Does The Timing of Exercise Affect Glucose Concentrations in Individuals with Type 2 Diabetes?

By

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Abstract

Background It is well known that exercise can improve glycemic control in individuals with type 2 diabetes (T2D). However, the glycemic response to exercise is highly variable. One of the primary causes of variability in response to a single bout of exercise may be timing in relation to meals. The timing of exercise has been shown to affect the glycemic response to subsequent meals but there is currently no consensus on the optimal time for exercise in individuals with T2D. Previous results from the Exercise, Physical Activity and Diabetes Glucose Monitoring (E-PAraDiGM) protocol found no significant differences in 24-hour glucose when exercise was performed 3-4 hours after lunch. The present study is a follow-up to the E-PAraDiGM protocol to determine if this result was due to the timing of the exercise.

Methods: Fourteen individuals with T2D were recruited and wore continuous glucose monitors (CGM) for 12 days. They completed the following four conditions: i. exercise in the morning before breakfast (MorEX) ii. exercise 3-4 hours after lunch (AftEX), iii. exercise 30 minutes after dinner (EveEX), and iv. seated control (CON). The exercise and control interventions were separated by 48-hour washout periods. Each participant completed the conditions according to a randomized, crossover design.

The exercise protocol consisted of 50 minutes of walking at 5.0 km/hr and 0.5% incline which is approximately equivalent to 3.5 metabolic equivalents (METS) . Standardized meals were provided for two days in each condition. Macronutrient profile was based on Diabetes Canada Guidelines of ~55% carbohydrate, ~30% fat, and ~15% protein.

Results: Eight males and six females were included in the analysis. On average they were 65 ±9.0 years old and had T2D for 10.5 ±6.8 years. The mean A1C for participants was 6.7 ±0.6 percent. Thirteen participants were treated with oral hypoglycemic medications and one

controlled their diabetes through diet and exercise. Mean glucose in the four conditions was 7.4 ±0.7mmol/L, 7.3 ±0.7mmol/L, 7.5 ±0.8mmol/L and 7.5 ±0.7mmol/L in the MorEX, AftEX, EveEX and CON conditions respectively. Overall, there was no significant difference in mean 24-hour glucose among the four conditions (P=0.55). When T tests were performed among the three exercise conditions, no significant difference was found between MorEX, AftEX, EveEX.

Conclusion: Fifty minutes of walking at three different times of day did not lower 24-hour glucose concentrations in people with T2D. These findings are not consistent with other studies of this nature. The reasons why exercise was not effective at lowering glucose are unclear at this time.

Preface

This thesis is original work by Matthew Munan. The research project that is a part of this thesis has received ethics approval from the University of Alberta Research Ethics Board, March 12, 2018 (Pro00078578-“E-PAraDiGM Exercise Timing”).

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Colossians 3:17 is a Bible verse I try to live by: “Whatever you whether in word or deed, do it all in the name of the Lord Jesus, giving thanks to God the Father through him.”

Table of Contents

List of Tables

List of Figures

Abbreviations

%-Percent

> -Greater than

< -Less than

A1C- Glycated hemoglobin

AMPK-adenosine monophosphate-activated protein kinase

ANOVA- Analysis of variance

ATP-Adenosine triphosphate

AUC-Area under the curve

BIA-Bioelectrical impedance analysis

BMI-Body mass index

BP-Blood pressure

BPM-Beats per minute

CGM-Continuous glucose monitors

MAGE-Mean amplitude of glycemic excursions

CONGA-Continuous overall net glycemic action

DBP-Diastolic blood pressure

DPP 4-Dipeptidyl peptidase-4 inhibitor

E-PAraDiGM-Exercise-Physical Activity and Diabetes Glucose Monitoring

GIP-Gastric inhibitory polypeptide

GIR-Glucose Infusion Rate

GLP-1-Glucagon like peptide 1

GLTEQ-Godin leisure-time exercise questionnaire

GLUT4-Glucose transporter type 4

HDL- High density lipoprotein

HGH-Human Growth Hormone

HR- Heart rate

iAUC- Incremental area under the curve

kg -Kilogram

LDL- Low density lipoprotein

METs- Metabolic equivalents

Min- Minutes

ml- Millilitres

mmHg- Millilitres of mercury

mmol/L- Millimols per litre

NA- Not applicable

O2 -Oxygen

OGTT- Oral glucose tolerance test

PHQ-8- Personal Health Questionnaire Depression Scale

PPG-Postprandial Glucose

PSQI- Pittsburgh Sleep Quality Index

RER- Respiratory exchange ratio

RMR- Resting metabolic rate

RPE -Rate of perceived exertion

SBP- Systolic blood pressure

SD- Standard deviation

SGLT2 inhibitors-Sodium glucose co-transporter 2 inhibitors

T2D- Type 2 diabetes

TZDS-Thiazolidinediones

umol/L- Micromole per litre

VO2max- Maximal oxygen consumption

WC- Waist circumference

Wt- Weight

yrs-Years

Chapter 1 Introduction

Diabetes mellitus is a disease characterized by high glucose concentrations in the blood. This disease has become a health crisis with estimates that 1 in 11 people have diabetes worldwide[1]. It is estimated that 415 million adults have diabetes, and that number is projected to grow to 642 million people living with diabetes by 2040[1]. The healthcare costs of diabetes are enormous with most countries spending between 5-20% of their annual healthcare expenditure on diabetes[1].

Type 2 diabetes (T2D) is a heterogenous disease in which blood glucose is elevated due to inadequate secretion of insulin by the body, reduced ability of the body to use insulin (insulin resistance), or a combination of both.[2] Individuals living with T2D manage their blood glucose through a combination of pharmacotherapies and lifestyle modification. Prolonged high blood glucose can have very adverse effects including micro and macrovascular complications such as blindness, kidney disease, heart disease, peripheral arterial disease, stroke and amputation.[3]

People with T2D often experience large increases in blood glucose postprandially. These "spikes" put individuals at higher risk for cardiovascular disease, which is the number one cause of death in people with T2D[4]. There is such a strong correlation between postprandial glucose and cardiovascular disease that the International Diabetes Foundation (IDF) developed guidelines for post meal glucose management. The IDF recommendations are that target glucose levels should be around 7.8 mmol/L 1-2 hours after a meal[5].

Postprandial glucose excursions have been shown to contribute to around 70% of overall hyperglycemia in patients with A1C values <7.3%[6]. These excursions may be a better predictor of cardiovascular disease than traditional measures such as A1C and fasting blood glucose[7]. Evidence from the Diabetes Intervention Study[6] has shown that post-breakfast glucose levels were related to myocardial infarction in people with T2D. Peak glucose concentrations occur in most individuals 60-90 minutes after a meal and for individuals with T2D, high glucose levels can stay elevated for several hours[7].

It is well known that long term exercise is effective in the treatment and management of T2D[8,9]. However,the glucose response to an acute bout of exercise is less understood and is variable among individuals[10]. One of the primary causes of the variability in response to a single

bout of exercise may be timing in relation to meals[11]. The timing of exercise has been shown to affect the glycemic response to subsequent meals[12,13] but there is currently no consensus on the optimal timing of exercise. The timing of exercise in relation to glucose excursions after meals (postprandially) may help to optimize the effect of exercise on glycemic control.

1.1 Purpose: The purpose of this study is to compare postprandial and 24-hour interstitial glucose levels in four different conditions: seated control, morning exercise (before breakfast in the fasted stated); afternoon exercise (3-4 hours after lunch and 30 minutes before dinner); and evening exercise (30 minutes after supper). This study will build upon methodologies and design principles used in the E-PAraDiGM (Physical Activity, Diabetes, Glucose Monitoring) study with a focus on the timing of exercise in relation to meals[14].

1.2 Hypothesis: Exercise performed in the morning before breakfast or 30 minutes after the evening meal will decrease 24-hour glucose concentrations more than exercise performed four hours after lunch.

1.3 Significance: Studies aiming to increase the amount of exercise performed in individuals with T2D have often shown short term success but poor adherence to exercise guidelines. The Canadian Society for Exercise Physiology (CSEP)[8] and Diabetes Canada[15] recommend that individuals perform 150 minutes per week of aerobic activity. This study focuses on optimizing the timing of exercise instead of attempting to increase the amount of time spent exercising. Many people with diabetes do engage in some physical activities or exercise and the outcomes of these activities may be further improved with simple recommendations regarding timing. It is our hope that by determining an optimal time for exercise in individuals with T2D, they will be better equipped to manage elevated blood glucose**.**

If a significant glucose lowering effect is seen in one of the conditions, we will attempt to expand this protocol to the other sites that have adopted the original E-PAraDiGM protocol across Canada. Ultimately the goal is to design an exercise protocol that is multi-site, has a large sample size and is statistically powerful enough to make recommendations to individuals with T2D on how to best manage high glucose levels through exercise interventions

1.4 Limitations, Delimitations and Scope: The population that we hope to generalize to is individuals with T2D. Type 2 diabetes is diagnosed by having one of the following: a fasting blood glucose value >7.0mmol/L, a two-hour plasma glucose >11.1mmol/L following a 75g oral glucose load, a random plasma glucose >11.1mmol/L measured any time throughout the day, or an A1C of >6.5%[2]. We will be analyzing the short term (24-hour) effect of an acute bout of exercise as measured by continuous glucose monitors (CGM). The participants were given standardized meals to eliminate variability in diet. We chose a standardized 50-minute treadmill walking speed at 5km/hr at 0.5 grade for all participants. This does not consider individual fitness levels, familiarity of treadmill walking or preference for other physical activities. This standardized treadmill protocol was chosen to allow for a protocol that most participants could adhere to and could be standardized at other sites. This study utilizes a moderate-intensity exercise bout and does not consider other intensities of exercise. Other studies such as Little (2014)[16] have looked at the response to a high intensity bout of exercise. Walking has been shown to be the most common exercise performed by individuals with T2D[17] and is practical and feasible in this population.

Randomized crossover designs are susceptible to a carryover effect because each participant is exposed to all conditions. This threat is minimized by the inclusion of a 48-hour washout day in between conditions. This design is also susceptible to an order threat as participants are asked to do an identical exercise session three separate times.

We relied on participants to adhere to the standardized diet and to self-report any deviations from the standardized diet. Continuous glucose monitors have limitations as they measure interstitial glucose as opposed to blood glucose. We are not drawing blood and analyzing glucose lowering hormones which limits the boundaries of our analysis.

Chapter 2 Review of Literature

2.1 Pathophysiology of Type 2 Diabetes

Type 2 diabetes is by far the most common form of diabetes, representing over 90% of cases[2]. Type 2 diabetes differs from type 1 diabetes in that it is closely linked to lifestyle factors such as obesity, nutritional status and physical activity. Type 2 diabetes has been previously referred to as "non-insulin dependent diabetes" or "adult onset diabetes"[18].

This disease is characterized by insulin resistance in target organs and beta cell (β-cell) dysfunction. The regulation of plasma glucose levels are tightly controlled by the actions of insulin and glucagon through negative feedback. Insulin and glucagon are peptide hormones secreted from alpha (glucagon) and beta (insulin) cells inside the Islets of Langerhans in the pancreas. These hormones work antagonistically to maintain euglycemia in the body.

Insulin is an anabolic hormone that acts mainly on the muscle, liver and adipose tissue to increase glucose uptake, resulting in a decrease in blood glucose. Beta cell secretion of insulin occurs in a biphasic pattern in which there is an early burst of insulin within the first 10 minutes in response to intravenous glucose followed by a progressively increasing phase that persists as long as the hyperglycemic stimulus is present[19]. The loss of first phase insulin secretion is one of the characteristics and early abnormalities of the progression of T2D[19].

Glucagon is a catabolic hormone that works mainly by breaking down glycogen and glucose (glycogenolysis and glycolysis) in the liver which results in its release into the bloodstream. Under post-absorptive conditions, half of hepatic glucose output is dependent on maintenance of normal basal glucagon levels[19]. After a meal, glucagon secretion is inhibited by hyperinsulinemia[19]. This results in hypoglucagonemia which contributes to the suppression of hepatic glucose production and maintenance of normal postprandial glucose concentrations[19].

Type 2 diabetes pathophysiology involves multiple organs and tissues including the pancreas, liver, skeletal muscle, gastrointestinal tract, adipose tissue, kidney and brain. Glucose homeostasis is impaired due to insufficient insulin secretion, insulin resistance in tissues and abnormalities in glucose uptake by the liver and gut[19] . The tissues shown in figure 1 can be categorized into either insulin dependent or insulin independent tissues. Insulin dependent tissues include skeletal muscle, liver and adipocytes while insulin independent tissues include the brain,

erythrocytes, and splanchnic tissues[20]. Skeletal muscle is the major site of glucose uptake in the postprandial state with 80% of glucose uptake occurring in the skeletal muscle in euglycemic hyperinsulinemic conditions[20].

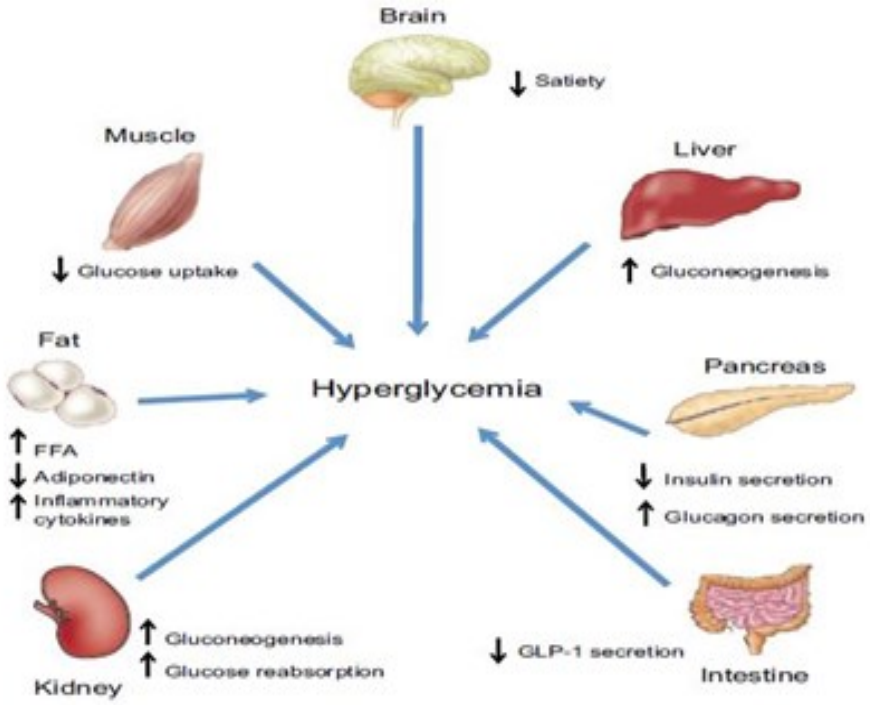

Figure 1. Multi-organ and Tissue Pathophysiology of Type 2 Diabetes. Taken with Permission from Cornell 2015[21]

2.2 Beta Cell dysfunction

The impairment of β-cell function and insulin action that characterizes T2D is thought to be due to factors including genetics, age, diet and exercise, glucotoxicity and lipotoxicity[21]. It has been shown that both glucotoxicity and lipotoxicity can lead to impaired insulin secretion[22,23,24] . The hypothesis that glucotoxicity leads to impaired insulin secretion can be supported by observations that improved glycemic control through diet, exercise, insulin therapy or metformin leads to enhanced insulin secretion[19]. Studies performed in animals directly support this hypothesis by showing that hyperglycemia in rat models results in impaired β cell function[22].

Lipotoxicity has been implicated in the development of T2D. The majority of individuals with T2D are overweight or obese and there are clear linkages between T2D and obesity[23].

Individuals with obesity have higher levels of free fatty acids (FFAs) in the blood which is known to contribute to insulin resistance and impaired β-cell functioning[24].

2.3 Incretins

Hormones in the gut known as incretins have been shown to stimulate insulin secretion when glucose is ingested orally[25]. Glucagon like peptide (GLP-1) and glucagon inhibitory peptide (GIP) have been identified as the two main incretin hormones responsible for the secretion of insulin[25]. In individuals with T2D, there is a defect in the secretion of GLP-1 and a reduced responsiveness to both GLP-1 and GIP[25,26].

2.4 Glucose Transport to Skeletal Muscle

Skeletal muscle is the major tissue involved in insulin mediated glucose uptake. It was shown by Defronzo in 1981[27] that skeletal muscle is responsible for 80% of insulin dependent glucose uptake in humans. Glucose uptake by skeletal muscle occurs through glucose transporter protein 4 (GLUT-4)[28]. Transporter GLUT-4 is a facilitated diffusion transporter and the only glucose transporter that is sensitive to insulin[29]. These GLUT-4 proteins are located in the cells of skeletal muscle and adipose tissue cells[29]. Both skeletal muscle contraction and insulin stimulate GLUT-4 translocation along the plasma membrane of skeletal muscle cells and facilitate glucose uptake by skeletal muscle[28]. The exercise response occurs in an intensity-dependent manner[30]. Figure 2 outlines the signaling pathways in which both exercise and insulin stimulate glucose uptake by skeletal muscle[31].

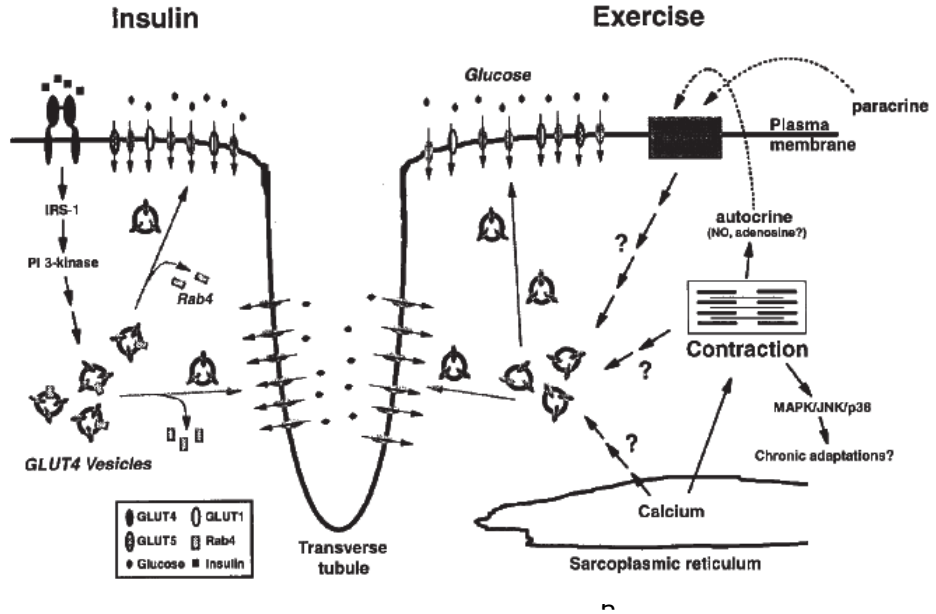

Figure 2. Glucose transport in response to insulin and exercise. Taken with Permission from Goodyear 1998[31]

In an individual with T2D, skeletal muscle becomes insulin resistant and there is a decrease in its insulin-mediated glucose uptake[32]. It is suggested that this is the initial defect in T2D and that it is present long before an individual is diagnosed with the disease[20]. Although individuals with T2D have reduced insulin-stimulated glucose uptake, the sensitivity of skeletal muscle to moderate exercise is not impaired:[28]. It has been shown that GLUT-4 expression on the plasma membrane is impaired in response to insulin but not to exercise in individual with T2D[28].

2.5 Glycemic Variability and Postprandial Glucose

Glycemic variability (GV) refers to blood glucose oscillations throughout the day[33]. A certain degree of variability is normal due to hormonal changes thoughout the day, however individuals with diabetes have increased variability[6]. Glycemic variability is related but not completely synonymous with postprandial glucose which refers to glucose excursion in a set amount of time after a meal (usually around two hours)[34]. A study performed by Cavalot et al.,[35] demonstrated that postprandial glucose was a stronger predictor of cardiovascular events than fasting glucose[35], however the clinical significance of GV outcomes alone has not been been fully elucidated in either type 1 or type 2 diabetes[34,36]. It is not clear from current literature if GV itself is an important parameter independent of having good glycemic control on cardiovascular risk factors[34].

There are many different methods of calculating GV with no consensus on a gold standard[33].Variability is determined with CGM outcomes such as standard deviation, J index, coefficient of variance, low blood glucose index, high blood glucose index, average daily risk rate, mean amplitude of glycemic excursions (MAGE), continuous overall net glycemic action (CONGA), and mean of daily differences[33]. The calculations for determining GV from each measure are shown in figure 2.3[37].

Variability measure	Formula	Explanation of symbols	Discriminating feature
SD	$\sqrt{\frac{\sum (x_i - \bar{x})^2}{k-1}}$	x_i = individual observation $\bar{x}$ = mean of observations k = number of observations	easy to determine, extensively used
CV	$\frac{s}{\bar{x}}$	s = standard deviation $\bar{x}$ = mean of observations	easy to determine, SD corrected for mean
adjusted M-value	$M_{GR} + M_W$ where $M_{GR} = \frac{\sum_{t=t_1}^{t_k} \left\| {}^{10}\log \frac{GR_t}{IGV} \right\|^3}{n}$ and $M_W = \frac{G_{max} - G_{min}}{20}$	M_{GR} = M-value for glucose readings M_W = correction factor for n <24 GR_t = glucose reading at time t IGV = ideal glucose value t_i = time in minutes after start of observations of the ith observation G_{max} = maximum glucose reading G_{min} = minimum glucose reading	not a pure variability measure
MAGE	$\sum \frac{\lambda}{n}$ if $\lambda \succ v$	λ = each blood glucose increase or decrease (nadir-peak or peak nadir) n = number of observations v = 1 SD of mean glucose for 24-hr period	used most extensively
CONGA	$\sqrt{\frac{\sum_{t=t_1}^{t_{k^*}} (D_t - \bar{D})^2}{k^* - 1}}$ where $D_t = GR_t - GR_{t-m}$ and $\bar{D} = \frac{\sum_{t=t_1}^{t_{k^*}} D_t}{k^*}$	k^* = number of observations where there is an observation n x 60 minutes ago $m = n \times 60$ D_t = difference between glucose reading at time t and t minus n hours ago	specifically developed for CGM
MODD	$\frac{\sum_{t=t_1}^{t_{k^*}} \left\| GR_1 - GR_{t-1440} \right\|}{k^*}$		inter-day variation

Figure 3. Methods for Determining Glucose Variability. Taken with Permission from Siegelaar et al. 2010

The most common method to assess GV is MAGE. It was first developed by Service et al., in 1970[38]. It is quantified by calculating the mean of blood glucose increases or decreases when both the ascending and descending segments are greater than one standard deviation of mean glucose for a 24-hour period[38].

2.6 Physiological Mechanisms by Which Exercise Affects Circulating Glucose

It is well known that exercise can improve insulin function and improve glucose control. A study performed in the 1970s have shown that trained individuals have a more rapid uptake of glucose with lower plasma insulin concentrations[39]. This increased glucose uptake is due to increased insulin sensitivity in peripheral tissues as a result of exercise training.

The liver plays a major role in glucose control. It is responsible for most of the body's endogenous glucose production through gluconeogenesis and glycogenolysis. Gluconeogenesis

is the production of glucose from non-carbohydrate substrates such as glycerol while glycogenolysis is glucose coming from the hydrolysis of glycogen. Exercise can affect hepatic glycogenolysis and gluconeogenesis. A study performed by Coggan et al., in 1995[40] showed that endurance training led to reductions in the rate of hepatic glycogenolysis and gluconeogenesis at rest.

Beta (β) cells are found in the pancreas in the Islets of Langerhans and are the site of insulin secretion. These cells have been a major focus of diabetes treatment and research. Exercise improves β cell disposition index (a measure of β cell insulin secretory compensation in response to insulin resistance)[41] however, these mechanisms are not well known and further studies are needed[42].

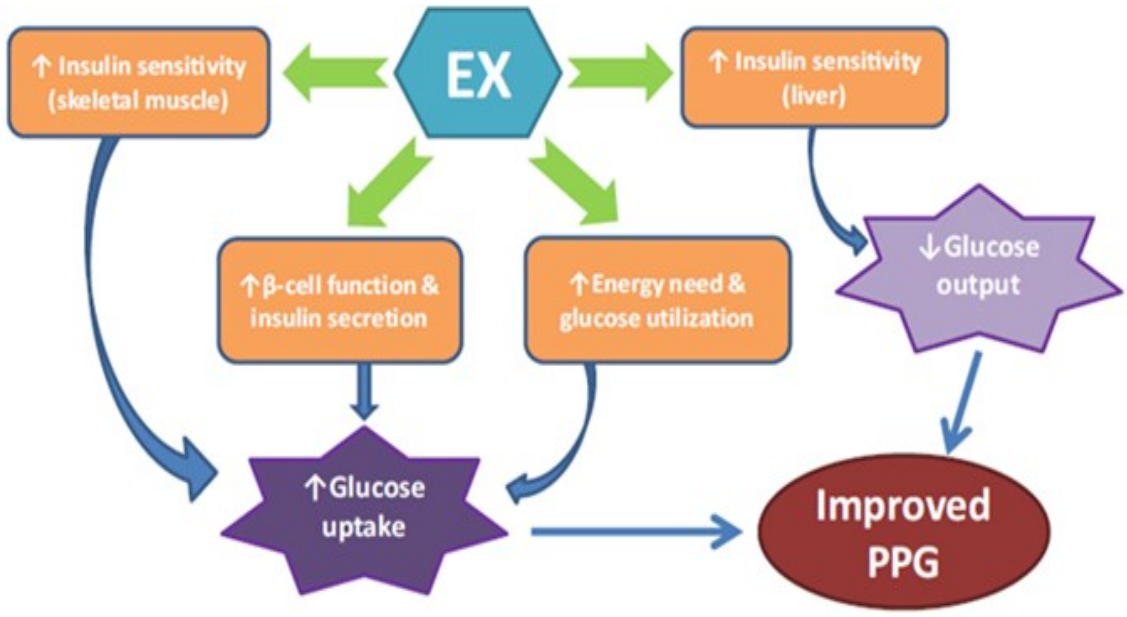

Figure 4. Pathways in Which Exercise Improves Glycemic Control from Kearney and Thyfault 2015[36]

2.7 Treatment Options for Type 2 Diabetes

Diabetes Canada recommends that individuals with T2D have blood glucose concentration between 4 and 7mmol/L before meals and between 5 and 10mmol/L two hours after starting a meal[43]. Glycated hemoglobin (A1C) is recommended to be under 7.0%[37] . To reach these goals, individuals with T2D are instructed to manage their disease through a combination of lifestyle interventions and pharmacotherapies. The current clinical care guidelines for Diabetes Canada recommend that metformin should typically be the initial antihyperglycemic agent[44]. The use of metformin is based on its effectiveness in lowering blood glucose, low cost, mild side effects and long- term safety record[38]. Metfomin is a biguanide that has a glucose lowering effect by reducing hepatic glucose output primarily through the down regulation of hepatic gluconeogenesis and increasing glucose uptake by skeletal muscle and adipocytes[45]. If metformin and lifestyle interventions are insufficient to maintain glycemic targets, other classes of drugs such as alpha-glucosidase inhibitors, incretin agents such as DPP-4 inhibitors and GLP-1 receptor agonists, insulin, insulin secretagogues, thiazolidinediones (TZDs) and sulfonylureas may be prescribed[46]. Each of these drugs have different mechanisms of action; DPP-4 inhibitors work by increasing insulin secretion and decreasing glucagon secretion in the pancreas[46]. Glucagon like peptide (GLP-1) receptor agonists act on the pancreas to increase glucose dependent insulin secretion, decrease gastric emptying, decrease inappropriate glucagon secretion, increase weight loss and increase β cell proliferation and regeneration[46]. Sodium glucose cotransporter-2 (SGLT-2) drugs target the kidney to increase the rate of glucose excretion in urine[46]. TZDs work to increase insulin sensitivity and sulfonylureas work on β-cells to stimulate insulin secretion[46].

2.8 Measurements of Glycemic Control

In clinical settings and research, glycemic control can be measured using finger stick capillary glucose devices, oral glucose tolerance tests (OGTT), glycated hemoglobin (A1C) measurements or continuous glucose monitors (CGM). Finger stick capillary glucose measurements are the most commonly used self monitoring method and involve sampling capillary blood via finger stick to be analyzed using test strips and a glucometer[47]. This method requires individuals to test themselves multiple times per day and can be negatively influenced by pain and time constraints[48].

Oral glucose tolerance tests (OGTTs) are used to diagnose diabetes[18] . These tests are performed by having the patient drink 75 grams of glucose in solution and measuring blood glucose concentration after 2 hours. OGTTs represent the integrated response of the intestines, liver and pancreas as well as insulin target tissue such as muscle and fat to glucose ingested by the mouth[48].

Glycated hemoglobin (A1C) is also used in the diagnosis of diabetes and is expressed as the percentage of hemoglobin molecules that are bound to glucose (i.e glycated). This percentage gives an indication of glycemic control over a period of 3-4 months. These measurements are used extensively by clinicians and have been considered the gold standard measurement for glycemic control due to their reliability in estimating mean blood glucose over a period of time [49]. Some of the limitations to A1C are that it takes a long time for changes to become apparent and it does not give an accurate indication of glycemic variability.

Real-time continuous glucose monitors (CGM) are a relatively new technology that allow individuals with diabetes to have a more complete view of glucose concentrations over a period of 1-2 weeks, depending on the device. One of the advantages of CGM is that they allow individuals to see fluctuations in glucose throughout the day. There are many different brands of CGM including Medtronic®, Dexcom® and Abbott®.

Figure 5. Medtronic Enlite Continuous Glucose Monitor with IPRO2

The CGM has a small flexible filament that is inserted into the subcutaneous tissue of the participant and measures interstitial glucose levels throughout the day. The Medtronic Enlite CGM takes a glucose measurement every 5 minutes. This device can be blinded to the participant and upon completion of the intervention, the data can be uploaded to a computer to show a complete view of changes in glucose levels over the previous days.

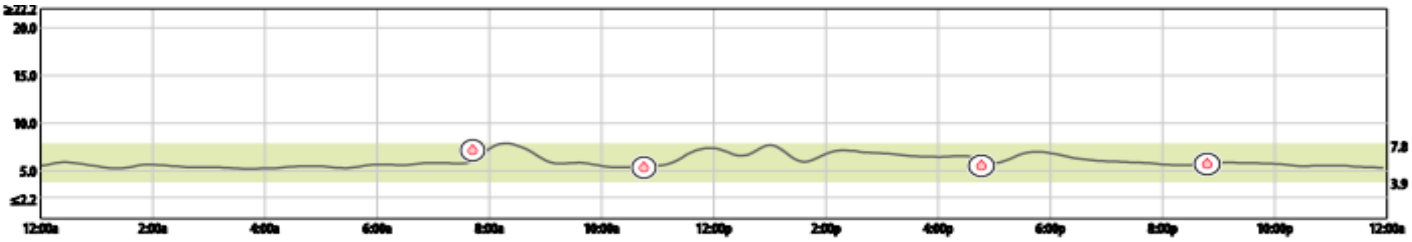

Figure 6. Example CGM Tracing

Continuous glucose monitors take readings from the interstitial fluid surrounding a cell but do not directly measure blood glucose levels. Since these monitors are measuring interstitial glucose levels rather than blood glucose, calibration with blood glucose monitors is required. Continuous glucose monitors operate under the assumption that interstitial glucose levels will be directly related to blood glucose levels due to the glucose exchange gradient across capillary walls.[50] It has been shown that there is time lag between plasma glucose and interstitial glucose[51]. The time lag is variable, but most researchers put the lag time between 5-15 minutes[51].

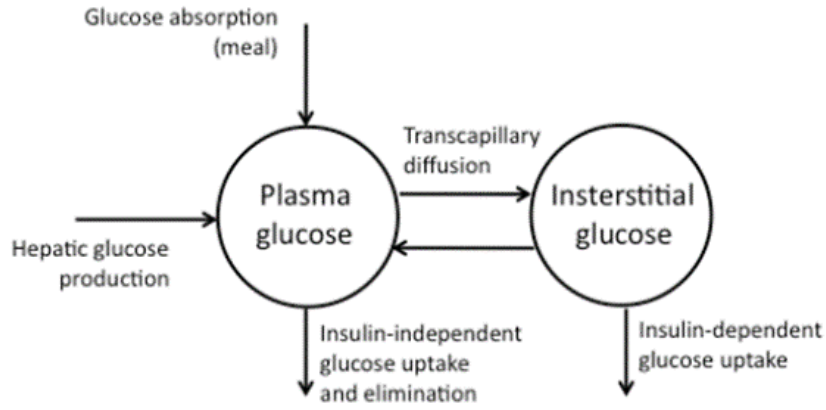

Figure 7. Glucose Exchange Across Capillary Walls Taken With Permission from Rosenetti et al., 2010[44]

2.9 Accuracy of Continuous Glucose Monitors

The accuracy of CGM has been examined in many studies including Figuera et al., 2012[51], Bally et al., 2015[52] and Aberer et al., 2017[53] . Figuera et al.,[51] showed that CGM are less accurate during aerobic exercise but it still an acceptable form of measurement when compared to finger stick capillary glucose (-11.3 ±16.5%), interclass class correlation (ICC)=0.8535[51]. Bally et al.,[52] assessed the accuracy of CGM in exercise conditions in individuals with type 1 diabetes and found a 13.6 ±2.8% difference between CGM and venous glucose levels[52] .

A study by Terada et al.,[54] (2014) assessed the test-retest reliability in continuous glucose monitors and found that the 22-hour average had a 3.9% coefficient of variation (R=0.95, P< 0.001)[54]. During exercise the coefficient of variation was 7.3% (R=0.95 P<0.001) and post exercise it was 8.9% (R=0.91 P<0.001) [54]. Taken together these studies show that CGM's are relatively accurate and reliable tools to measure glucose changes over a period of time.

2.10 The Effects of Exercise on Type 2 Diabetes

Exercise is a cornerstone in the treatment and prevention of T2D[8]. A meta-analysis performed by Umpierre et al., (2011)[55], demonstrated that structured exercise training led to reductions in A1C by -0.73% on average across 47 randomized controlled trials totaling 8538 patients[55]. Larose et al. (2011)[56] showed that changes in aerobic fitness indicators such as $V0_2$ max and ventilatory threshold correlate with reductions in A1C levels[56]. This study showed a reduction of 0.51% in A1C levels in the aerobic group after 6 months of training[56]. This outcome is consistent with a meta-analysis performed by Boulé et al (2001)[9] exercise was shown to reduce A1C levels by -0.66% across 12 aerobic training studies[9].

Meta-regression analysis has shown that the magnitude of improvement in glycemic control is partially predicted by baseline A1C. Umpierre et al.,[55] demonstrated that individuals with a greater baseline A1C show a larger magnitude of improvement after an exercise intervention (R^2=30.8 P=0.007)[55]. Similar results were found in the Diabetes Aerobic and Resistance Exercise (DARE) trial which found that participants with baseline A1C over 7.5% had greater decrease post exercise than individuals under 7.5%[57].

The intensity of exercise was found to be a predictor of the impact of exercise on A1C in a meta analysis by Boulé et al.,[58]., but not in a separate meta-analysis by Umpierre et al.,[55]. A

meta-analysis comparing energy matched head to head trials found that high intensity exercise decreased A1C by 0.22% more than moderate intensity exercise[59].It is possible that higher intensity exercise has a greater glucose lowering effect when compared to moderate intensity.

2.11 Acute Exercise and Glucose Concentrations

It has been shown that the insulin sensitizing effect of exercise persists for at least 16 hours[60] and up to 48 hours in other studies[61]. A meta-analysis conducted by MacLeod et al., (2013)[62] compiled all previous studies examining the effect of short term exercise on individuals with T2D using CGM[62]. Eight studies were included in the analysis. The authors demonstrated that exercise significantly reduced glucose concentrations by -0.8mmol/L ($p<0.01$) on average in the 24-hour period following the exercise[62].

Since that time many other studies have examined the effect of an acute bout of exercise on 24-hour glucose concentration in individuals with T2D. Our group is currently working on a updated meta-analysis on the effects both short term and long term exercise on 24-hour glucose. Among the 24 short-term and 5 long-term studies there was an average decrease of 0.5 mmol/L ;(95% CI -0.7, -0.3; $p<0.01$, I^2 =73% in short term studies and 0.5 mmol/L (95% CI -0.9, 0.1; $p<0.01$, I^2= 0%) in the long term [63]. The I^2 value is calculated to represent the variability due to heterogeneity rather than sampling error (chance). The short term studies have an I^2 value of 73% which represents a significant amount of heterogeneity among studies.[64]

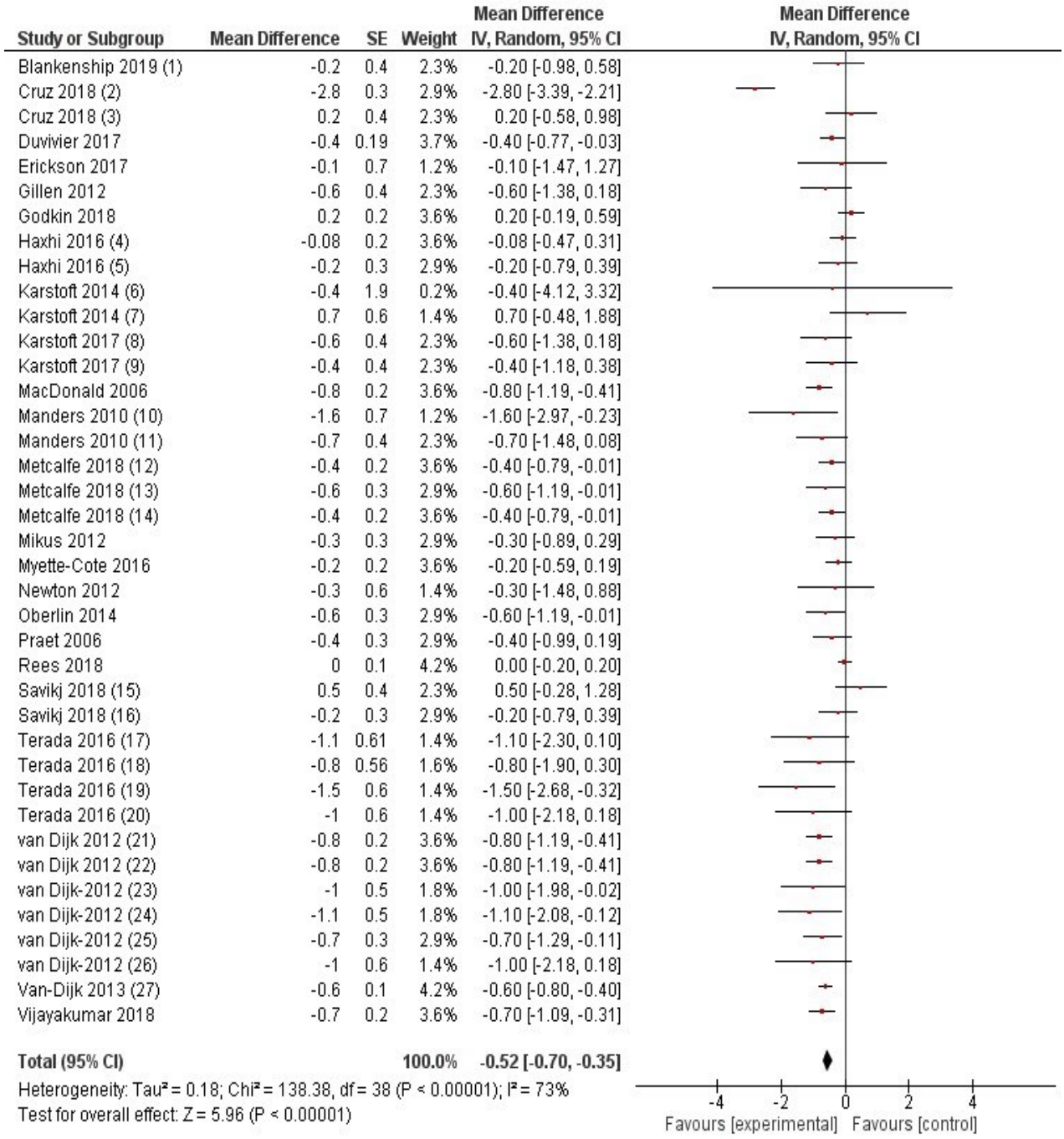

Figure 8. Combined Mean 24-Hour Glucose in Short Term Studies. Taken from Munan et al.,[63]

2.12 The E-PAraDiGM Protocol

The E-PAraDiGM protocol was developed in 2015 with the goal of standardizing an exercise protocol across eight different sites to allow for a greater sample size to compare inter-individual differences. This protocol allowed researchers to standardize meals, timing of exercise, method of measurement, exercise intensity, washout period etc. The primary outcome of interest was to compare the 24-hour glucose as measured by CGM following a 50-minute bout of aerobic exercise compared to 50 minutes of sitting. Over 70 participants complete the protocol across Canada making this the largest ever acute exercise study using CGM in individuals with T2D.

The E-PAraDiGM study used a randomized crossover design in which participants wore a CGM for 6 days and were asked to complete both the exercise and control session in a randomized order with a 48-hour washout day in between. The results from the 70 participants across eight sites have shown considerable variability and after statistical analysis there was no significant difference in 24-hour periods following the exercise and control day with mean (SD) glucose concentrations of 7.5 mmol/L (1.6) on both days[65].

2.13 Exercise Timing

One of the potential reasons for the results of the last study may be the timing of exercise in relation to meals. There has been some controversy regarding the optimal timing of exercise in relation to meals. It has been suggested that the optimal time for exercise is 30 minutes after a meal[66,67,57].The reasoning for this is that the 30-minute mark is the approximate time that the greatest amount of glucose from a meal will be entering the bloodstream[68]. It is at this 30-minute post meal window that glucose is thought to be most readily available for uptake by contracting skeletal muscle[68]. A 2013 review by Haxhi et al.,[13] concluded that premeal exercise was effective at controlling lipidemia, while postmeal exercise is more effective at reducing hyperglycemia[13].

Other studies however, have argued that fasted state exercise is more beneficial for lowering blood glucose[69]. Boulé and Terada[70] have questioned the assertion that 30 minutes postprandially is the optimal time for exercise and argued that fasted state exercise may be preferable to postprandial exercise in decreasing postprandial glucose excursions[70]. These authors reason that fasted state exercise has been shown to increase glycogen content, insulin

sensitivity and AMP-activated protein kinase (AMPK) activity more than postprandial exercise[70,71]. Exercising in the fasted state stimulates energy provision by fatty acid oxidation. For individuals who are consistently consuming a high fat diet, this may improve diet-induced insulin resistance[71]. A study performed by Terada et al., 2016[69] showed that fasted state high intensity exercise decreased postprandial hyperglycemia more than post breakfast exercise in people with T2D[69].

Subgroup analysis performed on the short-term studies in our meta-analysis found that aerobic exercise performed in the morning or in the fasted state decreased glucose in the 24 hour period following exercise more than exercise performed in the afternoon (shown in figure 9). It is important to point out that these results are heavily influence by the E-PAraDiGM study. A systematic review with 19 included randomized controlled trials (RCTs) concluded that exercise performed 30 minutes after a meal may lead to an increased glucose lowering response however definitive statements cannot be made due to a lack of head to head trials comparing exercise at different times throughout the day[72].

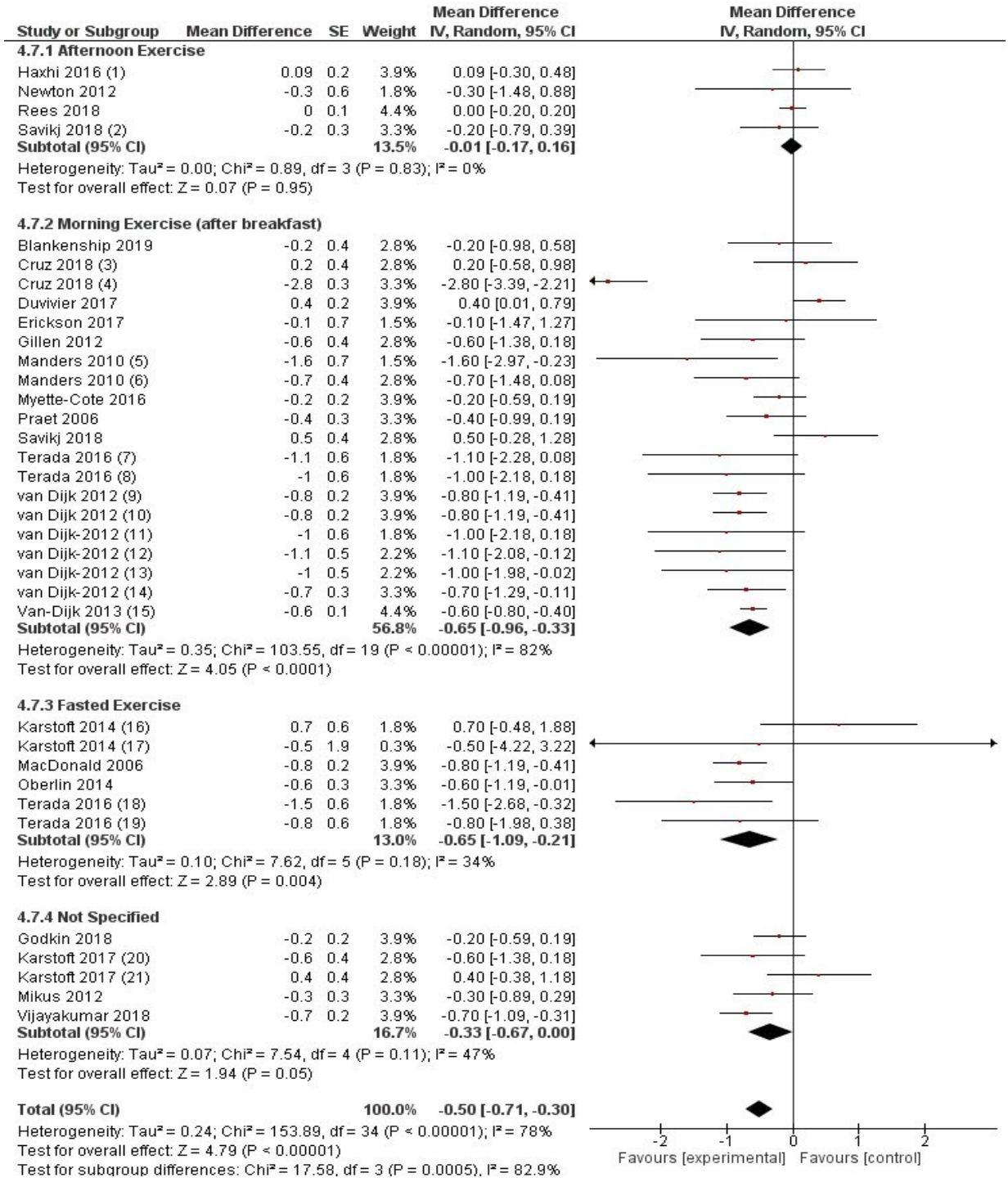

Figure 9. Exercise Timing Subgroups Taken from Munan et al.[63]

2.14 Glucose Excursions and The Circadian Rhythm

It has been shown that there is a diurnal rhythm in glucose tolerance[73]. Hepatic glucose production is influenced by the circadian rhythm[74]. In previous studies both glucose infusions and oral glucose tolerance tests result in higher blood glucose levels in the evening versus the morning[74]. In healthy humans, insulin sensitivity and β-cell response to glucose is lower at the evening meal compared to breakfast[74]. A 2014 study by Morris et al.,[75] looked at the difference in glucose tolerance at different times throughout the day and found that postprandial glucose levels were 17% higher in the evening (8 pm) versus the morning (8 am)[75]. Similarly, a study by Van Cauter et al., (1992)[76] found that the glycemic response to a standardized meal was modulated by the circadian rhythm: the glucose response to a meal consumed in the evening was elevated compared to a meal consumed in the morning[76]. The diurnal hormonal response is summarized in the figure 10.[77]

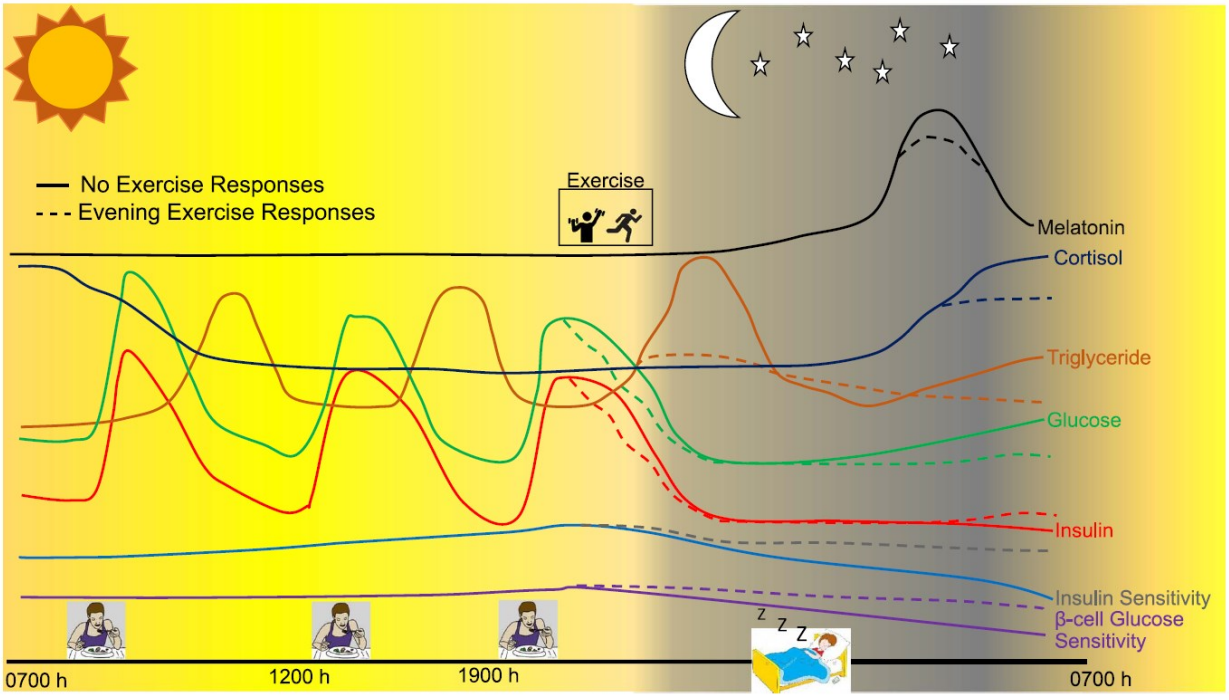

Figure 10. Hormonal and Metabolic Circadian Changes. Taken from Heden et al. 2018

2.15 The Dawn Phenomenon

The "Dawn Phenomenon" refers to a period of hyperglycemia occurring in the early hours before and after breakfast. This phenomenon was originally described by Schmidt et al.,[78] in the 1980s in individuals with type 1 diabetes[78]. It was then shown to occur in individuals with T2D[79]. Approximately 55% of individuals with T2D present with this phenomenon which has been shown to contribute to a 0.4% increase in A1C values.[80,81] The mechanisms of this rise in glucose in individuals with T2D is thought to be a result of an increase in hepatic glucose production (both glycogenolysis and gluconeogenesis) without compensatory insulin secretion[82].

2.16 Variability In Exercise Studies

On the following page is a table highlighting exercise studies examining glucose concentrations in individuals with or without T2D. As shown below, participants in these studies exercised at different times of the day and different intensities. The results show significant variability in glycemic response to exercise.

Table 1. Variability in Exercise Studies

Author	Population	Sample Size	Exercise Mode	Exercise Duration	Exercise Intensity	Exercise Timing	Results
Rees (Original E-PAraDiGM) 2019[65]	Type 2 diabetes	73	Treadmill walking	50minutes	~3.5 METS	3-4 hours post prandially	No significant difference in 24hr glucose concentrations.
Nygaard 2017[83]	Hyperglycemic individuals	12	Treadmill walking	60 minutes	12/20 RPE	ExBr-Fasted state BrEx-30 minutes post breakfast	No significant difference for 22hrs in either fasted state or postprandial exercise groups. The postprandial exercise group lowered the iAUC for the evening meal compared to fasted state.
Erickson 2017[84]	Active, healthy men	8	Treadmill walking	30mins (3x10min intervals)	50% $V0_{2peak}$	30 minutes post meal	Exercise lowered glucose for 2hrs following the morning meal. The effect was not sustained past this time.
Hatomoto 2017[85]	Active, healthy men	11	Treadmill	60 minutes	62.4 ±12.9 $V0_{2peak}$	Pre-prandial exercise Postprandial exercise Brief Periodic	No significant difference between groups over 24hrs or the AUC 2hrs postprandially. Brief periodic exercise was more effective than the other 2 conditions at lowering post breakfast glucose levels. Brief periodic exercise was more effect at lowering glucose following lunch than with postprandial exercise.
Reynolds 2016[86]	Type 2 diabetes	41	Walking	30 minutes	Not specified	Group 1-not specified Group 2-Right after each meal	The iAUC for glucose was lower when participants walked after each meal compared with one single block of time. The effect was most prevalent after evening meal.
Terada 2015[69]	Type 2 Diabetes	10	Treadmill Running/ Walking	60 minutes	HIITGroup40-100% V02 Peak. Moderate Intensity 50% V02 Peak	Fasted state or right after breakfast	Fasted state exercise attenuated post prandial hyperglycemia more than post breakfast. High Intensity fast group lowered mean 24hr glucose by 1.5mmol/L

Francois 2014[87]	Individuals with Insulin Resistance	9	Treadmill Running/ Walking	Group 1 (CONT) 30mins Group 2 (ES)6x1min intervals at 90% HRmax	CONT-60% HRmax Group 2 (ES) 90% HRmax interval training	ES-30minutes before each meal CONT-30 minutes before evening meal	Exercise Snacks attenuated mean 3hr postprandial glucose concentrations following breakfast. ES reduced the mean 24hr glucose concentration by 0.7mmol vs control.
Oberlin 2014[88]	Type 2 Diabetes	9	Treadmill Walking and Stationary Biking	60 minutes 20 minutes on treadmill, 20 on bike, 20 on treadmill	60% HRR	Fasted State	Exercise significantly reduced glucose during the first 24 hrs compared to the control.
Dipietro 2013[89]	Inactive older participants	10	Treadmill walking	45 minutes continuous (group 1)or 15 minutes 30 minutes after each meal (group 2).	3.0 METS	30 minutes post meal (15mins) Or CONT 10:30am or 4:30pm	Both continuous morning and post meal walking significantly improved 24hr glucose concentrations. Post meal walking was significantly more effective than both morning and afternoon continuous groups at lowering 3hr postprandial glucose.
Myette-Cotte 2013[90]	Type 2 Diabetes	10	Treadmill walking	50 minutes	85% of VT	2.75hrs after breakfast	Exercise increased the AUC for 2hr postprandial glucose compared to no exercise group.
Colberg 2009[12]	Type 2 Diabetes	12	Walking	20 minutes	Self Paced	Immediately before or 15 minutes after a meal	Postprandial exercise decreased blood glucose more than premeal exercise 90minutes after testing.

The table above shows variability in responses to exercise in the 24-hour mean glucose concentrations as well as no clear signal as to an optimal time for exercise. Terada et al., (2015)[69] showed that fasted state exercise produced a greater reduction in 24 hour glucose than postprandial exercise performed after breakfast[69]. Similarly, Oberlin et al., (2014)[88] showed a significant effect from fasted state exercise over the 24-hour period[88]. The E-PAraDiGM study[65] and the study by Dipietro et al., (2013)[89] did not show a significant glucose lowering effect when exercise was performed 3-4 hours postprandially[65,89]. These data suggest that fasted state exercise may be more effective for decreasing glucose than mid-afternoon exercise in individuals with T2D.

Reynolds et al., [86] had the second largest sample size (n = 41) behind the E-PAraDiGM study[86]. This study showed that the incremental area under the curve (iAUC) for glucose was lower when participants exercised after each meal as opposed to one continuous block with no specified timing. It is also interesting to note that the effect was greatest after the evening meal. In contrast to Terada et al., (2015), [69] Colberg et al., 2009[12] found that postmeal walking decreased glucose more premeal walking.

Upon analysis of the literature, the optimal time for exercise is most likely either fasted state or 30 minutes after the evening meal. To determine which of these states is optimal, we have developed a follow-up study to the original E-PAraDiGM study. This new study will allow us to compare fasted state exercise to 30 minutes postprandial exercise. Due to the time that has passed from the original E-PAraDiGM study to this follow up, we wish to also have participants perform the original E-PAraDiGM protocol in addition to the two new conditions.

Chapter 3 Methods

3.1 Study Design: This study built upon the original E-PAraDiGM study by comparing the original E-PAraDiGM protocol (exercise performed in the mid-postprandial period 3-4 hours after lunch) to an additional 6-day intervention in which individuals exercised in the following two conditions: fasted state (starting 1.5 hours before breakfast) and 30 minutes after dinner. Participants were asked to complete both 6-day interventions: the original E-PAraDiGM protocol (exercise 3-4 hours after lunch, seated control) and the follow-up study (exercise 30 minutes after dinner, exercise in the fasted state). These conditions were completed in a randomized order with a 48-hour washout period in between. A breakdown of the study is as follows:

Table 2. breakdown of 12 day intervention

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Insert CGM	Standardized meals **Session 1** (Randomized)	Standardized meals	Washout	Standardized meals **Session 2** (Randomized)	Standarized meals Remove CGM

Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Insert new CGM	Standardized meals **Session 3** (Randomized)	Standardized meals	Washout	Standardized meals **Session 4** (Randomized)	Standardized meals Remove CGM

3.2 Inclusion Criteria

• 30-90 years of age.

•No contra-indications to exercise.

•No previous myocardial infarction, stroke, diagnosed coronary artery disease.

•No changes in diabetes medication in the last 3 months.

•Not treated by insulin or corticosteroids.

•No significant changes in body weight (>5lbs in past 3 months).

•Blood pressure <160/100 mm/hg.

•Resting heart rate <100 beats per minute.

•Able to understand English or French and comply with study requirements.

3.3 Variables: The independent variable was the timing of the exercise. The exercise was performed either 3-4 hours postprandially, 30 minutes postprandially (after supper) or in a fasted state. The primary dependent variable was the mean 24-hour CGM glucose concentration. Secondary outcomes included; the change in 50-minute CGM glucose during exercise, 2 hour postprandial CGM glucose concentration, time above 10mmol/L, time below 4 mmol/L, fasting glucose and glucose variability as assessed by mean amplitude of glycemic excusions (MAGE).

3.4 Baseline Assessments: Baseline assessment included anthropometric measurements height, weight, waist and hip circumference. Body fat percentage was obtain from bio-electrical impedence (BIA) using the Tanita Body Composition Analyzer, TBF-300A®. Physiological assessments such as blood pressure and heart rate were also obtained. Physical activity habits were obtained by having participants complete the Godin Leisure Time Exercise Questionnaire[91]. Participants also completed the Patient Health Questionairre-8 (PHQ-8)[92], the Pittsburgh Sleep Quality Index (PSQI) and perform a 15-minute practice treadmill walking session. Participants were asked to bring their most recent lab results with A1C, LDL, HDL, total cholesterol and triglycerides taken within the last 6 months and serum creatinine measured within the last year. At the Edmonton site, A1C was also measured using DCA Vantage® Analyzer.

3.5 Methods of Measurement:

During the exercise session, heart rate was measured continuously throughout using a Polar® heart rate monitor. Ratings of perceived exertion (RPE) on the Borg scale were assessed every 5 minutes. During minutes 5-15 and 35-45 of exercise and the equivalent seated control days, expired gases were analyzed using a Parvo Medics TrueOne 2400® metabolic measurement system. This allowed for analysis of RER (respiratory exchange ratio) which is an indication of macronutrient oxidation.

3.6 Standardized Meals

Participants were provided with all of their food for the eight intervention days. The macronutrient profile of the meals, based on Diabetes Canada recommendations, consisted of ~55% carbohydrate, ~30% fats and ~15% protein[93]. The caloric needs of each participant was

determined using the Harris Benedict Formula[94]. This formula estimates resting metabolic rate (RMR) multiplied by a physical activity level (PAL) of 1.4 to reflect the energy requirements of a relatively sedentary day. The Harris Benedict Formula is shown below:

Males:RMR (kcal/day)=66.4730 + 13.7516W +5.0033H-6.07750A

Females:RMR (kcal/day)=665.0955+9.5634W + 1.8496H-4.6756A

W=Weight in kilograms H=Height in centimeters A=Age in years

To standardize meals and to make meals easily replicable at other Canadian sites using the E-PAraDiGM protocol, we used a combination of prepackaged foods from the Presidents Choice Blue Menu® and Subway® sandwiches in addition to fruits, vegetable, almonds breads etc. A list of foods chosen and sample menu is shown in Appendix B.

3.7 Exercise Intervention

The exercise bout consisted of 50 minutes of treadmill walking at 5.0 km/hr and 0.5% incline. This corresponds to ~3.5 METS. This intensity was chosen to align with the CSEP[15] and Diabetes Canada[8] Guidelines of 150 minutes of moderate to vigorous aerobic activity per week performed over three days. The warm up was included in the 50 minutes and consisted of 5 minutes at a pace of 3.5 km/hr at 0% grade. If a participant could not comfortably complete 15 minutes of walking at the specified intensity at the baseline screening visit the speed was reduced to 4.5 km/hr (i.e 2.8mph or 3.3 METS) or 4.0 km/hr (i.e 2.5 METS). During exercise heart rate and ratings of perceived exertion (RPE) were recorded every 10 minutes. Blood pressure and capillary glucose were monitored before and after exercise.

3.8 Analysis of Data

The differences in 24-hour glucose concentration were analyzed using a one-way repeated measures ANOVA to test the null hypothesis that all four conditions are equal. The 24-hour period started at the beginning of exercise for the fasted state, seated control and afternoon conditions and at the start of dinner in the evening condition. With four conditions, there is a possibility of six comparisons (see figure 11). With every comparison the risk of committing a type 1 error increases, therefore three primary between condition comparisons were performed. Since other studies have compared fasted state to control (Terada et al.)[69], afternoon to control

(Rees et al.)[65] and 30 minutes postprandially to control (Terada et al.)[69] The primary analyses included the following three questions:

- Is fasted state exercise different from afternoon exercise?
- Is fasted state exercise different from post dinner (evening exercise)?
- Is afternoon exercise different from post dinner (evening exercise)?

These three comparisons will be done using paired t-tests without adjusting the alpha. Our secondary analysis will include comparison between each exercise condition and control. Since this analysis is at high risk for type 1 error and no adjustment formula is used, these results will be interpreted with caution.

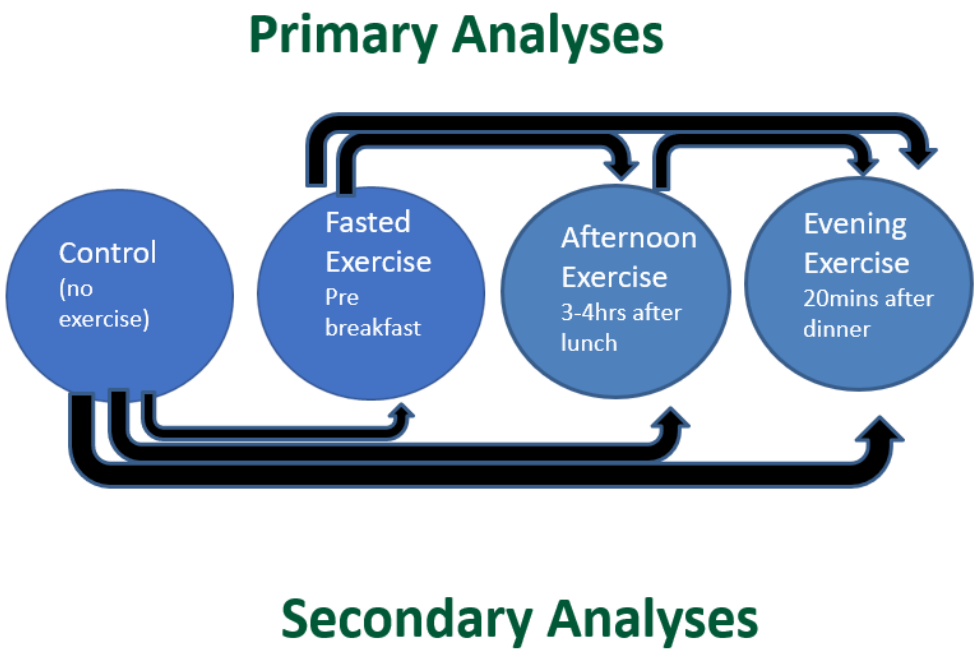

Figure 11. Primary and Secondary Statistical Analyses

3.9 Statistical Power

Previous studies have shown a mean difference of 0.8 mmol/L between fasted state exercise and a control condition (Terada et al.[69]). A difference of this magnitude was also observed in the 24 hours after an acute bout of exercise in a meta analysis by Macleod et al[62]. The standard deviation was 1.7 in Terada et al.,[69] and 0.7 in Macleod et al.,[62]. We estimated our sample to have a standard deviation of 1. Therefore the effect size would be 0.8. A power calculation was performed using the Lenth Java Applet for Power and Sample Size[95]. In order to have 80% power to detect an effect size of 0.8 with the alpha set at 0.05, 14 participants would be required. Differences below 0.8 mmol/L may still be clinically meaningful but our study was underpowered to detect such differences.

Chapter 4 Results

4.1 Participant Characteristics

Seventeen individuals were screened for inclusion between July and December 2018 at the University of Alberta Physical Activity and Diabetes Laboratory (PADL) and Augustana Campus in Camrose Alberta with 14 individuals completing the protocol. Reasons for exclusion were: A1C > 9% (n=1), blood pressure above 160/100mmhg (n=1), participant drop out before study completion (n=1).

Eight males and six females were included in the analysis. On average they were 65.0 ± 9.0 years, had T2D for 10.5 ± 6.8 years. The mean A1C for participants was 6.7 ± 0.6%. Thirteen participants were treated with oral hypoglycemic medications and one controlled their diabetes through diet and exercise.

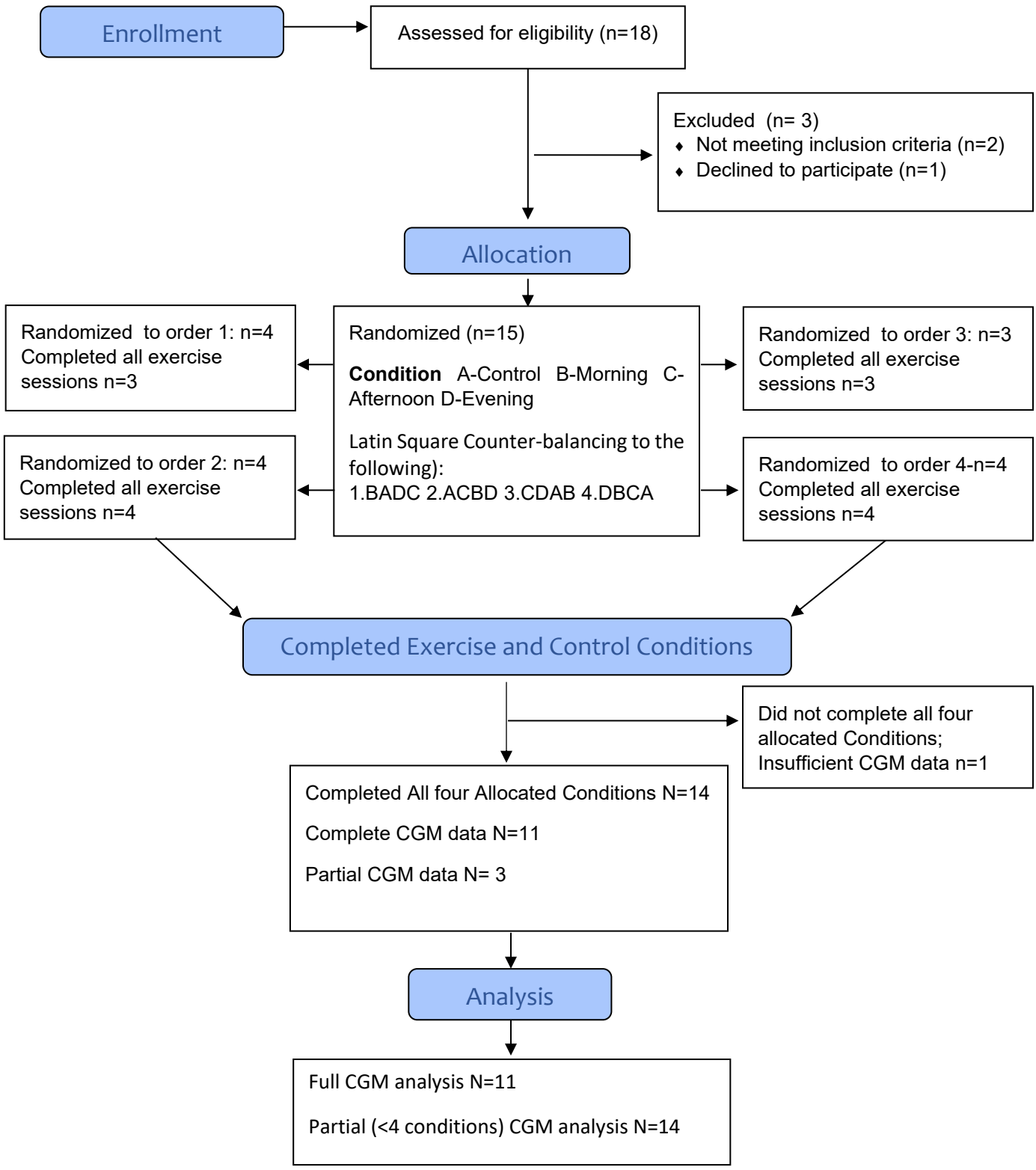
Enrollment
Assessed for eligibility (n=18)
Excluded (n= 3)
Not meeting inclusion criteria (n=2)
Declined to participate (n=1)
Allocation
Randomized to order 1: n=4
Completed all exercise sessions n=3
Randomized (n=15)
Condition A-Control B-Morning C-Afternoon D-Evening
Latin Square Counter-balancing to the following):
1.BADC 2.ACBD 3.CDAB 4.DBCA
Randomized to order 3: n=3
Completed all exercise sessions n=3
Randomized to order 2: n=4
Completed all exercise sessions n=4
Randomized to order 4-n=4
Completed all exercise sessions n=4
Completed Exercise and Control Conditions
Did not complete all four allocated Conditions; Insufficient CGM data n=1
Completed All four Allocated Conditions N=14
Complete CGM data N=11
Partial CGM data N= 3
Analysis
Full CGM analysis N=11
Partial (<4 conditions) CGM analysis N=14

Figure 12. Consort Trial Flow

Table 3. Participant Characteristics

Baseline Characteristics	All N=14 Mean ± SD
Sex M/F	8/6
Age (yrs)	65 ± 9.0
Weight (kg)	77.7 ± 14
Duration of T2D (yrs)	10.5 ± 6.8
A1C (%)	6.7 ± 0.6
SBP (mmhg)	120.6 ± 9.0
DBP (mmhg)	75.9 ± 11.0
RHR (BPM)	69.7 ± 11.6
HDL Cholesterol mmol/L N=10	1.4 ± 0.4
LDL Cholesterol mmol/L N=10	1.9 ± 0.6
Total Cholesterol mmol/L	3.9 ± 0.8
Triglycerides mmol/L	1.5 ± 0.6
Serum Creatinine μ mol/L	74.3 ± 23.7
Height (cm)	168.0 ± 11.6 (all) 175 ±0.4 M, 161.6 ±1.1 F
Weight (Kg)	77.7 ± 14.0 (all) 82.5 ±11.1 M, 78.7 ±13.4 F
BMI (kg/m^2)	27.2 ± 3.5 (all) 26.7 ±3.1 M, 29.4 ±3.3 F
Body Fat (%)	28.8 ± 8.7 (all) 22.9 ±4.0 M, 33.9 ±8.6 F
WC (cm)	98.5 ± 10.3 99.2 (all) ±10.0 M, 102 ±4.6 F
HC (cm)	104.0 ± 6.4 (all) 102.7 ±4.6 M, 105.2 ±8.1 F
Sleep (PSQI)	5.1 ± 2.8
Depression (PHQ-8)	3.7 ± 4.3
Physical Activity (GLTEQ)	50.8 ± 53.8

n=sample size, M=males, F=females, yrs=years, A1c=glycated hemoglobin, %=percent, mmol/L=millimole per litre, HDL=high density lipoprotein cholesterol, LDL=low density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides, umol/L = micromole per litre, SBP=systolic blood pressure, DBP=diastolic blood pressure, mmHg=millimeters of mercury, RHR=resting heart rate, bpm=beats per minute, cm=centimeters, kg=kilograms, BMI=body mass index, WC=waist circumference, HC=hip circumference, PSQI = Pittsburgh Sleep Quality Index, PHQ-8 = Patient Health Questionnaire, GLTEQ = Godin Leisure Time and Exercise Questionnaire (physical activity).

Table 4. Medication Information

Glucose Medications	Number of Participants
Metformin alone	10
Metformin + other	2 (DPP-4 Receptor Agonist, Sulfonylurea)
Other hypoglycemic agent	1 (SGLT-2 Inhibitor)
No hypoglycemic agent	1
Blood pressure medication	8
Lipid/cholesterol lowering agent	9

4.2 Dietary Intake

All participants were provided standardized meals for the day of the intervention and the day after. The macronutrient distribution fit within our goal of 55 ± 5% carbohydrate, 30 ± 5%, fats and 15 ± 5 protein per day. The average daily caloric content for the participants was 2125 kcal/day.

Table 5. Dietary Intake

Variable	All (N=14) Mean ±SD
Daily caloric content (Kcals)	2125 ± 337
carbohydrate intake (g/day)	265 ± 48
Fat intake (g/day)	79 ± 16
Protein intake (g/day)	83 ± 13
Carbohydrate (% per day)	54% ± 2%
Fat (% per day)	31% ± 3%
Protein (% per day)	14% ± 0.9%

4.3 Exercise Variables

The treadmill speed was set at 3.5 mph for 10 participants. It was decreased to 2.5 mph for one participant and 2.0 mph for three participants due to them being unable to safely perform the prescribed exercise. Across exercise conditions, the average intensity was 3.7 ± 0.5 METS. Between exercise conditions, morning exercise resulted in a significantly lower HR and RER when compared to afternoon or evening exercise. No significant difference was found between afternoon and evening exercise in either HR or RER as shown in table 6 (see supplementary material).

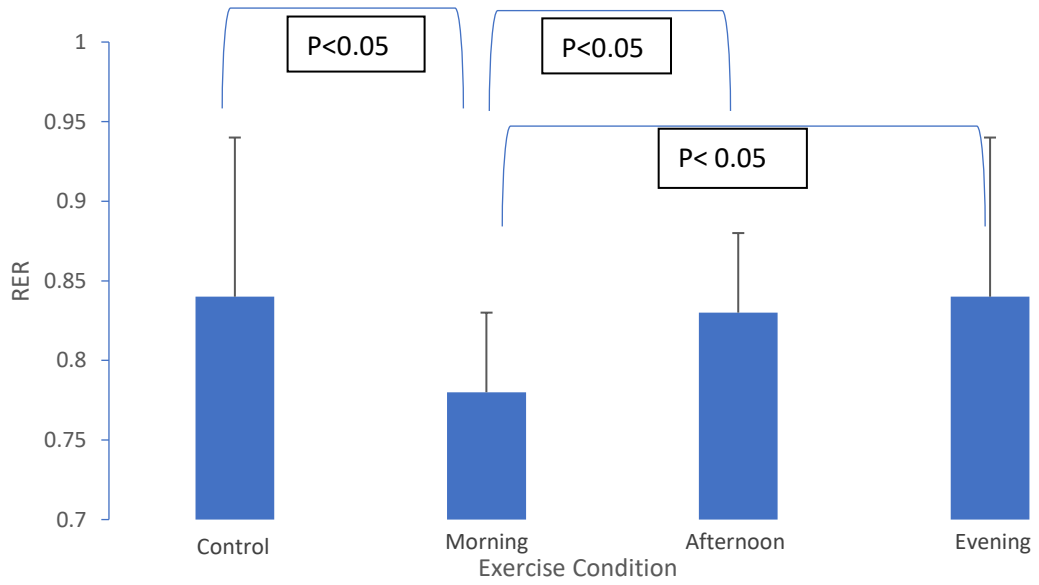

Figure 13. Mean Respiratory Exchange Ratio during 50 minutes of Exercise

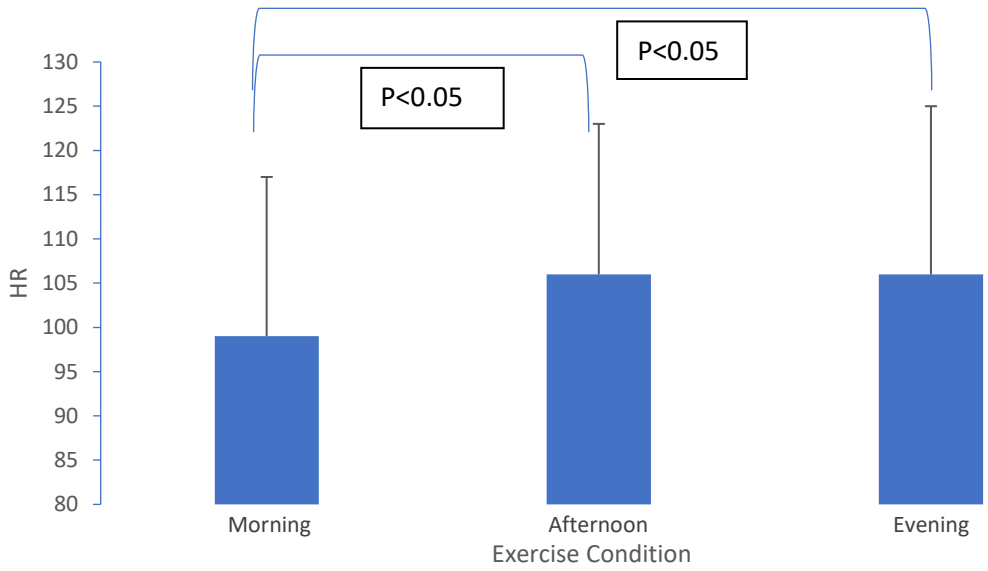

Figure 14. Mean Heart Rate during 50 Minutes of Exercise

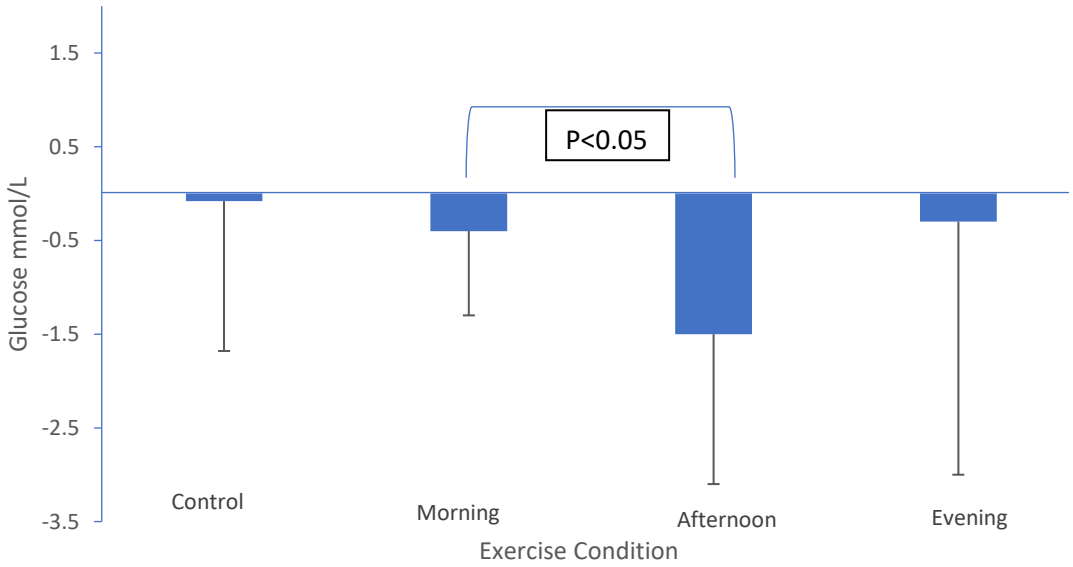

Figure 15. 50-Minute Mean Change in Glucose

4.4 Continuous Glucose Monitor Outcomes

Contrary to our hypothesis, there was no overall difference in 24-hour glucose among the four conditions in the 11 participants for whom 24-hour glucose was data was available. (P=0.55) (see table 7). When the conditions were compared using paired t-tests, afternoon exercise was associated with lower mean glucose compared to the resting control condition (P=0.006). There was no significant difference between any other combinations (see table 7).

Glycemic variability (MAGE) was obtained for each 24-hour period directly following exercise in the control, afternoon and morning conditions and directly following the pre-exercise meal in the evening condition. There was no significant difference among the four conditions or between conditions.

Complete postprandial glucose data was available for 10 participants and partial (postprandial mean available in two or three conditions) was available for three participants. One participant did not record meals in the logbook as requested. As a result, postprandial glucose could not be assessed. There was no significant difference between conditions in postprandial glucose when all three meals are averaged. When mean glucose for each meal is compared, there is no significant difference among conditions for the 2-hour period following breakfast, lunch or dinner. When paired t-tests were performed, the mean 2-hour period following lunch was significantly lower in the morning exercise condition compared to control P=0.035 and the mean 2-hour period following dinner in the afternoon exercise condition was significantly lower than control P=0.014.

There was no overall difference in fasting glucose among the four conditions, however when paired T-Tests were performed, fasting glucose on the morning following fasted exercise was lower than the fasting glucose on the morning after afternoon exercise, p=0.003 (see figure 24). There was no significant difference between any other combinations. There were very few incidences of hypoglycemia with one participant under 4mmol/L for 110 mins in the 24 hours after the seated control session and another under 4 mmol/L for 70 minutes in the 24 hours after morning exercise. There was no significant difference in time above 10 mmol/L among the four

conditions, however when paired t-tests were performed, afternoon exercise was associated with less time above 10 mmol/L compared to control (see figure 22).

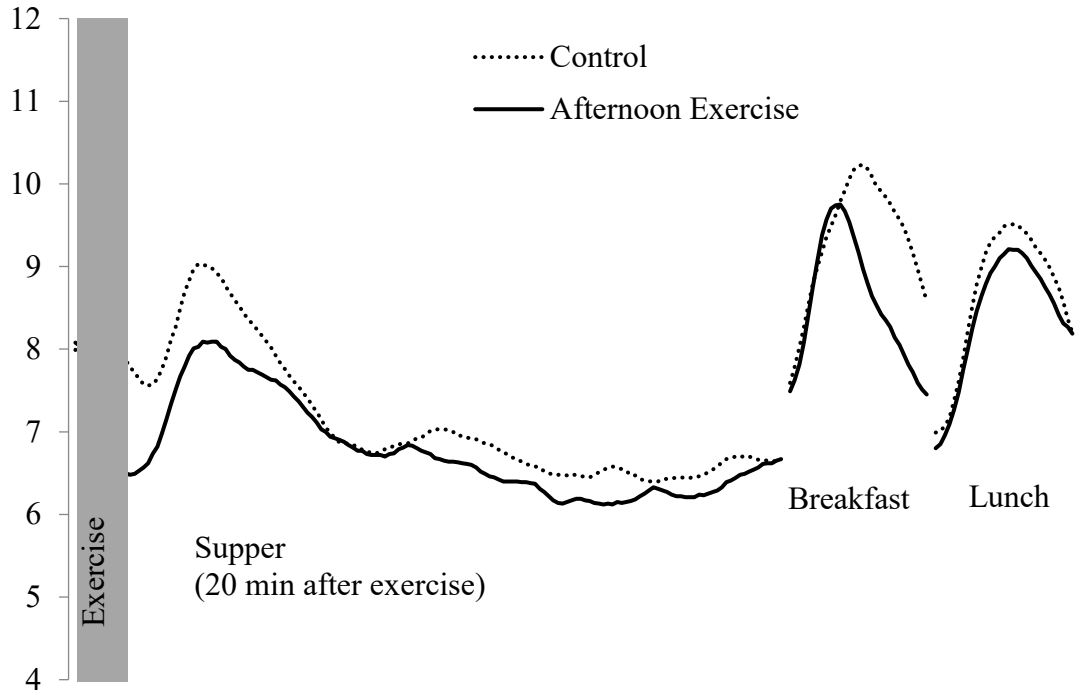

Figure 16. Glucose Curves Afternoon and Control

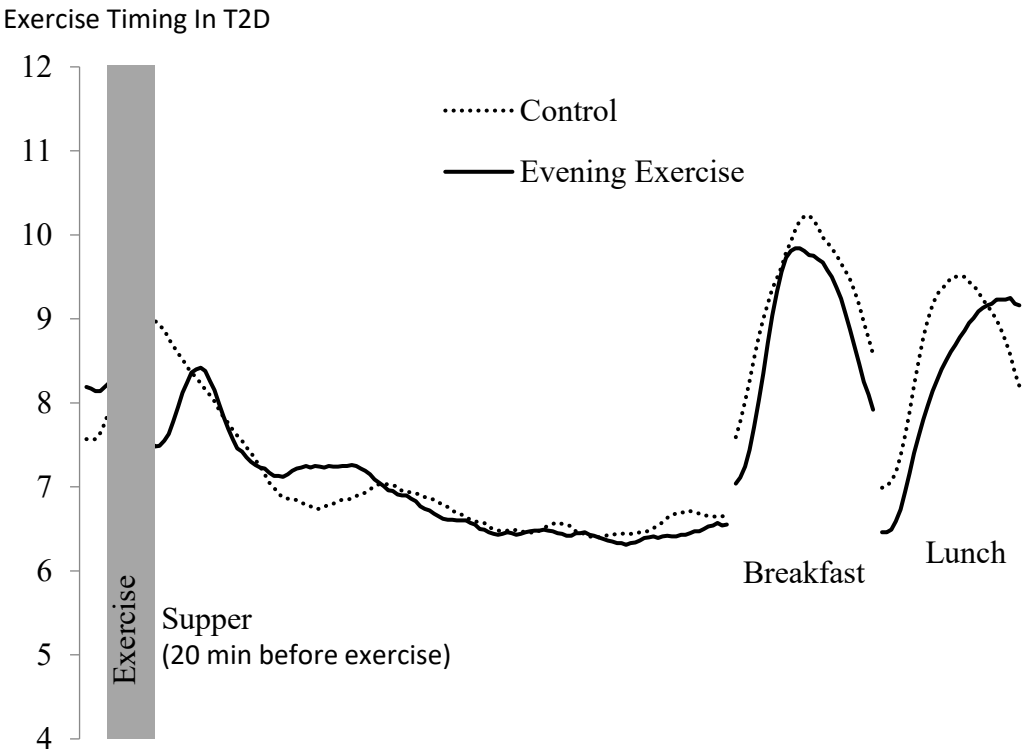

Figure 17. Glucose Curves Evening and Control

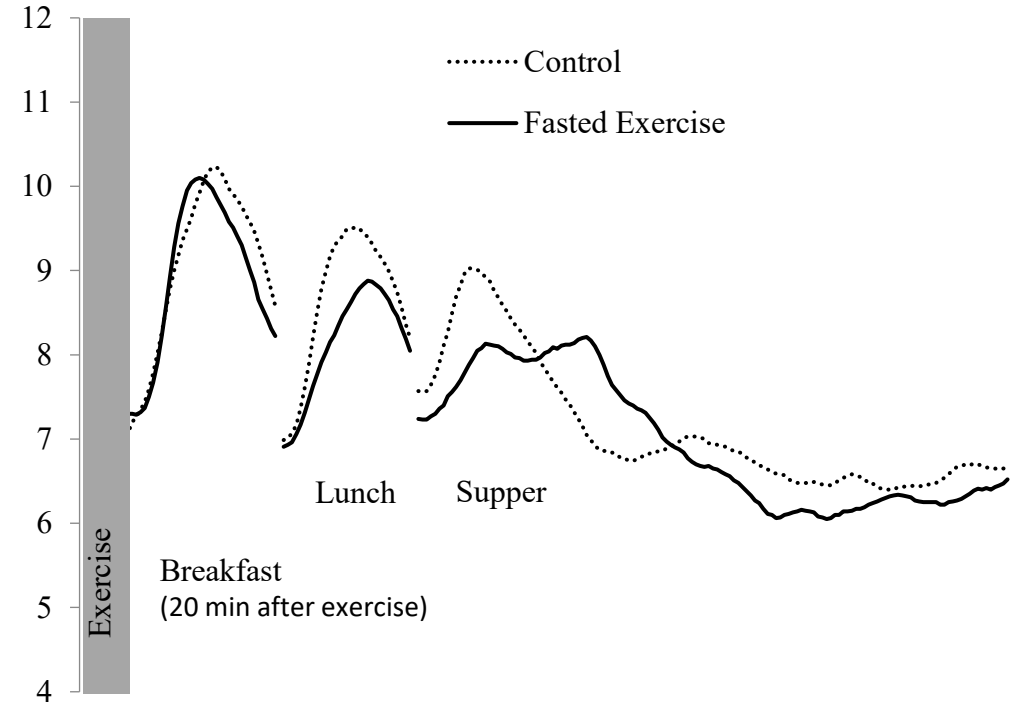

Figure 18. Glucose Curves Fasted (Morning) and Control

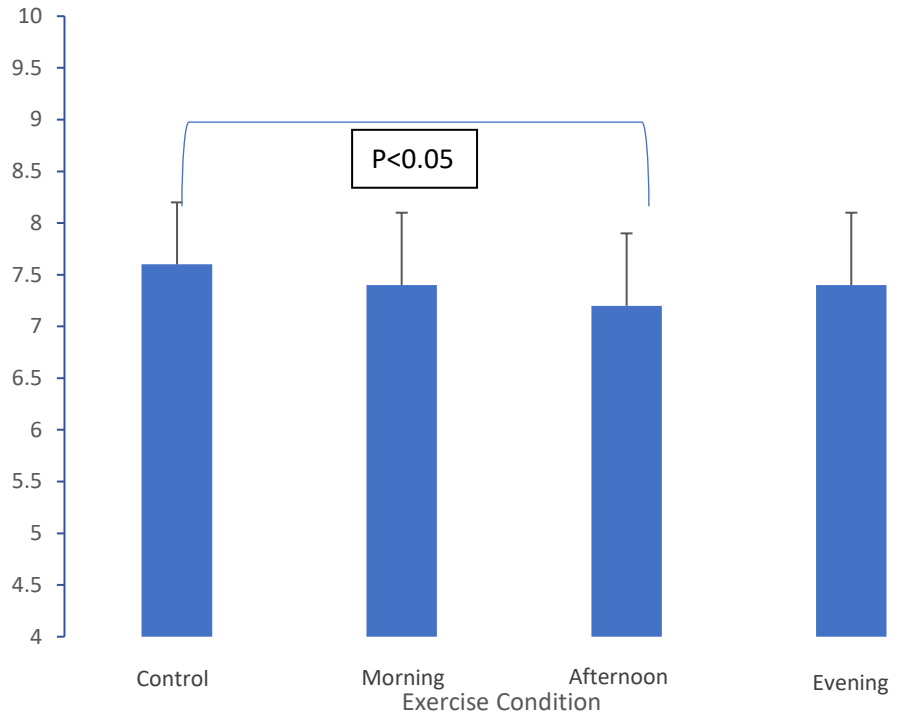

Figure 19. 24-Hour Mean Glucose

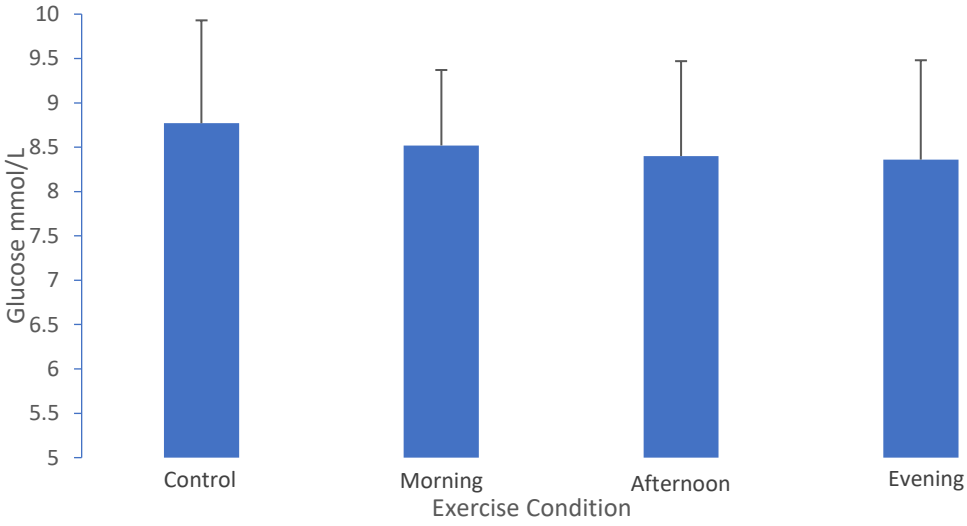

Figure 20. Mean 2-Hour Postprandial Glucose (Mean of Three Meals)

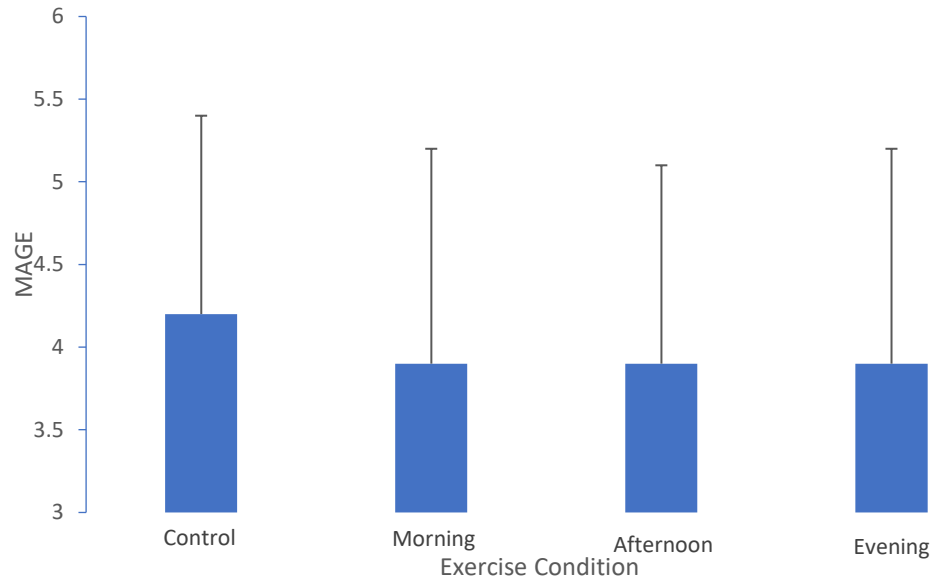

Figure 21. 24-Hour MAGE

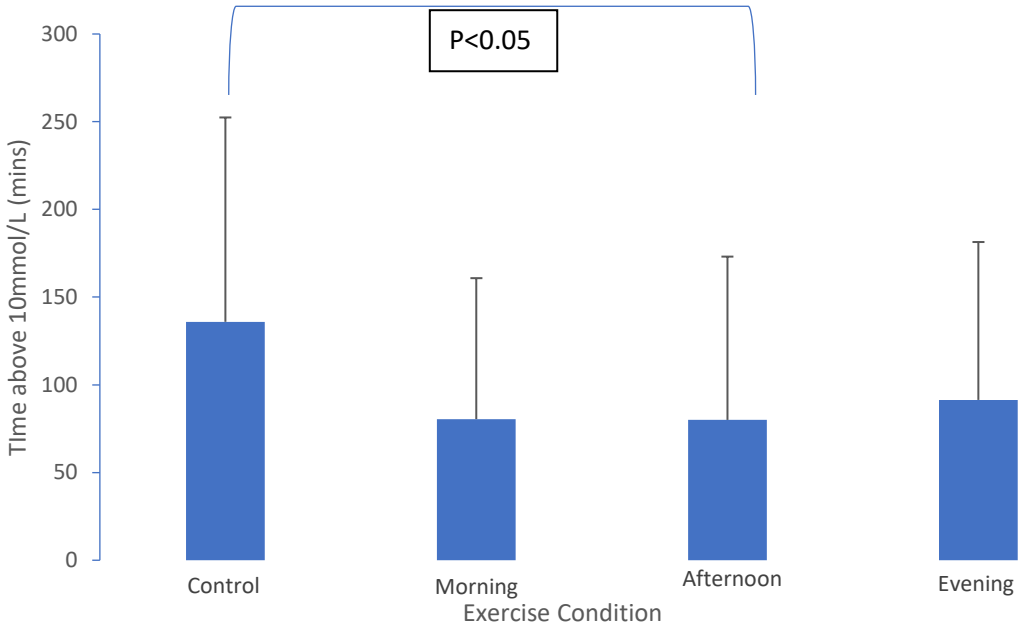

Figure 22. Time Spent Above 10mmol/L

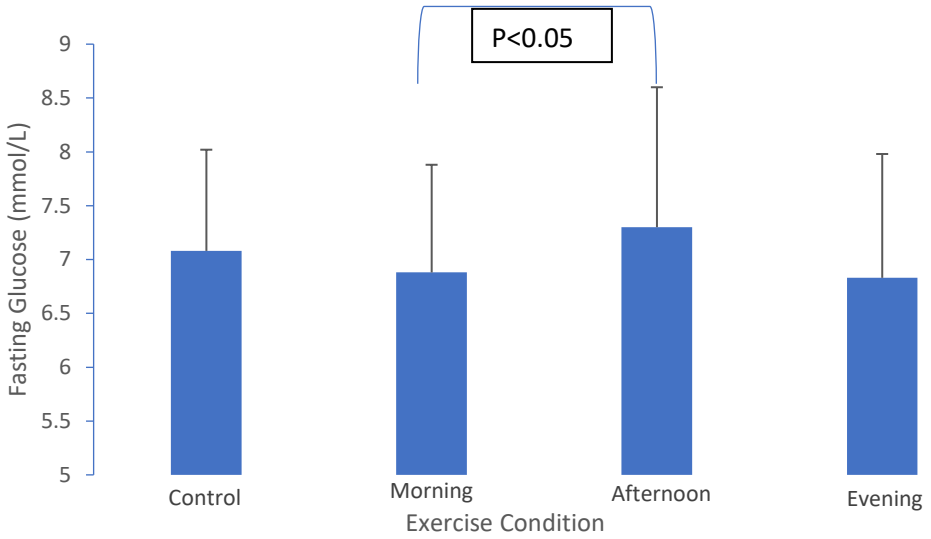

Figure 23. Fasting CGM Glucose

Chapter 5 Discussion

This study followed up on the E-PAraDiGM[65] study by comparing the exercise conditions from the original E-PAraDiGM (exercise performed 3-4 hours after lunch) to morning (pre-breakfast) exercise and postprandial exercise (20-30 minutes after the evening meal). The E-PAraDiGM study found no significant difference in 24-hour mean glucose between exercise and control[65]. We hypothesized that this was due to the timing of exercise. Our hypothesis was that exercise performed before breakfast or 20-30 minutes after the evening meal would decrease 24-hour mean glucose more than exercise performed in the afternoon. The results of this study were contrary to our hypothesis and, similar to the E-PAraDiGM protocol, no significant difference was found in the primary outcome.

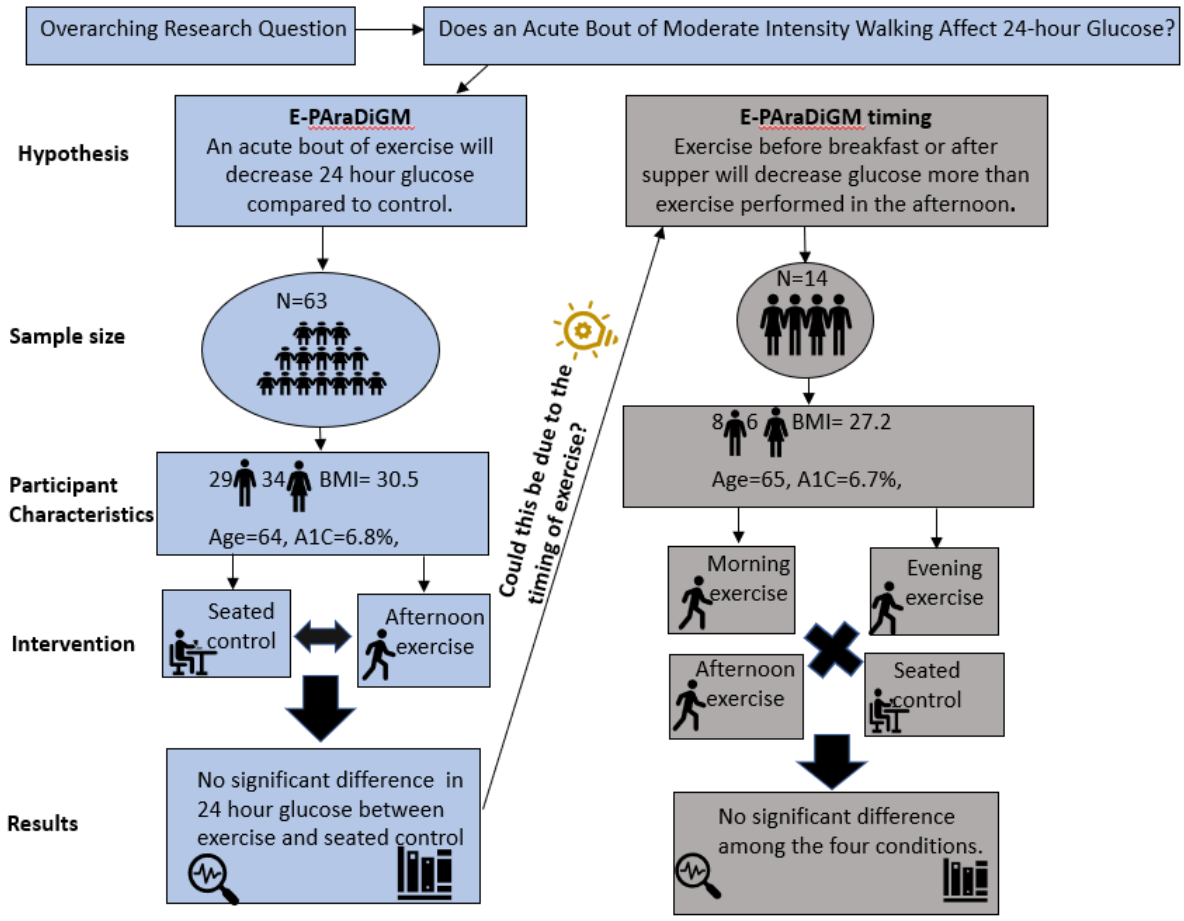

Figure 24. Similarities and differences between the E-PAraDiGM study and the present study.

5.1 Effect of Exercise on CGM outcomes

In this study, no significant difference was found in the mean 24-hour glucose among the four exercise conditions. When repeated measures t-tests are performed afternoon exercise was the only condition that was found to have a statistically significant reduction in 24-hour glucose when compared to control (-0.4 mmol/L; p=0.01). This reduction, however small is a surprising finding as the original E-PAraDiGM protocol had a much larger sample size and found no reduction in 24-hour glucose when exercise was performed in the afternoon (ref). It is important to point out that this comparison (afternoon to control) was performed as a secondary comparison and the results should be interpreted with caution due to the use of multiple comparisons without adjusting the alpha.

These results are contrary to previous studies that found a significant decrease in 24-hour glucose concentrations following an acute bout of exercise in individuals with T2D[62]. A recent meta-analysis performed by our lab compared the results of 24 short-term exercise studies using CGM. This analysis found a mean difference of -0.5 mmol/L (95% CI -0.7, -0.3) in the 24 hours post exercise[63]. When subgroup analysis was performed on these studies, it was found that those where exercise was performed in the afternoon there was no significant difference in glucose -0.0 mmol/L (95% CI -0.2, 0.2) whereas studies performing exercise in the morning fasted or after breakfast produced a mean decrease in glucose of -0.7 mmol/L (95% CI -1.0,-0.3) and -0.7 mmol/L (95% CI -1.1, -0.2) respectively[63].

The prescribed exercise type and intensity in this protocol was identical to the original E-PAraDiGM protocol. The walking protocol was chosen due to it being the preferred method of exercise for individuals with T2D[17] and was shown to be feasible and well tolerated for all participants. The average intensity of exercise that was achieved was 3.7 ± 0.5 METS as measured by indirect calorimetry. This was slightly higher than our goal intensity of 3.5 METS and slightly lower than the original E-PAraDiGM mean intensity of 3.9 ± 0.4. It is unclear whether the intensity of exercise affects 24-hour glycemia. The intensity of exercise has been shown to affect A1C response to exercise in one meta-analysis[58] but not another[55]. In a meta-analysis comparing head to head trials, it was found that high intensity exercise decreased A1C

by 0.22% more that moderate intensity exercise[96]. It is important to note that these head to head comparisons were not energy matched and that differences in intensity were much larger than what we observed between the two E-PAraDiGM protocols.

The participants in this study had very well controlled T2D as shown by a mean A1C of 6.7 ± 0.6%. It has been shown in a previous meta-analysis that the glucose lowering effect of exercise is greater in participants with an A1C over 7% (R^2=30.8 P=0.007)[55]. Similar results were found in the Diabetes Aerobic and Resistance Exercise (DARE) trial which found that participants with a baseline A1C over 7.5% had a greater decrease after a 6-month training intervention than participants whose baseline A1C was under 7.5%[57].

In our lab's meta-analysis, we used a regression to determine if elevated control glucose concentrations led to an increased glucose lowering effect of exercise. We found that participants with higher glucose during the control session have a greater glucose lowering effect in the 24-hours after exercise (R^2=0.37, P<0.001)[63]. The average glucose concentration during the control session in the present study was 7.5 mmol/L. As shown by the regression line below, most studies where participant mean glucose concentrations during the control session were in the 7-8mmol/L range have found very small, or no glucose lowering effect of exercise.

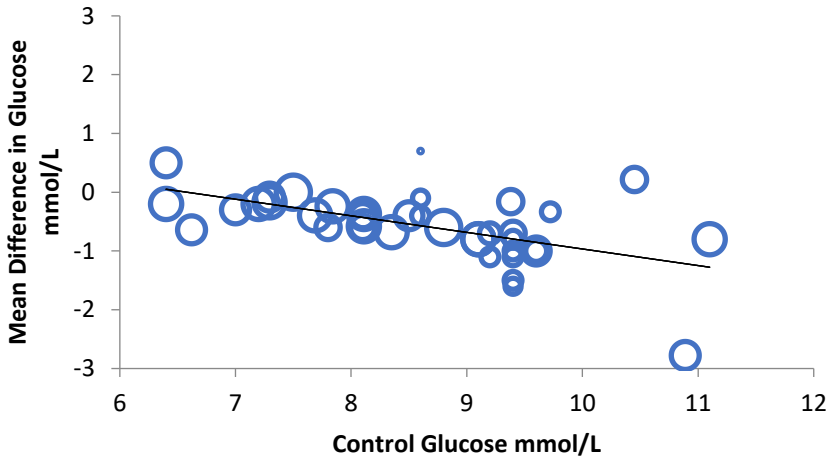

Figure 25. Meta Regression Analysis

Surprisingly, there was no overall significant difference among the four conditions with respect to postprandial glucose. This is contrary to many other studies which show a significant

postprandial glucose lowering effect after acute exercise[62]. It has been shown that the primary mechanism by which exercise improves glucose control is through increased insulin sensitivity and glucose uptake by skeletal muscle rather than an increase in hepatic insulin sensitivity[97]. Therefore, It would be intuitive to hypothesize that the effect of exercise would be most pronounced in the postprandial period due to increase glucose availability for uptake by skeletal muscle.

There are a number of possible explanations as to why exercise did not have a significant postprandial glucose lowering effect. One potential explanation could be the use of standardized meals. Participants were given all meals and snacks for two days in each condition, and our approach may have provided fewer calories and more healthy options than their normal diet. The average postprandial glucose for all four conditions was in the 8-9 mmol/L range. This is well within the current Diabetes Canada targets for glycemic control which states that people with T2D should aim for a 2-hour postprandial glucose (PPG) target of 5-10 mmol/L[43]. It is possible that the participants in our study already have very well controlled PPG and therefore the glucose lowering effect of exercise was too small to become statistically significant.

The use of the CGM allows for measurement of time in range (TIR). This is a new metric that allows researchers and clinicians to report time spent in hyperglycemia (usually defined as time >10 mmol/L) and time spent in hypoglycemia (usually defined as time <4 mmol/L.) The international consensus on CGM outcomes, has acknowledged that TIR is a valuable measure to be use alongside other glycemic outcomes to compare research interventions[98]. No significant difference in minutes spent over 10 mmol/L was found when all four conditions were compared to one another. However morning and afternoon exercise resulted in less time over 10 mmol/L when compared to the control condition. In the 24 hours following morning and afternoon exercise, participants spent 80.5 ±80.4 and 80 ±93.1 minutes in hyperglycemia compared with 135 ±116.5 minutes in the control condition. Other studies have reported similar findings that an acute bout of exercise reduced type spent in hyperglycemia[98,99,100]. However, only one study, Praet et al.,[100] reported a reduction in time >10 mmol/L with no significant different in 24-hour glucose[100]. It is unclear if there is a clinical significance associated with a reduction in time spent in hyperglycemia without a reduction in 24-hour or postprandial glucose. Time above 10 mmol/L likely reflects postprandial glucose and it is surprising that there is a significant difference in

time above 10 mmol/L in the afternoon compared to control but not in afternoon postprandial glucose compared to control. It is possible that participants did not accurately report meal times leading to an imprecise 2-hour postprandial calculation and increased variability in mean postprandial glucose.

Most of the participants (N = 12), were taking metformin. It has been shown that metformin may interfere with the glucose lowering effect acute of exercise[101,102]. The effect of metformin and acute exercise may not be additive[102]. The effect of exercise and metformin has not been shown to lead to an increase in insulin sensitivity when compared to metformin alone[102]. Studies addressing the concurrent use of metformin and exercise have shown mixed results. Erickson et al., (2017)[84] found that exercise performed after breakfast in people with T2D taking metformin led to a reduction in glucose in the 2-hour period after exercise when compared to a control condition[84]. It is interesting to note however, that the reduction was not sustained past the morning meal. Myette-Cote et al.,(2016)[90] performed a very similar study comparing metformin and exercise to a condition with no exercise and metformin treatment and found that the metformin and exercise condition led to a increased postprandial glucose iAUC. The mean 24-hour glucose and fasting glucose were not different among conditions[90]. It is possible that the use of metformin in our participants blunted the glucose lowering effect of exercise.

In summary, exercise did not decrease 24-hour or postprandial glucose among the four conditions in this study. This outcome could be explained by the characteristics of our sample (small sample size, well controlled T2D, already active), the combination of metformin and exercise therapy, and the use of standardized meals.

5.2 Effect of Exercise on Fasting Glucose

Impaired fasting glucose and impaired glucose tolerance are thought to be due to different mechanisms[103]. Although both are insulin resistant states, the site of insulin resistance is different[104]. It has been suggested that fasting glucose is related to hepatic insulin resistance, while postprandial glucose is related to insulin resistance in skeletal muscle[103]. Although no differences were found among all four conditions in mean fasting glucose, the fasting glucose following the morning condition was lower than that of the afternoon conditions when repeated

measures t-tests were performed. This is surprising, as the afternoon exercise condition had the lowest mean 24-hour glucose overall. These results should be interpreted with caution as fasting glucose was obtained using the mean of three CGM readings before a self-reported breakfast. Also, mean fasting CGM glucose following morning exercise is not significantly different when compared to control, but is significantly different from mean CGM glucose following afternoon exercise. Therefore it is difficult to draw conclusions based on this finding. Previous studies have found that acute exercise improves insulin sensitivity though improved peripheral sensitivity but not hepatic insulin sensitivity[104] and that acute exercise does not lower fasting glucose.[62]

It is unclear how many of the participants in our study experience the dawn phenomenon (see section 2.15). Though beyond the scope of the study, further analysis could be undertaken to examine CGM glucose from midnight under breakfast to look for nocturnal glucose nadirs and pre breakfast glucose[81]. This period of hyperglycemia has been shown to be due to decreased insulin sensitivity primarly to an increase in cortisol and free fatty acids but not human growth hormone (HGH) and glucagon[74] . Although the glucose tracings show a greater postprandial glucose concentation after breakfast compared to lunch and dinner, it is not apparent if this is due to the dawn phenomenon or to the composition of breakfast in comparison to lunch and dinner.

5.3 Differences in Fuel Utilization, Heart Rate and Glucose during the Exercise Session

Among the four conditions, there were significant differences in fuel utilization as estimated by RER. This difference is due to morning exercise having a greater reliance on fatty acid oxidation as shown by a lower RER. The reasons for this

The evening exercise session was performed 20-30 minutes following supper and it was hypothesized that this condition would elict the greatest reliance on carbohydrate metabolism. However, there was no difference between control, afternoon and evening exercise metabolism. This is likely due to the participants consuming an afternoon snack shortly before the afternoon exercise and control conditions. There was no specified time for the afternoon snack and many participants consumed it shortly before arriving at the laboratory for the afternoon exercise session.

Carbohydrate consumption before exercise has been shown to suppress fat oxidation for up to four hours after a meal[105]. Fasted exercise has previously been shown to result in an

increase in fat oxidation (lower RER) during exercise[106,107]. Although speculative, the pre-breakfast increase in counterregulatory hormones that is observed in the dawn phenomenon may have further contributed to an increase in fatty acid oxidation. It unknown whether the increase in fat oxidation persisted past the 50 minutes of exercise in the present study.

Heart rate was lower in the morning exercise condition compared to afternoon and evening exercise. This effect has been shown in previous studies and is likely due to a combination of decreased blood supply demand to digestive organs and the effect of less circulating metformin. Metformin has been shown to increase heart rate during exercise.[101] Since most participants were taking metformin with breakfast (after the morning exercise condition) there would be less circulating metformin in their system during the morning condition compared to the afternoon and evening conditions.

The mean reduction in capillary glucose during the 50-minute exercise session was highest in the afternoon condition -1.5 mmol/L when compared to morning -0.5 mmol/L and evening -0.4 mmol/L conditions. These results were surprising as one might expect the evening (20- 30 minutes after supper) condition to have the greatest decrease in CGM glucose as exercise is performed closest to a large meal. Chacko made the argument that beginning exercise 30 minutes after eating is best for decreasing glucose as this is the time that the greatest amount of glucose will be in the bloodstream and most readily available for uptake by skeletal muscle[66]. It has been shown that the peak postprandial glucose spike will occur at approximately 1 hour and 15 minutes after meal consumption and that in 80% of individuals with diabetes it will occur within the first 90 minutes[108]. This study also found that there was intraindividual differences in postprandial glucose with the glucose peak occurring under 30 minutes or greater than 120 minutes in 3 and 4% of participants respectively[108]. People with T2D should be cautions to rely on glucose changes during exercise as an indication of 24-hour glucose changes as these can over estimate the glucose lowering effect of exercise.

A study by Gaudet-Savard et al., (2007)[109] compared glucose responses during exercise performed at different intervals after a meal and found that exercise performed 2-5 hours after a meal led to the greatest decrease in glucose during exercise[109]. This decrease occurred regardless if participants began exercise with blood glucuose under 6 mmol/L, between 6 and 8 mmol/L and over 8 mmol/L[109]. This study found that pre-exercise glucose concentration were a determinant

of magnitude of change during exercise. The higher the pre-exercise glucose, the greater the decrease post exercise[109].

The variability of the change during exercise was very high, with some participants experiencing a much larger decrease than others. The variability was much higher in the evening condition as shown by a SD of ± 2.7 mmol/L compared to ± 1.6 mmol/L during the morning and afternoon conditions. This is an interesting result as the evening condition was performed at a standardized time interval after a standardized meal. One might expect this session to display the most consistent glucose change during exercise. The variability in response could be due to diabetic gastroparesis. Individuals with T2D have been shown to have delayed gastric emptying[110]. This gastroparesis is estimated to occur in approximately 30-50% of people with T2D[111] and could be a potential explanation of the variability in response shown here.

5.4 Limitations

The main limitation of this study was a small sample size which led to underpowered statistical comparisons. The study was powered for an effect size of 0.8 with a standard deviation of the change of 1.0, based on the Macleod et al. 2013[62], meta-analysis. The differences among conditions were much lower than 0.8 so it is difficult to reach statistical significance with a sample size of 14. However, it is unlikely that such a small reduction in glucose i.e 0.2-0.4 mmol/L is clinically relevant. We performed multiple comparison among the four conditions which led to an increased risk of committing a type 1 error. To migate this problem, we focused on three primary comparisons, as opposed to all six comparison. We also utilized a randomized crossover design to decrease confounding covariates by ensuring every participant was compared to themself.

Exercise studies present a challenge obtaining a representative sample of individuals with T2D. The participants may not be an accurate representation of the average individual with T2D as this study had participants with very well controlled T2D as shown by a mean A1C of 6.7%. There were a few participants who expressed interest in the protocol but were ineligible to due to an A1C over 9%. There was also a variety of fitness levels among the participants. Studies performed in our lab often have individuals who are already active and have well-controlled

T2D. Many of our participants were already physically active and well conditioned and others struggled with the assigned speed and grade and required a decrease.

On average the participants in the present study were very active as shown by a mean Godin Leisure Time Questionnaire score of 50.8. According to the scoring system, a score above 24 units (estimated to be greater than 14/kcal/kg/week) is classified as active[91]. Our results display a very large standard deviation (53.8) and heavily influence by an outlier scoring 227 on the instrument. When the outlier is removed the mean ±SD is 37.2 ±18.7 Only two participants in the study scored below 24 units. However, this is a self-report measure and it is possible that some participants over estimated their leisure time exercise or incorrectly filled out the instrument. Since many participants in this study already meet the Diabetes Canada Guidelines, they may not benefit as much as people who are not meeting the guidelines. Our sample may not be representative of the T2D population in general as is has been shown that approximately 60-70% of individuals with T2D are not sufficiently active[112].

The SD of the HR during exercise was 17-19 bpm depending on the condition. Some of the participants were exercising at close to 85% of their age-predicted max HR while others were exercising around 55-65%. It is unclear whether participants exercising at a higher percentage of age-predicted HR max had a greater reduction in glucose when compared to participants exercising at a lower percentage of HR.

Another limitation of this study was the use of a predicted equation to estimate resting metabolic rate and caloric needs. This equation does not take into account weight history and ethnicity and is less accurate in overweight women[113]. The used of self-reported compliance to standardized meals is another limitation of the study. The nature of the CGM allows for researchers to track glucose changes over time in free living conditions and therefore it would seem to be an added burden for participants to consume all meals in a lab setting. It is possible that participants did not accurately report the time of meal consumption and compliance to standardized meals.

5.5 Future Directions

The debate as to an optimal time for exercising in T2D continues. Short-term exercise studies have shown considerable variablility and mixed results when comparing exercise performed at different time points throughout the day. A longer term study is necessary to futher investigate the effects of training for over six weeks or more as opposed to a single bout of exercise. The effect of long-term exercise on glycemic outcomes such as A1C are well known[57,114] but to date there has never been a long-term study performed in T2D exploring the effects of exercising at different times throughout the day.

It is unknown whether a long-term study would find differences in glycemic control if exercise was performed in the fasted state compared with exercise performed in the postprandial state. A long term study would provide significant benefits as more stable glycemic outcomes such as A1C could be compared in addition to CGM outcomes. The effects of chronic versus acute exercise differ and cannot be measured in isolation[115]. Long term exercise has been studied extensively in individuals with T2D. Long-term training has been shown to decrease A1C, decrease LDL cholesterol, and increase HDL cholesterol[51,115]. One of the landmark studies on exercise training on metabolism the HERITAGE family study examined the effects of a 20-week endurance training program in healthly, sedentary people and found insulin sensitivity was improved by 10%[116].

A study that compared the effects of an acute bout of exercise and the same bout of exercise after a 6-week training session found that whole body glucose metabolism and rate of muscle glycogen synthesis were higher after training[117]. This evidence provides a significant rationale that long-term training augments the effect of a single bout of exercise and leads to greater benefits over time. It is necessary to point out that this study prescribed exercise based on a heart rate response and therefore as the week exercise intervention progressed, participants were performing more work. It is unlikely that this factor alone led to the significant difference in the training effect of long term exercise compared to the acute effect of a single bout.

It is well known that an acute exercise session leads to an increase in glucose transporter (primarily GLUT-4) number and activity[118]. Chronic exercise leads to an increase in GLUT-4 transporters in skeletal muscle that was shown to persist five days after the exercise training

sessions indicating that this effect is independent of the acute effect of exercise[119]. Chronic training also leads to an increase in capillarization in skeletal muscle[120], muscle glycogen and glucose uptake[121].

A recent review of fasted vs fed exercise [122], concluded that fasted long-term endurance training leads to greater improvements in insulin sensitivity and basal muscle fat oxidation in healthy subjects[122]. The authors suggest that these adaptations could have benefits for individuals with T2D[122]. It is not yet known if there is a difference between fasted and postprandial chronic exercise in individuals T2D. Van Proeyen et al., showed that in healthy males consuming a high fat diet (50% of daily calories), six weeks of training led to improvements in whole body glucose tolerance and insulin sensitivity in fasted training but not in postprandial training[71]. These increases in glucose tolerance and insulin sensitivity were driven by increases in GLUT 4 transporter protein and AMPK phosphorylation[71].

Despite no acute glucose lowering benefit of acute exercise performed at different times throughout the day in the present study, there is significant rationale that training in the fasted state could lead to a greater glucose lowering effect of exercise. It remains to be explored whether long term training in the fasted state would provide additional benefits to individuals with T2D when compared to post-prandial training. Since exercise is a first line treatment option for individuals with T2D and time is often a barrier to exercising, further studies exploring ways to optimize the effects of exercise are warranted.

5.6 Conclusion

Diabetes is an international health crisis and lifestyle interventions are among the foremost treatments for both the prevention and management of T2D. Since it is well-known that exercise is an effective management strategy, studies that seek to optimize exercise interventions are warranted. The use of CGM allows for a complete view of glucose fluctuations over the 12-day intervention making them valuable tools for understanding the effects of exercise on glucose.

This study followed up on the findings of the E-PAraDiGM study[65] to discern whether the timing of exercise can be optimized for individuals with T2D. This study found that 24-hour glycemia following an acute bout of exercise performed at different times throughout the day did not differ among the four conditions. Though this intervention did not find any differences, data

from the afternoon condition can be added to the E-PAraDiGM repository and may help to understand why some individuals respond to exercise and others do not. Ultimately, a long term exercise trial on the effects of fasted versus postprandial exercise is warranted to further understand the glycemic response to exercise performed at different times during the day.

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APPENDIX A

Additional Charts and Figures

Table 6. Exercise Session Outcomes

Mean ± SD	MorEX	AftEX	EvEX	CON	Within Subjects Effect	Primary Analysis (Paired t-test)	Secondary Analysis (Paired t-test)
HR (BPM)	99 ± 18	106 ± 17	106 ± 19	NA	**P<0.05**	Aft vs Mor **P=0.006** Mor vs Eve **P=0.005** Aft vs Eve P=1.000	NA
RER $VC0_2/V0_2$	0.78 ± 0.05	0.83 ± 0.05	0.84 ± 0.04	0.84 ± 0.10	**P<0.05**	Aft vs Mor **P<0.001** Aft vs Eve P=0.823 Eve vs Morn **P<0.001**	Mor vs Con **P=0.003** Aft vs Con P=0.663 Eve vs Con P=0.523
METS	3.6 ± 0.5	3.7 ± 0.5	3.7 ± 0.5	1.0 ± 0.1	**P<0.05**	Aft vs Mor p=0.055 Aft vs Eve P=0.643 Eve vs Mor **P=0.016**	Mor vs Con **P<0.001** Aft vs Con **P<0.001** Eve vs Con **P<0.001**
Glucuse (change from pre exercise) mmol/L	-0.4 ± 0.9	-1.5 ± 1.6	-0.3 ± 2.7	-0.1 ± 1.6	P=0.221	Aft vs Mor **P=0.018** Aft vs Eve P=0.123 Eve vs Mor P=0.920	Mor vs Con P=0.597 Aft vs Con P=0.067 Eve vs Con P=0.821

SD=standard deviation, MorEx=morning exercise, AftEx=afternoon exercise, EvEx=evening exercise, CON=control, HR=heart rate, BPM=beats per minute, RER=respiratory exchange ratio, VC02=volume of carbon dioxide, V02=volume of oxygen, METS=metabolic equivalent.

Table 7. CGM Outcome data

CGM Outcome	Condition	Mean ±SD	Within Subjects Effect (N=11)	Paired T-Tests (Primary analysis)	Paired T-Test (Secondary analysis)
24 hour glycemia	CON	7.6 ±0.6	Greenhouse Geisser P=0.420	AftEX vs MorEX P=0.570	AftEX vs CONEX **P=0.01**
	MorEX	7.4 ±0.7		AftEX vs EveEX P=0.423	MorEX vs CON P=0.347
	AftEX	7.2 ±0.7		MorEX vs EveEX P=0.824	EveEX vs CON P=0.447
	EveEX	7.4 ±0.7			
24 hour MAGE	CON	4.2 ±1.2	Sphericity Assumed P=0.803	AftEX vs MorEX P=0.535	AftEX vs CON P=0.102
	MorEX	3.9 ±1.3		AftEX vs EveEX P=0.856	MorEX vs CON P=0.393
	AftEX	3.9 ±1.2		MorEX vs EveEX P=0.663	EveEX vs CON P=0.556
	EveEX	3.9 ±1.3			
Mean 2hr Postprandial Glucose (all 3 meals)	CON	8.8 ±1.2	**N=10** Sphericity Assumed P=0.692	AftEX vs MorEX P=0.564	AftEX vs CON P=0.152
	MorEX	8.5 ±0.8		AftEX vs EveEX P=0.831	MorEX vs CON P=0.635
	AftEX	8.4 ±1.1		MorEX vs EveEX P=0.550	EveEX vs CON P=0.373
	EveEX	8.4 ±1.1			
Time above 10mmol/L (mins)	CON	135.9 ±116.5	Sphericity Assumed P=0.263	AftEX vs MorEX P=0.769	AftEX vs CON **P=0.031**
	MorEX	80.5 ±80.4		AftEX vs EveEX P=0.654	MorEX vs CON P=0.127
	AftEX	80.0 ±93.1		MorEX vs EveEX P=0.662	EveEX vs CON P=0.235
	EveEX	91.4 ±90.0			
Fasting Glucose	CON	7.1 ±0.9	Greenhouse Geisser P=0.311	AftEX vs Mor **P=0.003**	AftEX vs CON P=0.223
	MorEX	6.9 ±1.0		Aft vs Eve P=0.404	Mor vs CON P=0.388
	AftEX	7.3 ±1.3		Mor vs Eve P=0.979	Eve vs CON P=0.522
	EveEX	6.8 ±1.2			

Table 8. Mean 2-Hour Postprandial Glucose (Broken Down by Meal)

	Breakfast 2 hr mean ± SD postprandial	Lunch 2 hr ± SD postprandial	Dinner 2 hr mean ±SD postprandial	Within Subjects Effect Sphericity assumed	Paired t-test Primary Analysis	Paired t-test (Secondary Analysis)
CON	9.3 ± 1.5	8.7 ± 1.5	8.6 ± 1.4	**Breakfast** P=0.727 **Lunch** P=0.458 **Dinner** P=0.404	**Breakfast** AftEX vs MorEX P=0.236 AftEx vs EveEX P=0.628 MorEx vs EveEX P=0.416	**Breakfast** MorEX vs CON P=0.635 AftEx vs CON P=0.387 EveEx vs CON P=0.681
MorEX	9.5 ± 1.3	8.1 ± 1.0	8.0 ± 0.8		**Lunch** AftEX vs MorEX P=0.639 AftEx vs EveEX P=0.880 MorEx vs EveEX P=0.908	**Lunch** MorEX vs CON **P=0.035** AftEx vs CON P=0.457 EveEx vs CON P=0.143
AftEX	8.9 ± 1.0	8.3 ± 1.4	7.6 ± 1.4		**Dinner** AftEX vs MorEX P=0.452 AftEx vs EveEX P=0.594 MorEx vs EveEX P=0.924	**Dinner** MorEX vs CON P=0.302 AftEx vs CON **P=0.014** EveEx vs CON P=0.269
EveEX	9.3 ± 2.2	8.3 ± 1.4	8.0 ± 0.9			

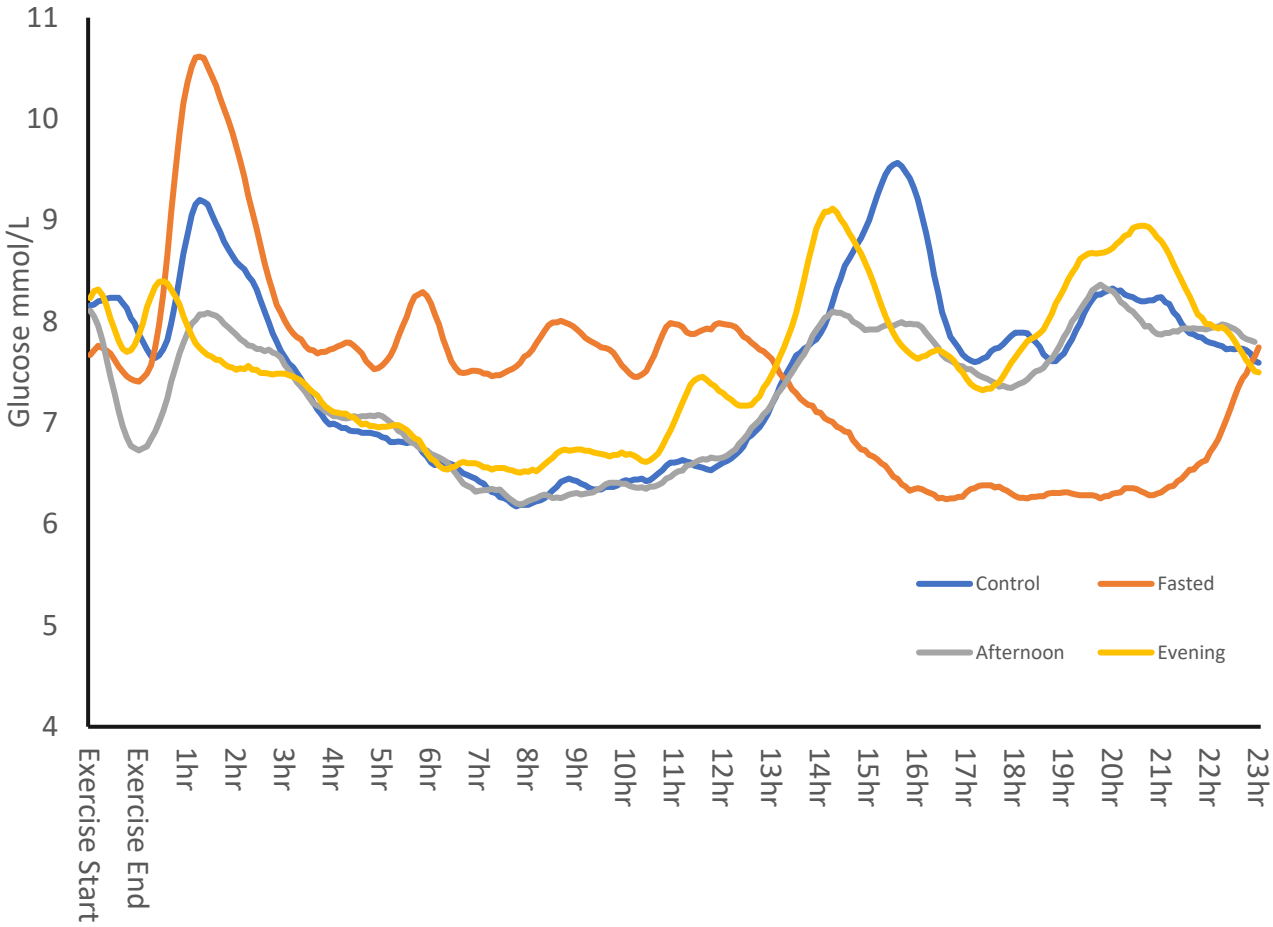


Figure 26. Glucose Tracing of all Four Conditions

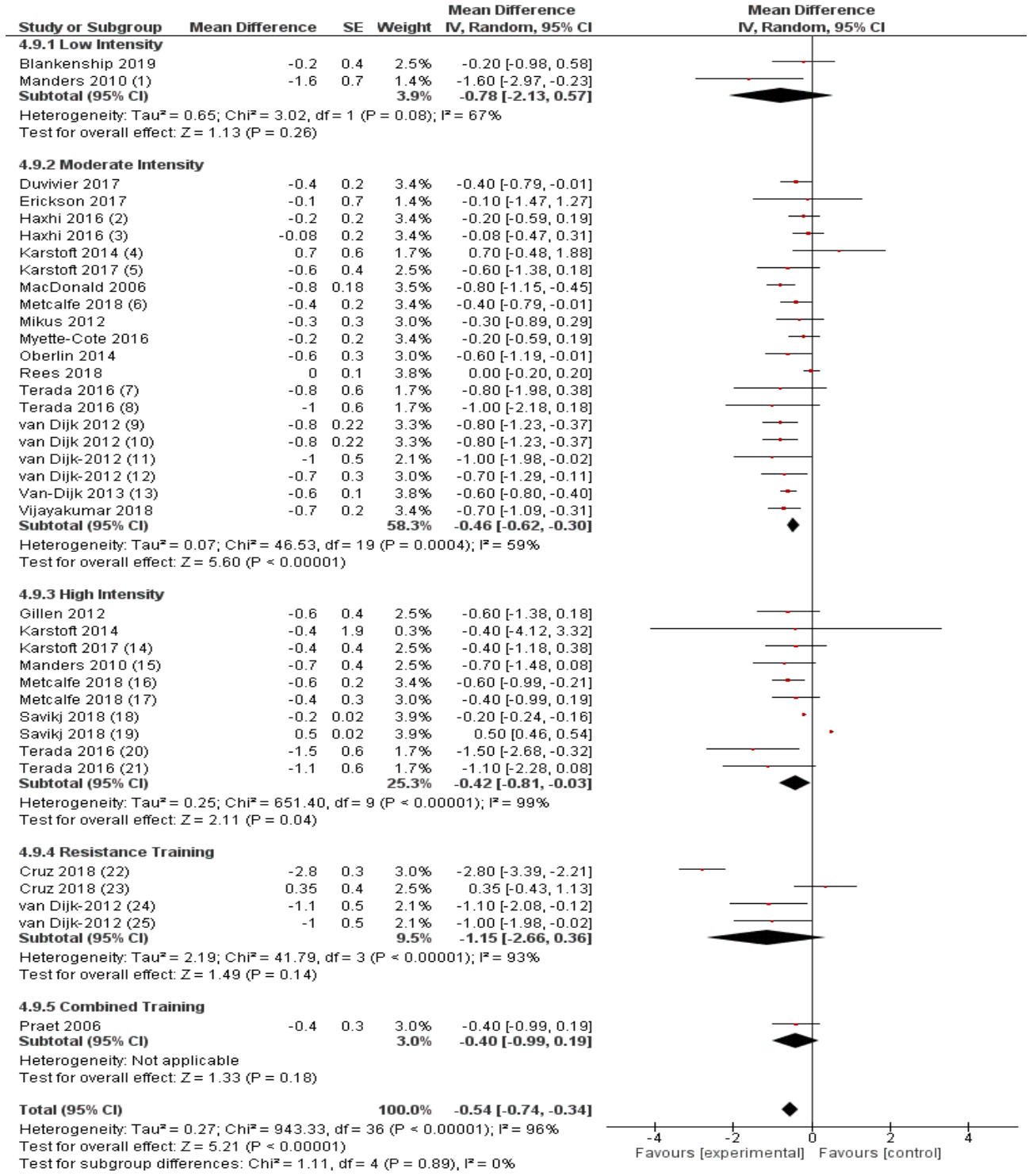


Figure 27. Exercise Type Subgroup Taken from Munan et al.[63]

APPENDIX B

Data Collection Forms

Form 2a

PARTICIPANT SCREENING AND MEDICAL INFORMATION FORM

Persons interested in taking part in the study are to complete this form with the Study Coordinator.

1. Have been diagnosed with type 2 diabetes? Y N

   If yes: How long ago? _____ (include if more than 6 months)

2. Are you between 30-90 years of age Y N

   If yes: What is your date of birth? (mm/dd/yr) _____

3. Do you currently take insulin? Y N

4. (Circle: Male Female)
   If female: When was your last menstrual cycle? _____

5. Are you able to walk for 45 minutes, continuously? Y N

6. Has your body weight changed by more than 5 lbs (~2.5 kg) within the last 3 months?
   Y N
   (Note: If weight is not stable, we could wait for stability before including)

7. Has your diabetes medication been changed in the last 3 months? Y N
   (Note: If medication not stable, we could wait for stability before including)

8. Please list any medications you are taking for diabetes, blood pressure, or cholesterol?

   _____
   _____
   _____
   _____

9. Please list other medications if applicable?
   If so, please specify. (Note: this includes Valium®, aspirin, antacids, vitamins)

   _____
   _____
   _____
   _____
   _____

(Note: treatment with corticosteroids are not eligible for this study)

10. To the best of your knowledge, have you ever suffered from any serious medical problems other than type 2 diabetes? (For example, heart attack or stroke) Y N

    If so, please specify.

    _____

    _____

    _____

    (Although not reasons for exclusion, particular note should be made of polycystic ovary syndrome (PCOS), Cushing's syndrome, musculoskeletal limitations, chronic obstructive pulmonary disease, heart disease such as possible cardiac deficiencies including arrhythmia and other heart conditions, high blood pressure, epilepsy, glaucoma, Parkinson's, hypo/hyperthyroidism and blood disorders such as anemia.)

11. Do you have a pacemaker for your heart or other implantable electronic devices? Y N

12. Are you aware of any allergies to drugs (e.g., to aspirin, penicillin, sulfonamides, phenothiazines or antihistamines)? Y N
    If so, please specify.

    _____

    _____

    _____

13. Do you have any other known allergies, including to certain foods? Y N
    If so, please specify.

    _____

    _____

    _____

14. Do you have any other dietary restrictions?
    If so, please specify.

    _____

    _____

    _____

15. Do you smoke more than one cigarette (cigar or other) per day?
    Y N

16. Do you consume alcohol? Y N
    If so, how many drinks do you consume per week on average? _____

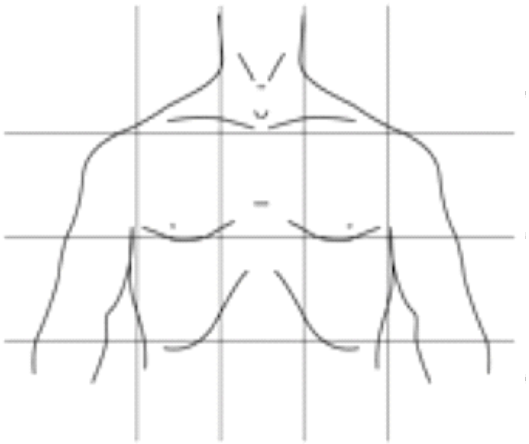
17. Within the last 12 months, have you experienced alcohol or substance abuse?
    Y N

Rose Angina Questionnaire

Please circle the appropriate response to the following questions:

1) Do you ever experience any pain or discomfort in your chest? **Yes / No**

2) Where do you get this pain or discomfort? Please mark '**X**' on the appropriate places in the diagram.



3) When you walk at an ordinary pace on level ground, does this produce the pain? **Yes / No**

4) When you walk uphill or hurry, does this produce the pain? **Yes / No**

5) When you get any pain or discomfort in your chest on walking, what do you do?

Stop / Slow down / Continue at same pace / Not Applicable

6) Does the pain or discomfort in your chest go away if you stand still? **Yes / No**

7) How long does it take to go away? **10 minutes or less / More than 10 minutes**

Definite Rose Angina is defined as chest pain or discomfort (yes to question 1) that fulfilled all of the following criteria:

(a) was brought on by exertion (yes to either question 3 or 4)

(b) was situated in the central or left anterior chest (site 4, 5, or 8 on diagram in question 2)

(c) forced the subject to slow down or stop (question 5)

(d) was relieved if the subject did so (yes to question 6)

(e) was relieved within 10 minutes (question 7)

This definition is further subcategorised into severe (grade II) if the exertional chest pain comes on when walking on level ground (yes to question 3) and not severe (grade I) if the exertional chest pain only comes on when hurrying or walking up hill (no to question 3 and yes to question 4).

*Lawler et al. J Epidemiol Community Health 2003;**57**:538-541*

Participant Information and Consent Form

Title: Does Exercise Timing Affect Glucose Levels in People with Diabetes?

Principal Investigator: **Normand Boulé PhD** **(nboule@ualberta.ca)**
(780) 492-4695

Study Coordinator: **Matt Munan** **(mmunan@ualberta.ca)**

INVITATION.

You are being asked to participate in a research study on exercise in type 2 diabetes. This study is looking at how glucose levels change when exercise is performed at different times throughout the day.

Before you make a decision one of the researchers will go over this form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form.

WHO IS CONDUCTING THE STUDY?

The study is being conducted by Dr. Normand Boulé, from the Faculty of Kinesiology, Sport and Recreation at the University of Alberta. The study is a follow-up to the Exercise-Physical Activity Diabetes Glucose Monitoring (E-PAraDiGM) Protocol.

BACKGROUND.

Exercise is recommended for people with type 2 diabetes. Often in exercise studies, researchers rely on single measures to describe the effects of exercise on blood glucose (sugar) control. For example, they measure glucose from a blood sample before and after exercise. More recently, **continuous glucose monitors (CGM)** have given researchers a wider lens to examine different aspects of glucose control. People wear these small devices to measure glucose in the body every 5 minutes. The CGM can be worn for many days in a row and gives researchers a more complete view of glucose concentrations at different points throughout the day.

PURPOSE.

This study seeks to examine the effect of a single bout of walking done at different times before or after eating on glucose levels in people with type 2 diabetes.This study will also compare two different types of continuous glucose monitors.

WHO CAN PARTICIPATE IN THE STUDY?
You may be able to participate in this study if:

- You are between the ages of 30-90 years.
- You have been diagnosed with type 2 diabetes for at least 6 months.
- You have an A1C less than 9%.
- You have never been diagnosed with heart disease, stroke, kidney disease (or any other chronic condition that may impact your ability to exercise).
- You are able to understand and comply with study requirements (e.g., attend visits during the day and eat the meals that will be provided to you).

WHAT DOES THE STUDY INVOLVE?

This study involves at total of **8 visits** to the laboratory at the University of Alberta. Each visit will last **1-2 hours** and will take place over a **2-week period**. Ideally these would be 2 weeks in a row, but they can be separated if needed.

Visit 1. Determining your eligibility (1-hour lab visit).

- **Initial Meeting.** You will come to the Physical Activity and Diabetes Laboratory (**PADL**) on the University of Alberta main campus. PADL is accessible by LRT. We will discuss any questions or concerns you may have about the study. If you agree to participate, we ask that you sign this consent form before any study procedures are done. Then you will complete an eligibility questionnaire. Questions include general information about your health, medications, and ability to exercise. We will also measure your blood pressure, heart rate and glycated hemoglobin (A1c). Your A1c will require a small finger prick to get a drop of blood. We will also assess your body fat using device called a bioelectrical impedance analysis (BIA). For the BIA, you will step on a platform, but you will not be able to feel the small current (0.0005 amps).
- **Treadmill Familiarization.** If your blood pressure is normal, you will complete 15 minutes of walking on a treadmill. This is to help you get comfortable with our suggested walking speeds and make changes if necessary. You will walk at 5 km/hr (i.e., 3.1 miles per hour.) under the supervision of an exercise professional.

Visit 2 and 5. Inserting the continuous glucose monitor (CGM) (30-minute lab visit).

You will be asked to come to PADL for a CGM insertion by a trained individual. The CGM is a small device that measures your blood glucose every 5 minutes. You will simultaneously wear 2 CGMs for the duration of the study. The CGM from Medtronic (called iPro 2) is worn on the abdomen and provides glucose data for 6 days. The CGM from Abbott Canada (called Freestyle Libre) is worn on the arm and provides glucose data for 14 days. The Medtronic CGM will need to be replaced by a new CGM after the first 6 days.

The CGM sensors have a small filament that is inserted under your skin with a small needle (less than 1 cm long). The needle is then removed and only the flexible filament remains under your skin. Tape will be placed over the CGM to hold it in place. These devices require you take finger pricks for capillary glucose measurements 4 times per day (iPro) or scan the device every 8 hours (Freestyle Libre). The CGM insertion should take no more than 5 minutes. During this lab visit you will be given a small booklet containing important information about the CGM, pedometer, and food log. You will also be given meals for the following 2 days.

Visit 3, 4, 6 and 7 Test days 1, 2, 3, and 4 (2-hour lab visit for each testing day).

For each of the test days you will arrive at the laboratory at your scheduled appointment time either in the morning before breakfast, 3-4 hours after lunch (on two occasions), or 30 minutes after dinner. You will complete a bout of walking or remain seated for 50 minutes. The order of these conditions will be random. Visit 3 must take place within 24 hours of visit 2. Visit 4 must take place exactly 3 days after Visit 3. Visit 6 must take place within 24 hours of visit 5, and visit 7 must take place exactly 3 days after visit 6. During these visits we will ask you questions about the food you ate on the previous day.

Walking Conditions. You will complete 50 minutes of walking at 5.0km/hr. The speed can be adjusted to allow you to finish comfortably. Your heart rate will be monitored during exercise. You will be asked to wear a device mask (similar to a snorkel) for a total of 10 minutes while you are walking. This will measure the amount of oxygen your body is using while you exercise. Blood pressure and capillary blood glucose will be measured before and after exercise.

Seated Control. You will sit quietly and be allowed to read, work on a computer, and/or watch a video for 50 minutes. Capillary blood glucose and blood pressure will be monitored before and after the 50 minutes of sitting.

Visit 8. CGM Drop Off (5-minute lab visit).

You will drop off your CGM at the PADL laboratory at a time convenient to you within 5 days of Visit 4.

Summary of Visits and Timeline.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Visit 2: CGM insertion and Food Journal	Standardized meals **Visit 3 Session 1** (walking conditions or sitting)	standardized meals (no lab visit)	No lab visit, no standardized meals	Standardized meals **Visit 4 Session 2** (walking conditions or sitting)	Standardized Meals (no lab visit)
Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Visit 5 Remove CGM and insert new CGM.	Standardized meals **Visit 6 Session 3** (walking conditions or sitting)	standardized meals (no lab visit)	No lab visit, no standardized meals	Standardized meals **Visit 7 Session 4** (walking condition or sitting)	**Visit 8** Standardized meals Remove CGM

CGM-Continuous Glucose Monitors

You are being asked to:

1) Show up to the lab at your scheduled appointment times.
2) Consume all standardized meals to the best of your ability.
3) Record any changes that you make to your meals in your food log.
4) Check your capillary glucose 4 times per day (i.e., finger prick glucose; supplies provided).
5) Report any noticeable changes in your health status (e.g., sickness, cold).

WHAT ARE THE POSSIBLE BENEFITS?

We hope this study will help us better understand how exercise affects glucose levels. You will receive information on how your blood glucose responds to exercise. You are not expected to receive any other benefits from participating in this study.

WHAT ARE THE POSSIBLE RISKS?

Continuous glucose monitoring. There is a small risk of infection and a very low risk of bruising from the insertion of the sensor. These could last for up to a few days. The insertion of the CGMs is done under sterile conditions by a trained researcher. The skin of some individuals is sensitive to the medical tape and can get red or itchy when the CGM is attached. There may be redness in the area where the tape was applied but this will usually disappear after a few days. The CGM also requires calibration from four capillary glucose measures per day. We will provide the capillary glucose monitor and strips. There is discomfort and a small risk of infection with these measures as well.

Adverse event during exercise. Exercise has many health benefits but it is possible that exercise will cause light headedness, muscle cramps, fatigue, nausea, and joint pain. The risks are minimized by supervision while you are walking on the treadmill. You are free to stop exercising if you feel any discomfort or do not wish to continue exercising. A questionnaire completed during screening will also ensure there is a low risk of an adverse event (e.g. heart attack) occurring with walking.

Low blood sugar. There may be a small risk of low blood sugar during or after exercise. We will assess your capillary glucose before and after exercise. This will help us make sure the appropriate steps are taken if your glucose is too low. In our experience with exercise studies in type 2 diabetes, we have not seen a hypoglycemia following moderate intensity exercise.

It is not possible to know all of the risks that may happen in a study. The researchers have taken all reasonable safeguards to minimize any known risks to a study participant.

WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, you have the right to request the withdrawal of your information collected during the study.

CONFIDENTIALITY.

During the study we will be collecting data about you. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your name will be released outside of the study investigator's office or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your information is kept private.

During research studies it is important that the data we get is accurate. For this reason, your data, including your name, may be looked at by people from: the University of Alberta auditors and members of the Research Ethics Board. By signing this consent form you are giving permission for the study investigator/staff to collect, use and disclose information about you as described above. After the study is done, we will still need to securely store your data that was collected as part of the study. At the University of Alberta, we keep data stored for 5 years after the end of the study.

COMPENSATION FOR INJURY.

If you become ill or injured as a result of this study, you will receive necessary medical treatment at no additional cost to you. By signing this consent form you are not releasing the investigator(s) and/or institution(s) from their legal and professional responsibilities. Inform the study personnel if you have been injured. They will help provide immediate aid and refer you to appropriate follow-up treatment.

REIMBURSEMENT OF EXPENSES.

Parking fees up to $15 per visit will be reimbursed. Public transportation fees (e.g. bus or LRT) will also be reimbursed up to $15 per visit.

CONTACT NAMES AND TELEPHONE NUMBER.

If you have any concerns about your rights as a study participant, please contact the Research Ethics Office at the University of Alberta: (780) 492-2615.This office is independent of the study investigators.

If you have any concerns or questions about the study, please contact the study coordinator (Matt Munan (780) 492-8079, mmunan@ualberta.ca), or the principal investigator (Normand Boulé (780) 492-4695, nboule@ualberta.ca).

Title of Project: **Exercise-Physical Activity Diabetes Glucose Monitoring (E-PAraDiGM) Protocol**

Principal Investigator	**Phone Number**
Dr. Normand Boulé PhD	(780) 492-4695
Research Coordinator	**Phone Number**
Matt Munan	(780) 492-8079

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

Who explained this study to you? _____

Signature of Research Participant _____

(Print Name) _____

Date: _____

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

Signature of Investigator or Designee _____ Date _____

FUTURE RESEARCH.

We would like your permission to contact you in the future to participate in other research studies related to diabetes and exercise. You can mark your choice below. Agreeing to be contacted does not mean you are agreeing to participate in future studies. You do not have to agree to be contacted for future research and your decision will not impact your participation in this study.

I agree to be contacted for future research: YES:____ NO:____

Baseline Assessment

Participant ID: _____ Date (dd-mm-yr):_____

1. Body Mass: 1st ___ ___ ___ . ___ Kg 3rd (if Δ>0.5cm) ___ ___ ___ . ___ Kg
   2nd ___ ___ ___ . ___ Kg **Average: ___ ___ ___ . ___Kg**

2. Standing Height: 1st ___ ___ ___ . ___ cm 3rd (if Δ>0.5cm) ___ ___ ___ . ___ cm
   2nd ___ ___ ___ . ___ cm **Average: ___ ___ ___ . ___cm**

3. Waist Circ.: 1st ___ ___ ___ . ___ cm 3rd (if Δ>0.5cm) ___ ___ ___ . ___ cm
   2nd ___ ___ ___ . ___ cm **Average: ___ ___ ___ . ___cm**

4. Hip Circ.: 1st ___ ___ ___ . ___ cm 3rd (if Δ>0.5cm) ___ ___ ___ . ___ cm
   2nd ___ ___ ___ . ___ cm **Average: ___ ___ ___ . ___cm**

5. Heart rate and Blood pressure. Cuff Size = _____

Systolic BP (SBP): Average of two consecutive measures with 5 mmHg?
(1)___ ___ ___mm Hg (2)___ ___ ___mm Hg (3)___ ___ ___mm Hg
(4)___ ___ ___mm Hg (5) ___ ___ ___mm Hg **Average SBP: ___ ___ ___mm Hg**

Diastolic BP (DBP): Average of two consecutive measures with 5 mmHg?
(1)___ ___ ___mm Hg (2)___ ___ ___mm Hg (3)___ ___ ___mm Hg
(4)___ ___ ___mm Hg (5)___ ___ ___mm Hg **Average DBP: ___ ___ ___mm Hg**

Resting Heart Rate (HR): Average of two consecutive measures with 5 bpm?
(1) ___ ___ ___bpm (2)___ ___ ___bpm (3)___ ___ ___bpm
(4)___ ___ ___bpm (5)___ ___ ___bpm **Average HR: ___ ___ ___bpm**

Blood pressure must be ≤ 160/100 mmHg to be eligible

6. A1C within last 6 months _____%

7. Within last 6 months: HDL-C _____mmol/L LDL-C _____mmol/L
   Total-Chol _____mmol/L TG _____mmol/L

8. Serum Creatinine within last year _____ µmol/L

9. For women
   a. Do you take hormone replacement therapy or contraceptives? Y N
   b. If so, please describe:

      _____
      _____
      _

   c. When was your last menstrual cycle? _____
      Note: The testing sessions should take place during the follicular phase. About ten days following first day of menstrual period in most women (may be prolonged with some contraceptives).

10. Practice/short exercise session.
    Predicted Max HR = 220- age = _____
    Predicted 70% of max HR = _____
    Gradually/safely bring the speed up to 5 kph or 3.1 mph with a 0% grade. Participants can hold rails for balance at the beginning, but try to minimize this.

	Speed (mph)	Grade (%)	HR	RPE
5 min				
10 min				
15 min				

    Ask participant: Do you think you would be able to continue at this speed for another 30 minutes? _____
    _____

11. Schedule date and time for CGM insertion
    Date: _____
    Time:_____

Form 5b - Exercise Session

Date:_____

Pre Exercise Blood Glucose:_____

Pre Exercise Blood Pressure:_____

Pre Exercise Step Count:_____

Note: The Standard speed and grade for the E-PAraDiGM protocol are written in the upper right corner of the cells. These speed and grades can be adapted as described in the manual (section 4).
Conversions: 5 km/h = 3.1 mph, 4.5 km/h = 2.8 mph, 4 km/h = 2.5 mph, 3.5 km/hr = 2.2 mph

Time (mins)	Speed (km/h)	Grade (%)	Heart Rate (bpm)	RPE	Indirect Calorimetry
0 - 5	3.5	0%			
5 - 10	5	0.5%			
10 - 15	5	0.5%			
15 - 20	5	0.5%			
20 - 25	5	0.5%			
25 - 30	5	0.5%			
30 - 35	5	0.5%			
35 - 40	5	0.5%			
40 - 45	5	0.5%			
45 - 50	3.5	0%			

Post Exercise Blood Glucose:_____

Post Exercise Blood Pressure:_____

Post Exercise Step Count:_____

Time of Dinner:_____
Additional Comments:

RATING OF PERCEIVED EXERTION

0	NOTHING AT ALL
1	VERY LIGHT
2	FAIRLY LIGHT
3	MODERATE
4	SOMEWHAT HARD
5	HARD
6	
7	VERY HARD
8	
9	
10	VERY VERY HARD (MAXIMAL)

Seated Control Session

Date:_____

Time of Arrival:_____

Pre Seated Control Blood Glucose:_____

Pre Seated Control Blood Pressure:_____

50 Minute Seated Control Start Time: _____

Time (mins)	Indirect Calorimetry
0 - 5	
5 - 10	
10 - 15	
15 - 20	
20 - 25	
25 - 30	
30 - 35	
35 - 40	
40 - 45	
45 - 50	

Post Seated Control Blood Glucose:_____

Post Seated Control Blood Pressure:_____

Time of Dinner:_____

Additional Comments:_____

Sample Participant Menu

DAY 1

Female

RMR (kcal/day) = 665.0955 + 9.5634W + 1.8496H - 4.6756A W=49.3 H=141.2 A=65

Caloric Target: 1531.32

	TOTAL CALORIES	CHO (g)	FAT (g)	PROTEIN (g)
BREAKFAST				
Milk Carton (237ml)	130	12	5	8
Bread, whole wheat, commercial (2 slices)	240	44	3	10
1 tbsp jam	25	6	0	0.1
TOTALS	**395**	**62**	**8**	**18.1**
SNACKS				
Roasted Almonds (~20)	170	5.5	15	6.3
TOTALS	**170**	**5.5**	**15**	**6.3**
LUNCH				
6'' Subway, Turkey Breast & Ham (with cheese & mayo)	450	48	20	20
Apple, med	80	22	0	0
TOTALS	**530**	**70**	**20**	**20**
SNACKS				
Carrots, chopped, 1 cup	41	9.58	0.24	0.93
Ranch Dip	160	3	16	1
TOTALS	**201**	**12.58**	**16.24**	**1.93**
Dinner				
Lean Cuisine Grilled Chicken and Vegetables (285g)	250	30	6	19
TOTALS	**250**	**30**	**6**	**19**
DAILY TOTALS	**1546**	**180.08**	**65.24**	**65.33**

Table 9 Commonly Used Foods with Macronutrient Contents

FOOD ITEM	Kcal	CHO (g)	Fat (g)	Protein (g)	CHO (%)	Fat (%)	Protein (%)	Total (%)	Fiber	Sugar
FRUITS & VEGGIES										
Banana, med	110	29	0	1	98%	0%	4%	102%	4	21
Apple, med	80	22	0	0	98%	0%	0%	98%	5	16
Orange, med	70	21	0	1	100%	0%	6%	106%	7	14
Grapes, 1 cup	69	18.1	0.16	0.72	102%	2%	4%	109%	0.9	15.48
Blueberries, 1 cup	57	14.49	0.33	0.74	93%	5%	5%	104%	2.4	9.96
Whole Strawberries, 1 cup	32	7.68	0.3	0.67	84%	8%	8%	100%	2	4.66
Carrots, chopped, 1 cup	41	9.58	0.24	0.93	79%	5%	9%	93%	3	4.54
BREAD/SPREADS										
Bread, whole wheat (2 slices)	173	33	2	9	71%	10%	21%	102%	5	4
Peanut Butter (1 tbsp)	95	3	8	4	11%	76%	17%	103%	1	1.5
Jam (1 tbsp)	42	11	0	0	100%	0%	0%	100%	1	10
Hummus (2 tbsp)	50	4	3	2	27%	53%	19%	99%	2	0
YOGURT										
Liberte 0% Vanilla Yogourt, 3/4 cup/ 175g	140	20	0	15	56%	0%	43%	99%	1	19
Oikos 2% Vanilla Yogourt, 150g	150	19.5	2.25	12	52%	14%	32%	98%	0	15
Liberte Apricot Museli Cups, 150g	160	20	3.5	11	50%	20%	28%	97%	0	17
Liberte Apple Museli Cups, 150g	160	21	3.5	11	51%	20%	28%	98%	1	18
PC Vanilla with Granola 2% Greek ,130g	170	23	4	12	53%	21%	28%	102%	1	13
BARS										
Natures Path Peanut Choco Crunch Granola Bar (2bars, 40g)	190	27	8	4	54%	38%	8%	100%	3	8
Natures Path Apple Pie Crunch Granola Bars (2 bars, 40g)	190	27	8	3	54%	38%	6%	98%	3	8
Natures Path Honey Oat Crunch Granola Bars (2 bars, 40g)	190	28	7	3	56%	33%	6%	95%	3	9
Cliff, Chocolate Chip Bar, (68g)	250	43	5	9	66%	18%	14%	98%	4	23
Cliff, Chocolate Chip Peanut Crucnch Bar (68g)	250	40	6	11	61%	22%	18%	100%	4	21
Kelloggs, All-Bran Honey Nut Bar (42g)	180	29	8	3	58%	40%	7%	104%	6	13
Kelloggs, All-Bran Oatmeal Cinnamon	180	29	8	3	58%	40%	7%	104%	6	12
Kelloggs, Special K, Cranberries & Almonds Bar (33g)	150	21	6	3	53%	36%	8%	97%	2	12
Kelloggs, Special K, Protein Double Chocolate Bar (45g)	170	24	5	10	51%	26%	24%	101%	5	15

CEREALS/GRANOLAS/NUTS										
Kelloggs, Special K, Vanilla Almond Cereal (3/4cup, 29g)	110	24	1	2	84%	8%	7%	99%	2	8
Kelloggs, Special K, Vanilla Low Fat Granola (1/2cup, 54g)	210	42	3	6	75%	13%	11%	100%	5	10
Natures Path, Pumpkin Flax Granola (3/4cup, 55g)	260	37	10	6	53%	35%	9%	97%	5	10
Natures Path, Flax Plus Oatmeal (50g)	210	38	3	6	68%	13%	11%	92%	5	10
PC Blue Menu, Maple & Brown Sugar Steel Cut Oats Instant Oatmeal (45g)	170	34	2.5	5	74%	13%	12%	99%	5	9
PC Blue Menu, Omega-3 Regular Whole Grain Instant Oatmeal (45g)	180	31	3.5	5	63%	18%	11%	92%	5	0
PC Blue Menu, Omega-3 Cranberry & Apple Whole Grain Instant Oatmeal (45g)	180	33	3	5	69%	15%	11%	95%	4	9
Dry Roasted Whole Almonds, 100g	597	19.1	53.2	21.3	9%	80%	14%	104%	10.77	4
PREPARED MEALS										
Subway Sandwiches: on white or whole wheat, no cheese, no condiments such as mayo.										
6" Subway, Roast Beef	290	46	4.5	17	60%	14%	23%	97%	5	7
6" Subway, Turkey Breast & Ham	290	47	4	18	61%	12%	25%	99%	5	7
6" Subway, Veggie Delight	230	44	2.5	8	72%	10%	14%	96%	5	6
Subway Salads: without dressing (can add specific dressing on website)										
Subway Oven Roasted Chicken Salad	120	9	3	15	23%	23%	50%	96%	4	4
Subway Turkey Breast Salad	110	12	2.5	11	36%	20%	40%	97%	4	5
FROZEN MEALS										
Lean Cuisine, Grilled Chicken Carbonara (244g)	280	38	8	21	53%	26%	30%	109%	2	4
Lean Cuisine, Grilled Chicken & Vegetables (285g)	250	30	6	19	46%	22%	30%	98%	3	4
Amy's Light & Lean Spinach Lasagna	250	40	5	11	60%	18%	18%	96%	5	6
Amy's Bean & Cheese Burrito (6.0 oz)	310	46	9	11	55%	26%	14%	95%	7	1
PC Blue Menu, Roasted Vegetable Lasagna (300g)	310	46	7	15	56%	20%	19%	96%	5	10
PC Blue Menu, Italian Lasagna (283g)	280	36	7	18	49%	23%	26%	98%	3	7
PC Blue Menu, Shepards Pie (275g)	300	28	9	28	35%	27%	37%	100%	3	6
PC Blue Menu, Chicken Carbonara (280g)	280	36	6	21	49%	19%	30%	99%	3	5
BEVERAGES										
Ensure, Milk Chocolate	220	33	6	9	59%	25%	16%	100%	1	15
Ensure, Vanilla	220	32	6	9	58%	25%	16%	99%	0	15
Glucerna, Vanilla (237 mL)	225	26.7	8.2	11.3	44%	33%	20%	97%	4.1	0
Glucerna, Vanilla (100 mL)	95	11.3	3.4	4.8	44%	32%	20%	96%	1.7	0