Carbohydrate Supplementation During Prolonged Aerobic Exercise for People Living with Type 1 Diabetes on Insulin Pump Therapy: The ExCarbs Study

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ABSTRACT

Moderate intensity exercise increases the risk of hypoglycemia in individuals with type 1 diabetes, making exercise more difficult in this population. The objective of this thesis was to assess the safety of three different carbohydrate and/or insulin strategies during fasted prolonged exercise and in recovery. Fifteen individuals with type 1 diabetes completed three 120-min treadmill exercise (~45% of VO_2peak) visits in a randomized crossover design. The three strategies included: 1) carbohydrate consumption of 0.3 g/kg/hr; 2) 50% basal rate reduction set 90 min pre-exercise; and 3) carbohydrate consumption of 0.3 g/kg/hr and 50% basal rate reduction at exercise start. Blood glucose level was higher in arm 3 compared to arm 1 and 2 after 105 min of exercise ($P < 0.05$), all with similar hypoglycemia incidence during exercise and in recovery. In arms 1, 2, and 3 the change in blood glucose was -2.7 ± 3.4 mmol/, -1.9 ± 2.5 mmol/L, and 0.3 ± 2.6 mmol/L respectively. Arm 2 had a lower RER (0.79 ± 0.04 vs 0.83 ± 0.04), increased ketones (0.4 ± 0.3 mmol/L vs 0.1 ± 0.1 mmol/L), higher net loss of energy (859.7 ± 239.6 kcal vs 709.2 ± 217.4 kcal), increased fat oxidation (0.51 ± 0.2 g/min 0.39 ± 0.1 g/min), and increased glucagon (30.9 ± 22.3 pg/mL vs. 18.1 ± 8.9 pg/mL) at exercise end, compared to arm 1 (all $P < 0.05$). Overall, all strategies had safe glucose levels throughout exercise, with arm 2 having the highest fat oxidation levels and improved counter regulatory function. These three strategies are all viable options to safely exercise with type 1 diabetes, depending on the goal of exercise and the planning of exercise.

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ABBREVIATIONS

AP	Artificial pancreas
APC	Antigen presenting cell
ATP	Adenosine triphosphate
BG	Blood glucose
BRR	Basal rate reduction
CaMKII	Calmodulin-dependent protein kinase II
CGM	Continuous glucose monitor
CHO	Carbohydrate only supplement
Combo	Combination of insulin reduction and carbohydrate supplement
CSII	Continuous subcutaneous insulin infusion
DKA	Diabetic ketoacidosis
EE	Energy expenditure
ExCarbs	Exercise carbohydrates
FFA	Free fatty acid
GLUT4	Glucose transporter 4
GV	Glycemic Variability
HR	Heart rate
HRR	Heart rate reserve
HIIT	High-intensity interval training
HbA_{1c}	Glycated hemoglobin
HPA	Hypothalamic pituitary adrenal
ISF	Insulin sensitivity factor
IFN	Interferon
IPAQ	International Physical Activity Questionnaire
MARD	Mean absolute relative difference
MDI	Multiple daily injections
PAR-Q+	Physical Activity Readiness Questionnaire for Everyone
RER	Respiratory exchange ratio
RPE	Rate of perceived exertion
SMBG	Self-monitoring of blood glucose
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TDD	Total daily dose
VO_{2max}	Maximum volume of oxygen consumption
VO_{2peak}	Peak volume of oxygen consumption

1.0 Introduction and Background

Moderate intensity exercise causes glucose to drop and frequently results in hypoglycemia in individuals with Type 1 Diabetes (T1D). In order to prevent this drop in blood glucose (BG), individuals with T1D have different options, including a meal bolus reduction, basal rate reduction (BRR) or carbohydrate feeding.

An insulin bolus reduction for a meal prior to exercise requires pre-planning and increases the risk of hyperglycemia before exercise (1,2). Exercise has been shown to only delay the peak in BG caused by under-bolusing rather than prevent it (2). A BRR also requires pre-planning in order to prevent the drop in BG during exercise. A hypoglycemia-predicted basal rate suspension algorithm, designed to suspend insulin infusion when BG was predicted to drop below 4.4 mmol/L within 30 minutes, still resulted in hypoglycemic events 32% of the time with only 30 minutes of exercise (3). In another study testing aggressive BRRs at the onset of exercise, the mean BG still decreased on average by 3.3 mmol/L after only 30 minutes of exercise (4). The Omni-TIME study showed that aggressive BRRs were required 90 minutes in advance of exercise to prevent exercise-induced hypoglycemia (5). Advocates for the newer insulin delivery systems which are controlled by BG levels must consider their limited capacity to prevent a drop in BG with unplanned aerobic exercise without carbohydrate feeding. Most research groups now acknowledge that some carbohydrate feeding will be necessary for insulin delivery systems, yet questions remain about the timing and amount of carbohydrate feeding required to prevent exercise-induced BG excursions and the impact of time of day, as hormonal responses during exercise of the same modality have been shown to differ between morning and afternoon (6,7).

The effects of carbohydrate feeding on the glycemic responses to exercise has been studied in patients living with T1D. Carbohydrate dose clearly varies depending on the timing of exercise

following a meal and the duration of exercise. In published studies, the carbohydrate dose ranges from ~0.4-1.6g/kg/hr, but the results are inconsistent and the carbohydrate dosage is typically not calculated based on body weight (8–12). One study found BG increased by 2.6 mmol/L during 45 minutes of cycling when 30g carbohydrates was ingested in the morning fasted state (7). Similarly, a recent study under Dr. Riddell's supervision found that 40g of carbohydrates was excessive, causing hyperglycemia during 45 minutes of brisk walking in the fasted state (13). This may be due to a greater counterregulatory response (cortisol and perhaps other hormones) during early morning exercise, thus suggesting that far less carbohydrates may be needed for morning versus afternoon exercise.

BRRs and meal bolus reductions need to be made in advance of aerobic exercise to prevent a drop in glycemia. Basal rate suspension at exercise onset is not effective at preventing this drop in BG and it can lead to increased hyperglycemia after exercise (14). However, because it is not always possible to pre-plan exercise, effective strategies are needed for spontaneous exercise bouts. An individual dose of carbohydrate supplementation for spontaneous aerobic exercise, based on body size and time of day, needs to be established as a preventative measure for hypoglycemia in individuals with T1D. Furthermore, few studies have examined aerobic exercise lasting longer than 60 minutes in the fasted state. Through further investigation we will have a better understanding of changing carbohydrate needs as exercise duration increases.

2.0 Review of Scientific Literature

2.1 Glucose Metabolism in Healthy Individuals

2.1.1 Dietary Carbohydrates

Dietary carbohydrates are found in a large variety of foods, which include sugars, starches and fibres (15). After ingestion, carbohydrates are broken into monosaccharides that can move across the intestinal wall and into the circulatory system to be transported to the liver. Hepatocytes either pass the glucose on through the circulatory system or store excess glucose as glycogen (16). Monosaccharides can then be utilized during cellular respiration through glycolysis to produce adenosine triphosphate (ATP).

2.1.2 Islet of Langerhans

There are at least five intermingled endocrine cells in the islet of Langerhans within the human pancreas. These endocrine cells produce hormones including insulin from the β-cells, glucagon from the α-cells, pancreatic polypeptide from the γ-cells, somatostatin from the δ-cells, and ghrelin from the ε-cells (17).

When glucose enters the circulatory system, it must be taken up by muscle or adipose tissue to maintain blood glucose (BG) regulation. This is done via an insulin mediated pathway called glucose-stimulated insulin secretion (18). Insulin stimulates glucose transport up to 40-fold in adipocytes compared to fasting conditions (19). The rate-limiting factor in this process is the number of glucose transporters present in the plasma membranes of the cells. Insulin acts on these cells by altering the distribution of glucose transporter 4 (GLUT4) from intracellular stores to the plasma membrane (20,21). GLUT4 are present in both adipose tissue and skeletal muscle. They fuse with the cell's plasma membrane via SNARE proteins (22). Stimulators of GLUT4 expression

or translocation can therefore improve insulin sensitivity (21). Following insulin secretion and glucose uptake, GLUT4 are recycled back into the cell for storage (22).

A counterregulatory hormone to insulin is glucagon, which also plays a critical role in maintaining BG levels. The glucagon producing α-cells contain insulin receptors which allows for intra-islet communication and the regulation of glucose metabolism (23). Glucagon promotes hepatic glucose output through increased glycogenolysis and gluconeogenesis and decreased glycogenesis and glycolysis (24). For these reasons, glucagon is released into the bloodstream when BG levels are low, such as in a fasted state. During these fasted states, insulin levels are also low. However, following a meal, glucagon declines and insulin rises, promoting liver glucose uptake, glycogen synthesis and suppressed production of glucose (25). Effective glucose regulation relies on the body's ability to sense BG levels and release islet hormones efficiently (17).

2.1.3 Cortisol

The interplay between insulin and glucagon allows BG levels to be maintained in a very tight range of 4.0 to 6.0 mmol/L (26). Other hormones in the body can also impact glucose homeostasis. For example, glucocorticoids are known to impact insulin resistance (27). Cortisol is a glucocorticoid produced in the adrenal gland and released into the blood. Most cells have cortisol receptors and therefore, cortisol has many different actions such as playing a role in inflammation, blood pressure regulation and memory formulation (28). Cortisol is released in a diurnal rhythm, meaning that it is high in the early morning and decreases throughout the day (29). The highest secretion of cortisol is seen around hour six of sleep up until the first hour of waking (30). The secretion of cortisol is mainly controlled by the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol affects the metabolism of carbohydrate, fats and proteins. Excess cortisol is associated

with glucose intolerance by opposing the action of insulin (29) and stimulating glucagon release (31). Cortisol infusion in healthy individuals stimulates lipolysis (31). Healthy individuals that have interrupted sleep patterns have also been found to have decreased insulin sensitivity likely due to increased cortisol levels (32). Since cortisol increases insulin resistance, in order to regulate BG levels in the early morning, there is a transient rise in insulin to prevent hyperglycemia.

Higher cortisol in the evening is predictive of the development of impaired glucose tolerance or development of type 2 diabetes (T2D) (33). Although cortisol impairs insulin action, cortisol's influence on adipose tissue metabolism is dependent on insulin levels. If insulin levels are low, cortisol stimulates lipolysis (34), on the other hand, if insulin levels are high, cortisol stimulates lipogenesis (35). Taken together, cortisol levels impact glucose oxidation and endogenous glucose production, impacting glucose homeostasis (36).

2.1.4 Ketone Metabolism

Under conditions where nutrients are not readily available, such as in fasted states, post-exercise, or when adhering to a low carbohydrate diet, ketone bodies can provide energy (37). Ketone bodies serve as fuel for tissues such as the brain, heart, or skeletal muscle, and spare the supply of glucose by reliance on fat as a substrate (38). This occurs when glucose oxidation decreases. Ketones are produced predominantly in the liver and then transported to other tissues for oxidation (37). The circulating levels of ketone bodies are determined by the rate of production and utilization. When levels of ketone bodies are elevated, the body is in a state of ketosis, which can quickly be abolished by the administration of glucose or the main factor, insulin (39). Under regular conditions, individuals typically have ketone levels <0.5 mM, however they can reach up to 7.5 mM during prolonged fasting or exercise conditions when insulin is low (40,41). When

circulating ketones reach abnormally high levels in the body, they can interfere with normal cellular functioning.

2.2 Metabolism During Exercise

2.2.1 Glucose Metabolism

Exercise impacts glucose metabolism in different ways. In general, exercise augments glucose uptake and insulin sensitivity, resulting in metabolic and transcriptional changes. Exercise can contribute to the transcription of GLUT4 in healthy individuals. The exact mechanism is still being studied, but muscle contraction causing elevated Ca^{2+} in the cytosol is thought to increase GLUT4 expression through the activation of the calcium/calmodulin-dependent protein kinase II (CaMKII) signaling cascade (42). Exercise also increases the AMP/ATP ratio, activating the AMPK pathway and augmenting GLUT4 gene expression (21). Therefore, people with high levels of activity tend to have increased expression of GLUT4 (43).

Exercise, specifically the muscles contracting, can also cause GLUT4 to translocate to the plasma membrane, promoting the utilization of glucose for energy (22,44). In both healthy individuals, and those with type 2 diabetes, an acute bout of cycling exercise activated the translocation of GLUT4 in skeletal muscle by 71-74% compared to rest (45). This cellular mechanism activated by exercise provides evidence for enhancing muscle glucose uptake, despite altered insulin sensitivity.

Substrate metabolism is complex depending on the duration and intensity of exercise being performed. One study showed that an increase in plasma glucose uptake was seen with increasing exercise intensity, whereas when intensity was held constant at 65% VO_{2max}, plasma derived substrate oxidation increased over time (46). In general, moderate intensity exercise increases whole body glucose uptake by 2-3mg/kg/min, which translates into a glucose requirement of 8.4

to 12.6g for 60 minutes of exercise in a 70kg individual (47). In response to this increased demand of glucose and increased translocation of GLUT4 to the plasma membrane, insulin levels decrease and glucagon levels increase. This increase in glucagon allows for glucose production from the liver to match increased glucose utilization maintains BG levels (48). This heightened activity of the GLUT4 proteins during exercise remains elevated during recovery, most likely as a way to replenish glycogen stores (49).

2.2.2 Fasted and Prolonged Exercise

Exercising immediately after a meal or consuming carbohydrates during exercise stimulates BG to contribute to the increased energy demand by contracting muscles (50,51). This fed state also allows athletes to oxidize carbohydrates from sources other than muscle glycogen (52). However, exercising in the fasted state or following a high-fat meal, stimulates energy from fat oxidation (53). The most efficient way to oxidize fat is to lower carbohydrate intake that results in nutritional ketosis (54). A meta-analysis of exercise performed in the fasted state versus fed concluded that fasted exercise induces higher fat oxidation, with lower plasma insulin and glucose levels (55). Consequently, individuals exercising in the fasted state may fatigue faster and reach hypoglycemia thus limiting their performance (52). Individuals may choose to exercise in the fed state when performing longer duration activities to prevent fatigue or choose to exercise in the fasted state if weight loss by increased fat oxidation is the goal. There is some evidence to suggest that training in the fasted state may lead to metabolic adaptations to prevent fatigue (56) and improved basal muscle fat uptake capacity and oxidation (57).

Exercise duration also impacts the primary fuel source used. As duration increases, fat oxidation increases and carbohydrate oxidation decreases. This is likely due to a reduction in muscle glycogen stores (58) leading to a greater reliance on lipids.

2.2.3 Cortisol Response

Different types of exercise can also stimulate the HPA axis, resulting in an increase in cortisol levels (59). Salivary cortisol increased compared to rest values in 12 female cyclists after training, and this increase correlated with the increase in training load (60). A similar increase in cortisol in response to high-intensity exercise was also observed in both competitive athletes and sedentary individuals (61). However, a study in 12 males performing 30 minutes of exercise at varying intensities, found that the cortisol response was elevated in the higher intensity activities, with no significant change in cortisol at low intensity exercise (62).

2.2.4 Sex Differences

There are differences in metabolism based on sex when performing intensity matched exercises. Women tend to have lower respiratory exchange ratios (RERs) during moderate intensity exercises, which indicates less reliance on carbohydrates for oxidation (63). Females thus tend to derive more energy during exercise from fat oxidation (64). Despite this difference in fuel utilization, males typically have a lower body fat percentage compared to females (64). Females also have less reliance on glycogen from muscle and the liver during this type of exercise (63) and reduced O_2 carrying capacity (65). The main controller of these differences are estrogen levels in females compared to males (63). Other factors may also play a role, such as differences in free fatty acid (FFA) levels due to higher lipolysis in females and action of other hormones (64).

The different phases of the menstrual cycle in females also play a role in exercise metabolism. During the luteal phase when estrogen and progesterone are elevated, females use less glycogen than males, but this is not seen during the follicular phase (66). There is also evidence to suggest that estrogen enhances performance during endurance exercise by altering substrate metabolism, whereas progesterone antagonizes this (67). Estrogen promotes glucose availability

for carbohydrate metabolism to be used as the main fuel source, whereas progesterone can inhibit this (67). A study looking specifically at fuel metabolism in females during moderate-intensity exercise found no differences between the different phases of the menstrual cycle (68). The females during the luteal phase did however have higher glucose and insulin levels compared to the early follicular phase (68).

2.3 Type 1 Diabetes

2.3.1 Pathogenesis

T1D is an autoimmune disease characterized by the destruction of β-cells in the pancreas resulting in an inability to produce insulin, thus causing a lifetime reliance on exogenous insulin therapy. People with T1D make up 5-10% of the diabetic population in Canada, around 300,000 people (69). A more recent longitudinal study of T1D incidence in the United States found the highest incidence was in youth aged 10 to 14 years old, with an increase in incidence rate ratio in males compared to females (70). T1D is occurring more frequently in the United States but varies strongly from region to region (70). The incidence of T1D is increasing worldwide by three percent annually (71) and can cause life expectancy to be shortened by as much as 15 years (69).

Although the exact cause of T1D remains unknown, it is suggested that the combination of genetic susceptibility (72) and environmental triggers cause an upregulation of interferon(IFN)-α and a downregulation of T regulatory cells (73) leading to the production of autoantibodies against autoantigens, allowing CD4+ and CD8+ T cells to destroy β-cells (73). Islet antigen presenting cells (APCs) are highly active in antigen presentation in autoimmune diabetes of mice (74), which is believed to be central to the development of T1D. However, it is not known how the antigenic material is transferred from β-cells to the APCs (74). With few to no β-cells, insulin production is minimal or non-existent leading to hyperglycemia. Autoantibodies against islet antigens are

actually detected prior to clinical onset of T1D, suggesting that these events precede hyperglycemia for months to years, as it takes time for the majority of the β-cells to be destroyed (73). Individuals can be tested by TrialNet Pathway to Prevention Study for anti-islet autoantibodies to determine if they are at risk of developing T1D (73). Individuals with two or more anti-islet autoantibodies were found to have a 70% risk for developing T1D within 10 years and almost 100% risk in their lifetime (75). Relatives of individuals with T1D screened through TrialNet that have a high chance of developing the disease are offered close monitoring and given access to prevention trials (76,77). Once the disease has progressed to having clinical hyperglycemia, common symptoms of undiagnosed T1D are polyuria, polydipsia, polyphagia and severe weight loss (78).

2.3.2 Treatment- Exogenous Insulin

The only treatment for T1D is exogenous insulin, through multiple daily injections (MDI) or a continuous subcutaneous insulin infusion (CSII). Research has led to modifications in the production of exogenous insulin to peak faster to better mimic endogenous insulin production (79). A commonly used insulin is insulin aspart which peaks earlier and returns to baseline faster than the previously used regular insulin (80). This is attributed to more rapid absorption from subcutaneous tissues. MDI patients use insulin aspart for a bolus of insulin for carbohydrate intake or to correct hyperglycemia. Insulin aspart is used in combination with insulin glargine, a long-acting insulin, which provides the minimum amount of insulin needed throughout the day, called a basal rate. CSII is an intensive insulin therapy delivered through an insulin pump that uses only insulin aspart for both delivery of small doses throughout the day to serve as a basal rate and manually added boluses for food and correction doses. CSII allows for greater flexibility as the user can temporarily adjust their basal rate throughout the day and give multiple boluses of insulin

as needed; for example, before a meal. The insulin pump used for CSII uses inputted BG and carbohydrate values to calculate the bolus of insulin, taking into account the amount of active insulin previously delivered to the body. In order to use CSII, the basal rates for the 24 hours of the day, the insulin-to-carbohydrate ratio and the insulin sensitivity factor; the expected drop in BG levels if one unit of insulin is delivered, must be entered into the insulin pump (81). It is typically suggested that the basal rate should cover approximately 50% of total daily dose (TDD) of insulin, however current research is shifting towards 30-40% of TDD (81). A meta-analysis found that CSII is cost-effective compared to MDI, and is most likely associated with reductions in average glucose control, hemoglobin A_{1c} (HbA_{1c}), and decreased incidence of hypoglycemia (82). A study in children found that those using CSII had decreased severe hypoglycemia, diabetic ketoacidosis (DKA) and better glycemic control compared to those using MDI (83). In adults it was found that initiating CSII improved glucose control in previous MDI users (84).

2.3.3 Treatment- Blood Glucose Monitoring

To allow for accurate insulin dosing, BG levels must be regularly monitored. This is often done via self-monitoring of blood glucose (SMBG) using a glucometer, where capillary blood is produced using a lancet device and applied to a test strip inserted in the glucometer. More recently for diabetes care, continuous glucose monitoring (CGM) systems have emerged. These are devices that contain a small electrode that sits underneath the skin in the interstitial fluid with a transmitter attached externally. The glucose molecules in the interstitial fluid initiate a reaction for electrons to be released along the electrode, proportional to the interstitial glucose levels (85). This signal is then converted by the transmitter into glucose values which are displayed on an external device, such as a cellular phone or insulin pump every five to fifteen minutes (85). Wearing CGM devices for treatment of T1D allows for a more accurate reflection of glucose excursions to be detected

(86,87). CGMs can alert to high or low BG while sleeping (86), can identify trends to allow for therapy optimization (86), can reduce stress, anxiety and improve sleep for the caregiver of the individual with T1D (88), all while reducing the frequency of SMBG (86). CGM use can reduce the incidence of severe hypoglycemia and improve HbA_{1c} (89).

The individuals using these CGM devices depend on their accuracy to replace SMBG. Accuracy is often evaluated using the international standard ISO 15197:2013 criteria (90) and measuring mean absolute relative difference (MARD). ISO 15197:2013 determines the accuracy of glucose monitors using the following criteria: (a) compared to a laboratory method at least 95% of the glucose measurements have to be within 0.8 mmol/L at glucose concentrations <5.5 mmol/L and within ± 15% at ≥ 5.5 mmol/L and (b) in a consensus error grid analysis at least 99% of results have to be within zones A and B (90). A consensus error grid analysis compares measured glucose values to a reference value and plots them in zones. Values in zones A and B would lead to appropriate diabetes treatment, zone C would lead to unnecessary treatment, zone D would be a failure to detect hypoglycemia or hyperglycemia, and zone E indicates that the user is confusing hypoglycemia and hyperglycemia with one another (Appendix A). MARD is also often used to evaluate the accuracy of CGM systems, comparing those values to a reference system. It was proposed by the American Diabetes Association (ADA) that a system with a MARD of less than 10% is reliable enough to make treatment decisions (91). An in-silico study showed that further accuracy in these systems did not contribute substantially to better glycemic control (92). The Dexcom G5 Mobile CGM System was the first CGM to be approved as non-adjunctive therapy, replacing the need for SMBG for treatment. There are different commercially available CGMs in Canada, with conflicting reports of accuracy between systems (93–96). There is often increased MARD with increasing rate of change in BG values (95) or during hypoglycemia, with Dexcom

overestimating true BG (93). Exercise also poses as a problem for sensor accuracy. During aerobic exercise (97) and high intensity interval training (HIIT) (98) the Dexcom CGM was found to lag behind SMBG with an increase in MARD. Other competing CGM systems had similar inaccuracies during exercise (99–101). Despite the increase in inaccuracy of CGM during exercise, these systems still provide additional benefit to individuals exercising compared to not wearing a CGM (102).

Another use of CGM is to assess overall glycemic control. Currently, to assess glycemic control, individuals with T1D often have a blood analysis called an HbA_{1c} test that reflects their average BG level over the past three months. However, this test is unable to detect glycemic variability (GV) over shorter periods of time and is thus, a limited indication of glycemic control (103). CGM data is more frequently used to evaluate glycemic control, highlighting time in a specific glucose target range and incidence of hypoglycemia.

2.3.4 Hypoglycemia and Hyperglycemia

Individuals with T1D must manage their insulin dosing, carbohydrate intake, ketones, exercise, and possible other hormones to maintain their BG levels (104). Since people with T1D use exogenous insulin and are not always able to dose accordingly to these factors, they are at risk of having hypoglycemic events, typically defined as BG values below 3.9 mmol/L (103). However, the International Hypoglycemia Study Group recommends reporting values in clinical trials below 3.0 mmol/L or levels that cause cognitive impairment as severe hypoglycemia (105). Hypoglycemia may result in autonomic warning symptoms such as sweating, shaking, confusion, and altered speech and behavior, which can result in death if left untreated (106). The threshold for which these symptoms occur is not a fixed value and varies both between individuals and within the same individual (105). In some cases, hypoglycemia unawareness can occur, where

neuroglycopenia occurs before autonomic warning symptoms (107). Treatment of non-severe hypoglycemia is often treated with orally ingested fast-acting carbohydrates, such as dextrose tablets. In more severe cases, a glucagon injection may be necessary.

Hyperglycemia, which is clinically defined as BG values above 10.0 mmol/L also often occurs in individuals with T1D (103). Episodes of hyperglycemia may cause polyuria, polydipsia, and polyphagia (78). Prolonged hyperglycemia can lead to microvascular and macrovascular complications or to a state of DKA. DKA is often marked by acidosis, ketosis and hyperglycemia, (108) caused by lack of insulin (109). This very dangerous condition is associated with younger age, higher HbA1c, infection, CSII failure, and lower physical activity level (110).

2.3.5 Glucagon

In addition to inability to produce insulin, individuals with T1D have abnormal glucagon secretion (24). The dysfunction of the beta cells impacts the other islet cell types, such as the alpha cells. The initial lack of insulin prior to diagnosis of T1D and common hyperglycemia following initiation of exogenous insulin is thought to contribute to abnormal glucagon secretion (111). A lack of suppression of high glucagon levels has been shown to contribute to postprandial glucose intolerance in T1D (112), which plays an important role in initiating and maintaining hyperglycemia (24). During hypoglycemia in individuals with T1D, glucagon counterregulation appears to be impaired at an average of 8 months after diagnosis, with the earliest seen just after 1 month (113). Hyperinsulinemia may contribute to insulin's inability to regulate liver metabolism (114). The problem of improper glucagon secretion is a contributing factor to the development of hypoglycemia and hyperglycemia in T1D (115), however this dysfunction is complex and changes throughout the course of the disease (111).

Injectable glucagon previously only used for severe hypoglycemia, is now being developed as a stable form for everyday use in T1D therapy, such as mini-doses or continuous infusion for the prevention of hypoglycemia (116). Recently, an intranasal, more convenient form of glucagon was approved by the FDA for treatment of severe hypoglycemia (117).

2.3.6 Ketones in Diabetes

Ketone bodies serve as an alternative fuel source when glucose is not readily available or unable to be utilized. This occurs in uncontrolled or undiagnosed diabetes, where ketone levels can reach up to 25 mM due to not having enough circulating insulin (39). Although ketones provide fuel for the body, when they reach such high levels in these circumstances, they can also have detrimental effects and can cause oxidative stress (118). High ketone levels increase the risk of complications in T1D. Hyperketonemia is often associated with hyperglycemia in these circumstances and marks a dysfunction of the metabolic system rather than an adaptation (118). Individuals with T1D must monitor their ketone levels in order to better treat their BG and avoid DKA. Hyperketonemia can cause insulin resistance, making it more difficult for BG regulation (118). Individuals with T1D may also have impaired clearance of ketones (118), making it more difficult to regulate ketone levels.

2.3.7 Cortisol in Diabetes

In healthy individuals, cortisol is released in a diurnal rhythm and increases insulin resistance in the early morning. In T1D, the "dawn phenomenon" was coined to describe a natural rise in BG levels in the early morning, or a need for increased insulin delivery to prevent fasting hyperglycemia (119). Studies in individuals with T1D found the rise in BG levels in the early morning was consistent with a rise in cortisol and growth hormone, but not with insulin or glucagon concentrations (120,121), however the exact pathway involved is unknown (122).

Following the early morning cortisol surge, cortisol declines rapidly during the day. Glucose disappearance is negatively correlated with plasma cortisol in individuals with T1D. Individuals with T1D must take this into account when dosing their insulin. One study found the fall in glycemia in the morning was attributable to rising insulin sensitivity which in turn appeared to be associated with declining cortisol (123). Despite the impact of cortisol on BG levels, individuals with T1D were found to have lower free cortisol concentration compared to healthy controls overnight, possibly indicating an impaired HPA axis in T1D (124). A review of the "dawn phenomenon" also found that approximately only 54% of individuals with T1D experience this natural increase in insulin demand (122) and that it occurs unpredictably within the same individual (125). These differences between individuals and within the same individual make it increasingly difficult to target CSII therapy to correct for early morning hyperglycemia. On study showed that programming CSII to combat early morning hyperglycemia may contribute to more hypoglycemia and be hazardous to the patient (125).

2.3.8 Estrogen and Progesterone

As pointed out in a review paper by Yardley et al. (126), very little is known about the impact of confounding variables such as age and sex on BG levels during exercise in individuals with T1D. Most studies focus on young, male individuals with T1D, overlooking the impact of changing hormone levels, such as estrogen, throughout the menstrual cycle in women. This is important because many studies in healthy individuals without T1D found differences in fuel metabolism between males and females, as females have a greater shift towards lipid metabolism (127,128). These sex differences are likely to also be present in those with T1D and this could impact BG levels in women with T1D during exercise and in recovery. Estrogen is a major contributor to differences seen between males and females, as it promotes lipid oxidation and glycogen sparing

during exercise (129). With the production of these hormones, females of reproductive age will have different estrogen levels depending on the phase of the menstrual cycle they are in. In females with T1D, there is often increased hyperglycemia and decreased insulin sensitivity in the luteal phase compared to the early follicular phase (130,131). However, this trend appears to only occur in some premenopausal women and not others (132). There is no research on the impact of the menstrual cycle on BG levels during exercise and in recovery in people with T1D (126).

2.4 Type 1 Diabetes and Exercise

2.4.1 Benefits of Exercise

The Canadian Physical Activity Guidelines for adults state that they should be engaging in at least 150 minutes of moderate- to vigorous-intensity activity per week in bouts of ten minutes or more (133). Despite difficulties of BG management around exercise, people with T1D are recommended to engage in regular exercise due to the health benefits. Exercise improves weight control and cardiovascular risk in those with T1D (134), including improvements in lipid profiles (135). A meta-analysis found that in addition to improvements in cardiovascular profile in people with T1D, those that underwent fitness training also had increased aerobic fitness capacity and decreased daily insulin needs, indicating improved insulin sensitivity (135). Although there is not a general consensus as to whether exercise improves overall glycemic control, more recently studies are showing a reduction in HbA1c with increased exercise (135–137). Active adults with T1D were found to have altered mitochondrial ultrastructure within skeletal muscle compared to those without T1D (138). Even with activity, this metabolic deficiency shows the impact living with T1D has, and it needs to be evaluated whether or not increased exercise can combat this problem. Children and adolescents with T1D tend to be less fit than those without diabetes (139,140), most likely because of the added barriers to exercising with T1D. However, a higher

level of physical activity in adolescents with T1D promoted a higher level of resilience which in turn, increased quality of life (141). Overall, despite the added barriers of exercising with T1D, the benefits of activity outweigh the disadvantages and it is highly recommended people with T1D exercise regularly.

2.4.2 Glucose Metabolism During Exercise

When individuals without T1D undergo physical activity, the hormonal responses allow BG levels to be maintained in a tight range and fuel to be utilized efficiently. In contrast, individuals with T1D use exogenous insulin and their bodies cannot increase or decrease these levels. This, along with abnormal glucagon secretion in T1D, makes it difficult to accommodate for the metabolic changes that occur during exercise in T1D. Before engaging in physical activity, individuals with T1D must consider different strategies to maintain euglycemia and take into account the duration, type and timing of the activity (142). Exercise in T1D results in disturbed energy substrate use, which can lead to either hypoglycemia or hyperglycemia (143). Moderate intensity continuous activity (< 80% VO_2max) lasting more than 30 minutes is likely to require insulin reduction or carbohydrate supplementation strategies (142) since the increase in glucose utilization is not met with a natural decline in insulin levels. However, high intensity activity may result in hyperglycemia due to excessive circulating catecholamines which is not met by an increase in insulin levels (143). Insulin aspart, a commonly used exogenous insulin, peaks approximately one hour after injection and takes between three to four hours to clear (144). The long half-life of exogenous insulin makes it impossible to rapidly clear insulin from circulation at exercise onset leading to increased glucose disposal.

In individuals without T1D, as exercise duration increases, there is more of a reliance on fat oxidation for energy. However, as exercise time increases it is not clear whether carbohydrate

oxidation rates increase or decrease in individuals with T1D. One study showed a steady decline in carbohydrate oxidation and increase in fat oxidation during a three hour walk in individuals with T1D (145); but it is important to note that BG levels before a bout of exercise will impact fuel oxidation rates and therefore the shift in glycaemia. Commencing an exercise bout within the euglycemic levels results in a greater shift towards lipid oxidation, similar to those without T1D, whereas hyperglycemia shifts towards carbohydrate metabolism (146). Timing since the last meal also impacts oxidation rates in individuals with T1D. Carbohydrate oxidation is lower and lipid oxidation is higher when exercising 30 minutes after a meal compared to 120 minutes postprandial (147). In addition to this, overall glycemic control will impact the response to exercise (148). In individuals with better control, there may be better counterregulatory function, or they may not have an exaggerated counterregulatory response, making control during exercise even more unpredictable.

2.4.3 Effect of the Type of Exercise

The type and duration of an exercise bout impacts BG levels in individuals with T1D in different ways. Exercise can be classified into two forms; aerobic and anaerobic, based on the primary metabolic energy source used during activity (149). Moderate intensity aerobic exercise (VO_{2max} < 80%) lasting longer than twenty minutes (such as swimming, running and jogging/walking) that depend primarily on oxidative metabolism are more aerobic in nature (150). This type of activity depends on a continuous supply of oxygen to the cells allowing for ATP production through oxidative phosphorylation. The risk of hypoglycemia is associated with moderate-intensity aerobic exercise due to increased glucose demand. There is an increase in insulin absorption from subcutaneous tissue and delivery to skeletal muscle most likely due to increased exercise-induced capillary recruitment (151). In addition, the insulin-independent

glucose uptake pathway in muscle is activated during exercise (148). With aerobic exercise, there appears to be a U-shape in the relationship between intensity and glucose disposal, with the highest risk of hypoglycemia occurring at about 50% of the individual's maximal aerobic capacity (152).

In contrast, higher intensity aerobic exercise (> 80% VO_{2max}) tends to cause a rise in BG levels (149,153). High intensity exercises defined in terms of percentage of VO_{2max}, typically last 2-3 minutes at a time and rely primarily on anaerobic glycolysis (150). Once the initial ATP stores are depleted, anaerobic glycolysis produces ATP and lactic acid to sustain this type of exercise. During intense activity, counterregulatory hormones, such as catecholamines, increase along with lactate, causing an increase in gluconeogenesis by the liver (154). This increase in glucose output is not matched by glucose uptake and can cause hyperglycemia in those with T1D.

As a means to prevent hypoglycemia with moderate intensity exercise, HIIT exercise may be performed between bouts of moderate intensity exercise. After only 25 minutes of HIIT in those with T1D, 90% of the trials showed hyperglycemia requiring a bolus of insulin to correct (155). Despite the differences in how these exercises impact BG levels during activity, there was no difference in time spent in hypoglycemia, hyperglycemia or euglycemia 24 hours after moderate or HIIT exercises (156). Another form of anaerobic exercise is resistance training, which is not thought to impact BG values as significantly. A study with individuals performing both aerobic and resistance exercise found stable BG levels throughout resistance training and a better outcome when the aerobic exercise was performed after resistance compared to before (157). Another study found that resistance training improves glycemic control compared to a day without activity, with less hypoglycemia compared to a day with aerobic training (158).

During sports or spontaneous play, with both moderate-intensity activity and short intense bursts of high-intensity activity, a drop in glycemia may be attenuated (159) or cause a rise in BG

(160), making glycemic control difficult around these times. In addition to type and duration of activity, individuals with T1D must take into account the timing of activity, degree of stress involved, metabolic control, as well as insulin and food supply (148).

2.4.4 Strategies to Prevent Hypoglycemia During Exercise

The occurrence of hypoglycemia in T1D poses an immediate risk to the individual. Since fear of hypoglycemia is a barrier to exercising (161), research has been done to evaluate the best strategy for exercising with T1D. Currently, the three most commonly used options to prevent hypoglycemia while exercising are to reduce a pre-exercise bolus of insulin, reduce the basal rate of insulin, or to supplement with carbohydrates.

2.4.5 Pre-meal Bolus Reduction

One strategy to prevent hypoglycemia during moderate intensity exercise is to reduce the amount of bolus insulin given with the meal before the onset of exercise. This requires knowledge of the timing, duration and intensity of the upcoming exercise. A study implementing a bolus reduction of 50-75% given 90 minutes before exercise showed an increase in BG levels before exercise onset and one hour after exercise (1). Another study which compared no bolus reduction, 50% reduction, 65% reduction, and 100% reduction two hours before exercise found that the 50-65% reduction had similar glycemia during the exercise bout compared to a control rest day (2). However, after exercise stopped, hyperglycemia ensued, showing exercise only delayed the peak in BG levels with a bolus reduction (2). Although a bolus reduction may prevent hypoglycemia, reducing a bolus with food may cause significant hyperglycemia prior to the onset of exercise and afterwards. Therefore, more research needs to be done to determine the optimal strategy for exercise following a meal.

2.4.6 Basal Rate Reduction

Another strategy to prevent hypoglycemia during moderate-intensity exercise is to reduce basal insulin levels. Individuals using MDI can reduce their daily basal insulin on days of exercise. Five consecutive days of moderate exercise resulted in a greater time spent in euglycemia when 75% of usual insulin glargine was given compared to the full dose (162). CSII users are able to set temporary changes to their basal insulin for any length of time. A basal insulin suspension strategy for 60 minutes of exercise decreased hypoglycemia incidence compared to no basal adjustment, but resulted in more frequent hyperglycemia after exercise (14). Alternatively, an algorithm that predicts hypoglycemia occurrence within 30 minutes and stops basal insulin infusion was designed to control the CSII (163) and despite a reduction in the incidence of hypoglycemia during 30 minutes of exercise, Abraham et al. found that 32% of the participants still experienced hypoglycemia during exercise with this strategy (3). A similar strategy implementing aggressive BRRs during exercise, ranging from 50-80%, still resulted in an average BG drop of 3.3 mmol/L during 30 minutes of exercise (4). A fourth strategy recently implemented is to reduce basal insulin levels prior to exercise onset. This strategy was tested by McAuley et al. by using a 50% BRR set 60 minutes before a bicycle exercise and found that it was not enough to significantly reduce circulating free insulin by exercise start (164). Three out of the fourteen individuals performing just 30 minutes of cycling needed to be treated for hypoglycemia (164). Similarly, a more aggressive BRR of 80% set 0, 20, or 40 minutes prior to exercise still had a comparable occurrence of hypoglycemia between the three arms (165). Recently, a BRR of 50-80% set 90 minutes before exercise onset was shown to greatly reduce the risk of hypoglycemia compared to suspending insulin at exercise start (5). These studies continue to provide evidence that BRRs must be made

well in advance of exercise start in order to reduce circulating insulin. As highlighted earlier, this requires pre-planning and may not always be feasible.

2.4.7 Carbohydrate Supplementation

With the need to pre-plan insulin reduction strategies for exercise, carbohydrate supplementation is often implemented when exercise is unplanned. Research has been done evaluating carbohydrate consumption during exercise. Compared to a placebo, carbohydrate intake has been shown to attenuate the drop in BG often observed with exercise (166). When comparing carbohydrate supplementation and insulin dosage reduction, irrespective of the exercise duration or intensity, carbohydrate supplementation appears to be the more effective strategy at reducing hypoglycemia (11). A study using 0, 15 or 30g ingestion of carbohydrate for 60 minutes of moderate intensity cycling found that each strategy still needed dextrose infusion to prevent hypoglycemia, and despite this, a 3.1 mmol/L drop in BG in the 30g arm still occurred (167). However, a similar study using carbohydrate supplements of different glycemic index before, during and after exercise found that most cause mild hyperglycemia (168). The variability in carbohydrates needed during exercise may be due to the generalizing of carbohydrate dosage for all individuals. A few studies used carbohydrate dosing based on body weight in order to prevent hypoglycemia (8,9) but hypoglycemia still occurred in these trials and there are inconsistencies in the dosage needed, ranging from ~0.4g carbohydrate per kg of body weight per hour of exercise to 1.6g/kg/hr. These trials were also done while postprandial and it is unclear how the dosage may change for fasted exercise. The time after a meal that exercise occurred and the duration of exercise differed between studies, likely contributing to the variability in results.

As the time between a meal and exercise onset increases, the amount of carbohydrates needed to prevent hypoglycemia decreases, with a maximum carbohydrate dosage needed at 1

hour postprandial exercise (169). A study matching carbohydrate dosage with total carbohydrate utilization only had hypoglycemic events occur in 15% of the individuals during 60 minutes of moderate intensity cycling compared to 45% with no supplementation (170). Despite being a fairly effective strategy, matching carbohydrate utilization is not applicable to real-life exercising in an uncontrolled setting. Another strategy that was implemented in children with T1D was a decision chart that used the values and trend arrows produced by a CGM to determine carbohydrate consumption during a sports camp (171). For example, if BG was in normal range and rapidly dropping indicated by two downward arrows, the individual would be instructed to consume 20g carbohydrates, but if BG was slowly dropping indicated by one downward arrow, they were instructed to consume 16g carbohydrates. While in many scenarios the decision chart was protective against hypoglycemia, when BG levels were below 5.0 mmol/L, hypoglycemia occurred 32% of the time despite carbohydrate intake (171). This highlights that attempting to prevent hypoglycemia while exercising with BG values in the low to normal range may not be successful and carbohydrates should be consumed before exercise starts as a preventative measure.

2.4.8 Fasted Exercise

Exercise performed in the fasted state eliminates the option of reducing a meal bolus beforehand to prevent hypoglycemia. There is very little research on fasted exercise in T1D, however there are benefits to performing this type of activity that may reduce the risk of hypoglycemia. In the morning, individuals with T1D only have basal insulin, meaning circulating insulin levels are low. It is hypothesized that because of the low circulating insulin levels throughout the night, the counterregulatory functions, such as glucagon production, may be enhanced (7). Exercise performed in the morning has a lower risk of hypoglycemia compared to the afternoon, with higher cortisol and lower insulin levels when first waking (172). Guidelines

suggest supplementing with carbohydrates by as little as 0.2-0.5g/kg/hr if circulating insulin levels are low (142). However, this small amount of carbohydrate supplementation has not been studied. Two studies performed 45 minutes of exercise in the fasted state and showed a small dose of carbohydrates ranging from 13-30g, was too much and tended to cause hyperglycemia during exercise (7,173). A more accurate dosage of carbohydrates needs to be determined for this type of activity.

2.4.9 Extreme Prolonged Exercise

Most exercise studies done in individuals with T1D look at only short duration activity. A case study of an individual with T1D showed that performing extreme activity, a 68-hour bicycle race, is possible but needs additional planning and can result in hyperglycemia as a result of trying to avoid hypoglycemia (171). Another study where 7 individuals with T1D completed a 42km run required less insulin and more carbohydrates before, during and after the completion of the race to avoid hypoglycemia (172). Four men participating in an ultramarathon significantly reduced their insulin and increased carbohydrate intake resulting in some hyperglycemia during the race but not ketoacidosis (173). Ten individuals with T1D participated in three consecutive days of prolonged walking of 40 or 50km, and had increased carbohydrate intake with decreased insulin and a modest increase in GV (174). It is clear that prolonged exercise will greatly impact insulin and carbohydrate consumption compared to a day without exercise. High carbohydrate intake is recommended in individuals without T1D, however it is not known what is best for those with T1D. Three days consisting of 7-10 hours of cross-country skiing by individuals with T1D showed that despite increased activity, a high carbohydrate load throughout the day required significantly more insulin to maintain in range BG levels (11). It is not clear what the best strategy for extreme activity in individuals with T1D is. There are no set guidelines on the best way to reduce GV

during prolonged exercise while simultaneously eliminating hypoglycemia and preventing rebound hyperglycemia. More research needs to be done to understand changes in oxidation rates and insulin needs during prolonged activity and in recovery.

2.5 Technological Advancements in Diabetes Treatment

Treatment for T1D has come a long way since the initial discovery of insulin in 1921. The development of newer insulins, CGM and CSII have allowed for greater flexibility and better control of diabetes. More recently, research has gone into the development of systems called the single-hormone Artificial Pancreas (AP) which integrate CGM with CSII (175). Single-hormone AP systems have a constant glucose reading via CGM, which is fed into an algorithm and changes insulin delivery rates based on these values. These systems reduce the burden of accurately dosing insulin throughout the day, which can change one-third to threefold on a daily basis, while reducing the risk of hypoglycemia, bettering glucose control (176). A meta-analysis of single-hormone AP use in an outpatient setting found more time in euglycemic range compared to usual care (177). Other systems incorporate glucagon infusion into the algorithm, called dual-hormone AP. The added benefit of glucagon allows a counterregulatory hormone to be present to better protect against hypoglycemia (178), however glucagon is a fairly unstable hormone and not yet feasible for T1D usual care. Studies comparing time in euglycemia between single- and dual-hormone AP systems, found similar results with less hypoglycemia in the dual-hormone system (179). Despite the promising results of using an automated system, AP systems still have challenges with BG control. The pharmacokinetics of rapid insulins are not the same as endogenous insulin, and this poses a problem around times of rapidly changing BG levels, such as during exercise or meals (180). The lag time of CGM compared to SMBG as discussed earlier also makes dosing decisions of AP systems more inaccurate.

When disturbances to BG are introduced, such as exercise, the single-hormone AP systems may encounter problems maintaining euglycemia (181). Studies show safety of the systems when exercise is announced well in advance of commencement. Typically, the systems temporarily raise target BG, set a BRR, or suggest carbohydrate intake (182,183). However, these systems do not eliminate the possibility of hypoglycemia or completely eliminate hypoglycemia occurrence (184). A study using an AP for one hour of unannounced exercise still encountered hypoglycemia, even with some pre-exercise carbohydrate consumption as per the individuals' usual routines (185).

Despite the challenges of these systems to keep up with rapidly changing glucose, when used properly they reduce the burden of living with T1D and reduce exposure to hypoglycemia when engaging in exercise (186). However, the only commercially available AP system, Medtronic Minimed 670G, still requires user input to stay in the BG driven insulin program (187), and there is not a product available that does not require frequent user input. The addition of glucagon in a dual-hormone AP also outperforms the single-hormone AP by reducing the incidence of hypoglycemia during unannounced exercise (188). However, only single-hormone systems are currently available and glucagon as a preventative to hypoglycemia is not yet utilized as common T1D therapy.

A fully automated AP must be able to detect things that can impact BG and respond appropriately. It is believed that exercise wearables will eventually feed into these systems to better manage changing BG (189). A study that incorporates heart rate to detect exercise into an AP found decreased hypoglycemia incidence compared to a system without heart rate detection (190). Overall, AP systems show promise for better T1D management and reducing the burden of the disease. Research continues to grow on how to best deal with exercise and T1D.

3.0 Study Overview, Objectives and Hypotheses

3.1 Study Overview

The purpose of this project was to determine the best carbohydrate and/or insulin strategy during aerobic exercise for a prolonged period of time in adults (n = 15) with T1D. A similar project was carried out in the Riddell laboratory, called the OmniTIME project, which highlighted the success of an insulin reduction only strategy (5). This project extends off key concepts learned from that trial with some important differences. This study compares exercise strategies that do not require pre-planning to the strategy used in the OmniTIME project. This study also has a longer duration of exercise that is typically not evaluated in T1D treatment. Lastly, this study is done in the morning fasted state when circulating insulin levels tend to be lowest, whereas the OmniTIME study was done in the afternoon post-absorptive state.

The ExCarbs study was funded by Insulet Corporation and carried out at York University. The results from this study may aid in education for safely exercising with T1D and to assist in the development of AP systems.

3.2 Primary Objectives

The primary objective of this study is to determine which strategy of preventing hypoglycemia during prolonged aerobic exercise is the most effective in maintaining euglycemia. The target range is defined as BG levels measured by SMBG between 4.0 and 10.0 mmol/L.

3.3 Secondary Objectives

The secondary objectives of this study were:

- to compare the time below target glucose range (<4.0 mmol/L)
- to compare the time above target glucose range (>10.0 mmol/L)
- to compare the incidence of hypoglycemia during exercise (<4.0 mmol/L for ≥ 15 mins)

- to compare the time and incidence of hypoglycemia 6 hours following exercise, overnight and 24 hours following exercise (interstitial glucose <4.0 mmol/L)
- to compare blood glucose changes over the time of exercise (capillary)
- to compare plasma insulin levels over the time of exercise
- to compare plasma glucagon levels over the time of exercise
- to compare plasma cortisol levels pre- and post-exercise
- to compare ketone levels pre- and post-exercise (capillary)
- to compare the total carbohydrates needed
- to compare amount of rescue carbohydrates needed
- to compare perception of glycemia and symptoms of hypoglycemia during exercise
- to compare energy expenditure during exercise
- to compare fuel utilized during exercise (RER)
- to compare total daily insulin dose and carbohydrate intake post-exercise
- to compare glucose response between different phases of the menstrual cycle in females

3.4 Hypotheses

The primary hypothesis was that all three arms would allow for safe prolonged exercise with increased fat oxidation and counter regulatory response in the basal rate reduction arm only. The arms were (A) a carbohydrate strategy of 0.3 g/kg/hr, (B) a basal rate reduction of 50% set 90 minutes before exercise, and (C) the combination of a carbohydrate dose of 0.3 g/kg/hr and 50% basal rate reduction at exercise onset. The secondary hypotheses included:

- Arm B would have a very modest decline in BG and protect against hypoglycemia for the duration of exercise, similar to that of the OmniTIME study (5).

- Arm A would have stable BG levels throughout exercise without rebound hyperglycemia. Previous research has shown that carbohydrate supplementation worked better than insulin only strategies (11), and the robustness of this strategy compared to the insulin only strategy was hypothesized to allow BG levels to be better targeted to euglycemia.
- Arm C would be the most effective treatment for exercising in the prevention of hypoglycemia. This strategy was hypothesized to be similar to the carbohydrate supplementation arm until about 60-90 minutes of exercise, when the insulin reduction would start working and would distinguish Arm A from Arm C.
- Arm A would need more grams of carbohydrates compared to Arm C.
- Arm B would shift to fat burning with higher ketone levels compared to the two other strategies requiring carbohydrate feeding.
- Following exercise, Arm C would best protect against hypoglycemia in recovery.
- Arm A would have the highest occurrence of hypoglycemia due to no reduction of insulin levels and heightened insulin sensitivity (49).
- The pre-exercise circulating insulin levels were hypothesized to be lowest in Arm B compared to two other arms which had normal basal insulin rates right before exercise onset, in agreement with the OmniTIME study (5). The post-exercise circulating insulin levels were hypothesized to be lower in Arm C compared to Arm A with no insulin adjustment.
- The circulating glucagon levels were hypothesized to be low or absent in all arms with a possible increase during exercise in Arm B due to such low circulating insulin levels (7).
- Cortisol levels were hypothesized to be similar between all three arms, with a decrease post-exercise compared to pre-exercise, due to its diurnal circadian rhythm (29).

- For the sub-analysis portion of this study, it was hypothesized that there would be a rise in BG during exercise with carbohydrate supplementation in the luteal phase of the menstrual cycle compared to the early follicular phase because the luteal phase has decreased insulin sensitivity and increased hyperglycemia (130).

4.0 Research Design and Methods

4.1 Study Participants

The experimental protocol was approved by the Research Ethics Board at York University, Toronto, Ontario, Canada (Certificate #: e2018-306). Fifteen individuals with type 1 diabetes were recruited for this study. All participants were screened for cardiometabolic complications using the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) (191). Physical Activity levels were assessed using the International Physical Activity Questionnaire (IPAQ) (192). Hypoglycemia awareness was assessed using the questionnaires developed by Clarke et al. (193) and Gold et al. (194) as they correlate strongly with impaired awareness in individuals with T1D (195). All females of reproductive capacity were given a calendar to track their menstrual cycle throughout the study.

4.2 Study Protocol

Participants visited the laboratory on four separate occasions (females of reproductive capacity had an additional visit). Anthropometrics were measured and a fitness assessment test was performed during the initial baseline visit. During the following three experimental visits, individuals performed a 2-hour treadmill walk at 40-50% of Heart Rate Reserve (HRR) with different insulin adjustments and carbohydrate intakes. These visits occurred in the morning fasted state.

4.3 Fitness Assessment (Visit 1)

Subject anthropometrics, including height, body mass, blood pressure, body fat percentage and waist circumference were measured and medical history recorded after consent, personal contact information and emergency contact information was obtained. Height was measured using a wall-mounted stadiometer, weight and body fat percentage were measured using the Tanita BF-

350 Total Body Composition Analyzer Scale (Tanita Corportation, Tokyo, Japan). Waist circumference was measured around the abdomen at the iliac crest (196). Blood pressure and resting heart rate (HR) were measured in duplicate using the OMRON M7 Intelli IT (OMRON Corporation, Kyoti, Japan) while participants were sitting, relaxed with their legs uncrossed (197). Current and past medication use was recorded. Current insulin settings in the individuals' pumps, including basal rates, insulin-to-carbohydrate ratios, insulin sensitivity factor (ISF), and type of insulin used and insulin pump and glucometer model was recorded as well as diabetes diagnosis date. Diabetes-related complications were recorded, including high blood pressure, retinopathy, nephropathy, neuropathy, cardiovascular disease, low BG symptoms and treatment, severe hypoglycemia history, DKA, average daily insulin dose. Capillary blood was obtained to measure HbA_{1c} using a point of care device (A1C Now+ SelfCheck, Bayer©, Leverkusen, Germany).

Participants then completed a VO_{2peak} test using an incremental-to-maximum effort treadmill protocol, consisting of a self-selected run on a Spirit CT850 treadmill (Dyaco International, Taipei, Taiwan) with an increase in incline every two minutes until exhaustion. Prior to exercising, subjects' last meal, insulin dose and site, and most recent hypoglycemic event were recorded. Subjects were then fitted with two HR monitor chest straps (Polar H10 and Garmin HRM-Dual™) and a metabolic system harness (K5; COSMED, Rome, Italy). Once the metabolic system mask was fitted to the subject, they underwent a seated five-minute rest period. During this time, the individual's BG was measured in duplicate. Once on the treadmill, subjects underwent four minutes of walking at a speed of 3.0 miles per hour (mph) with 0% incline for the first two minutes followed by two minutes at 5% incline. Following this walk, subjects began running at a self-selected pace at 2% incline. Treadmill running speed during the peak test ranged from 3.8-6.5 mph. Every two minutes, incline was increased by 2% until exhaustion, with a

maximum incline of 15%. Subject exhaustion was analyzed using Borg Category-Ratio 10 Rating of Perceived Exertion (RPE) Scale (198). When subjects terminated the run, they then had a 2-minute walking cool down at 2.5mph and 0% incline. Peak oxygen consumption (VO_{2peak}) was measured using a portable metabolic unit (K5; COSMED, Rome, Italy) and peak HR was measured using a chest strap HR monitor (Polar H10, Kempele, Finland). Following the VO_{2peak} test, subjects had another five-minute seated rest period where BG was measured in duplicate, and recovery HR recorded. The metabolic system harness and HR monitors were then removed. Following the exercise test, subjects who were not currently wearing a CGM device (G5; Dexcom, San Diego, CA) were set up on it using their cellular devices and a self-created account. The subject chose where the CGM device was placed (abdomen, arms, or buttocks) and instructed on how to use the device. All subjects were instructed to use a Contour® Next Link (Ascensia Diabetes Care, New Jersey, USA) glucometer when calibrating the CGM. They were then verbally informed on how to prepare for the remaining experimental visits and scheduled in.

4.4 Experimental Testing (Visits 2-5)

This study is a randomized, cross-over study, evaluating three different exercise and blood glucose management strategies to optimize time in target range in physically active subjects with T1D using insulin pump therapy. Females of reproductive capacity performed all three visits in the early follicular phase and repeated one exercise arm in the luteal phase. A graphical presentation of the study design is provided in Appendix B. The 3 different strategies are:

A. CHO: Carbohydrate dose of 0.3g/kg/hr with no basal rate reduction (i.e. 100% basal)
B. BRR: Basal rate reduction of 50% (i.e. 50% of usual basal rate) made 90 minutes pre-exercise
C. Combo: Basal rate reduction of 50% with carbohydrate dose of 0.3g/kg/hr at exercise onset

For the carbohydrate supplementation arms (A and C), the carbohydrates were given every 30 minutes throughout exercise (i.e. 0.15g/kg for every 30 minutes). The supplements were given at t= -5, 30, 65, and 105min of exercise. For each arm, the subjects were given a 5-minute rest period for every 30 minutes of exercise, with a 10-minute rest mid-exercise. The carbohydrate were given at the start of the five-minute rest periods, and halfway through the 10-minute rest period. The carbohydrates were pre-weighed and calculated based on the subjects' weight. The carbohydrates were a small amount of fruit flavoured candy (Skittles™, Mars, Inc., McLean, Virginia, USA), containing primarily sucrose, with hydrogenated vegetable oil, fruit juice, citric acid and natural and artificial flavours (199). This choice of carbohydrate was shown to be just as effective at treating hypoglycemia compared to glucose tablets (200).

For the basal rate reduction (BRR) arm (B), subjects were contacted one hour prior to their arrival in lab, and instructed to set a temporary basal rate reduction using their insulin pump. The BRR was set at 50% of their usual rate for a duration of six hours. Confirmation of this action was done upon the subjects' arrival in laboratory by looking at the pump history.

Prior to the subjects' scheduled date of testing, they were contacted via e-mail as a reminder of their visit and provided instructions on what to do leading up to the visit. Subjects were instructed to ensure they were wearing a CGM at least 24 hours prior to the visit, not to perform moderate to vigorous exercise 24 hours prior to the visit and refrain from caffeine and alcohol 12 hours prior to the visit. Subjects were instructed to not eat after 11:30pm the night before arriving at the laboratory and to not give a bolus of insulin or adjust their basal rate after 2:00am on the same day as their exercise visit. If significant hyperglycemia or hypoglycemia occurred after 11:30pm, subjects were instructed to treat their diabetes as they normally would and to report it. They were asked to ensure that their insulin pump sites and CGM sites would not need to be

changed during the in-clinic visit. Subjects were instructed to try to arrive at the laboratory with their BG between 4.0-15.0mmol/L, with no active insulin, in the fasted state. Subjects were also contacted the morning of the in-clinic visit to ensure they were ready and in a BG range of 4.0-20.0mmol/L to exercise.

Subjects arrived at the laboratory between 6:00am and 10:00am. Each individual decided what time they wanted to begin exercise at and this was kept consistent between the three arms. BG was measured at arrival and shown to the subject. If BG was < 3.9mmol/L, participants treated their low BG with 12g carbohydrates. If BG was > 15.0mmol/L, participants were tested for ketones (Freestyle Precision Neo, Abbott Laboratories, Illinois, USA). All BG measurements after this time point were blinded to the subject. They were also asked to refrain from looking at their CGM values on their smartphone from this point onwards. Weight and body fat percentage were measured, and individuals were fitted for two chest strap HR monitors. Most recent food consumption, insulin dose, injection site, hypoglycemic episode and past exercise was recorded. Sleep timing estimation and interruptions in sleep were recorded. Ten minutes prior to exercise onset, saliva samples were collected into a cryotubes (Diamed Lab Supplies Inc., Mississauga, Canada) via a saliva collection aid (Salimetrics, LLM, California, USA). Blood was then collected into two K2-EDTA blood collection tubes (Sarstedt Inc., Numbrecht, Germany) via finger stick capillary poke. For Arm A, subjects' BG and ketones were tested, and according to the decision table, were given carbohydrates five minutes prior to exercise onset. For Arm B, subjects' BG and ketones were tested and according to the decision table, started exercise. For Arm C, subjects' BG and ketones were tested, basal insulin rate was reduced by 50%, and according to the decision table, were given carbohydrates five minutes prior to exercise onset. After these actions for each arm, individuals wore the metabolic system and began exercise on the treadmill. The speed and

incline of the treadmill were adjusted to target the individuals HRR of 40-50% based on the baseline VO_{2peak} test. HRR was calculated prior to exercise onset using the Karvonen formula (201):

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

BG was measured after every 15 minutes of exercise on the treadmill and upon subjects request. HR, RPE, carbohydrate consumption and speed and incline of the treadmill were recorded every 15 minutes of exercise. The metabolic system was worn for 15 minutes at a time during exercise, at time points 0min, 75min, and 125min of the exercise protocol. A seated rest occurred after every 30 minutes of exercise. At these time points, carbohydrate consumption occurred based on the decision table. An Edinburgh Hypoglycemic Symptom Scale (202) questionnaire was also conducted by the researcher and the subject estimated their BG levels every 30 minutes of exercise (Appendix D). At time points 65min and 140min, additional finger stick capillary blood was collected for later analysis. Following completion of exercise at 140min and blood collection, a final saliva sample was collected, and the subject was shown current and previous BG measurements. HR straps and the metabolic system harness were removed and BG was measured following a 20min rest.

If BG was < 4.0 mmol/L on the glucometer at any point during exercise, exercise was stopped and subjects were treated with 12g of carbohydrates and informed of their BG level. After waiting 15 minutes, BG was checked and if it was ≥ 4.0mmol/L, exercise was resumed. If subjects experienced ≥ 3 episodes of hypoglycemia during exercise, exercise was terminated. If BG was > 10.0 mmol/L during exercise, the carbohydrate dose was not given if in the carbohydrate feeding arms (Arm A and C). If BG was ≥ 20.0mmol/L and/or ketones were ≥ 1.5mmol/L, exercise was

terminated and usual diabetes care was initiated. The decision-making strategies are outlined in Appendix C.

Following the final BG measurement, subjects left the laboratory and were able to consume food. Subjects were asked to keep their food consumption similar for all treatments arms and to track their insulin dosing and carbohydrate consumption throughout the day (Appendix E). In accordance with diabetes and exercise guidelines (133), subjects were instructed at their own discretion, to reduce their bolus insulin amounts by 25% to protect against post-exercise hypoglycemia (203). Subjects were also instructed to set a BRR by 20% for six hours when they went to sleep the night of the in-clinic exercise to protect against nocturnal hypoglycemia (142). Subjects were also given exercise logs to track their activity prior to and following the in-clinic visit (Appendix F).

4.5 Study Design

This study used a randomized, cross-over design. The main advantage of cross-over studies is that subjects serve as their own controls, reducing the inter-subject variability. The control arm in this study was the arm performing a 50% basal insulin reduction administered 90 minutes pre-exercise, as studied previously in the Riddell lab (5).

4.6 Selection of Study Population

4.6.1 Inclusion Criteria

01. Male or Female

02. Clinical diagnosis of presumed autoimmune T1D

03. Age 18-65 years, inclusive

04. Duration of T1D ≥ 18 months

05. Using insulin pump therapy for at least 3 months

06. Exercise regularly: i.e. ≥ 30 minutes of moderate or vigorous aerobic activity ≥ 3 times/week for a minimum of 90 minutes weekly
07. HbA1c ≤ 9.9% at screening visit
08. In good general health with no known conditions that could influence the outcome of the trial, and in the judgement of the Investigator is a good candidate for the study based on review of available medical history and clinical laboratory evaluations
09. Willing to adhere to the protocol requirements for the duration of the study

4.6.2 Exclusion Criteria

01. Pregnant or lactating
02. Physician diagnosis of active diabetic retinopathy that could be worsened by exercise
03. Physician diagnosis of peripheral neuropathy or autonomic neuropathy
04. Any evidence of unstable cardiovascular disease, disorders or abnormalities
05. Currently following a very low calorie or other weight-loss diet which may impact glucose control and mask the primary and secondary outcome measures
06. More than one episode of severe hypoglycemia with seizure, coma or requiring assistance of another person during the past 6 months
07. Known hypoglycemia unawareness
08. Participation in other studies involving the administration of an investigational drug or device during the duration of the current study
09. Medications other than insulin that might impact outcome measures:
    - Beta blockers
    - Agents that affect hepatic glucose production such as beta-adrenergic agonists and antagonists, xanthine derivatives

- Pramlinitide
- Any non-insulin diabetes therapy

4.6.3 Removal of Patients from the Study

If during the study, subjects revealed having an exclusion criteria, treatment discontinuation occurred. Subjects were able to withdraw from the study if they decided to do so, at any time and for any reason. The primary investigator was also able to decide to withdraw a subject from the study based on an inability of the subject to adhere to the obligations of the study or for the safety of the subject. All documents pertaining to subject discontinuation were kept.

4.6.4 Methods of Assigning Patients to Treatment Groups

Subjects who met the eligibility defined at the baseline visit were randomly assigned to the order in which they complete the three treatment groups. This order was generated via an online list randomizer.

4.6.5 Blinding

This is an open-label study and neither the subjects nor the investigator were blinded to the treatment arm. Subjects were blinded to their BG during exercise for the experimental visits.

4.6.6 Usual Therapy

Subjects were asked to maintain their usual therapy throughout the study period without drastic changes to insulin dosing, activity level or diet.

4.7 Data Collection Methods

4.7.1 Continuous Glucose Monitoring

Subjects were instructed to wear the Dexcom G5 CGM throughout the study period (Visits 2-4) and ensure that the device was inserted a minimum of 24 hours prior to the experimental exercise sessions. Their data was remotely collected with permission through the Dexcom

CLARITY® website. The live time glucose data was monitored via the Dexcom Follow™ App leading up to and following in-clinic visits.

4.7.2 Blood Collection

Blood for BG and ketone measurements were collected via a self-poke of the subjects' finger using the subjects' personal lancet device. Both measurements were done using a handheld meter device. The Contour® Next Link was used as the laboratory glucose meter as it was shown to have a high level of accuracy compared with a laboratory standard(204). Prior to collection, subjects were instructed to clean their finger using an alcohol swab, air dry their finger, use their lancet device to draw blood, clean the first drop of blood with a tissue, and then push more blood from their fingertip for the test strips (205). All BG measurements were taken in duplicate and averaged, or in triplicate if the first two values had a >1.0mmol/L difference.

Plasma for glucagon and insulin assays were taken via capillary blood generated from a lancet device. The subjects often performed multiple pokes to their fingertips to generate enough blood, or turned up the depth of the lancet device. Blood was collected via K2-EDTA blood collection tubes, which were immediately spun at 10,000g for 5 min. The supernatant plasma was collected in two microcentrifuge tubes (Eppendorf, Hamburg, Germany) at each time point. Samples were immediately placed on ice and then stored in -80°C freezer until all samples were analyzed together.

Half the plasma collected at each time point (-5min, 65min, and 140min) was analyzed for circulating free insulin concentrations (Insulin ELISA; Crystal Chem, Illinois, USA). To remove antibody-bound insulin, polyethylene glycol 6000 (BioShop, Ontario, Canada) was used to create a precipitate (modified from Nakagawa et al (206)). A total of 50uL of 25% aqueous polyethylene glycol 6000 and phosphate buffer solution (pH 7.4) was added to 50uL of each plasma sample and

vortexed for 30 s. Samples were centrifuged at 10,000g for 15 min in refrigerated centrifuge, and this supernatant was extracted and analyzed for circulating free insulin concentrations according to the manufacturer's recommendations.

The other half of the plasma collected at each time point (-5min, 65min, and 140min) was analyzed for glucagon concentrations (Glucagon ELISA; Mercodia, Uppsala, Sweden).

4.7.3 Saliva Collection

Saliva was collected pre- and post-exercise via a saliva collection aid into cryotubes. Subjects were instructed to fill over the quarter way mark of 2.0 mL tubes. They were instructed to allow saliva to pool in the mouth with the head slightly tilted forward to go through the saliva collection aid. After collection into the cryotube, the collection aid was discarded and the samples were immediately placed on ice and then stored in a -80°C freezer until all samples were analyzed together. Saliva samples were analyzed for cortisol concentrations (Cortisol Saliva ELISA; Chrystal Chem, Illinois, USA). Prior to kit use, the saliva samples were centrifuged for 5 min at 4,000g and the supernatant was collected into clean tubes and analyzed.

4.7.4 Exercise Equipment Fitting

Subjects were fitted for two chest HR monitors (Polar H10 and Garmin HRM-Dual™ monitor), a metabolic system harness and a metabolic system mask. Water was placed on the HR monitors where they make contact with the skin to allow better conductance. They were placed just below the sternum, with the Polar H10 placed just above the Garmin HRM-Dual™ monitor with no overlapping of straps. Straps were fitted tightly to ensure they were not moving throughout exercise, but not uncomfortable for the subject. The Polar H10 transmitted the HR to a smartphone device via the Polar Beat application and Garmin HRM-Dual™ transmitted its signal to the OMNIA Cardiopulmonary Diagnostic Suite (version 1.6.5, COSMED, Rome, Italy) database on

the laboratory computer. The metabolic system harness was fitted to each subject to ensure a tight fit with limited movement of the device throughout exercise. The straps were adjusted according to the subject's height and torso circumference, with one fitted tightly around the chest and the other around the thorax region. The metabolic system was placed on the harness in the mid-back region. The subjects were fitted for the masks to sit on their faces without any visible leaks in the system. The masks were tightened with a head strap to seal the mask to the face and to fit comfortably.

4.8 Females of Reproductive Capacity

Females of reproductive age were studied in the early-follicular phase (days 1-6) of their menstrual cycle for all three treatment arms (A, B and C), and repeated Arm A in the luteal phase (days 18-24) of their menstrual cycle. Females using oral contraceptives were studied during their placebo pill week for all three treatment arms and repeated Arm A during week 3 (days 15-21) of their pills. Subjects tracked their own menstrual cycle using their usual tracking system. Upon arrival at the laboratory for their luteal study visit, subjects not using oral contraceptives were tested to confirm ovulation using urine analysis strips (Ovulation Double Check®, Proov). Subjects performed the analysis themselves after being instructed on how to use the urine strips. The strips tested for Pregnanediol Glucuronide (PdG), a urine metabolite of progesterone, which if positive, will show a single line on the urine strip. This single line confirms PdG levels above the 5ug/ml threshold, indicating ovulation. Females of reproductive capacity also tracked their menses on a hard-copy calendar provided for the study.

4.9 Data Analysis

4.9.1 Downloads and Analysis

All BG data was recorded on a lab created form and later entered into a computerized form. Time in target range was defined as BG values between 4.0-10.0 mmol/L during exercise. Data from the Polar H10 monitor automatically uploaded to the Polar Flow software system, which was later downloaded from the server. All data from the metabolic system and Garmin HRM-Dual™ was transmitted to the OMNIA software via bluetooth, which was later downloaded. CGM data was connected via an online system (Dexcom CLARITY®) which was downloaded a minimum of 24 hours after the in-clinic visit.

CGM data was used to analyze recovery data; 6hr post-exercise, 24hr post-exercise, and overnight (00:00-6:00am) glucose data. Hyperglycemia was defined as glucose values above 10.0 mmol/l, hypoglycemia was defined as glucose values < 4.0 mmol/L, severe hypoglycemia was defined as values < 3.0 mmol/L, and euglycemia was defined as values between 4.0-10.0 mmol/L in accordance with the International Consensus on use of CGM (207). Mean glucose was calculated for these time periods and GV was calculated for 24hr post-exercise. The number of hypoglycemic events was defined as a minimum of three consecutive values < 4.0 mmol/L.

RER, VO_2/kg, and energy expenditure (EE) were obtained from gas collection and the average was calculated from the last five minutes of wear from the start, middle and end of exercise. Fuel utilization was calculated from data output from gas collection (208).

HR was calculated throughout exercise by averaging the values that were recorded every 15 minutes. Total walking distance was calculated using the duration of exercise and speed on the treadmill. RPE was analyzed over the course of the exercise and between the three arms of

exercise. Estimations of BG levels provided by the subjects throughout exercise were compared to the averaged SMBG measured at the same time point.

Total carbohydrate consumption was calculated by summing each of the four rounds of carbohydrate feeding and any carbohydrates used for treatment of hypoglycemia. Difference in carbohydrate feeding was analyzed by separating the first hour of carbohydrate feeding from the second hour. Caloric intake was calculated based on total grams of carbohydrates consumed, using the manufacturers nutritional values provided.

TDD of insulin was recorded for each in-clinic study day and compared to an average TDD over the previous two weeks before enrolling in the study. Total carbohydrate consumption on the in-clinic study days was recorded and compared between the three arms.

4.9.2 Statistical Analysis

All statistical analyses were conducted using GraphPad Prism version 7.0 (GraphPad Software, California, USA). Statistical significance was set at $P < 0.05$ and a Tukey post hoc test was used if significance was found. The changes in glucose concentrations during exercise, RER, carbohydrate oxidation, fat oxidation, ketones, energy expenditure, hormone levels, Edinburgh values, estimated glucose MARD, and CGM 24-hr and overnight tracings were compared using two-way repeated measures ANOVA (condition by time). A one-way repeated measures ANOVA was used to compare exercise intensity, baseline glucose, change in BG from start to end of exercise, nadir glucose, carbohydrate consumption, recovery mean BG, hypoglycemia frequency, GV and severe hypoglycemia, CGM time in euglycemia, hyperglycemia, and hypoglycemia range, and TDD. A paired t-test was used in place of a one-way repeated measures ANOVA for the menstrual phase data. Data are presented as mean (SD).

The sample size of this study was calculated using the change in BG levels over exercise as the outcome measure. The minimal difference in change in BG to be detected was set as 1.0 mmol/L, with 80% power, and an alpha level of 0.05. Using G*Power (Heinrich Heine University Düsseldorf, Düsseldorf, Germany, version 3.1.9.3), the sample size calculated was 12 subjects.

5.0 Results

5.1 Participant Characteristics

A total of 16 participants were recruited for this study and 15 participants (9 females) completed all arms of the study. One participant dropped out after completing two of the three arms of the study due to personal medical reasons unrelated to the trial. Participants were all adults (aged 35.5 ± 14.9 years), with a BMI of 25.0 ± 5.5 kg/m^2 and HbA_{1c} of 6.9 ± 0.9 %. Table 1 describes the general patient characteristics of those who completed the study and Table 11 separated between males and females.

All participants were using CSII (67% Omnipod Insulin Management System Users), and either using insulin lispro (Humalog; Eli Lilly and Company, Indianapolis, IN) (n = 5) or insulin aspart (Novorapid or Fiasp; Novo Nordisk, Bagsvaerd, Denmark) (n = 10). Table 2 describes the diabetes specific characteristics of those who completed the study.

Based on two questionnaires used to assess hypoglycemia awareness (Gold score = 2.6 ± 1.2 and Clarke score), 2 participants had reduced hypoglycemia awareness and 13 were hypoglycemia aware. Based on the International Physical Activity Questionnaire – Short From, one participant had low activity levels, 6 participants were moderately active, and 8 participants highly active (metabolic equivalent of task-minutes per week = 3,227 ± 2,286); overall the participant group could be categorized as active.

5.2 Data Loss

No data was lost during in-clinic measurements. However, CGM data was lost during 6 exercise sessions as a result of participants' CGM expiring and failure to replace it prior to initiation of exercise session, as well CGM data was lost during 2 recovery sessions due to personal cellular device malfunctions.

5.3 In-Lab Exercise

5.3.1 Exercise Characteristics

Table 3 describes the cardiometabolic outcome variables throughout the three arms of exercise. Participants covered an average of 11.8 ± 0.5 km during the two hours of exercise, with an average incline of 3.3 ± 1.4 %. Participants were exercising at 47.3 ± 7.5%, 46.7 ± 6.9% and 46.6 ± 7.6% of their VO_{2peak} (Table 3, $P = 0.68$), and 46.3 ± 5.2%, 46.3 ± 5.5% and 45.2 ± 5.2% of their HRR (Table 3, $P = 0.68$) for the CHO, 50% BRR and Combo arm, respectively. RPE did not differ between the three arms, with CHO, 50% BRR and Combo having an average RPE throughout exercise of 4.3 ± 1.3, 4.4 ±1.5 and 4.0 ± 1.4, respectively (Table 3, $P = 0.08$).

5.3.2 Blood Glucose Data During Exercise

Figure 1*A* represents the absolute glucose concentrations from 30 minutes pre-exercise until 20 minutes post-exercise. Glucose concentration at exercise start was 9.0 ± 3.5 mmol/L, 9.2 ± 3.0 mmol/L and 8.9 ± 3.7 mmol/L for the CHO, 50% BRR and Combo arm, respectively (Table 4, $P > 0.05$). BG concentration was similar between the three arms from 20 minutes pre-exercise until halfway through exercise (Fig. 1*A,* all $P > 0.05$). After 90 minutes of exercise, the Combo arm had significantly higher glucose concentrations compared to the 50% BRR arm (Fig. 1*A*, $P < 0.05$), but not the CHO feeding arm. After 105 minutes of exercise until 20 minutes into recovery, the Combo arm had higher glucose concentrations compared to both the 50% BRR arm and the CHO feeding arm (Fig. 1*A*, all $P < 0.01$). Mean glucose following 2 hours of exercise was 6.3 ± 2.3, 7.3 ± 2.5, and 9.2 ± 2.7 mmol/L in the CHO, 50% BRR and Combo arm, respectively.

Figure 1*B* shows the change in BG concentrations from 30 minutes pre-exercise until 20 minutes into recovery, normalized to starting exercise glucose level. Change in BG was similar between the three arms for the first 65 minutes of exercise, with a decline in BG of -1.2 ± 2.5, -1.2

± 1.9 and -0.7 ± 2.4 mmol/L in the CHO, 50% BRR, and Combo arm, respectively (Fig. 1*B*, all $P > 0.05$). After 90 minutes of exercise, the 50% BRR arm had the greatest drop in BG of -1.1 mmol/L compared to the Combo arm that had a modest increase of 0.5 mmol/L (Fig. 1*B*, $P < 0.01$). After 105 minutes of exercise, the Combo arm had the smallest change in BG compared to both the CHO arm and the 50% BRR arm (Fig. 1*B*, both $P < 0.01$). By the end of exercise, the Combo arm had a modest increase in BG of 0.3 ± 2.6 mmol/L, compared to the CHO arm with a decline of -2.7 ± 3.4 mmol/L and the 50% BRR arm with a decline of -1.9 ± 2.5 mmol/L (Table 4). From the end of exercise until 20 minutes into recovery, all arms had a modest incline in BG of 0.7 ± 1.4, 0.6 ± 0.8 and 0.6 ± 0.9 mmol/L in the CHO, 50% BRR and Combo arm, respectively (Table 4, all $P > 0.05$). Nadir glucose during exercise was 5.8 ± 1.9 mmol/L, 6.7 ± 2.2 mmol/L and 7.4 ± 2.8 mmol/L for the CHO, 50% BRR, and Combo arm, respectively (Table 4, all $P > 0.05$).

The most number of hypoglycemic events occurred in the CHO arm (3 events in 2/15 [13%] individuals), as compared with the 50% BRR arm and Combo arm (both 1 event in 1/15 [7%] individuals) (Table 4, all $P > 0.05$). The greatest number of hypoglycemic events occurred in the CHO arm, at 65min of exercise and during two time points at the end of exercise (Table 4). The 50% BRR arm had one hypoglycemic event at 125min of exercise and the Combo arm at 65min of exercise (Table 4).

Glucose time in range (TIR) during exercise was highest in the CHO with 81.5 ± 24.4%, followed by the 50% BRR arm with 76.3 ± 33.6% and the Combo arm with the lowest TIR of 62.2 ± 36.8% (Table 4, all $P > 0.05$).

5.3.3 Carbohydrate Data

Table 5 represents the carbohydrate consumption throughout exercise in each of the arms. The total grams of carbohydrates consumed in the CHO, 50% BRR and Combo arm were 38.0 ±

18.8g, 0.8 ± 3.1g and 29.5 ± 16.2g, respectively (Table 5). The 50% BRR arm required less grams of carbohydrates of Skittles™ during exercise (ExCarbs) throughout exercise compared to the other two arms (Table 5, both $P < 0.001$). The average dose to body weight for the CHO, 50% BRR and Combo arm was 0.25 ± 0.1 g/kg/hr, 0.01 ± 0.0 g/kg/hr and 0.20 ± 0.1 g/kg/hr, respectively (Table 5). When separated between the first and second hour, the ExCarb consumption required between the three arms in the second hour was highest in the CHO arm at 0.26 ± 0.1 g/kg/hr, followed by the Combo arm at 0.20 ± 0.1 g/kg/hr and the 50% BRR arm at 0.01 ± 0.0 g/kg/hr (Fig. 2, all $P <$ 0.05).

5.3.4 Energy Expenditure

Table 3 describes the energy expenditure (EE) characteristics throughout the three arms of exercise. The RER values between the three arms after 15 minutes of exercise were similar, with an average of 0.80 ± 0.06. However, after 90 minutes of exercise the 50% BRR arm had a lower RER of 0.80 ± 0.05 compared to the CHO arm at 0.84 ± 0.04 (Fig. 3*A*, $P < 0.05$). During the last 15 minutes of exercise the RER of the 50% BRR arm was significantly lower than that of the CHO feeding arm, at 0.79 ± 0.04 and 0.83 ± 0.04, respectively (Fig. 3*A*, $P < 0.05$), but the Combo arm was not different from either at 0.81 ± 0.03. After two hours of exercise, there was an increase in RER in both the CHO and Combo arm by 0.03 ± 0.06 and 0.01 ± 0.05, respectively, and a decrease in the 50% BRR arm by -0.02 ± 0.05.

Carbohydrate oxidation was similar between all three arms in the first 15 minutes of exercise and halfway through exercise with an average of 1.71 ± 0.87 g/min and 1.71 ± 0.77 g/min, respectively, for all three arms combined. At the end of exercise, carbohydrate oxidation was highest in the CHO feeding arm and lowest in the 50% BRR arm, at 1.69 ± 0.7 g/min and 1.38 ± 0.6 g/min, respectively (Fig. 3*B*, $P = 0.20$). All arms had a modest decline in carbohydrate

oxidation over two hours. Fat oxidation was similar between all three arms in the first 15 minutes of exercise with an average of 0.50 ± 0.03 g/min. Halfway through exercise, fat oxidation was higher in the 50% BRR arm at 0.47 ± 0.1 g/min compared the CHO arm at 0.37 ± 0.1 g/min (Fig. 3*C*). During the last 15 minutes of exercise, fat oxidation continued to increase in the 50% BRR arm at 0.51 ± 0.2 g/min compared to the CHO arm at 0.39 ± 0.1 g/min (Fig. 3*C*, $P < 0.05$). Fat oxidation in the Combo arm fell in between the CHO and 50% BRR arm during exercise (0.51 ± 0.2 g/min, 0.39 ± 0.1, and 0.44 ± 0.1, for middle and end of exercise, respectively) (Fig. 3*C*).

Ketone levels measured pre-exercise were similar between the three arms, starting with an average of 0.2 ± 0.1 mmol/L. Following exercise, there was a significant difference in ketone levels between the three arms, with 50% BRR having the highest levels, followed by the Combo arm and then the CHO arm, at 0.4 ± 0.3 mmol/L, 0.3 ± 0.2 mmol/L and 0.1 ± 0.1 mmol/L, respectively (Fig. 4, all $P < 0.05$). The 50% BRR arm had a significant increase in ketone levels from pre- to post-exercise (Fig. 4, $P < 0.05$). The highest reported post-exercise ketone levels in the CHO, 50% BRR and Combo arm were 0.2 mmol/L, 0.9 mmol/L and 0.4 mmol/L, respectively.

EE was transient within all conditions, but values remained unchanged between conditions during the start, middle and end of exercise (Table 3, all $P > 0.05$). EE during the first 15 minutes of exercise was higher than at the middle and end of exercise, at 7.6 ± 1.9 kcal/min, 7.1 ± 1.9 kcal/min and 6.9 ± 1.9 kcal/min, respectively (Table 3, both $P < 0.0001$). Total average calories burned during the two hours of exercise was 864.2 ± 225.1 kcal. The net loss in calories was highest in the 50% BRR arm (859.7 ± 239.6 kcal) compared to the CHO arm (709.2 ± 217.4 kcal) and the Combo arm (736.8 ± 200.9 kcal) (Table 3, both $P < 0.01$).

5.3.5 Hormone Levels

Figure 5 represents salivary free cortisol pre- and post-exercise in each of the three conditions. The CHO and Combo arm had a significant decline in cortisol levels over the time course of exercise, with the CHO levels decreasing from 44.3 ± 19.4 ng/mL to 28.8 ± 14.0 ng/mL and the Combo levels decreasing from 40.7 ± 15.5 ng/mL to 27.7 ± 9.5 ng/mL (both $P < 0.01$). The 50% BRR arm had a non-significant decline in cortisol levels from 41.3 ± 15.5 to 32.7 ± 14.8 ng/mL ($P = 0.21$). Combining all three arms, the participants slept an average of 6.7 ± 1.3 hours with 1.4 ± 1.9 interruptions to their sleep the night before exercise. The individuals were awake for an average of 2.4 ± 0.9 hours before commencing exercise. There was no difference between the three arms in hours slept, interruptions to sleep and waking hours prior to exercise commencing (all $P > 0.05$).

Figure 6*A* represents circulating glucagon concentrations across all conditions. In the CHO arm, glucagon concentrations were similar throughout exercise at 16.3 ± 13.0 pg/mL, 15.5 ± 15.5 pg/mL and 18.1 ± 8.9 pg/mL at the beginning, middle and end of exercise, respectively (Fig. 6*A*, $P > 0.05$). In the 50% BRR arm, glucagon concentrations significantly increased by the end of exercise (30.9 ± 22.3 pg/mL), compared to the beginning (15.1 ± 8.9 pg/mL) (Fig. 6*A*, $P > 0.05$) and middle of exercise (21.3 ± 14.5 pg/mL) (Fig. 6*A*). A similar increase in glucagon concentration was observed in the Combo arm, where glucagon at the end of exercise (22.7 ± 19.2 pg/mL) was higher compared to the start (11.7 ± 7.0 pg/mL) and the middle of exercise (13.9 ± 7.5 pg/mL) (Fig. 6*A*, both $P > 0.05$). The final glucagon concentration in the 50% BRR arm was higher than the final glucagon concentration in the CHO arm (Fig. 6*A*, $P > 0.05$).

Figure 6*B* represents circulating free insulin concentrations across all conditions. Insulin concentrations were similar in all three conditions over all three time points. Both the CHO and

50% BRR arm had a small decline in insulin concentration during exercise (Fig. 6*B*) of 14.47 ± 14.3 mU/L, 13.1 ± 21.7 mU/L, and 12.7 ± 13.0 mU/L for the CHO arm and 15.9 ± 22.8 mU/L, 13.7 ± 30.8mU/L, and 9.0 ± 16.4 mU/L for the 50% BRR arm. The Combo arm had a decrease in insulin halfway (65min) through exercise (6.8 ± 5.4 mU/L) followed by an increase at the end (140min) of exercise (20.5 ± 43.3 mU/L).

5.3.6 Edinburgh and Glucose Estimation

Figure 7 represents the Edinburgh Hypoglycemic Symptom questionnaire scores. There was a significant trial by time interaction for the total score ($P = 0.04$). More specifically, at time points 65 and 105 minutes of exercise, the Combo arm had a lower total score compared to both the CHO and 50% BRR arm (Fig. 7*A*, all $P < 0.01$). This difference between the Combo arm compared to CHO and 50% BRR arm at time points 65 and 105 minutes of exercise is also seen in autonomic scoring (Fig. 7*B*, all $P < 0.01$). At the end of the exercise session, the Combo arm had a lower total score compared to the 50% BRR arm only (Fig. 7*A*, $P = 0.01$). The Combo arm had a lower autonomic score compared to the 50% BRR arm at all time points (Fig. 7*B*, all $P < 0.05$).

Figure 8 represents Clarke error grid between estimated BG and SMBG taken every half hour throughout exercise. The CHO arm had 93.4% guesses fall in zones A and B, 4.0% in zone C, and 1.3% in each of zone D and E. The 50% BRR arm had 100% of the guesses fall in zones A and B. The Combo arm had 98.7% guesses fall in zone A and B, and 1.3% in zone D. The CHO arm had a higher MARD in estimated BG and SMBG compared to the Combo arm at 105 minutes of exercise ($P = 0.02$), and a higher MARD compared to both the 50% BRR arm and Combo arm at 140 minutes of exercise (both $P < 0.01$). At this time, the MARD in estimated BG and SMBG

of the CHO arm was 52.4 ± 42.4% compared to the 50% BRR arm at 28.8 ± 27.5% and the Combo arm at 24.8 ± 16.9%.

5.4 Recovery Data

Table 6 describes the recovery data following the exercise session in each of the three conditions. Six hours, 24 hours and overnight following exercise, the Combo arm had the highest incidence of hyperglycemia compared to the other two arms at 35.5 ± 32.0%, 35.0 ± 21.0%, and 52.6 ± 38.4%, respectively (Table 6, all $P > 0.05$). The CHO arm had the highest TIR of 72.6 ± 21.6%, 73.3 ± 18.6%, and 67.3 ± 38.2% at six hours, 24 hours and overnight post-exercise (Table 6, all $P > 0.05$). Hypoglycemia incidence was 3.3 ± 3.1%, 3.8 ± 5.1%, and 4.2 ± 5.5% 24 hours post-exercise for the CHO, 50% BRR and Combo arm, respectively (Table 6, all $P > 0.05$).

GV 24-hr post-exercise was 29.6 ± 6.9%, 33.2 ± 6.6% and 32.5 ± 8.2% for the CHO, 50% BRR and Combo arm, respectively (Table 6, all $P > 0.05$). Six hours following exercise, the 50% BRR arm had a higher mean glucose of 9.4 ± 2.9 mmol/L compared to the CHO arm of 7.9 ± 2.0 mmol/L (Table 6, $P = 0.02$). The three conditions had a similar frequency of hypoglycemic events and severe hypoglycemia 24 hours following exercise, with an average of 1.0 ± 0.4 events per 24 hours and 0.5 ± 0.1%, respectively.

Figure 9*A* shows the CGM tracing in each of the three conditions 24 hours following the completion of exercise. The Combo arm had higher interstitial glucose levels compared to the CHO arm immediately following exercise for 65 minutes (Fig. 9*A*, all $P < 0.05$). Figure 10 shows the overnight CGM tracing in each of the three conditions from midnight until 6:00 AM following the in-lab exercise. The Combo arm had higher interstitial glucose levels from 2:10 AM until 4:10 AM compared to the CHO arm (Fig. 10, all $P < 0.05$). There was no difference in total daily dose of insulin on exercise days compared to a control day without exercise (Table 6).

5.5 Correlations

The ExCarbs consumed in both the CHO and Combo arm combined are correlated with body weight (Figure 11*A,* $r^2 = 0.17$, $P = 0.02$) and starting BG levels (Figure 11*B*, $r^2 = 0.60$, $P < 0.01$). The starting cortisol levels are correlated with hours awake (Figure 11*C*, $r^2 = 0.34$, $P < 0.01$), but not with total hours slept or interruptions to sleep (both $P > 0.05$). BG levels were not correlated with glucagon levels throughout exercise (Figure 11*D*, $r^2 = 0.00$, $P = 0.85$).

5.6 Follicular and Luteal Phase Exercise

A sub-analysis was carried about between the CHO arm during the luteal phase and follicular phase of female participants (n = 7). Participants were all women of reproductive capacity (age 27.7 ± 5.5 years) with a BMI of 27.1 ± 7.5 kg/m^2 and HbA1c of 6.9 ± 0.6%. Descriptive statistics of the participants in this sub-analysis are found in Table 7. The cardiometabolic outcomes are shown in Table 8. The relative exercise intensity in the luteal arm and follicular were 43.5 ± 4.9% and 45.6 ± 5.8 of maximum aerobic capacity, and 43.3 ± 6.6% and 46.8 ± 3.3% of HRR (Table 8, both $P > 0.05$), respectively. The RER and carbohydrate oxidation did not differ significantly between the two conditions or over time (Table 8, $P > 0.05$). Fat oxidation rates did not differ between the two conditions (Table 8, $P > 0.05$), but in the follicular condition, fat oxidation decreased as exercise time increased (Table 8, $P < 0.01$). Ketones pre- and post-exercise did not differ between the two conditions (Table 8, $P > 0.05$). Both the luteal and follicular conditions had similar EE (6.0 ± 1.1 kcal/min and 6.3 ± 1.0) and net loss of energy (569.7 ±127.0 and 573.3 ± 69.7), respectively (Table 8, $P > 0.05$ for both).

Figure 12*A* represents the absolute glucose concentrations from 30 minutes pre-exercise until 20 minutes post-exercise. There is no difference in BG between the conditions at any time point (Fig. 12*A*, all $P > 0.05$). The glycemic outcomes are shown in Table 9. The luteal and

follicular condition had 82.5 ± 21.1% and 87.3 ± 19.7% time in range with a mean BG of 8.4 ± 1.7 mmol/L and 8.0 ± 1.8 mmol/L during exercise, respectively (Table 9, $P > 0.05$ for both). Figure 12*B* shows the change in BG concentrations from 30 minutes pre-exercise until 20 minutes into recovery, normalized to starting exercise glucose level. Change in BG was similar between the luteal and follicular arm (Table 9, all $P > 0.05$). The luteal arm had a decrease of -1.8 ± 2.7 mmol/L in BG throughout exercise and the follicular arm a decrease of -1.2 ± 1.7 mmol/L (Table 9, $P > 0.05$). There was one incidence of hypoglycemia in the luteal condition and none in the follicular condition (Table 9, $P > 0.05$). ExCarbs were similar between the two arms, ranging between 0.26-0.28g/kg/hr throughout the first and second hour of exercise ($P > 0.05$). Nadir glucose was identical between both the follicular and luteal arm at 6.4 mmol/L (Table 9).

When comparing the estimated BG versus SMBG, there was no difference in accuracy between the two conditions (all $P > 0.05$). In the luteal arm, MARD in estimated BG and SMBG ranged from 19.1 ± 12.4% to 33.7 ± 53.8% at different time points. In the follicular arm, MARD ranged from 10.5 ± 7.3 to 51.5 ± 26.4% at different time points. There was no difference in Edinburgh questionnaire scores between the luteal and follicular arm (all $P > 0.05$).

Figure 13 represents salivary free cortisol pre- and post-exercise in each condition. Both the luteal condition ($P = 0.07$) and follicular condition ($P = 0.31$) had decreasing cortisol levels from start to end of exercise (Figure 13). The participants slept for an average of 6.5 ± 1.2 hours the night prior with 2.1 ± 2.0 interruptions, and were awake for 2.2 ± 1.1 hours prior to commencing exercise. There was no difference between the two conditions (all $P > 0.05$). Figure 14*A* represents circulating glucagon concentrations throughout exercise in both conditions. The luteal arm (27.5 ± 25.2 pg/mL) had higher glucagon concentrations pre-exercise compared to the follicular arm (12.9 ± 11.8 pg/mL). Figure 14*B* represents circulating free insulin concentrations

across the two conditions. There was no difference between the two conditions (Fig. 14*B*, all $P > 0.05$).

Table 10 outlines the recovery data following both the luteal and follicular exercise session. In recovery, the follicular arm had increased interstitial glucose TIR compared to the luteal arm, both 6- and 24-hours post-exercise (Table 10, both $P > 0.05$). The luteal arm had decreased time in range compared to the follicular arm overnight, at 41.3 ± 44.4% and 78.77 ± 29.8%, respectively with increased time in hyperglycemia in the luteal arm at 58.7 ± 44.4% compared to the follicular arm at 21.2 ± 29.8% (Table 10, both $P < 0.05$). No difference was observed between the two arms in time spent in hypoglycemia, severe hypoglycemia, and frequency of hypoglycemia for 24-hours following exercise (Table 10, all $P > 0.05$).

Figure 15*A* represents the 24-hour interstitial glucose levels following exercise in both conditions. There were no differences between the follicular and luteal arm (Fig. 15*A*, all $P > 0.05$). Figure 15*B* represents the overnight interstitial glucose levels the night following exercise in both conditions. At all time points, the luteal arm had a higher average glucose compared to the follicular arm (Fig. 15*B*, all $P > 0.05$).

6.0 Discussion

6.1 Principal Findings

This study demonstrated three different strategies to safely engage in moderate-intensity exercise in the morning fasted state. With a total of 45 exercise visits, only 4 (9%) had instances of hypoglycemia. The incidence of participants experiencing hypoglycemia in the CHO arm (13%) was modestly higher than the Combo arm and 50% BRR arm (both 7%). The carbohydrate dosage of 0.3 g/kg/hr appears to be an effective strategy (Table 4). The 50% BRR arm had a similar response in BG to the CHO arm in the first hour of exercise, both with a decline of -1.2 mmol/L and in the second hour with an overall decrease in BG of -1.9 ± 2.7 mmol/L in the 50% BRR arm and -2.7 ± 3.4 mmol/L in the CHO arm (Figure 1*B*). Both arms had similar starting BG, despite reducing insulin 90 minutes prior to exercise commencing in the 50% BRR arm. These two strategies provide a solution for pre-planned exercise (50% BRR set 90 minutes pre-exercise) or spontaneous exercise (carbohydrate dose of 0.3 g/kg/hr).

Adjustments often need to be made with insulin dosage and/or carbohydrate intake in order to prepare for activity. Previously in the Riddell lab, an insulin reduction of 50-80% set 90 minutes before activity in the post-absorptive state was an effective strategy for an hour of moderate aerobic activity (5). However, this strategy requires significant pre-planning for exercise and may not be possible if activity is occurring early in the morning. Therefore, the aim of the current study was to compare this strategy to strategies that could be implemented at exercise start. Insulin reduction strategies alone at exercise start were not able to prevent a drop in glycemia (5,164,165,209) and carbohydrate dosage reported is variable (167,168,210).

All three arms had stable BGs for the first 30mins of exercise, with an average change of -0.1 mmol/L, -0.5 mmol/L and -0.2 mmol/L for the CHO, 50% BRR, and Combo arm, respectively.

A similar study found that there was low exogenous glucose demand in the first 20 mins of exercise irrespective of BG (211). The Combo arm had the most stable BG levels over two hours of exercise, with a -0.7 ± 2.4 mmol/L decline after one hour, followed by a 0.3 ± 2.6 increase after two hours of exercise. However, this arm spent only 58.3% time in target glucose range compared to the CHO arm at 81.5% and the 50% BRR arm at 77.1%. Despite having minimal BG changes throughout exercise, the Combo arm spent more time in hyperglycemia. This hyperglycemia during exercise is often seen when there is overcompensation to protect against hypoglycemia in T1D (210). Having a temporary BRR set for two hours of exercise with the addition of carbohydrate consumption caused BG levels to rise in the second hour of exercise. It was at this time (75-90 mins of exercise) that the Combo arm had significantly higher BG levels than the other two arms. Since previous research has shown that it takes approximately 90 mins for the BRR to take effect (5), the last carbohydrate dose at 90 mins of exercise may not be necessary in the Combo arm. This is also shown when looking at the amount of ExCarbs needed in each arm. The CHO arm needs a higher dose of 0.26 g/kg/hr in the second hour compared to 0.20 g/kg/hr in the Combo arm (Table 5, $P < 0.05$), whereas in the first hour of exercise no difference in ExCarbs is observed. The ExCarb dose is slightly less than the estimated 0.3 g/kg/hr due to individuals starting above the cut-off of 10.0 mmol/L or reaching this cut-off during exercise. It is important to note that starting BG levels were more strongly correlated with ExCarbs consumed throughout exercise compared to body weight (Fig. 11*A* and *B*). This shows how important it is to take into consideration starting BG levels prior to exercise to determine how many ExCarbs should be consumed.

The 50% BRR arm had only 1/15 (7%) individual require 12g of carbohydrates, whereas 14/15 (93%) participants exercised for 120 mins without any exogenous carbohydrate

consumption. It was in the 50% BRR arm where the lowest RER was observed (Table 3). RER is greatly influenced by the substrate type used for energy production (212). A lower RER, is indicative of higher lipid substrate utilization compared to carbohydrate utilization. This is supported with increased fat oxidation in the 50% BRR arm and decreasing carbohydrate oxidation. Exercising in the fasted state induces fat to be utilized more, as observed with the CHO arm having a higher RER, higher carbohydrate oxidation and lower fat oxidation compared to the 50% BRR arm (Table 3). The 50% BRR arm more heavily relying on fat oxidation was also evidenced in the elevated ketone levels (Figure 4). Ketone bodies spare the carbohydrate supply by using fat as a substrate (38). Insulin levels are the main driver of whether ketone bodies are used as fuel (40). With the 50% BRR arm having the lowest exogenously administered insulin, the highest ketone levels were seen here, followed by the Combo arm with lowered basal insulin levels, and unchanged ketones in the CHO arm which had unchanged basal insulin. It is important to note that no individuals reached unsafe ketone levels (≥ 1.5 mmol/L) during exercise (210). Although the CHO arm and Combo arm had similar ExCarbs intake, the lower insulin in the Combo arm caused higher fat utilization in this arm.

Participating in physical activity for individuals with T1D has many health benefits, such as improved glycemic control, overall wellbeing, and life expectancy with decreased cardiovascular disease and insulin resistance (213). Despite these benefits, there is reduced physical activity levels in T1D because of barriers, the main being increased risk of hypoglycemia (161). With decreased activity in this population, obesity is becoming a concern (214) and there is little research addressing how to combat this problem (215). With only one hypoglycemic event occurring in both the 50% BRR arm and Combo arm, these are two effective strategies for increased fat burning and may help in weight control in T1D.

The role of insulin concentration is one of the main factors in determining amount of carbohydrates needed during exercise (216). The current study, being done in the morning fasted state, had all subjects exercising with low circulating insulin levels in all three arms. By being able to exercise with such a low exogenous glucose supply, all three strategies had caloric deficit with minimal hypoglycemia during exercise. This caloric deficit with good BG control may be favourable for individuals with T1D who are looking for safe weight loss strategies.

The very low exogenously delivered insulin in the 50% BRR arm also impacted hormone regulation in the body. There was an increase in glucagon levels by the end of exercise in the 50% BRR arm compared to the starting levels in all three arms, and CHO arm at the end of exercise (Figure 6*A*). Typically, the rise in glucagon to promote hepatic glucose output to protect against low BG levels is blunted in T1D (115). A study looking at either 30 or 60 mins of exercise following a meal found no glucagon response (1), similar to that of the CHO arm in the present study. A similar study to the current, following 120 mins of moderate exercise, found a rise in glucagon at the end of exercise compared to the start, irrespective of BG levels (146). The 50% BRR arm may have had an increase in glucagon due to having such low circulating insulin levels and having performed a long duration of exercise. It is unlikely that the BG levels during exercise impacted glucagon levels, as there was no correlation between the two (Fig. 11*D*). Cortisol also appeared to be impacted by the aggressive BRR. Typically, upon awakening, there is a decline in cortisol as it is released in a diurnal rhythm. Although higher intensity activities may cause an increase in cortisol (60), this was not observed in the present study. A significant decline in cortisol was observed only in the CHO and Combo arm. Previous studies found that caloric restriction (217) and low carbohydrate diets (218) can cause elevated cortisol levels during exercise due to higher stress on the body. The 50% BRR arm had individuals fasting for a minimum of 8 hours

with no food consumption during exercise, which may have resulted in higher cortisol levels. The low insulin levels also allow cortisol to promote lipolysis (34), further promoting fat oxidation in the 50% BRR arm. Cortisol also stimulates glucagon release (31), which may have aided in this arm during exercise. It is important to note that the hours awake prior to exercise beginning correlated with starting cortisol levels (Figure 11*C*), which may in turn impact insulin sensitivity when planning exercise. Individuals with T1D may find they are least insulin sensitive if exercising immediately upon waking up.

The identical 50% BRR strategy used in the Zaharieva et al. study had a reduction in BG levels of -2.6 ± 2.8 mmol/L over 60 mins of exercise (5), which is more than what was observed in 120 mins of exercise in the current study. The observed differences may be due to increased cortisol levels in this current morning exercise compared to the afternoon exercise in the Zaharieva et al. study. Exercise in the morning, with higher cortisol and higher insulin resistance, may further protect against hypoglycemia.

The Edinburgh Hypoglycemic Symptom Score questionnaire used in the present study had an increase in all arms in the autonomic scoring. This sub-section of the questionnaire contains the symptoms of sweating and hunger, which would be common during exercise in the fasted state. The 50% BRR arm and CHO arm had significantly higher total and autonomic scores as exercise progressed compared to the Combo arm. Although not indicative of hypoglycemia, the two arms with the largest drop in BG levels experienced higher scores on this questionnaire. This may indicate that the overlap in symptoms between exercise and hypoglycemia may be heightened when BG levels are dropping. The CHO arm had the highest MARD and most guesses of BG outside of zones A and B (Figure 8). Individuals may either be unable to detect the biggest drop in

BG that occurred in this arm, or their decision may be influenced by the amount of ExCarbs they are receiving, thinking that the supplement should prevent a drop in BG.

Following exercise, insulin sensitivity can stay heightened for up to 17 hours (154), which could increase the risk of hypoglycemia in individuals with T1D (219). Nocturnal hypoglycemia is a common problem in T1D following prolonged activity (220). The current study had minimal hypoglycemia overnight, ranging between 1.3-3.4% in the three different arms. This is most likely a result of the 20% BRR set to protect against this occurrence. The highest time spent in hypoglycemia was in the CHO arm six hours following exercise at 6.8%. This arm had no insulin reduction which could have caused increased risk of hypoglycemia.

The 50% BRR arm had an increased mean BG six hours following exercise compared to the CHO arm. The elevated ketones and aggressive insulin reduction throughout exercise may have contributed to higher BG levels. Individuals were asked to reduce their meal bolus following exercise, which may not have been necessary for this arm. The Combo arm also tended to have increased BG levels following exercise, which is most likely a result of finishing the exercise with higher BG and possibly overfeeding with ExCarbs. Overall, all three arms had similar recovery and GV was not impacted by the different strategies. GV ranged from 29.6% to 33.2%, which is below the 36% threshold set for stable glucose control (221).

The sub-analysis evaluating the effect of the menstrual cycle on glucose control during exercise showed a similar response between the luteal and follicular phase. Both groups had a similar drop in BG levels throughout the two hours of exercise, with one hypoglycemic episode in the luteal phase (Table 9). Previous studies found increased time spent in hyperglycemia, elevated BG levels around meals (131), decreased insulin sensitivity (130), and increased insulin resistance in the luteal phase which was positively associated with estradiol and progesterone levels (222).

These patterns were not evident throughout the exercise. However, the luteal phase did have elevated starting cortisol and glucagon levels compared to the follicular phase. Previous studies report higher cortisol levels in the luteal phase compared to the follicular phase (223,224). A study in healthy ovulating women also found elevated glucagon concentrations in the luteal phase compared to the follicular phase of the menstrual cycle which was believed to be attributed to higher progesterone levels since alpha cells contain receptors for this hormone (225). This relationship between progesterone and glucagon, to our knowledge, has not been observed in T1D previously, and could be a contributing factor to commonly observed hyperglycemia in the luteal phase. Despite the similar profile during exercise, the luteal phase did consistently have lower TIR and higher time spent in hyperglycemia during recovery, especially overnight (Table 10). This is consistent with what is seen in the literature. In the present study, it appears that insulin resistance and hyperglycemia, often present during the luteal phase, did not occur during exercise, but impacted recovery.

6.2 Strengths

There are three main strengths of the in-lab design of this project. Having a prolonged exercise period allowed important changes in BG levels, hormone levels, carbohydrate needs and fuel utilization to be observed between the three different strategies. Measuring hormone levels identified changes in glucagon and cortisol to be evident dependent upon the strategy used. Lastly, this study had a randomized crossover design.

Providing CGM devices and asking subjects to keep meals consistent after their visits allowed differences in recovery to be observed. This study had a diverse population, with 60% females, age ranging from 18 years to 60 years, diabetes duration from 4 years to 39 years, and BMI ranging from 19.4 kg/m^2 to 43.0 kg/m^2, making the results applicable to a wide range of

individuals with T1D. Lastly, females were also studied in two different phases of their menstrual cycle, which there is little existing research on.

6.3 Limitations

Although there are clear strengths of this project, there were also several limitations. To begin with, the CGM data loss decreased the sample size when evaluating the recovery data. Sample size was also small (n = 7) in the sub-analysis of menstrual cycle changes. Meals were not standardized between subjects and within subjects. Although asked to keep days similar, type of carbohydrates consumed was not always identical throughout the day. More precise differences in recovery, such as TDD or TIR may have been found between the three arms if food was provided following exercise. Exercise was only performed at one time of day and one intensity, which may not suit the type of activity that individuals with T1D typically perform. Ketone measurements were not done in recovery, and it could have been very important to see whether ketone levels continued to increase post-exercise in the 50% BRR arm. Lastly, the population studied was Caucasian and all using CSII, which does not fully represent the T1D population in Canada.

6.4 Future Directions

This study provides more information about how future exercise strategies can be further manipulated to work in different scenarios. Firstly, a different time of day for exercise needs to be evaluated, as well as exercise performed not in the fasted or post-absorptive states. Exercising after a meal could greatly impact carbohydrate and insulin reduction needs for exercise compared to fasted exercise. Secondly, the Combo arm in the present study has a lot of potential to be an unplanned strategy with increased fat oxidation, however there was greater time spent in hyperglycemia, making it unfavourable. With the current knowledge, a better targeted ExCarbs strategy in the latter half of exercise could now be proposed and hyperglycemia could be reduced.

The 50% BRR arm, although safe, still has a reduction in BG levels. The addition of a very small amount of ExCarbs may stabilize BG but still have favourable fat oxidation effects, and should be studied. Lastly, mini-dose glucagon for exercise is just starting to be examined in T1D. This alternative to ExCarbs should be studied in a similarly designed study to the current one.

The population needs to be more diverse to better represent all individuals with T1D. This includes children who will typically have a lower body weight, requiring much lower ExCarbs according to the current calculation of 0.3 g/kg/hr.

Lastly, the differences in menstrual cycle during exercise and in recovery has not been evaluated greatly in T1D. This needs to be evaluated in a larger population over multiple trials. Different strategies to control BG around exercise and in recovery may need to be implemented during different phases of the menstrual cycle.

6.5 Conclusions

Overall, this thesis dissertation reveals three effective strategies in exercising safely for a prolonged period of time in the fasted state. We found the CHO arm had good glucose control during exercise and in recovery, whereas the other two arms had slightly elevated glucose levels. The 50% BRR arm had many advantages if the goal is weight loss in T1D. By exercising fasted with low circulating insulin levels, fat oxidation and ketone levels increased without any caloric intake over two hours. Manipulating hormone levels that are impacted by insulin levels is difficult in T1D, but was achieved in the current study. This also provides a safe exercise strategy for individuals who follow low-carbohydrate or ketogenic diets. Another major benefit of the 50% BRR arm was that there was not continuous decision making about ExCarbs throughout exercise, unlike the other two arms. With a standard insulin reduction, irrespective of BG levels, there was a lot of success in this arm without targeting the BG to be in range. However, although decisions

needed to be made in the CHO and Combo arms, this only occurred every 30 mins of exercise and could be incorporated into a management decision algorithm. All arms, despite the long duration of exercise, had minimal hypoglycemia in recovery, likely due to the protective insulin strategies implemented in recovery.

7.0 References

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8.0 Tables

Table 1. Baseline characteristics of study population. Participant characteristics for study (n = 15). Data are mean ± SD [range].

Characteristic	Total (n = 15)
Gender, M / F	6 / 9
Age (years)	35.5 ± 14.9 [18 - 61]
Weight (kg)	75.7 ± 17.1 [57.8 – 125.8]
Height (cm)	174.1 ± 10.7
Body Mass Index (kg/m^2)	25.0 ± 5.5 [19.4 – 43.0]
Body Fat Percentage (%)	26.1 ± 11.0 [11.3 – 50.5]
VO_{2peak} (mL/kg/min)	43.3 ± 10.5 [25.3 – 61.8]
Caucasian, n (%)	15 (100)
Waist Circumference (cm)	88.7 ± 12.2 [73.0 – 126.0]
METS per Week	3,227.4 ± 2,285.7

Table 2. Diabetes characteristics of study population. Participant characteristics of diabetes history (n = 15). Data are mean ± SD [range].

Diabetes Characteristics	**Total (n = 15)**
HbA_{1c} Now Meter (%)	6.9 ± 0.9 [5.2 – 8.7]
Last Laboratory HbA_{1c} (%)	7.1 ± 0.8 [6.0 – 8.7]
Diabetes Duration (years)	17.2 ± 11.6 [4 – 39]
Total Daily Dose (units)	37.8 ± 15.3
Total Daily Dose (units/kg)	0.5 ± 0.1
Omnipod Insulin Management System Users, n (%)	10 (67)
Insulin Type	
Aspart	10 (67)
Lispro	5 (33)
Hypoglycemia Awareness by Clarke, n (%)	2 (13)
Hypoglycemia Gold Score	2.6 ± 1.2

Table 3. Cardiometabolic outcome variables for each of the three treatment arms. Exercise outcomes for the study participants in each of the three treatment arms (n = 15 for each arm). Values are presented as mean ± SD. *Significantly different from the other two treatment arms ($P < 0.05$, one-way ANOVA or two-way RM ANOVA). #Significantly different from round 2, same arm ($P < 0.05$, two-way RM ANOVA). †Significantly different from round 3, same arm ($P < 0.05$). ∞Significantly different from 50% BRR treatment arm ($P < 0.05$).

Cardiometabolic Outcome Variables			
	CHO	**50% BRR**	**Combo**
Relative VO_2 (%)	47.3 ± 7.5	46.7 ± 6.9	46.6 ± 7.6
Relative Heart Rate (%)	46.3 ± 5.2	46.3 ± 5.5	45.2 ± 5.2
Rate of Perceived Exertion	4.3 ± 1.3	4.4 ±1.5	4.0 ± 1.4
Respiratory Exchange Ratio			
R1	0.80 ± 0.07 #	0.80 ± 0.07	0.80 ± 0.06
R2	0.84 ± 0.04∞	0.80 ± 0.05	0.83 ± 0.04
R3	0.83 ± 0.04∞	0.79 ± 0.04	0.81 ± 0.03
Carbohydrate Oxidation (g/min)			
R1	1.80 ± 0.8	1.69 ± 1.0	1.66 ± 0.9
R2	1.82 ± 0.8	1.55 ± 0.7	1.77 ± 0.8
R3	1.69 ± 0.7	1.38 ± 0.6	1.54 ± 0.7
Fat Oxidation (g/min)			
R1	0.52 ± 0.2#†	0.48 ± 0.1	0.51 ± 0.2#
R2	0.37 ± 0.1	0.47 ± 0.1	0.39 ± 0.1
R3	0.39 ± 0.1∞	0.51 ± 0.2	0.44 ± 0.1
Ketones Pre- and Post-Exercise (mmol/L)	0.2 ± 0.1 0.1 ± 0.1	0.2 ± 0.2# 0.4 ± 0.3*	0.2 ± 0.2 0.3 ± 0.2*
Energy Expenditure (kcal/min)			
R1	7.7 ± 1.8#†	7.5 ± 2.2†	7.6 ± 2.0#†
R2	7.1 ± 1.9	7.1 ± 1.9	7.1 ± 2.0
R3	6.9 ± 1.9	7.0 ± 2.0	6.9 ± 1.9
Total Energy Burned (kcal)	868.9 ± 218.2	863.1 ± 241.3	860.6 ± 230.8
Caloric Intake (kcal)	159.7 ± 79.0	3.4 ± 13.0*	123.8 ± 68.1
Net Loss of Energy (kcal)	709.2 ± 217.4	859.7 ± 239.6 *	736.8 ± 200.9

Table 4. Exercise glycemic outcome variables. Glycemic outcomes for all participants in each treatment arms (n = 15 for each arm). Values are presented as mean ± SD. *Significantly different from CHO arm (one-way ANOVA, $P < 0.05$).

Glycemic Outcome Variables			
	CHO	**50% BRR**	**Combo**
Blood Glucose (mmol/L) at exercise start	9.0 ± 3.5	9.2 ± 3.0	8.9 ± 3.7
Δ Glucose (mmol/L) from start to end of exercise	-2.7 ± 3.4	-1.9 ± 2.7	0.3 ± 2.6*
Δ Glucose (mmol/L) from start to mid-exercise	-1.2 ± 2.5	-1.2 ± 1.9	-0.7 ± 2.4
Δ Glucose (mmol/L) from 30-min pre-exercise to exercise start	-0.3 ± 0.7	-0.7 ± 0.5	-0.1 ± 0.9
Δ Glucose (mmol/L) from end of exercise to 20-min post-exercise	0.7 ± 1.4	0.6 ± 0.8	0.6 ± 0.9
Time in range (4.0 - 10.0 mmol/L) during exercise (%)	81.5 ± 24.4	76.3 ± 33.6	62.2 ± 36.8
Nadir Glucose (mmol/L) during exercise	5.8 ± 1.9	6.7 ± 2.2	7.4 ± 2.8
Number of hypoglycemic events	3	1	1
Time to first hypoglycemic event (min)	65, 140, 140	125	65

Table 5. Consumption of exercise carbohydrates. Carbohydrate consumption for all participants during three exercise conditions (n = 15 for each arm). Values are presented as mean ± SD. *Significantly different from the other two treatment arms ($P < 0.01$, one-way ANOVA). #Significantly different from Combo arm ($P < 0.05$, one-way ANOVA).

Exercise Carbohydrates			
	CHO	**50% BRR**	**Combo**
Carbohydrates consumed during exercise (g)	38.0 ± 18.8	0.8 ± 3.1*	29.5 ± 16.2
ExCarbs during exercise (g/kg/hr)	0.25 ± 0.1	0.01 ± 0.0*	0.20 ± 0.1
ExCarbs during first hour (g/kg/hr)	0.23 ± 0.1	0.00 ± 0.0*	0.20 ± 0.1
ExCarbs during second hour (g/kg/hr)	0.26 ± 0.1#	0.01 ± 0.0*	0.20 ± 0.1

Table 6. Glycemic outcomes during recovery period. The recovery CGM glycemic outcomes following each of the three exercise treatment arms. Values are presented as mean ± SD. *Significantly different from the CHO treatment arm ($P < 0.05$, one-way ANOVA).

Recovery Glycemic Outcomes			
	CHO	**50% BRR**	**Combo**
Total Daily Dose (Units)	32.7 ± 10.3	33.0 ± 11.2	36.3 ± 13.2
Time in range (4.0 - 10.0 mmol/L) 6-hr post-exercise (%)	72.6 ± 21.6	62.5 ± 32.2	62.9 ± 30.8
Time in range (4.0 - 10.0 mmol/L) 24-hr post-exercise (%)	73.3 ± 18.6	65.2 ± 14.6	60.9 ± 20.3
Time in range (4.0 - 10.0 mmol/L) night following exercise (%)	67.3 ± 38.2	59.3 ± 40.9	44.0 ± 36.9
Time in hypoglycemia (≤ 3.9 mmol/L) 6-hr post-exercise (%)	6.8 ± 7.9	4.6 ± 10.7	1.6 ± 4.5
Time in hypoglycemia (≤ 3.9 mmol/L) 24-hr post-exercise (%)	3.3 ± 3.1	3.8 ± 5.1	4.2 ± 5.5
Time in hypoglycemia (≤ 3.9 mmol/L) night following exercise (%)	1.3 ± 2.9	1.4 ± 5.0	3.4 ± 7.7
Time in hyperglycemia (> 10.0 mmol/L) 6-hr post-exercise (%)	20.5 ± 23.2	32.9 ± 35.3	35.5 ± 32.0
Time in hyperglycemia (> 10.0 mmol/L) 24-hr post-exercise (%)	23.4 ± 19.6	30.8 ± 17.9	35.0 ± 21.0
Time in hyperglycemia (> 10.0 mmol/L) night following exercise (%)	31.4 ± 39.2	39.3 ± 42.0	52.6 ± 38.4
Glycemic variability 24-hr Recovery (%)	29.6 ± 6.9	33.2 ± 6.6	32.5 ± 8.2
Mean glucose 6-hr following exercise (mmol/L)	7.9 ± 2.0	9.4 ± 2.9*	9.1 ± 2.4
Mean glucose 24-hr following exercise (mmol/L)	8.4 ± 1.3	9.0 ± 1.7	8.9 ± 1.9
Mean glucose overnight following exercise (mmol/L)	9.3 ± 2.6	10.0 ± 3.5	10.5 ± 4.1
Frequency of hypoglycemia (≤ 3.9 mmol/L) 24-hr post-exercise (events)	1.1 ± 1.0	1.4 ± 1.7	0.6 ± 0.7
Time in severe hypoglycemia (≤ 3.0 mmol/L) 24-hr post-exercise (%)	0.4 ± 0.7	0.6 ± 1.3	0.6 ± 1.2

Table 7. Baseline characteristics of study sub-population. Participant characteristics for study population that enrolled in the menstrual phase sub-analysis (n = 7). Data are mean ± SD [range].

Sub-Analysis Characteristics of Menstrual Cycle	Total (n = 7)
Age (years)	27.7 ± 5.5 [24 – 39]
Body Mass Index (kg/m^2)	27.1 ± 7.5 [19.8 – 43.0]
Body Fat Percentage (%)	33.0 ± 10.0 [20.6 – 50.5]
VO_{2peak} (mL/kg/min)	39.3 ± 7.0 [25.3 – 47.8]
Waist Circumference (cm)	89.5 ± 17.8 [73.0 - 126.0]
HbA_{1c} Now Meter (%)	6.9 ± 0.6 [5.8 – 7.5]
Diabetes Duration (years)	11.7 ± 6.9 [4 – 23]
Total Daily Dose (units/kg)	0.5 ± 0.1
Oral Contraceptive Users, n (%)	2 (28.6)

Table 8. Cardiometabolic outcome variables for the two treatment arms. Exercise outcomes for the sub-study participants in the two treatment arms (n = 7 for each arm). Values are presented as mean ± SD. *R1 vs R2 and R3, both arms ($P < 0.01$, two-way RM ANOVA).

Menstrual Cycle Cardiometabolic Outcomes		
	Luteal	**Early-Follicular**
Relative VO_2 (%)	43.5 ± 4.9	45.6 ± 5.8
Relative Heart Rate (%)	43.3 ± 6.6	46.8 ± 3.3
Rate of Perceived Exertion		
First Half	3.6 ± 1.1	4.0 ± 1.2
Second Half	4.4 ± 1.3	4.8 ± 1.4
Respiratory Exchange Ratio		
R1	0.80 ± 0.04	0.78 ± 0.04
R2	0.82 ± 0.02	0.82 ± 0.03
R3	0.81 ± 0.02	0.81 ± 0.02
Carbohydrate Oxidation (g/min)		
R1	1.40 ± 0.45	1.29 ± 0.30
R2	1.30 ± 0.30	1.35 ± 0.37
R3	1.27 ± 0.26	1.22 ± 0.30
Fat Oxidation (g/min)		
R1	0.45 ± 0.12	0.54 ± 0.12*
R2	0.36 ± 0.08	0.37 ± 0.09
R3	0.37 ± 0.06	0.38 ± 0.06
Ketones Pre- Post-Exercise (mmol/L)		
	0.3 ± 0.5	0.1 ± 0.1
	0.1 ± 0.1	0.1 ± 0.1
Energy Expenditure (kcal/min)	6.0 ± 1.1	6.3 ± 1.0
Total Energy Burned (kcal)	725.1 ± 134.9	750.3 ± 117.9
Caloric Intake (kcal)	155.4 ± 52.3	177.0 ± 74.6
Net Loss of Energy (kcal)	569.7 ±127.0	573.3 ± 69.7

Table 9. Sub-analysis of glycemic and carbohydrate outcome variables during exercise. Glycemic outcomes for the menstrual cycle sub-analysis during exercise for all participants in the two treatment arms (n = 7 for each arm). Values are presented as mean ± SD.

Menstrual Cycle Glycemic and Carbohydrate Outcomes		
	Luteal	**Early-Follicular**
Blood Glucose (mmol/L) at exercise start	9.1 ± 2.6	7.9 ± 1.7
Δ Glucose (mmol/L) from start to end of exercise	-1.8 ± 2.7	-1.2 ± 1.7
Δ Glucose (mmol/L) from start to mid-exercise	-0.3 ± 2.4	0.2 ± 2.0
Δ Glucose (mmol/L) from end of exercise to 20-min post-exercise	0.1 ± 1.0	0.4 ± 0.8
Time in range (4.0 - 10.0 mmol/L) during exercise (%)	82.5 ± 21.1	87.3 ± 19.7
Average Exercise Blood Glucose (mmol/L)	8.4 ± 1.7	8.0 ± 1.8
Nadir Glucose (mmol/L) during exercise	6.4 ± 1.6	6.4 ± 1.8
Number of hypoglycemic events	1	0
Time to first hypoglycemic event (min)	50	N/A
CHO consumed during exercise (g)	37.0 ± 12.5	42.1 ± 17.8
ExCarbs during exercise (g/kg/hr)	0.26 ± 0.1	0.27 ± 0.1
ExCarbs during first hour (g/kg/hr)	0.26 ± 0.1	0.28 ± 0.1
ExCarbs during second hour (g/kg/hr)	0.26 ± 0.1	0.26 ± 0.1

Table 10. Recovery glucose outcome for sub-analysis. The recovery CGM glycemic outcomes following each of the two treatment arms for the menstrual cycle sub-analysis. Values are presented as mean ± SD. *Significantly different from each other ($P < 0.05$, paired t-test).

Menstrual Cycle Recovery Glycemic Outcome		
	Luteal	**Early-Follicular**
Total Daily Dose (Units)	33.3 ± 12.7	32.4 ± 12.1
Time in range (4.0 - 10.0 mmol/L) 6-hr post-exercise (%)	71.0 ± 26.6	76.2 ± 25.0
Time in range (4.0 - 10.0 mmol/L) 24-hr post-exercise (%)	67.5 ± 17.0	77.53 ± 20.0
Time in range (4.0 - 10.0 mmol/L) night following exercise (%)	41.3 ± 44.4*	78.77 ± 29.8*
Time in hypoglycemia (≤ 3.9 mmol/L) 6-hr post-exercise (%)	1.4 ± 3.7	7.1 ± 9.6
Time in hypoglycemia (≤ 3.9 mmol/L) 24-hr post-exercise (%)	1.6 ± 2.4	3.6 ± 3.5
Time in hypoglycemia (≤ 3.9 mmol/L) night following exercise (%)	0.0 ± 0.0	0.0 ± 0.0
Time in hyperglycemia (> 10.0 mmol/L) 6-hr post-exercise (%)	27.6 ± 28.0	16.7 ± 27.5
Time in hyperglycemia (> 10.0 mmol/L) 24-hr post-exercise (%)	31.0 ± 15.6	18.9 ± 20.7
Time in hyperglycemia (> 10.0 mmol/L) night following exercise (%)	58.7 ± 44.4*	21.2 ± 29.8*
Glycemic variability 24-hr Recovery (%)	30.8 ± 8.9	27.1 ± 5.0
Mean glucose 6-hr following exercise (mmol/L)	8.5 ± 1.9	7.6 ± 2.3
Mean glucose 24-hr following exercise (mmol/L)	9.1 ± 1.3	8.2 ± 1.3
Mean glucose overnight following exercise (mmol/L)	11.3 ± 3.9	9.0 ± 1.5
Frequency of hypoglycemia (≤ 3.9 mmol/L) 24-hr post-exercise (events)	0.7 ± 1.1	1.1 ± 1.1
Time in severe hypoglycemia (≤ 3.0 mmol/L) 24-hr post-exercise (%)	0.3 ± 0.6	0.6 ± 0.9

Table 11. Baseline characteristics of study population separated between males and females. Participant characteristics for study (n = 15). Data are mean ± SD [range].

Male and Female Baseline Characteristics	**Female (9)**	**Male (6)**
Age (years)	34.9 ± 15.0 [23 – 61]	36.5 ± 16.0 [18 – 58]
Body Mass Index (kg/m^2)	26.4 ± 6.7 [19.8 – 43.0]	22.9 ± 2.4 [19.4 – 26.6]
Body Fat Percentage (%)	32.8 ± 8.7 [20.6 – 50.5]	16.2 ± 4.5 [11.3 – 21.3]
VO_{2peak} (mL/kg/min)	37.5 ± 7.1 [25.3 – 47.8]	52.0 ± 8.7 [39.9 – 61.8]
HbA_{1c} Now Meter (%)	6.8 ± 0.6 [5.8 – 7.5]	6.9 ± 1.3 [5.2 – 8.7]
Duration of diabetes (years)	16.7 ± 11.8 [4 – 39]	18.0 ± 12.5 [4 – 35]
Total Daily Dose (units/kg)	0.47 ± 0.1 [0.34 – 0.68]	0.53 ± 0.1 [0.39 – 0.62]

9.0 Figures

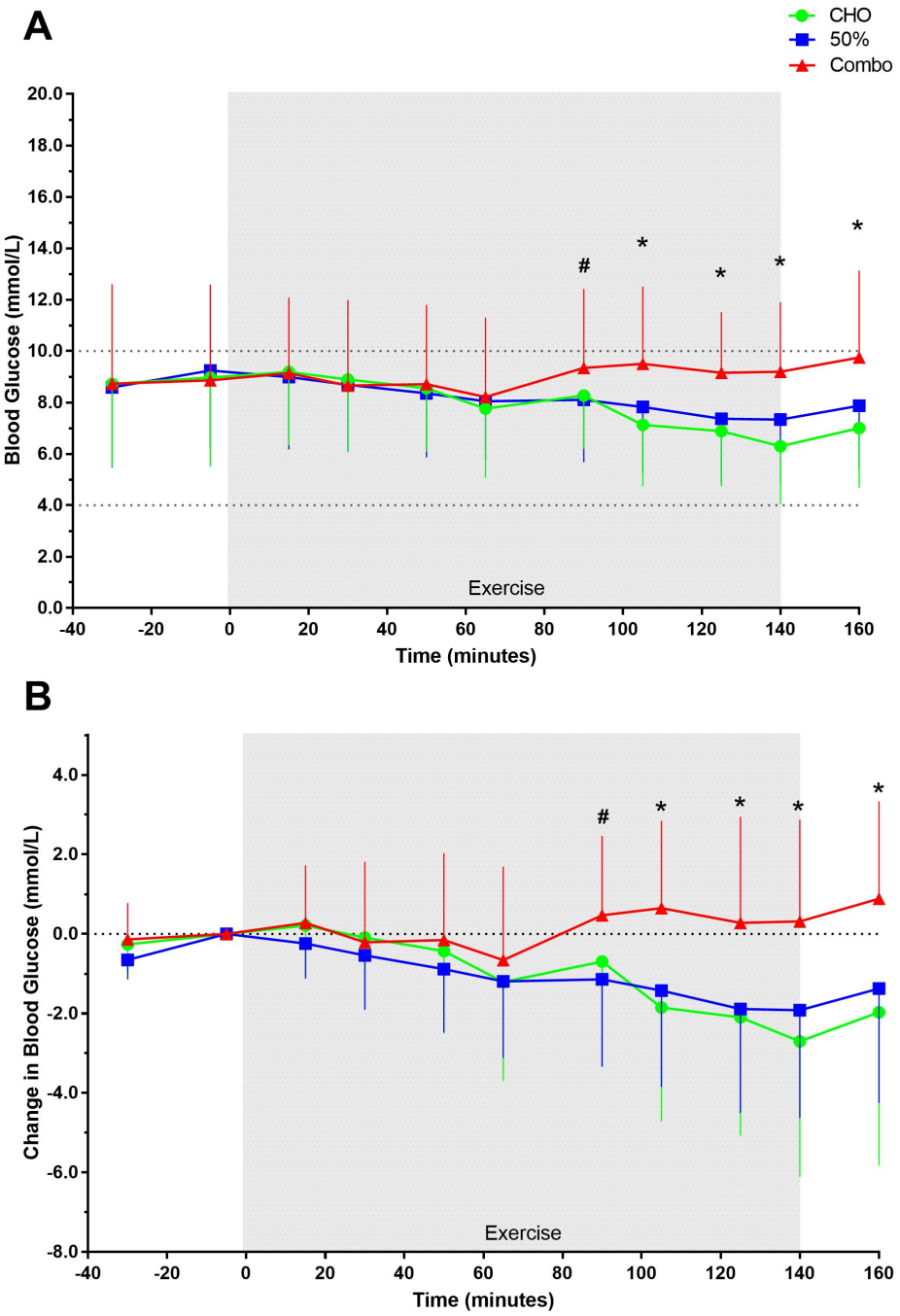


Figure 1-A. Absolute blood glucose concentrations during exercise and 20 minutes in recovery across three treatment arms. B. Relative change in blood glucose (Δ in BG) concentrations during exercise and in recovery across treatment arms. *Combo arm significantly different versus both CHO and 50% BRR arm (two-way RM ANOVA, $P < 0.05$). #50% arm significantly different from combo arm ($P < 0.05$). Data presented as mean ± SD.

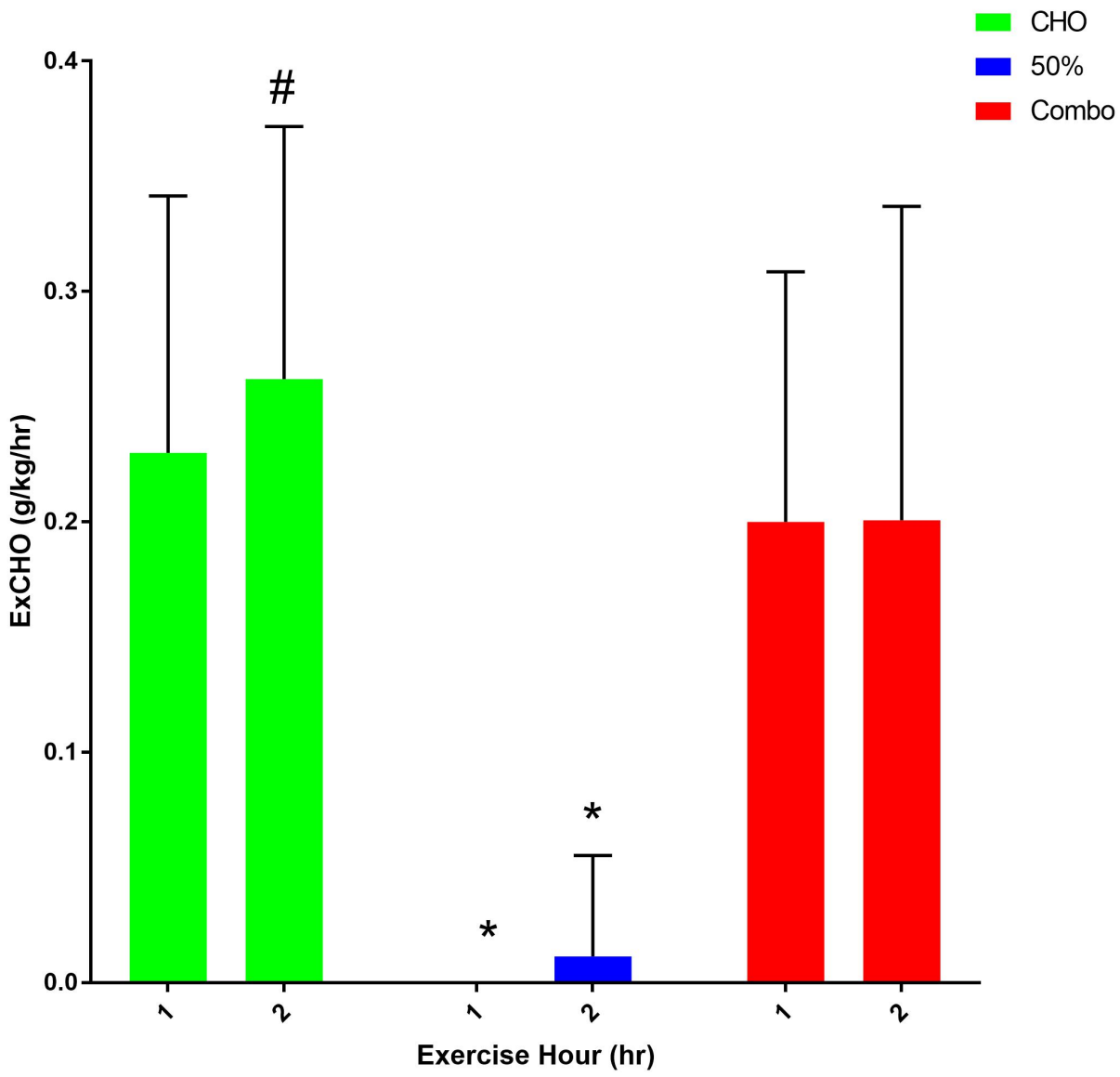


Figure 2. Carbohydrate consumption during two-hour exercise across all treatment arms. The fast-acting carbohydrates consumed, according to individual body weight, separated between the first and second hour of exercise. *Significantly different from the other two treatment arms ($P < 0.01$). #Significantly different from combo arm, both hours ($P < 0.05$).

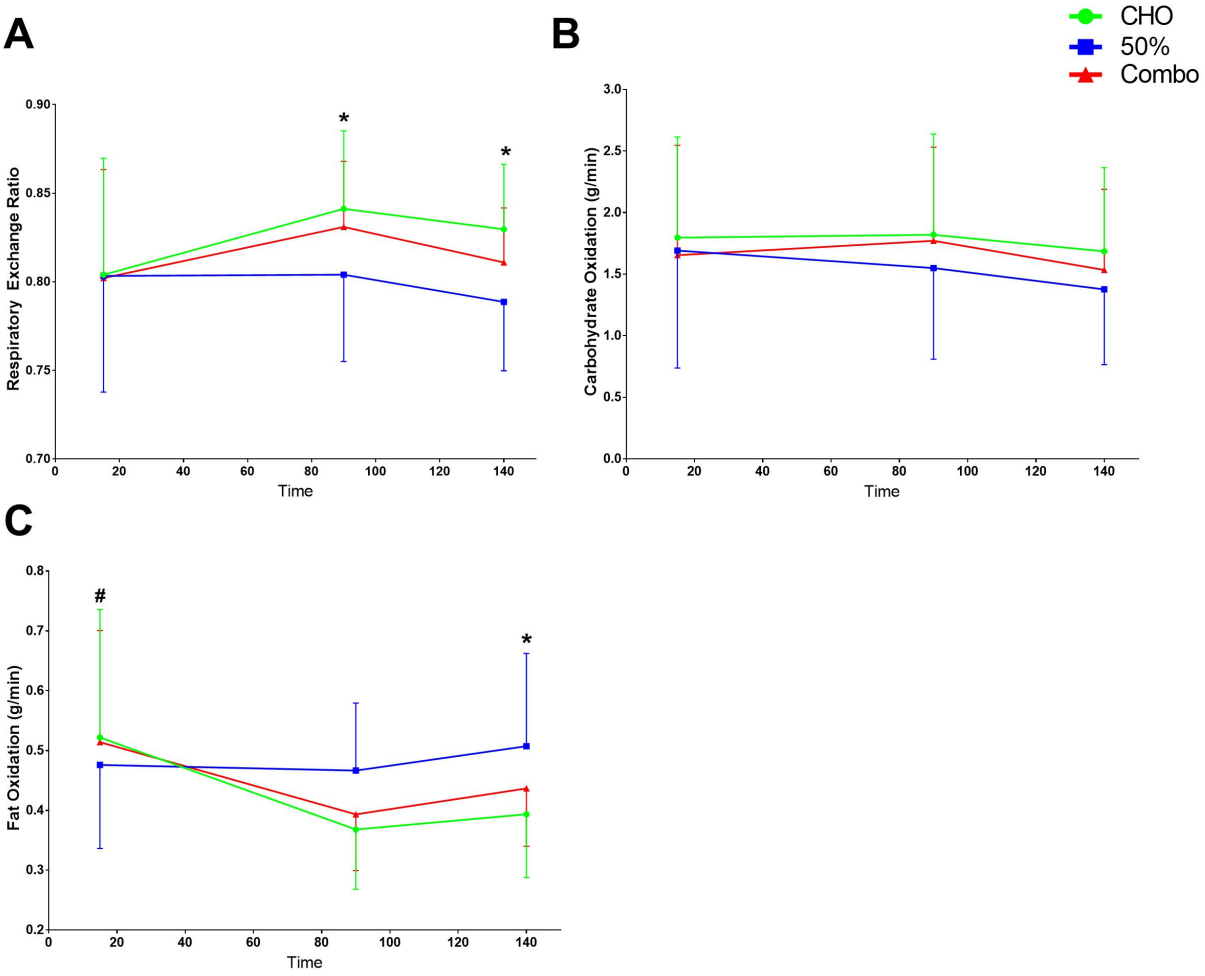


**Figure 3-A. Respiratory exchange ratio at start, middle and end of exercise across all treatment arms. B. Carbohydrate oxidation at start middle and end of exercise across all treatment arms. C. Fat Oxidation at start, middle and end of exercise across all treatment arms. ***CHO arm significantly different from 50% BRR arm ($P < 0.05$). #CHO 15min arm vs. CHO 90min and 140min ($P < 0.05$).

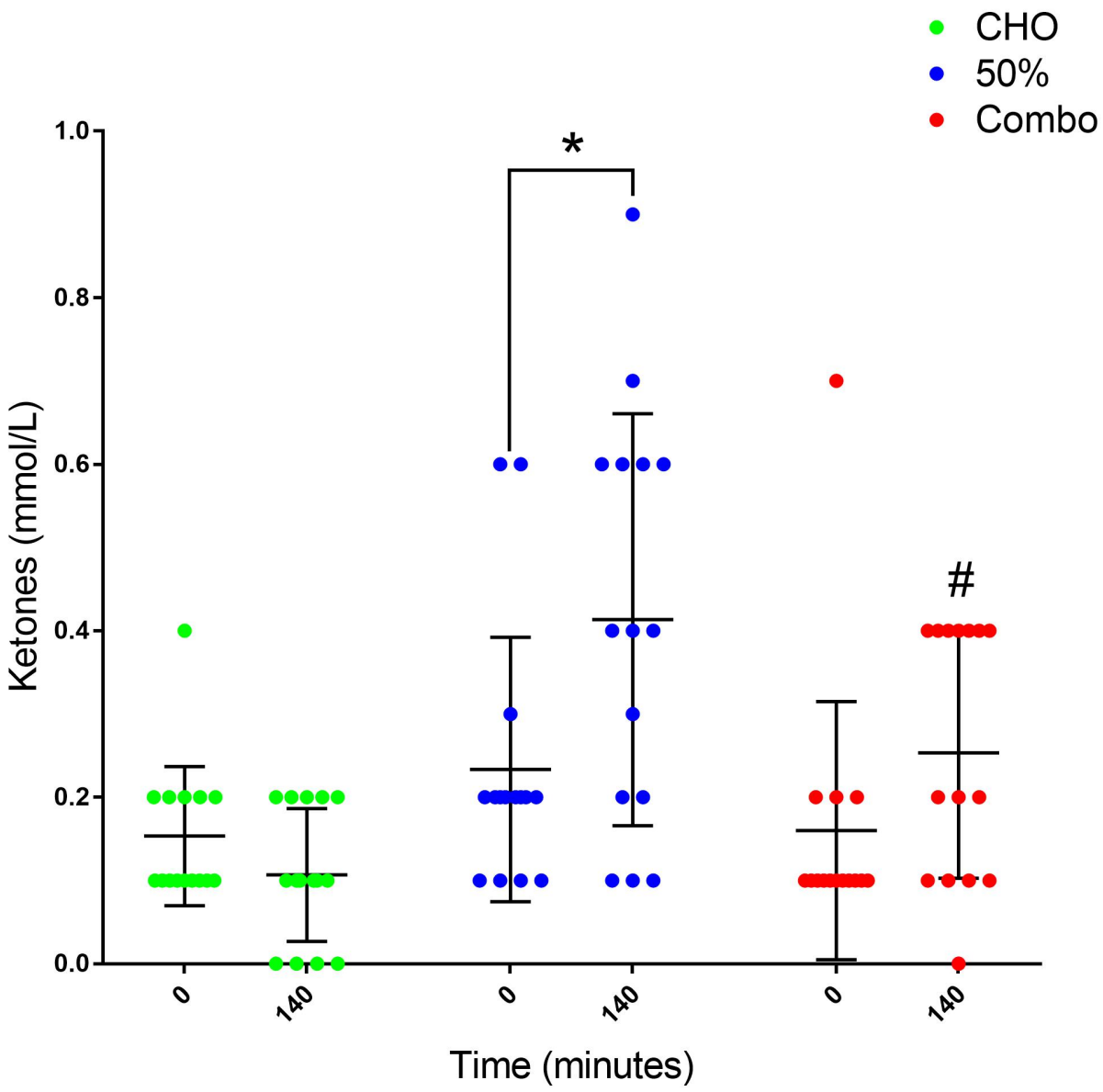


Figure 4. Ketones pre- and post-exercise across all treatment arms. Data presented as mean ± SD (n=15**).** *Significantly different from pre- to post-exercise. #Significantly different from CHO and 50% BRR arm, post-values.

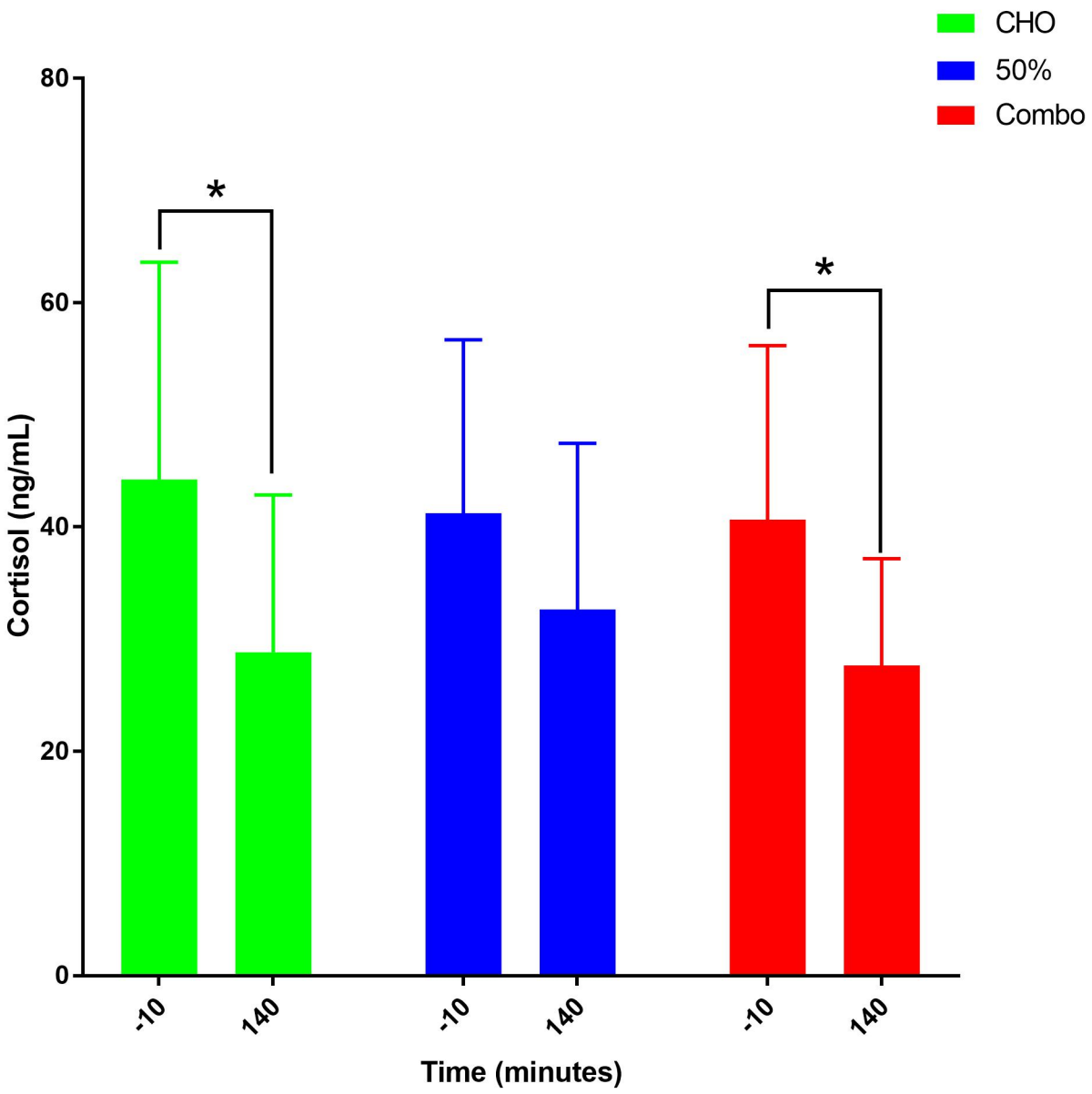


Figure 5. Salivary free cortisol pre- and post-exercise in each of the three conditions.
*Significantly different over time for CHO and Combo arm ($P < 0.05$).

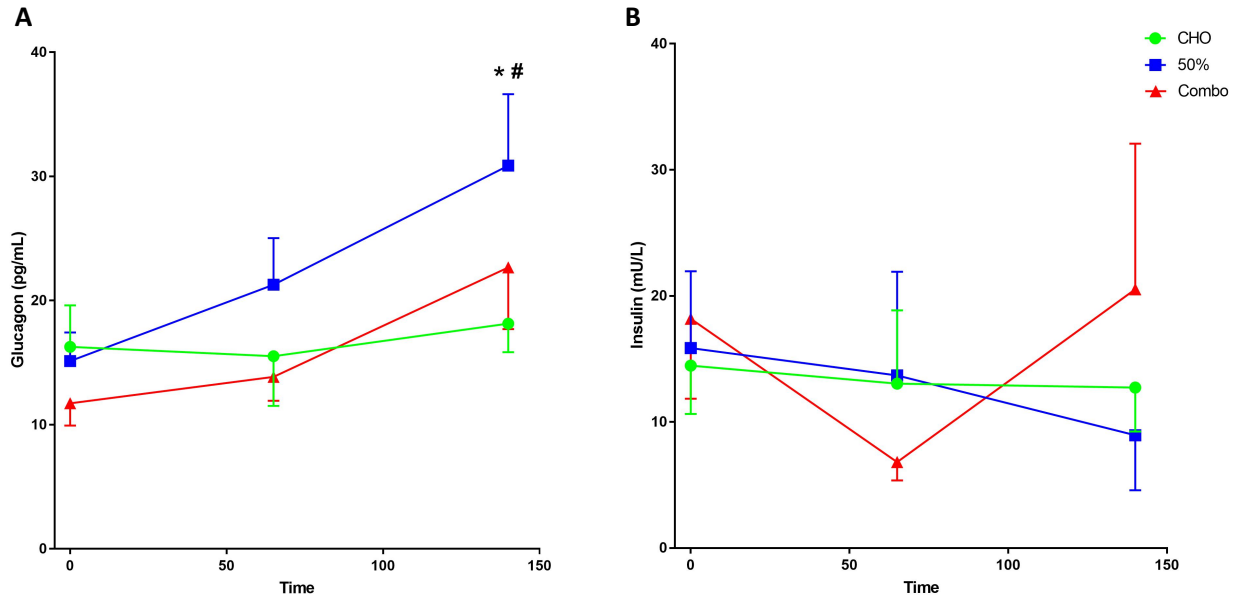


Figure 6-A. Circulating glucagon concentrations at start, middle and end of exercise across all three treatment arms. 6-B. Circulating insulin concentrations at start, middle, and end of exercise across three treatment arms. Data present as mean ± SEM. *50% BRR arm vs. CHO time 0, CHO time 65, Combo time 0, Combo time 65, 50% time 0 ($P < 0.05$). #50% BRR arm vs. CHO ($P < 0.05$).

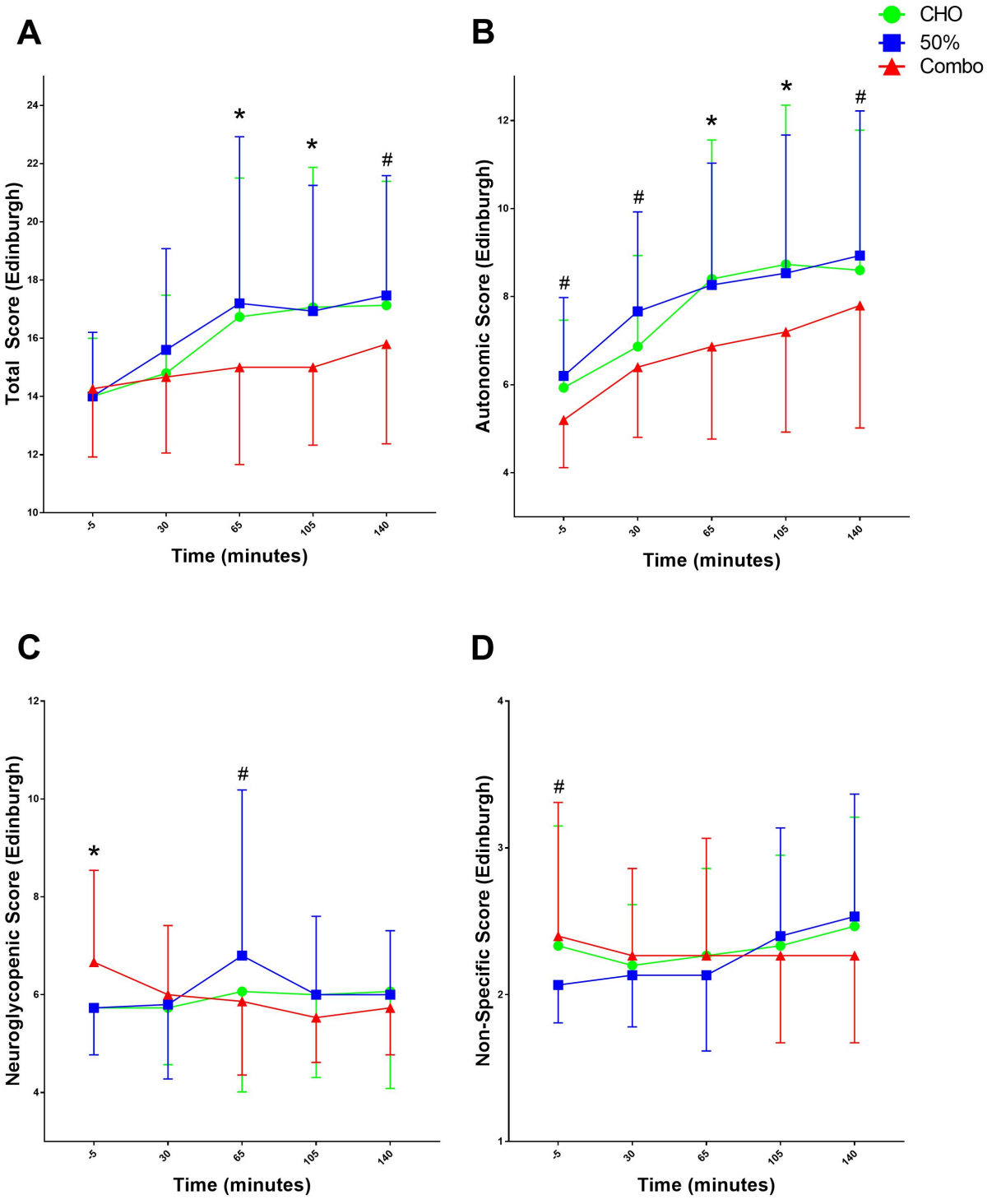
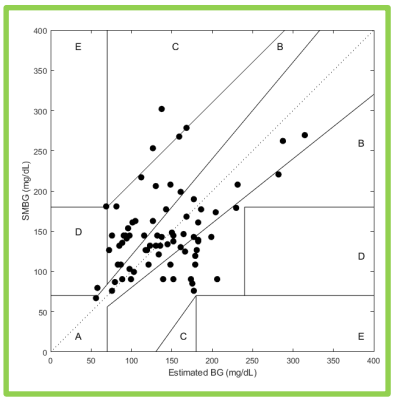


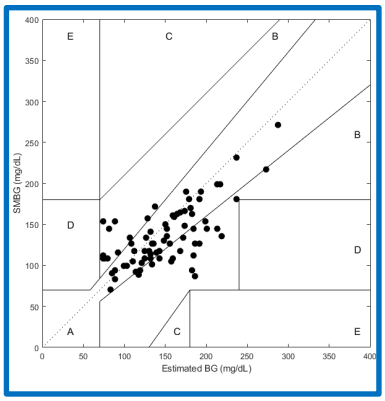
Figure 7. Edinburgh questionnaire (A) total scores, (B) autonomic scores, (C) neuroglycopenic scores, and (D) non-specific scores across all three treatment arms. *Combo significantly different from other two treatment arms ($P < 0.05$). #Combo significantly different from 50% BRR arm ($P < 0.05$).

A



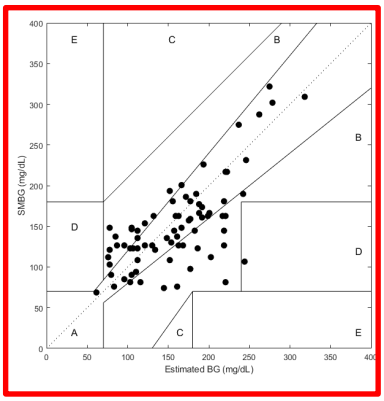
Zone	%
A	42.7
B	50.7
C	4.0
D	1.3
E	1.3

B



Zone	%
A	58.7
B	41.3
C	0
D	0
E	0

C



Zone	%
A	56.0
B	42.7
C	0
D	1.3
E	0

Figure 8. Clarke error grid comparing measured to estimated blood glucose in (A) CHO, (B) 50% BRR, and (C) Combo arm. Blood glucose values reported in mg/dL. Tables calculating percentage of points in each zone.

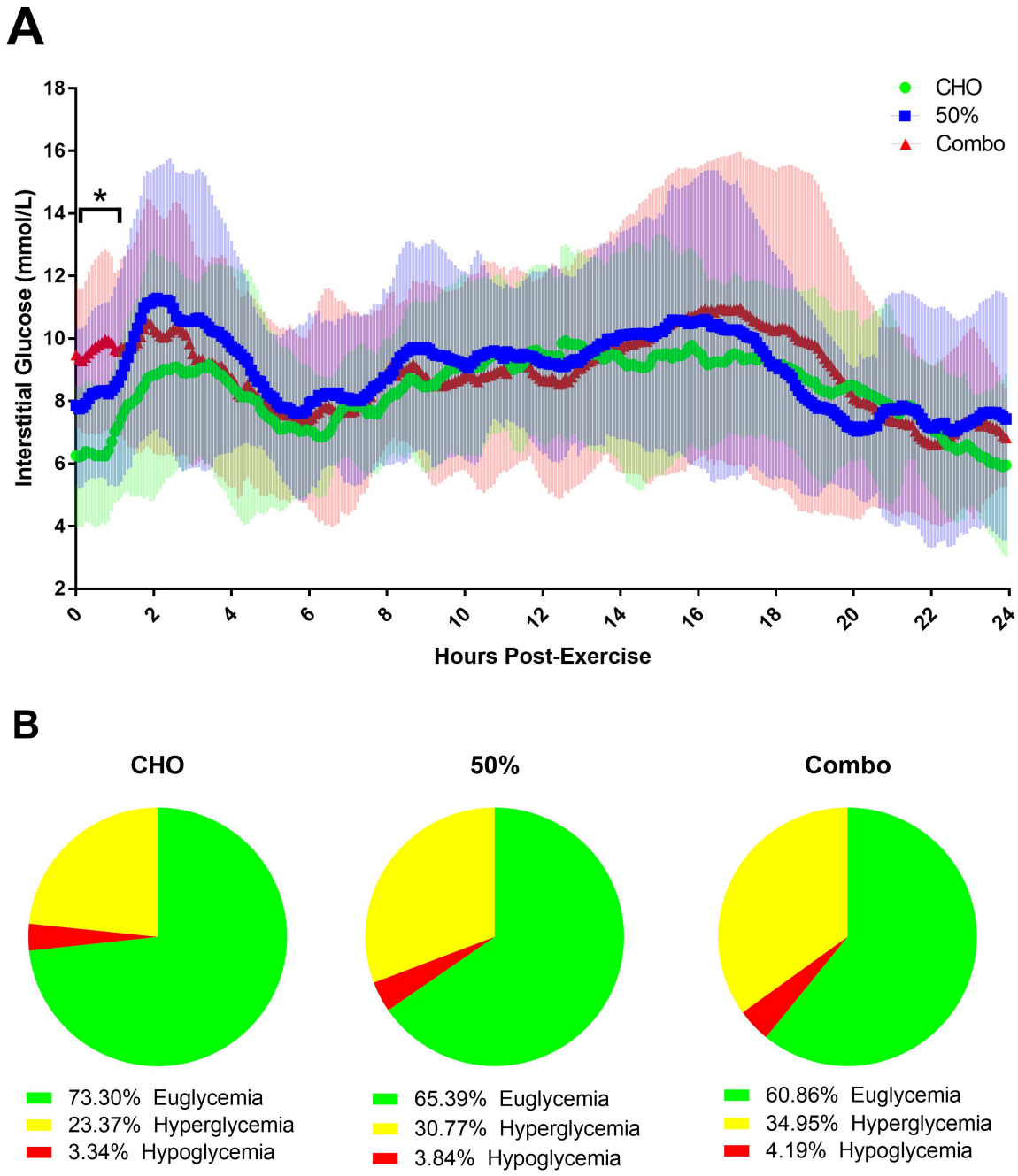


Figure 9-A. Continuous glucose monitor tracing over 24-hours following exercise across three conditions. 9-B. Percent time spent in euglycemia, hyperglycemia and hypoglycemia (n=13). Tracing data presented as mean ± SD. *Combo arm significantly different from CHO arm ($P < 0.05$).

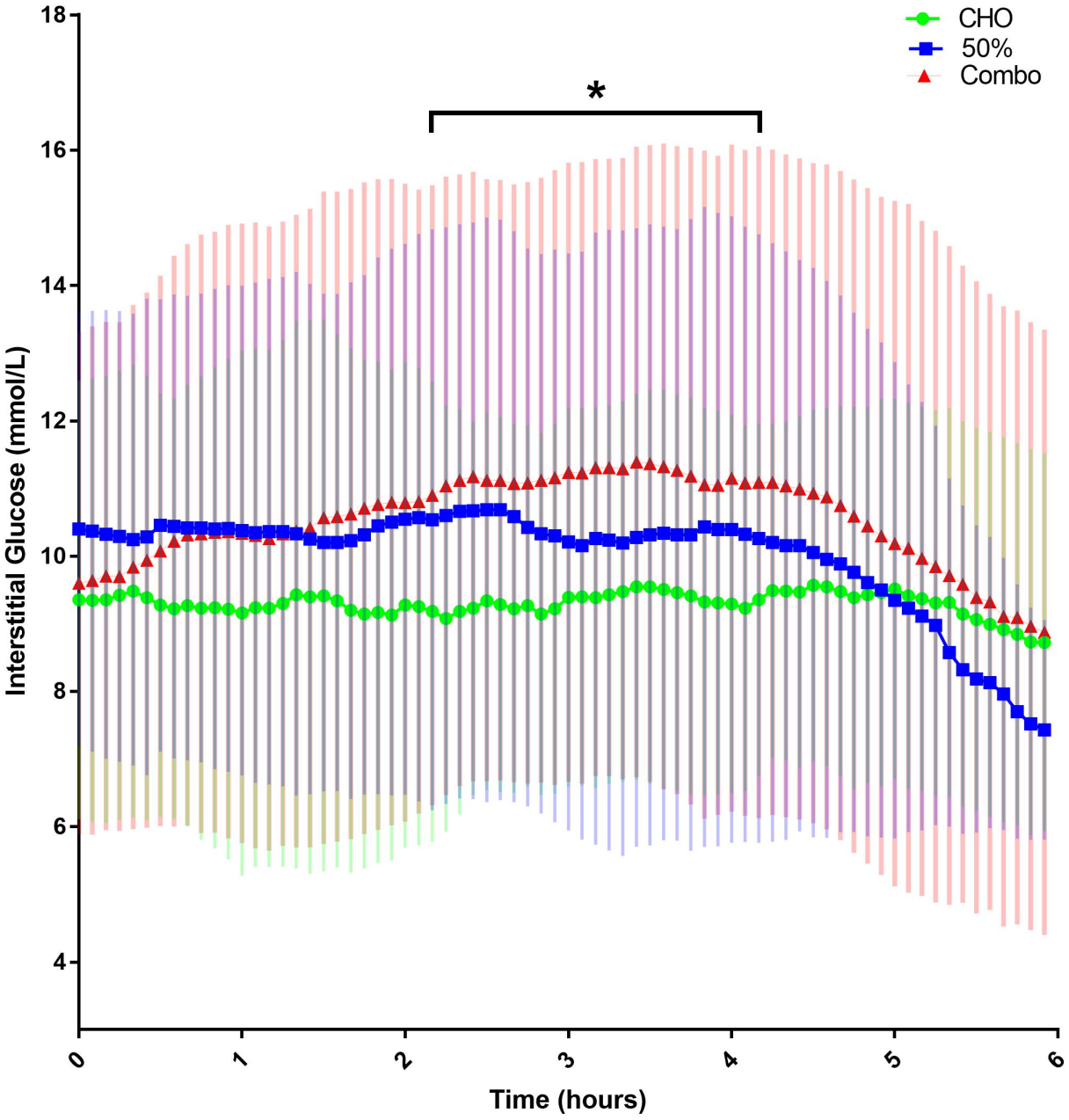


Figure 10. Continuous glucose monitor tracing overnight from 12:00 AM until 6:00 AM following exercise visit across three conditions. *Combo arm significantly different than CHO arm ($P < 0.05$).

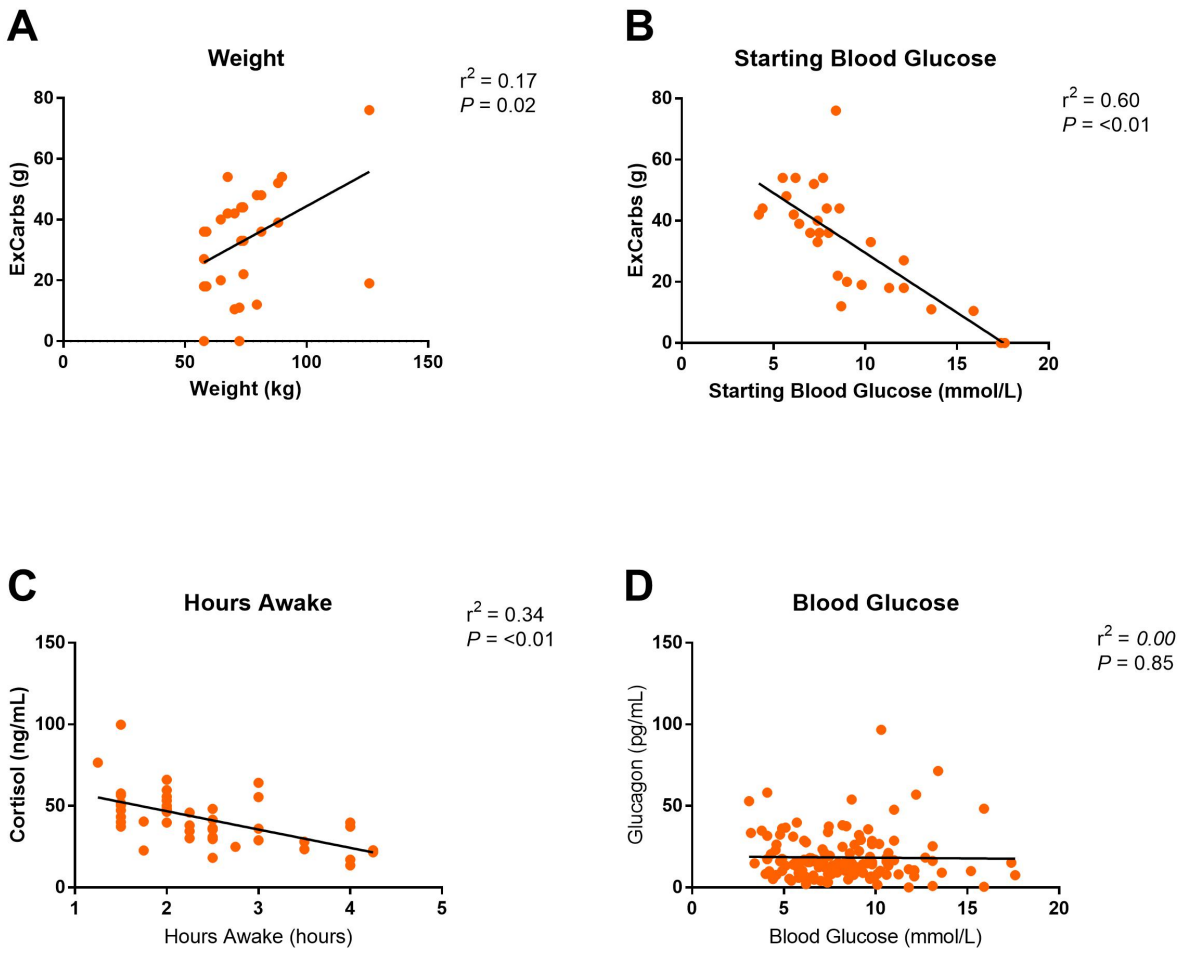


Figure 11. Correlation plots for ExCarbs and (A) Weight and (B) Starting Blood Glucose, (C) Cortisol and Hours Awake, and (D) Glucagon and Blood Glucose. Values on graph represent r^2 values and *P*-values from linear regression analysis.

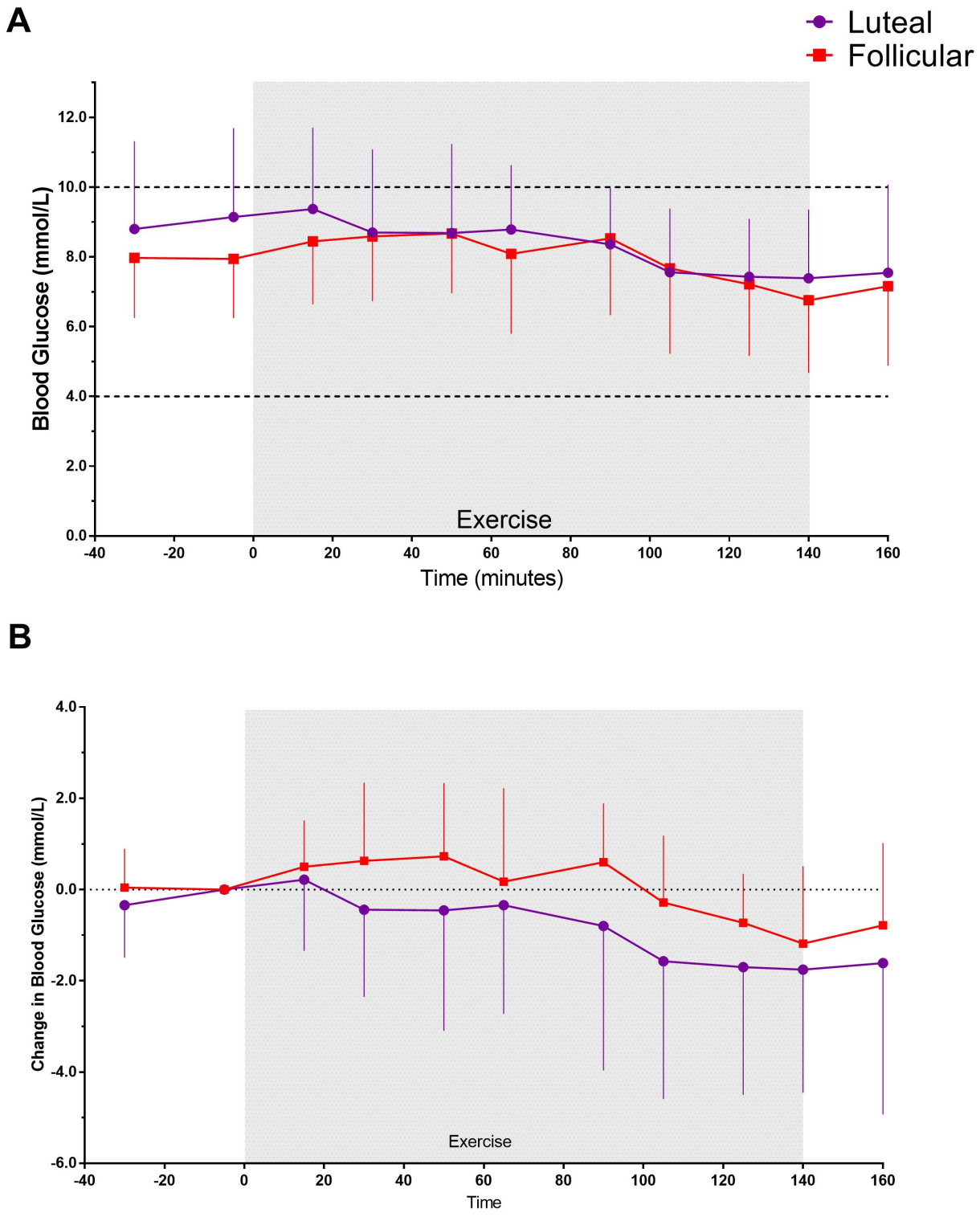


Figure 12-A. Absolute blood glucose concentrations during exercise and 20 minutes in recovery across two treatment arms. 12-B. Relative change in blood glucose (Δ in BG) concentrations during exercise and in recovery across two treatment arms. No statistical difference between the two arms in both (A) and (B).

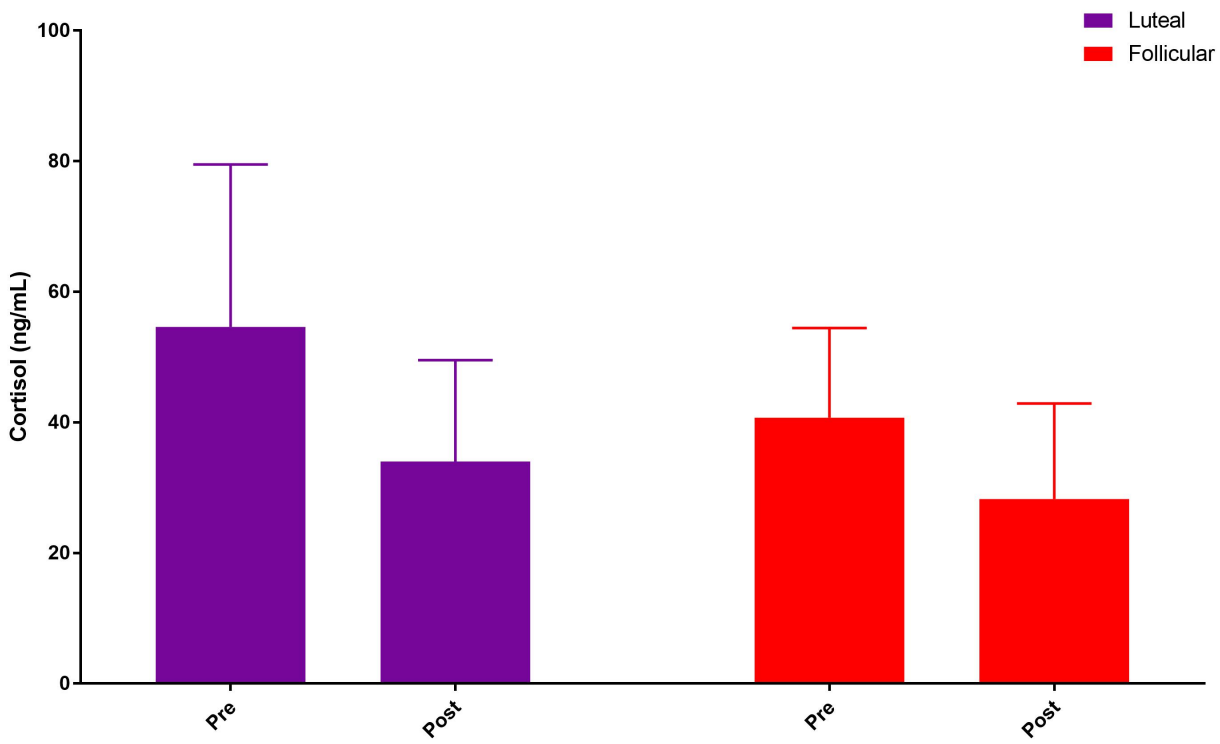


Figure 13. Salivary free cortisol pre- and post-exercise in Luteal and Follicular arm. Data presented as mean ± SD (n = 7).

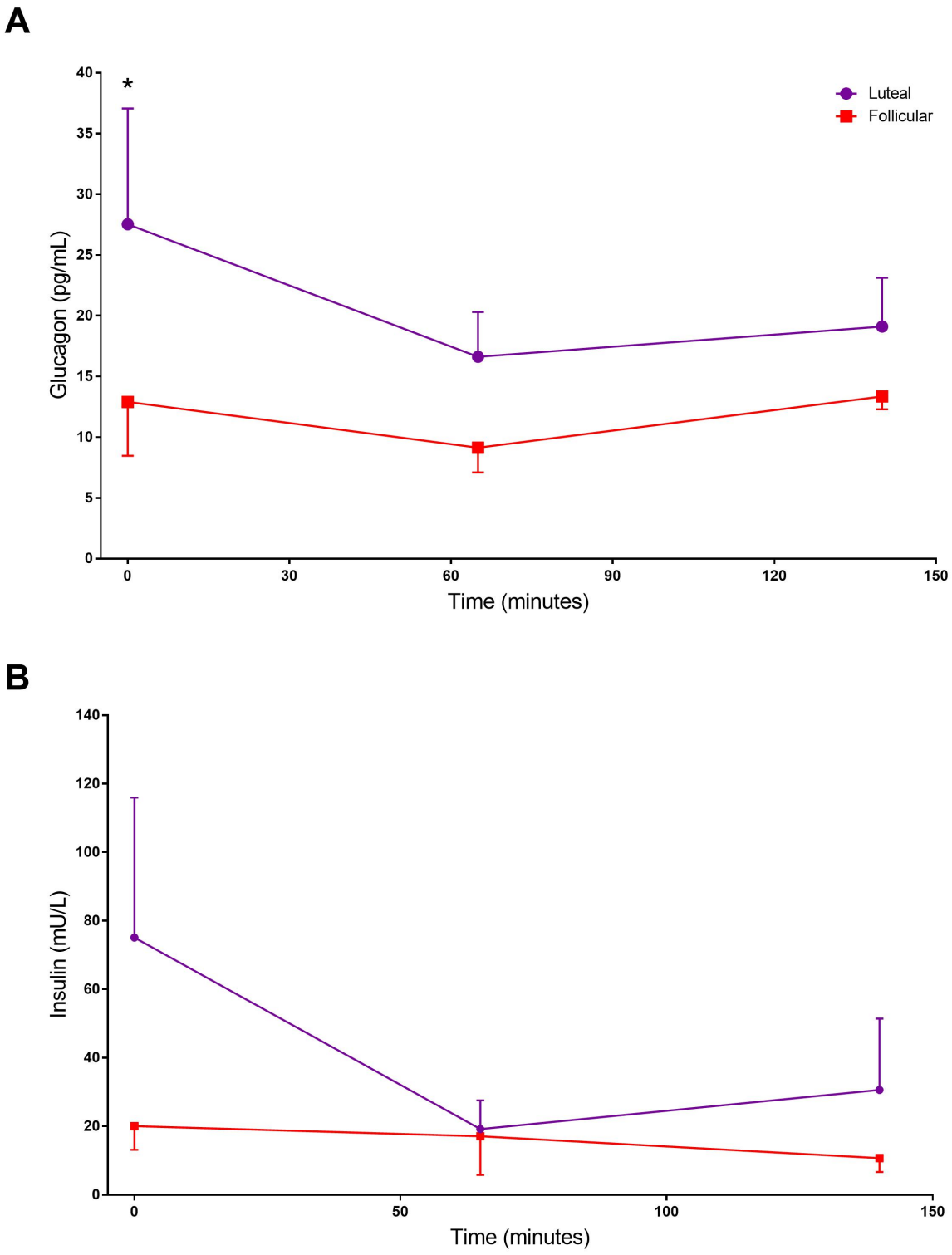


Figure 14-A. Circulating glucagon concentrations at start, middle and end of exercise across in Follicular and Luteal arm. 14-B. Circulating insulin concentrations at start, middle, and end of exercise in both treatment arms. Data presented as mean ± SEM. *Luteal vs all other measurements ($P < 0.05$).

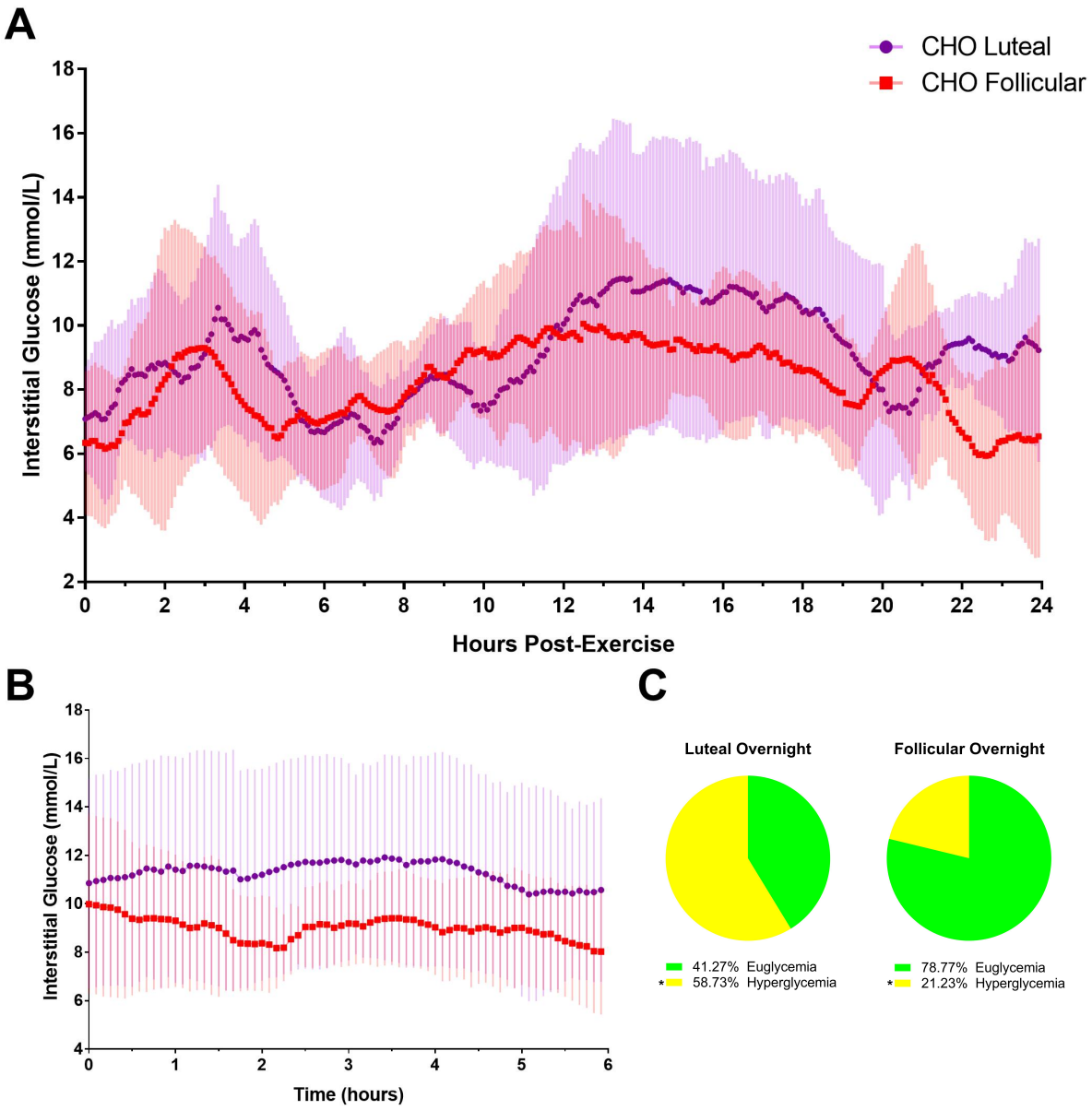
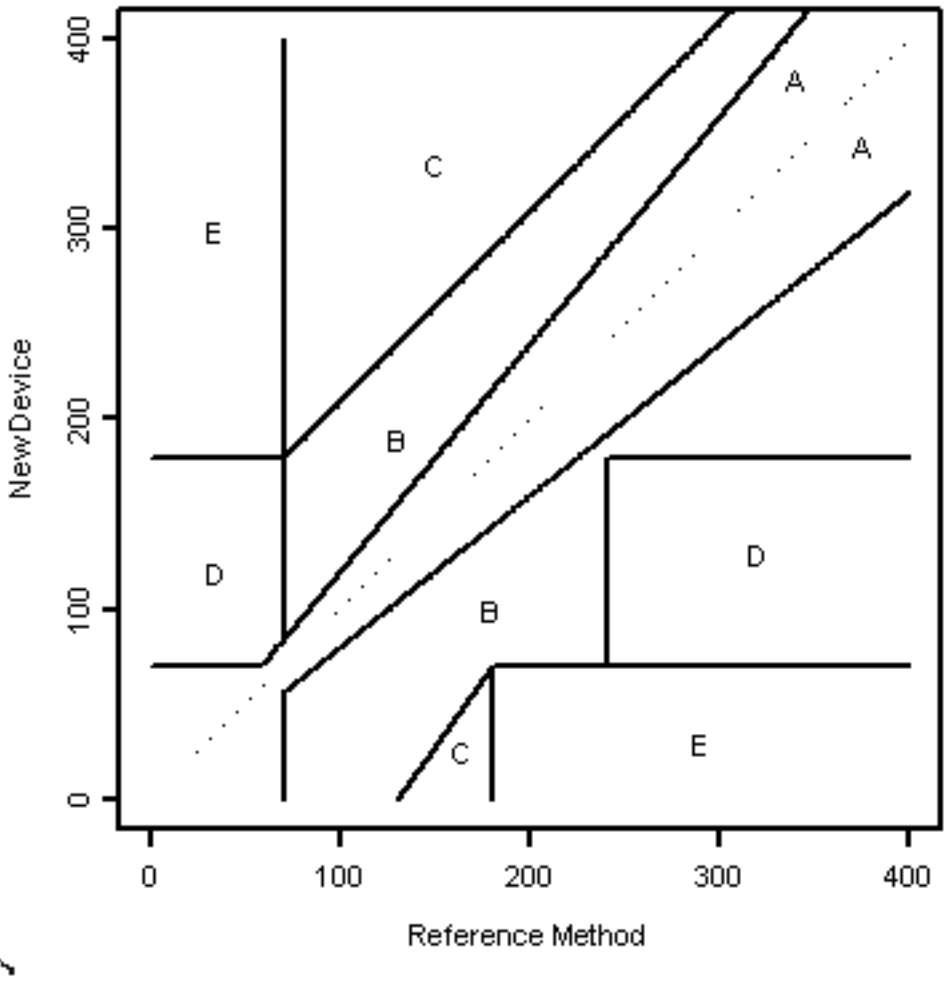


Figure 15. Continuous glucose monitor tracing over (A) 24-hours and (B) overnight following exercise across Luteal and Follicular arm. 16-C. Percent time spent in euglycemia, hyperglycemia and hypoglycemia overnight in recovery (n=7).

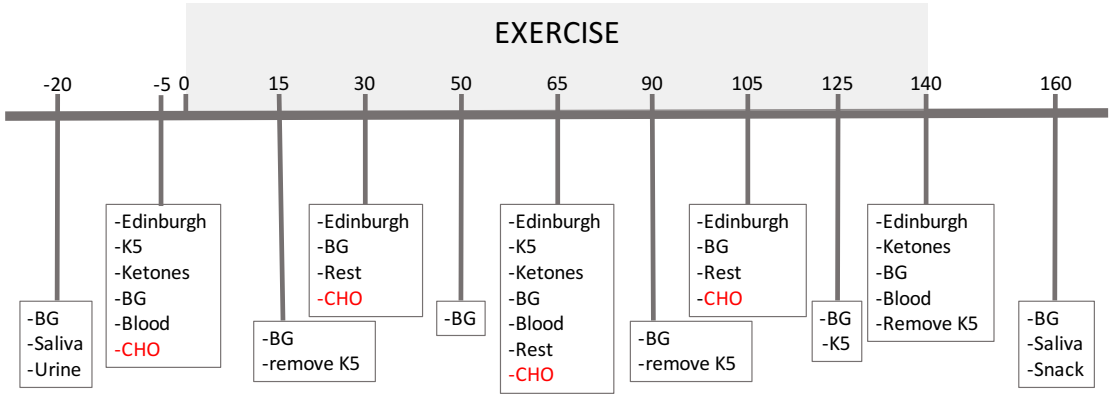
10.0 Appendices

Appendix A. Clarke Error Grid Zones. A graphical representation of the zones in a Clarke Error Grid. Zone A: values within 20% of reference, Zone B: points outside of 20% but not leading to inappropriate treatment, Zone C: leading to unnecessary treatment, Zone D: leading to potentially dangerous failure to detect hypoglycemia or hyperglycemia, and Zone E: confusing hypoglycemia with hyperglycemia and vice versa (226).

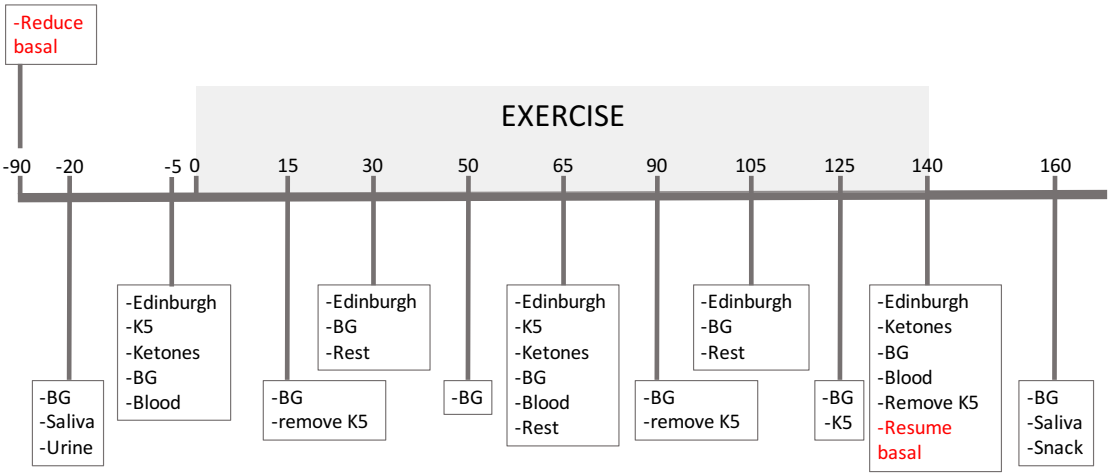


Appendix B: Study Layout. A graphical representation of the in-lab ExCarbs study layout.

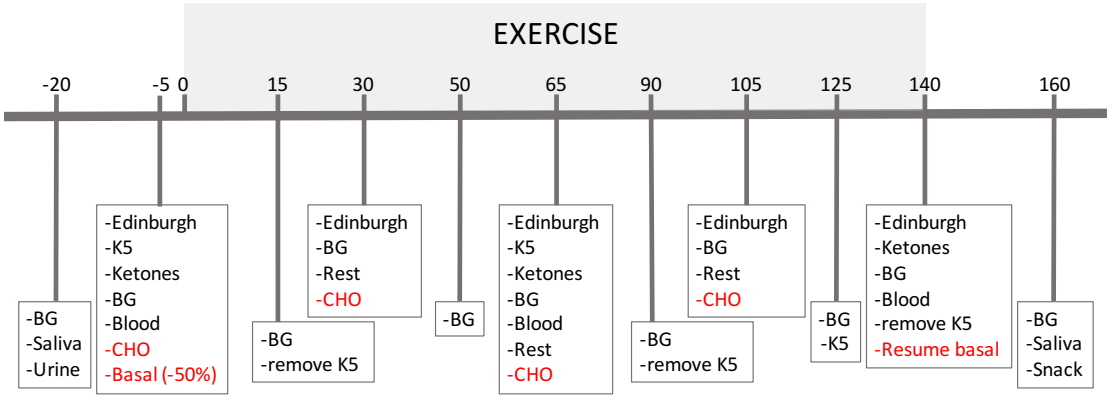
(A) CARBOHYDRATE FEEDING (0.3g/kg/hr)



(B) BASAL REDUCTION (-50%)



(C) CARBOHYDRATE FEEDING (0.3g/kg/hr) AND BASAL REDUCTION



Appendix C: Decision making chart. The decision strategy for in-lab exercise when blood glucose measurements are taken.

DECISION TABLE

BLOOD GLUCOSE LEVEL	ACTION	DECISION
≤3.9mmol/L	Stop Exercise, Treat with 12 skittles	Wait 15 minutes until BG is ≥4.0mmol/L to resume exercise
4.0-10.0mmol/L	None	Continue exercise and treatment plan
10.1-14.9mmol/L	None	Terminate carbohydrate feeding
≥15.0mmol/L	Test for ketones	Terminate carbohydrate feeding, If ketones ≥1.5mmol/L terminate exercise
≥20.0mmol/L	Test for ketones	Terminate exercise and treatment plan
**** If three separate hypoglycemic events occur during the exercise, the treatment plan and exercise will be terminated ****		
**** If ketone levels are ever ≥1.5mmol/L, exercise and treatment plan will be terminated ****		
****STARTING BG: Must be between 4.0-20.0mmol/L or exercise will be rescheduled****		

Appendix D: Edinburgh Hypoglycemic Symptom Scale Questionnaire.

ExCarbs Study

DATA COLLECTION FORM

Participant ID (Subject ID #): _____

Date Form Completed (dd /mm/ yyyy): __ __ / __ __ / 20__ __

Form Completed By: __ __

Edinburgh Hypoglycemic Symptom Score

Randomization: **0.3g/kg/hr OR -50% Basal Reduction OR Combo**

Time Point: **-5 30 65 105 140**

	Not Present						**Very Intense**
Hunger	1	2	3	4	5	6	7
Palpitations	1	2	3	4	5	6	7
Sweating	1	2	3	4	5	6	7
Shaking	1	2	3	4	5	6	7
Autonomic Score							
Drowsiness	1	2	3	4	5	6	7
Confusion	1	2	3	4	5	6	7
Odd Behavior	1	2	3	4	5	6	7
Speech Difficulty	1	2	3	4	5	6	7
Incoordination	1	2	3	4	5	6	7
Neuroglycopenic score							
Nausea	1	2	3	4	5	6	7
Headache	1	2	3	4	5	6	7
Non-specific Score							
TOTAL SCORE							
What do you think your current blood glucose is?							

INSTRUCTIONS FOR USE

Each symptom is graded on a Likert scale ranging from 1 (non present) to 7 (very intense). A symptom is scored as definitely present if it is rated progressively higher than the baseline at two or more points during hypoglycemia. A symptom score is also considered to be unequivocal if the rating increases by factor of 2 at any time even if it returns to baseline thereafter.

Appendix E: Food and insulin log.

ExCarbs Study
DATA COLLECTION FORM
Participant ID (Subject ID #): _____ (e.g. Omni01) Date Form Completed (dd /mm/ yyyy): __ __ / __ __ / 20__ __ Form Completed By: __ __

STUDY DAY TRACKER

Randomization: **0.3g/kg/hr OR -50% Basal Reduction OR Combo**

TIME	BLOOD GLUCOSE	CARBS	INSULIN

Total Daily Dose of Insulin: _____

Appendix F: Exercise log.

ExCarbs Study

DATA COLLECTION FORM

Participant ID (Subject ID #): _____ (e.g. Omni01)

Date Form Completed (dd /mm/ yyyy): __ __ / __ __ / 20__ __

Form Completed By: __ __

omnipod®

At-Home Log Instructions

1. Complete the log for all days.
2. Bring the completed log and all physical activity sheets to your next scheduled in-clinic exercise session.
3. Record the following information each time you do ***Physical Activity where exertion is at least 2 or more on the RPE scale provided. Examples of physical activity include walking for >5 minutes, gardening, household chores, shopping, sports and training, etc.)***:
   - Type of Activity
   - Intensity (Defined by the 0-10 RPE scale provided)
   - Activity Start Time
   - Duration (Minutes)