± 0.65	2.44*	16.9	0.79*	0.22-0.94
[b]$MAGE_{abs.gos}$ (mmol·L^{-1})	2.32 ± 0.79	2.11 ± 0.57	1.13	13.2	0.77*	0.14-0.94
CONGA (mmol·L^{-1})						
[b]$CONGA_1$	0.93 ± 0.30	0.94 ± 0.27	-0.22	7.0	0.96***	0.84-0.99
[b]$CONGA_2$	1.22 ± 0.40	1.22 ± 0.37	-0.06	8.6	0.95***	0.81-0.99
[b]$CONGA_4$	1.56 ± 0.55	1.41 ± 0.51	1.37	15.8	0.86**	0.48-0.96
[b]$CONGA_6$	1.69 ± 0.68	1.32 ± 0.44	2.44*	25.3	0.76*	0.11-0.94
[b]$CONGA_8$	1.76 ± 0.68	1.37 ± 0.39	2.18	23.3	0.59	-0.54 to 0.89
[b]$CONGA_{10}$	1.75 ± 0.65	1.42 ± 0.64	1.29	29.5	0.26	-1.77 to 0.80
[b]$CONGA_{12}$	1.51 ± 0.56	1.05 ± 0.32	2.68*	30.1	0.41	-1.13 to 0.85

[a]CV= SD/mean x 100, [b]n=11 after excluding one outlier, [c]individuals who showed no time spent in glycemia >10.0 mmol/L were excluded (n=7).
$t_{>10.0\ mmol/L}$: time spent in hyperglycemia, SD_w: glucose standard deviation within each 22-hour CGMS measurement, $MAGE_c$: mean amplitude of glycemic excursions, $MAGE_{ave}$: mean amplitude of glycemic excursion calculated from both upward and downward glycemic excursions, $MAGE_{abs.gos}$: MAGE by the group of signs method, CONGA: continuous overlapping net glycemic action. $\%cv_w$: percent coefficient of variation, CI: confidence interval. *p<0.05, **p<0.01, ***p<0.001

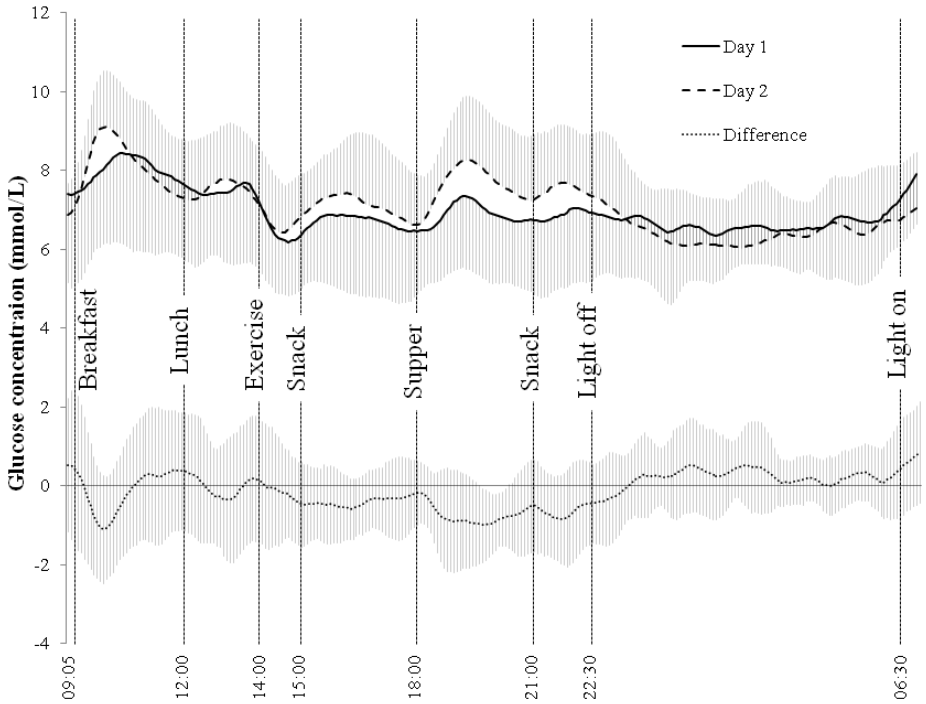

Figure 4.1 Mean ± SD glucose concentrations over two 22-hour periods using continuous glucose monitoring system devices.

Meals were provided at 09:05, 12:00, and 18:00 hour. Exercise was performed from 14:00 to 14:35 hour. Participants were instructed to sleep from 22:30 to 06:30 hour. Participants performed sedentary activities of their choice between instructed tasks.

CHAPTER 5

Study 4: Exercise intensity and timing to target specific changes in glycemic profiles in type 2 diabetes.

5.1 Introduction

Elevated glycemic parameters, such as postprandial and fasting hyperglycemia(1), as well as labile glycemic concentrations(2) have been identified as independent risk factors for the development of diabetic complications. There have been several meta-analyses demonstrating that, on average, exercise has a clinically meaningful impact on overall glycemic control as measured by glycated hemoglobin (HbA1c) in individuals with type 2 diabetes(3,4). However, it is less clear whether exercise can be tailored to favour preferential reductions in specific glycemic parameters.

A recent systematic review investigating the effects of exercise on glycemic parameters measured by continuous glucose monitoring systems (CGMS) showed that aerobic exercise typically lowers postprandial but not fasting glucose(5). Postprandial hyperglycemia is considered to be more strongly associated with insulin resistance at the level of skeletal muscles, whereas fasting glycemia reflects hepatic insulin resistance(6). Thus, it is possible that muscular contractions improved muscular insulin sensitivity but had little effects on the hepatic insulin sensitivity. Nonetheless, because fasting glucose concentration is often measured on the day subsequent to exercise, it is also possible that the negligible effect of exercise on fasting glucose concentrations is due to a short-lasting effect of traditionally used exercise interventions.

Modification to exercise interventions in order to favour different effects on muscle versus liver glycogen could have different effects on various glucose parameters. Two such strategies may be high intensity and fasted-state exercise. An increasingly appreciated approach to increase exercise intensity in type 2 diabetes is high intensity interval exercise (HIIE)(7-10), which involves alternating between repetitions of high intensity exercise bouts followed by lower

intensity recovery periods. HIIE, but not traditionally used moderate intensity continuous exercise (MICE), has been shown to induce delayed onset of hypoglycemia in individuals with type 1 diabetes(11). In addition, Borer et al. demonstrated that, in elderly women, exercise prior to meals results in more sustained reduction of glucose concentration presumably due to greater depletion of hepatic glycogen stores compared to postprandial exercise(12). Therefore, the effects of HIIE and fasted-state exercise on glycemic parameters may differ from those of traditionally recommended MICE and postprandial exercise.

To date, no study has directly compared the acute effects of HIIE versus MICE matched for exercise duration and volume, and the effects of fasted-state and postprandial exercise on glycemic parameters of individuals with type 2 diabetes as determined by continuous glucose monitoring system (CGMS). In addition, it is unknown if the combination of HIIE and fasted-state exercise has additive effects on lowering glycemia. The primary purpose of the study was to compare the glycemic responses between HIIE and MICE, and between fasted-state and postprandial exercise. A secondary purpose was to contrast the glycemic responses associated with the four conditions (fasted-state HIIE and MICE, and postprandial HIIE and MICE) with a sedentary day.

5.2 Methodology

Research Design: A randomized controlled crossover research design was used. Each participant was studied under five separate experimental conditions: fasted-state HIIE ($HIIE_{fast}$), post-breakfast HIIE ($HIIE_{fed}$), fasted-state MICE ($MICE_{fast}$), post-breakfast MICE ($MICE_{fed}$), and breakfast with no exercise (control), in random order separated by at least 48 hours(13). Each experimental period consisted of 24 hours during which the effects of each intervention on glycemic parameters were assessed using CGMS.

Participants: Ten individuals were recruited. Inclusion criteria for the study were: 1) diagnosed with type 2 diabetes; 2) non-smoker; 3) between 45-75 years of age; 4) post-menopausal for at least one year; 5) not on exogenous insulin; 6)

blood pressure below 140/90; 7) HbA1c below 10% (<64 mmol·mol^{-1}), 8) no previous history of type 2 diabetes-related complications and/or myocardial infarction. All participants provided written informed consent. Ethical approval was obtained from the University of Alberta Health Research Ethics Board.

Preliminary-testing: Volunteers reported to the Physical Activity and Diabetes Laboratory at the University of Alberta to complete the physical activity readiness questionnaire (PAR-Q+)(14), participant screening and medical information forms, and to measure baseline HbA1c, blood pressure, and anthropometric characteristics. Weight and height were measured with a stand-on balance beam scale (Health o meter®, McCook, IL) and wall-mounted stadiometer (seca 216, Chino, CA), respectively. HbA1c was measured by a validated(15) point-of-care immunoassay analyzer (DCA 2000; Siemens Healthcare Diagnostics Inc. Tarrytown, NY). On a separate day, participants performed a graded exercise test on a treadmill (Freemotion Fitness, Flaman Fitness, Saskatoon, SK) while connected to an electrocardiograph (ECG; CardioCard™ System, Nasiff Association, Inc, Brewerton, NY) under the supervision of a physician to confirm the absence of underlying cardiac contraindications to performing high intensity exercise and to determine peak oxygen consumption (VO_{2peak}). During exercise, expired gases were analyzed by a calibrated TrueMax® metabolic measurement system (ParvoMedics, Sandy, UT). The exercise test started with a comfortable walking speed with 0% slope. The slope was increased by 1% every minute thereafter. The end-point was achieved when one of the following was observed: volitional exhaustion or failure of VO_2 to increase with increases in exercise intensity. Metabolic data were acquired every 15 seconds and the highest VO_2 (ml·kg^{-1}·min^{-1}) was used as VO_{2peak}.

Exercise protocols: The exercise sessions that occurred during the experimental conditions lasted for 60 minutes and were performed on a treadmill. Exercise intensity was prescribed as a percentage of VO_{2peak}. In contrast to the exercise intensity estimation based on American College of Sport Medicine (ACSM)

equations used in Chapter 2 and 3, exercise intensities were determined based on measured VO_{2peak} as pilot work in preparation of this study showed this method yields similar exercise volume between HIIE and MICE. Walking speed and slope that corresponded 100%, 40%, and 55% VO_{2peak} during the baseline graded exercise test were determined. During MICE, participants performed continuous exercise at treadmill speeds and inclines adjusted to elicit 55% VO_{2peak}. During HIIE, participants performed repetitions of three minutes at 40% followed by one minute at 100% VO_{2peak} (i.e., total of 15 high intensity bouts, mean calculated relative VO_{2peak} =55%).

Familiarization sessions: Before participating in the experimental conditions, eligible individuals participated in two familiarization exercise sessions per week for three weeks to be accustomed to the exercise protocols. Each week, participants performed both HIIE and MICE. The duration of the exercise sessions were 30, 45, and 60 minutes for the first, second, and third week, respectively. All exercise sessions were supervised.

Continuous glucose monitoring system (CGMS): One day before the first experimental condition, each participant was fitted with Medtronic iPro2 CGMS (Medtronic, Northridge, CA). A detailed protocol for CGMS preparation is described elsewhere(16). Typically, the CGMS was used for two experimental conditions before being removed from participants. A new sensor was inserted approximately within two centimeters of the initial insertion site one day before the next experimental condition.

Experimental conditions: Experimental conditions were separated from the last familiarization session by at least four days to minimize the carryover effects. Each participant reported to the laboratory at the same time in the morning following a 12-hour overnight fast. Participants were instructed to refrain from intense physical activity on the days preceding the testing, and reported to the laboratory by car or using public transport. Upon arrival, capillary blood glucose

was measured. Subsequently, resting VO_2 and CO_2 production (VCO_2) were measured by TrueMax® metabolic measurement system, and heart rate (HR) by Polar HR monitor (Polar Electro Canada, Lachine, QC), respectively, for a minimum of 10 minutes. The days on which exercise preceded breakfast, participants performed either HIIE or MICE, which was followed by breakfast one hour after the termination of the exercise bout. The days on which breakfast preceded exercise, participants performed either HIIE or MICE one hour after breakfast. Schematic presentation of the experimental conditions is provided in Figure 1.

During the exercise bouts, HR, VO_2 and VCO_2 were measured from minutes 20-30 and 50-60. Four-minute average VO_2, VCO_2, RER, and HR values were used for analyses because workload over the four-minute window (i.e., three minutes at low plus one minute at high intensity for HIIE) was calculated to yield the same mean relative VO_{2peak} between HIIE and MICE. The metabolic measures obtained over the mid and last 10 minutes of exercise were used to estimate total exercise energy expenditure(17). On the control day, participants ate breakfast and remained sedentary for one hour in the laboratory. Medication was withheld in the morning on the testing days.

In all five conditions, participants were provided a standardized healthy breakfast (50% carbohydrate, 20% protein, and 30% fat, determined with ESHA Food Processing software version 8.3.0: ESHA Research, Salem, OR). The caloric content of breakfast corresponded to 25% of daily caloric expenditure which was estimated by multiplying basal metabolic rate(18) by a physical activity level (PAL) of 1.5. Each participant was instructed to eat the entire breakfast within 30 minutes.

After the completion of the designated intervention in the laboratory, participants' glucose parameters continued to be monitored under standardized diet and medication but otherwise free-living conditions. All participants were asked to maintain their habitual daily routine but to refrain from both structured and recreational physical activity. Participants were equipped with pedometers (Walk4Life Inc, Plainfield IL) before leaving the laboratory and recorded step

counts at the end of each testing day. The participants also recorded their food intake and the time of food consumption throughout each 24-hour experimental condition, and administered medication as instructed by physicians. The diet and medication were kept consistent over the test days and recorded in the food diary. A validated(19) One Touch Ultra® 2 (LifeScan Milpitas, CA. USA) handheld glucose monitor was provided for capillary glucose measurement upon arriving to the lab, as well as before lunch, dinner, and bed.

Glycemic profiles: CGMS-stored signals were exported as previously described(16). Glycemic parameters over the 24-hour period starting from the arrival at the laboratory were analysed. Exercise-induced glucose concentration changes (post-exercise – pre-exercise glucose concentrations), postprandial, nocturnal (0:00 to 5:00 hour) and fasting (one hour mean following eight hours of fasting(20)) glucose concentrations, as well as 24-hour mean glucose concentrations, glycemic variability, time spent in hyperglycemia (glucose concentration >10.0 mmol·l^{-1} [$t_{>10.0\ mmol\cdot l^{-1}}$]) and low glucose (<4.0 mmol·l^{-1} [$t_{<4.0\ mmol\cdot l^{-1}}$]) were determined. The postprandial glycemia was determined as two-hour mean and as the incremental area under the blood glucose response curve (iAUC) following breakfast, lunch, and supper. Also, mean and total iAUC of all three meals were determined. The iAUC was calculated as an area enclosed by pre-meal glucose concentration and glucose curve above the pre-meal concentration, ignoring the glucose areas below pre-meal concentration. Glycemic variability was assessed by mean amplitude of glycemic excursion (MAGE)(21) and standard deviation (SD) of all of the measurements over the 24-hour period (SD_w)(22). All included variables showed high test-retest reliability except for MAGE and $t_{>10.0\ mmol\cdot l^{-1}}$(16). MAGE and $t_{>10.0\ mmol\cdot l^{-1}}$ were included as the former was shown to be a predictor of oxidative stress, one of the factors that leads to diabetic complications(2), while the latter has frequently been used in studies assessing the effects of exercise using CGMS(5).

Data analysis: Linear mixed model was used for all statistical analyses. Primary outcomes were analyzed using exercise type (HIIE versus MICE), meal status (fasted versus postprandial), and the interaction of exercise type and meal status as fixed effects, and participants as random effects. In addition, using the five experimental conditions as a fixed effects and participants as random effects, we compared each of the four exercise conditions to control with a Bonferroni correction to adjust for multiple comparisons.

Based on the nature of the data, we assumed equal variances arising from all conditions. We also assumed constant covariance from participants (i.e., multiple measures were treated as independent in time but correlated because of uniqueness of the participants(23)). Thus, the compound symmetry covariance pattern was fitted. The model was compared against unstructured covariance structure using Schwarz's Bayesian Criterion, and more parsimonious model was chosen. The same analyses were performed for oxygen consumption, substrate oxidation and HR measured at rest and during exercise, as well as for food intake and step counts. The model residuals were examined for normality using Kolmogorov-Smirnov test and data was log-transformed where necessary. All data are presented as mean ± SD unless otherwise stated. P values <0.05 were considered significant. Statistical analyses were performed with SPSS statistical software (SPSS Inc., Chicago, IL, USA).

5.3 Results

Participants: Eight males and two females with type 2 diabetes (age, 60±6 years old; height, 172.4±9.4 cm; weight, 91.4±17.1 kg; BMI, 30.8±5.4 $kg \cdot m^{-2}$; VO_{2peak}, 25.5±6.6 $mL \cdot kg^{-1} \cdot min^{-1}$; time since the diagnosis of type 2 diabetes, 6.8±4.6 years [ranged from 1-13 years]; HbA1c 7.1±1.0% or 53.9±10.9 $mmol \cdot mol^{-1}$) participated in the study. One participant only completed three testing conditions due to injury not related to the study. Of the ten participants, five were treated with metformin alone; five with metformin+sitagliptin, metformin+glyburide, metformin/sitagliptin+gliclazide, metformin+gliclazide, or metformin+saxagliptin+glyclazide.

Laboratory measures: Fasting capillary blood glucose, HR, RER and VO_2 measured upon arrival at the laboratory did not differ across the testing conditions. Speed and slope [mean (SD)] for exercise intensity corresponding to 100%, 55%, and 40% were 4.2 (0.8) $km \cdot hr^{-1}$ and 14.0 (3.4)%, 3.9 (0.9) $km \cdot hr^{-1}$ and 3.9 (2.2)%, and 3.6 (1.0) $km \cdot hr^{-1}$ and 0.9 (1.2)%, respectively. Mean exercise intensities estimated by $\%VO_{2peak}$ were close to the estimated 55% and did not differ between HIIE and MICE. However, $\%VO_{2peak}$ was higher for postprandial exercise than fasted-state exercise over 50-60 minutes ($p<0.05$). Similarly, estimated energy expenditure did not differ between HIIE and MICE, but was ~18 kcal higher over the 60 minutes for postprandial exercise than fasted-state exercise ($p<0.05$). HR was also higher when exercise was performed postprandially. As expected, meal consumption and higher exercise intensity significantly elevated RER (both $p<0.01$). Glucose concentrations immediately before exercise, as well as exercise-induced glucose concentration changes (post-exercise – pre-exercise glucose concentrations), were greater for postprandial exercise than fasted-state exercise (both $p<0.001$). There was no difference in the degree of glucose reduction between HIIE and MICE. These laboratory measures are summarized in **Table 5.1**.

Daily activity and diet: Step counts for the remainder of the day were not statistically different between HIIE and MICE [mean (SD)= 4977 (6317) versus 5090 (5927)] and between fasted-state and postprandial exercise [4308 (6259) versus 5759 (5953)]. Food diaries were screened and the days on which caloric intake deviated from the other testing days were identified. Two participants consumed extra calories with supper on one condition ($HIIE_{fed}$ and $MICE_{fast}$, respectively). Consequently, glucose parameters that were affected by the change (i.e., post-supper mean and iAUC, 24-hour mean, MAGE, SD_w, $t_{>10.0\ mmol \cdot l^{-1}}$, nocturnal and fasting glycemia) were excluded from analysis. One participant failed to take medication with lunch on one condition ($HIIE_{fast}$) and consumed extra calories with supper on another ($HIIE_{fed}$). Glycemic parameters affected by

these changes were also excluded. Lastly, one participant failed to complete dietary record over two testing days ($MICE_{fast}$ and $MICE_{fed}$). All glycemic parameters from the days were thus excluded. In the remaining data, there was no difference in energy intake among the testing conditions.

CGMS-estimated glycemic profiles: No gaps in glucose data were observed on the testing days. **Figure 5.2** shows the glycemic responses comparing HIIE and MICE, and postprandial and fasted-state exercise. Although the two-hour mean postprandial glucose concentrations were not affected by exercise types or timing, fasted-state exercise significantly lowered iAUC following breakfast ($p<0.05$) and lunch ($p<0.001$) compared to postprandial exercise, which is also reflected in lower total post meal iAUC ($p<0.05$). Fasted-state exercise also reduced glycemic variability as estimated by MAGE ($p=0.015$) but not by SD_w ($p=0.066$). Mean nocturnal and fasting glucose measured on the day following interventions were lower after HIIE compared to MICE (both $p<0.05$).

When each of the four exercise conditions was compared to control, $HIIE_{fast}$ and $MICE_{fast}$ lowered MAGE, SD_w, total post-meal mean and iAUC (all $p<0.05$). However, $HIIE_{fast}$ additionally reduced fasting glucose (-1.0 $mmol \cdot l^{-1}$; $p<0.05$), 24-hour mean glucose (-1.5 $mmol \cdot l^{-1}$; $p<0.01$) and $t_{>10.0\ mmol \cdot l^{-1}}$ (-283 minutes; $p<0.05$) relative to control. Low glucose was observed in only one participant for a total of 90 and 40 minutes on $MICE_{fed}$ and control conditions, respectively, but not in response to fasted-state exercise. CGMS-estimated glycemic responses are summarized in **Table 5.2**.

5.4 Discussion

The novel findings of this study are that: 1) fasted-state exercise reduces MAGE and total postprandial incremental AUC more than postprandial exercise; 2) HIIE decreases nocturnal and fasting glycemia to a greater extent than MICE; and 3) compared to a non-exercise day, HIIE performed under fasted condition (i.e., $HIIE_{fast}$) improves the most aspects of glycemic parameters (i.e., 24-hour mean, MAGE, $t_{>10.0\ mmol \cdot l^{-1}}$, postprandial and fasting glucose). Importantly, these

differences emerged despite a similar reduction in the 24-hour mean glucose concentration and without increasing the risk of low glucose ($t_{<4.0\ mmol \cdot l^{-1}}$).

Our finding that fasted-state exercise lowers postprandial glucose increments to a greater extent than postprandial exercise are similar to those of Oberlin et al., who showed exercise performed before breakfast lowers post-lunch and tends to lower post-breakfast glycemic responses more than those observed on non-exercise days(24). However, our study adds to the current knowledge by showing that fasted-state exercise is more effective in attenuating overall postprandial glycemic increment than postprandial exercise. This is interesting given that, to date, postprandial exercise has generally been considered more beneficial for glucose control as it acutely (within a few hours following an exercise bout) blunts meal-induced hyperglycemia(25), a risk factor for diabetic complications(1).

The smaller glycemic increments in response to meals may in part be due to the fact that our postprandial exercise started one hour after breakfast and was therefore unable to affect the first hour of post-breakfast glycemic increment. However, it is important to note that this difference persisted in the post-lunch period. Our observations are similar to those of Borer and colleagues(12). However, they used two bouts of exercise lasting two hours prior to meals. Thus, our protocol was less demanding and maybe more applicable to individuals with type 2 diabetes. It has been shown that limited exogenous carbohydrate availability increases glycogen degradation to meet the energy demand while ample carbohydrate intake results in glycogen sparing(26). Consequently, we speculate that the greater glycogen depletion and enhanced cellular stress during exercise(27) facilitated the transfer of glucose from blood to muscle cells in response to subsequent meals. In support of this notion, emerging evidence in non-diabetic individuals suggests that fasted-state exercise facilitates muscular glycogenolysis(26) and increases AMPK activity(27), which are known stimulants for improved insulin sensitivity during recovery(28). Consequently, while postprandial exercise acutely reduces meal-induced glycemia, it is possible

that a high exogenous carbohydrate availability during exercise hampers favourable changes in glucose that persist hours after exercise.

Another important finding from the fasted-state exercise data was reduced glycemic variability as estimated by MAGE. Attenuated post-meal glycemic increments likely contributed to the reduced MAGE. While SD_w did not reach statistical significance ($p=0.066$), it also tended to be lower following fasted-state exercise. The degree of difference between fasted-state and postprandial exercise (1.01 for MAGE and 0.24 for SD_w, respectively) were comparable to administering oral anti-hyperglycemic medications.

The second major finding of the present study is that HIIE has a greater nocturnal and fasting glucose lowering effect. This is interesting given evidence from a recent meta-analysis indicating negligible acute effects of aerobic exercise on fasting blood glucose(5). In addition, a large epidemiological study also indicated that fasting glycemia was insensitive to increased amount of physical activity(30). Fasting hyperglycemia predominantly reflects hepatic insulin resistance(6). Therefore, we speculate that greater release of catecholamine and glucagon(31) in response to HIIE may have stimulated greater mobilization of hepatic glucose stores, which in turn enhanced hepatic insulin sensitivity. Our observation is similar to that of Kirwan and colleagues who reported suppression of hepatic glucose production in individuals with type 2 diabetes following seven days of vigorous aerobic exercise training(32). Devlin et al., also demonstrated reduced endogenous glucose production in individuals with type 2 diabetes on the morning after HIIE(33).

Lastly, our results showed that only $HIIE_{fast}$ concurrently improves 24-hour mean glucose, $t_{>10.0\ mmol \cdot l^{-1}}$, MAGE, SD_w, total postprandial and fasting glucose in comparison to the control condition. This suggests that $HIIE_{fast}$ may be the most effective way to improve dysglycemia among the conditions tested in the present study. However, we were unable to find significant differences among the four exercise conditions (data not shown). The observed 24-hour mean glucose reduction of -0.8 to -1.5 $mmol \cdot l^{-1}$ is comparable to the CGMS-measured mean

glucose reduction with the addition of a dipeptidyl peptidase-4 inhibitor (~1.3 $mmol \cdot l^{-1}$) to the treatment of type 2 diabetes(34).

Previous studies have suggested that different energy expenditure was primarily responsible for different degrees of acute glycemic responses following exercise of different intensity(35,36). Thus, we attempted to match energy expenditure between the exercise conditions. Among the variables measured during exercise, no differences were observed between HIIE and MICE except for RER. These laboratory measures highlight that, while the degree of carbohydrate oxidation differed between HIIE and MICE, exercise volume was equal and does not explain the differences in CGMS-measures. Additionally, while HR, RER, VO_2, and thus energy expenditure were higher during postprandial exercise presumably due to thermic effects of food(37), fasted-state exercise induced greater reduction in total postprandial glucose increment and MAGE. These points, together with no differences in mean step counts or fasting capillary glucose and resting energy metabolism before implementing each condition negate the potential of our results being explained by these factors.

A major limitation of this study is that we can only speculate on possible physiological mechanisms resulted in different glycemic responses. The mechanisms involved should be studied to clarify the observed effects of HIIE and fasted-state exercise. Another limitation to our study is the relatively small sample size used. Our a priori sample size calculation was based on the previous study reporting 24-hour mean glucose concentrations in response to HIIE and MICE(4). However, with the exclusion of some data due to violation of our testing protocols, the chance of committing type I error might have been high. We attempted to retain statistical power by using crossover study design, linear mixed model, and two-by-two factorial analysis as these methods reduce error residuals, allow the inclusion of incomplete data, and pool available data for comparison (e.g., $HIIE_{fast}$+$HIIE_{fed}$ versus $MICE_{fast}$+$MICE_{fed}$), respectively. Nonetheless, there is no denying the possibility that the lack of difference we observed in some variables may simply be attributable to lack of power. Furthermore, adjusted α-level by the number of comparisons used to address our secondary purpose may

have compromised our statistical power. For example, when we reran the analyses without Bonferroni adjustment, we found that all the four exercise conditions lowered 24-hour glucose to a greater extent than control. The identification of several significant differences despite a small sample size suggests relatively large and/or consistent effect of the interventions. Nevertheless, larger and longer-term studies would be required to confirm the efficacy of the interventions.

With regard to generalizability of our findings, although no gender disparity in the patterns of glycemic responses to our exercise interventions was observed, small number of females (n=2) in our study limits the generalizability of our results to females. Additionally, the population we studied were individuals with relatively well controlled type 2 diabetes (HbA1c 7.1±1.0% or 53.9±10.9 $mmol \cdot mol^{-1}$), who are previously demonstrated to tolerate HIIE(3). With a number of studies showing the feasibility of a similar HIIE protocol to ours on patients with cardiac complications(38-39), we speculate that HIIE is applicable to a variety of clinical population. Nonetheless, it is currently unknown whether HIIE is generalizable to less fit individuals with more advanced type 2 diabetes. Lastly, while all exercise sessions were completed in the laboratory in the present study, a study showing that HIIE can be used under free-living, unsupervised conditions and still induces better glyemic responses over MICE(4) suggest the applicability of HIIE to outside the laboratory settings.

5.5 Conclusion

In conclusion, our results showed the potential to tailor exercise intervention to target specific aspects of dysglycemia. High intensity interval exercise may be incorporated to reduce nocturnal and fasting glucose, while fasted-state exercise can be used to target postprandial glucose excursions. Given that deteriorated fasting and postprandial glucose contribute differently to the overall hyperglycemia(40), tailoring exercise interventions to target specific aspects of glycemia may lead to more effective use of exercise for better glycemic control. An intervention combining high intensity interval exercise and fasted-

state exercise may also be more advantageous than other more traditional forms of exercise in lowering various aspects of dysglycemia.

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5.6 References

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patients - Variations with increasing levels of HbA1c. Diabetes Care 2003;26(3):881-885.

Table 5.1 Metabolic and glycemic responses upon arriving at the laboratory and during exercise

	Conditions, mean (SD)					P-value	
	Control	$HIIE_{fast}$	$HIIE_{fed}$	$MICE_{fast}$	$MICE_{fed}$	HIIE vs. MICE	fasted vs. fed
Pre-test							
Fasting glucose ($mmol \cdot l^{-1}$)	8.8 (2.2)	8.5 (2.0)	8.6 (2.0)	8.9 (2.5)	8.6 (1.4)	0.473	0.432
$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	2.8 (0.2)	2.9 (0.2)	2.9 (0.3)	2.9 (0.3)	3.0 (0.3)	0.708	0.984
HR ($beat \cdot min^{-1}$)	67 (12)	65 (10)	70 (10)	68 (11)	68 (10)	0.745	0.178
RER	0.83 (0.04)	0.86 (0.08)	0.82 (0.04)	0.87 (0.06)	0.85 (0.06)	0.271	0.219
Exercise (20-30 min)							
% $\dot{V}O_{2peak}$		55.0 (6.3)	55.1 (3.6)	53.2 (4.8)	54.6 (5.6)	0.317	0.259
$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)		13.8 (0.9)	14.3 (1.0)	13.5 (1.1)	14.3 (1.3)	0.699	0.208
HR ($beat \cdot min^{-1}$)		111 (15)	114 (16)	109 (12)	114 (13)	0.644	0.040
RER		0.86 (0.05)	0.89 (0.05)	0.82 (0.04)	0.85 (0.05)	0.007	0.001
Exercise (50-60 min)							
% $\dot{V}O_{2peak}$		53.5 (5.7)	57.0 (3.3)	54.0 (5.3)	55.1 (4.9)	0.518	0.021
$\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)		13.5 (3.4)	15.0 (4.2)	13.7 (3.6)	14.5 (3.9)	0.611	0.024
HR ($beat \cdot min^{-1}$)		116 (16)	120 (15)	111 (13)	120 (12)	0.500	0.012
RER		0.83 (0.04)	0.88 (0.03)	0.81 (0.04)	0.85 (0.03)	<0.001	<0.001
Exercise (0-60 min)							
Pre-exercise glucose ($mmol \cdot l^{-1}$)		8.1 (1.7)	11.0 (2.2)	8.7 (1.8)	11.4 (4.7)	0.268	0.001
Glucose change ($mmol \cdot l^{-1}$)		-0.9 (1.0)	-3.4 (2.2)	-0.4 (0.6)	-2.8 (1.7)	0.177	<0.001
Energy expenditure (kcal)		354 (85)	371 (94)	351 (88)	362 (101)	0.410	0.026

HR: heart rate, % $\dot{V}$O2peak: percent peak oxygen consumption, $\dot{V}O_2$: oxygen consumption, RER: respiratory exchange ratio, $HIIE_{fed}$=postprandial high intensity interval exercise; $HIIE_{fast}$=fasted-state high intensity exercise; $MICE_{fed}$=postprandial moderate intensity continuous exercise; $MICE_{fast}$=fasted-state moderate intensity continuous exercise.

Glucose change was estimated by post exercise - pre exercise CGMS glucose concentrations. No significant interaction observed between exercise type (HIIE vs. MICE) and meal status (fasted vs. fed) for any of the variables. No significant differences were observed between the four exercise conditions vs. control. No significant interaction effects observed for any of the variables.

Table 5.2 Effects of exercise intensity and meal status on various glycemic profiles.

Glucose parameters	Control mean (SD)	Changes from control: $HIIE_{fast}$ (95% CI) (n=9 or 10)	$HIIE_{fed}$ (95% CI) (n=7 or 9)	$MICE_{fast}$ (95% CI) (n=8 or 9)	$MICE_{fed}$ (95% CI) (n=8)	P-value: HIIE vs. MICE	fasted vs. fed	Ex x meal interaction
24-hour mean glucose ($mmol \cdot l^{-1}$)	9.4 (2.5)	**-1.5*** **(-2.6 to -0.4)**	-1.1 (-2.3 to 0.1)	-0.8 (-2.0 to 0.2)	-1.0 (-2.1 to 0.1)	0.207	0.986	0.443
$t_{>10.0\ mmol \cdot L\text{-}1}$ (min)	486 (432)	**-283†** **(-527 to -38)**	-167 (-422 to 87)	-120 (-374 to 135)	-127 (-382 to 128)	0.122	0.474	0.201
MAGE ($mmol \cdot l^{-1}$)	5.03 (2.10)	**-1.79*** **(-3.18 to -0.41)**	-0.26 (-1.70 to 1.18)	**-1.54†** **(-2.98 to -0.10)**	-0.98 (-2.42 to 0.46)	0.507	**0.015**	0.239
SD_w ($mmol \cdot l^{-1}$)	2.03 (0.81)	**-0.74*** **(-1.20 to -0.28)**	-0.16 (-0.83 to 0.51)	**-0.52†** **(-1.14 to 0.10)**	-0.45 (-1.08 to 0.18)	0.814	0.066	0.094
Post breakfast 2-hour mean ($mmol \cdot l^{-1}$)	12.2 (3.3)	**-2.9*** **(-4.9 to -1.0)**	-1.1 (-3.0 to 1.0)	-1.9 (-3.9 to 0.1)	-1.9 (-4.0 to 0.1)	0.823	0.149	0.072
Post breakfast iAUC ($mmol \cdot 120\ min \cdot l^{-1}$)	355 (166)	-88 (-208 to 32)	-41 (-164 to 82)	**-157*** **(-281 to -34)**	-115 (-243 to 13)	0.251	**0.032**	0.932
Post lunch 2-hour mean ($mmol \cdot l^{-1}$)	10.7 (3.4)	**-2.7*** **(-4.6 to -0.8)**	-1.7 (-3.6 to 0.3)	**-2.1†** **(-4.0 to -0.3)**	**-2.3†** **(-4.2 to -0.4)**	0.938	0.623	0.215
Post lunch iAUC ($mmol \cdot 120\ min \cdot l^{-1}$)	175 (122)	**-154‡** **(-280 to -29)**	-40 (-214 to 133)	**-167‡** **(-294 to -40)**	-68 (-145 to 9)	0.265	**<0.001**	0.721
Post supper2-hour mean ($mmol \cdot l^{-1}$)	9.8 (3.5)	-1.3 (-3.2 to 0.6)	-1.1 (-3.2 to 1.0)	-1.8 (-3.8 to 0.2)	-1.6 (-3.6 to 0.4)	0.335	0.941	0.958
Post supper iAUC ($mmol \cdot 120\ min \cdot l^{-1}$)	163 (177)	-12 (-126 to 102)	-77 (-268 to 115)	-61 (-253 to 131)	-55 (-228 to 118)	0.715	0.806	0.872
Total post meals mean ($mmol \cdot l^{-1}$)	10.9 (3.1)	**-2.3*** **(-3.9 to -0.7)**	-1.5 (-3.3 to 0.3)	**-2.0†** **(-3.7 to -0.4)**	**-1.9†** **(-3.6 to -0.2)**	0.884	0.545	0.418
Total post meals iAUC ($mmol \cdot 360min \cdot l^{-1}$)	693 (263)	**-367*** **(-634 to -95)**	-185 (-479 to 109)	**-470†** **(-751 to -188)**	**-316†** **(-598 to -33)**	0.099	**0.042**	0.892
Nocturnal glucose ($mmol \cdot l^{-1}$)	8.2 (2.4)	-0.6 (-1.4 to 0.2)	-0.8 (-1.6 to 0.1)	0.2 (-0.6 to 1.0)	0.1 (-0.7 to 0.9)	**0.012**	0.471	0.814
Fasting glucose ($mmol \cdot l^{-1}$)	8.0 (1.9)	**-1.0†** **(-1.9 to -0.1)**	-0.8 (-1.8 to 0.2)	-0.1 (-1.0 to 0.9)	-0.1 (-1.1 to 0.9)	**0.047**	0.937	0.869

CI=confidence interval; iAUC=incremental area under curve; MAGE: mean amplitude of glycemic excursions; SD_w=standard deviation within a day; $HIIE_{fed}$=postprandial high intensity interval exercise; $HIIE_{fast}$=fasted-state high intensity exercise; $MICE_{fed}$=postprandial moderate intensity continuous exercise; $MICE_{fast}$=fasted-state moderate intensity continuous exercise; and n=number of data points. For $HIIE_{fast}$, n=10 for post breakfast variables, whereas n=9 for all the remaining variables. For $MICE_{fast}$, n=9 for post breakfast and lunch variables, whereas n=8 for all the remaining variables. For $HIIE_{fed}$, n=9 for post breakfast and lunch variables, whereas n=7 for all the remaining variables.
†$p<0.05$, *$p<0.01$ and ‡$p<0.001$ vs. control. P-values were multiplied by four to adjust for the number of multiple comparisons vs. control.

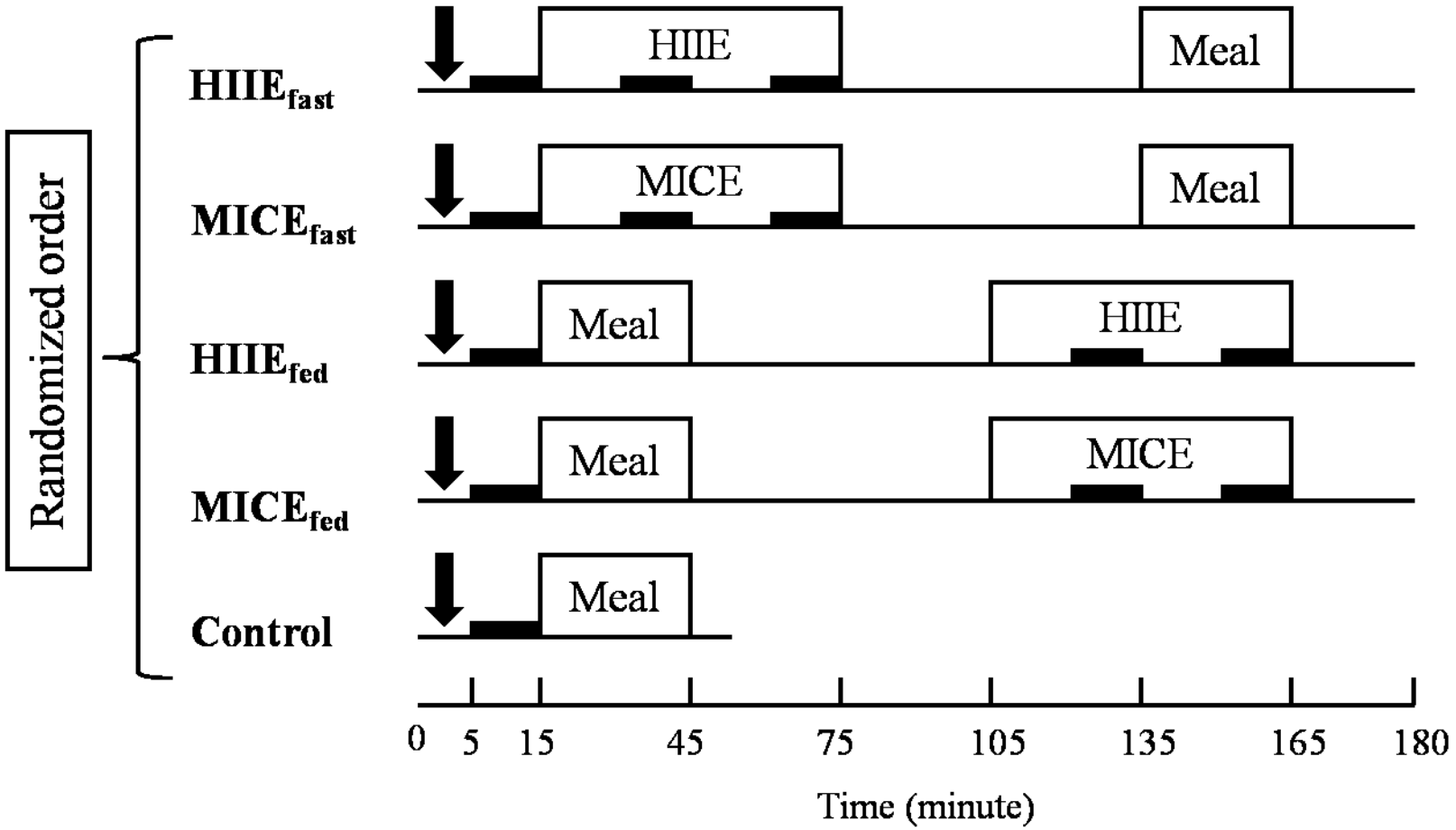
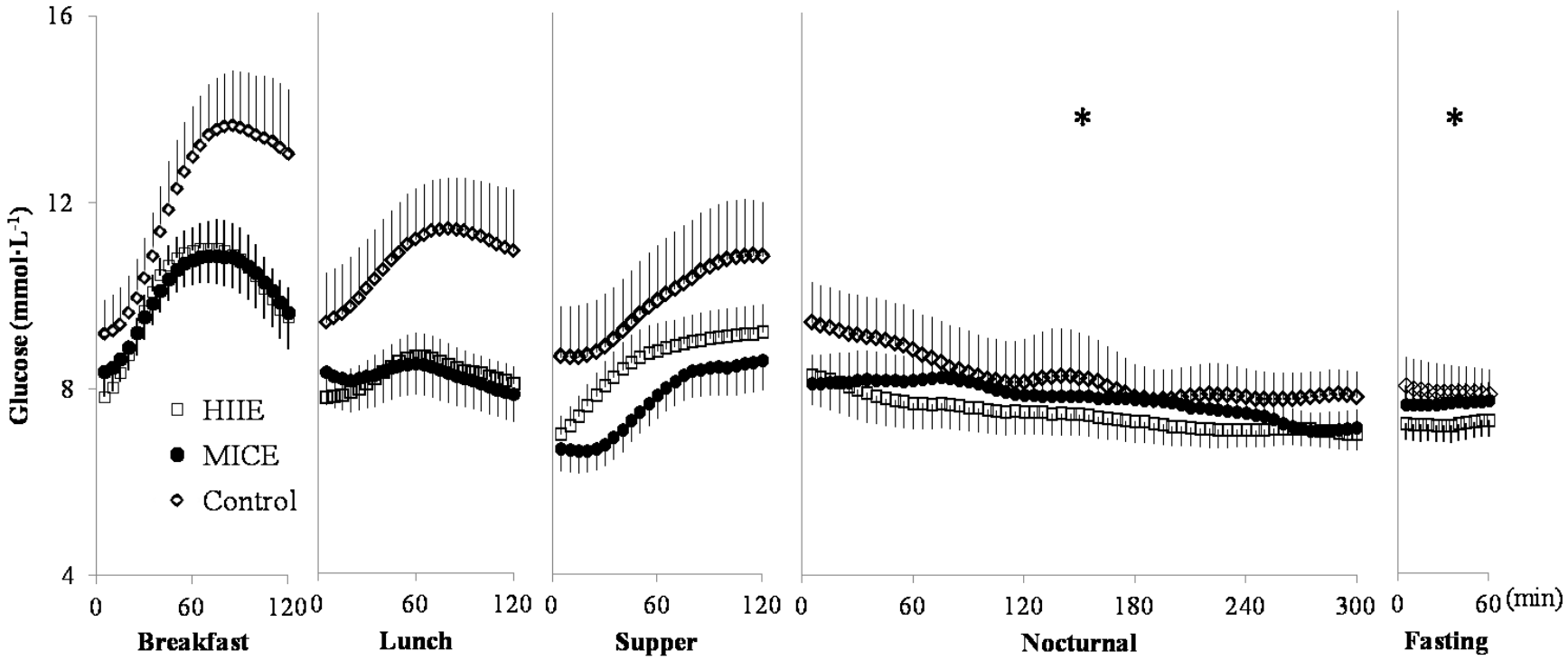


Figure 5.1 Schematic presentation of the experimental design during the laboratory visits.
$HIIE_{fed}$=postprandial high intensity interval exercise; $HIIE_{fast}$=fasted-state high intensity exercise; $MICE_{fed}$=postprandial moderate intensity continuous exercise; $MICE_{fast}$=fasted-state moderate intensity continuous exercise. Black boxes represent metabolic cart and heart rate measurements. Arrows represent capillary glucose measurement.

A


16
12
8
4
Glucose (mmol·L-1)
HIIE
MICE
Control
*
*
0
60
120
180
240
300
(min)
Breakfast
Lunch
Supper
Nocturnal
Fasting

B

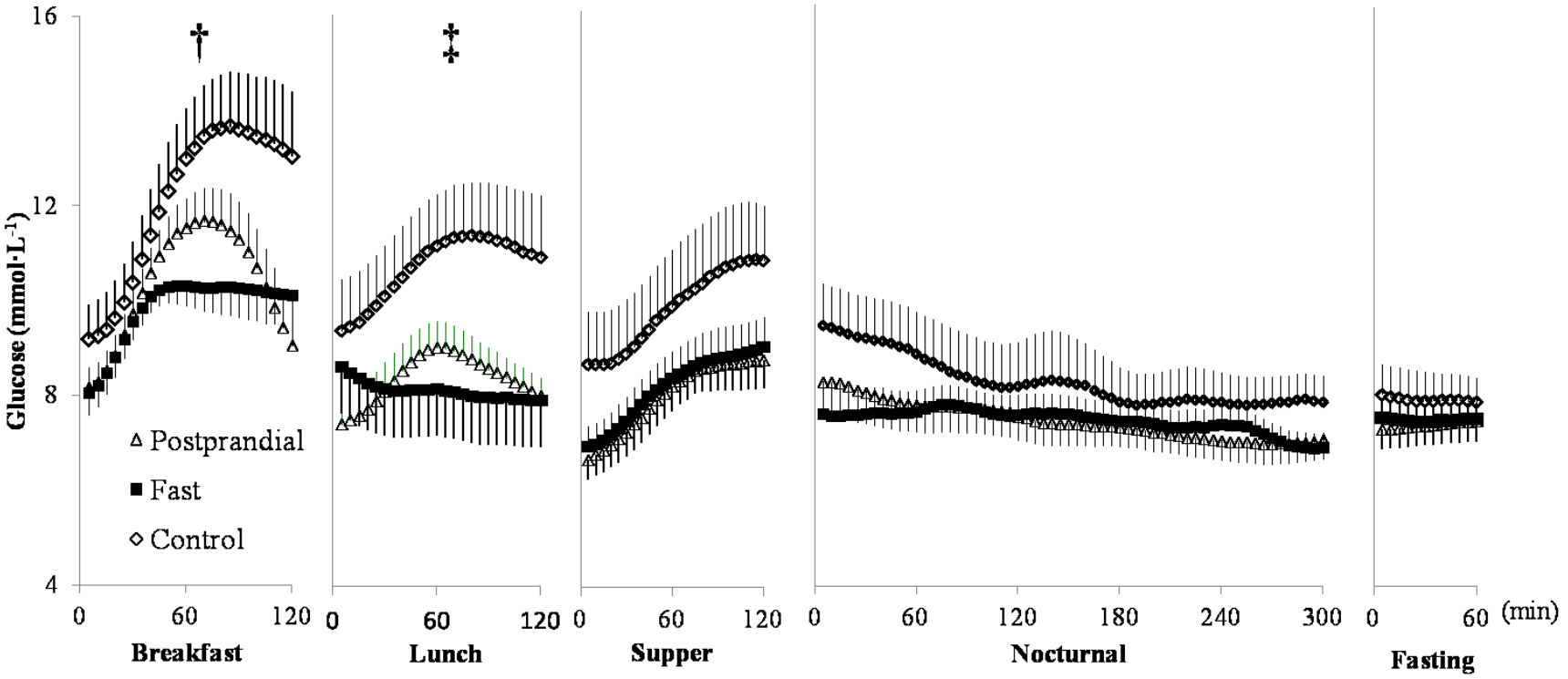


Figure 5.2 A Glycemic responses to A:HIIE (□) vs. MICE (♦) vs. control (◊) and **B**: fasted (■) vs. postprandial (Δ) vs. control (◊). Results are expressed as means ± SE. *Significant difference ($p<0.05$) between HIIE and MICE. †Significant difference between fed vs. fasted ($p<0.05$). ‡Significant difference between postprandial vs. fasted ($p<0.001$).
Nocturnal glucose was measured between 0:00 and 5:00. Fasting glucose was one-hour average glucose concentration following eight hours of fasting. HIIE=high intensity interval exercise, MICE=moderate intensity continuous exercise**.**

CHAPTER 6

Discussion

There is ever-increasing appreciation of the importance of physical activity in the management of T2D. The effects of exercise on individuals with diabetes have been well received and contributed extensively to recent evidence-based guidelines in several countries. However, at the time of undertaking this thesis research, knowledge regarding the therapeutic benefits of high intensity interval exercise (HIIE) in individuals with T2D was limited. In addition, the effects on HIIE on different glycemic profiles, i.e., fasting glucose, postprandial glucose, glycemic variability, and A1c, had not been explored despite each profile's contribution to the development of diabetic complications (1). The purposes of this chapter are: 1) to briefly review the key findings from each study; 2) to integrate the findings from these studies; and 3) to discuss the overall limitations and future directions.

6.1 Feasibility of HIIE training in individuals with T2D

While HIIE may be a potent therapeutic intervention to improve glucose profiles of individuals with T2D (2), there had not been a randomized trial reported in the literature comparing the feasibility of HIIE and traditionally recommended MICE. Consequently, the feasibility of HIIE in individuals with T2D was assessed. The results indicated that adherence and retention, as well as self-efficacy and psychological distress were similar between HIIE and MICE. In addition, satisfaction assessed at the end of study did not differ between HIIE and MICE, and no injury or symptoms of hypoglycemia were observed following both types of exercise. Collectively, **Study 1** (Chapter 2) demonstrated that short to medium term HIIE (12 weeks) is as feasible as MICE and well-tolerated by individuals with T2D. This information was essential in planning the subsequent studies in this dissertation. With the establishment of the feasibility of HIIE in

individuals with T2D, detailed glycemic responses to HIIE were further investigated.

Hypothesis statement: The hypothesis that HIIE is as feasible as MICE in individuals with T2D was supported.

6.2 Glucose changes during HIIE and MICE

While exercise has been shown to lower overall glucose concentrations, clinically meaningful heterogeneity in the glycemic responses to exercise have been documented (3). Similarly, glycemic changes during high intensity exercise have been inconsistent with some studies showing greater (4,5) or equal (6,7) reduction compared to MICE, while another study showed markedly elevated glucose concentration (8). Accordingly, to elucidate the heterogeneous glucose responses during exercise, **Study 2** (Chapter 3) examined glycemic responses during HIIE and MICE while concurrently considering several other factors (i.e., pre-exercise glucose concentration, meal and medication timing in relation to exercise, exercise duration and modality).

The results showed that heterogeneous glycemic responses during exercise were largely attributable to pre-exercise glucose concentrations. High glucose concentrations prior to exercise were associated with a greater reduction in glucose during exercise, whereas low glucose concentrations prior to exercise were associated with small changes. This finding emphasizes the clinical stability of the exercise interventions. Specifically, unlike some anti-hyperglycemic medications (e.g., sulfonylurea or insulin (9)), exercise attenuates high glycemic excursions while posing a small risk of hypoglycemia when glucose concentration is relatively low.

After adjusting for the differences in glucose concentrations before exercise, a greater reduction was associated with HIIE compared to MICE. Moreover, longer exercise duration, meal and medication consumption prior to exercise were independently associated with greater reductions in glycemia during exercise. Exercise bouts within two hours following meal intake led to a greater

reduction compared to exercise performed more than six hours after the most recent meal. Similarly, oral anti-hyperglycemic medication within six hours of an exercise bout augmented glucose reduction more than no medication within six hours. This study identified some of the factors associated with heterogeneous glycemic responses during exercise.

Hypothesis statement: The findings supported the hypothesis that HIIE lowers glucose concentrations to a greater extent than MICE. However, the hypothesis was true only after pre-exercise glucose concentration differences were taken into account. When adjusted for pre-exercise glucose concentrations, the findings also supported the other hypothesis that meal and medication intake prior to exercise accentuate the reduction in blood glucose concentrations.

6.3 Acute glycemic responses to HIIE and MICE

A question that remained to be addressed following the completion of **Study 2** was how the glycemic changes during exercise influence glycemia following the termination of exercise. In addition to HIIE, meal timing in relation to exercise was of particular interest because, despite our results and other studies (10,11) showing the effects of previous meal consumption on glycemic responses, combined effects of HIIE and meal timing on acute glycemia had not been directly examined.

Accordingly, **Study 4** investigated acute glycemic responses to HIIE and MICE under fasted and postprandial states using a randomized controlled repeated measure design. CGMS-measured glycemic profiles that showed high test-retest reliability (**Study 3**, Chapter 4) were chosen as outcome variables. **Study 4** was designed to directly address the potential interaction between exercise intensity and meal timing. In addition, as opposed to **Study 2** which was associative by nature, **Study 4** randomly assigned participants to a two-by-two factorial design (i.e., HIIE versus MICE and fasted versus postprandial conditions), and added an important control condition that was absent in **Study 2**.

By tracing glucose concentrations over an extended time, **Study 4** showed that, while HIIE lowered nocturnal and fasting glycemia to a greater extent than MICE, MICE was more effective in lowering total post-meal glycemic increment than HIIE. This was primarily because HIIE performed following a meal had little effect on postprandial glycemia. Indeed, although fasted-state HIIE was effective in lowering various aspects of dysglycemia (24-hour mean glucose, glycemic variability, fasting and postprandial glycemia), postprandial HIIE did not lower any of the glycemic profiles compared to the non-exercise sedentary day despite the greatest reduction in glucose concentration during exercise. These findings suggest that, when incorporating HIIE to the exercise intervention for individuals with T2D, it should be done in the fasted-state for better results.

The suggestion of the additive effects of modification to exercise intensity and timing in relation to a meal is uncommon in the field of exercise and nutritional science. This type of research may reveal previously unknown synergies which could help people with T2D receive additional benefits without increasing exercise volume. In addition, with more varied types of medication being available, prescription is now more individualized to target specific aspects of dysglycemia. In this regard, it may also be important to address the timing and type of exercise in an exercise prescription to meet individual needs.

Hypothesis statement: The hypothesis that HIIE and exercise under fasted condition would lower glycemic profiles to a greater extent than MICE or postprandial exercise was partially supported. Fasted-state exercise lowered glycemic profiles to a greater extent than postprandial exercise as hypothesized. Similarly, HIIE lowered nocturnal and fasting glycemia to a greater extent than MICE. Nonetheless, HIIE was less effective in lowering postprandial glucose than MICE.

6.4 Long-term glycemic responses to HIIE and MICE

Despite the exercise prescription of both HIIE and MICE groups exceeding the recommendation made by national guidelines (accumulation of a

minimum of 150 minutes of moderate to vigorous-intensity aerobic exercise each week (12,13), A1c was not improved in either group (**Study 1**). In fact, three out of seven in HIIE and four out of eight in MICE group had an increase in their A1c after three months of exercise training. While the lack of difference may be attributable to the combination of small sample size and relatively well controlled glycemia of the study participants (3), the long-term heterogeneous glycemic responses to exercise suggest that meeting exercise volume alone may not be enough to induce overall improvement in glycemia.

The long-term glycemic benefit of exercise training has been suggested to be the sum of the effects of each successive bout (14). Thus, acute glycemic responses may not have been of a sufficient magnitude to induce long-term improvement in glycemia. Indeed, 24-hour mean glucose concentrations in response to MICE and HIIE were not significantly lower than the sedentary day (**Study 4**) except for HIIE performed under the fasted-state. In this regard, the long-term effect of HIIE under fasted conditions is of interest given that fasted-state HIIE resulted in improvements of all aspects of dysglycemia. A summary of the dissertation is provided in the integration figure below (**Figure 6.1**).

Hypothesis statement: The hypothesis that HIIE lowers A1c to a greater degree than MICE was rejected.

Figure 6.1 Glycemic profiles in response to HIIE and MICE**.**
Relative changes in A1c and during exercise were calculated as percentage reductions from pre-training and pre-exercise glucose concentrations, respectively. Twenty-four hour postprandial, next day fasting, and 24-hour mean glucose were estimated as relative changes from a non-exercise control day. Glycemic responses to the same exercise performed under fasted condition were included to indicate the potential advantage of fasted-state exercise.
HIIE=high intensity interval exercise; MICE=moderate intensity continuous exercise; and A1c=glycosylated hemoglobin A1c.

6.5 Integration: HIIE and T2D

Clinical practice guidelines published by the Canadian Diabetes Association recommend "People with diabetes should accumulate a minimum of 150 minutes of moderate- to vigorous-intensity aerobic exercise each week (13)". However, there is currently no reference to any forms of HIIE for people with T2D. In order to integrate the findings from this dissertation within the broader context of physical activity recommendation, this section discusses the safety, applicability, and the health benefits of HIIE.

Safety, potential side effects, and applicability: Concerns exist over the risk of cardiovascular events (15) and microvascular complications (12) from participating in high intensity exercise. Because of the potentially increased susceptibility to adverse events, guidelines (12,13) obscurely advise an exercise stress ECG examination for the majority of individuals with T2D (i.e., age >40 years or individuals with possible risks for CVD or microvascular complications) that are willing to partake in intense exercise, despite no strong evidence to support the benefit from the testing (16). The indication of an exercise stress test is a major barrier to recommending HIIE as it increases the cost and delays the commencement of the exercise program.

While HIIE can be categorized as a high intensity exercise, it is unknown whether it induces the same degree of cardiovascular susceptibility as more prolonged high intensity exercise. Several studies have shown the safety of HIIE in individuals with various heart conditions (17-22). Moreover, one retrospective study showed a very low incidence of cardiovascular events in patients with coronary heart disease undertaking HIIE at cardiac rehabilitation centers (one non-fatal cardiac arrest per 23,182 hours) (23).

In the present dissertation, individuals with relatively well-controlled diabetes participating in HIIE training showed no injuries or episodes of symptomatic hypoglycemia (**Study 1**). Similarly, among a total of 34 individuals identified in published HIIE training studies (baseline mean A1c ranging from 6.8 to 8.5% (24-27)), no adverse effects were reported. In contrast, despite no

hypoglycemic events, one study showed several cases of microvascular complication (two developed background retinopathy and eleven showed loss of peripheral sensation) (28). Nonetheless, the study is more than 20 years old and individuals were treated with diet only despite their high mean baseline A1c of 12.2%. Lack of anti-hyperglycemic medication is unusual for individuals with such high glycemia under current standards. Thus, it is not clear if the complication was induced by HIIE or occurred as a result of untreated hyperglycemia.

Acute adverse events in responses to HIIE were not observed in **Study 2** or **Study 4.** Consistently, no injuries or symptoms of hypoglycemia were reported among 28 individuals with T2D (A1c ranging from 6.0 to 10.5%) identified in acute HIIE studies (6,29-31). These limited data suggest that HIIE unlikely poses hypoglycemic risks in otherwise healthy individuals with T2D. Thus, the occurrence of adverse events during HIIE would be considered to be rare at least in individuals with relatively well controlled T2D (A1c <10%). Considering the health benefits of partaking in HIIE (discussed in the following section) and the low risk of adverse events, the necessity of exercise stress test in individuals with T2D is questionable and requires a larger investigation that will more adequately address the safety issue. Caution needs to be practiced in individuals with more advanced T2D.

The low risk of the adverse events is essential for HIIE to be accepted as a therapeutic exercise option for individuals with T2D. Another important factor is the applicability of HIIE. The positive perception towards HIIE has been noted in recreationally active males, who reported HIIE to be more enjoyable than MICE (32). Anecdotal evidence also suggests that HIIE is enjoyable in individuals with T2D. Little et al. indicated that individuals with T2D participating in HIIE perceived the protocol enjoyable (24). Similarly, although it is possible that the responses were biased since HIIE may have been perceived as the novel intervention that was being examined, some individuals participating in the present dissertation also anecdotally indicated HIIE more enjoyable compared to MICE that was felt to be more monotonous. No participants suggested that they

preferred MICE. Despite these limited data, HIIE may be applicable and safe at least in relatively well-controlled individuals with T2D. Trials to expand these findings to longer-term real-life settings are needed.

Health benefits of HIIE. In comparison to a non-exercise condition, randomized controlled HIIE training studies of individuals with T2D have consistently shown improved A1c (25,27). In addition, two studies reported an improvement in A1c following HIIE training (24,28). The implementation of HIIE also acutely lowered fasting glucose (26,30), postprandial glucose (24,29), and 24-hour mean glucose concentrations (24). The observations from the present dissertation were in agreement with these latter results (**Study 4**). Several studies have also shown increases in activities of intermediaries considered to increase glucose transport to a greater extent following HIIE than MICE (see HIIE vs. MICE in Appendix for further detail). These data, and the present dissertation, suggest that HIIE is a therapeutic exercise option for a glucose control in individuals who are capable of performing high intensity exercise.

Although controlling glucose is an important aspect of treatment for individuals with T2D, the management of diabetes has been characterized as too "glucocentric" (33) and controversy remains regarding the contribution of various forms of hyperglycemia (34) (or hypoglycemia (35)) to cardiovascular complications. In this regard, it is worth mentioning that several studies report HIIE improves aerobic power (36), body composition (37), insulin sensitivity (38), and endothelial function (21,39) to a greater extent than MICE (see "HIIE in older individuals" in Appendix for more detail). Given that these factors contribute to macrovascular complications, positive effects of HIIE on these parameters need to be considered along with its effects on glycemia.

The demonstration that HIIE lowers the risk factors for T2D complications to a greater extent than MICE is essential if this form of exercise is recommended as an alternative for MICE. While more studies are needed to elucidate if HIIE confers additional benefits to MICE in terms of glucose control, currently

available evidence suggests that HIIE is as effective as, if not more effective than, MICE in providing various health benefits.

6.6 Limitations

The main limitation of the collection of studies from this thesis is the absence of detailed measurements that would help provide a better understanding of how the exercise interventions affect various indicators of glycemic control. (e.g., changes in hormonal concentrations, enzymatic activity and protein content). Changes in glucose concentrations are just one outcome of exercise responses and may not reflect other important physiological changes. For example, despite the same glucose concentrations following an exercise bout, insulin sensitivity can differ depending on the concentration of insulin. Improved insulin sensitivity is one important benefit of exercise because hyperinsulinemia or insulin resistance reduces nitric oxide production and create a pro-inflammatory condition (40). Nonetheless, such changes were not captured in the present dissertation.

Another limitation related to the investigation of acute glycemic responses to HIIE and MICE (**Study 4**) was the absence of oral anti-hyperglycemic medication in the morning before exercise. The decision to remove the morning dose of medication was made to avoid different types of medication interacting with exercise and meal intake, and to minimize the risk of hypoglycemia induced by a combination of exercise and medication. The removal of medication favored the glycemic responses to HIIE and MICE, as well as fasted- and fed states exercise in a more controlled context. However, taking anti-hyperglycemic medication in the morning is a common practice for individuals with T2D who often manifest the highest peak in glycemia in the morning. It is of practical importance to evaluate if similar glycemic responses can be obtained with the presence of medication in the morning.

Exercise studies are often powered to detect differences between exercise training and a sedentary control group. It has been established that exercise interventions can improve glycemia compared to a non-exercise condition (e.g.,

A1c (41)). However, prospective studies with sufficient power to compare different exercise interventions on A1c may be difficult. For example, a retrospective sample size calculation based on A1c results from **Study 1** revealed that, to detect the changes using one-way ANOVA comparing two groups with power level of 0.80 and alpha at 0.05 (two-tailed), 143 participants per group are required. Thus, the study assessing long-term effects of HIIE (**Study 1**) was underpowered and the probability of type II error was high.

Lastly, among a total of 34 participants recruited for the four studies, five participated in multiple studies. This decreases generalizability of the results. Similarly, because the studies were performed only on individuals with relatively well-controlled T2D, the results may not be applicable to those with more advanced T2D.

6.7 Future directions

In the present dissertation, the training effect of HIIE on A1c was investigated without considering timing to perform such exercise. Allowing participants to exercise at the time of their convenience may have increased the adherence and retention to the training program, but it did not allow the investigation of long-term effects of HIIE under different meal states. Based on the results from **Study 4** (Chapter 5) which indicated fasted-state HIIE acutely reduces most glycemic profiles, standardizing exercise timing in relation to meals may have shown different outcomes. In this regard, it would be of interest to examine the long-term effects of fasted-state HIIE.

In addition to investigating the timing to perform HIIE, different forms of HIIE also requires further investigation. HIIE can be performed in various forms by manipulating duration, intensity, or frequency of the high intensity bouts and/or recovery periods. The main strength of the HIIE protocol employed in the present dissertation is its same exercise duration and volume as MICE. Although this protocol enabled the investigation to focus on the effects of high intensity bouts compared to MICE while controlling other potential factors that may

influence glycemic responses, it compromises some of the important advantage of low-volume HIIE.

A major advantage of low-volume HIIE is that, despite its shorter time commitment and smaller exercise volume, it provides similar benefits to other lower intensity prolonged exercise. Seminal studies showed positive effects of low-volume HIIE on glucose (24,29) and insulin sensitivity (42-44). Nevertheless, it is not clear if such exercise induces similar glycemic responses as observed in the present dissertation, or induces better glycemic outcomes compared to MICE. Further investigation using low-volume HIIE is required.

6.8 Conclusion

In summary, the findings in this thesis indicated that HIIE is well tolerated by individuals with relatively well-controlled T2D and effectively improves various aspects of glycemic profiles. In addition, compared to MICE, high intensity interval exercise was shown to induce greater reductions in nocturnal and fasting glucose concentrations on the day subsequent to exercise. These results suggest that HIIE has some potential advantage over MICE in improving specific aspects of glycemia. While performing high intensity interval exercise in the fasted-state attenuated the reduction of glucose concentration during exercise, it lowered most aspects of dysglycemia measured over ~24 hours following the exercise bouts. Postprandial HIIE, on the other hand, resulted in the greatest reduction in glycemia during exercise; however, no acute glucose profiles were improved as compared to a sedentary day. These results suggest the importance of performing HIIE during a fasted-state for lowering additional measures of glycemic profiles. Whether acute glycemic improvements following fasted-state HIIE translate into a better long-term effect as reflected by A1c is yet to be seen.

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Appendix I: Literature Review

Introduction

Exercise has long been prescribed as a first line therapeutic approach to control abnormal blood glucose concentrations seen in individuals with T2D. To date, a variety of exercise interventions have been used to optimize the effects of exercise on blood glucose concentrations. Nonetheless, it is still not clear whether high intensity interval exercise (HIIE) has an advantage over traditionally used moderate intensity continuous exercise (MICE) in controlling blood glucose of individuals with T2D. Moreover, it also remains inconclusive how physiological conditions, such as exogenous nutrient availability, interact with different forms of exercise. This literature review focuses on 1) pathogenesis of disturbed glucose profiles, 2) a device used to capture the glucose profiles, 3) the potential impact of HIIE, and 4) the potential effects of exercise under fasting and fed conditions.

Glucose profiles of T2D and associated risks

It has generally been established that hyperglycemia increases oxidative stress in a variety of tissues and causes cellular damage that leads to late complications (1). Some of the potential mechanisms by which hyperglycemia contributes to vascular complications include its effect on endothelial cell functions by inducing oxidative stress via the generation of free radicals and through the production of advanced-glycosylation end product (AGE), both of which have been implicated to be associated with endothelial damage (2,3). Naturally, regulation of blood glucose is one of major targets of T2D treatment.

Since elevated fasting blood glucose (FBG), glycosylated hemoglobin A1c (A1c), and postprandial glucose (PPG) are strong predictors of the development of diabetic complications (4-8), these measures have been used to assess the severity of the condition. Recently, in addition to this so-called glucose triad, another factor that arguably exacerbate the condition (9) has been identified and under intensive research. This is glycemic variability (GV), the swing or

fluctuation of glucose concentrations (10). The following sections will review the current understanding on the glucose quartet independently, as well as their associations with one another.

Glycosylated Hemoglobin A1c (A1c)

Since the finding that hemoglobin becomes glycosylated upon incubation with glucose, glycosylated hemoglobin A1c (A1c) has gradually become the "gold standard" for assessing the overall condition of T2D over the previous 12-16 weeks (11). Plasma glucose concentrations and A1c levels are independent continuous risk factors for cardiovascular disease (CVD) with no apparent threshold (12). Large prospective randomized controlled trials assessing the relationship between A1c and T2D-related complications, such as the United Kingdom Prospective Diabetes Study (UKPDS) (8) and Kumamoto study (6,7), established close association between elevated A1c and the risks for microvascular complications.

Based on its stability against acute perturbations (stress, exercise, or diet) and biological variability (13), A1c has been used extensively in a clinical test to investigate the condition of T2D. Moreover, its strong association with diabetic complications (8) has frequently made A1c a primary outcome to assess the effectiveness of various interventions. American Diabetes Association (ADA) recommends individuals with T2D to target < 7% to avoid microvascular and neuropathic complications (14). However, while attaining A1c < 7% has been a benchmark of successful diabetes therapy, it represents average glycemic control over time and does not necessarily reflect other potential pathogenic glucose profiles, such as postprandial glucose spikes and daily glycemic variability. Because individuals with similar A1c can have dissimilar glycemic patterns, it is important to assess the association between the other glycemic profiles and diabetic complications.

Fasting Blood Glucose (FBG)

During the periods between meals, glucose concentrations of healthy individuals are maintained within a narrow range by finely regulated hepatic glucose production. In individuals with T2D, however, hepatic glucose production is not sufficiently suppressed. This increased hepatic insulin resistance predominantly characterizes impaired FBG (15,16).

T2D can be clinically defined as an 8-hour fasting plasma glucose greater than 7.0 $mmol \cdot L^{-1}$ (14). However, with prolonged effects of meal-induced hyperglycemia, "true" fasting state is a rare state in individuals with T2D that can only be observed in the morning before breakfast (17). More generally, ADA recommends adults with T2D maintain preprandial glucose (not true fasting, but glucose values before each meal) values of 3.9 to 7.2 $mmol \cdot L^{-1}$ (14).

Based on its well-documented positive association with risk for mortality (18,19), FBG has frequently been used as a marker to examine the existence/severity of diabetes. However, because postprandial glucose (PPG), blood glucose responses to meals, normally deteriorates before FBG (20), relying solely on FBG may not be an appropriate approach to detect T2D at an early stage. The co-existence of normal FBG and uncontrolled PPG can contribute to undetected elevation of overall mean daily glycemia. In addition, Sorkin et al. demonstrated that among individuals with similar FBG, those who have more deteriorated PPG manifest a greater risk of mortality (19). This also indicates that achieving target FBG does not necessarily mean that blood glucose concentrations are under control throughout the day(21). Indeed, the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study, a large collaborative prospective study, found that FBG alone may not be enough to identify individuals at increased risk of mortality associated with hyperglycemia and showed the importance of assessing glycemic response to oral glucose load by oral glucose tolerance test (22).

Postprandial Blood Glucose (PPG)

Postprandial hyperglycemia is another potential pathogenic factor. Lack of rapid insulin secretion from β-cells in response to an increase in plasma glucose concentration fails to adequately stimulate glucose uptake by the liver, muscle, kidney, and adipose tissues (23). Because the skeletal muscle comprises the major depot for the glucose storage (24), individuals with T2D who manifest a high glucose spike after a meal often have moderate to severe muscle insulin resistance (15,16).

Despite the fact that FBG and A1c have dominated in the clinical assessment of glycemia, the DECODE study showed not FBG but high blood glucose concentrations 2 hours after oral glucose ingestion is associated with an increased risk of mortality (22). Similarly, 11-year follow up of early T2D patients demonstrated impaired PPG but not FBG is an independent risk factor for myocardial infarction and all-cause mortality (25). Strong positive associations were also observed between PPG and the occurrence of cardiovascular events (26,27), and between PPG and the occurrence of diabetic retinopathy (28).

Possible deleterious effects of PPG surges on endothelial functions have been well documented by studies completed by Ceriello's groups (10,29-34). In the series of studies, the author has indicated that PPG excursion enhances oxidative stress and oxidative damage incurred by reactive oxygen species; both of which negatively affect endothelial walls and subsequently increases the rate of CVD occurrence. In accordance with the proposed mechanism, studies indicated that 2-hour PPG concentrations are more strongly associated with carotid intima-media thickness, a well-established surrogate marker for early signs of atherosclerosis, than FBG or A1c (35,36). Another study reporting significant correlation between meal-induced glucose fluctuations and oxidative stress also corroborates the harmful nature of uncontrolled PPG (37). Not surprisingly, PPG has now been designated as an independent risk factor that contributes to the development of CVD (27,38). International Diabetes Federation (IDF) recommends implementing treatment strategies to lower PPG (39).

Although still based on the results from epidemiological, observational, and experimental studies rather than large-scale interventional studies (40), currently available evidence suggests, and expert panels agree, that the PPG excursion is a marker for metabolic abnormalities responsible for the development of diabetic complications(34). Administration of oral anti-hyperglycemic medication that selectively increases meal-related early insulin secretion, such as Repaglinide, was shown to more effectively regress carotid intima-media thickness and C-reactive proteins, another surrogate measure for the risk factors associated with atherosclerosis, than another form of oral anti-hyperglycemic medication in patients with T2D (41). Similarly, intensive insulin therapy that mimics the physiological pattern of postprandial insulin secretion has been shown effective in reducing the occurrence of diabetes-related complications (6,7). Given that muscular insulin sensitivity is enhanced following an exercise bout, exercise intervention may also be an appropriate intervention to target the PPG spikes. Two-hour PPG goal of < 7.8 and peak PPG of < 10.0 $mmol \cdot L^{-1}$ have been recommended by IDF (39) and ADA (14), respectively.

Glycemic variability (GV)

As indicated earlier, A1c has traditionally been used as a valid surrogate to assess the condition of T2D and ubiquitously been used in clinical practice. However, there is a growing body of evidence suggesting that A1c is not sufficient to predict the development of diabetes related complications (42) as transient hyperglycemia may be offset by hypoglycemia and results in little changes in A1c. Glucose variability (GV), the oscillation of plasma glucose concentrations from either high to low or low to high, is now considered a strong stressor that increases cellular oxidative stress (37). GV is, in many ways, similar to PPG. However, while PPG is limited to meal-induced glucose excursions, GV includes fluctuations throughout the period of interest. Thus, a large PPG spike can be a major contributor to GV, but GV also includes other circadian fluctuations in blood glucose concentrations.

An acute glucose swing exerts its deleterious effects on endothelial cells in a similar way a PPG glucose spike does, that is by triggering oxidative stress (37). Brownlee et at. demonstrated that highly oscillating plasma glucose concentrations is a strong predictor of total free radical production (43), substances that enhances oxidative stress and results in an increased rate of endothelial cellular dysfunctions (44) and apoptosis (45). Other studies on individuals with T2D have also demonstrated that intermittent high glucose concentrations induce more oxidative stress by measuring urinary excreted 8-iso prostaglandin, a well-recognized marker of oxidative stress (37,46), and poses greater deleterious threat on endothelial function by reducing flow-mediated dilation to a greater extent than consistently high glucose concentrations (37).

In keeping with this finding, when 344 patients with T2D were divided into CAD and non-CAD groups based on coronary artery angiography, the CAD group had significantly more labile glucose profile despite similar A1c and FBG (47). Although this does not show labile glucose concentrations cause CAD, it is possible that highly oscillating plasma glucose concentrations exert greater oxidative stress on endothelial function than chronic hyperglycemia and increase the risk of developing CVD (17) and microvascular complications (48). A systematic review showing that GV has a significant association with diabetic retinopathy, cardiovascular events and mortality independent of A1c levels in individuals with T2D further supports the possibility (49).

In addition to the role GV may play on oxidative stress, some evidence suggests negative association between GV and antioxidants. In one study, significant correlations have been reported between acute glucose fluctuations and depressed antioxidant markers, adiponectin and glutathione (50). In another *in vitro* study, it has been shown that while both consistent hyperglycemia and intermittent hyperglycemia exacerbate the gene production and protein concentration of adiponectin, intermittent hyperglycemia induced significantly greater effects (51). Consequently, it is possible that GV contributes to increased risk of diabetic complications by increasing oxidative stress, as well as by reducing antioxidant activities.

While mounting evidence indicates that GV is an important target to avoid diabetic complications, the precise role of GV in the development of complications still remains an open question (9,52) as the link between the intermittent high glucose concentration and its deleterious effects has only been established in experimental settings and no human intervention study has established a causal relation between GV and oxidative stress (53). It has been argued that randomized prospective intervention studies linking GV and the development of diabetic complications may help further establish the missing link (54).

Interrelation among glucose profiles

While A1c represents duration and magnitude of chronic hyperglycemia, it may be insensitive to acute changes in glucose concentrations (55). The fact that A1c does not reveal any information on the extent and frequency of acute glycemic changes may suggest that A1c can show adequate glycemic control in patients who are susceptible to CVD by exhibiting acute marked glucose fluctuations.

While it is still debatable how much proportion of A1c can be explained by FBG and PPG, it is generally agreed that PPG contributes more to A1c than FBG in those with relatively well controlled A1c (56). Monnier and colleagues have reported that PPG deteriorates at earlier stage of T2D than FBG, and showed that the regulation of PPG is more important in this subgroup of T2D (20). The contribution of FBG to A1c, on the other hand, increases with the worsening of overall glycemic control (57-59). Consistent to these observations, dietary modification aiming to improve PPG was shown to improve A1c significantly in individuals with T2D whose A1c ranges between 6.5-7.0 % (60). Consistently, it is now generally accepted that abnormalities in insulin secretion and action (primarily involved in PPG regulation (15,16)) contribute to the development of T2D, whereas less controlled endogenous glucose production (primarily involved in FBG regulation) is a later phenomenon (61). Yet, with one study showing that A1c correlates with FBG but not with PPG in similar population (A1c < 7%) (62),

the associations among glucose profiles may require further investigation. With regard to GV, the degree to which GV contributes to A1c is inconclusive. Kuenen et al. demonstrated that GV only modestly influences A1c for a given mean plasma glucose in T2D (63); however, the investigation was limited to participants with relatively well-controlled A1c (mean A1c =6.8%).

Taken together, there may be a limitation in describing the condition of T2D thoroughly with a single glucose profile. Assessing the condition of T2D by A1c alone is hampered as high PPG and GV can still be manifested in individuals with relatively well controlled T2D. Simultaneous assessment of different glucose profiles is warranted for better diagnostic purposes. Only with the detailed evaluation of glycemic phenotype can intervention be tailored for the most appropriate treatment.

Glucose profiles summary

In recent decades, A1c and FBG have often been used as clinical markers to determine the existence or severity of T2D. However, emerging evidence now suggests that relatively well-controlled A1c or FBG does not necessarily reflect favourable PPG and/or GV, both of which can worsen the conditions of T2D if uncontrolled. Although common definitions and metrics for optimum health are yet to be standardized for PPG and GV (64), therapeutic intervention targeting all four aspects of the glycemic profiles may be required to more optimally avoid diabetic complications. The following section will focus on the instrument that can capture the glucose profiles that are overlooked by conventional A1c and self-measured blood glucose assessment.

Diabetic complications

Individuals with type 2 diabetes (T2D) are at increased risk of cardiovascular conditions due to elevated glycemia. This elevated glycemia in combination with hyperinsulinemia, insulin resistance, and hyperlipidemia, to name a few are modifiable risk factors that contribute to the development and progression of

cardiovascular complications (65). This section introduces some of the factors associated with the development and progression of vascular complications and possible roles exercise may play in counteracting the exacerbation of vasculature.

Hyperglycemia

Hyperglycemia, a condition characterized by elevated blood glucose concentrations, are an important risk factor for cardiovascular complications. Elevated glucose concentration in the circulatory system promotes the binding of glucose to proteins, which accelerate the generation of advanced glycated end products (AGE) (66). AGE, in turn, binds to specific receptors on endothelial cells and initiate coagulant activities (67). In addition, the glycation of proteins also interferes with molecular and cellular functions throughout the body and promotes the release of highly oxidizing side products, such as hydrogen peroxide and free radicals (66). These reactive oxygen species (ROS) decrease the function of endothelial nitric oxide (NO) synthase (eNOS) and reduce the half-life of NO (68). Because NO protects vasculature by inhibiting vascular smooth muscle cell proliferation and migration and mitigating oxidative stress (69), reduced NO bioavailability due to elevated glycemia results in vascular dysfunctions.

Hyperinsulinemia

In addition to the adverse effects of hyperglycemia on vasculature, hyperinsulinemia has also been reported to cause pro-inflammatory condition by reducing NO production (70). Because insulin stimulates eNOS activity through a series of signal transduction initiated by the binding of insulin to its cellular receptors, insulin resistance reduces NO bioavailability (69).

Insulin binding to an insulin receptor initiates a series of reaction that involves phosphatidylinositol 3-kinase (PI3K) and Akt (71). The activation of PI3K and Akt not only stimulates the translocation of GLUT4 vesicles for glucose uptake but also promotes the activation of eNOS (72). Because the activated eNOS promotes the conversion of L-arginine to NO (71), disrupted eNOS activity with presence of insulin resistance has negative consequences on vasculature.

Another pathway that can suppress the production of NO involves mitogen-activated protein kinase (MAPK). Although insulin resistance affects the PI3K and Akt mediated pathway and decreases the production of NO, another insulin mediated pathway that involves MAPK is not affected by the presence of insulin resistance (71). This is problematic because the activation of the pathway involving MAPK is proatherogenic and leads to decreased NO production and increased vascular smooth muscle cell proliferation (69). Thus, with the presence of insulin resistance, both disrupted PI3K and Akt pathway, as well as unaffected MAPK pathway may be responsible for reduced NO availability and creating a prothrombotic condition.

Hyperlipidemia

In the insulin-resistant state, insulin-dependent lipase in the adipocyte is less well prohibited. This increases flux of free fatty acids from adipose tissues to the liver and promotes triglyceride synthesis and the secretion of low-density lipoprotein (LDL) cholesterol (73,74). In addition, under insulin-resistant states, enzymes, such as hepatic lipase and endothelial lipase, are upregulated and promote hypercatabolism of HDL (73,75). Thus, insulin resistance is associated with elevated circulation of triglycerides, a decrease in high-density lipoprotein (HDL) cholesterol, and an increase in low-density lipoprotein (LDL) (76), all of which contribute to the creation of a prothrombotic condition. Naturally, control of lipid has been recommended to protect against vascular events (14,77). By raising levels of HDL while decreasing LDL, exericse decreases the risk of developing cardiovascular complications (78).

Exercise and vasculature

Endothelial dysfunction is defined as an imbalance in which the effects of vasoconstrictors outweigh the effects of vasodilators, and this imbalance generally results from decreased NO bioavailability (69). Regular aerobic exercise can slow down the losses in endothelial function supposedly by restoration of NO

availability and by evoking specific adaptations in several tissues, such as the upregulation of antioxidant defense mechanisms (79).

Exercise improves insulin sensitivity by activating the PI3K-Akt pathway and promoting GLUT4 translocation in response to insulin (80). This activation of PI3K and Akt through exercise also suggests the activation of eNOS and enhanced production of NO. Another way by which exercise improves vasculature is through shear stress, a parallel friction force applied to endothelium by increased pulse pressure (79). The characteristics of shear stress are an important consideration as low arterial shear stress is associated with pro-thrombotic state which contributes to the development of vascular complications (81). Pulsatile shear stress during exercise stimulates the vascular endothelium to synthesize and release substances such as NO (82). Furthermore, by suppressing angiotensin II production, a hormone known to increase blood pressure and suppress eNOS (69). exercise increases NO production.

Taken together, through various possible pathways, exercise enhances the production of NO and decreases the risk of developing cardiovascular disease in diabetes. Increased NO bioavailability is expected to be vascular protective as it inhibits inflammation, oxidative stress, vascular smooth muscle cell proliferation and migration (69). Exercise training has been readily and consistently demonstrated in subjects in whom antecedent endothelial dysfunction exists (83).

Intramyocellular triglyceride and insulin resistance

Skeletal muscle takes up plasma free fatty acids and stores them as intramyocellular triglyceride (IMTG), the amount of which correlates strongly with insulin resistance (84). The accumulation of triglyceride due to either increased uptake or decreased oxidation of free fatty acids reflects an important defect of muscles in response to insulin. However, it was suggested (85) and now widely agreed that IMTG alone does not confer insulin resistance but rather act as a surrogate for other potential detrimental lipid metabolites. Diacylglycerol (DAG), glyceride consisting of two fatty acid chains bound to a glycerol

molecule, and ceramide, sphingolipid molecule composed of sphingosine and a fatty acid, are widely recognized mediators of insulin resistance (86,87).

Through a series of signaling, DAG suppresses PI3K activity (90) and promotes PKC activity (88,89), whereas ceramide promotes PKC activity (90) and inhibits a pathway involving Akt (91), all of which lead to the suppression of GLUT4 translocation. Under conditions of lipid oversupply, hydrolysis of IMTG increases the contents of DAG and ceramide (90). Thus, when energy supply exceeds energy requirement, IMTG can act as a precursor for lipotoxic intermediates that mediate insulin resistance.

Endurance-trained athletes also possess a high IMTG content. However, skeletal muscles of trained individuals are characterized by high lipid oxidative capacity and enhanced insulin sensitivity (90). Exercise training has been shown to promote an increase in IMTG but reduce both ceramide and DAG concentrations (92), possibly by improving the contents of mitochondria and enzymes associated with lipid oxidation (87,93). A high turnover rate of the IMTG pool in trained athletes is proposed to reduce accumulation of lipotoxic intermediates interfering with insulin signaling, whereas in sedentary obese and type 2 diabetes, reduced oxidative capacity and a mismatch between IMTG lipolysis and beta-oxidation may be detrimental to insulin sensitivity by generating lipotoxic intermediaries (94).

Continuous Glucose Monitor System (CGMS)

In the past, self-monitored blood glucose (SMBG) throughout the day provided diabetologists and family doctors with the information necessary for planning the most appropriate anti-diabetic treatment to optimize blood glucose (95). While SMBG is important, it is invasive, cumbersome, and predominantly episodic in nature, making it difficult to capture rapid changes in glucose concentrations in response to everyday stimulus. Recently, to fill in gaps between point measures, continuous glucose monitor systems (CGMS) have been developed. CGMS provides glucose concentrations in a continuous temporal line of data, allowing the analysis of glucose concentrations in context of its direction, periodicity, and

amplitude. With the use of the device, the effectiveness of treatment on FBG, PPG, and GV can be examined in detail.

As of 2014, CGMS manufactured by Medtronic and DexCom are approved by Health Canada. The device used in the present dissertation was the latest version developed by Medtronic as of June 2013 (iPro2, Medtronic Northridge, CA). Because iPro2 was a new device with only limited information available, the following sections summarized the general features and current understanding of CGMS with special emphasis on earlier versions of CGMS manufactured by Medtronic.

CGMS System Overview

In general, CGMS measures interstitial fluid glucose concentration using the glucose-oxidase enzyme technology. A needle-based glucose sensor embedded with glucose oxidase is implanted subcutaneously at the anterior abdomen with the help of a spring-loaded device, Sen-serter (Medtronic Northridge, CA). The insertion of the electrochemical sensor is followed by the attachment of a CGMS monitor. Once inserted, the enzyme embedded in the sensor catalyzes the reduction of glucose to gluconic acid and hydrogen peroxide (glucose + H_2O → gluconic acid + H_2O_2) (96). Hydrogen peroxide is then dissociated to $^2H^+$, O_2, and $2e^-$, which create electrical current measured in nA (96). Thus, the CGMS measures the magnitude of the electrical charge produced by the chemical reaction which is proportional to interstitial glucose concentrations. The glucose sensor signal is acquired from interstitial fluid every 10 seconds (97,98), with an average of the acquired signals stored in the sensor every 5 min for up to 7 consecutive days (99). The stored nA readings are retrospectively converted to glucose values at the time the data are downloaded to a personal computer with the use of calibration values measured via a SMBG monitor (97).

This technology to measure glucose concentration is defined as minimally invasive because it compromises skin barrier without puncturing any blood vessels (100). However, the measurement from interstitial fluid with the

assumption of the glycemic equilibrium between interstitial fluid and blood is the most frequently encountered criticism of the device. Glucose can freely and rapidly diffuse across a concentration gradient between blood and interstitial fluid (101,102), and then taken up into the cells within the compartment (**Figure A.1**). Accordingly, glucose concentrations in the interstitial fluid reflect the blood glucose concentration. However, because there is a consistent difference between interstitial and plasma glucose concentrations, proper calibration is required in order for CGMS to accurately reflect the plasma glucose concentration (103). In addition, since the rate of glucose flow from blood to interstitial fluid is subjected to a variety of factors, such as the rate of blood flow and metabolic glucose concentration changes, time lag before the interstitial fluid accurately reflects blood glucose concentration is not consistent and reported to vary between 2 to 45 minutes (102) depending on the sites of measures (104), the type of sensor making the measurement (105), and the direction of the blood glucose concentration changes (i.e., rising, stable, or falling). When the sensor was inserted to anterior abdominal wall, the time differences between blood and interstitial glucose ranged from 4 to 10 min, and the suggested mean lag time was 6.7 minutes (98).

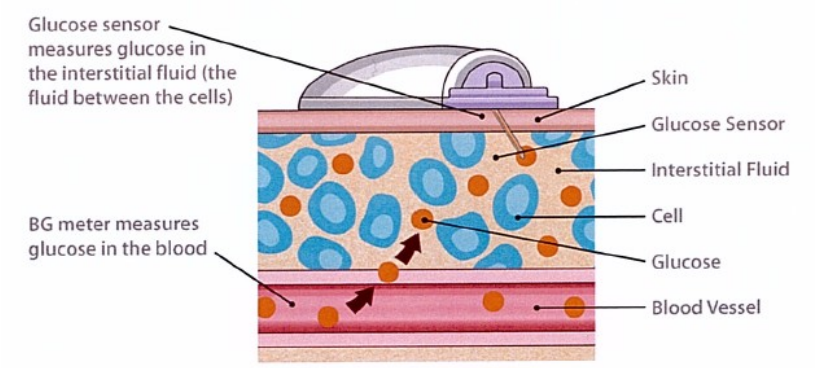

Figure A.1. Schematic presentation of iPro2. (adopted from iPro2 training guide (99))

CGMS Accuracy

Although the accuracy of iPro2 has yet to be determined, other Medtronic CGMS which use the same technology, such as Guardian glucose monitoring system, has been shown to correlate highly with reference blood glucose measures of critically ill patients at both very high and very low concentrations (106). However, in healthy individuals undergoing an oral glucose challenge, real-time CGMS from Medtronic has demonstrated statistically significant mismatches against reference measures; most notably due to delayed response to an increase in blood glucose during rapid rise in glucose concentrations (107). The accuracy of Minimed CGMS (Medtronic Northridge, CA), a type similar to iPro2 on the other hand, although it tended to overestimate glycemia, was shown statistically acceptable during exercise (108,109).

While above studies investigated the accuracy of CGMS performance using conventional statistical methods, the difficulty in determining the accuracy of the CGMS measures requires attention. One important concept that needs to be taken into consideration is the difference between statistical and clinical accuracy. For example, while reporting glucose concentration of 6 $mmol \cdot L^{-1}$ when the actual value is 5 $mmol \cdot L^{-1}$ can result in a statistically significant difference depending on variability and sample size, the difference has relatively minor clinical importance. Accordingly, to examine the clinical accuracy of the device, error-grid analyses were introduced and frequently used to assess the CGMS performance.

Point accuracy error-grid analysis (P-EGA) was first developed to investigate the clinical accuracy of SMBG readings (110). Briefly, it compares the measured values against reference values and examines if the difference has significant clinical implications. The difference between measured and reference values at each data point is categorized into zone A: clinically accurate; zone B: benign error (within 20% of reference); zone C: overcorrection error; zone D: failure to detect; and zone E: erroneous errors (111), with the size of

accurate/acceptable zones adjusted in accordance to clinical importance (**Figure A.2**). Therefore, the differences that have little clinical importance are categorized acceptable while the differences that could possibly lead to inaccurate therapeutic decision are deemed clinically inaccurate.

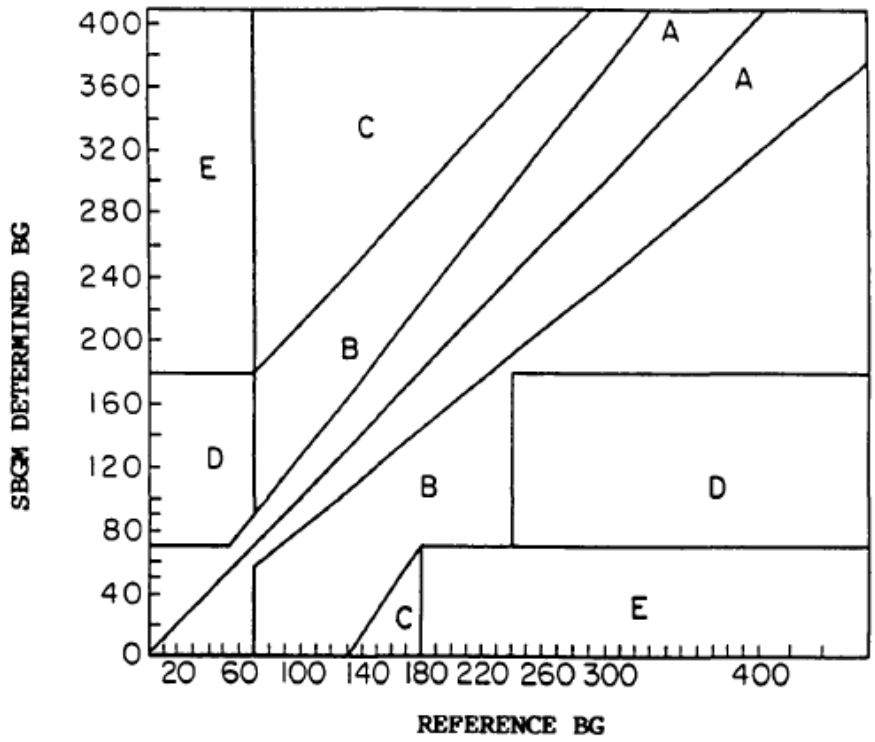

Figure A.2. Schematic presentation of point accuracy error-grid analysis (adapted from Kovatchev et al. (112))

Because P-EGA only compares measured data at each point against the corresponding reference value, the delay in interstitial fluid during a rapid concentration change inflates the difference (112). Consequently, continuous error-grid analysis (CG-EGA) was developed (112) to investigate clinical accuracy while taking the temporal component into account. This method expands the boundaries of accurate zones when there is a rapid fluctuation in the rate of the glucose concentration change.

Using CG-EGA, Minimed demonstrated good clinical accuracy with 98.3 % of readings in either accurate or benign error ranges (clinically acceptable)

(111). The accuracy, however, was somewhat deteriorated in a hypoglycemic range. In keeping with this report, another study also showed high clinical accuracy during euglycemia and somewhat deteriorated accuracy during hypoglycemia (113). Another Medtronic manufactured CGMS, a CGMSgold sensor also showed a similar trend (114).

One shortcoming of the determination of CGMS accuracy is that, even when EGA is applied, the data points are still compared as isolated points despite the temporal structure of data (112). Because of high inter-dependency of nearby CGMS data points, the chance of obtaining sequential inaccurate readings is high, which might have contributed to more erroneous observations during hypoglycemia (113,114). In summary, CGMS accuracy is still being questioned and general consensus is that its accuracy is inferior to that of SMBG (105). Although the device undoubtedly provides important information that is often overlooked by SMBG system, FDA states that CGMS should be used as an adjunct to, but not a replacement for, information obtained from SMBG.

Statistical analyses for glycemic variability (GV)

Besides mean daily blood glucose values and area under the curve, CGMS provides an important temporal glucose concentration change. Nevertheless, while sequentially collected data provides a large amount of information and allows detection of GV, the statistical disadvantage of the CGMS data stream is that all data points are highly interdependent. This high dependency of the data violates the statistical assumption and complicates its analysis (115).

Standard deviation (SD) has often appeared in literature as a means to investigate the temporal GV. However, the use of SD as a measure of GV may be misleading because patients with T2D tend to spend more time in hyperglycemia and thus their glucose distribution tends to skew towards higher values. Because the use of SD is only accurate when the glucose readings are symmetrically distributed around the mean, the description becomes inaccurate with more glucose concentrations distributed in hyperglycemia (116). Another important shortcoming of the use of SD is that it fails to include the pattern for fluctuations.

For example, a patient who demonstrates one major fluctuation can have the same SD as another patient with moderate fluctuations throughout the day (**Figure A.3**) (44).

To date, several methods have been developed and proposed to capture GV. However, currently, no consensus has been achieved as to which analytical method(s) should be used (49). The following section summarizes two of the methods used to assess the GV from CGMS data. Among several methods, continuous overlapping net glycemic action (CONGA) and mean amplitude of glycemic excursions (MAGE) are of particular interest as the former is specifically developed to analyze CGMS data and the latter is widely used analytical protocol (53).

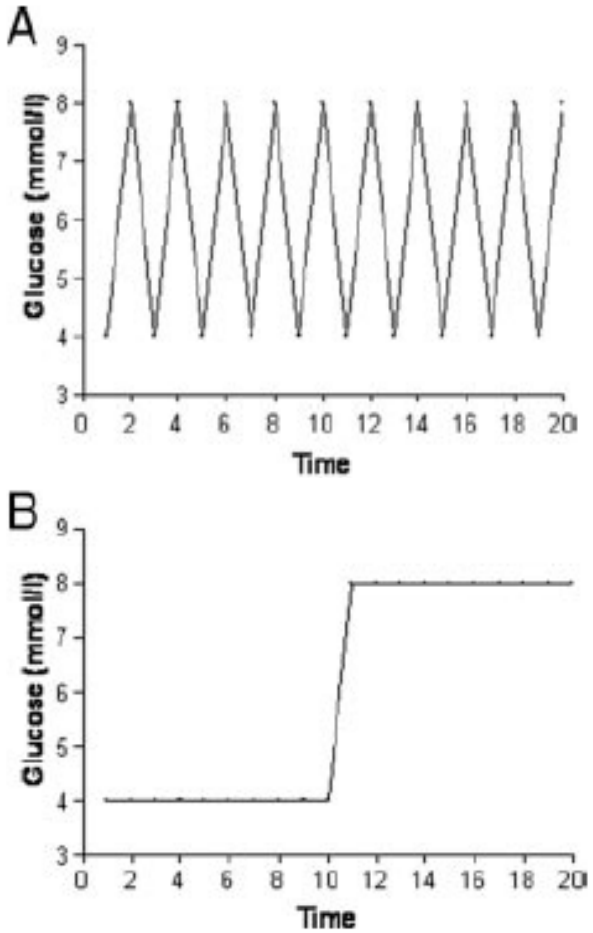

Figure A.3. Two potential glucose patterns that lead to identical mean and SD (adapted from Siegelaar et al. (53))

Continuous overlapping net glycemic action (CONGAn)

Continuous overlapping net glycemia action ($CONGA_n$) is an analytical method specifically designed to analyze CGMS data. As described above, raw glucose concentration values are often skewed toward hyperglycemia. However, changes in blood glucose concentrations over a given timeframe tend to be more symmetrical (117). CONGA measures GV by calculating the SD of the glucose concentration differences (118).

First, the time segment, or size of the window, used to measure the GV is defined as n. For example, $CONGA_1$, $CONGA_2$, and $CONGA_4$ each represent CONGA with different window sizes. For $CONGA_1$, the difference between a glucose value and another value 1 hour prior to the observation is calculated for each data point. The differences are subsequently used to calculate the SD. Similarly, for $CONGA_4$, the SD of the differences between observed glucose values and the values 4 hours prior to the observations are calculated. Higher CONGA values represent labile glucose concentrations whereas smaller values represent less variable glucose concentrations.

CONGA values range between 0.4 and 1.2 $mmol \cdot L^{-1}$ in normal non-diabetic individuals while CONGA values above 1.5 indicate glycemic instability (118). Mean values for non-diabetic individuals are reported to be 0.72, 0.88, and 1.01 $mmol \cdot L^{-1}$ for $CONGA_1$, $CONGA_2$, and $CONGA_4$, respectively (119). CONGA is accredited with its objective and valid indices to measure intraday GV (11).

Mean Amplitude of Glycemic Excursion (MAGE)

Mean amplitude of glycemic excursion (MAGE) is a simple arithmetic average of the amplitudes of all major GV introduced by Service et al. (120). Briefly, nadirs to peaks or peaks to nadirs glucose concentration changes that exceed 1SD are graphically identified. Fluctuations within 1 SD are considered not attributable to

the patients' condition and excluded from analysis, giving more weight on major glucose oscillations. A unique feature of the method is that it only includes 1-way fluctuations. For example, if the first fluctuation that exceeds 1 SD is from nadir to peak, subsequent fluctuations to be included are limited to nadir to peak only. If the first fluctuation is from peak to nadir, then the subsequent fluctuations from nadir to peak are excluded from analysis. All 1-way fluctuations that exceed 1SD are averaged for the final MAGE value.

MAGE has been regarded as a gold-standard for measuring intraday glucose variability (37). However, some inherent limitations of the method include: 1) it does not discern the total number of fluctuations (one large fluctuation results in large MAGE value); 2) determination of 1 SD as a cutoff was an arbitrary determination; and 3) the central 68 % of all glucose profiles (i.e., within 1 SD) used in MAGE is ignored and only outliers are considered for investigation (121). In addition, when data are acquired over more than a day, MAGE does not specify which SD should be used (122) (i.e., SD from 1 day or over the measurement).

Despite the limitations, MAGE is still the most widely used technique to calculate GV with a variety of computer programs developed to make computation easy (123,124). In non-diabetic individuals, the MAGE value of 2.22 $mmol \cdot L^{-1}$ is accompanied by normal level of endothelial surrogate measures, suggesting that this is the target value for GV (125). MAGE for non-diabetic individuals ranges from 1.11 to 3.33 $mmol \cdot L^{-1}$, and the values become higher as glucose concentrations become more labile (126). Previously reported mean values for non-diabetic individuals are 1.78 $mmol \cdot L^{-1}$ (119). An interesting feature of MAGE is that it is independent of mean glycemia (127,128).

Effect of exercise on the glucose profiles of T2D

Recently, a number of rigorous studies have surfaced molecular mechanisms underpinning contraction-induced blood glucose uptake. This section

focuses on molecular mechanisms associated with acute effects of exercise, as well as how different exercise interventions affect the molecular responses.

Potential mechanism of action

Glucose transporter 4 (GLUT4)

One of the mechanisms by which exercise augments muscular glucose uptake during and after exercise is via the translocation of glucose transporter 4 (GLUT4) to the cell membrane and t-tubule (129). It has been well established that exercise and insulin enhance glucose uptake via two separate pathways targeting different pools of intracellular GLUT4 vesicles (130), whose translocation to the cell membrane is the major mechanism by which glucose uptake into cells is enhanced (131).

Immediately after an acute bout of exercise, an insulin-independent contraction-induced increase in trafficking of GLUT4 vesicles to cell surface is prominent (132). In human muscles, a single bout of exercise increases GLUT4 gene expression (133) and GLUT4 protein content in cell membrane (134). This exercise-induced increase in GLUT4 mRNA expression subsides as time elapses. Interestingly, however, the down-regulation of GLUT4 mRNA does not necessarily reflect blunted GLUT4 protein concentrations. Using rats, Kuo and colleagues found that down-regulation of GLUT4 mRNA occurs in parallel with an increase in GLUT4 mRNA translation, which increases muscle GLUT4 protein considerably following exercise (135). Furthermore, subsequent to an exercise bout, the increased muscular GLUT4 content takes place with the presence of insulin (136). Thus, after contraction-induced, insulin-independent increase in glucose uptake subsides, insulin-dependent translocation of GLUT4 to the cell surface still persists (132). This increase in GLUT4 protein is accompanied by a proportional increase in glucose uptake by the muscle hours after exercise (135,137).

Several putative upstream kinases are involved in enhanced GLUT4 transcription. Over the past decade, 5’ adenosine monophosphate-activated

protein kinase (AMPK) has been recognized as an important signaling intermediary that leads to an increase in glucose uptake into muscle cells by facilitating cell-surface expression of GLUT4 (138-140). The decrease in high-energy-phosphate, ATP, during contractile activity stimulates AMPK, which is expected to trigger the processes that result in GLUT4 translocation (141). Collectively, activation of AMPK is, at least in part, responsible for the translocation of GLUT4.

5' adenosine monophosphate-activated protein kinase (AMPK)

An increase in energy expenditure needs to be coupled with an increased uptake and metabolism of fuels. Contraction-induced metabolic disturbance, glycogen depletion, and mechanical stresses activate several key kinases and phosphatases involved in signal transduction leading to increased glucose uptake (142). One of the key players responsible for enhanced glucose uptake is AMPK, especially AMPK α2 isoform abundant in skeletal muscles (143). Enhanced glucose uptake paralleled by GLUT4 expression in conjunction with AMPK activation has been well documented (138-140).

AMPK is an energy-sensing enzyme, such that the enzymatic activity is increased when the cell is under conditions associated with energy depletion (144). In response to increasing energy demand, AMPK was hypothesized to increase fatty acids oxidation and glucose uptake (145). It has been documented that in rats skeletal muscles 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), a compound known to activates AMPK, increases fatty acid oxidation and glucose uptake (146). Winder and Buhl demonstrated that AMPK activation by AICAR injection increases acetyl-CoA carboxylase (ACC), which subsequently reduces the activation of malonyl CoA, a known inhibitor of fatty acids oxidation, thereby enhancing fatty acid oxidation (147,148). Furthermore, they also showed that AICAR injection increases GLUT4 protein content in fast-twitch fibers and enhances insulin-stimulated glucose uptake, suggesting an important therapeutic implication for individuals with T2D who are characterised by higher component of fast-twitch muscle fibers (149) and reduced

oxidative metabolism. Hayashi et al. also confirmed that AMPK is centrally involved in regulating glucose transport in contracting muscle during metabolic stress associated with intracellular fuel depletion by indicating a close association between increases in AMPK activity and increases in GLUT4 (150). To further support this observation, transgenic mice, a dominant inhibitory mutant of AMPK showed impaired glucose uptake in response to contraction (151). At present, it is generally agreed that AMPK plays an important role in the signaling cascade that activates the intracellular signaling pathway to facilitate GLUT4 translocation and glucose uptake (152,153).

Another important feature of AMPK is that it promotes GLUT4 translocation to the cell membrane following exercise to replenish glycogen store (154). This is one of the important mechanisms by which insulin resistant or hyperglycemic individuals benefit from participating in exercise. Following exercise, activation of AMPK initiates the process that leads to increased insulin sensitivity for many hours by augmenting the translocation of more GLUT4 to the cell surface (155). Moreover, AMPK activation in the liver also reduces the post-exercise hepatic glucose production of individuals with T2D, further contributing to better glycemic concentration following exercise (156).

As can be expected from a normal GLUT4 response to acute exercise in T2D (157), acute AMPK activity induced by exercise is also intact in these individuals (158). Thus, it can be speculated that the exercise intervention which stimulates AMPK to a greater extent may be a more potent stimulus to improve glycemia in T2D. The possible roles different exercise intervention and different physiological conditions play on AMPK activation and glucose uptake will be covered in the latter sections.

Peroxisome proliferator-activated receptor-γ coactivator (PGC-1α)

While the precise pathway bridging AMPK activation to the expression of GLUT4 is yet to be elucidated, recently the phosphorylation of peroxisome proliferator-activated receptor-γ coactivator (PGC-1α), a protein also known to facilitate mitochondrial biogenesis, is considered a candidate that mediates the

reaction (159). Indeed, a modest increase in PGC-1α, as often seen following an exercise bout, has been shown to be associated with improved insulin sensitivity in mammalian muscles in vivo, the change of which appears to be attributable to the up-regulation of GLUT4 protein expression (160).

In addition to the implicated link between the activation of PGC-1α and enhanced GLUT4 gene (161) and protein (160) expression, using transgenic mice expressing a dominant-negative mutant of AMPK in muscles, Zong et al. demonstrated that AMPK activation-induced mitochondrial biogenesis is mediated by PGC-1α activation (162). While controversy still exists owing to inconsistent responses observed in vivo and in vitro, available evidence now suggests that compromised PGC-1α and mitochondrial dysfunction play a role in the pathogenesis of insulin resistance in T2D (163). This may be a reasonable observation given the close relationship between mitochondrial function and fatty acid oxidation. Dysregulated metabolism and reduced mitochondrial content and function (164) can lead to intramyocellular fatty acid metabolites and insulin resistance (165). Accordingly, the function of PGC-1α to stimulate mitochondrial biogenesis and GLUT4 protein expression may have an important clinical implication in individuals with T2D who have been reported to indicate smaller and in some cases severely damaged mitochondria (166).

Exercise stimulates transient increases in PGC-1α transcription and mRNA content in human skeletal muscles (167). In rats, it has been reported that prolonged low intensity exercise increases PGC-1α mRNA levels (168) possibly via the activation of AMPK (169). Also, another rats study showed that PGC-1α protein abundance increases in training duration/intensity-dependent manner in fast twitch muscle fibers (170). In human skeletal muscles, it has been demonstrated that both acute exercise and exercise training elicit a marked increase in transcription and mRNA content of the PGC-1α with its sensitivity enhanced after training (167). Given the close positive correlation between skeletal muscles oxidative capacity and insulin sensitivity (171), stimulation of PGC-1α and its associated improvement in oxidative capacity may play an

important role in improving the condition of T2D. Putative mechanisms summarizing previous findings are summarized in **Figure A.4**.

Figure A.4. Schematic presentation of the putative acute and chronic mechanisms leading to the improvement of T2D condition.

AMPK: 5' adenosine monophosphate-activated protein kinase; GLUT4: glucose transporter 4; PGC-1α: Peroxisome proliferator-activated receptor-γ coactivator; ACC2: acetyl-CoA carboxylase 2; Malonyl CoA: Malonyl coenzyme A.

Glycogen

Exercise degrades glycogen and results in dynamic changes in skeletal muscle glycogen stores. The breakdown of glycogen to meet the energy demand is advantageous as it creates room for glucose deposition, which is required to maintain high insulin sensitivity (172). A high positive correlation between exercise-induced glycogen degradation and increases in insulin sensitivity suggests that skeletal muscle glycogen could play a role in signal transduction (173).

A series of studies on rodents have established a link between decreased glycogen content and improved insulin sensitivity. In 1982, Fell and colleagues observed an association between a low muscle glycogen content and an increased

rate of glucose transport into muscles (174). More recently, another study reported enhanced insulin-stimulated glucose uptake in muscles with low glycogen content compared with muscles with normal or high glycogen (175). In support of these findings, it has been shown that glycogen depletion is associated with enhanced insulin-stimulated glycogen synthase activity (176) and with enhanced GLUT4 expression (177), both of which facilitate the removal of blood glucose to replenish glycogen stores.

Potential advantages of high intensity exercise

More than 40 years ago, Pruett et al. showed post-exercise glucose uptake into cells in response to glucose infusion increases in proportion to an increase in exercise intensity rather than total energy expenditure in healthy individuals (178). With greater fiber recruitment as well as higher metabolic stress on active fibers, higher intensity exercise has been indicated to increase glucose uptake (179). To support this finding, a study comparing the effect of different exercise intensity on insulin resistance of obese Zucker rats found that the oral glucose tolerance test (OGTT)-derived insulin sensitivity in muscle improves in an exercise intensity specific manner (180). Moreover, in inactive old women, high intensity exercise training (80% VO_{2peak}) has been shown more effective than moderate to light intensity exercise training in improving insulin sensitivity (181).

Recently elucidated molecular mechanisms support the important role of exercise intensity. For example, the activation of AMPK in response to exercise occurs in exercise intensity-dependent manner both in rats (182-184) and in human skeletal muscles (185-188). With a previously demonstrated association between AMPK activity and GLUT4 content in cell membrane (150), it is tempting to speculate a positive correlation between exercise intensity and glucose uptake. Indeed, Chen et al. demonstrated that, in humans, AMPK activity remains similar to the resting condition during light intensity exercise and progressively increases in proportion to increasing workload thereafter, which is paralleled by a greater glucose disappearance rate (189). It is speculated that a greater proportion of type II fiber recruitment during high intensity exercise

explains the different molecular responses to exercise of different intensities (190).

Besides its potentially exaggerated molecular responses, another potential advantage associated with high intensity exercise is greater magnitude of muscle glycogen depletion (189,191). An impact of exercise intensity on insulin sensitivity has been investigated based on the premise that high intensity exercise reduces muscle and liver glycogen to a greater extent (192) and thus leads to greater insulin sensitivity. Indeed, post-exercise glycogen depletion is associated with insulin action, which is reversed with the replenishment in muscle glycogen levels (193). Given that post-exercise insulin sensitivity is correlated with the magnitude of glycogen utilisation during exercise (194) and that individuals with T2D show greater reliance on plasma glucose than muscle glycogen during moderate intensity exercise(40% VO_{2max}) as compared to non-diabetic individuals (195), higher intensity exercise that augments glycogen depletion may facilitate insulin action. Although total amount of work was unadjusted, one study showed that higher exercise intensity induces better insulin sensitivity in sedentary individuals (196).

Glycemic responses to different intensity/duration exercise in T2D

Only a few studies have examined the effect of exercise duration on glycemic responses presumably due to a consistent outcome. In individuals with T2D, Paternostro-Bayles showed that the magnitude of glycemic reduction in response to exercise (50-55% of age predicted maximum HR) depends on exercise duration (197). Jeng et al. also showed that exercise duration is the significant determinant of glycemic reduction and its effect does not interact with exercise intensity (198). Direct oxidation is expected to increase in proportion to an increase in exercise duration, which may explain the positive correlation between exercise duration and glucose reduction.

With regard to the effects of exercise intensity on glycemia, while a glucose disappearance rate increases in proportion to an increase in exercise

intensity, different degrees of hepatic glucose output induce different glycemic responses. Among the existing studies examining the impact of high intensity exercise on glycemia, varied glycemic outcomes have been reported in individuals with T2D. Some studies directly comparing the acute effects of high intensity and lower intensity exercise showed a greater reduction in glucose concentration immediately after higher intensity exercise (198-200). However, when the caloric demand was matched between high and moderate intensity exercise by adjusting exercise duration, the difference in the degree of reduction in plasma glucose was nonexistent (191,201). In another study, a graded bike exercise bout to the intensity of 110 % predetermined VO_{2max} significantly elevated blood glucose concentrations (202). Enhanced glucose production stimulated by high plasma catecholamine concentrations exceeded glucose uptake by muscles, which contributed to persistent hyperglycemia for up to 1-2 hours following an exercise bout (203). Interestingly, although high intensity exercise acutely elevated blood glucose concentrations, it significantly enhanced insulin-stimulated glucose clearance measured 24 hour after the exercise bout (202). In accordance to this finding, Devlin et al. demonstrated that, in individuals with T2D, a single bout of high intensity exhausting exercise significantly increases peripheral and hepatic insulin sensitivity and lowers fasting glucose concentration 12-16 hours later as a result of an increase in non-oxidative glucose disposal to enhance glycogen storage (204).

In summary, while longer duration exercise has been shown to have positive impact on glycemia, whether exercise intensity per se confers greater benefits in terms of acute glycemic regulation remains largely inconclusive. Limited attempts to elucidate the effects of exercise intensity on post-exercise glycemic control also hinder the understanding of exercise intensity on glycemia. A gap between immediate response (i.e., during exercise and a few hours following exercise) and the acute effect of exercise (i.e., 12-48 hours after exercise) also needs to be filled to elucidate the glycemic response to high intensity exercise.

Acute effects of exercise

It is generally agreed that, in the absence of changes in body composition, improved insulin sensitivity is mainly attributable to the individual effect of a bout of exercise preceding the measurement (205,206). In keeping with this theory, although physically trained individuals have normal glucose tolerance with reduced insulin secretion, this adaptation is lost within 10 days of physical inactivity (207).

Acute exercise induces prolonged reduction of blood glucose concentrations that results from the replenishment of depleted liver and muscle glycogen stores (208). After the cessation of exercise, the insulin-independent GLUT4 translocation elevates glucose uptake for about two hours, followed by insulin-facilitated GLUT4 translocation for glycogenesis (209). While the precise pathway involved in enhanced insulin sensitivity after exercise is under intensive research, improved insulin sensitivity is, at least partially, related to the improved ability of insulin to translocate GLUT4 to the cell membrane (210).

The extent to which exercise improves glycemia following an exercise bout in individuals with T2D has been reported in a few studies. A continuous glucose monitoring system showed that this enhanced glucose uptake lasts for at least 24 hours following an exercise bout for one hour at a power output corresponding to 90% of lactate threshold (108). High intensity interval exercise (~8 bouts of 2-minute at 85% of VO_{2max} interspersed by 3-minute rest) showed increased insulin sensitivity as measured via insulin clamp technique at least 12-16 hours following the exercise bout (204). This acute effect of exercise was prolonged after exercise training but the improvement was minimal when measured 72 hours after the last exercise bout (211). As glycogen replenishment is considered the main cause of residual effects of exercise on insulin sensitivity, Rogers proposed that exercise stimulus must be relatively intense to elicit persistent improvement in glucose metabolism (212). Considering the duration of residual effect of exercise on insulin sensitivity, an exercise frequency of three times a week is recommend as an absolute minimum to obtain worthwhile health benefits (213,214).

High intensity interval exercise (HIIE)

High intensity interval exercise (HIIE) alternates between high intensity exercise bouts and lower intensity recovery periods. During high intensity interval bouts, exercise intensity normally exceeds the intensity that can be maintained for continuous exercise albeit for shorter periods of time. While HIIE can encompass a wide range of work-to-rest ratios, for the purposes of this dissertation, HIIE is defined as exercise involving repeated bouts of short duration (≤5 minutes), intense bouts (>60% VO_{2peak} or HRR, or >70% HR_{max}), interrupted by the same or longer periods of rest or lower intensity exercise.

HIIE and its molecular responses

A repetitively reported major advantage of HIIE is that, with markedly smaller total amount of work, it improves aerobic fitness to a similar extent to more prolonged moderate intensity continuous exercise (MICE) (215,216). This improvement in aerobic fitness with small amount of total exercise volume is important not only because of established strong association between improved aerobic fitness and reduced risk of CVD (217) but also because molecular mechanisms responsible for the improvement in aerobic fitness may also be associated with improved insulin sensitivity or glucose control.

While precise mechanism by which HIIE induces positive aerobic adaptation is yet to be elucidated, exercise intensity briefly exceeding the anaerobic threshold may pose greater stress than MICE to elicit enhanced mitochondrial biogenesis and enzymatic markers associated with aerobic metabolism (218). One proposed mechanism is through activation of phosphatises and kinases involved in signal transduction (219). AMPK, among many others, is one of the kinases known to facilitate mitochondrial biogenesis by up-regulating PGC-1α (154). In human skeletal muscles, significant correlation between improved VO_{2max} and PGC-1α protein levels have previously been reported in response to HIIE (220). Also, enhanced PGC-1α protein expression is paralleled

by a shift in fiber type composition to more oxidative type I fibers and increased GLUT4 expression (221). Interestingly, the effects of HIIE on PGC-1α activity has been reported to increase in proportion to exercise intensity following HIIE, but is blunted in response to supramaximal exercise (133% VO_{2max}) (222).

Collectively, the activation of AMPK may induce mitochondrial biogenesis and also facilitates the translocation of GLUT4 to the cell membrane (154), a transduction of which may also be mediated by PGC-1α (223). In rodents, Koshinaka et al. showed that 160 seconds of HIIE (8 x 20-second swimming with a weight of 18% body mass attached interspersed by 40-second rest) enhances AMPK activity to a greater extent than MICE and elicits significantly greater glucose uptake immediately after an exercise bout (224,225). In line with these observations, Terada and colleagues have demonstrated that a single session of very short HIIE (280 seconds in total) induces a greater increase in AMPK than prolonged aerobic exercise (6 hours in total) (226). In another study completed by the same author, eight days of the same HIIE training elicited a similar degree of GLUT4 translocation and glucose transport activity to MICE despite considerably smaller total amount of work completed (227). Eight weeks of HIIE training five days per week performed by rats with metabolic syndrome also indicated that HIIE confers greater benefits in improving aerobic fitness, endothelial function, blood pressure, and insulin action than MICE matched for exercise volume (228). In these studies, HIIE-induced AMPK activation consistently increased insulin independent glucose uptake immediately after exercise.

In keeping with the studies on rats, several human studies also demonstrated that HIIE up-regulates GLUT4 contents (229-231). Improved insulin sensitivity has also been observed in response to HIIE in healthy individuals (232,233). Accordingly, available evidence suggests that the brief bursts of intense efforts induce intracellular perturbation that results in rapid activation of several intermediaries in the pathways leading to enhanced blood glucose uptake (230,231,234-239).

HIIE and glycogen

Another possible mechanism by which HIIE improves glycemic control of individuals with T2D is by augmenting glycogen breakdown. Given well-established relationship between exercise intensity and degree of glycogen breakdown (i.e., higher exercise leads to greater degradation of glycogen (192)), HIIE can deplete the glucose reservoir and may create a favorable condition for promoting glucose uptake subsequent to the cessation of an exercise bout. Kawanaka and colleagues showed that HIIE in rats enhances muscle glycogen depletion, the degree of which was significantly correlated with the rate of post-exercise glucose transport (240). In addition, the brief breakdown of glycogen resulted in increased size of glycogen contents following recovery. Previous studies have shown that, if sufficiently replenished, the glycogen depletion induced by HIIE can result in increased glycogen content with as few as six sessions in healthy individuals (230). Another longer-term study on similar population also indicated that HIIE increases muscle glycogen contents by 59% (231). Because muscle glycogen is a major depot of blood glucose it is tempting to speculate that the increase in glycogen content after HIIE may indicate an increase in the size of glucose reservoir and enhanced capacity to extract blood glucose.

In summary, glycogen content after exercise or the amount of glycogen used during exercise is a strong predictor of insulin sensitivity in the recovery period. Given that individuals with T2D rely more on plasma glucose than glycogen for energy during moderate intensity exercise (241) and that the rate of glycogen breakdown is positively correlated with exercise intensity (192), it is speculated that HIIE depletes glycogen store to a greater extent than traditional MICE and results in better insulin sensitivity and glycemic control following an exercise bout.

HIIE in young healthy individuals

A brief all-out type of HIIE has been shown effective in improving aerobic power of athletes (242-246). This observation challenged the concept that aerobic performance can only be enhanced by aerobic endurance training (247). The use of repeated bouts of all-out exercise demonstrated that, with markedly smaller amount of work, HIIE can induce a similar degree of improvement in performance and muscular adaptation to MICE (215,216). Accordingly, HIIE has been proposed as a time-efficient way to induce beneficial aerobic responses (215).

Studies investigating the effects of HIIE on body composition, insulin sensitivity, blood glucose, and potential intermediaries leading to enhanced glucose uptake of young, healthy non-diabetic individuals are summarized in **Table A.1**. In review of these results, vigorous training that involves periods of very strenuous exercise appears a powerful stimulus to increase aerobic power, PGC-1α, GLUT4 translocation, insulin sensitivity, and lowers blood glucose with relatively short bouts of exercise.

Table A.1. Major responses to HIIE on young healthy individuals. Studies are listed in an alphabetical order

study	Intervention	# of sessions	participant characteristics (n)	Age (SD)	VO_{2max} (ml/kg/min) (SD)	major findings
Allemeier(248) (1994)	3 x (30-sec Wingate + 20-min rest)	15	healthy men (11)	22 (5)	48.7 (6.7)	↑ 20.3% type IIa fibers ↓ 41.7% type IIb fibers
Babraj(232) (2009)	4-6 x (30-sec Wingate + 4-min rest or low cadence with no resistance)	6	recreationally active or sedentary (16)	21 (2)	48 (9)	↑ 23 % insulin sensitivity (Cederholm index) ↓ 12 % BG-AUC ↓ 37% insulin-AUC No change in fasting BG
Bartlett(249) (2012)	7min warm up at 70% + 6 x (3-min 90% + 3-min 50%) + 7-mni cool down at 70% VO_{2max}	1	recreationally active (10)	20 (1)	52 (7)	↑50% AMPK ↑320% PGC-1α mRNA 3h post exercise
Burgomaster (235) (2007)	4-6 x (30-sec Wingate + 4 min recovery at 30W)	6	Active (8)	22 (1)	50 (2)	↑ ~20% GLUT4 after 6 wk of detraining
Burgomaster (216) (2008)	4-6 x (30-sec Wingate + 4.5 min recovery 30W)	18	recreationally active (10)	24 (3)	41 (6)	↑ 7.3% VO_{2peak} ↑ ~100% PGC-1α protein ↑ fat oxidation

Ciolac(250) (2010)	2-min at 50-60% + 1-min at 89-90 % VO_{2max} for 40 min	48	young normotensive women of hypertensive parents (16)	24 (3)	29.3 (3.6)	↓35.4% fasting insulin ↑30.7% insulin sensitivity (HOMA) ↑15.7% VO_{2max}
Daussin(251) (2008)	4-7 x (4-min at power output at VT + 1-mina t 90% PO_{max})	24	sedentary (11)	45 (9)	~28 (6)	↑15 % VO_{2max} ↑36% skeletal muscle mitochondrial oxidative capacity
Gurd(252) (2010)	10 x (4-min at ~90% VO_{2peak} + 2-min rest)	18	recreationally active (9)	23 (3)	n/a	↑11% VO_{2peak} ↑16% PGC-1α protein
Little(230) (2010)	8-12 x (1-min ~100% VO_{2peak} + 75-sec 30W)	6	recreationally active (7)	21 (1)	46 (2)	↑ 24% PGC-1α protein content ↑ 119% GLUT4 protein content ↑ 17% muscle glycogen
McKay(253) (2009)	5-min warm up + 8-12 x (1-min VO_{2max} + 1-min rest)	8	young adult males (6)	~25	46 (5)	↑ 4% VO_{2peak} ↑18.5% LT ↓2.5% body mass
Macpherson (243) (2011)	4-6 x (30-sec max effort + 4-min rest or active recovery)	18	young healthy recreationally active (10)	24 (3)	46.8 (5.1)	↑11.5% VO_{2max} ↓12.4% % body fat
Metcalfe(254) (2012)	3-min at 60W cycle + 1-2 x (10-20sec Wingate + 4:50-min at 60W)	18	young sedentary male (7)	26 (7)	36.3 (5.8)	↑ 28% insulin sensitivity (Cederholm index) ↑15% VO_{2peak}
Metcalfe(254) (2012)	3-min at 60W cycle + 1-2 x (10-20sec Wingate + 4:50-min at 60W)	18	young sedentary female (8)	24 (8)	32.5 (4.2)	↑ 12% VO_{2peak} ↓ 6.1% BG-AUC
Morton(255) (2009)	10-min warm up at 70% VO_{2max} + 5 x (3-min at 90% + 1.5-min at 25% + 1.5-min at 50% VO_{2max}) + 10-min cool-down at 70%.	24	recreationally active males (8)	20 (1)	56.9 (7.3)	↑ 8% VO_{2max} ↑ PGC-1α protein
Niklas(256) (2010)	7 x (30-sec at ~187% VO_{2peak} + 4-min at 50W at 110rpm)	1	elite cyclist (10)	24 (10)	67.8 (3.5)	↑500-600% PGC-1α mRNA
Nybo(257) (2010)	5-min warm up with light jog + 5 x (2-min at >95% HR_{max} + 1-min with lower intensity) (total of ~480 min including warm-up)	24	untrained men (8)	37 (8)	36.3 (4.8)	↑14% VO_{2peak} ↓8.8 % fasting BG ↓16.4% OGTT BG
Oliveira(258) (2010)	8 x (1-min at max aerobic velocity + 1-min at 50% max aerobic velocity	1	recreationally active (10)	25 (5)	n/a	↑39.6% capillary BG measured 3-min after exercise
Perry(231) (2008)	10 x (4-min at 90% VO_{2peak} + 2-min rest)	18	recreationally active (8)	24 (2)	n/a	↑ 9% VO_{2peak} ↑ 21% GLUT4 ↑ 12% fat oxidation at 55% VO_{2peak} ↑ 59% glycogen
Richards(233) (2010)	4-7 x (30sec-Wingate + 4-min rest)	6	sedentary or recreationally active (12)	29 (10)	32.7 (7.3)	↑insulin sensitivity 72h post exercise (hyperinsulinemic euglycemic clamp)

Richards(233) (2010)	4-7 x (30sec-Wingate + 4-min rest)	1	sedentary or recreationally active (9)	24 (3)	38 (13.5)	no change in insulin sensitivity 72 h post exercise (hyperinsulinemic euglycemic clamp)
Russell(221) (2003)	~10-min light run + stretching + 5-6 x (1-3 min at 70-80% + 1 min at 50% $VO_{2max)}$ twice a wk. 40-min continuous exe at 60% VO_{2max} once a wk.	18	healthy males (7)	34 (5)	54 (4)	↑ 10% VO_{2max} ↑ 170% PGC-1α mRNA ↑ 59% GLUT4 ↑ 18% type I fibers ↓ 12% type IIa fibers ↓ 7% type IIx fibers
Sandvei(259) (2012)	5-10 x (30-sec near max sprint + 3-min rest)	24	young healthy (11)	~25 (3)	50.9 (6.0)	↑5.3 % VO_{2max} ↓3.8 % fasting BG (n=9) ↑12.4% insulin sensitivity (n=9) (HOMA β-cell index)
Shepherd(260) (2013)	4-6 x (30-sec Wingate + 4.5-min active recovery at 30W)	18	sedentary healthy males (8)	22 (2)	41.9 (5)	↑ 7% VO_{2peak} ↓ 17% BG-AUC ↓ 33% insulin-AUC ↑ 56 % insulin sensitivity (Matsuda-ISI) ↑39% mitochondria density ↑ IMTG breakdown during moderate intensity exe.
Talanian(261) (2007)	10 x (4-min 90% VO_{2peak} + 2 min rest)	7	moderately active women (7)	22 (1)	36.3 (9.8)	↑ 36% fat oxidation at 60% VO_{2peak} ↑ 13% VO_{2peak} No change in glycogen
Trapp(262) (2008)	5-min warm up + maximum 60 bouts x (8-sec maximum effort + 12-sec active recovery) + 5-min cool down	45	inactive healthy women (11)	22 (2)	28.8 (7.0)	↑23.8% VO_{2peak} ↓9.5% % trunk fat ↑33% insulin sensitivity (HOMA-IR)
Tremblay(263) (1994)	25-30 min at 60-85% HRR + 19 sessions of 5-min warm up at 50% + 10-15 x (15-30 sec at 60- 75% VO_{2max}) + 16 sessions of -min warm up at 50% + 5 x (60-90 sec at 70-85% VO_{2max})	n/a	young healthy adults (17)	18-32	n/a	↓14.8 % sum of 6 sites skinfold
Tsekouras(264) (2008)	5-min warm up + 4 x (4-min at 60% + 4-min at 90% VO_{2peak})	24	healthy recreationally active (7)	20-40	36.7 (7.1) (Predicted)	↑18% VO_{2peak} No changes in % body fat
Wang(265) (2009)	5-min warm up at 25% + 12-sec at 120% + 18-sec at 20% VO_{2max} for 90-min	1	healthy sedentary (9)	26 (3)	40.9 (6)	↑1200% PGC-1α mRNA

Values are Mean (SD). % changes were extracted or calculated.
GLUT4: Glucose transporter 4; VT: ventilator threshold; HOMA-IR: homeostasis model assessment of insulin sensitivity; BG: blood glucose; AUC: area under curve.

HIIE in older individuals

While HIIE has been shown effective in improving aerobic power and regulating blood glucose of young, healthy individuals, its suitability to less active individuals is questionable. To increase the practicality of the method, several studies investigated the effects of less intense HIIE (i.e., not all-out type but still involves high intensity [>60% VO_{2peak}] bouts). Lower intensity HIIE has the potential to allow individuals to complete relatively larger amount exercise volume as compared with more intense all-out types of HIIE. It can be expected that this type of training will accumulate energy expenditure over training period without compromising total exercise volume and lead to the improvement of body composition.

Importantly, studies demonstrated that HIIE with high intensity intervals ranging from 61-100% to be safe and well-tolerated by elderly individuals without (266) or with various comorbidities such as patients with stable coronary heart disease (CHD) (267), chronic stroke (268), coronary artery disease (CAD) (269,270), post-infarction heart failure (220,271), chronic obstructive pulmonary disease (272), intermittent claudication (273), and overweight and obesity (274). Thus, while intense exercise has been advocated to be associated with a greater risk of sudden cardiac event, the feasibility and safety of HIIE has been demonstrated in various populations. To corroborate the feasibility, using patients with chronic congestive heart failure, one study demonstrated that HIIE poses no additional cardiac stress as measured by left ventricular function during and after exercise to work-matched MICE (275). Other studies showed that HIIE involving 100% peak power output does not induce ventricular arrhythmias or abnormal blood pressure on patients with heart failure and reduced ejection fraction (276,277), or does not induce deleterious effects on vascular walls of CHD patients (278). The incidence of cardiovascular events in CHD patients performing HIIE bouts involving 85-95% HR_{max} was very low in large retrospective study (one per 23,182 hours) (279).

With the gradual establishment of the feasibility, multifaceted effects of HIIE on individuals with various comorbidities have been documented. One study

investigated the effects of HIIE in middle aged sedentary individuals and demonstrated increases in GLUT4 contents, PGC-1α activity, and insulin sensitivity (237). Moreover, a series of studies have indicated that, to a greater extent than traditionally recommended exercise care, HIIE improves aerobic power (220,239,280,281), insulin sensitivity (239,282), endothelial function (220,239), and elicits more prolonged reduction in blood glucose (283). Studies have also demonstrated that HIIE has superior effects in attenuating the endothelial dysfunction in response to high fat meals in middle-aged healthy individual (284) and reduces blood pressure of hypertensive patients to a similar extent to MICE (250). Collectively, these studies suggest that HIIE is applicable to individuals who suffer from various pathophysiological conditions, including individuals with T2D. The impact of HIIE on older sedentary individuals with or without various pathophysiological conditions is summarized in **Table A.2**.

Table A.2. HIIE on older individuals with or without comorbidity. Studies are listed in the order of the participants' conditions.

study	Intervention	Sessions frequency	participant characteristic (n)	age (yr) (SD)	VO_{2peak} (ml/kg/min)	major outcome
Reitman(285) (1984)	5-min at 60-90% VO_{2max} + 2-min rest for 20-40 min	5-6d/wk 6-10 wk	T2D (6)	26 (7)	40.0 (4.5)	↑ 17 % VO_{2peak} ↓ 24% fasting BG ↓ 32% glucose response to oral glucose load
Schneider (211) (1984)	8 x (4-min at 50-75% VO_{2max} + 1.5-min rest)	3d/wk 6wks	T2D (20)	46 (17)	26.2 (4.9)	↑ 8.4% VO_{2max} ↓ 12.3% A1c ↑ insulin response to OGTT
Mourier(286) (1997)	2 continuous exe + 1 HIIE per wk. continuous exe: 45-min at 75% VO_{2peak}. HIIE: repetition of 2-min at 85% + 3-min at 50% VO_{2peak}	6 run-in sessions + 3d/wk 8 wks	T2D (10)	45 (6)	23.0 (3.8)	↑ 41% VO_{2peak} ↑ 46% insulin sensitivity(ITT) ↓48% abdominal visceral fat ↓18% subcutaneous fat ↓ 27.1% A1c

Little(234) (2011)	6 x (1-min ~90% HR_{max} + 1-min rest or at 50W)	6d/2wk	T2D (8)	63 (8)	n/a	↓13.2% mean 24 BG, ↓29.6% sum of 3-meal PPG AUC) ↓13.5% AUC over 24h ↑369% GLUT4
Coquart(287) (2008)	8 x (2-min 80% of power at VT + 2-min at 120% of power at VT)	3d/wk 10wk	women with T2D (10)	52 (7)	13.8 (3.7)	↓4.4% change in A1c
Praet(288) (2008)	4-8 x (30-sec cycling at 50-60% PO_{max} + 60-sec with no load) combined with resistance exe. (both number of bouts and intensity progressed)	3d/wk 10wk	Male patients with T2D with poly-neuropathy on exogenous insulin (11)	59.1 (7.5)	24.3 (1.4)	HIIE is feasible in individuals with advanced T2D No change in VO_{2peak}
Devlin(204) (1987)	2-min at 85% VO_{2max} + 3-min rest until fatigue (mean = 41.1 min)	Single session	T2D (5)	37 (4)	2.98 (0.83) L/min	↑ non-oxidative Glucose disposal ↓20.3% endogenous glucose production on the morning after exe ↓16.8% fasting BG
Devlin(289) (1985)	2-min at 85% VO_{2max} + 3-min rest until fatigue (mean = 33.1 min)	Single session	T2D (6)	33 (5)	2.69 (0.24) L/min	↑63.8% non-oxidative glucose disposal at 40mU/m2/min
[a]Gillen(290) (2012)	10 x (1-min 90% HR_{max} + 1-min rest)	Single session	T2D (7)	62 (3)	n/a	↓65% time in G>10 mmol/L ↓36% sum of 3-meal PPG AUC
Larsen(201) (1999)	4 x (3-min 50% + 4 min 100% VO_{2max} + 6-min rest)	Single session	T2D (8)	56 (5)	29.2 (5.7)	↓9.5% BG during exe ↓26.6% 4h post breakfast AUC BG
Mackenzie (291) (2012)	6 x (5-min 120% LT + 5-min passive recovery)	Single session	T2D (8)	58 (6)	n/a	↓BG 24h after Exercise HOMA β-cell index did not change 48h post exe

Stensvold (292)(2010)	4 x (4-min 90-95% HR_{max} + 3-min HR_{max})	3d/wk 12wk	metabolic syndrome (11)	49 (10)	34.2 (9.8)	↑ 11% VO_{2peak} ↑ 2% endothelial function (FMD)
Ahmaidi(266) (1998)	HR measured at VT + active recovery for 30-60 min.	2d/wk 3mo	Sedentary elderly adults (11)	62 (4)	2.4 (0.6)	↑20% VO_{2max}
Trilk(293) (2011)	4-min cycle with no resistance + 4-7 x 30-sec Wingate + 4-min with no resistance.	3d/wk 4wk	Over weight/obese women (14)	30 (6)	43.1 (5.5)	↑12 % VO_{2max}
Moreira(294) (2008)	120% AT + rest (2:1 ratio) for a total of 20-60 min	3d/wk 12wk	Sedentary overweight (8)	~40 (8)	n/a	↓1.5% body mass ↓ 2.5% waist to hip ratio ↓ 2.9% %body fat (BIA) ↓ fasting BG
Sartor(295) (2010)	4-min at 90% VO_{2peak} + 2-3 min rest up to 10 times (combined with low CHO diet)	3d/wk 2wk	Sedentary obese (10)	37 (10)	27 (5)	↑16 % VO_{2peak} ↑ 5% oral glucose insulin sensitivity ↓ 2.5% trunk fat ↑ resting fat oxidation No changes in fasting- and 2h-BG and insulin
Wallman(296) (2009)	1-min at 90% VO_{2peak} + 2-min at 30% VO_{2peak} for 30-min	4d/wk 8wk	Overweight or obese (7)	40 (11)	~23 (~5)	↑24 % VO_{2peak} Tendency of android fat loss (7.9%)
Morikawa (297) (2011)	3-min at ≥ 70% VO_{2peak} + 3-min at ≤ 40% VO_{2peak} for ~50 min (unsupervised)	≥4d/wk for 4 months	Middle-aged and older Japanese males (198)	68	20.6 (4.2)	↑15.0 % VO_{2peak} ↓ 9.8% % body fat ↓2.6% body weight ↓4.0% BG
Morikawa (297) (2011)	3-min at ≥ 70% VO_{2peak} + 3-min at ≤ 40% VO_{2peak} for ~50 min (unsupervised)	≥4d/wk for 4 months	Middle-aged and older Japanese females (468)	66	21.5 (4.3)	↑15.8% VO_{2peak} ↓5.6% % body fat ↓2.5% body weight ↓3.2% BG
Nemoto(298) (2007)	2-4 x (2-3 min at 40% + 3-min at 70-85% VO_{2peak}) for ~53-min	~4.5 d/wk, 5 months	Middle age and older Japanese (42)	~65	~22.6	↑9% VO_{2peak} ↓blood pressure

Hood(237) (2011)	10 x (1-min at ~60% VO_{2peak} + 1-min recovery)	6d/wk 2 wks	Sedentary healthy	45 (5)	30 (3)	↑56% PGC-1α ↑260% GLUT4 ↑35% insulin Sensitivity (ISI)
Morris(299) (2002)	30 x (1-min at 70-75% VO_{2peak} + 1-min rest)	3d/wk 10 wks	Older men	65 (3)	28.4 (2.8)	↑18.4% VO_{2peak}
Tjonna(239) (2008)	10-min warm up at 70% + 4 x (4-min 90% + 3-min at 70% HR_{max}) + 5-min cool down	3d/wk 16 wks	metabolic syndrome (11)	52 (3)	33.6 (8.7)	↑138% PGC-1α ↑35 % VO_{2max} ↑19.4% insulin sensitivity (HOMA-IR) ↑9 % FMD
Tjonna(283) (2011)	10-min at 70% HR_{max} + 4 x 4-min at 90-95% with 3-min 70% HR_{max} active recovery in between + 5 min cool-down	Single session	metabolic syndrome - same as Tjonna2008 (11)	n/a	n/a	↓10% fasting BG for at least 72hr ↑54.5% endothelial function (FMD)
Schjerve(238) (2008)	10-min warm up at 50-60% + 4 x (4-min at 85-95% + 3-min at 50-60% HR_{max}) + 5-min cool down	3d/wk 12 wks	obese (14)	46 (8)	39.7 (25.4)	↑ 33 % VO_{2peak} ↑PGC-1α ↑FMD ↓2% body weight ↓2.2% body fat (DXA)
Sijie(300) (2012)	10-min warm up (walking, jogging, stretching) + 5 x (3-min at 85% + 3-min at 50% VO_{2max}) + 5-min cool down (slow walking, stretching)	5d/wk 12wks	Overweight female university students (17)	19 (1)	33.3 (3.9)	↓9.9% body fat (DXA) ↑8.4% VO_{2max} ↑11.1 % VT
Whyte(301) (2010)	4-6 x (30-sec Wingate + 4.5-min recovery at 30W)	6d/2wk	sedentary overweight obese (10)	32 (8)	32.8 (4.4)	↑ 8.6% VO_{2max} ↑15% resting fat oxidation ↑23.3% insulin sensitivity (ISI)
Whyte(301) (2013)	4 x (30-sec Wingate + 4.5-min recovery at 30W)	Single session	sedentary overweight obese males (10)	26 (6)	42.0 (2.4)	No change in insulin sensitivity (ISI & HOMA-IR) ↑63% resting fat oxidation next day

Venables (302) (2008)	5-min at 25% + 5-min at 65% VO_{2max} for 30-60 min	5d/wk 4wks	Sedentary obese males (8)	40 (7)	31.1 (5.2)	No change in VO_{2max} No change in % fat No change in insulin sensitivity (ISI)
Tyldum(284) (2009)	10-min warm up at 50-60% + 4 x (4-min at 85-95% + 3-min at 50-60% HR_{max}) + 5-min cool down	Single session	healthy men (8)	42 (11)	52.6 (7)	↑45 % FMD (FMD remained high after high fat meal)
Eguchi(303) (2012)	10 x (2.5-min at 45% + 0.5-min at 75% VO_{2max})	3d/wk 12wk	healthy female (10)	50 (11)	23.4 (3.7)	↑11.5% VO_{2max} No changes in % body fat, fasting BG, or A1c
Gjellesvik (268)(2012)	4 x (4-min 85-95% HR_{max} + 3-min 50% HR_{max})	5d/wk 4wk	post stroke (8)	48 (10)	30.1 (3.2)	↑10.8% VO_{2peak}
Moholdt(271) (2012)	4 x (4-min 85-95% HR_{max} + 3-min 70% HR_{max})	3d/wk 12wk	Post MI patients (30)	56 (10)	31.6 (5.8)	↑12.7% VO_{2max} ↑31.1% endothelial Function (FMD)
Rognmo(269) (2004)	5-min at 50-60% + 4 x (4-min 80-90% + 3-min 50-60%) + 3-min cool down at 50-60% VO_{2peak}	3d/wk 10wk	CAD patients (8)	62 (11)	31.8 (9.3)	↑15.9% VO_{2max}
Warburton (270) (2005)	10-min warm up + (2-min at 85-95% + 35-45% HRR) for 30-min + resistance training + cool down + 30-minat 60-70% HRR	2d /wk 16 wks 3d /wk 16 wks	CAD patients (7)	55 (7)	~33	↑31.8% AT ↑VO_{2peak}
Anagnostakou (280)(2011)	26 x (30-sec 50% PO_{max} + 60-sec rest)	3d/wk 3mo	Chronic heart failure (14)	52 (11)	15.7 (4.0)	↑9% VO_{2peak}
	13 x (same as above) + 20-min resistance training	3d/wk 3mo	Chronic heart failure (14)	54 (10)	15.7 (6.0)	↑14% VO_{2peak}

Freyssin(304) (2012)	10-min warm up at 5W+ 3 x (12 x (30-sec at 50% PPO + 60-sec rest) + 5- min rest) for the first 4 wks and 3 x (12 x (30-sec at 80% PPO + 60-sec rest) + 5- min rest)	5d/wk 8wks	Chronic heart failure (12)	54 (9)	10.7 (2.9)	↑27%VO_{2peak} ↑22%VO_2 at VT
Fu(281) (2013)	3-min warm up at 30% + 5 x (3-min at 80% + 3-min at 40%) + 3-min cool down at 30% $VO_{2peak.}$	3d/wk 12 wks	Heart failure patients	67 (6)	16.0 (3.9)	↑22.5%VO_{2peak} No changes glucose or A1c
Meyer(305) (1996)	10 x (30-sec at 50% PO_{max} + 60-sec 15W)	5d/wk	Severe chronic heart failure (8)	52 (8)	12.2 (3.0)	↑19.7%VO_{2peak} ↑23.7% VT
	5 x (60-sec at intense speed + 60-sec at 0.9 mph)	3d/wk				
	20-min of strength and conditioning,	3d/wk 3wk total				
Roditis(306) (2007)	30-sec at 100-120% peak workload + 30-sec rest for 40-min	3d/wk 12 wks	Chronic heart failure (11)	63 (2)	14.2 (3.1)	↑8.5% VO_{2peak}
Dimopoulos (307) (2006)	30-sec at 100-130% peak workload + 30-sec rest for 40-min	3d/wk 12 wks	Chronic heart failure (10)	59 (12)	15.4 (4.7)	↑8% VO_{2peak}
Wisloff(220) (2007)	10-min at 50-60% VO_{2peak} + 4 x (4-min at 90-95% + 3-min 50-70% HR_{max} active recovery) + 3 min cool-down	3d/wk 12 wks	Post-infarction heart failure (9)	76 (9)	13.0 (1.6)	↑46 % VO_{2peak} ↑endothelial function (FMD) ↑47% PGC-1 α

Munk(308) (2009)	10-min warm up + few bouts x (4-min at 80-90% + 3-min at 60-70% HR_{max}) + 5-min cool down + 10-min strength training + 5-min stretching (1h total)	3d/wk 6 wks	CAD patients with stent implantation (6 had T2D) (20)	57 (14)	23.2 (5.7)	↑16.8 % VO_{2peak} ↑30.8 % VT ↑5.2 % endothelial function (FMD) ↑47% PGC-1 α
Groot(309) (2003)	3-min at 70-80% HRR + 2-min rest for 1h	3d/wk 8 wks	Patients with spinal cord injuries (3)	52 (2)	n/a	↑50% VO_{2peak}
Tordi(310) (2001)	6 x (4-min at 50% + 1-min at 80% PO_{max})	3d/wk 4 wks	Patients with spinal cord injuries (5)	27 (8.1)	21 (17-33)	↑18 % VO_{2peak}
Coppoolse (311) (1999)	2-min at 60% + 9 x (1-min at 90% + 2-min at 40% peak workload) + 30-min at 60% peak work load	3d/wk 2d/wk 8 wks	COPD (9)	63 (8)	~15.2 (2.4)	No change in VO_{2max}
Varga(312) (2009)	7.5-min warm up at 50% + 5 x (2-min at 90% 1-min at 50%) + 7.5-min cool down at 50% PO_{max}	3d/wk 8wks	COPD (17)	67 (10)	16.4 (4.6)	↑7.3% VO_{2peak}
Slordahl(273) (2005)	8 x (2-min at 80% VO_{2peak} + 3-min rest)	3d/wk 8 wks	intermittent claudication (8)	70 (6)	20.6 (1.9)	↑16% VO_{2peak}

Values are mean (SD).
EE: energy expenditure; HRR: heart rate reserve; ITT: intravenous insulin tolerance test; PO_{max}: maximum power output; HR_{max}: maximum heart rate; LT: lactate threshold; VT: ventilator threshold; CS: citrate synthase; PPG: postprandial plasma glucose; AUC: area under curve; BG: blood glucose; MI, myocardial infarction; CAD, coronary artery disease; FMD: flow-mediated dilation; ISI: insulin sensitivity index; n/a: not available.
[a]the results are based on the data obtained from the same population used in Little's study (2011)

HIIE vs. MICE on aerobic power and body composition

When comparing the effects HIIE and MICE, HIIE has consistently showed greater or equal degree of improvement in aerobic power (**Table A.3**). In addition, a number of studies have demonstrated the potential benefits of HIIE over exercise volume-matched MICE. HIIE training was shown to improve aerobic power of sedentary individuals (313)**,** CAD patients (269), and patients with heart failure (220,281) to a greater extent than exercise volume-matched MICE. Although there is one study conducted on COPD patients showing that MICE improves VO_{2peak} to a greater extent than HIIE (311), it is likely that this was owing to the significant higher VO_{2peak} of HIIE group at baseline.

The improvement in aerobic power is important as it is often closely linked with improved indices of lifestyle-related diseases, namely blood pressure, blood glucose, and body composition (297). Changes in muscle fiber types in response to high intensity exercise may at least partially explain the change. Allemeier and Russell showed that repetitive bursts of high intensity exercise increase the abundance of oxidative muscle fibers (20.3% and 18% increases in type IIa and I fibers, respectively (221,248). Augmented PGC-1α activity following HIIE (216,221,249,249,252,255,265) may increase mitochondrial density and thus aerobic power and fat oxidation. Indeed, Shepherd showed that HIIE training with markedly smaller total exercise volume induces comparable increases in mitochondrial density to MICE (260). These beneficial peripheral changes, along with central adaptation, such as an increase in stroke volume and thus cardiac output documented in heart failure patients participated in HIIE training but not in MICE (281), may explain the superior effect of HIIE on improving aerobic power.

In addition to its potential benefits on enhancing aerobic power, Trapp et al. and Sijie et al. reported, respectively, a greater reduction in trunk adipose tissue following HIIE than MICE of similar energy expenditure (262) and greater improvement in percent body fat following HIIE than MICE of similar total exercise duration (300).

When unadjusted for energy expenditure or exercise volume, studies showed that HIIE training; 1) reduces percent body fat to a similar extent to MICE despite remarkably smaller total time commitment (0.75 vs. 13.5 hours) (243); 2) reduces subcutaneous adiposity more profoundly than MICE of greater energy expenditure (263); and 3) is less efficacious in reducing body weight and percent body fat than MICE of greater energy expenditure (257). Consequently, while some evidence suggests that HIIE may be a stronger stimulus to improve body composition, to what extent increased exercise intensity exerts its effect over work volume has not been established. Furthermore, in the second study mentioned above (263), the baseline percent body fat was significantly higher in the HIIE, making it difficult to attribute the outcome to the intervention.

While the effects of HIIE in comparison with MICE on body composition await more concrete evidence, there are possible mechanisms that may explain the phenomenon of accelerated fat loss. For example, a greater degree of AMPK after high intensity exercise (185-187,187,188) and its greater suppressive effects on acetyl-CoA carboxylase (ACC) activity, which subsequently suppresses the activity of malonyl-CoA that inhibits fat oxidation (314), may result in enhanced fatty acids oxidation. Also, greater catecholamine concentrations associated with HIIE training can contribute to greater mobilization of free fatty acids (315). The elevated fatty acid mobilization and oxidation in combination with elevated metabolism following exercise may result in favourable changes in body composition. Brockman et al. showed that a total of 14 minutes of HIIE results in significantly higher post-exercise oxygen consumption than two hours of low intensity exercise (316). Hazell and colleagues also demonstrated that, despite significantly smaller oxygen consumption during exercise, HIIE elicits comparable 24-hour total oxygen consumption to MICE (317). When amount of total work is equated, HIIE has previously been demonstrated to be associated with greater post exercise energy expenditure as compared with moderate intensity exercise (318). These studies suggest that acute HIIE causes a substantial increase in metabolic rate that continues into recovery. Collectively, increased

energy metabolism and fat oxidation following HIIE may contribute to better body composition.

HIIE vs. MICE on insulin sensitivity and glucose regulation

Importantly, insulin sensitivity and glucose regulation improve not only following a long-term result of improved body composition but also acutely after exercise, possibly through its grater activation of AMPK and PGC-1α. The studies comparing the effects of HIIE and MICE on glycemia have shown conflicting results. One study showed that acute HIIE has more prolonged effects on improving FBG of metabolic syndrome patients (283), while another showed lack of improvement in insulin sensitivity in active individuals on the following day of HIIE despite significant improvement in MICE (319). This discrepancy may be attributable to different study populations as well as outcome measures.

In terms of long-term effects on blood glucose and insulin sensitivity, studies have indicated that HIIE improves insulin sensitivity (239) to a greater extent than energy expenditure-adjusted MICE. Furthermore, with profoundly smaller total exercise volume, several studies have demonstrated that HIIE improves oral glucose tolerance (257), β-cell sensitivity to glucose (259), blood glucose area under curve (AUC) and insulin sensitivity (260). In contrast to these findings, one study performed on sedentary obese individuals showed that MICE is superior to HIIE in improving insulin sensitivity (302). Nonetheless, in this study the intensity used for high intensity bursts was low (65% of VO_{2max}). This may indicate that intensity for HIIE needs to be relatively high to induce favourable outcomes.

In summary, potential benefits of HIIE over MICE on people with various pathophysiological conditions include greater improvement in 1) aerobic power (220,238,239,257,313,320,321), 2) endothelial function (220,238,239,239), greater activation of intermediaries involved in translocation of GLUT4 (220,238,239), insulin sensitivity (239,282,282), and body composition (262,263,300). Studies comparing the effects of HIIE and MICE are summarized in **Table A.3**.

Table A.3 HIIE vs. MICE.

study	Exercise description	Duration	participant characteristic	age	major outcome
Rognmo(269) (2004) & Amundsen(322) (2008)	5-min at 50-60% + 4 x (4-min 80-90% + 3-min 50-60%) + 3-min cool down at 50-60% VO_{2peak}	3d/wk 10 wks	CAD Patients (8)	62 (11)	[ab]↑17.9% VO_{2peak}
	41-min at 50-60% VO_{2peak} (same O_2 uptake)	3d/wk 10 wks	CAD Patients (9)	61 (7)	[b]↑7.9% VO_{2peak}
Nybo(257) (2010)	5-min warm up with light jog + 5 x (2-min at >95% HR_{max} + 1-min with lower intensity) (total of ~480 min including warm-up)	2d/wk 12 wks	untrained men (8)	37 (8)	[ab]↑14% VO_{2peak} [b]↓ 8.8 % fasting BG [b]↓16.4% 2-hr OGTT BG
	60-min at 80% HR_{max} (total of ~1800 min)	2.5d/wk 12 wks	untrained men (9)	31 (5)	[b]↑7% VO_{2peak} [b]↓8.9 % fasting BG [b]↓18.0 % 2-hr OGTT BG [b]↓1.2% body mass [b]↓7.0% %fat
Bartlett(323) (2012)	6 x (3-min 90% + 3-min 50% VO_{2max})	acute	Recreationally active (10)	20 (1)	[b]↑50% AMPK [b]↑320% PGC-1α mRNA 3h post exercise
	50-min at 70% VO_{2max} (matched for average intensity, duration and distance)	acute	recreationally active (10)	20 (1)	[b]↑50% AMPK [b]↑350% PGC-1α mRNA 3h post exercise
Trombold(324) (2013)	2-min at 25% and 2-min at 90% VO_{2peak} for ~40-45-min	acute	recreationally active (6)	25 (2)	[ab]↓15.5% postprandial plasma triglyceride No changes in glucose or insulin responses to a subsequent meal.

	~60-min at 50% VO_{2peak} (isoenergetic, crossover design)	acute	recreationally active (6)		[b]↓13.5% postprandial plasma triglyceride No changes in glucose or insulin responses to a subsequent meal.
Shepherd(260) (2013) & Cocks(325) (2013)	4-6 x 30-sec Wingate interspersed with 4.5-min active recovery at 30W	3d/wk 6 wks	Sedentary healthy men (8)	22 (2)	[b]↑7% VO_{2peak} [b]↓17% BG-AUC [b]↓33% insulin-AUC [b]↑56 % insulin sensitivity (ISI) [b]↑39% mitochondria density in type I [b]↑39% mitochondria density in type II [b]↑IMTG breakdown during exercise
	40-60 min at ~65% VO_{2peak}	5d/wk 6 wks	Sedentary healthy men (8)	21 (2)	[b]↑15% VO_{2peak} [b]↓12% BG-AUC [b]↓18% insulin-AUC [b]↑29% insulin sensitivity (ISI) [b]↑46% mitochondria density in type I [b]↑50% mitochondria density in type II [b]↑IMTG breakdown during exercise
Eguchi(303) (2012)	10 x (2.5-min at 45% + 0.5-min at 75% VO_{2max})	3d/wk 12 wks	Healthy female (10)	50 (11)	[b]↑11.5% VO_{2max} No changes in % body fat, fasting BG, or A1c
	30-min at 50% VO_{2max} (similar caloric expenditure)	3d/wk 12 wks	Healthy female (10)	50 (6)	[b]↑10.0% VO_{2max} [b]↓2.3% A1c No changes in % body fat, or fasting BG

Tremblay(263) (1994)	25-30 min at 60-85% HRR + 19 sessions of 5-min warm up at 50% + 10-15 x (15-30 sec at 60- 75% VO_{2max}) + 16 sessions of -min warm up at 50% + 5 x (60-90 sec at 70-85% VO_{2max})	15wk	young healthy adults (17)	18-32	[a]↓14.8 % sum of 6 sites skinfold
	30-45 min at 60-85% HRR	4-5d/wk 20wk	young healthy adults (10)	13-32	↓ 4.5 % sum of 6 Sites skinfolds
Trapp(262) (2008)	5-min warm up + maximum 60 bouts x (8-sec maximum effort + 12-sec active recovery) + 5-min cool down	3d/wk 15 wks	Inactive healthy young women (11)	22 (2)	[b]↑23.8% VO_{2peak} [ab]↓9.5% trunk fat [b]↓31% fasting insulin
	5-min warm up at comfortable pace + 10-40 min at 60% VO_{2peak} + 5-min cool down (similar estimated total energy expenditure)	3d/wk 15 wks	Inactive healthy young women (8)	21 (2)	[b]↑19.3% VO_{2peak}
Moreira(294) (2008)	exercise at 120% AT + rest (2:1 ratio) for a total of 20-60 min	3d/wk 4 wks	Sedentary overweight (7)	~40 (8)	[ab]↑AT [b]↓1.5% body mass [ab]↓2.5% waist to hip ratio [b]↓2.0% %body fat (BIA) [b]↓fasting BG
	20-60 min continuous exercise at 90% AT (similar energy expenditure to HIIE)	3d/wk 4 wks	Sedentary overweight (8)	~40 (8)	[b]↑AT [b] ↓1.7% body mass [b]↓2.8% %body fat (BIA) [b]↓fasting BG
Schjerve(238) (2008)	10-min warm up at 50-60% + 4 x (4-min at 85-95% + 3-min at 50-60% HR_{max}) + 5-min cool down	3d/wk 12 wks	Obese (14)	46 (8)	[ab]↑ 33 % VO_{2peak} [ab]↑PGC-1α [ab]↑FMD [b]↓2% body weight [b]↓2.2% body fat (DXA)

	47-min at 60-70% HR_{max} (isocaloric)	3d/wk 12 wks	Obese (13)	44 (7)	[b]↑ 16 % VO_{2peak} [b]↑FMD [b]↓3% body weight [b]↓2.5% body fat (DXA)
Niklas(256) (2010)	7 x (30-sec at ~187% VO_{2peak} + 4-min at 50W at 110rpm)	acute response	elite cyclist (10)	24 (4)	[b]↑500-600% PGC-1α mRNA
Crossover design	3 x (20-min at ~87% VO_{2peak} + 4-min at 50 W) (Lower intensity interval)	acute response	elite cyclist (10)	24 (4)	[b]↑500-600% PGC-1α mRNA
Macpherson(243) (2011)	4-6 x (30-sec max running + 4-min active recovery)	3d /wk 6 wks	young, recreationally active (10)	24 (3)	[b]↑11.5% VO_{2max} [b]↓12.4% fat mass (BodPod)
	30-60 min at 65% VO_{2max}	3d /wk 6 wks	young, recreationally active (10)	22 (3)	[b]↑12.5% VO_{2max} [b]↓5.8% fat mass (BodPod)
Warburton(270) (2005)	10-min warm up + (2-min at 85-95% + 35-45% HRR) for 30-min + resistance training + cool down + 30-minat 60-70% HRR	2d /wk 16 wks 3d /wk 16 wks	CAD patients (7)	55 (7)	[ab]↑ 31.8% AT [b]↑ VO_{2peak}
	10-min warm up + 30-min at 65% HRR + resistance training + 10-min cool down (similar average training volume) + 30-minat 60-70% HRR	2d /wk 16 wks 3d /wk 16 wks	CAD patients (7)	55 (8)	[b]↑ 15.0% AT [b]↑ VO_{2peak}
Gorostiaga(326) (1991)	30-sec at max work + 30-sec rest for 30-min	3d/wk 8 wks	Young sedentary-recreationally active (6)	~27	[b]↑ 16% VO_{2max}
	50% max work for 30-min (same absolute work)	3d/wk 8 wks	Young sedentary-recreationally active (6)	~27	No change in VO_{2max}

McKay(253) (2009)	5-min warm up + 8-12 x (1-min VO_{2max} + 1-min rest)	8sessions over 19d	Young adult males (6)	~25	[b]↑ 4% VO_{2peak} [b] ↑ 18.5% LT [b]↓ 2.5% body mass
	MICE 90-120-min at 65% VO_{2max}	8sessions over 19d	Young adult males (6)	~25	[b]↑ 7% VO_{2peak} [b] ↑ 27.3%LT [b]↓ 3.3% body mass
Wallman(296) (2009)	1-min at 90% VO_{2peak} + 2-min at 30% VO_{2peak} for 30-min	4d/wk 8 wks	Overweight or obese (7)	~23 (~5)	[b]↑24% VO_{2peak} Android fat tended to decrease (7.9%) (DXA)
	50% VO_{2peak} for duration that results in the same total energy expenditure	4d/wk 8 wks	Overweight or obese (6)	~24 (~3)	[b]↑19% VO_{2peak}
Helgerud(321) (2007)	47 x (15-sec at 90-95% + 15-sec 70% HR_{max}) for 45-min	24	Healthy moderately trained males (10)	~24 (3)	[ab]↑5.5% VO_{2max}
	4 x (4-min at 90-95% + 3-min 70% HR_{max}) for 45-min (same total work)	24	Healthy moderately trained males (10)	~24 (3)	[ab]↑7.2% VO_{2max}
	70% HR_{max} for 45-min (same total work)	24	Healthy moderately trained males (10)	~24 (3)	
	85% HR_{max} for 24.25-min (same total work)	24	Healthy moderately trained males (10)	~24 (3)	
Coppoolse(311) (1999)	2-min at 60% + 9 x (1-min at 90% + 2-min at 40% peak workload) + 30-min at 60% peak work load	3d/wk 2d/wk 8 wks	COPD (9)	63 (8)	No change in VO_{2max} (VO_{2max} was significantly higher at baseline)
	30-min at 60% peak work load (same total workload)	5d/wk 8 wks	COPD (10)	67 (3)	[b]↑17% VO_{2max}
Roditis(306) (2007)	30-sec at 100-120% peak workload + 30-sec rest for 40-min	3d/wk 12 wks	Patients with CHF (11)	63 (2)	[b]↑8.5% VO_{2peak}

	40-min at 50-60% peak workload (same duration and total work as HIIE)	3d/wk 12 wks	Patients with CHF (10)	61 (3)	[b]↑8.5% VO_{2peak}
Varga(312) (2007)	7.5-min warm up at 50% + 5 x (2-min at 90% 1-min at 50%) + 7.5-min cool down at 50% PO_{max}	3d/wk 8 wks	Patients with COPD (17)	67 (10)	[b]↑7.3% VO_{2peak}
	45-min at 80% PO_{max}	3d/wk 8 wks	Patients with COPD (22)	61 (12)	[b]↑8.5% VO_{2peak}
Dimopoulos(307) (2006)	30-sec at 100-130% peak workload + 30-sec rest for 40-min	3d/wk 12 wks	Patients with stable CHF (10)	59 (12)	[b]↑8% VO_{2peak}
	50-65% peak workload for 40-min (same work output as HIIE)	3d/wk 12 wks	Patients with stable CHF (14)	61 (7)	[b]↑6% VO_{2peak} [b]↑10% AT
Slordahl(273) (2005)	8 x (2-min at 80% VO_{2peak} + 3-min rest)	3d/wk 8 wks	Patients with intermittent claudication (8)	70 (6)	[a]↑16% VO_{2peak}
	30-min at 60% VO_{2peak}	3d/wk 8 wks	Patients with intermittent claudication (8)	61 (7)	↑9% VO_{2peak}
Poole(327) (1985)	10 x (2-min at 105% VO_{2max} + 2-min rest)	3d/wk 8 wks	Sedentary young males (6)	24 (2)	[b]↑15.2% VO_{2max} [ab]↑47.7% VT
	35-min continuous exercise at ~70% VO_{2max} (isocaloric)	3d/wk 8 wks	Sedentary young males (6)	23 (3)	[b]↑20.0% VO_{2max} [b]↑28.5% VT
	55-min continuous exercise at ~50% VO_{2max} (isocaloric)	3d/wk 8 wks	Sedentary young males (5)	24 (7)	[b]↑14.7% VO_{2max} [b]↑18.8% VT
Gaesser(320) (1988)	10 x (2-min at 100% VO_{2peak} + 2-min rest)	3d/wk 6 wks	Young healthy males (3 were fairly active runners) (6)	22 (1)	[ab]↑7.5% VO_{2peak}

	40-min at 50% VO_{2peak}	3d/wk 6 wks	Young healthy males (2 were fairly active runners) (5)	21 (0)	
Cunningham(328) (1979)	2-min at 90-100% VO_{2max} + 1-min rest for 14.6-15.5-min	4d/wk 12 wks	Healthy sedentary women (5)	18-25	[b]↑20.5% VO_{2max}
	20 min at 70 – 80% VO_{2max} (same total work)	4d/wk 12 wks	Healthy sedentary women (5)	18-25	[b]↑23.2% VO_{2max}
Warburton(329) (2004)	2-min at 90% + 2-min at 40% VO_{2max} for the duration that yielded the same amount of total work as MICE	3d/wk 12 wks	Normally active males (6)	30 (5)	[b]↑22.2% VO_{2max}
	30-48 min at 64.3% VO_{2max} (same amount of work as HIIE)	3d/wk 12 wks	Normally active males (6)	30 (4)	[b]↑22.8% VO_{2peak}
Brestoff(319) (2009)	5 x (30-sec at 125 VO_{2peak} + 4-5 min active recovery	Acute response	Healthy recreationally active (12)	21 (1)	
Crossover design	45-min at ~75% VO_{2peak}	Acute response	Healthy recreationally active (12)	21 (1)	[a]↑insulin sensitivity (HOMA-ISI)
Mcrae(330) (2012)	8 x (20-sec aerobic-resistance training + 1-0-sec rest)	4d/wk 4 wks	Recreationally active females (7)	20 (1)	[b]↑7.0% VO_{2max}
	30 min at ~85% HR_{max}	4d/wk 4 wks	Recreationally active females (7)	21 (2)	[b]↑6.7% VO_{2max}
Daussin(313) (2007)	4-min at 49% and 1 min at 90% PO_{max} for 20-35 min	3d/wk 8 wks	Healthy sedentary individuals (10)	47 (9)	[ab]↑34% VO_{2max} [b]↑27% LT
Crossover design	61% PO_{max} for 20-35 min (isoenergetic)	3d/wk 8 wks	Healthy sedentary individuals (10)	47 (9)	[b]↑22% LT
Eddy(331) (1977)	1-min at 100% VO_{2max} + 1-min rest for 98.1-274.6KJ	4d/wk 7 wks	College age subjects (7)	20 (0)	[b]↑14.3% VO_{2peak}

	Continuous exercise at 70% VO_{2max} for 98.1-274.6KJ (same total work)	4d/wk 7 wks	College age subjects (7)	21 (3)	[b]↑15.2% VO_{2peak}
Berger(332) (2006)	20 x (1-min at 100% VO_{2peak} + 1-min rest)	3d/wk 2wks + 4d/wk 4wks	Young healthy sedentary (8)	23 (4)	[b]↑21.4% VO_{2peak}
	30-min at 60% VO_{2peak} (the same work output)	3d/wk 2wks + 4d/wk 4wks	Young healthy sedentary (8)	24 (5)	[a]↑21.3% VO_{2peak}
Tabata(246) (1996)	20 x (20-sec at 170% VO_{2max} + 10-sec rest)	5d/wk 6wks	Young physically active (7)	23 (1)	[b]↑14.5% VO_{2max}
	70% VO_{2max} for 60 min 4d/wk + 30-min at 70% + 4 x (20-sec at 170% VO_{2max} + 10-sec rest)	5d/wk 6wks	Young physically active (7)	23 (1)	[b]↑9.8% VO_{2max}
Burgomaster(216) (2008)	4-6 x (30-sec Wingate + 4.5 min recovery at 30W)	3d/wk 6 wks	Young healthy (10)	24 (3)	[b]↑7.3% VO_{2peak} [b]↑ PGC-1 α [b]↑ lipid oxidation
	40-60 min at ~65% VO_{2peak} (10 folds greater total training volume)	5d/wk 6 wks	Young healthy (10)	23 (3)	[b]↑9.8% VO_{2peak} [b]↑ PGC-1 α [b]↑ lipid oxidation
Hazell(242) (2010)	4-6 x (30-sec wingate + 4-min unloaded cycling)	3d/wk 2wks	Young physically active (13)	~24 (3)	[b]↑9.3% VO_{2max}
	4-6 x (10-sec wingate + 4-min unloaded cycling)	3d/wk 2wks	Young physically active (11)	~24 (3)	[b]↑9.2% VO_{2max}
	4-6 x (30-sec wingate + 2-min unloaded cycling)	3d/wk 2wks	Young physically active (12)	~24 (3)	↑3.8% VO_{2max}
Bailey(333) (2009)	4-7 x (30-sec Wingate + 4-min at < 30W	6d/2wks	Young recreationally active (8)	21 (5)	[ab]↑8 % VO_{2max}

	90% gas exchange threshold for ~21 min (identical total work)	6d/2wks	Young recreationally active (8)	20 (4)	
Daussin(251) (2008)	4-7 x (4-min at power output at VT + 1-mina t 90% PO_{max})	3d/wk 8wks	Sedentary (11)	45 (9)	[b]↑15 % VO_{2max} [b]↑36% skeletal muscle mitochondrial oxidative capacity
Crossover design	20-35 min at 61% PO_{max} (similar total work and duration)	3d/wk 8wks	Sedentary (11)	45 (9)	[b]↑9 % VO_{2max}
Iaia(334) (2008)	8-12 x (30-sec at 90-95% max speed run + 3-mni rest)	3-4d/wk 4wks	Moderately trained endurance runner (8)	33 (3)	No change in VO_{2max}
	9-12 km over 45-60 min	3-5d/wk 4wks	Moderately trained endurance runner (7)	55.8 (3)	No change in VO_{2max}
Tyldum(284) (2009)	10-min warm up at 50-60% + 4 x (4-min at 85-95% + 3-min at 50-60% HR_{max}) + 5-min cool down	Acute response	Healthy men (8)	42 (11)	[b]↑45 % FMD (FMD remained high after high fat meal)
Crossover design	47-min at 70% HR_{max} (isocaloric)	Acute response	Healthy men (8)	42 (11)	[b]↑20 % FMD (FMD decayed after high fat meal)
†Tjonna(283) (2011)	95% with 3-min 70% HR_{max} active recovery in between + 5 min cool-down	Acute response	Metabolic syndrome	n/a	↓fasting BG for at least 72 hr
	47-min at 70% HR_{max} (isocaloric)	Acute response	Metabolic syndrome	n/a	↓fasting BG, normalized at 24 hr
Tjonna(239) (2008)	10-min warm up at 70% + 4 x (4-min 90% + 3-min at 70% HR_{max}) + 5-min cool	3d/wk 16 wks	Metabolic syndrome (11)	55 (13)	[ab]↑138% PGC-1α [ab]↑35 % VO_{2max} [ab]↑19.4% insulin sensitivity (HOMA-IR) [ab]↑9 % FMD

	47-min at 70% HR_{max} (similar caloric expenditure)	3d/wk 16 wks	Metabolic syndrome (8)	52 (10)	[b]↑16% VO_{2peak} [b]↑5 % FMD
Sandvei(259) (2012)	5-10 x (30-sec near max sprint + 3-min rest)	3d/wk 8 wks	Young, healthy (11)	~25 (3)	[b]↑5.3 % VO_{2max} [b]↓3.8 % fasting BG (n=9) [b]↓5.5 % OGTT-AUC (n=9) [b]↑12.4% insulin sensitivity (n=9) (HOMA β-cell index)
	30-60 min at 70-80% HR_{max}	3d/wk 8 wks	Young, healthy (12)	~25 (3)	[b]↑3.8% VO_{2max} [b]↓3.6% fasting BG (n=10)
Sijie(300) (2012)	10-min warm up (walking, jogging, stretching) + 5 x (3-min at 85% + 3-min at 50% VO_{2max}) + 5-min cool down (slow walking, stretching)	5d/wk 12wks	Overweight female university students (17)	19 (1)	[ab]↓9.9% body fat (DXA) [ab]↑8.4% VO_{2max} [ab]↑11.1 % VT
	10-min warm up (walking, jogging, stretching) + 40-min at 50% VO_{2max} + 5-min cool down (slow walking, stretching)	5d/wk 12wks	Overweight female university students (16)	19 (0)	[b]↓5.2% body fat (DXA) [b]↑4.7% VO_{2max} [b]↑7.1% VT
Venables(302) (2008)	5-min at 25% + 5-min at 65% VO_{2max} for 30-60 min	5d/wk 4wks	Sedentary obese males (8)	40 (7)	No change in VO_{2max} No change in % fat
Crossover design	30-60min at 44% VO_{2max} (isocaloric)	5d/wk 4wks	Sedentary obese males (8)	39 (7)	[ab]↑27% insulin sensitivity 48h after exe (ISI) [b]↑44% fat oxidation during exe No change in VO_{2max} No change in % fat

Wang(265) (2009)	5-min warm up at 25% + 12-sec at 120% + 18-sec at 20% VO_{2max} for 90-min	Acute response	Healthy sedentary (9)	26 (3)	[b]↑1200% PGC-1α mRNA
Crossover design	5-min warm up at 25% VO_{2max} + 90-min at 60% VO_{2max} (identical work and duration)	Acute response	Healthy sedentary (9)	26 (3)	[b]↑900% PGC-1α mRNA
Nemoto(298) (2007)	2-4 x (2-3 min at 40% + 3-min at 70-85% VO_{2peak}) for ~53-min	~4.5 d/wk, 5 months	Middle age and older Japanese (42)	65	[ab]↑ 9% VO_{2peak} [ab]↓ blood pressure
	~62-min at 50% VO_{2peak}	~4.5 d/wk, 5 months	Middle age and older Japanese (51)	64	
Ciolac(335) (2010)	2-min at 50-60% VO_{2max} + 1-min at 80-90% VO_{2max} for 40-min	3d/wk 6 wks	Young normotensive women of hypertensive parents (11)	24 (3)	No change in BG [b]↓ 35.4% insulin [b]↑ 30.7% insulin sensitivity (HOMA) [b]↑ 15.7% VO_{2max}
	40-min at 60-70% VO_{2max} (same total training load)	3d/wk 6 wks	Young normotensive women of hypertensive parents (11)	26 (4)	No change in BG [b]↓ 27.8% insulin [b]↑ 27.1% insulin sensitivity (HOMA) [b]↑ 8.0 % VO_{2max}
Fu(281) (2013)	3-min warm up at 30% + 5 x (3-min at 80% + 3-min at 40%) + 3min cool down at 30% VO_{2peak}	3d/wk 12 wks	Patients with heart failure	67 (6)	No change in BG, A1c [ab]↑ 22.5% VO_{2peak}
	3-min warm up + 30-min at 60% + 3-min cool down at 30% VO_{2peak}	3d/wk 12 wks	Patients with heart failure	66 (8)	No change in BG, A1c

Freyssin(304) (2012)	10-min warm up at 5W+ 3 x (12 x (30-sec at 50% PPO + 60-sec rest) + 5- min rest) for the first 4 wks and 3 x (12 x (30-sec at 80% PPO + 60-sec rest) + 5- min rest)	5d/wk 8 wks	Chronic heart failure	54 (9)	[b]↑27% VO_{2peak} [ab]↑22% VO_2 at VT
	10-min warm up at 5W + 45-min at HR at VT + 5-min cool down	5d/wk 8 wks	Chronic heart failure	55 (12)	
Wisloff(220) (2007)	10-min at 50-60% VO_{2peak} + 4 x (4-min at 90-95% + 3-min 50-70% HR_{max} active recovery) + 3 min cool-down	3d/wk, 1/d performed at home 12 wks	Postinfarction heart failure (9)	76 (9)	[ab]↑46% VO_{2peak} [ab]↑endothelial function (FMD) [ab]↑PGC-1 α
	47-min at 70-75% HR_{max} (isocaloric)	3d/wk, 1/d performed at home 12wks	Postinfarction heart failure (9)	74 (12)	[a] ↑14% VO_{2peak} [a] ↑endothelial function (FMD)

[a]Significantly greater improvement than its comparison group
[b]Significant within group improvement
DXA: dual-energy X-ray absorptiometry; OGTT: oral glucose tolerance test; HOMA-IR: homeostasis model assessment of insulin sensitivity; CHF: chronic heart failure; BIA: bioelectrical impedance analysis
† used the same protocol and participants from Tyldum (284)

HIIE in individuals with T2D

While seminal studies set the stage for investigation of HIIE in individuals with T2D, studies investigating the impact of HIIE on T2D are limited. As of March 2013, 11 studies assessing the effects of HIIE on glycemic regulation in T2D were retrieved. Of the 11 studies, two used CGMS (based on the same data) (234,290) and one had an MICE comparison group (291). Identified studies were included in **Table A.2**.

With regard to acute responses to HIIE, Devlin et al. demonstrated that HIIE increases non-oxidative glucose disposal and decreases endogenous glucose production, which decreased FBG (204,289). This effect was seen 12 to 16 hours

after the cessation of exercise. Likewise, HIIE was shown to lower blood glucose during exercise (201) and its glucose lowering effect was evident 24 hours after a single bout (291). Using CGMS, Gillen showed that a single bout of HIIE reduces time spent in hyperglycemia (>10 mmol/L) and PPG-AUC (290). Furthermore, although this has only been observed in individuals with T1D, HIIE but not MICE has been reported to induce delayed onset hypoglycemia and lowers blood glucose (336). While the study demonstrated that HIIE may not be a desirable approach for individuals with T1D, it may confer additional benefits in controlling the blood glucose of those who show chronically elevated glycemia, such as individuals with T2D. Thus, while its effectiveness over MICE warrants further research, HIIE appears promising intervention for better glycemic regulation.

Training effects of HIIE has shown consistent positive outcomes on glycemia while its superiority over MICE remains inconclusive. Although they did not include an MICE comparison group, several studies showed that HIIE training improves FBG (285), mean 24-hour blood glucose (234), A1c (211,286,287), and PPG-AUC (234,285). These studies suggest that HIIE is a potent stimulus to improve glycemia of individuals with T2D. Possible mechanisms by which individuals with T2D benefit from HIIE are summarized in **Figure A.5**.

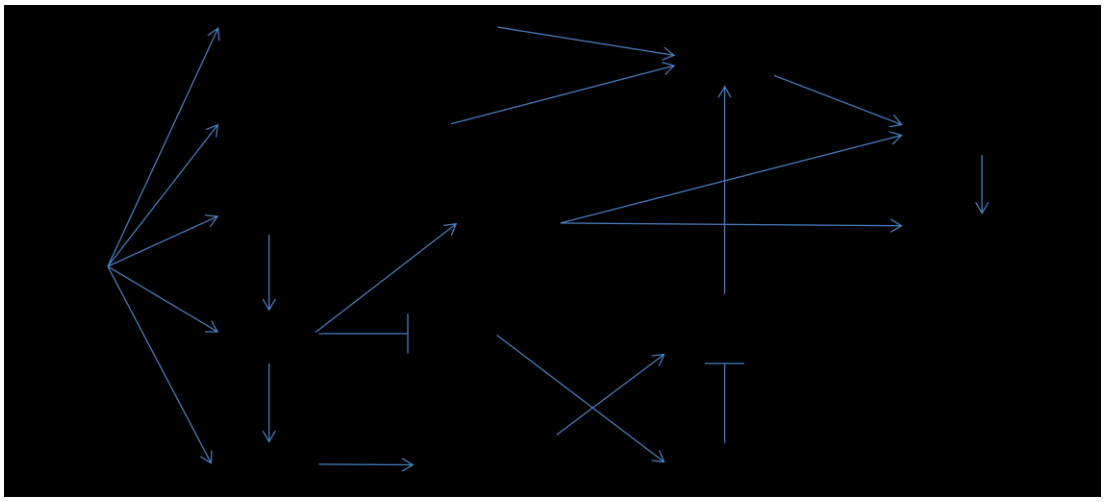

Figure A.5. Schematic presentation of putative mechanisms by which HIIE improves the condition of T2D.
AMPK: 5' adenosine monophosphate-activated protein kinase; GLUT4: glucose transporter 4; PGC-1α: Peroxisome proliferator-activated receptor-γ coactivator; ACC2: acetyl-CoA carboxylase 2; Malonyl CoA: Malonyl coenzyme A.

Exercise and exogenous carbohydrate

In order to understand the effects of exercise intensity on glycemic regulation, physiological conditions affecting the glycemic responses to exercise need to be clarified. Among many potential factors that interact with an association between exercise and glycemia, several studies showed that nutrients availability plays an important role.

Exercise intensity and carbohydrate availability

One of the difficulties in understanding the relationship between exercise intensity and blood glucose concentrations may arise from different carbohydrate availability. When the effects of acute moderate intensity exercise (60% VO_{2peak}) was investigated in relation to time interval from the most recent meal in individuals with T2D, Poirier et al. found the greatest decrease in blood glucose when exercise was performed three to five hours after the last meal (337). Using the same exercise intervention, Gaudet-Savard and Ferland also showed the greatest decrement in blood glucose when exercise was performed two to five

hours after the meal (338,339), whereas no change in blood glucose concentrations or a slight increase if performed in the fasting condition. These observations indicate the glucose-lowering effect of exercise is influenced by carbohydrate availability.

When exercise is performed after a meal, high glucose and insulin concentrations induced by the meal blunt hepatic glucose output despite increased glucose demands by working muscles (340). This imbalance between glucose production and utilization typically results in lower glucose concentrations regardless of exercise intensity. Under fasting conditions, however, glucose responses differ depending on the intensity of exercise performed. For example, high intensity exercise performed in the fasting state elevates glucose concentration in individuals with T2D (202). Similarly, trained athletes performing HIIE during Ramadan period showed a marked increase in post-exercise glucose concentration, whereas the glucose value decreased when the same exercise was performed in the fed states (341).

During high intensity exercise, the inconsistent response between fasting and fed conditions primarily reflects the different magnitude of counter-regulatory hormonal responses. High catecholamine response under fasting condition stimulates greater hepatic glucose production that exceeds glucose utilization, whereas less pronounced catecholamine response under fed states does not stimulate hepatic glucose output to the same extent. In fact, fasting combined with high intensity exercise has been shown to induce large counter-regulatory response, which results in elevated glycemia in healthy individuals (342). Glucose ingestion prior to intense exercise, on the other hand, results in hyperinsulinemia and low epinephrine responses (343).

Interestingly, although high intensity fasting exercise has been shown to cause acute hyperglycemia, a few studies have shown increased insulin sensitivity in response to high intensity fasting exercise >12 hours after the cessation of the exercise bout (202,204). How acutely elevated counter-regulatory hormones and glycemia in response to high intensity fasting exercise affect glycemic regulation during the recovery period (between acute and >12 hours) is not clear.

Fasted-state Exercise

Diet is a potent modulator of many of the adaptive responses to exercise (142). In individuals with T2D, postprandial (within four hours of meal consumption (344)) exercise has been proposed advantageous over fasted-state (12 hours after meal consumption (344)) exercise because it blunts hyper-glycemic and insulinemic responses (345) which are independent risk factors for cardiovascular (346) and micro and macrovascular complications (347).

In non-diabetic individuals, however, emerging evidence suggests that training under limited carbohydrate availability may stress physiological systems differently and elicit different metabolic responses. Notable difference between exercise performed under fed and fasting conditions involves more intense adrenergic responses under fasting condition, which stimulates the mobilization of endogenous glucose stores. Exercise under fasted-states was shown to facilitate glycogenolysis (348) and increase AMPK activity (143). Because AMPK is a known stimulant of GLUT4 translocation at least partly to resynthesize the depleted glycogen stores (139,140,194), endurance training under fasting conditions can lead to higher GLUT4 (349) and glycogen contents (349,350). In line with these observations, one study showed significantly elevated muscle glycogen, GLUT4, and AMPK contents, and improved whole-body glucose tolerance and insulin sensitivity as a result of fasted but not fed exercise training (351). A greater degree of intramuscular triglyceride depletion associated with fasting exercise may also fuel the increases in insulin sensitivity and glucose uptake during exercise recovery periods (352). Based on their study on healthy individuals, Van Proeyen et al. concluded that early morning exercise in the fasted state is more potent than an identical amount of exercise in the fed state to improve glucose tolerance and induce adaptations in muscles cells that contribute to improved insulin sensitivity (351). Indeed, one study demonstrated that, in individuals with T2D, performing exercise prior to breakfast attenuates glucose excursions in responses to subsequent meals (353). Borer et al. also found exercise under limited exogenous carbohydrate availability or under deficiencies

in circulating carbohydrates is a critical condition for sustained reduction in blood glucose concentrations of obese females (354).

Lastly, carbohydrate availability may also explain inconsistent exercise effects on some of the important metabolic transcriptional factors, such as PGC-1α. Studies showed the absence of PGC-1α activity when exercise was performed on the day following high carbohydrate consumption (355), whereas enhanced PGC-1α activity following standardized diet (167). Considering that PGC-1α is a target of AMPK, these findings fit nicely with aforementioned studies. Taken together, while postprandial exercise acutely reduces hyper-glycemia and insulinemia, high exogenous carbohydrate availability during exercise may hamper some of the important adaptive responses observed under fasting exercise. Further study is warranted to elucidate how exogenous carbohydrate availability affects glucose profiles.

Exogenous carbohydrate supplementation during and after exercise

Nutrient timing during and after exercise can also influence many of the adaptive responses probably through altering blood-born nutrients and hormonal concentrations (142). Similar to meal consumption prior to exercise, in non-diabetic human, oral glucose ingestion during exercise has been shown to attenuate muscle AMPK activities (143) and blunts GLUT4 expressions (356,357). Therefore, while carbohydrate ingestion during exercise is beneficial in preserving glycogen and maintaining high exercise performance, it may at the same time mask some of the important molecular responses.

There is a close association between glycogen level and insulin sensitivity (194). A number of studies have demonstrated reduced insulin sensitivity with carbohydrate ingestion following glycogen depleting exercise both in rats and in humans (358,359). Dietary consumption of carbohydrate rich food following glycogen-depleting exercise leads to the replenishment of glycogen content to the level that exceeds pre-exercise normal glycogen contents, a condition termed glycogen super-compensation. Once achieved, glycogen super-compensation masks AMPK activity (360) and both contraction-stimulated and insulin-

stimulated GLUT4 translocation in rat skeletal muscle (360-362). This suppressive effect of carbohydrate ingestion after exercise on GLUT4 mRNA was consistently found in human skeletal muscles (363).

Conversely, studies on rats showed that avoidance of glycogen repletion by decreasing exogenous carbohydrate availability after exercise prolongs the exercise-induced insulin sensitivity (193,364) and promotes non-oxidative disposal of carbohydrate (359). It was shown that rats can display persistent increases in GLUT4 protein and insulin-stimulated glucose transport for at least three days when skeletal muscle glycogen super-compensation is avoided by restricting dietary carbohydrate consumption (365). Derave et al. consistently showed that the ingestion of low carbohydrate diet following glycogen depleting exercise maintains high GLUT4 content on the cell surface in rats' skeletal muscles (366). These finding highlights that glycogen is a strong regulator of insulin sensitivity. Restricting exogenous carbohydrate availability is likely to slow glycogen repletion, which may stimulate activation of important metabolic proteins.

Literature review summary

This literature review indicated that not only A1c and FBG but also PPG and GV may be important pathogenesis of diabetic complications. Until recently, technical limitation had often hampered detailed investigation of PPG and GV. With the advent of CGMS, however, capturing the fluctuations in glycemia otherwise overlooked by traditionally used self-measured blood glucose became possible. With the use of CGMS, the effects of exercise intervention on glycemia may be better established.

HIIE is of particular interest in this dissertation as it has been shown promising in ameliorating various conditions of individuals with various disorders. This review demonstrated potential mechanisms by which the glycemic profiles of individuals with T2D can be improved with the use of HIIE. The review also showed the need to demonstrate whether HIIE is more efficacious in improving the glycemic profiles of individuals with T2D than traditionally used

MICE protocol, along with the need for concomitant consideration of carbohydrate availability as it can interfere with exercise intensity and its blood glucose responses. Because studies investigating the effectiveness of HIIE on T2D population are limited, this dissertation aims to examine if it induces different responses from more often used MICE.

Appendix II: Example: exercise intensity estimation for **Study 1 and 2**.

For a given participant who reached VO_{2peak} at a speed of 3.3 mph and a slope of 15%, the ACSM equations (367) would predict a VO2 of 36.2 $ml \cdot kg^{-1} \cdot min^{-1}$. The speed and slopes corresponding to 40% and 20% of 36.2 $ml \cdot kg^{-1} \cdot min^{-1}$ could then be estimated in the same manner.

speed (mph)	speed (m/min)	Slope (%)	slope (fraction)	Estimated VO_2	VO_2R (%)
3.3	88.51	15.0	0.15	36.2	100.0
3.3	88.51	10.0	0.10	28.3	75.7
3.3	88.51	5.0	0.05	20.3	51.4
3.3	88.51	0.0	0.00	12.4	27.0
3.0	80.47	10.0	0.10	26.0	68.8
3.0	80.47	5.0	0.05	18.8	46.7
3.0	80.47	3.5	0.04	16.6	40.1
3.0	80.47	0.0	0.00	11.5	24.6
2.5	67.06	0.0	0.00	10.2	20.5
2.4	64.37	0.0	0.00	9.9	19.7

For a given participant who reached VO_{2peak} at a cadence of 65 rpm and a resistance of 2.5 kp, the ACSM equation (367) would predict a VO_{2peak} of 29.5 $ml \cdot kg^{-1} \cdot min^{-1}$. The cadence and resistance corresponding to 40% and 20% of 29.5 $ml \cdot kg^{-1} \cdot min^{-1}$ could then be estimated in the same manner.

cadence (rpmh)	Resistance (kp)	power output (W)	Estimated VO_2	VO_2R (%)
65.0	2.5	159.4	29.5	100.0
65.0	2	127.5	25.0	82.7
65.0	1.5	95.6	20.5	65.4
65.0	1	63.8	16.0	48.1
62.0	0.8	48.7	13.9	39.9
65.0	0.7	44.6	13.3	37.7
60.0	0.5	29.4	11.2	29.4
60.0	0.3	17.7	9.5	23.0
60.0	0.2	11.8	8.7	19.8

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