

# **The Acute Effects of Aerobic and Resistance Exercise on Blood Glucose Levels in Type 1 Diabetes**

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## **Abstract**

Aerobic exercise interventions involving individuals with type 1 diabetes have had little positive effect on blood glucose control as reflected by hemoglobin A<sub>1c</sub>. The few existing interventions involving resistance exercise, either alone or combined with aerobic exercise, while small in sample size, have had better outcomes. The purpose of this research program was to examine the changes in blood glucose levels during activity and for 24 hours post-exercise (as measured by continuous glucose monitoring) when resistance exercise is performed, either on its own or combined with aerobic exercise, as compared to aerobic exercise alone or no exercise. Twelve physically active individuals with type 1 diabetes performed 5 separate exercise sessions in random order separated by at least five days: 1) no exercise/control; 2) aerobic exercise (45 minutes of treadmill running at 60%  $\dot{V}O_{2peak}$ ); 3) resistance exercise (45 minutes of weight lifting – 3 sets of 8 repetitions of 7 different exercises); 4) aerobic then resistance exercise (2 and 3 combined with the aerobic exercise first); 5) resistance then aerobic exercise (2 and 3 combined with the resistance exercise first). We found that resistance exercise was associated with a lower risk of hypoglycemia during exercise, less carbohydrate intake during exercise, less post-exercise hyperglycemia and more frequent (but less severe) nocturnal hypoglycemia than aerobic exercise. When aerobic and resistance exercise were combined, performing resistance exercise prior to aerobic exercise (rather than the reverse) resulted in attenuated declines in blood glucose during aerobic exercise, accompanied by a lower need for carbohydrate supplementation during exercise and a trend towards milder post-exercise nocturnal hypoglycemia.

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## **1.0 INTRODUCTION**

## 1.1 Background

Type 1 diabetes is an auto-immune disorder that causes the destruction of the insulin-producing  $\beta$ -cells of the pancreas. More than 300,000 Canadians are currently living with this disease, with the incidence increasing at a rate of 3% per year (1). Affected individuals are dependent on exogenous insulin to control their blood glucose, and consequently, for survival. Since they have very little or no endogenous insulin, they cannot have the moment-to-moment physiological regulation of insulin secretion from which nondiabetic individuals benefit. Therefore, people with type 1 diabetes face constant struggles to balance insulin dose, carbohydrate consumption, and physical activity to maintain tight control over blood glucose levels. Chronic hyperglycemia (high blood glucose) increases the risk of both macrovascular (heart disease), and microvascular (peripheral vascular disease, and eye, kidney and neural disorders) complications considerably (2, 3). Conversely, very tight glycemic control can lead to weight gain and acute hypoglycemia (low blood glucose) potentially resulting in immediate and sometimes severe health consequences.

Regular physical activity is associated with improved longevity and reduced burden of diabetes-related complications in individuals with type 1 diabetes (4). In spite of the fact that exercise is recommended for this population, there is still debate as to which type of exercise training would be most beneficial. Studies examining the effects of exercise on blood glucose control in this population have reported conflicting results. The mechanisms by which exercise training might improve blood glucose control also require further exploration. For those with type 1 diabetes who do exercise regularly, there is often a fear of hypoglycemia which may limit an individual's desire to perform exercise sessions of

appropriate duration or to maintain adequate levels of intensity during activity (5). In addition, there may be a tendency to consume more carbohydrate than necessary or decrease insulin intake excessively, potentially negating several of the health benefits of exercise training on the risk of macrovascular and microvascular diseases.

The majority of studies examining the effects of physical activity in type 1 diabetes so far have focused on aerobic exercise. Aerobic exercise is defined as any activity, such as walking, jogging, cycling or swimming, involving large muscle groups in repeated and continuous movements for extended periods of time (6). The benefits of this type of activity for individuals with type 1 diabetes include increases in cardiovascular fitness (7-10), decreased abdominal fat (11), as well as improved lipid profiles (9, 12), endothelial function (13) and insulin sensitivity (10, 12, 14, 15). Glycemic control, as measured by hemoglobin A<sub>1c</sub> levels, has shown inconsistent responses to aerobic exercise training with small improvements (decreases) found in some studies (14, 16), no significant change seen in several studies (7-11, 15, 17, 18), and either non-significant (12, 13, 18) or statistically significant increases (19) demonstrated in others.

Resistance exercise, defined as exercise in which muscular strength is used in working against a resistive load or moving a weight (6), has only been included in a very small number of studies involving participants with type 1 diabetes. The data from these very small studies (n=8-13) seem to suggest that, whether alone or in combination with aerobic activity, resistance exercise training might improve glycemic control (20-24). The mechanisms by which this occurs have yet to be elucidated.

Advancements in technology since the publication of the majority of these studies can now allow the investigator to monitor blood glucose in participants with type 1

diabetes for much longer periods. While continuous glucose monitoring (CGM) systems were designed to assist patients with diabetes in documenting the period(s) where they may have less than optimal glycemic control (otherwise unidentified periods of hypoglycemia or hyperglycemia), they can now be used by researchers to examine patterns of glucose variation associated with particular stimuli over a period of up to three days. In the case of physical activity, where antecedent hypoglycemia can affect exercise-related glucose counter-regulatory responses (25-27), the information provided by CGM can be invaluable: a participant's blood glucose levels can be monitored for many hours before, during, and after an exercise session, rather than the few hours that the participant is in the laboratory. Studies have also shown that CGM is accurate during exercise, with fewer than 5% of points falling outside the 95% confidence intervals in one study (28) and 92.9% of points falling within the A zone of the Clarke error grid in another (29).

## **1.2 Objectives**

This research program was designed to examine the acute effects of resistance exercise, alone or in combination with aerobic exercise, on blood glucose both during and after the exercise session in physically active individuals with type 1 diabetes. It also aimed to understand these changes in blood glucose by means of examining concurrent changes in regulatory hormones and metabolites in the blood. Finally, this research aimed to determine whether the order in which exercise is performed (aerobic before resistance or vice versa) would produce different hormonal and blood glucose outcomes if both exercise modalities were performed in a single exercise session.

Evidence from this study could eventually be used to justify larger randomized controlled trials examining the effects of aerobic and resistance exercise (either individually or combined) as well as the effects of different types of resistance exercise programs in type 1 diabetes. It could contribute to better the understanding of how the type, intensity and duration of physical activity affect blood glucose control in individuals with type 1 diabetes, thereby contributing to improved exercise prescriptions for this population.

### **1.3 Research Questions**

#### **a) Primary Research Questions:**

- 1) In physically active type 1 diabetes mellitus patients, how does resistance exercise – alone or in combination with aerobic exercise – affect blood glucose control both during exercise and over a 24 hour post-exercise period as measured by CGM when compared to aerobic exercise alone or no exercise?
- 2) When exercise modalities are combined, how does the order in which the exercises are performed (aerobic before resistance or vice versa) by physically active individuals with type 1 diabetes affect blood glucose control both during and over a 24 hour post-exercise period as measured by CGM?

#### **b) Secondary Research Question:**

- 1) How do changes in non-esterified fatty acids (NEFA), insulin, glucagon, cortisol and growth hormone assist in explaining the changes in blood glucose observed during and after an exercise session in physically active individuals with type 1 diabetes?

## 1.4 Research Hypotheses

- 1) Resistance exercise would produce smaller decreases, or possibly increases, in blood glucose during the exercise session as compared to aerobic exercise.
- 2) Resistance exercise, which is more reliant on phosphocreatine and muscle glycogen as a fuel source than aerobic exercise (where plasma glucose and lipids provide more energy), might be associated with a greater risk of late post-exercise hypoglycemia (blood glucose  $<3.5$  mmol/l as measured by CGM) due to the need to replenish glycogen stores.
- 3) Combined aerobic and resistance exercise sessions would be associated with a decreased risk of hypoglycemia during the exercise session as compared to aerobic exercise alone.
- 4) Combining aerobic and resistance exercise would be associated with a greater risk of late-onset post-exercise hypoglycemia (blood glucose  $<3.5$  mmol/l as measured by CGM) due to greater energy expenditure, and the need to replenish glycogen stores.

These questions and hypotheses have been addressed in three separate articles. The first article compares changes in blood glucose, along with NEFA, insulin, cortisol and growth hormone, among testing sessions that consist of rest/no exercise (control), aerobic exercise alone and resistance exercise alone. The second article examines how changes in blood glucose (along with NEFA, insulin, cortisol and growth hormone) differ during an aerobic exercise session when it is performed subsequent to a bout of resistance exercise as compared to when it is performed on its own. Finally, the third paper examines how the order in which resistance and aerobic exercise are performed during combined exercise sessions affects changes in blood glucose, along with NEFA, insulin, cortisol and growth hormone. Glucagon analyses were excluded from all of these papers due to inconsistency

in assay results. In all three of these papers, trends in post-exercise blood glucose levels as examined by means of continuous glucose monitoring systems are also presented. The conclusions drawn from the results are summarized in order to make exercise recommendations based on the present state of knowledge, as well as to suggest new areas of research in need of exploration.

## **2.0 REVIEW OF THE LITERATURE**

## **2.1 Glucose Homeostasis in Healthy Individuals**

At rest in individuals without diabetes, normal blood glucose levels are maintained within a narrow range, generally between 3.9 and 6.1 mmol/l in the fasting state and no higher than 7.8 mmol/l after meals (2). For this purpose, the body is equipped with a very sensitive hormone-based regulatory system that senses and adapts to the slightest changes in circulating glucose levels. The pancreatic hormones, insulin and glucagon, are the most predominant of the glucoregulatory hormones when the body is at rest. Insulin promotes energy storage while glucagon promotes energy release.

### ***2.1.1 Fasting Metabolism***

The liver plays a vital role in the maintenance of blood glucose levels at rest when a period of several hours has elapsed since food has been ingested. As glucose is the main energy source for the brain and the major organs in the body, it is important that a certain amount of glucose remains circulating in the blood at all times. Between meals, when blood glucose levels begin to drop, the release of insulin is inhibited, and the secretion of its antagonist, glucagon, is promoted. Glucagon exerts its main effect on the liver, stimulating the breakdown of glycogen stores (glycogenolysis) and the production of glucose from amino acid precursors (gluconeogenesis) for subsequent release into the blood stream (2). These processes then increase the circulating level of glucose, ensuring an adequate supply for the body's basic metabolic needs.

In extreme situations, such as during a period of extended fasting, where the balance of insulin and glucagon is insufficient to maintain glucose homeostasis, further neural and endocrine responses will occur in order to prevent hypoglycemia (low blood

glucose – usually defined as glucose concentration  $< 3.9$  mmol/l). Initial releases of cortisol will increase the availability of amino acids for gluconeogenesis, often through protein catabolism. Growth hormone will also be released as a response to low blood glucose, stimulating fat metabolism, and indirectly suppressing carbohydrate oxidation (30). Increases in epinephrine and norepinephrine can occur in healthy individuals when blood glucose levels drop below 3.9 mmol/l. The role of the catecholamines is initially to stimulate glycogenolysis and, if hypoglycemia is prolonged, to increase gluconeogenesis in an attempt to restore appropriate blood glucose levels (31). The role of cortisol and growth hormone in stimulating glucose production in resting individuals with low blood glucose seems to be less pronounced than that of glucagon and the catecholamines, especially where recovery from hypoglycemia is concerned (32).

### ***2.1.2 Postprandial Metabolism***

The breakdown of food from a meal or snack eventually results in an increase in plasma glucose levels. While there is always a low level of circulating insulin present in the blood, within 8 to 10 minutes of an increase in blood glucose levels additional release of insulin from the  $\beta$ -cells in the pancreas is stimulated. Once in the blood, insulin binds to receptors on the surface of striated muscle (skeletal and cardiac) and adipose cells, bringing the Glut-4 glucose transporters to the surface, and resulting in the transport of glucose into these cells. Transport of glucose into the liver by Glut-2 transporters, that are sensitive to concentration gradients, also takes place when blood glucose levels are elevated (30). The storage of glucose in the form of glycogen is promoted in muscle and hepatic cells, and  $\alpha$ -glycerol phosphate levels are increased in adipose cells for the storage

of triglycerides. Conversely, processes that would increase the levels of glucose in the blood (glycogenolysis, gluconeogenesis and lipolysis) are inhibited by insulin. Peak concentrations of insulin are generally reached within 30 to 45 minutes of food consumption, and then return rapidly to baseline (in parallel with blood glucose concentration) within 90 to 120 minutes (2).

### ***2.1.3 Acute Effects of Aerobic Exercise on Glucose Homeostasis***

The basic physiological reactions to the initiation of aerobic activity in individuals without diabetes are generally well understood. Muscle glycogen provides most of the energy necessary for the first five to ten minutes of exercise after which blood-borne substrates (glucose and non-esterified fatty acids (NEFA)) become the main source of fuel. If moderate aerobic activity is sustained for several hours, NEFA becomes the primary fuel source (33).

Throughout moderate-intensity aerobic exercise blood glucose levels remain relatively unchanged. Glucose demands by the exercising muscles are increased. Insulin secretion is diminished and glucagon release is promoted in response. Contraction-mediated (insulin independent) regulation of Glut-4 glucose transporters allows continued glucose transport into the muscle cells in spite of lower insulin levels in order to provide fuel for the working muscles. The change in the molar ratio of glucagon to insulin at the portal vein encourages a substantial (two to four-fold) (34) increase in glucose released by the liver to meet the elevated demand for glucose in the muscle. Upon exercise termination, insulin levels will rise and glucagon secretion will decrease while both glucose utilization and production return to baseline levels. Decreases in blood glucose

levels during moderate intensity exercise may eventually lead to hypoglycemia in healthy humans if exercise lasts for several hours without caloric intake, and glucose utilization begins to exceed hepatic glucose production (35).

Similar to the resting state, cortisol plays a minor role in maintaining blood glucose levels when they begin to drop during exercise in individuals without type 1 diabetes. Cortisol levels generally peak within the first 30 minutes of exercise, increasing protein catabolism and freeing amino acids to be used for gluconeogenesis in the liver (30). Growth hormone, which also increases and remains elevated during aerobic activity, plays a similar role in maintaining blood glucose levels by stimulating lipolysis and indirectly suppressing carbohydrate metabolism (30). Further decreases in blood glucose levels as a result of prolonged mild to moderate exercise combined with inadequate food intake result in the release of catecholamines (epinephrine and norepinephrine) as a defense against hypoglycemia. This will result in an increase in glycogenolysis, both in the muscles and in the liver, and will eventually produce an increase in gluconeogenesis as well, ensuring that a safe level of circulating glucose is maintained (30).

#### ***2.1.4 Acute effects of Anaerobic Exercise on Glucose Homeostasis***

Very intense (greater than 85% of an individual's aerobic capacity) exercise, where anaerobic metabolism supplies the majority of the energy needed, is generally not sustainable for more than 15 minutes by most individuals. In response to high intensity activity, epinephrine and norepinephrine levels increase substantially, augmenting the rate of hepatic glucose production (36), and diminishing the role of insulin and glucagon in glucoregulation. The increased catecholamine levels can produce a 5 to 10 fold increase in

glucose production, and a resulting increase in blood glucose concentration as the rate of glucose production exceeds the rate of utilization (36-38). Upon exercise completion this may result in hyperglycemia (high blood glucose levels) in individuals without diabetes, as the rate at which glucose is being used decreases faster than the rate at which it is produced (36-38). In response to the high plasma glucose levels, the regular mechanisms of glucose control will recommence: insulin release will be stimulated, glucose storage will resume, and normal blood glucose levels will be restored.

In addition to the catecholamine response, high intensity exercise can elicit both growth hormone and cortisol responses in individuals without diabetes. Growth hormone secretion has been shown to increase with exercise intensity (39), with higher levels generally being found in females (40), and a lower magnitude of response seen in older individuals (41). These, once again, are thought to play a role in fuel metabolism during exercise, albeit a small one in comparison to the action of catecholamines.

### ***2.1.5 Acute Effects of Resistance Exercise on Glucose Homeostasis***

As a form of anaerobic activity, bouts of resistance exercise elicit very similar metabolic and hormonal responses to those of constant high intensity running or cycling (30, 42). A wide variety of resistance training protocols exists depending on the goals of the individual training program. The amount of weight lifted (in terms of a percentage of the person's maximum lifting ability or one repetition maximum (1RM)), the number of times it is lifted per set (repetitions), the number of sets performed, the speed with which each movement is made, and the amount of rest between sets will affect metabolic and hormonal responses to the activity (42, 43).

Similar to other forms of exercise, changes in insulin and glucagon secretion will be mostly dependent on levels of circulating glucose. Catecholamine release, as is the case with other anaerobic activities, increases in proportion to the intensity of the resistance exercise being performed (44). This can, once again, cause hyperglycemia both during, and for a short time after exercise, as the catecholamine-enhanced rate of glucose production through hepatic glycogenolysis exceeds peripheral utilization (44, 45). Resistance exercise programs with moderate to high intensity, a high volume of repetitions, short rest intervals and a focus on large muscle groups have also been shown to increase growth hormone and cortisol release in both males and females (43, 46), leading to the suggestion that release of these hormones may be related to the amount of lactate accumulated as a result of the activity. It is interesting to note that carbohydrate supplementation during resistance exercise has been shown to alter hormonal responses significantly, by increasing insulin secretion and blunting the cortisol response (47, 48). Performing aerobic exercise prior to resistance exercise has also been shown to alter hormonal responses, by increasing circulating NEFA and attenuating the release of growth hormone (49). In individuals without type 1 diabetes, a return to baseline glucose concentration will generally occur within an hour of exercise, as glucagon secretion will decrease and insulin release increase according to circulating glucose levels in order to correct any exercise-induced hyperglycemia.

## **2.2 Type 1 Diabetes Mellitus**

Type 1 diabetes mellitus is a metabolic disease resulting from defects in insulin secretion as a result of autoimmune destruction of the  $\beta$ -cells of the pancreas (50). This

form of the disease accounts for approximately 5 to 10% of all cases of diabetes, and is generally associated with absolute insulin deficiency (51). The lack of insulin production leads to difficulty in controlling blood glucose levels, often resulting in chronic hyperglycemia. For individuals with diabetes, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is used as a measure of blood glucose control over the previous 2-3 months. In those without diabetes, HbA<sub>1c</sub> levels of approximately 4 to 6% of total hemoglobin can be expected. The chronic hyperglycemia that is often found in poorly controlled diabetes, leads to an increase in the glycosylation of hemoglobin, and therefore a higher level of HbA<sub>1c</sub>.

### ***2.2.1 Management of Type 1 Diabetes***

In the general (mainly nondiabetic) population, HbA<sub>1c</sub> levels lower than 5% are associated with the lowest rates of cardiovascular disease, with a relative risk of death (all causes) of 1.24 and 1.28 for men and women respectively for every percentage point increase thereafter even within the “normal” range (52). In type 1 diabetes it is usually not feasible to achieve HbA<sub>1c</sub> in the normal range; most national diabetes guidelines suggest that the target HbA<sub>1c</sub> in people with diabetes should be 7% or lower, as levels higher than this are associated with an increased risk of both microvascular and macrovascular complications (53) including retinopathy, nephropathy, neuropathy and cardiovascular disease (51).

Where physiological control of insulin is impaired or absent, it becomes necessary for the individual to find an appropriate balance among diet, exogenous insulin injections, and physical activity to maintain appropriate blood glucose levels. Correct use of these tools, in combination with self-monitoring of blood glucose concentration, can lead to

relatively stable blood glucose levels. If, however, mistakes are made in the composition, quantity or timing of any of these three, the resulting hypoglycemia or hyperglycemia carries with it the risk of both immediate and chronic complications.

### ***2.2.2 Insulin therapy***

Recent years have seen the development of several new types of insulin, as well as insulin delivery systems, which have helped individuals with diabetes to mimic more closely the physiological production of insulin by the pancreas. Insulin preparations, which are generally produced by recombinant DNA technology, are classified according to their duration of action (see Table 2.1 below) (54). For individuals using insulin injections, several formulations are now available from ultra-short acting, the effects of which begin within 20 minutes of injection and generally last up to 4-5 hours, to long-acting, which is relatively peakless and lasts approximately 24 hours. Using a combination of long or intermediate and short acting insulin in multiple daily injections (MDI) allows an individual with diabetes to maintain adequate insulin levels in between meals (basal), and to increase insulin availability when food is to be consumed (bolus). Continuous subcutaneous insulin infusion (CSII) devices, otherwise known as insulin pumps, can also be used to deliver continuous infusions of ultra-short acting insulin, often with diurnal variations in rate, throughout the day to maintain basal insulin levels, while allowing for immediate administration of an insulin bolus when food is consumed.

It is important that individuals with type 1 diabetes match their insulin administration appropriately to the quantity, timing and composition of food that they ingest (2). Irregular meal times or incorrect calculations of carbohydrate content in

consumed foods can cause a mismatch between the insulin present in the system, and the amount of glucose ingested, resulting in either hypoglycemia or hyperglycemia (2). The recent innovations in ultra-fast acting insulin and CSII currently allow for more flexibility in mealtimes and finer insulin adjustments, making this less of a concern than it has been in the past. In spite of this, patients with diabetes still have to take into account the fact that absorption rates of different types of carbohydrates can vary, causing blood glucose to rise either faster or to a greater extent with some foods when compared to others, and that concurrent consumption of fats and proteins can substantially alter the speed with which the carbohydrates are digested and absorbed (2).

**Table 2.1 – Types of insulin and their characteristics (adapted from (54))**

Insulin Type	Name (trade name)	Onset	Peak	Duration
Rapid-acting insulin analogues	• Insulin aspart (NovoRapid)	10-15 min	1-1.5 h	3-5 h
	• Insulin lispro (Humalog)	10-15 min	1-2 h	3.5-4.75 h
	• Insulin glulisine (Apidra)	10-15 min	1-1.5 h	3-5 h
Short-acting insulins	• Humulin-R	30 min	2-3 h	6.5 h
	• Novolin ge Toronto	30 min		
Intermediate-acting	• Humulin-N	1-3 h	5-8 h	Up to 18 h
	• Novolin ge (NPH)			
Long-acting basal insulin analogues	• Insulin detemir (Levemir)	90 min	N/A	16 to 24 h
	• Insulin glargine (Lantus)			Up to 24 h

The risk of severe hypoglycemia (hypoglycemia requiring the assistance of another person) can be increased two to three-fold among those receiving intensive therapy (3). Hypoglycemia can produce both neurogenic (e.g. trembling, palpitations, sweating, anxiety, nausea) and neuroglycopenic (e.g. confusion, weakness, drowsiness, difficulty

speaking, dizziness) symptoms (55). In addition to the dangers that these can present in everyday situations (such as driving or operating other machinery) hypoglycemia in its most severe form can result in seizures, unconsciousness, brain damage or death. Repeated occurrences of hypoglycemia can also lead to a lessening of symptoms and therefore decreased awareness of low blood glucose levels, thereby increasing the risk of adverse outcomes.

### **2.2.3 Diet**

The frequency and composition of meals play an important role in determining blood glucose levels in those with type 1 diabetes. As such, individuals with type 1 diabetes are encouraged to maintain consistency in carbohydrate intake, and to eat their meals and snacks at both frequent and regular intervals (56). The macronutrient composition of recommended food intake falls in line with Canada's Food Guide, consisting of no less than 45% carbohydrate (<10g/day of sugar alcohols, and only up to 10% of total daily energy intake as sucrose), no more than 35% fat (while restricting the intake of saturated fats), and approximately 15 to 20% protein (56). In addition, individuals with type 1 diabetes are encouraged to choose food sources of carbohydrates with a low glycemic index, rather than high glycemic index, and to ensure adequate levels of dietary fibre from a variety of sources (including cereal and soluble fibres) (56). Knowledge of the type and amount of carbohydrate consumed as well as the appropriate amount of insulin with which this needs to be matched are essential tools in the management of blood glucose levels in type 1 diabetes.

### ***2.2.4 Physical Activity***

Although it is considered an important tool in diabetes management, it is often difficult to balance physical activity with appropriate carbohydrate ingestion and insulin administration. The increased insulin sensitivity associated with physical activity can lead to a decrease in the need for exogenous insulin (3), with adjustments often being made on a trial and error basis. The timing and quantity of insulin injection with respect to the start of exercise, the site at which insulin is injected, as well as the timing of the individual's last meal or snack, will all affect the individual's ability to exercise safely, without the risk of either high, or low blood glucose during the exercise session. To fully appreciate the complexity of these interactions and how they may affect long term blood glucose control, it will be essential to understand how the physiological and metabolic responses to both acute and chronic physical activity in individuals with type 1 diabetes differ from those of non-diabetic individuals.

#### **2.2.4a General Considerations for Exercise in Type 1 Diabetes**

Regardless of the type of activity being performed, several factors will influence the blood glucose response of individuals with type 1 diabetes during exercise. While the intensity and duration of exercise will be the two most predominant factors, the type, dose and site of pre-exercise insulin administration (57-60), the pre-exercise level of blood glucose (61), as well as the timing of injections and meals (62, 63) before exercise will also affect the outcome. As a result, glucose levels may increase, decrease, or even remain unchanged during physical activity, depending on the balance of these factors.

The muscle contraction that takes place during exercise, regardless of intensity or modality, stimulates the uptake and oxidation of circulating glucose, even in the absence of insulin. As it was mentioned above, the slightest decrease in blood glucose levels in individuals without diabetes leads to the suppression of insulin secretion and promotes the release of glucagon, to ensure glucose availability for the exercising muscles. This fine-tuned interaction is not possible in individuals with type 1 diabetes, and finding the ideal conditions of low insulin and adequate blood glucose concentration to provide fuel appropriately for the working muscles is often difficult. As endogenous insulin production is absent, the level of circulating insulin will be determined entirely by exogenous insulin intake. Any error in producing the right level of active insulin in the system during physical activity will result in a failure to maintain blood glucose in a healthy range. High levels of circulating insulin (hyperinsulinemia) can be the result of poor injection timing (so that insulin is exerting its peak effect during exercise), performing exercise post-prandially without adequate insulin bolus reductions, or injecting insulin into a limb that is used during exercise thereby speeding up insulin absorption. Under hyperinsulinemic conditions, muscle, adipose and hepatic cells will be transporting glucose from the blood stream for storage at the same time as the skeletal muscles are increasing their uptake to fuel the work being performed. The normal exercise-induced stimulation of glucose uptake into the contracting muscle is accelerated by the presence of excessive insulin, and the release of glucose from storage (which occurs mostly in the liver) is inhibited. These interactions are further complicated by the action of catecholamines during high intensity exercise, which will be discussed in greater detail in Section 2.4.2.

Unless appropriate adjustments are made to insulin dosage prior to exercise, or additional carbohydrates are consumed, hyperinsulinemia often leads to hypoglycemia during physical activity in individuals with type 1 diabetes, especially during aerobic exercise. Glucagon secretion, which may also be impaired in individuals with type 1 diabetes, is often insufficient to counteract the effects of high insulin levels (64). As a result, the body is unable to release sufficient glucose to meet the demand of the exercising muscles, and blood glucose levels drop (64, 65). In addition, counter-regulatory responses to low blood glucose can be blunted if the individual has encountered recent incidents of hypoglycemia (25-27, 66-68).

Low levels of circulating insulin may also have a negative effect on exercise metabolism in individuals with type 1 diabetes. With inadequate insulin levels, glucose uptake by the exercising muscles may be reduced, and hepatic glucose production, especially during high intensity exercise, may exceed demand. Counter-regulatory responses to exercise (catecholamines, growth hormone, cortisol, glucagon) may be increased (69), leading to even higher levels of hepatic glucose production. With the supply of glucose exceeding the demand, the end result is often hyperglycemia (70).

Managing circulating insulin levels involves a delicate balance of timing and composition. Faster absorbing insulin analogues can lead to hyperinsulinemia (and therefore an increased risk of hypoglycemia) if administered too close to the exercise session (71). Conversely, if sufficient time has elapsed since injection, or if pre-exercise dosage has been reduced, individuals with type 1 diabetes are more likely to achieve an appropriate level of insulin (58). One study suggested that reducing pre-exercise insulin dosage by 50% is sufficient to achieve appropriate levels of insulinemia for mild to

moderate exercise (72). Others have found that, regardless of insulin levels, carbohydrate supplementation either before, during, or after activity routinely reduces the risk of hypoglycemia (73-78) and has the added benefit of permitting more spontaneity in the timing of activities.

The use of continuous subcutaneous insulin infusion (CSII) may also assist active individuals with type 1 diabetes in fine-tuning their insulin dosage to match their exercise needs. As this technology provides a constant low-dose infusion of short-acting insulin, small adjustments in infusion rates can be made to account for meals, exercise, or other unrelated fluctuations in blood glucose. A recent systematic review found that CSII therapy, both in adults and in adolescents with type 1 diabetes, resulted in lower levels of HbA<sub>1c</sub>, without an increased risk of hypoglycemia (79). The ability to lower insulin infusion rates during and after exercise has been shown to lower the risk of hypoglycemia in individuals with type 1 diabetes (59) as it better mimics the physiological decrease in insulin during activity seen in individuals without type 1 diabetes.

### **2.3 Physical Activity in Type 1 Diabetes**

In spite of the fact that physical activity is recommended for individuals with type 1 diabetes, a study by Plotnikoff et al. (80) found that 63.7% of Canadian individuals with type 1 diabetes were considered insufficiently active. Higher levels of physical activity in those with type 1 diabetes were associated with a younger age, being single, higher income, lower level of perceived disability and not smoking (80). A separate study found that individuals with type 1 diabetes tend to perceive more barriers and fewer benefits with respect to physical activity, than their counterparts without diabetes (81), with the fear of

hypoglycemia being the most reported obstacle to physical activity within this population (5, 82).

### ***2.3.1 Potential Benefits of Physical Activity in Individuals with Type 1 Diabetes***

Higher levels of physical activity are associated with increased life expectancy as well as decreased frequency of diabetic complications in individuals with type 1 diabetes (4, 83-88). A recent cross-sectional analysis of survey data collected to investigate the influence of time spent using a computer on metabolic control in individuals with type 1 diabetes found no relationship between computer use and HbA<sub>1c</sub> levels, but did find a negative and significant correlation between weekly time spent on physical activity and levels of HbA<sub>1c</sub> (83). These results were consistent with a prospective study that followed 548 patients with type 1 diabetes for 7 years and found that those who had higher self-reported activity levels at baseline had a lower risk of developing microvascular complications (4). After adjusting for age, body mass index, diabetic complications and smoking, the investigators reported that sedentary (< 1,000 kcal/week expended on physical activity) male patients were three times more likely to die than those reporting higher (>2,000 kcal/week) physical activity levels (4). A similar trend was found among the female patients, but it failed to reach statistical significance.

Regular physical activity has also been associated with several health benefits in children and adolescents with type 1 diabetes. A cross-sectional analysis of survey data from over 18,000 pediatric patients found that HbA<sub>1c</sub> levels were lower in those who performed regular physical activity more often (84). This relationship was consistent for both sexes and in all age groups examined. The same survey data also found that higher

physical activity levels were associated with a lower body mass index, more favourable lipid profiles and lower diastolic blood pressure (84, 85).

Physical activity may also play a role in decreasing the severity of several type 1 diabetes-related complications. One randomized clinical trial showed that regular exercise prevented the onset and delayed the progression of peripheral neuropathy over a 4-year period in individuals with type 1 or type 2 diabetes (89). When longitudinal data were collected on 1680 individuals with type 1 diabetes, women with lower levels of self-reported leisure time physical activity were found to have poor glycemic control in comparison to their more active counterparts (87). The same study also found that men and women reporting higher levels of physical activity had higher insulin sensitivity (87). When a follow-up study was performed involving 1945 individuals with type 1 diabetes, the frequency and severity of diabetic complications, including nephropathy, retinopathy, and cardiovascular disease was greater among those reporting very little or relatively low intensity leisure time physical activity in comparison to those who were more frequently and vigorously active (86).

Existing exercise intervention studies involving individuals with type 1 diabetes have generated conflicting results, which will be discussed further in section 2.4. Differences in study design (timing, duration, intensity and frequency of exercise sessions, changes in carbohydrate and insulin intake, etc.) among interventions will likely explain a great deal of this variation. In order to fully understand how these factors can interact to affect blood glucose levels, it is essential to understand the mechanisms of blood glucose control, both at rest, during, and after an exercise session in individuals with type 1 diabetes.

## **2.4 The Chronic and Acute Effects of Exercise in Type 1 Diabetes**

### ***2.4.1 Aerobic Exercise***

#### **2.4.1a General Adaptations to Aerobic Exercise Training**

Regular aerobic activity has been associated with a multitude of physical benefits which often increase in proportion to the volume of exercise performed and the intensity of the exercise sessions (30). Aerobic training produces greater plasma volume and muscle capillary density thereby increasing blood flow to the working muscles during peak exercise (30). Overall, this results in greater oxygen provision to and carbon dioxide removal from the tissues. The ability to bring oxygen into the body is also augmented by improved lung function and cardiac output (30). In individuals who exercise regularly, the oxidative metabolic system becomes more efficient as the volume of oxidative enzymes in the tissues increases, eventually leading to a shift in the type of substrates that are used to supply the energy demands of physical activity, with free fatty acids (through lipolysis) providing a greater proportion of the energy needs. Glucose transport into muscle tissue is also improved, with an increase in muscle Glut-4 glucose transporter content (90). In addition, regular aerobic exercise has been associated with a lower body mass index, lower serum triglyceride levels, and an increase in high-density lipoprotein (providing less atherogenic lipid and lipoprotein profiles) (91, 92). Aerobic exercise training has also been associated with increased muscle and hepatic insulin sensitivity (93) as well as greater insulin-mediated glucose uptake (94).

#### **2.4.1b Studies Examining Aerobic Exercise Training in Type 1 Diabetes**

Several studies have examined the effects of aerobic exercise on blood glucose control in type 1 diabetes (7-12, 14, 15, 17-19, 95, 96). To determine if control has improved, HbA<sub>1c</sub> is generally measured both before and after a training intervention, as it can be used as an indication of blood glucose levels over the 12 to 15 week period preceding the test (2). To date, aerobic exercise interventions in type 1 diabetes have yielded mixed results. While some studies have found that aerobic exercise can significantly lower HbA<sub>1c</sub> levels (14, 16, 96), others have found non-significant decreases in HbA<sub>1c</sub> (8, 9, 11), have shown no effect (7, 10, 15, 17, 18, 95), or have even resulted in non-significant (12, 13, 18) or significant (19) increases in HbA<sub>1c</sub> by the end of the study period. The inconsistent results may be due to shortcomings in the studies' designs including short study duration (8, 9, 11), inadequate exercise intensity (13, 15), low participant compliance (13, 17, 19), or significantly increased caloric intake (11, 12, 15, 17, 18). In spite of failing to lower HbA<sub>1c</sub> levels, the exercise interventions provided several other health benefits including improved cardiorespiratory fitness (9, 12, 18), greater muscle mass (7), increased insulin sensitivity (12), lower body fat (9), increases in the HDL/LDL ratio (9, 12, 18) and improved psychological well being (97).

#### **2.4.1c Acute effects of Aerobic Exercise on Blood Glucose in Type 1 Diabetes**

Individuals with type 1 diabetes can partake in exhaustive aerobic activity for several hours if insulin and carbohydrate are adjusted and monitored appropriately (98-100). In conditions of adequate glycemia and insulinemia similar patterns of fuel selection during aerobic activity of long duration can be found in individuals with type 1 diabetes as

compared to those without diabetes, with a gradual shift towards lipid oxidation occurring with increasing exercise duration (61). These ideal conditions, however, are difficult to achieve and may change from day to day for any given individual. This can result in either hypoinsulinemia or hyperinsulinemia at the time of exercise, thereby altering the individual's blood glucose response to exercise. Hyperinsulinemia, which often occurs when exercise is performed too soon after a meal, can be especially deleterious: the risk of hypoglycemia is greatly increased as hepatic glucose production (inhibited by a higher than normal insulin to glucagon ratio at the hepatic portal vein) will be unable to keep pace with utilization.

Table 2.2 –Responses to aerobic exercise in individuals with and without type 1 diabetes

<b>EXERCISE RESPONSE</b>	<b>NO DIABETES</b>	<b>TYPE 1 DIABETES</b>
<i>Change in Glucose Uptake</i>	↑↑↑	↑↑↑
<i>Initial Blood Glucose Response</i>	↓	↓
<i>Insulin Response</i>	↓↓	↔
<i>Glucagon Response</i>	↑↑	↑ or ↔
<i>Catecholamines Response</i>	↑	↑
<i>Hepatic Glucose Production</i>	↑↑↑	↑
<i>Resulting Blood Glucose Levels</i>	↔ (euglycemia)	↓↓ (hypoglycemia)

With the exception of insulin, aerobic activity in individuals with type 1 diabetes elicits many of the same hormonal responses as it does in those without diabetes (Table 2.2). Assuming that the participant has generally been euglycemic prior to activity, the onset of aerobic exercise will lead to increases in glucagon, epinephrine, norepinephrine,

cortisol and growth hormone (25-27, 101), all of which will work to ensure that glucose is released from storage to meet the demands of the exercising muscles. Hormonal responses will generally increase in parallel with the intensity and/or the duration of exercise. There is, however, evidence to indicate that glucagon responses are impaired in individuals with type 1 diabetes (102, 103) which may place more emphasis on the other counter-regulatory hormones in maintaining blood glucose during exercise.

All of these responses, however, can be blunted should the individual encounter periods of hypoglycemia prior to exercise (25-27, 101). The size of the blunting effect seems to be dependent on the magnitude and duration of the hypoglycemic episode (27) and is more prominent in males than in females (101). In the absence of antecedent hypoglycemia, there is evidence to indicate that secretion of growth hormone may in fact be elevated during aerobic exercise in individuals with type 1 diabetes, when compared to their non-diabetic counterparts (98), although this response can also be diminished if individuals with type 1 diabetes undertake exercise in a hyperglycemic rather than a euglycemic state (104).

While the composition of the fuel used during physical activity is similar in individuals with type 1 diabetes to that of their counterparts without diabetes, the provenance of the fuels may be different. It has been found that individuals with type 1 diabetes may have lower reliance on hepatic glycogen stores during low intensity aerobic activity than those without diabetes (105). In the presence of high insulin levels, a greater reliance on exogenous glucose for fuel during aerobic exercise was found, in spite of the fact that glycogen stores were not spared (106). Hyperglycemia during exercise has also produced alterations in fuel selection, leading to greater carbohydrate metabolism than in

euglycemia, accompanied by blunted cortisol and growth hormone responses (61). Studies have also shown a greater reliance on muscle glycogenolysis and gluconeogenesis to meet the energy requirements of aerobic activity in type 1 diabetes than would be found in individuals without diabetes (105, 107).

The effects of aerobic activity on blood glucose levels can often last for several hours after exercise completion in individuals with type 1 diabetes. As a result of needing to replenish glycogen stores, which may be depleted to a greater degree after exercise for individuals with type 1 diabetes (105, 107), glucose uptake by the exercising muscles may be enhanced for many hours and often overnight (108). Some forms of prolonged aerobic exercise can lead to an increased risk of hypoglycemia for several hours post-exercise. Conversely, certain types of prolonged exercise, such as a marathon run, can increase lipid oxidation for several hours post-exercise, decreasing the reliance on glucose as a fuel source, and therefore diminishing the immediate risk of a drop in blood glucose (99). The risk of hypoglycemia associated with aerobic activity, however, is likely to increase an individual's propensity to consume excess carbohydrate before, during, or after exercise, potentially negating the glucose lowering benefits of performing aerobic activity in the first place.

## ***2.4.2 Anaerobic Exercise***

### **2.4.2a General Adaptations to Anaerobic Exercise Training**

Many of the adaptations to anaerobic exercise training occur at the cellular rather than the systemic level. Regular high intensity activity increases the body's ability to produce anaerobic power by improving the provision of fuels during short intense bouts.

With training, the main fuels for short powerful bursts (adenosine triphosphate and phosphocreatine) are stored in greater supply within the muscle tissue, increasing the individual's ability to sustain higher absolute exercise intensities for a greater length of time (30). Additional adaptations to high intensity training include reduced glycogenolysis during high-intensity exercise, a lower accumulation of muscle lactate and hydrogen ions (109), increased activity of oxidative enzymes (109-112) and increased peak oxygen consumption (109-112). Increases in epinephrine and norepinephrine that are seen during high intensity exercise are also enhanced in trained individuals, causing even greater increases in glucose during strenuous bouts of exercise (36).

#### **2.4.2b Studies Examining Anaerobic Exercise Training in Type 1 Diabetes**

There are very few studies examining the effects of anaerobic exercise training in type 1 diabetes. A small study by Harmer *et al.* (113, 114) examined the effects of a 7-week anaerobic exercise training period where participants (n=8 individuals with type 1 diabetes, n=7 controls without type 1 diabetes) performed four to ten 30-second sprints interspersed with four minute rest periods three times per week. Over the 7 week study, HbA<sub>1c</sub> levels in the participants with type 1 diabetes showed a non-significant (P=0.09) decrease from 8.6±0.8% to 8.1±0.6% (114). During intense exercise, it was found that both individuals with and without type 1 diabetes showed higher peak ventilation and lower carbon dioxide output, plasma lactate, muscle lactate, glycogenolytic and glycolytic rates, and ATP degradation after seven weeks of training. Training also produced higher activity rates in glycolytic enzymes (hexokinase and citrate synthase) and increased fat oxidation during submaximal exercise in participants both with and without type 1 diabetes

(113). The authors surmise that the enhanced muscle oxidative metabolism produced by high intensity training may have clinically important health benefits for individuals with type 1 diabetes, in spite of not having found significant changes in HbA<sub>1c</sub> during the study (113).

#### 2.4.2c Acute Effects of Anaerobic Physical Activity in Type 1 Diabetes

Regardless of insulin levels, high intensity exercise may cause hyperglycemia both during and after exercise in individuals with type 1 diabetes. Strenuous exercise leads to an increase in counter-regulatory hormones, especially catecholamines, which can increase glucose production to a level that exceeds peripheral utilization (70, 115-118) (Table 2.3). In individuals without diabetes, insulin levels would naturally increase post-exercise in order to return glycemia to resting levels. As this does not occur in type 1 diabetes, prolonged hyperglycemia can result (70, 115, 117, 118), unless a correction dose of exogenous insulin is administered.

Table 2.3 – Response to anaerobic exercise in individuals with and without type 1 diabetes

<b>EXERCISE RESPONSE</b>	<b>NO DIABETES</b>	<b>TYPE 1 DIABETES</b>
<i>Change in Glucose Uptake</i>	↑↑↑	↑↑↑
<i>Catecholamines Response</i>	↑↑↑↑	↑↑↑↑
<i>Insulin Response (exercise)</i>	↓	↔
<i>Glucagon Response (exercise)</i>	↑↑	↑ or ↔
<i>Hepatic Glucose Production</i>	↑↑↑↑	↑↑↑↑
<i>Insulin Response (post-exercise)</i>	↑↑	↔
<i>Resulting Blood Glucose Levels</i>	↔ <b>(euglycemia)</b>	↑↑ <b>(hyperglycemia)</b>

The higher levels of blood glucose that can be produced by high intensity exercise may actually be an effective way of maintaining safe blood glucose levels and preventing exercise-related hypoglycemia. Two studies by Bussau *et al.* (119, 120) demonstrated that a single 10-second maximal sprint performed either at the end (119) or at the beginning (120) of 20 minutes of low intensity ( $40\% \dot{V}O_{2\text{peak}}$ ) cycling led to significantly smaller decreases in blood glucose levels post-exercise as compared to exercise sessions where no sprint was performed. In a series of similar studies performed by Guelfi *et al.* exercise sessions where participants cycled continuously at constant moderate intensity ( $40\% \dot{V}O_{2\text{peak}}$ ) led to greater post-exercise declines in blood glucose than sessions where 4-second sprints were performed every 2 minutes throughout the exercise session (121, 122). It should be noted, however, that glycemia was only monitored for 120 minutes after exercise in all of these studies, when a trend towards late onset (nocturnal) post-exercise hypoglycemia was found after high intensity activity in a small study using continuous glucose monitoring (CGM) (123). Another study using CGM comparing the effects of intermittent high intensity exercise to moderate aerobic exercise also found that the frequency of nocturnal hypoglycemia was higher after the high intensity interval protocol than the moderate continuous exercise (124). Further studies with larger sample sizes are necessary to confirm the effects of high intensity exercise on both early and late post-exercise hypoglycemia in individuals with type 1 diabetes.

### ***2.4.3 Resistance Exercise***

#### **2.4.3a General Adaptations to Resistance Exercise Training**

Regular heavy resistance exercise training can lead to gains in muscle mass ranging from 3 to 12% (125, 126), and increases in muscle strength of greater than 30% (127, 128) within the first couple of months of training. Elderly subjects tend to benefit the most from this type of training with relative increases in both muscle mass and strength typically being higher (125, 129). Initial gains in strength generally do not involve any changes in lean muscle mass (hypertrophy) but rather occur as a result of improved muscle recruitment (peripheral nervous system adaptation). The amount of muscular hypertrophy that occurs as a result of resistance exercise training will depend on the type of program followed, with high volume-low resistance exercise training favoring muscular endurance, moderate volume-moderate resistance exercise training producing a greater degree of muscular hypertrophy, and low volume-heavy resistance exercise training leading to greater strength gains (130).

There is evidence to indicate that regular resistance exercise training can change the patterns of response for certain hormones that result from an acute bout of resistance exercise. As is the case with other anaerobic activities, the catecholamine response to resistance exercise is enhanced in trained individuals (131), potentially leading to greater degrees of hyperglycemia during exercise. A review of resistance training studies, however, found that no consistent pattern of change could be found in the cortisol response to acute resistance exercise after regular resistance exercise training, as both reduced and enhanced responses, as well as no change in response have been found in various training studies (42). Inconsistent outcomes have also been found in studies examining the effect

of progressive resistance exercise training on growth hormone secretion during resistance exercise (107, 121), although this may be related to the type of exercise stimulus used.

#### **2.4.3b Studies Examining Resistance Exercise Training in Type 1 Diabetes**

Only two studies have been published to date examining the effects of resistance exercise training (on its own) on blood glucose control in type 1 diabetes. The first was performed by Durak *et al.* (21) who randomized eight subjects into 2 groups: Group A (n=4) took part in a 10 week resistance exercise training program prior to taking a 6 week break and group B (n=4) partook in the 10 weeks of resistance exercise training after an initial 6 week period without exercise. At the end of the non-training periods, mean HbA<sub>1c</sub> was 6.9±1.4%, while the 10 week training session ended with participants showing a mean HbA<sub>1c</sub> level of 5.8±0.9% (P=0.05) (21). The resistance training sessions (lasting approximately an hour and performed three times weekly) also produced decreases in serum cholesterol and self-monitored blood glucose (21).

The second study was performed by Ramalho *et al.* (22), and involved sixteen previously sedentary participants with type 1 diabetes who were randomized to either 12 weeks of aerobic exercise training, or 12 weeks of resistance exercise training, with each type of activity being performed three times per week. By the end of the training period, both groups had reduced their mean waist circumference, insulin dosage and self-monitored blood glucose, but statistical significance for these variables was only reached in the aerobic exercise group (22). It should be noted, however, that a non-significant decrease in HbA<sub>1c</sub> (from 8.2±2.9% to 7.6±1.6%) was found in the resistance exercise training group, while aerobic exercise training resulted in a significant increase (from 8.7±1.6% to 9.8±1.8%; P<0.05) (22).

There are equally few studies that examine the combination of both aerobic and resistance exercise training in individuals with type 1 diabetes. In addition, small sample sizes (n=8 to 13) and the lack of concurrent non-exercising control groups with diabetes makes interpretation for some of these studies difficult. An early study by Petersen *et al.* (132) found that an 8 month training program consisting of a 5 minute warm-up, 15 minutes of cycling and 15 minutes of resistance training resulted in a significant decrease in HbA<sub>1c</sub> (from 10.3% to 7.6%), a decrease in blood pressure, heart rate and mean body fat, as well as an improvement in nerve conduction in 10 individuals with type 1 diabetes. Patients also received monthly evaluations by a physician, strict glucose monitoring instructions and weekly group meetings. As there was no control group in this study, it is difficult to know how much of the improvement in blood glucose control can be attributed to the exercise, rather than to the improvements in patient blood glucose monitoring. Another study by Mosher *et al.* (24) consisted of 10 adolescents with type 1 diabetes performing a combination of endurance and strength activities for 45 minutes three times a week over a 12-week period. While this study once again lacks a non-exercising comparison group, the study participants were found to have improved strength and cardiorespiratory endurance, increased lean body mass, and significant improvements in HbA<sub>1c</sub> (from 7.72±1.26 to 6.76±1.07%) at the end of the intervention period.

There are two recent studies that examined the effects of combined exercise training in adolescents with type 1 diabetes (20, 23) where non-exercising control groups were included. D'Hooge *et al.*, (20) found that a 20 week supervised program, performed twice weekly, consisting of a combination of strength (30 minutes) and aerobic training (30 minutes), produced improvements in muscular strength and endurance, but had no

significant effect on body composition or HbA<sub>1c</sub>. The lack of significant findings may be attributable to the relatively low compliance rates (mean attendance of 63%), potential changes in diet (not monitored during the study), and the relatively small sample size (n=8 for each group). They did, nonetheless, find a significant decrease in insulin dosage in the exercise group, while insulin needs increased in the control group throughout the study period (20).

Reductions in insulin dosage were also found in a recent randomized controlled trial by Salem *et al.*(23) involving a combination of aerobic, anaerobic (1 to 2 minutes at  $>85\% \dot{V} O_{2\text{peak}}$ ) and resistance exercise, along with stretching, neuromuscular and balance exercises in adolescents with type 1 diabetes. The study involved two different exercising groups (one performing the exercise protocol once per week (n=75), the other performing it three times per week (n=73)) and a non-exercising type 1 diabetic control group (n=48). While the authors observed a non-significant increase in HbA<sub>1c</sub> (from 8.3±2.1 to 8.9±1.4%) in the control group, both exercise groups showed significant decreases, with the more frequently exercising group demonstrating greater improvements (from 8.9±1.6 to 7.8±1% (P=0.03) versus 8.9±1.4 to 8.1±1.1% (P=0.01). Similarly, improvements in weight, BMI, waist circumference and lipid profiles were found in both exercise groups but not in the control group, with greater improvements being associated with increased exercise volume (23). As the training protocol involved several different types of exercise training, it is impossible to ascertain which training modality would have had the greatest effect. From the few studies that have been completed, it would, nonetheless, seem that resistance exercise, whether on its own or in combination with aerobic or other types of

exercise, may have a beneficial effect on blood glucose control. The reasons for this remain to be clearly elucidated.

#### **2.4.3c Acute Effects of Resistance Exercise in Type 1 Diabetes**

There are currently no studies available in the published literature examining the acute hormonal and resulting blood glucose responses to resistance exercise in type 1 diabetes. In individuals without diabetes, resistance exercise has been shown to produce elevated levels of epinephrine, thereby enhancing hepatic glucose production and causing a rise in blood glucose (45). Resistance exercise is also associated with lactate accumulation (43), which could potentially stimulate gluconeogenesis, and increases in growth hormone (42) that could enhance lipolysis, creating less of a dependency on plasma glucose for fuel. As studies examining other types of anaerobic exercise (short sprints, high intensity intervals) have shown that young, fit individuals with type 1 diabetes have similar catecholamine (117, 119, 121), and lactate (70, 115) responses to their counterparts without diabetes, it is likely that resistance type activities of sufficient intensity will lead to either increases in blood glucose, or attenuated rates of decline, as compared to aerobic activity in individuals with type 1 diabetes.

### **2.5 Continuous Glucose Monitoring**

A continuous glucose monitoring (CGM) system generally consists of a sensor which is somehow connected (either physically via a wire, or telemetrically) to a pager size monitor, worn by the individual. The recently developed CGM iPro™ (Medtronic, Northridge, CA) has gone one step further and now stores data on a small chip within the

transmitter itself which can be downloaded at the end of three days, thereby removing the need to carry a monitor, or interact in any way with the device during this time. The sensor technology, however, has remained essentially unchanged in spite of new developments in the monitoring units themselves. The sensor is inserted in the subcutaneous tissue, so that it sits in the interstitial fluid and can be worn for up to 72 hours. Electrochemical detection of glucose in the interstitial fluid then takes place through its reaction with glucose oxidase in the tip of the sensor. This electrical signal is relayed to the monitor every 10 seconds where the information is converted into 5 minute averages and is stored for subsequent downloading and viewing. The monitor can read glucose values between 2.2 and 22.0 mmol/l.

With the exception of one study showing that sensor-augmented insulin-pump therapy can improve HbA<sub>1c</sub> levels in inadequately-controlled type 1 diabetes (133) the use of CGM has not been shown to significantly lower HbA<sub>1c</sub> levels (134). It does, however, appear to be helpful in identifying periods of asymptomatic nocturnal hypoglycemia that could otherwise go unnoticed (134). Using CGM technology, several studies have shown that nocturnal hypoglycemia occurs frequently among individuals with type 1 diabetes (81, 135, 136), with frequency of hypoglycemia being related to lower HbA<sub>1c</sub> (137) as well as lower bedtime glucose levels (135).

As recent evidence indicates that nocturnal hypoglycemia, generally occurring between midnight and 4am, might be more common after late afternoon exercise than it is on non-exercise days (108), these monitoring systems have also been used in recent studies to examine late onset post-exercise hypoglycemia (123, 124, 138). In a small study examining the effects of high intensity cycling on blood glucose, it was determined from

overnight CGM data that three out of the five participants with type 1 diabetes experienced asymptomatic nocturnal hypoglycemia post-exercise (123). Similarly, in monitoring twelve participants at a sports camp for individuals with type 1 diabetes it was found that all twelve monitored participants experienced hypoglycemia over the 60 hour monitoring period, with 45 of the 75 hypoglycemic episodes taking place at night, and the lowest average glucose levels occurring at 3:45am (138). When the effect of 30 minutes of intermittent high intensity exercise (IHE) was compared to 30 minutes of moderate (MOD) aerobic exercise in individuals with type 1 diabetes, it was found that, although blood glucose levels tended to be higher after the IHE protocol when participants left the laboratory 150 minutes post-exercise, the frequency of nocturnal hypoglycemia as detected by CGM was actually lower after the MOD protocol (124).

For the most part, studies that have included an examination of the accuracy of continuous glucose monitoring systems have found a high correlation between either plasma glucose or capillary glucose values and the interstitial glucose values recorded by the CGM (28, 29, 123, 139). Iscoe *et al.* (123) found a correlation of  $r=0.89$  ( $p<0.0001$ ) between CGM values, and self-monitored capillary glucose values recorded by their study participants. Fayolle *et al.* (29) found that 97% of values fell within clinically acceptable zones on the Clarke's Error Grid when glucose levels in venous blood samples were compared to CGMS data. Similarly, MacDonald *et al.* (28) found that fewer than 5% of points fell outside the 95% confidence intervals. The accuracy of the monitoring systems themselves also depends to a certain extent on the compliance of the participants, as accuracy is generally improved when at least three calibrations are performed, especially if those calibrations take place during periods of relative glucose stability (139).

It has also been noted that there are a few limitations to the use of CGM and the interpretation of the resulting data in clinical studies. As the limits of measurement are set at 2.2 and 22.0 mmol/l, the severity of certain hypoglycemic or hyperglycemic events can be underestimated. A time lag of 4 to 10 minutes has been found between glucose values from venous samples, and those read in the interstitial tissue by the CGM (140).

Variability has also been found within the sensors themselves, with differences of  $6.7 \pm 5.1$  minutes being found between sensors being worn simultaneously by individual research participants (140). One study found a tendency for the CGM data points to be higher than self-monitored blood glucose (capillary test) values (123), while another found that when glucose values were changing rapidly, such as during exercise, that sensor values tended to decrease less rapidly (29). In using the older CGM systems (such as the CGMS System Gold<sup>TM</sup>) wires catching on surrounding objects and or being damaged through friction with clothing can lead to errors in recording data, especially during exercise. Sensors becoming dislodged through contact with clothing or other articles are also potential problems with all types of CGM systems. Finally, as the software associated with most CGM devices is programmed to average several readings over either a three or five minute period while filtering out outlier noise, small transients shifts in glucose that last less than three to five minutes may not be detected at all by the continuous glucose monitor (140, 141).

Nonetheless, when all factors are taken into account, most researchers and clinicians agree that continuous glucose monitoring is an effective way to track glucose fluctuations and determine trends over a relatively extended period of time, making them a useful research tool.

### **3.0 PAPER 1**

## **Resistance exercise impacts blood glucose less than aerobic exercise in type 1 diabetes**

Prepared for submission to Diabetologia

# Resistance exercise impacts blood glucose levels less than aerobic exercise in type 1 diabetes

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## ABSTRACT

**Aims/hypothesis:** To compare changes in blood glucose during resistance exercise to those of aerobic exercise and no exercise, both during activity and for 24 hours post-exercise in individuals with type 1 diabetes.

**Methods:** 12 (10 male, 2 female) physically active individuals (aged  $32.7 \pm 13.7$  years) with type 1 diabetes ( $HbA_{1c} = 7.1 \pm 1.0\%$ ) performed 45 minutes of resistance exercise (3 sets of 7 exercises at 8 repetition maximum), 45 minutes of aerobic exercise (running at 60% of  $\dot{V}O_{2peak}$ ) or no exercise (control) on separate days, starting at 1700 h. Glucose was measured by continuous glucose monitoring (CGM) for 24 hours both pre- and post-exercise. Blood samples were collected every 5 to 15 minutes during exercise and recovery (60 minutes) for measurement of glucose, insulin, cortisol, growth hormone (GH) and NEFA.

**Results:** Plasma glucose decreased from  $9.2 \pm 3.4$  to  $5.8 \pm 2.0$  mmol/l ( $P=0.001$ ) during aerobic exercise and from  $8.4 \pm 2.7$  to  $6.8 \pm 2.3$  mmol/l ( $P=0.008$ ) during resistance exercise while no significant changes were seen during the control session. During recovery, glucose did not change significantly after resistance exercise but increased by  $2.2 \pm 0.6$  mmol/l ( $P=0.023$ ) after aerobic exercise. Higher mean CGMS glucose was found from 3 to 6 hours post-exercise ( $P<0.05$ ) after aerobic compared to resistance exercise.

**Conclusions/interpretation:** Aerobic exercise produces greater declines in blood glucose during activity, but results in higher late post-exercise glucose levels than resistance exercise or no exercise. This may account for the lack of  $HbA_{1c}$  reduction in most studies of aerobic exercise in type 1 diabetes.

**Key words:** continuous glucose monitoring, hypoglycemia, resistance exercise, aerobic exercise, type 1 diabetes.

### **Abbreviations**

CGM	continuous glucose monitoring
CSII	continuous subcutaneous insulin infusion
GH	growth hormone
MDI	multiple daily injections
$\dot{V} O_{2\text{peak}}$	peak oxygen consumption
8RM	8 repetition maximum

## INTRODUCTION

A recent cross-sectional study of self-reported data found that the frequency and severity of complications in individuals with type 1 diabetes, including nephropathy, retinopathy and cardiovascular disease is greatest among individuals reporting little leisure time physical activity in comparison to individuals with higher activity levels [1].

However, it remains unclear whether exercise is beneficial for glycemic control in type 1 diabetes. Aerobic exercise interventions have, for the most part, shown little effect on blood glucose control as reflected by HbA<sub>1c</sub> levels [2]. In contrast, the few studies evaluating resistance exercise alone [3, 4] or combined with aerobic exercise [5-7] have shown some HbA<sub>1c</sub> reductions, but sample sizes were, for the most part, very small (n=8 to 13).

Aerobic activities are associated with large and rapid decreases in blood glucose during exercise in type 1 diabetes, and therefore an increased risk of hypoglycemia [8, 9]. Conversely, recent studies have shown that other activities involving a substantial contribution of anaerobic metabolism (e.g. short sprints, high intensity intermittent exercise) on their own or combined with aerobic exercise, result in smaller declines in blood glucose during activity and up to 2 hours post-exercise than moderate-intensity aerobic activity alone [10-13]. However, two small studies using continuous glucose monitoring (CGMS) have suggested that the risk of hypoglycemia associated with anaerobic activity is delayed until several hours post-exercise [14, 15].

The acute effects of resistance exercise, another form of anaerobic activity, in this population has yet to be examined. Therefore, the aim of this study was to determine the effects of resistance exercise on blood glucose during, immediately after and for 24 hours

post-exercise, in comparison to aerobic exercise alone and no exercise in individuals with type 1 diabetes.

## **METHODS**

### **Participants**

The study was approved by the Research Ethics Boards of the University of Ottawa and the Ottawa Hospital. Twelve (10 male, 2 female) non-obese (BMI<30), non-smoking adults with complication-free type 1 diabetes were recruited to take part. Participants needed to be performing both aerobic and resistance exercise at least three times a week, and to have  $HbA_{1c} \leq 9\%$ . Participants were receiving insulin using either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII).

### **Experimental Design**

Testing took place in the Human and Environmental Physiology Research Unit at the University of Ottawa. Participants took part in two preliminary visits and three experimental trials. During the preliminary visit, participants were informed of the purpose, research protocol, and possible risks of the study prior to giving informed consent and completing exercise readiness questionnaires. OneTouch® UltraSmart® glucometers (Lifescan, Johnson & Johnson, Milpitas, USA) and coded strips (same code throughout the study) were provided for capillary glucose tests. Participants returned on a separate day for maximal exercise stress testing with electrocardiogram monitoring (Quinton Q4500, Quinton, Bothell, Washington) using a ramp protocol on a treadmill to determine peak oxygen consumption ( $\dot{V} O_{2peak}$ ).  $\dot{V} O_{2peak}$  was determined by measuring expired oxygen and

carbon dioxide concentrations (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry, Pittsburgh, PA, USA). Muscular strength (8RM) was measured as the maximum weight that participants could safely lift 8 times for each of the following exercises: chest press, leg press, lat pulldown down, shoulder press, leg curl, and seated row to determine the weight to be lifted during the resistance exercise test. Venous blood samples were collected for determination of HbA<sub>1c</sub>, which was measured by automated heterogeneous immunoassay with latex enhanced turbidimetric detection on a Roche Cobas Integra 800 analyzer (Roche Diagnostics Corporation, Indianapolis, IN).

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

Continuous glucose monitoring (CGM) sensors (CGMS<sup>®</sup> System Gold<sup>™</sup>, Medtronic, Northridge, CA) were inserted subcutaneously at 8:30 am the day before the testing session. The CGMS<sup>®</sup> System Gold<sup>™</sup> was specifically selected for use so that participants would be blinded to their real-time values and would not change their regular behavior patterns. Participants were instructed on the operation of the CGM and were asked to test capillary glucose 4 times per day for calibration purposes, using the meter provided. On the third day, at least 24 hours after the end of the exercise (or control) session, CGM units were retrieved and data were downloaded via the com-Station using the Minimed Solutions Software version 3.0c (Medtronic, Northridge, CA).

Over each monitoring period participants could choose their own foods, but were asked to maintain as much consistency as possibly by consuming the same breakfast, lunch, dinner and snacks at as close to the same times as possible and recording their food and insulin intake on log sheets provided by the investigators. Participants refrained from

exercise for 24 hours prior to the insertion of the sensor (48 hours prior to the experimental session), and were asked to avoid caffeine and alcohol during the monitoring period.

### ***Experimental sessions***

Participants arrived at the lab at 1600 hours. This time of day was chosen as it represents the most common time of day that individuals choose to exercise. Female participants were using monophasic oral contraceptives and were tested during the active pill consumption (high exogenous hormone) phase. Each participant performed the following sessions, under thermoneutral (21°C, 20% relative humidity) conditions, separated by at least five days:

- 1) Aerobic exercise session: 45 minutes of treadmill running at 60% of  $\dot{V} O_{2peak}$ .
- 2) Resistance exercise session: Three sets of 8 repetitions at the maximum weight that could be lifted 8 times (8 RM) of supine bench press, leg press, shoulder press, abdominal crunches, lat pulldown, leg curl and seated cable row with 90 seconds rest between sets (total exercise duration ~ 45 minutes).
- 3) Resting control session: 45 minutes of resting in an upright seated position.
- 4) Aerobic exercise before resistance exercise session (**AR**): A combination of sessions 1 and 2 as described above, with aerobic exercise being performed before resistance exercise.
- 5) Resistance exercise before aerobic exercise session (**RA**): A combination of sessions 1 and 2 as described above, with resistance exercise being performed prior to aerobic exercise.

All sessions were followed by 60 minutes of monitored resting recovery. Control sessions were performed first. The remaining sessions were randomly assigned. In this paper we will present the results of sessions 1 through 3 above.

## **Measurements**

### ***Insulin adjustments and glucose supplementation***

Participants were asked to reduce their insulin doses on exercise days by either making a 10% decrease in intermediate or long acting insulin (MDI), or a 50% decrease in basal rate starting an hour prior to exercise for those using CSII. If blood glucose was below 5 mmol/l upon arrival at the laboratory, those on CSII decreased their basal rate a further 25%. Reduced basal rates were maintained until the end of exercise. Participants consumed a standard snack (Glucerna Chocolate Graham Snack Bars (Abbott Laboratories, Abbott Park, IL)) at 1600 h on every day of sensor wear.

Capillary glucose was checked upon arrival at the laboratory, 30 minutes before exercise and during the baseline blood draw before exercise to ensure glucose levels between 5.5 and 13.9 mmol/l. If capillary glucose was less than 4.5 mmol/l, participants consumed 32 g of glucose in tablet form (Dex 4®, AMG Medical, Montreal). If values were between 4.5 and 5.4 mmol/l, participants consumed 16 g of glucose. Glucose levels were also monitored during exercise using venous blood and the study glucometers. If capillary glucose fell below 4.5 mmol/l during exercise, exercise was interrupted and 16 g of glucose was provided. Capillary glucose was then checked at 10 minute intervals with an additional 16 g of glucose being provided if levels had not increased to 5.5 mmol/l. Exercise resumed when levels reached 5.5 mmol/l.

### ***Energy Expenditure and Heart Rate***

Heart rate was monitored using a Polar Vantage heart rate monitor (Polar Electro, Kempele, Finland) and oxygen consumption was measured for 20 minutes before exercise, as well as during exercise and for 60 minutes post-exercise using an automated portable gas analysis system (Oxycon Mobile, Jaeger; Hoechberg, Germany). Energy expenditure was calculated as described elsewhere [16].

### **Blood sampling and analyses**

Venous blood samples were collected through an IV catheter at baseline, 5, 10, 15, 30, and 45 minutes during exercise/control, and 5, 10, 15, 20, 30, 40, 50 and 60 minutes during recovery for all three sessions. Blood was drawn using 5-ml sterile plastic syringes and transferred immediately into 5.4-ml serum (no additive) and plasma (K<sub>2</sub>EDTA) BD Vacutainer® tubes (BD, Franklin Lakes, NJ, USA). One ml of blood was added to a 16X100 borosilicate tube containing 1 ml of aprotinin (Trasylol) solution for subsequent analysis of glucagon. Serum tubes (no additive) were kept at room temperature to clot for 20 minutes before centrifugation at 4000 rev/min for 4 minutes. Tubes containing aprotinin and K<sub>2</sub>EDTA were mixed by inversion and centrifuged immediately. Serum and plasma aliquots were transferred into 1.5-ml microcentrifuge tubes and stored at -80°C until analyzed.

The hexokinase timed endpoint method was used to determine plasma glucose throughout testing for all 12 participants. Analysis was performed on the Beckman Coulter Unicel ®DxC600 Synchron® Clinical Analyzer (Beckman Coulter Inc., Fullerton, CA, USA) using the SYNCHRON CX® Systems GLUCOSE reagent (Cat#442640). For

determination of plasma NEFA, an Enzymatic Colorimetric Method was employed using RANDOX NEFA reagent (Randox Laboratories, Antrim, UK). Serum cortisol and human growth hormone (GH) concentrations were determined by enzyme immunoassay (Alpco Diagnostics™, Salem, NH, USA). A synthetic insulin enzyme immunoassay kit (Alpco Diagnostics™, Salem, NH, USA) was used to determine plasma insulin levels and a glucagon enzyme immunoassay kit (Alpco Diagnostics™, Salem, NH, USA) was used to determine plasma glucagon levels. The sensitivities of the EIA kits were 11.04 nmol/l for cortisol, 1.13 nmol/l for GH, 32.99 pmol/l for insulin, and 50 ng/l for glucagon. Intra- and inter-assay coefficients of variation were 2.9 to 9.4% and 3.8 to 8.1% for serum cortisol, 2.2 to 2.9% and 3.0 to 4.4% for serum GH, 2.15 to 8.42% and 7.42 to 10.18% for plasma synthetic insulin, and 3.3 to 5.1% and 7.3 to 18.9% for plasma glucagon. Due to budgetary constraints, hormone analyses were run on only 6 of the 12 subjects that were representative of the overall study population in terms of gender, age, weight, and fitness. Due to equipment and budgetary constraints, we were unable to perform catecholamine assays.

### ***Statistical Analyses***

Exercise and recovery were examined separately. Glucose, cortisol, NEFA, GH and insulin levels were compared among conditions using two separate (one for exercise and one for recovery) two-way (time and condition) repeated measures ANOVAs. The exercise period consisted of the 5, 10, 15, 30, and 45 minute time points, while the recovery period consisted of the 50, 55, 60, 65, 75, 85, 95, and 105 minute time points. Paired samples t-tests were used to perform pair-wise post-hoc comparisons for each time point between

conditions (aerobic, resistance or control) within exercise and recovery separately, and to examine changes from baseline as well as the changes from the end of exercise within each exercise condition. The level of significance was set at 0.05 and alpha level was adjusted for multiple comparisons so as to maintain the rate of Type 1 error at 5% during the Holm-Bonferroni post-hoc analysis.

CGMS data were examined in the following windows: 24 hours pre-exercise, overnight (2400 to 0600 h) pre-exercise, 1 to 6 hours post-exercise, overnight post-exercise and 24 hours post-exercise. In examining the data in the 1 to 6 hour post-exercise time frame, 15 minute averages of CGM data were compared among conditions using a two-way (condition and time) repeated measures ANOVA. Paired sample t-tests were then used to perform pair-wise post-hoc comparisons to examine differences among conditions for each 15 minute segment. Thresholds for hypo- and hyperglycemia were set at 3.5 and 10.9 mmol/l respectively. The minimum, maximum and mean blood glucose, amount of time spent in hypoglycemia and hyperglycemia, and area under the curve (AUC) for time spent in hypo- and hyperglycemia was determined for each window. Pre-exercise values were compared to post-exercise values within exercise conditions using related-samples Wilcoxon Signed Ranks test. Differences among conditions were examined using related-samples Friedman's Two-Way ANOVA by Ranks. The accuracy of CGMS data was assessed by performing separate Pearson correlations between sensor glucose and self-recorded capillary glucose values measured over three days during non-exercise periods for the control, aerobic and resistance trials.

Daily total insulin and carbohydrate intake were calculated based on the food items and quantities provided by participants in their food and insulin diaries. Comparisons

among groups for each day were performed using related samples Friedman's Two-Way ANOVA by Ranks. Where significant results were found, related samples Wilcoxon Signed Ranks tests were performed to determine where the differences lay. Analyses were performed using SPSS 18.0 for Windows (SPSS Inc. Chicago, IL, USA). Data are presented as means  $\pm$  SD.

## **RESULTS**

Participant characteristics are presented in Table 1. There were no significant differences among groups with respect to the amount of time spent in hypoglycaemia, AUC for hypoglycemia overnight or in the full 24 hours before exercise. There were also no differences among the groups in the number of hyperglycemic events, time spent in hyperglycemia, AUC for hyperglycemia, or mean blood glucose prior to exercise.

Energy expenditure was lowest during the control trial ( $933\pm 136$  kJ for resting and recovery combined). The aerobic exercise trial (including both the exercise and the recovery periods) involved expending twice as much energy as the resistance exercise trial ( $3276\pm 574$  kJ for aerobic exercise versus  $1631\pm 279$  kJ for resistance).

### **Exercise**

All means ( $\pm$ SD) and P-values for the post-hoc comparisons during exercise are listed in Table 2. Glucagon was excluded from statistical analyses as consistent assay results were not obtained.

***Glucose:***

A significant interaction of time and condition ( $P < 0.001$ ) was found in the analysis of mean glucose levels during exercise (Figure 1). There were no significant differences among conditions at baseline. No significant changes from baseline were detected throughout the first 45 minutes of the control session. A small but gradual decline in plasma glucose was seen with resistance exercise, resulting in levels that were significantly lower than baseline by the end of exercise. During aerobic exercise, glucose declined more rapidly, resulting in significant changes from baseline within the first 10 minutes. Glucose then continued to decline until the end of aerobic exercise resulting in lower glucose levels during the aerobic session as compared to the control session after 30 minutes of activity. There were no statistically significant intergroup differences at each time point between the resistance exercise and control sessions, or between the resistance and aerobic exercise sessions.

***NEFA, cortisol, insulin and GH:***

In the subsample chosen for blood analysis, NEFA levels did not change significantly within each condition and were not different among conditions (Figure 2A). A significant effect of time ( $P = 0.007$ ) but no effect of condition was found with respect to changes in cortisol levels (Figure 2B) throughout exercise. Cortisol (Figure 2B) decreased from baseline in all exercise conditions in the first 5 minutes of exercise but these failed to retain significance after adjustment for multiple comparisons. An interaction of time and condition was found in the analysis of insulin levels ( $P = 0.004$ ) and GH levels ( $P = 0.006$ ) throughout exercise. There were no inter-group differences in insulin levels throughout

exercise (Figure 2C). GH (Figure 2D) stayed constant during the control session while it increased during both the aerobic and resistance exercise sessions. These changes were only significant with aerobic exercise.

## **Recovery**

Mean ( $\pm$ SD) data and P-values for all post-hoc comparisons during recovery are listed in Table 3.

### ***Glucose:***

Throughout recovery, there was once again an interaction of time and condition with respect to mean plasma glucose levels ( $P < 0.001$ ). There were no significant changes in blood glucose during recovery in the control condition, or after resistance exercise. Throughout most of recovery, glucose levels were lower than baseline in the resistance exercise session ( $P < 0.05$ ), but these were not statistically significant after the adjustment for multiple comparisons. The aerobic exercise condition produced a significant increase in plasma glucose from the end of exercise throughout recovery ( $P = 0.002$ ). As a result, glucose was not significantly different from the baseline value at the end of recovery in the aerobic exercise trial. Intergroup differences at each time point throughout recovery were also not statistically significant.

### ***NEFA, cortisol, insulin and GH:***

During recovery, there was a marginal effect of both condition ( $P = 0.06$ ) and time ( $P = 0.06$ ) in the analysis of NEFA levels. NEFA increased during the first 5 minutes of

recovery ( $P=0.003$ , not significant after adjustment for multiple comparisons) in the aerobic exercise session but did not change in the control or resistance exercise trials (Figure 2A). Cortisol levels saw a decreasing trend throughout recovery after resistance exercise but showed very little change in the control or aerobic exercise sessions (Figure 2B). Differences among conditions at each time point were not significant throughout recovery with respect to cortisol. A significant effect of time was found in the analysis of insulin levels ( $P=0.004$ ). Insulin levels did not change significantly in any condition from the end of exercise throughout recovery, however insulin levels were lower than baseline values in the aerobic condition (Figure 2C). This resulted in lower insulin levels in the aerobic condition at the end of recovery as compared to both the control and resistance exercise conditions. These trends were not statistically significant after adjustments for multiple comparisons. There was a significant effect of condition ( $P=0.010$ ), time ( $P<0.001$ ) and an interaction of time and condition ( $P=0.017$ ) with respect to GH. GH (Figure 2D) decreased throughout recovery after aerobic exercise but levels still remained significantly higher than baseline in this condition for the first 15 minutes of the recovery. There were no significant changes in GH after the resistance exercise or control sessions. GH levels were elevated throughout recovery in both the aerobic and resistance exercise sessions when compared to control ( $P<0.05$ ), however these differences were no longer significant after adjustment for multiple comparisons.

***CGM data:***

Due to equipment malfunction, CGM data were only available for 11 of 12 participants in the control trial, and 10 of 12 in the aerobic exercise trial. In total there were

124 paired meter and CGM values for the control condition, 113 for the aerobic exercise condition and 115 for the resistance exercise condition. The Pearson correlations between capillary and sensor values were 0.94, 0.90 and 0.95 during non-exercise periods in the control, aerobic, and resistance exercise sessions respectively. Analysis of CGM data as 15 minute averages in the 1 to 6 hour post-exercise time frame revealed a marginal effect of time ( $P=0.073$ ). A trend towards higher mean CGM glucose was found in the 4<sup>th</sup> and 5<sup>th</sup> hours post-exercise (Figure 3) after aerobic exercise when compared to resistance exercise ( $P=0.018$  at 5 hours post-exercise). There were no significant differences between aerobic exercise and control, or resistance exercise and control throughout this time.

No statistically significant differences were found among measures of post-exercise nocturnal hypoglycemia determined from CGM data (Table 4), although there were twice as many hypoglycemic excursions after the resistance exercise session (9 in total) as compared to the aerobic exercise and control sessions (4 for each). A trend towards more time spent in hypoglycemia was seen in the aerobic exercise condition when comparing 24 hours pre-exercise to 24 hours post-exercise ( $P=0.09$ ). There was also a trend towards more nocturnal hyperglycemia after resistance exercise ( $P=0.059$ ) when compared to the pre-exercise night.

### ***Carbohydrate intake and insulin dosage:***

During testing, two participants had to be provided with glucose tablets during the control trial, three participants during the resistance trial and nine participants during the aerobic trial. In total, 41 g of additional carbohydrate were provided during the control session, 290 g during the aerobic exercise session, and 56 g during the resistance exercise

session. These differences were significant between aerobic exercise session in comparison to the control ( $P=0.007$ ) and resistance exercise ( $P=0.05$ ) sessions. Differences between the control and resistance exercise sessions were not significant. Five participants required an interruption during exercise (average break time of 20 minutes) for carbohydrate supplementation during the aerobic exercise session, while no breaks were required during the control, or resistance exercise sessions. In spite of the extra carbohydrate supplementation, there were no statistically significant differences in carbohydrate intake among conditions on the day before or the day after the laboratory testing session (Table 5), however carbohydrate intake was higher on the testing day in the aerobic exercise session when compared to the resistance exercise session ( $P=0.013$ ), but not the control session ( $P=0.182$ ).

Insulin adjustments varied slightly among the participants. Of those using CSII, three chose to suspend basal insulin entirely for both the aerobic and resistance exercise trials, 2 chose a 50% decrease for both exercise sessions, while the final two suspended their basal insulin for aerobic exercise while maintaining a 50% basal rate for resistance exercise. Only three participants on CSII chose to deliver an insulin bolus with the pre-exercise snack during the aerobic exercise session, while 5 participants took insulin with the snack during the resistance exercise session. Of the participants using MDI, the lunchtime bolus was the same for three participants in both aerobic and resistance exercise trials, 2 units higher for one participant, and 2 units lower for one participant in the aerobic compared to the resistance exercise session. With the exception of one individual adjusting for high blood glucose during the aerobic exercise session, none of the MDI patients took

insulin with their pre-exercise Glucerna bar. Overall, there were no statistically significant differences in insulin intake during the 3 days of sensor wear.

## **DISCUSSION/CONCLUSION**

We found that aerobic exercise resulted in a greater decline in blood glucose during exercise than resistance exercise or no exercise in individuals with type 1 diabetes. A greater amount of carbohydrate supplementation was required during the aerobic exercise session as compared to the resistance exercise and control sessions, which may have actually diminished the overall decline in blood glucose and therefore decreased the magnitude of the effect of exercise on blood glucose during this session. Post-exercise, there was a consistent increase in blood glucose after the aerobic exercise session (probably as a result of glucose demands decreasing faster than the levels of circulating counter-regulatory hormones), where blood glucose remained unchanged in the resistance exercise and control sessions. This led to a trend towards higher glucose levels after aerobic activity between 3 and 6 hours post-exercise as measured by CGM.

We found no differences among conditions with respect to levels of insulin and cortisol. This is consistent with other studies of high intensity activity (cycling) in individuals with type 1 diabetes [10-13]. This would indicate that these hormones are not responsible for the differences in glucose responses in type 1 diabetic participants seen among the conditions during exercise. However, the lower insulin levels found after aerobic exercise in our study may have contributed to the higher blood glucose levels detected by CGM between the 3<sup>rd</sup> and 6<sup>th</sup> hours post-exercise.

Our blood sample analysis also revealed comparable elevations in GH during the aerobic and resistance exercise sessions. As Bussau et al. [10, 11] and Guelfi et al. [12, 13] found approximately 1.5 to 2 times greater elevations in GH with intermittent high intensity activity as compared to constant aerobic activity we expected to find slightly higher GH values in resistance exercise compared to aerobic exercise. It should be noted, though, that the aerobic exercise in the studies by Bussau et al. [10, 11] and Guelfi et al. [12, 13] was performed at 40%  $\dot{V}O_{2\text{peak}}$  while we chose 60%  $\dot{V}O_{2\text{peak}}$  for ours. GH release has been shown to increase in proportion to exercise intensity which may be why GH levels were similar between the resistance and aerobic conditions in our study [17]. We did note in our study, however, that GH levels decreased more rapidly after aerobic exercise as compared to resistance exercise, leaving the possibility that these remained elevated for a longer period post-exercise in the resistance exercise condition. This could have prevented any further decreases in glucose in this condition by stimulating lipolysis for a more extended period of time post-exercise.

While we did not have the laboratory facilities to measure catecholamines, it has been shown that resistance exercise increases epinephrine and norepinephrine substantially in individuals without type 1 diabetes [18, 19]. We are unaware of studies measuring catecholamine secretion during resistance exercise in individuals with type 1 diabetes, however, short sprints on a bike and sustained high intensity cycling (both involving the contribution of anaerobic metabolism) have been shown to cause increases in catecholamines that can persist up to 20 minutes post-exercise in individuals with type 1 diabetes [10, 20]. Even short, high-intensity bouts (4 to 10 seconds) of exercise interspersed throughout aerobic activity have caused elevated catecholamine levels

compared to aerobic exercise alone [10-13]. This has been shown to either increase [20, 21] plasma glucose or attenuate decreases in plasma glucose during and post-exercise [10-13] in individuals with type 1 diabetes. These increases and attenuated declines are attributed to higher rates of glycogenolysis, causing the rate of glucose production to either match or exceed glucose utilization. As catecholamine secretion is known to be similar [21-23] or slightly attenuated [20, 24] in those with type 1 diabetes compared to those without diabetes, it is possible that greater catecholamine secretion during the resistance exercise session could have attenuated decreases in blood glucose both during and after exercise in this session.

Resistance exercise protocols similar to the one we used have also been shown to cause a 4 to 5-fold increase in blood lactate [25]. While we are unaware of published data on lactate production during resistance exercise in individuals with type 1 diabetes, high intensity cycling has been shown to produce elevated lactate levels that can persist up to 30 minutes post-exercise in this population [10-13, 21]. The present study did not measure lactate, but it is likely that resistance exercise would have increased blood lactate levels to a greater extent than aerobic exercise. This could have also assisted in attenuating declines in blood glucose by stimulating gluconeogenesis.

While our CGM data revealed a higher frequency of post-exercise nocturnal hypoglycemia after resistance exercise (50% versus 20% of participants experiencing low blood glucose for resistance and aerobic exercise respectively) it should be noted that the occurrence of hypoglycemia was significantly lower post-exercise than it was the night before exercise in the resistance exercise condition. There were no statistically significant differences among the conditions with respect to the measures of hypoglycemia that we

chose for our study and mean nocturnal blood glucose was also similar across conditions (Table 2). While the frequency of hypoglycemia is in agreement with the outcome of a study by Maran et al. [14] which found that intermittent high intensity intervals on a cycle ergometer resulted in more episodes of nocturnal hypoglycemia (7 episodes versus 2) than continuous moderate aerobic exercise, our outcomes contrast in that we did not find significantly lower overnight mean glucose levels after resistance exercise. The difference between the outcomes of our study and that of Maran et al. may be due to our participants being fit and regularly active, while their participants were not.

McMahon et al. [26] found that adolescents with type 1 diabetes had a higher glucose infusion requirement to maintain euglycemia between the hours of midnight and 4 am after performing evening exercise than if no exercise had been performed. This would indeed coincide with the time where the lowest nocturnal glucose levels were found after the aerobic and resistance exercise sessions in our study (Figure 3) however differences in glucose levels among conditions in our study were not significant. As McMahon et al. surmise that the delayed increase in post-exercise glucose needs are related to replenishment of glycogen stores [26], a higher frequency of low blood glucose after resistance exercise (where there was probably a greater reliance on glycogen for fuel) might be expected. Meanwhile, it is important to note that hypoglycemic events were of similar duration and intensity after resistance exercise as they were when no exercise was performed, and they also tended to be shorter and less severe than those occurring after aerobic exercise (Table 4).

We chose to have subjects go about their usual activities (other than exercise), and allowed each to choose his/her preferred foods for meals. If we had instead brought them

into the laboratory or a hospital setting for 3 days and provided identical meals to all subjects, there would probably have been less variability in our findings. However, we chose the current design because it provides a better reflection of real-life conditions. We did take measures to minimize extraneous variability by having each participant consume the same breakfast, same lunch, and same supper every day of all trials, and by having them exercise only during the same specific time of day. We also tried to minimize the effect of any previous exercise sessions by having participants avoid physical activity for 48 hours before and 24 hours after the exercise session. While many exercise studies have had their exercise session mid-morning [10-13, 20, 21], we chose to schedule it at the time that is most popular for exercise – about 1700 h, which would be right after work for many who work full-time.

This study is also limited by the great deal of both inter and intra-individual variation found in the variables that were measured. It was difficult to find statistical significance in many instances where trends in the data can be seen. A larger sample would probably provide more significant changes as well as significant differences among conditions. In the case of cortisol and growth hormone a more homogeneous sample may have also yielded more significant differences as these markers are known to have different responses to exercise depending on the age and sex of the individual [27, 28]. We were also unable to measure catecholamines, lactate and glucagon, which would have been useful in providing more explanation for some of the observed glucose trends.

The outcomes of this study reflect the need for additional research on the effects of resistance exercise in individuals with type 1 diabetes. Resistance exercise involved less of a decline in blood glucose during exercise, leading to less of a necessity to supplement

with additional carbohydrates, and resulted in a better range of blood glucose levels in the hours following exercise. These results could, in part, explain why several exercise interventions involving resistance exercise (alone or combined with aerobic exercise) have shown more consistently positive results with respect to improvements in HbA<sub>1c</sub> [3, 5-7] as compared to aerobic exercise interventions in this population [2]. Future studies should seek to determine whether or not the time of day that exercise is performed, the relative intensities of aerobic and resistance exercise (or a combination thereof), the fitness level or the level of metabolic control of the participants will affect the outcomes.

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## **Tables and Figures<sup>1</sup>**

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<sup>1</sup> Tables 2 and 3 may be submitted as online appendices

**Table 1.** Participant characteristics

N	12 (10 male, 2 female)
Age (yrs)	31.8 ± 15.3
Height (m)	1.77 ± 0.07
Weight (kg)	79.2 ± 10.4
BMI (kg/m <sup>2</sup> )	25.3 ± 3.0
$\dot{V} O_{2\text{peak}}$ (mLO <sub>2</sub> ·kg <sup>-1</sup> ·min <sup>-1</sup> )	51.2 ± 10.8
HbA <sub>1c</sub> (%)	7.1 ± 1.1
Diabetes duration (yrs)	12.5 ± 10.0
Insulin delivery	Multiple Daily Injection = 5, Insulin pump = 7

Data are presented as mean ± SD. BMI, body mass index.  $\dot{V} O_{2\text{peak}}$ , peak oxygen consumption

**Table 2.** Changes in glucose, non-esterified fatty acids, cortisol, insulin and growth hormone (GH) throughout exercise

<b>Glucose (mmol/l)</b>	Control (CON)	P (CON change from baseline)	Aerobic (AER)	P (AER change from baseline)	P (AER vs. CON)	Resistance (RES)	P (RES change from baseline)	P (CON vs. RES)
0 min	8.4±3.5		9.2±3.4		0.467	8.4±2.7		0.543
5 min	8.5±3.5	0.534	8.9±3.7	0.266	0.731	8.3±2.7	0.664	0.658
10 min	8.6±3.5	0.166	8.1±3.6	0.007*	0.614	7.8±2.6	0.122	0.865
15 min	8.8±3.6	0.053	7.6±3.3	0.004*	0.279	7.8±2.6	0.197	0.747
30 min	8.8±3.8	0.152	6.1±2.7	0.000*	0.008*	7.3±2.6	0.065	0.438
45 min	8.6±3.8	0.585	5.8±2.0	0.001*	0.020	6.8±2.3	0.008*	0.237
<b>NEFA (µmol/l)</b>								
0 min	193±57		211±70		0.340	264±97		0.261
5 min	202±60	0.065	190±52	0.363	0.628	263±144	0.995	0.430
10 min	205±67	0.345	223±93	0.742	0.708	256±127	0.766	0.511
15 min	220±101	0.232	251±130	0.440	0.676	254±132	0.783	0.674
30 min	206±112	0.649	267±187	0.463	0.532	268±142	0.896	0.499
45 min	204±122	0.735	260±200	0.544	0.588	194±91	0.010	0.900
<b>Cortisol (nmol/l)</b>								
0 min	343.29±102.53		364.48±174.32		0.782	382.80±165.42		0.506
5 min	329.62±95.73	0.011	327.38±151.08	0.030	0.972	353.62±149.74	0.037	0.629
10 min	335.85±114.59	0.572	309.41±136.86	0.108	0.615	333.12±131.85	0.035	0.947
15 min	320.03±104.55	0.224	306.92±114.95	0.125	0.748	310.45±114.83	0.034	0.770
30 min	300.96±110.8	0.105	300.62±113.96	0.197	0.995	277.38±93.65	0.032	0.302
45 min	272.68±96.72	0.024	323.74±216.33	0.587	0.626	260.83±105.11	0.014	0.609
<b>Insulin (pmol/l)</b>								
0 min	98.90±28.66		62.28±9.88		0.051	77.52±22.01		0.204
5 min	112.08±46.79	0.276	73.16±13.58	0.092	0.119	86.54±28.64	0.152	0.314
10 min	99.08±33.75	0.977	80.68±21.63	0.123	0.219	81.11±26.14	0.394	0.323
15 min	99.90±39.59	0.888	80.61±27.33	0.198	0.203	89.22±27.34	0.121	0.596
30 min	86.88±30.32	0.178	90.48±44.77	0.242	0.757	78.34±29.98	0.905	0.623
45 min	76.23±22.94	0.017	81.28±37.90	0.349	0.637	76.80±28.41	0.927	0.938
<b>GH (nmol/l)</b>								
0 min	1.26±0.72		0.74±0.97		0.326	8.52±8.90		0.093
5 min	0.96±0.53	0.029	0.82±0.96	0.392	0.776	9.32±11.67	0.709	0.133
10 min	1.11±0.85	0.343	0.96±0.98	0.093	0.800	6.51±7.91	0.202	0.138
15 min	1.24±1.04	0.957	2.19±2.35	0.179	0.368	5.95±6.96	0.181	0.130
30 min	1.72±1.80	0.488	6.58±4.51	0.017*	0.041	5.27±4.56	0.216	0.125
45 min	1.88±2.13	0.446	9.83±5.96	0.008*	0.036	10.16±8.41	0.776	0.068

Data are presented as mean ± SD. n=12 for glucose, n=6 for non-esterified fatty acids (NEFA), insulin and growth hormone (GH), n=5 for cortisol. \* denotes statistical significance after Holm-Bonferroni adjustment.

**Table 3.** Changes in glucose, non-esterified fatty acids, cortisol, insulin and growth hormone (GH) throughout recovery

Glucose (mmol/l)	Control (CON)	P (CON change from baseline)	Aerobic (AER)	P (AER change from baseline)	P (AER vs. CON)	Resistance (RES)	P (RES change from baseline)	P (CON vs. RES)
50 min	8.9±4.1	0.387	6.4±2.0	0.007	0.062	6.8 ± 2.4	0.016	0.281
55 min	8.6±3.9	0.650	6.4±2.1	0.008	0.080	6.7 ± 2.5	0.016	0.288
60 min	8.6±3.9	0.736	6.5±2.1	0.013	0.108	6.8 ± 2.5	0.020	0.328
65 min	8.6±4.0	0.703	6.5±2.2	0.021	0.130	6.7 ± 2.6	0.021	0.308
75 min	8.5±3.6	0.931	7.0±2.5	0.069	0.293	6.7 ± 2.7	0.037	0.337
85 min	8.5±3.3	0.925	7.6±2.3	0.226	0.855	6.8 ± 2.7	0.070	0.262
95 min	8.3±3.2	0.811	7.9±2.0	0.317	0.630	6.6 ± 2.6	0.050	0.234
105 min	8.1±3.1	0.662	8.0±2.4	0.419	0.356	6.6 ± 2.7	0.057	0.315
<b>NEFA (µmol/l)</b>								
50 min	215±118	0.504	474±259	0.053	0.092	232 ± 112	0.108	0.849
55 min	195±93	0.956	543±418	0.106	0.126	237 ± 128	0.229	0.616
60 min	192±90	0.976	501±346	0.094	0.113	250 ± 138	0.686	0.501
65 min	202±81	0.751	484±320	0.094	0.120	223 ± 115	0.105	0.766
75 min	210±82	0.591	488±307	0.096	0.111	250 ± 135	0.604	0.632
85 min	217±73	0.456	549±446	0.146	0.155	349 ± 218	0.169	0.256
95 min	239±102	0.362	614±538	0.147	0.170	419 ± 272	0.098	0.219
105 min	263±103	0.168	575±367	0.075	0.115	534 ± 309	0.057	0.123
<b>Cortisol (nmol/l)</b>								
50 min	274.94±104.71	0.041	347.86±286.68	0.879	0.616	265.71 ± 91.25	0.028	0.756
55 min	275.09±91.60	0.049	369.36±337.00	0.971	0.581	275.28 ± 82.28	0.054	0.996
60 min	279.04±80.44	0.120	392.04±367.60	0.853	0.548	275.04 ± 65.35	0.100	0.926
65 min	300.18±96.17	0.398	409.63±389.98	0.782	0.591	264.60 ± 68.85	0.073	0.549
75 min	277.27±80.27	0.149	345.71±289.07	0.879	0.651	234.92 ± 83.21	0.025	0.463
85 min	281.12±111.73	0.037	364.78±313.35	0.998	0.630	239.40 ± 86.55	0.025	0.492
95 min	273.13±98.70	0.017	364.35±288.52	0.999	0.570	232.82 ± 84.44	0.020	0.436
105 min	262.42±105.98	0.006*	534.32±291.20	0.941	0.583	213.73 ± 82.61	0.017	0.360
<b>Insulin (pmol/l)</b>								
50 min	75.72±18.11	0.028	65.60±14.06	0.715	0.236	74.17 ± 24.63	0.661	0.889
55 min	72.92±19.70	0.022	56.62±7.32	0.122	0.094	68.87 ± 18.96	0.284	0.822
60 min	69.70±14.15	0.025	54.25±7.70	0.026	0.065	67.82 ± 20.93	0.120	0.901
65 min	71.33±17.69	0.031	53.50±6.13	0.027	0.069	64.73 ± 19.99	0.088	0.696
75 min	71.22±11.81	0.036	49.86±6.87	0.022	0.040	62.38 ± 17.75	0.070	0.498
85 min	68.18±8.60	0.044	47.38±6.94	0.007	0.010	70.04 ± 24.77	0.213	0.700
95 min	68.34±8.74	0.031	47.74±5.07	0.008	0.014	76.35 ± 38.63	0.923	0.559
105 min	68.62±6.04	0.051	48.76±7.12	0.008	0.007	74.01 ± 34.80	0.758	0.353
<b>GH (nmol/l)</b>								
50 min	1.56 ± 1.72	0.649	9.49±5.72	0.008*	0.031	9.27 ± 7.07	0.884	0.052
55 min	1.27 ± 1.47	0.976	7.79±3.73	0.002*	0.019	8.64 ± 6.14	0.982	0.039
60 min	1.04 ± 1.10	0.640	6.78±3.85	0.006*	0.023	6.92 ± 4.46	0.741	0.028
65 min	0.86 ± 0.82	0.348	5.59±3.41	0.012	0.030	6.78 ± 4.53	0.721	0.028
75 min	0.58 ± 0.26	0.086	4.33±2.94	0.015	0.024	6.69 ± 3.48	0.692	0.008
85 min	0.46 ± 0.25	0.038	2.82±1.89	0.016	0.028	5.95 ± 4.26	0.593	0.025
95 min	0.46 ± 0.22	0.051	1.85±1.08	0.012	0.020	4.57 ± 3.62	0.376	0.041
105 min	0.55 ± 0.53	0.128	1.25±0.72	0.121	0.034	3.71 ± 2.96	0.278	0.062

Data are presented as mean ± SD. n=12 for glucose, n=6 for non-esterified fatty acids (NEFA), insulin and growth hormone (GH), n=5 for cortisol. \* denotes statistical significance after Holm-Bonferroni adjustment.

**Table 4.** Summary of overnight continuous glucose monitoring data for the night following exercise

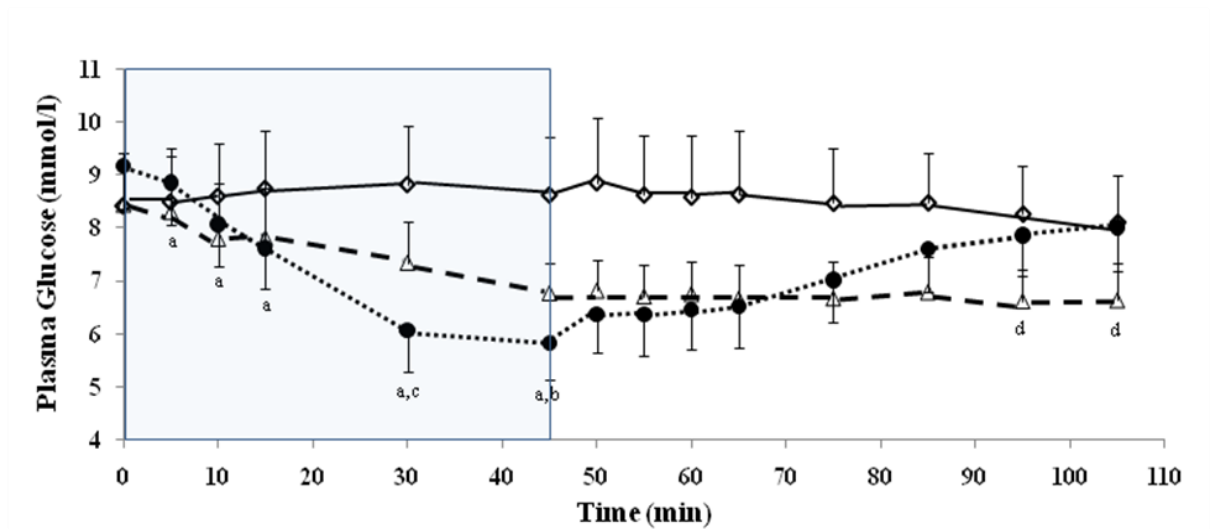
	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>
Number of participants experiencing nocturnal hypoglycemia (<3.5 mmol/L)	4/11 (36%)	2/10 (20%)	6/12 (50%)
Total number of hypoglycemic episodes	4	4	9
Mean duration of hypoglycemia per episode (minutes)	40 ± 7	53 ± 48	40 ± 27
Mean area under the curve for hypoglycemia per episode	35 ± 14	51 ± 55	31 ± 26
Mean overnight glucose (mmol/l)	7.2 ± 2.1	7.0 ± 2.8	6.8 ± 2.5

Data are presented as mean±SD.

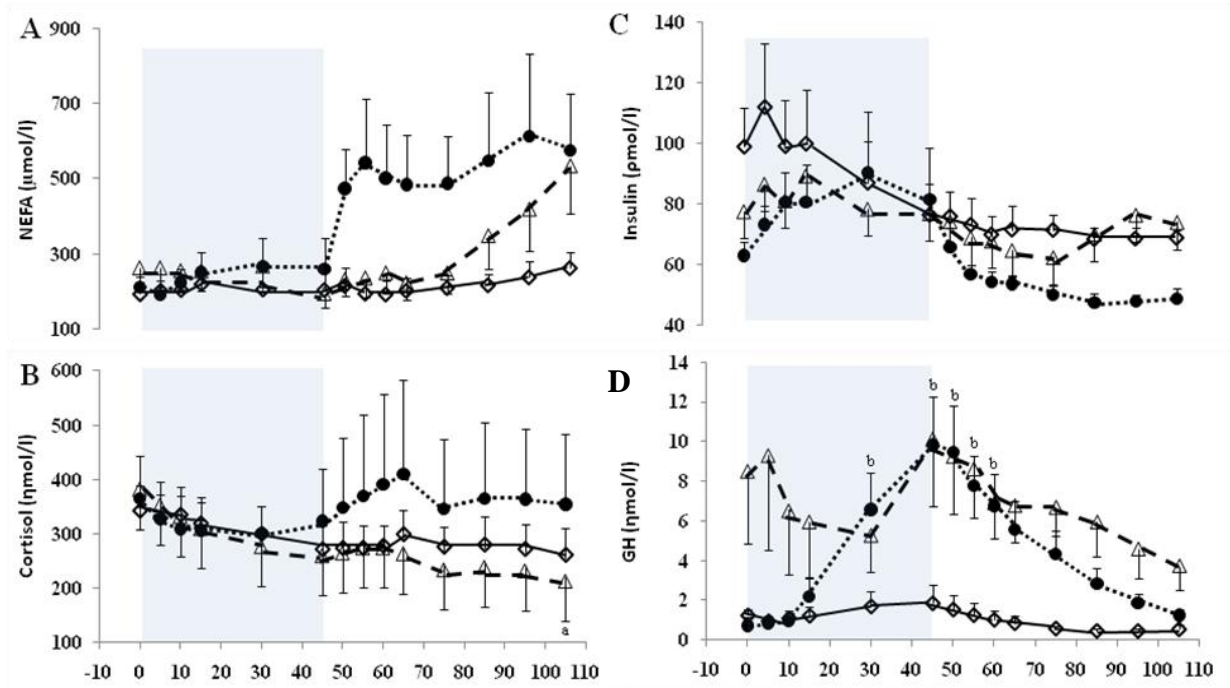
**Table 5.** Carbohydrate and insulin intake calculated from patient food and insulin diaries.

	<b>Control (Resting)</b>			<b>Aerobic</b>			<b>Resistance</b>		
	Day 1	Day 2	Day 3*	Day 1	Day 2	Day 3*	Day 1	Day 2	Day 3*
Carbohydrate (g)	268±77	283±97	157±40	272±92	310±110	156±60	270±107	276±109	163±61
Insulin dosage (U)	45±17	47±20	37±18	47±19	48±20	39±16	51±21	47±20	39±18

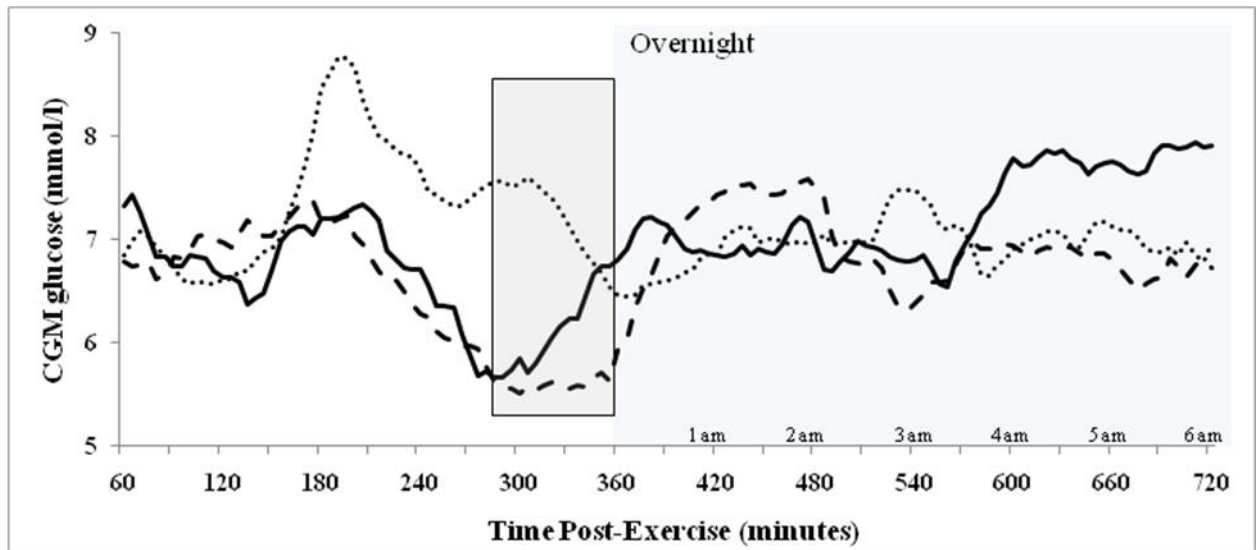
Values reported as mean ±SD. n=12, exercise sessions were performed on day 2 starting at 1700h. \*Day 3 does not include evening meal.



**Figure 1.** Plasma glucose during 45 minutes of exercise (represented by box) and 60 minutes of recovery (n = 12).  $\diamond$  = control session,  $\Delta$  = Resistance exercise session,  $\bullet$  = aerobic exercise session. a = statistically significant change from baseline in aerobic exercise; b = statistically significant change from baseline in resistance exercise; c = statistically significant difference between control session and aerobic session where; d = statistically significant change throughout recovery after aerobic exercise. Differences were only considered statistically significant if still significant after Holm-Bonferroni corrections for multiple comparisons. Data are presented as mean $\pm$ SD.



**Figure 2.** Effect of 45 minutes of exercise (represented by box) and 60 minutes of recovery on mean ( $\pm$ SE) non-esterified fatty acid (NEFA) (A)  $n=6$ , cortisol (B)  $n=5$ , insulin (C)  $n=6$  and growth hormone (GH) (D)  $n=6$ . ◇ = control session, △ = resistance exercise session, ● = aerobic exercise session. a = statistically significant change from baseline in control session; b = statistically significant change from baseline in aerobic exercise. Differences were only considered statistically significant if still significant after Holm-Bonferroni corrections for multiple comparisons.



**Figure 3.** Mean glucose as measured by continuous glucose monitoring from 1 to 12 hours post-exercise. The solid line represents the control trial, the dotted line represents the aerobic exercise session and the dashed line represents the resistance exercise session. The box represents period of time where glucose was significantly higher after aerobic exercise as compared to resistance exercise ( $p < 0.05$ ).  $n=11$  (control),  $n=10$  (aerobic),  $n=12$  (resistance)

## **4.0 PAPER 2**

### **Resistance exercise attenuates declines in blood glucose during subsequent aerobic exercise in type 1 diabetes**

Prepared for submission to Diabetes Care

# Resistance exercise attenuates declines in blood glucose during subsequent aerobic exercise in type 1 diabetes

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## ABSTRACT

PURPOSE: To examine the changes in blood glucose during activity and for 24 hours post-exercise when aerobic exercise is performed with or without prior resistance exercise in individuals with type 1 diabetes.

METHODS: 12 (10 male, 2 female) physically active individuals (aged  $32.7 \pm 13.7$ ) with type 1 diabetes ( $HbA_{1c} = 7.1 \pm 1.0\%$ ) performed 45 minutes of aerobic exercise (treadmill running at 60% of  $\dot{V}O_{2peak}$ ) either on its own (A) or after 45 minutes of resistance exercise (3 sets of 7 exercises at 8 repetition maximum) (RA) on separate days, starting at the same time of day (1700h). Glucose was measured by continuous glucose monitoring (CGM) for 24 hours pre- and post-exercise. Blood sampling was performed every 5 to 15 minutes throughout exercise and 60 minutes of recovery for measurement of glucose, insulin, cortisol, growth hormone (GH) and non-esterified fatty acids (NEFA). Carbohydrate supplementation was given per protocol if participant glucose levels dropped below 4.5 mmol/l during exercise.

RESULTS: Plasma glucose decreased significantly over the course of the A session (from  $9.2 \pm 3.4$  to  $5.8 \pm 2.0$  mmol/l;  $P=0.001$ ) but saw no statistically significant changes from baseline in RA after correction for multiple comparisons (from  $9.2 \pm 4.0$  to  $6.9 \pm 3.1$ ;  $P=0.04$ ). Nine (75%) of the participants required carbohydrate supplementation in A but only six (50%) required supplementation in RA.

CONCLUSIONS: Performing resistance exercise prior to aerobic exercise attenuates exercise-related declines in blood glucose in active individuals with type 1 diabetes.

Key words: type 1 diabetes, resistance exercise, aerobic exercise, continuous glucose monitoring, hypoglycemia,

## INTRODUCTION

The physiological decreases in plasma insulin that occur during physical activity in non-diabetic individuals are absent in those with type 1 diabetes. The lack of change in insulin levels is due to the use of exogenous synthetic insulin, which often results in a relative state of hyperinsulinemia during exercise in individuals with diabetes. As moderate aerobic exercise increases insulin sensitivity and enhances glucose uptake and utilization in skeletal muscle, it creates an elevated risk of hypoglycemia both during and after exercise in individuals with type 1 diabetes (1).

In contrast, 10 to 15 minutes of very high intensity exercise, ~87% of maximum oxygen consumption ( $\dot{V} O_{2\max}$ ), where anaerobic metabolism is responsible for much of the energy expended, has been shown to increase glucose production throughout exercise, resulting in post-exercise hyperglycemia in individuals with type 1 diabetes (2-4). Shorter bouts of anaerobic exercise (4-second sprints) interspersed at regular intervals in an aerobic exercise session have also been shown to maintain higher levels of blood glucose and therefore decrease the risk of hypoglycemia both during and for up to two hours post-exercise (5, 6). Even as little as a 10-second sprint performed before or after 20 minutes of moderate aerobic activity has been shown to have a protective effect against exercise-induced hypoglycemia in individuals with type 1 diabetes (7, 8).

Resistance exercise is activity like weight lifting that uses muscular strength to move a weight or work against a resistant load. To date, there remains a paucity of information about the acute effects of resistance exercise (a form of anaerobic activity) on blood glucose in type 1 diabetes. We have previously shown that plasma glucose falls less

during resistance exercise than during aerobic exercise in individuals with type 1 diabetes (9). We are unaware of previous research on whether a bout of resistance exercise might attenuate the usual decrease in plasma glucose during subsequent aerobic exercise. This study aims to determine the effects of aerobic exercise on blood glucose in individuals with type 1 diabetes, both during and after exercise, if it is performed on its own or subsequent to a bout of resistance exercise. We evaluated the hypothesis that, similar to short sprints, a session of resistance exercise immediately before aerobic exercise would attenuate the usual decrease in plasma glucose during subsequent aerobic exercise. We also evaluated the hypothesis that this may lead to an increase in late onset post-exercise hypoglycemia overnight in order to replenish glycogen stores in the muscles.

## METHODS

### *Participants*

The study was approved by the Research Ethics Boards of the University of Ottawa and the Ottawa Hospitals. Twelve (10 male, 2 female) physically active, non-obese (BMI<30), non-smoking adults with complication-free type 1 diabetes were recruited for the study. Participants were required to be regularly performing both aerobic and resistance exercise a minimum of three times a week, and to have  $HbA_{1C} \leq 9\%$ . Participants were receiving insulin either by multiple daily injections (MDI) or by continuous subcutaneous insulin infusion (CSII).

### *Experimental Design*

This was a randomized, crossover study in which each subject was studied for two separate 3-day periods. All participants were required to participate in two preliminary and two experimental visits. Testing took place in the Human and Environmental Physiology Research Unit at the University of Ottawa.

### *Preliminary visits*

Participants were informed of the study purpose, protocol, and possible risks before providing informed consent and completing exercise readiness questionnaires (PAR-Q, AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire). They were provided with OneTouch® UltraSmart® glucometers (Lifescan, Johnson & Johnson, Milpitas, USA) and coded strips (same code throughout the study) for capillary glucose tests. On a separate day a maximal exercise stress test was performed with a monitored electrocardiogram (Quinton Q4500, Quinton, Bothell, Washington) using a ramp protocol on a treadmill. Peak oxygen consumption ( $\dot{V}O_{2\text{peak}}$ ) was determined by measuring expired oxygen and carbon dioxide concentrations (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry, Pittsburgh, PA, USA). Muscular strength was measured as the 8 repetition maximum of the following exercises: chest press, leg press, seated row, leg curl, shoulder press and lat pulldown. Venous blood samples were collected for determination of HbA<sub>1c</sub>, which was measured by automated heterogeneous immunoassay with latex enhanced turbidimetric detection on a Roche Cobas Integra 800 analyzer (Roche Diagnostics Corporation, Indianapolis, IN).

### *Continuous Glucose Monitoring*

At 8:30 am on the day prior to the testing session, Continuous Glucose Monitoring System<sup>®</sup> (CGMS) sensors (CGMS System Gold<sup>™</sup>, Medtronic, Northridge, CA) were inserted subcutaneously. The System Gold does not have real-time glucose display, leaving participants blinded to CGM values and therefore not adjusting their usual behavior based on the readings. Participants were instructed on the operation of the CGM and were asked to test capillary glucose 4 times per day for calibration purposes, using the meter provided. On the third day, at least twenty-four hours post-exercise the sensors were removed and CGM units were retrieved. Data were downloaded via the com-Station using the Minimed Solutions Software version 3.0c (Medtronic, Northridge, CA).

While wearing the sensor participants could choose their own foods, but were asked to consume the same breakfast, lunch, dinner and snacks each day at as close to the same times as possible and to record their food and insulin intake. Log sheets were provided by the investigators for this purpose. Participants were asked to avoid exercise for 24 hours before sensor insertion (48 hours before the experimental session) and to avoid caffeine and alcohol during the monitoring period.

### *Experimental sessions*

Participants arrived at the laboratory at 1600 h. Female participants were tested during the active pill consumption (high exogenous hormone) phase of oral contraceptive use. Each participant performed the following sessions under thermoneutral (21°C, 20% relative humidity) conditions:

- 1) Aerobic exercise only (A): 45 minutes of treadmill running at 60% of  $\dot{V} O_{2\text{peak}}$ .

2) Resistance exercise only (R): Three sets of 8 repetitions at the maximum weight that could be lifted 8 times (8RM) of supine bench press, leg press, shoulder press, abdominal crunches, lat pulldown, leg curl and seated cable row with 90 seconds rest between sets (total exercise duration ~ 45 minutes).

3) Resting control session: 45 minutes of resting in an upright seated position

4) Combined aerobic before resistance exercise session (AR): A combination of sessions 1 and 2 as described above, with resistance exercise being performed prior to aerobic exercise.

5) Combined resistance before aerobic exercise (RA): A combination of sessions 1 and 2 as described above, with resistance exercise being performed prior to aerobic exercise. All exercise sessions were followed by 60 minutes of monitored resting recovery in the laboratory. The experimental trials were randomly assigned and separated by at least 5 days. Data presented in this paper result from sessions 1 and 5 above.

## MEASUREMENTS

### *Insulin adjustments and glucose supplementation*

Participants were provided with guidelines for insulin reduction on exercise days. A 10% reduction in intermediate or long acting insulin was recommended for those using MDI and a 50% reduction in basal infusion starting one hour before exercise and continuing until the end of exercise was recommended for those using CSII. Where blood glucose was measured below 5 mmol/l upon arrival at the laboratory, a further 25% decrease in basal rate was made for those using CSII. Standardized snacks (Glucerna

Chocolate Graham Snack Bars (Abbott Laboratories, Abbott Park, IL)) were also provided and consumed at 1600 h on every day of the study.

Participants were required to have capillary glucose levels between 5.5 and 13.9 mmol/l before starting exercise. Capillary glucose tests were performed upon arrival at the laboratory, 30 minutes before exercise and during the baseline blood draw prior to exercise. If glucose was less than 4.5 mmol/l, 32 g of glucose in tablet form (Dex 4®, AMG Medical, Montreal, QC, Canada) was provided, and 16 g of glucose were provided if levels were between 4.5 and 5.4 mmol/l. Glucose levels were monitored during exercise using venous blood tested on the glucometer provided to the participant at the beginning of the study. Exercise was stopped and 16 g of glucose provided if blood glucose levels fell below 4.5 mmol/l during exercise. Capillary glucose tests were performed every 10 minutes with an additional 16 g of glucose being provided if glucose levels had not increased. Exercise was resumed once levels were above 5.5 mmol/l.

### *Blood sampling*

Venous blood samples were collected at baseline 5, 10, 15, 30, and 45 minutes of resistance exercise for the combined resistance and aerobic exercise session, baseline, 5, 10, 15, 30 and 45 minutes of aerobic exercise for both sessions and 5, 10, 15, 20, 30, 40, 50 and 60 minutes during recovery (after cessation of exercise). Five-ml sterile plastic syringes were used to draw blood through an IV catheter. Samples were transferred immediately into 5.4 ml serum (no additive) and plasma (K<sub>2</sub>EDTA) BD Vacutainer® tubes (BD, Franklin Lakes, NJ, USA). One ml of blood was added to a 16X100 borosilicate tube containing 1 ml of aprotinin (Trasylol) for subsequent analysis of glucagon. Blood

contained in serum tubes sat at room temperature to clot for 20 minutes before centrifugation while tubes containing K<sub>2</sub>EDTA and aprotinin were mixed by inversion and centrifuged immediately (4000 rev/min for 4 minutes). Serum and plasma aliquots were then stored in 1.5 ml microcentrifuge tubes at -80°C until analyzed.

Plasma glucose for each time point was determined using the hexokinase timed endpoint method on the Beckman Coulter Unicel <sup>®</sup>DxC600 Synchron<sup>®</sup> Clinical Analyzer (Beckman Coulter Inc., Fullerton, CA, USA) with SYNCHRON CX<sup>®</sup> Systems GLUCOSE reagent (Cat#442640). Due to budgetary constraints, non-esterified fatty acids (NEFA), insulin, cortisol and growth hormone (GH) were only analyzed on a subsample of 6 participants that were representative of the overall study population in terms of gender, age, weight, and fitness. Plasma NEFA levels were determined using an Enzymatic Colorimetric Method with RANDOX NEFA reagent (Randox Laboratories, Antrim, UK). Enzyme immunoassays were used to determine serum cortisol, serum GH, plasma synthetic insulin and plasma glucagon (Alpco Diagnostics <sup>™</sup>, Salem, NH, USA). The sensitivities of the EIA kits were 11.04 nmol/l, 1.13 nmol/l, 32.99  $\mu$ mol/l, 50 ng/l respectively. Intra- and inter-assay coefficients of variation were 2.9 to 9.4% and 3.8 to 8.1% for serum cortisol, 2.2 to 2.9% and 3.0 to 4.4% for serum GH, 2.15 to 8.42% and 7.42 to 10.18% for plasma synthetic insulin and 3.3 to 5.1% and 7.3 to 18.9% for plasma glucagon. Due to equipment and budgetary constraints, we were unable to perform catecholamine assays.

## STATISTICAL ANALYSES

Two separate two-way (time and condition) ANOVA analyses were performed to examine exercise and recovery periods separately for glucose, cortisol, NEFA, GH and insulin levels. Paired samples t-tests were used to perform pair-wise post-hoc comparisons for each time point (0, 5, 10, 15, 30 and 45 minutes for aerobic exercise, and 5, 10, 15, 20, 30, 40, 50, and 60 minutes for recovery) between conditions and to examine within-condition changes from baseline. The level of significance was set at 0.05 and alpha level was adjusted during multiple comparisons so as to maintain the rate of Type 1 error at 5% during the Holm-Bonferroni post-hoc analysis.

CGMS data were grouped and summarized for the following time periods: 24 hours pre-exercise, overnight pre-exercise (2400h to 0600h), 1 to 6 hours post-exercise, overnight post-exercise and 24 hours post-exercise. To examine the 1 to 6 hour post-exercise time period 15 minute averages were calculated and compared between conditions using a two-way repeated measures ANOVA (time and condition). Post-hoc comparisons were made using paired sample t-tests. The thresholds were set at 3.5 mmol/l for hypoglycemia and at 10.9 mmol/l for hyperglycemia. For each time period of interest the minimum, maximum and mean blood glucose, amount of time spent in hypoglycemia and hyperglycemia, and area under the curve (AUC) for time spent in hypoglycemia and hyperglycemia was determined. AUC was calculated by multiplying the absolute distance above or below threshold in mmol/l by the duration of the episode. Related-samples Wilcoxon Signed Ranks test was used to compare pre-exercise values to post-exercise values and to compare between conditions for each of these parameters. Separate Pearson correlation analyses were performed for A and RA sessions to compare capillary glucose

values recorded during non-exercise periods by the participants to CGMS data, in order to assess the accuracy of CGMS measurements. Daily total insulin and carbohydrate intake were calculated based on the details provided by the participants in their food and insulin diaries. Comparisons between conditions for each day were performed using related samples Wilcoxon Signed Ranks tests. Analyses were performed using SPSS 18.0 for Windows (SPSS Inc. Chicago, IL, USA). Data are presented as means  $\pm$  SD.

## RESULTS

Twelve healthy physically active male (n=10) and female (n=2) volunteers with type 1 diabetes (aged  $31.8 \pm 15.3$  years, HbA1c  $7.1 \pm 1.1\%$ , BMI  $25.3 \pm 3.0 \text{ kg/m}^2$ ,  $\dot{V}O_{2\text{peak}}$   $51.2 \pm 10.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , type 1 diabetes duration  $12.5 \pm 10$  years [means $\pm$ SD]) took part in the study. Participant characteristics are presented in Table 1. Both female participants used monophasic oral contraceptive pills. During non-exercise periods, there were 114 and 105 capillary glucose readings for the A and RA exercise sessions respectively. The Pearson correlations between capillary readings and sensor readings were 0.90 for A (P<0.01) and 0.91 for RA (P<0.01). The average minimum glucose value reached by the participants overnight on the night prior to exercise was lower in RA than in A ( $4.6 \pm 0.9$  versus  $3.8 \pm 1.2 \text{ mmol/l}$ ; P=0.036). However, rates of hypoglycemia and hyperglycemia, time spent in hypoglycemia or hyperglycemia and AUC for both of these were statistically similar between conditions both overnight and in the full 24 hours prior to the exercise testing sessions.

## EXERCISE

All data (mean  $\pm$  SD) for glucose, NEFA, insulin, cortisol and GH can be found in Table 1. Statistical analyses were not performed on glucagon values as the assays performed failed to yield consistent results.

### *Plasma Glucose*

Mean plasma glucose levels were comparable in both conditions at the beginning of the 45 minutes of aerobic exercise. Significant effects of time ( $P=0.001$ ) and an interaction of condition and time ( $P=0.046$ ) were found when examining blood glucose levels throughout exercise. Plasma glucose decreased significantly from baseline in A within the first 10 minutes of aerobic activity and remained significantly lower than baseline until the end of the exercise (Figure 1). Conversely, there were no statistically significant declines in blood glucose throughout exercise in the RA condition. In spite of seeing no significant change from baseline in RA, differences in plasma glucose levels between conditions at each time point were not statistically significant.

### *NEFA, GH, insulin, and cortisol*

A significant effect of time was found for NEFA and GH levels during exercise ( $P=0.016$  and  $P<0.001$  respectively). There were no significant differences in NEFA levels between conditions at each time point, nor were there any significant changes from baseline within each condition (after Holm-Bonferroni adjustment) (Figure 2A). GH was higher in RA than in the A session (Figure 2B) for the first 15 minutes of exercise after which a significant increase in GH occurred in A so that groups were not significantly

different from one another by the end of exercise. No significant intergroup differences were observed for plasma insulin (Figure 2C) or serum cortisol (Figure 2D) throughout exercise.

## RECOVERY

All data (mean  $\pm$  SD) for glucose, NEFA, insulin, cortisol and GH can be found in Table 2.

### *Plasma Glucose*

During recovery, a significant effect of time was found with respect to plasma glucose levels ( $P=0.016$ ). Glucose increased from the end of exercise throughout recovery in both groups, but increases only reached significance in the A condition (Table 2). There were no intergroup differences with respect to plasma glucose throughout recovery.

### *NEFA, GH, insulin, and cortisol*

A significant effect of time was found in the analysis of NEFA ( $P=0.001$ ), GH ( $P<0.001$ ), insulin ( $P<0.001$ ) and cortisol ( $P=0.001$ ) levels. NEFA levels increased in the first 5 minutes of recovery in both conditions (Figure 2A) but the change from the end of exercise was only statistically significant in A. GH decreased post-exercise in both groups but changes were only statistically significant in A after adjusting for multiple comparisons (Figure 2B). Insulin levels were lower than baseline during recovery from AE ( $P<0.05$ ) but these failed to retain significance after adjustment for multiple comparisons (Figure 2C).

There were no significant changes in cortisol (Figure 2D) and no significant intergroup differences were measured for any of these markers throughout recovery.

#### *Carbohydrate and insulin intake*

All participants using subcutaneous insulin infusion made identical adjustments to their basal insulin rates for both trials with the exception of one, who suspended their basal insulin for A, but only reduced basal insulin by 50% for RA. Similarly, those using multiple daily injections had identical insulin intake with their last meal prior to exercise with the exception of two participants who had to increase their insulin intake prior to the RA exercise condition (by 2 and 13U respectively, in order to correct for high blood glucose levels. Of the 12 participants, 8 took the same insulin bolus for the pre-exercise snack in both exercise conditions while 2 had a slightly higher bolus for A (by 0.7 and 1.7U respectively) and 2 had a slightly higher bolus for RA (both by 1U). Insulin dosage was similar between conditions on all three days of sensor usage. There was also no difference between the first (non-exercise) day and the second (exercise) day within conditions with respect to total daily insulin dose (A: Day 1=47±19U, Day 2=48±20U; RA: Day 1=50±19U, Day 2=48±21U).

There was a greater need for carbohydrate supplementation in the A condition during exercise as compared to the RA condition. Nine out of 12 participants required glucose supplementation in A vs. 6 out of 12 in RA. Only 3 participants required interruptions during exercise for carbohydrate supplementation in RA (with breaks lasting on average 10 minutes) versus 5 participants in the A session, where breaks lasted an average of 20 minutes. Overall there were no statistically significant differences in

carbohydrate intake both between days within conditions and across conditions for the same day.

### *Continuous Glucose Monitoring*

Due to equipment malfunction, CGM data was only available for 10 out of 12 participants for the aerobic only trial. There was a significant interaction of time and condition with respect to mean CGM glucose from 1 to 6 hours post-exercise ( $P=0.004$ ), with peaks occurring at different times post-exercise (Figure 3). When pre-exercise CGM data was compared to post-exercise data (24 hour and overnight) within the A condition there were no significant differences between rates of hypoglycemia or hyperglycemia. Time spent in hypoglycemia, time spent in hyperglycemia and AUC for both hypoglycemia and hyperglycemia were also similar before and after exercise, as were the average minimum, maximum, and mean glucose levels among the participants. Within the RA condition, the average minimum glucose level recorded among the participants was higher in the 24 hours post-exercise than the 24 hours before (pre =  $3.0\pm 0.8$  mmol/l, post =  $3.4\pm 1.1$  mmol/l,  $P=0.028$ ), and the average nocturnal maximum glucose level was lower (pre =  $9.5\pm 3.0$  mmol/l, post =  $8.8\pm 4.0$  mmol/l;  $P=0.041$ ). There were no differences between the conditions with respect to all measures of hypoglycemia and hyperglycemia both overnight and 24 hours post-exercise.

## DISCUSSION

The results of this study support our hypothesis that performing a 45 minute bout of resistance exercise would assist in preventing exercise-induced hypoglycemia in

individuals with type 1 diabetes. Declines in blood glucose were delayed and of a smaller magnitude when aerobic exercise was preceded by resistance exercise than when aerobic exercise was performed on its own. In spite of a greater amount of exercise being performed during the RA exercise sessions, there was a trend towards less glucose supplementation during the aerobic portion of this session, and rates of overnight hypoglycemia were no greater. It is also likely that the extra carbohydrate consumed and the additional interruptions in exercise during the A as compared to the RA exercise session actually led to less of a decline in glucose during A than would have otherwise been expected and subsequently an underestimation of the difference between the two exercise conditions.

Sustained high intensity exercise ( $>80\% \dot{V} O_{2\text{peak}}$ ) involving a contribution of anaerobic metabolism is known to cause increases in blood glucose during exercise, as well as post-exercise hyperglycemia in individuals with type 1 diabetes (2, 4). Sigal et al. (2) found that approximately 13 minutes of cycling at 89 to 98% of  $\dot{V} O_{2\text{peak}}$  resulted in significantly higher post-exercise glucose levels (from  $5.4 \pm 0.3$  to  $6.9 \pm 0.4$  mmol/l in the group that started in euglycemia and from  $8.6 \pm 0.3$  to  $9.8 \pm 0.5$  mmol/l in the group that started in hyperglycemia) in individuals with type 1 diabetes. Similarly, Purdon et al. (4) observed an increase in plasma glucose from  $4.8 \pm 0.2$  to  $7.2 \pm 1.1$  mmol/l after a ~12-min bout of high-intensity cycling to exhaustion. Short bursts of anaerobic activity (sprints) have also been shown to attenuate decreases in blood glucose when performed in association with aerobic exercise (5-8). Where a 10-second sprint at the conclusion of low intensity ( $40\% \dot{V} O_{2\text{peak}}$ ) aerobic exercise on a cycle ergometer prevented a further fall in

glycemia post-exercise in individuals with type 1 diabetes, a similar session without sprints resulted in decreases in blood glucose of  $3.6 \pm 1.2$  mmol/l in the 2 hours post-exercise (7). The same sprint performed prior to 20 minutes of low intensity cycling also attenuated post-exercise decreases in blood glucose, but for a shorter period of time (45 minutes). Similarly, Guelfi et al. (6) found that 4-second sprints performed at 2-minute intervals during 30 minutes of light intensity ( $40\% \dot{V}O_{2\text{peak}}$ ) cycling resulted in less of a decline in blood glucose throughout exercise ( $-4.4 \pm 1.2$  mmol/l in the control group vs.  $-2.9 \pm 0.8$  mmol/l in the sprint group,  $P=0.006$ ) as well as fewer changes in post-exercise blood glucose levels when compared to the non-sprinting group.

Increases in blood glucose concentration associated with exhaustive cycling or high intensity sprint intervals are generally attributed to elevations of epinephrine and norepinephrine stimulating higher levels of glycogenolysis, and thereby causing rates of glucose production to exceed those of utilization (3, 4). Elevated levels of catecholamines have been shown to last for up to 20 minutes post-exercise in individuals with type 1 diabetes (2, 8). While we are unaware of data describing changes in catecholamine levels during resistance exercise in individuals with type 1 diabetes, resistance exercise in individuals without diabetes has been shown to cause considerable increases in catecholamines as well as blood glucose (10), with epinephrine secretion increasing in proportion to the intensity and duration of the exercise (11). Previous research would indicate that catecholamine secretion is indeed elevated during high intensity exercise in individuals with type 1 diabetes (3, 4, 12) although there is some evidence to indicate that this response may be blunted in comparison to individuals without diabetes (2, 13). It is very likely that resistance exercise caused an increase in epinephrine secretion in our

participants and that these levels remained elevated after the completion of the resistance exercise. This could explain why there were no significant changes in blood glucose until the end of aerobic exercise in the RA condition (Figure 1), as opposed to the immediate and rapid decline in glucose levels that were seen in the A condition.

A study by Goto et al. (14) examined the effects of resistance exercise on substrate oxidation during subsequent aerobic exercise in moderately active individuals without type 1 diabetes. The researchers found that a bout of resistance exercise similar to that used in our study (3 sets of 10 repetitions for 6 exercises) resulted in elevated levels of NEFA and GH during the subsequent low intensity aerobic exercise session when compared to aerobic exercise alone. Using indirect calorimetry, they showed that fat oxidation contributed almost twice as much towards energy production during aerobic exercise when it was preceded by a bout of resistance exercise. The authors suggest that the elevated GH levels may have enhanced the lipolytic action of epinephrine in the adipose tissue through modification of the beta-adrenergic pathway (14).

Similar to the Goto et al. (14) study, we found significantly higher levels of GH during aerobic exercise when it was performed subsequent to resistance exercise (Figure 2B). Elevated GH levels have also been found in studies involving high intensity exercise in type 1 diabetes. Guelfi et al.(5, 6) and Bussau et al.(7, 8) measured elevated levels of GH persisting for 30 minutes post-exercise where short sprints were included either throughout or at the end of a low intensity cycling session (5-7). GH could have contributed to the attenuated decrease in glucose in the RA session by increasing the mobilization of fatty acids, thus increasing insulin resistance. While we did not find any significant differences between the conditions with respect to NEFA levels, a trend

towards levels that were higher than baseline ( $P=0.032$  – not significant after Holm-Bonferroni correction) was found in NEFA concentration by the end of aerobic exercise in the RA condition, but not in the A condition. It is possible that with a larger sample size we may have been able to detect a difference between conditions also.

Resistance exercise protocols similar to the one used in our study have been shown to increase lactate to approximately four to five times resting levels in individuals without type 1 diabetes (15). While we are not aware of published data describing lactate responses to resistance exercise in type 1 diabetes, other forms of high intensity exercise have been shown to increase plasma lactate in this population (2, 4). In a study by Purdon et al.(4), 12 minutes of exhaustive cycling increased blood lactate from  $0.67\pm 0.06$  to  $12.51\pm 1.30$  mmol/l. Similarly, intermittent maximal intensity sprint intervals have been associated with elevated lactate levels for up to 40 minutes post-exercise in individuals with type 1 diabetes (5-8). It has been suggested that elevated lactate levels could stimulate gluconeogenesis, thereby increasing the rate of glucose appearance both during and after high intensity exercise (8). If individuals with type 1 diabetes have a similar lactate response to resistance exercise as they do to other forms of anaerobic activity, higher lactate levels and a higher rate of gluconeogenesis may also be partly responsible for the attenuated declines in plasma glucose seen during the RA session.

Similar to previous studies of high intensity exercise in type 1 diabetes (5-7), we did not find any significant differences between conditions with respect to cortisol levels during both exercise and recovery. This is also consistent with studies examining hormonal responses to resistance exercise in individuals without diabetes, where no significant changes in cortisol levels were found with a similar resistance exercise protocol (15). There

were also no significant differences between conditions with respect to insulin levels, which therefore were probably not responsible for any intergroup differences in blood glucose response.

Surprisingly, there were no differences between conditions with respect to measures of nocturnal hypoglycemia. A previous study has suggested that high intensity exercise is associated with an increased frequency of post-exercise nocturnal hypoglycemic events than moderate aerobic exercise (7 episodes versus 2 respectively) (16), possibly as the result of delayed replenishment of glycogen stores (16, 17). We were, therefore, expecting to find increases in our measures of post-exercise hypoglycemia after the RA condition, where both a greater amount of work was performed, and the additional work would have been fueled by anaerobic metabolism consisting mostly of phosphocreatine and muscle glycogen (18). However, both conditions in our study produced very similar post-exercise overnight glucose profiles which were also very similar to those that had been measured on the non-exercise night prior to the testing sessions in both conditions. Notable exceptions were the higher minimum glucose and lower maximum glucose found after the RA session in comparison to the non-exercise night, indicating a healthier range of glucose levels after the combined exercise session. If, as we have suggested, there was a greater tendency to fuel exercise with lipid oxidation and gluconeogenesis during aerobic exercise in the RA condition, it could have contributed to less of a depletion of glycogen stores during the 45 minute aerobic exercise bout. It should be noted that the participants in the above-mentioned CGM study were not regularly training, while those in our study were. This may have contributed to some of the discrepancy in the frequency of post-exercise nocturnal hypoglycemia. As the frequency and severity of nocturnal

hypoglycemia was not different after 48 hours without exercise as it was in the overnight hours following exercise, it is possible that low blood glucose at night in our participants is the result of intensive insulin therapy (19), rather than exercise per se.

In contrast to several other studies (2, 4-8), we chose to have our participants exercise in the late afternoon (i.e., 1700 hours), as this is a popular time for those who work to perform their daily exercise. If the participants had remained in the laboratory for 24 hours before and after the exercise sessions, and had all been provided with identical meals at the same times, we could have decreased the variability in the data. We feel, however, that the current study design is more representative of real-life conditions. While participants went about their regular daily activities and were able to choose their own foods, we did take several measures to minimize variability throughout the study: each participant was asked consume the same breakfast, same lunch, and same supper every day of all trials, exercise took place at the same time of day for every trial, and participants avoided physical activity for 48 hours before and 24 hours after the testing sessions.

This study would have been strengthened by having the ability to measure glucagon, lactate and catecholamines, as these may have been useful in explaining some of the changes in blood glucose levels that were observed. It should also be noted that all of our participants were quite fit, and that the applicability of the outcomes to inactive individuals with type 1 diabetes may be limited. Finally, as the number of female participants taking part in the research was small (only 2 out of 12 participants) it was impossible to ascertain whether or not there were sex-related differences in the blood glucose (and hormonal) responses to the various exercise stimuli.

The outcome of this study highlights the need for more research on the effects of resistance exercise on blood glucose in type 1 diabetes. The data indicate that the inclusion of resistance-type activities prior to aerobic exercise both delays and attenuates declines in blood glucose thereby decreasing the risk of hypoglycemia during aerobic exercise, in spite of greater amounts of work being performed. This may also lead to a decreased need for carbohydrate supplementation during exercise, and consequently less hyperglycemia post-exercise for active individuals with type 1 diabetes (9). Over time, this could translate into improvements in HbA<sub>1c</sub> where resistance exercise is included, which would be consistent with the results found in the few intervention studies involving resistance exercise in individuals with type 1 diabetes (20-22). Further research will be necessary to determine whether the same effects are found in individuals with type 1 diabetes who have poor glucose control, or who are not regularly active.

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## **Tables and Figures<sup>2</sup>**

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<sup>2</sup> Tables 1 and 2, as well as figure 3 may be submitted as online appendices

**Table 1.** Changes in glucose, non-esterified fatty acids (NEFA), cortisol, insulin and growth hormone (GH) throughout exercise

Glucose (mmol/l)	Aerobic Only (A)	P (change from baseline in A)	Combined Resistance & Aerobic (RA)	P (change from baseline in RA)	P (A vs RA)
Baseline	9.2 ± 3.4		9.2 ± 4.0		0.966
5 min	8.9 ± 3.7	0.266	9.5 ± 3.7	0.219	0.569
10 min	8.1 ± 3.6	0.007*	9.6 ± 3.5	0.211	0.240
15 min	7.6 ± 3.3	0.004*	9.4 ± 3.7	0.586	0.137
30 min	6.1 ± 2.7	0.000*	8.0 ± 3.4	0.129	0.137
45 min	5.8 ± 2.0	0.001*	6.9 ± 3.1	0.040	0.345
<b>NEFA (µmol/l)</b>					
Baseline	211 ± 70		328 ± 139		0.155
5 min	190 ± 52	0.363	290 ± 145	0.247	0.141
10 min	223 ± 93	0.742	317 ± 178	0.813	0.230
15 min	251 ± 130	0.440	361 ± 213	0.585	0.293
30 min	267 ± 187	0.463	391 ± 214	0.271	0.386
45 min	260 ± 200	0.544	418 ± 164	0.032	0.267
<b>Cortisol (nmol/l)</b>					
Baseline	364.48 ± 174.32		317.97 ± 139.22		0.133
5 min	327.38 ± 151.08	0.030	313.09 ± 153.10	0.716	0.643
10 min	309.41 ± 136.86	0.108	333.82 ± 201.03	0.728	0.577
15 min	306.92 ± 114.95	0.125	376.47 ± 251.68	0.447	0.410
30 min	300.62 ± 113.96	0.197	424.46 ± 281.55	0.341	0.321
45 min	323.74 ± 216.33	0.587	522.12 ± 380.07	0.246	0.348
<b>Insulin (pmol/l)</b>					
Baseline	62.28 ± 9.88		61.72 ± 10.06		0.797
5 min	73.16 ± 13.58	0.092	60.12 ± 7.90	0.351	0.174
10 min	80.68 ± 21.63	0.123	64.34 ± 11.51	0.471	0.294
15 min	80.61 ± 27.33	0.198	73.92 ± 24.44	0.340	0.867
30 min	90.48 ± 44.77	0.242	75.61 ± 31.20	0.387	0.685
45 min	81.28 ± 37.90	0.349	69.79 ± 24.88	0.498	0.739
<b>GH (nmol/l)</b>					
Baseline	0.74 ± 0.97		12.07 ± 13.54		0.099
5 min	0.82 ± 0.96	0.392	11.34 ± 9.07	0.782	0.040
10 min	0.96 ± 0.98	0.093	12.50 ± 9.98	0.871	<0.001*
15 min	2.19 ± 2.35	0.179	13.28 ± 10.62	0.632	0.001*
30 min	6.58 ± 4.51	0.017*	16.25 ± 14.08	0.198	0.185
45 min	9.83 ± 5.96	0.008*	15.12 ± 13.96	0.379	0.432

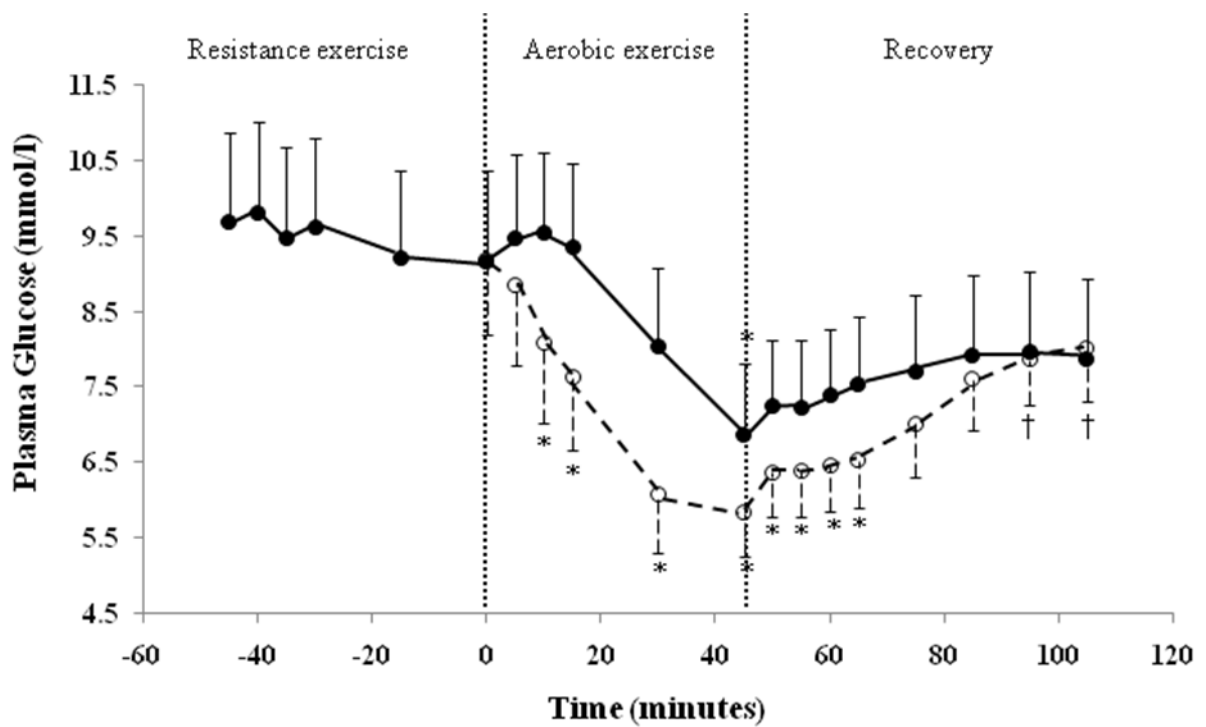
Data are presented as mean ± SD. \* denotes statistical significance after Holm-Bonferroni adjustment.

Glucose: n=12 for aerobic only (A) session, n=11 for combined resistance and aerobic (RA) session. Non-esterified fatty acids (NEFA), insulin and growth hormone (GH): n=6. Cortisol: n=5.

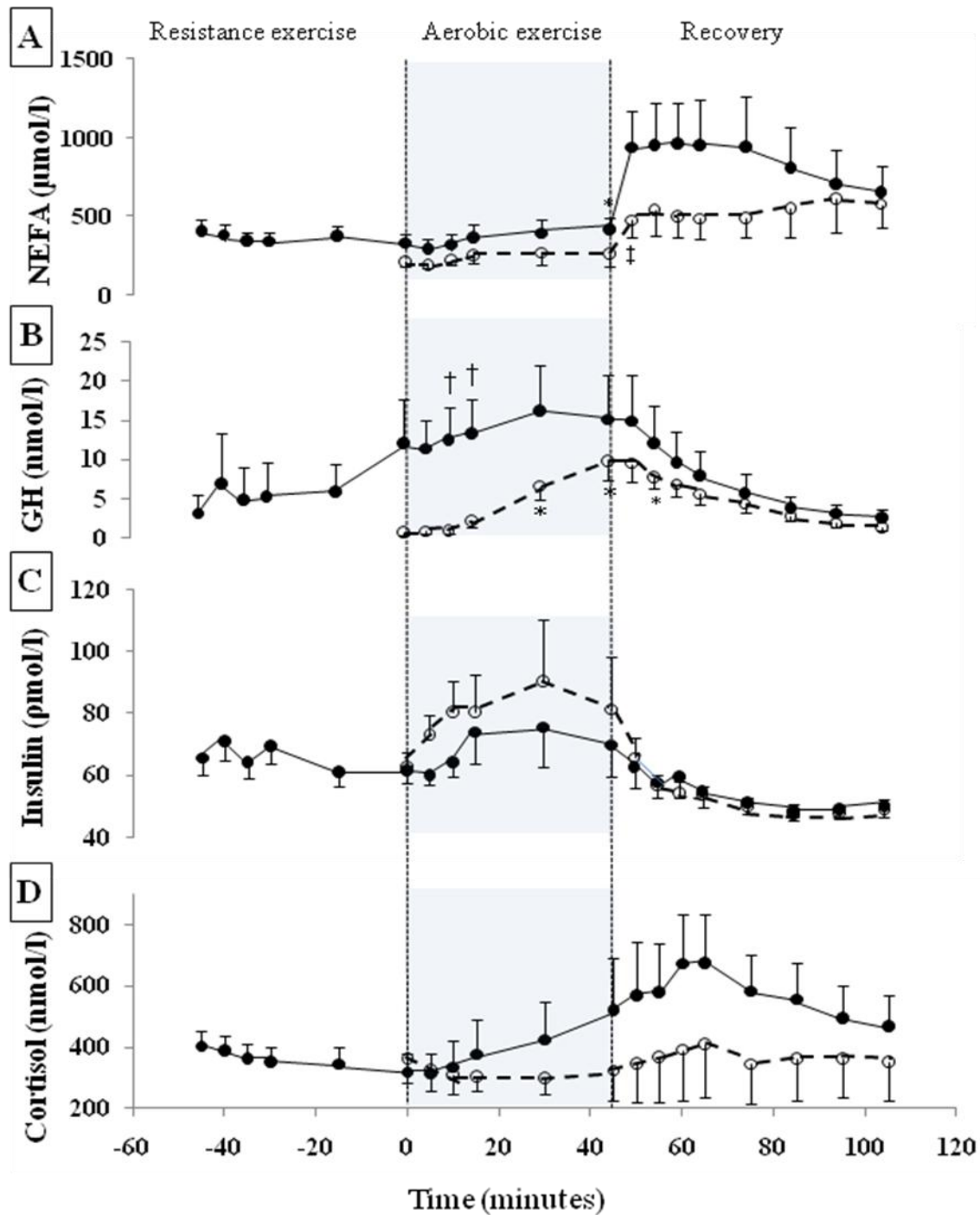
**Table 2.** Changes in glucose, non-esterified fatty acids NEFA, cortisol, insulin and growth hormone (GH) throughout recovery

Glucose (mmol/l)	Aerobic Only (A)	P (change from baseline in A)	P (change from end exercise in A)	Combined Resistance & Aerobic (RA)	P (change from baseline in RA)	P (change from end-exercise in RA)	P (A vs RA)
50 min	6.4±2.0	0.015	0.018	7.3±2.9	0.103	0.100	0.434
55 min	6.4±2.1	0.008	0.064	7.2±3.0	0.108	0.145	0.482
60 min	6.5±2.1	0.013	0.120	7.4±2.9	0.145	0.097	0.452
65 min	6.5±2.2	0.021	0.141	7.5±3.0	0.204	0.113	0.427
75 min	7.0±2.5	0.069	0.067	7.7±3.3	0.284	0.130	0.635
85 min	7.6±2.3	0.226	0.011	7.9±3.6	0.376	0.125	0.761
95 min	7.9±2.0	0.317	0.002*	8.0±3.6	0.400	0.142	0.920
105 min	8.0±2.4	0.419	0.004*	7.9±3.5	0.400	0.264	0.857
<b>NEFA (µmol/l)</b>							
50 min	474±259	0.053	0.003*	937±564	0.028	0.032	0.152
55 min	543±418	0.106	0.031	95 ±653	0.047	0.054	0.312
60 min	501±346	0.094	0.020	959±647	0.048	0.058	0.228
65 min	484±320	0.094	0.022	951±703	0.068	0.085	0.232
75 min	488±307	0.096	0.078	940±796	0.115	0.149	0.267
85 min	549±446	0.146	0.180	810±632	0.123	0.172	0.439
95 min	614±538	0.147	0.188	705±540	0.168	0.253	0.778
105 min	575±367	0.075	0.106	652±414	0.145	0.254	0.740
<b>Cortisol (nmol/l)</b>							
50 min	347.86±286.68	0.879	0.530	570.24±381.08	0.170	0.110	0.323
55 min	369.36±337.00	0.971	0.483	578.50±354.43	0.147	0.189	0.368
60 min	392.04±367.60	0.853	0.404	671.07±362.80	0.085	0.042	0.284
65 min	409.63±389.98	0.782	0.373	673.01±353.64	0.079	0.049	0.311
75 min	345.71±289.07	0.879	0.667	582.66±263.30	0.071	0.443	0.214
85 min	364.78±313.35	0.998	0.532	555.41±270.28	0.077	0.642	0.317
95 min	364.35±288.52	0.999	0.555	494.75±239.76	0.121	0.717	0.434
105 min	354.32±291.20	0.941	0.658	467.61±231.03	0.135	0.537	0.478
<b>Insulin (pmol/l)</b>							
50 min	65.60±14.06	0.715	0.225	62.63±17.12	0.911	0.085	0.946
55 min	56.62±7.32	0.122	0.191	57.67±12.52	0.508	0.081	0.635
60 min	54.25±7.70	0.026	0.185	59.40±16.65	0.784	0.030	0.307
65 min	53.50±6.13	0.027	0.167	54.80±12.73	0.282	0.060	0.510
75 min	49.86±6.87	0.022	0.169	51.10±8.08	0.761	0.076	0.451
85 min	47.38±6.94	0.007	0.145	48.44±7.87	0.626	0.057	0.740
95 min	47.74±5.07	0.008	0.134	49.13±8.14	0.634	0.067	0.499
105 min	48.76±7.12	0.008	0.157	50.04±9.07	0.676	0.085	0.591
<b>GH (nmol/l)</b>							
50 min	9.49±5.72	0.008	0.631	14.92±14.49	0.611	0.799	0.463
55 min	7.79±3.73	0.002*	0.153	12.14±11.40	0.984	0.064	0.447
60 min	6.78±3.85	0.010	0.026	9.61±9.63	0.462	0.036	0.549
65 min	5.59±3.41	0.019	0.028	7.88±7.55	0.320	0.053	0.558
75 min	4.33±2.94	0.015	0.009	5.71±5.94	0.159	0.038	0.657
85 min	2.82±1.89	0.016	0.010	3.77±3.61	0.117	0.044	0.563
95 min	1.85±1.08	0.033	0.011	3.05±3.04	0.110	0.044	0.406
105 min	1.25±0.72	0.121	0.010	2.56±2.64	0.116	0.048	0.314

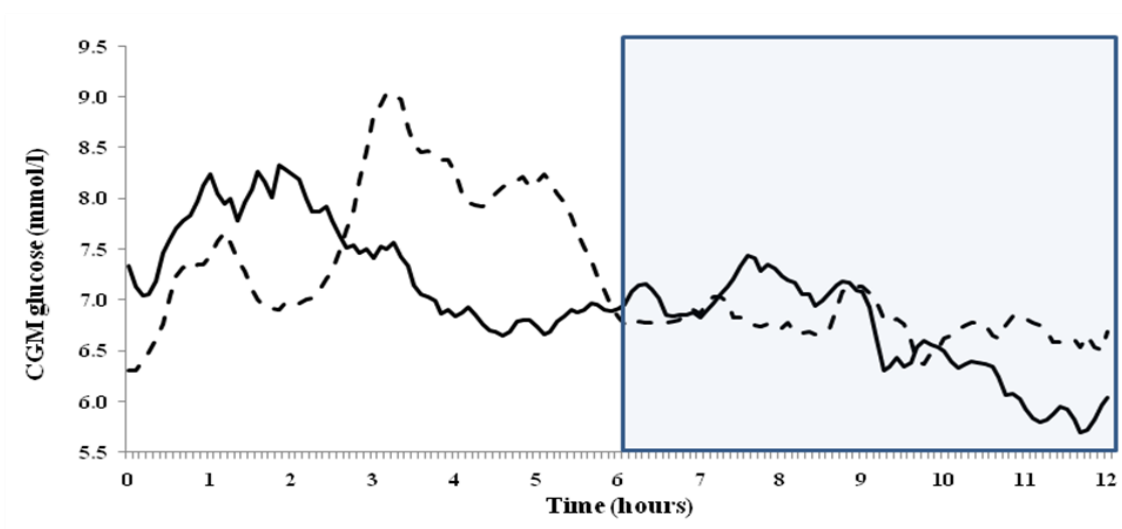
Data are presented as mean ± SD. \* denotes statistical significance after Holm-Bonferroni adjustment. n=12 for aerobic only (A) session, n=11 for combined resistance and aerobic (RA) session. Glucose: n=12 for aerobic only (A) session, n=11 for combined resistance and aerobic (RA) session. Non-esterified fatty acids (NEFA), insulin and growth hormone (GH): n=6. Cortisol: n=5.



**Figure 1** –Plasma glucose during 45 minutes of aerobic exercise on its own (A – dashed line with open symbols ○) or after resistance exercise (RA – solid line with closed symbols ●). Data are presented as means and error bars represent SE (n=12 for aerobic only session, n=11 for combined resistance then aerobic session). \* indicates statistical significance for changes from baseline (after Holm-Bonferroni adjustment). † indicates statistical significance for changes from the end of exercise (after Holm-Bonferroni adjustment).



**Figure 2** –Effect of 45 minutes of aerobic exercise on its own (A – dashed line with open symbols  $\circ$ ) or after resistance exercise (RA – solid line with closed symbols  $\bullet$ ) on (A) non-esterified fatty acids (NEFA)  $n=6$ , (B) growth hormone  $n=6$ , (C) insulin  $n=6$  and (D) cortisol  $n=5$ . Data are presented as mean  $\pm$  SE. \* indicates significant changes from baseline values, † represents significant differences between groups, ‡ indicates significant change from the end of exercise. Differences were only considered statistically significant if still significant after Holm-Bonferroni corrections for multiple comparisons.



**Figure 3** – Mean glucose as measured by continuous glucose monitoring during the 12 hours post-exercise. The dashed line represents the aerobic exercise only (A) session and the solid line represents the resistance then aerobic exercise (RA) session. The overnight period corresponds to the time between 12am and 6am (represented by box). n=10 for aerobic only, n=12 for resistance then aerobic exercise.

## **5.0 PAPER 3**

**Effects on glycemia of performing resistance exercise before versus after  
aerobic exercise in type 1 diabetes**

Prepared for submission to Diabetologia

# **Effects on glycemia of performing resistance exercise before versus after aerobic exercise in type 1 diabetes**

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## ABSTRACT

**Aims/hypothesis:** To determine the effects of combining resistance and aerobic exercise, as well as the effect of exercise order, on blood glucose in individuals with type 1 diabetes.

**Methods:** 12 (10 male, 2 female) physically active individuals (aged  $32.7 \pm 13.7$  years) with type 1 diabetes ( $HbA_{1c} = 7.1 \pm 1.0\%$ ) performed either aerobic exercise (45 minutes of running at  $60\% \dot{V}O_{2peak}$ ) prior to 45 minutes of resistance training (3 sets of 8, 7 different exercises) (**AR**), or performed the resistance exercise prior to running (**RA**). Blood samples were collected for measurement of glucose, insulin, cortisol, growth hormone (GH) and NEFA. Glucose was measured by continuous glucose monitoring systems (CGMS) 24 hours prior to, during and 24 hours post-exercise.

**Results:** Significant declines in blood glucose levels were seen in **AR** but not in **RA** throughout the first 45-minute exercise bout, resulting in higher glucose levels in **RA** (**AR** =  $5.5 \pm 0.7$  mmol/l, **RA** =  $9.2 \pm 1.2$  mmol/l,  $P = 0.006$ ). Glucose subsequently decreased in **RA** and increased in **AR** over the course of the second 45 minute exercise bout resulting in levels that were not significantly different by the end of exercise (**AR** =  $7.5 \pm 0.8$  mmol/l, **RA** =  $6.9 \pm 1.0$  mmol/l,  $P = 0.436$ ). While there were no differences in frequency of post-exercise hypoglycemia, the duration (105 minutes versus 48 minutes) and severity (AUC of 112 U·min versus 59 U·min) of hypoglycemia was greater after **AR** in comparison to **RA**.

**Conclusions/interpretation:** Performing resistance exercise before aerobic exercise may reduce the risk of hypoglycemia both during and post-exercise for individuals with type 1 diabetes.

**Key words:** continuous glucose monitoring, hypoglycemia, resistance exercise, aerobic exercise, type 1 diabetes

### **Abbreviations**

AR	aerobic then resistance exercise session
CGMS	continuous glucose monitoring system
CSII	continuous subcutaneous insulin infusion
GH	growth hormone
MDI	multiple daily injections
RA	resistance then aerobic exercise session
$\dot{V}O_{2\text{peak}}$	peak oxygen consumption
8RM	8 repetition maximum

## INTRODUCTION

Regular physical activity is associated with greater longevity and lower frequency and severity of diabetic complications in individuals with type 1 diabetes [1, 2]. Which type of exercise to recommend for this population, however, is still a matter of debate. Intervention studies of aerobic exercise training have failed to find consistently positive effects on blood glucose control, as measured by HbA<sub>1c</sub> [3]. Some studies examining the chronic effects of resistance exercise training (a form of anaerobic activity) on blood glucose control in type 1 diabetes have found reductions in HbA<sub>1c</sub> [4, 5] but both were very small (n=8-10). It has recently been shown that including short bursts of intense activity, where anaerobic metabolism plays a major role in providing fuel, may assist in preventing hypoglycemia both during and up to 2 hours post-exercise in individuals with type 1 diabetes [6-9]. However, two small studies using continuous glucose monitoring systems (CGMS) have suggested that the risk of nocturnal hypoglycemia after such exercise sessions may also be high [10, 11] and perhaps even greater than that associated with moderate aerobic activity [11].

We previously found that aerobic exercise causes a more rapid decrease in blood glucose and therefore a greater need for carbohydrate supplementation during exercise than resistance exercise [12]. We are unaware of previous research examining the acute effects of combining these exercise modalities in a single session, or whether the order in which they are undertaken makes a difference in patients with type 1 diabetes. This research, therefore, seeks to examine the effects of a combined aerobic and resistance exercise program, and the order in which the exercises are performed, on blood glucose both during and post-exercise (as measured by CGMS) in individuals with type 1 diabetes.

In individuals without diabetes, an increased reliance on lipids as a fuel source has been demonstrated during aerobic exercise when it is performed immediately subsequent to resistance exercise [13]. Similarly, growth hormone (GH) response to resistance exercise has been shown to be attenuated by prior endurance exercise [14]. We therefore hypothesized that performing resistance exercise prior to aerobic exercise would lead to less of a decline in blood glucose during exercise in individuals with type 1 diabetes than when the opposite order of exercise was performed. As performing resistance exercise first may result in less of a reliance on carbohydrate as a fuel source during exercise, we anticipated that less nocturnal hypoglycemia would be found after the exercise session where aerobic exercise was preceded by resistance exercise.

## **METHODS**

### **Participants**

The experimental protocol was approved by the Research Ethics Boards of the University of Ottawa and the Ottawa Hospitals. Fit (regularly performing both aerobic and resistance exercise at least three times per week), lean, non-smoking, adults with type 1 diabetes mellitus (as defined by the 2008 Canadian Diabetes Association guidelines)[15] were recruited to take part in the study. Participants had normal resting and exercise 12-lead electrocardiograms, fair to good control of their diabetes ( $HbA_{1c} \leq 9.0\%$ ) and no evidence of diabetic complications. Insulin was administered either by multiple daily injections (MDI) or by continuous subcutaneous insulin infusion (CSII).

## **Experimental Design**

The research took place in the Human and Environmental Physiology Research Unit at the University of Ottawa. After being informed of the purpose, protocol, and possible risks of the study, participants gave consent and completed physical activity readiness questionnaires (PAR-Q, AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire). OneTouch® Ultra® glucometers (Lifescan, Johnson & Johnson, Milpitas, CA) and test strips (with identical code) were provided for capillary glucose tests. On a separate visit, participants underwent an incremental workload test on a treadmill with a monitored electrocardiogram (Quinton Q4500, Quinton, Bothell, Washington) to determine peak oxygen consumption ( $\dot{V} O_{2\text{peak}}$ ).  $\dot{V} O_{2\text{peak}}$  was determined by measuring expired oxygen and carbon dioxide concentrations (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry, Pittsburgh, PA). Strength tests were performed to determine the maximum weight that participants could lift 8 times (8 RM) while maintaining proper form for each of the following exercises: chest press, leg press, seated row, leg curl, shoulder press and lat pulldown. A blood sample was drawn for determination of HbA<sub>1c</sub>, which was measured by automated heterogeneous immunoassay with latex enhanced turbidimetric detection on a Roche Cobas Integra 800 analyzer (Roche Diagnostics Corporation, Indianapolis, IN).

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

At least 24 hours prior to each experimental session, the sensor of the Continuous Glucose Monitoring System® (CGMS System Gold™, Medtronic, Northridge, CA) was inserted subcutaneously either in the abdomen, or in the upper gluteal area. The CGM

System Gold™ does not have a real-time display of glucose values, and would therefore not alter participant behavior. Training on the calibration and operation of the CGM units was provided. Participants were instructed to perform capillary glucose tests and calibrate the CGM unit 4 times daily using the glucometer provided. On the third day, at least 24 hours after the end of exercise, sensors were removed by the participant and the monitoring units subsequently retrieved by the investigators. Data were downloaded using a Medtronic com-Station and Minimed Solutions Software version 3.0 (Medtronic, Northridge, CA).

Participants maintained detailed diaries of food intake and insulin administration while wearing the CGM sensor. They were asked to eat the same breakfast, same lunch and same supper each day they were being studied, and to keep their insulin doses the same each of these days to the greatest extent possible. Participants were asked to avoid exercise for at least 24 hours before inserting the sensor (therefore at least 48 hours before each study exercise session), and to avoid caffeine and alcohol during the three days of CGM measurement.

### ***Experimental sessions***

Participants were asked to arrive at the lab at 1600 h. Tests for female participants on oral contraceptives were scheduled during the high exogenous hormone (active pill consumption) phase. Intravenous catheters were inserted soon after arrival. Each participant performed two experimental sessions in random order, under thermoneutral (21°C, 20% relative humidity) conditions, separated by at least 5 days:

- 1) Resting control session: 45 minutes of resting in an upright seated position.

- 2) Aerobic exercise session: 45 minutes of treadmill running at 60% of  $\dot{V}O_{2\text{peak}}$ .
- 3) Resistance exercise session: Three sets of 8 repetitions at the maximum weight that could be lifted 8 times (8 RM) of supine bench press, leg press, shoulder press, abdominal crunches, lat pulldown, leg curl and seated cable row with 90 seconds rest between sets (total exercise duration ~ 45 minutes).
- 4) Aerobic exercise before resistance exercise session (**AR**): A 45 minute bout of moderate aerobic exercise (treadmill running at 60%  $\dot{V}O_{2\text{peak}}$ ) followed by a 45 minute bout of resistance training (same as above)).
- 5) Resistance exercise before aerobic exercise session (**RA**): The same exercises performed in session 4) were performed again with the resistance exercise bout taking place before the aerobic exercise.

All sessions were immediately followed by one hour of monitored resting recovery in the laboratory. This paper presents the data from sessions 4 and 5.

## Measurements

### *Pre-exercise glucose and insulin adjustments*

On the days exercise was scheduled (day 2 of each 3-day monitoring period), participants administering insulin by MDI were asked to decrease their long or intermediate-acting doses by 10% and those using CSII were asked to decrease their basal rates by 50% one hour before exercise. A further 25% decrease in basal rate was made for those using CSII if their capillary glucose was measured at or below 5 mmol/l upon arrival at the laboratory. Adjusted basal rates were maintained until the end of exercise.

Standardized snacks (Glucerna Chocolate Graham Snack Bars (Abbott Laboratories, Abbott Park, IL)) were provided and consumed at 1600 h each day of glucose monitoring.

Prior to the start of exercise, participants were required to have blood glucose levels between 5.5 and 13.9 mmol/L. Capillary glucose tests were performed upon arrival at the laboratory, 30 minutes prior to exercise and immediately prior to exercise. If capillary glucose levels were less than 4.5 mmol/l participants were provided with 32 g of glucose in tablet form (Dex4 ®, AMG Medical, Montreal, Canada) before checking levels again 15 minutes later. Similarly, if initial readings were between 4.5 and 5.4 mmol/l, participants were provided with 16 g of glucose. If a level of at least 5.5 mmol/l was not achieved, these steps were repeated. Venous blood and the study glucometers were used to monitor glucose levels during exercise. When glucose levels were measured below 4.5 mmol/l, exercise was interrupted and participants were provided with 16 g of glucose in tablet form. A capillary glucose test would then be performed every 10 minutes and an additional 16 g of glucose provided when necessary until a level of at least 5.5 mmol/l was achieved and exercise could resume.

### ***Blood sampling and analyses***

Venous blood samples were collected at baseline, 5, 10, 15, 30, 45, 50, 55, 60, 75, and 90 minutes during exercise (participants changed modalities at 45 minutes) and at 5, 10, 15, 20, 30, 40, 50 and 60 minutes post-exercise through the IV catheter. Blood was drawn using 5 ml sterile plastic syringes and transferred immediately into 5.4 ml serum (no additive) and plasma (K<sub>2</sub>EDTA) BD Vacutainer® tubes (BD, Franklin Lakes, NJ, USA). One ml of blood was mixed with 1 ml of aprotinin (Trasylol) solution in 16X100

borosilicate tubes for subsequent analysis of glucagon. Samples collected in serum tubes sat at room temperature to clot for 20 minutes before centrifugation at 4000 rev/min for 4 minutes. Tubes containing aprotinin and K<sub>2</sub>EDTA were mixed by inversion and centrifuged immediately. Serum and plasma aliquots were transferred into 1.5 ml microcentrifuge tubes and stored at -80°C until analyzed.

The hexokinase timed endpoint method was used to determine plasma glucose concentration during each sampling time point for all 12 participants. Analysis was performed on the Beckman Coulter Unicel <sup>®</sup>DxC600 Synchron<sup>®</sup> Clinical Analyzer (Beckman Coulter Inc., Fullerton, CA, USA) using the SYNCHRON CX<sup>®</sup> Systems GLUCOSE reagent (Cat#442640).

Due to budgetary constraints we were only able to perform analyses for NEFA, growth hormone (GH), insulin, glucagon and cortisol on a subsample of six participants. The six participants were representative of the overall study population in terms of gender, age, weight, and fitness. Plasma NEFA levels were measured using an Enzymatic Colorimetric Method with RANDOX NEFA reagent (Randox Laboratories, Antrim, UK). Serum cortisol and (GH) concentrations were determined by enzyme immunoassay (Alpco Diagnostics <sup>™</sup>, Salem, NH, USA). A synthetic insulin enzyme immunoassay kit (Alpco Diagnostics <sup>™</sup>, Salem, NH, USA) was used to determine plasma insulin levels and aprotinin-treated plasma samples were analyzed for glucagon with a glucagon enzyme immunoassay kit (Alpco Diagnostics <sup>™</sup>, Salem, NH, USA). The sensitivity of the EIA kits was 11.04 nmol/l, 1.13 nmol/l, 32.99  $\mu$ mol/l, and 50ng/l respectively for cortisol, GH, insulin and glucagon. We did not have the budget or the laboratory equipment necessary to perform catecholamine assays.

### *Statistical Analyses*

Exercise and recovery periods were examined separately for all hormones and metabolites. Differences in glucose, cortisol, NEFA, GH and insulin were compared between conditions using two-way repeated measures ANOVA with the factors of time (5, 10, 15, 30, 45, 50, 55, 60, 75 and 90 minutes during exercise and 5, 10, 15, 20, 30, 40, 50, and 60 minutes during recovery) and condition (**RA** or **AR**). The glucagon assays failed to produce consistent results and were therefore excluded from the analysis. Paired sample t-tests were used to perform pair-wise post-hoc comparisons between conditions for each time point to examine within condition changes from baseline (during both exercise and recovery), and changes from the end of exercise throughout recovery. The level of significance was set at 0.05 and alpha level was adjusted during multiple comparisons to maintain the rate of Type 1 error at 5% during the Holm-Bonferroni post-hoc analysis.

CGM data were grouped and summarized for the following time periods: 24 hours and overnight (2400 to 0600h) pre-exercise, as well as 24 hours and overnight post-exercise. Hypoglycemia was defined as any value of less than 3.5 mmol/l detected by the CGM sensor and values above 10.9 mmol/l were categorized as hyperglycemic. The amount of time spent in hypoglycemia, euglycemia, and hyperglycemia for the pre-determined periods as well as the area under the curve (AUC) for all time spent both hypo- and hyperglycemic was determined along with the maximum, minimum and mean blood glucose for each time period. AUC was calculated by multiplying the absolute distance above or below threshold in mmol/l by the duration of the episode. All of these variables were then compared between exercise conditions, and pre- and post-exercise values were

compared within conditions using related samples Wilcoxon Signed Ranks tests. These tests were also used to examine differences in insulin and carbohydrate intake (calculated from the details provided in the participants' food and insulin diaries) between days within exercise conditions (day 1 versus day 2), and between exercise conditions (days one through three). Pearson correlation analyses were performed comparing capillary glucose values recorded by the participants during non-exercise periods to CGM data in order to assess the accuracy of the sensors throughout each 3 day measuring period. All analyses were performed using SPSS 18.0 for Windows (SPSS Inc. Chicago, IL, USA). Data are presented as means  $\pm$  SD.

## **RESULTS**

Participant characteristics are presented in Table 1. Both female participants used monophasic oral contraceptive pills. The Pearson correlations between capillary glucose readings taken during non-exercise periods and sensor readings over the monitoring period were 0.95 and 0.91 for the **AR** and **RA** sessions respectively ( $P < 0.001$ ). There were no statistically significant differences between conditions with respect to measures of hypoglycemia and hyperglycemia (number of excursions, time, AUC) as well as mean, maximum and minimum glucose either on the night before or 24 hours prior to exercise.

### **Exercise**

All means ( $\pm$ SD) for glucose, NEFA, insulin, cortisol and GH can be found in Table 2.

### ***Plasma glucose:***

A significant effect of time ( $P=0.001$ ) and an interaction of condition and time ( $P=0.004$ ) were found in examining plasma glucose levels (Figure 1). Differences between conditions were not significant at baseline. During the first 45 minutes, the aerobic exercise performed in the **AR** condition caused a substantial decline in blood glucose (from  $9.1\pm 2.4$  at baseline to  $5.5\pm 2.4$  mmol/l at 45 minutes;  $P<0.01$ ). Glucose then increased during resistance exercise, resulting in levels that were not lower than baseline by the end of exercise. Conversely, in the **RA** condition, no significant changes from baseline were measured during the resistance exercise portion. After the change in exercise modality in **RA**, glucose levels measured at the end of aerobic exercise were not significantly different from baseline after adjustment for multiple comparisons. Glucose was significantly lower in the **AR** condition as compared to the **RA** condition between 30 and 50 minutes (the last 15 minutes of the first exercise modality, and the first 5 of the second) of exercise.

### ***NEFA, insulin, cortisol, and GH:***

An interaction of time and condition was found with respect to NEFA (Figure 2A) levels and plasma insulin (Figure 2B) throughout exercise ( $P=0.008$  and  $0.01$  respectively). NEFA was higher in **AR** throughout most of the second exercise modality but these differences were no longer significant after adjustment for multiple comparisons. Intergroup differences and changes from baseline within each condition were not significant for plasma insulin. There was no significant effect of condition or time with respect to cortisol levels (Figure 2C) although decreases ( $p<0.05$  but not significant after

adjustment for multiple comparisons) in cortisol levels were seen in both groups. An effect of time ( $P<0.01$ ) and an interaction of time and condition ( $P=0.003$ ) were found during exercise in GH concentrations (Figure 2D). There were no differences between conditions at baseline or during the first 45 minutes of exercise. GH increased in **RA** between 45 and 90 minutes of exercise, while decreasing in **AR** resulting in higher GH levels in **RA** during this time ( $p<0.05$  for all time points between 50 and 90 minutes) which were not statistically significant after adjustment for multiple comparisons.

### **Recovery**

All means ( $\pm$ SD) for glucose, NEFA, insulin, cortisol and GH can be found in Table 3.

#### ***Plasma glucose:***

During recovery, there was a significant effect of time ( $P<0.01$ ) for the change in plasma glucose, but no effect of condition. Significant increases in plasma glucose from the end of exercise were seen throughout recovery in the **AR** condition whereas no significant changes were observed after the **RA** exercise session.

#### ***NEFA, cortisol, GH and insulin:***

An interaction of time and condition was also found with respect to NEFA levels and insulin levels during recovery ( $P<0.001$  and  $0.023$  respectively). NEFA levels increased from the end of exercise in both groups within the first 5 minutes, and continued to increase throughout recovery in **AR** but not in **RA** (Figure 2A). Mean NEFA values

were higher in **AR** at the end of recovery but intergroup differences were not statistically significant. While there was a significant effect of time for plasma insulin levels during the recovery period ( $P < 0.001$ ) changes from baseline within each condition were not statistically significant. A significant effect of time was also found for cortisol throughout the recovery ( $P = 0.002$ ). Cortisol levels (Figure 2C) were higher in **RA** during recovery, but these failed to retain significance after adjustment for multiple comparisons. An effect of condition ( $P = 0.043$ ), time ( $P < 0.001$ ) and an interaction of condition and time ( $P < 0.001$ ) were found with respect to GH throughout recovery (Figure 2D). GH decreased throughout recovery in both conditions ( $P < 0.05$  for changes from the end of exercise at 15, 20 and 30 minutes for **AR** and at 15, 30, 40, 50, and 60 for **RA** - not significant after adjustment for multiple comparisons) resulting in final values that were not different between conditions, or different from baseline within conditions.

#### ***Carbohydrate intake and insulin dosage:***

Participants using CSII made identical pre-exercise adjustments to their basal rates for both exercise sessions. Those using MDI had identical dosage of long-acting insulin between conditions, with the exception of one participant whose dosage was increased by 5U for the **RA** session. Eight out of 12 participants delivered the same bolus with the pre-exercise snack, while two had a slightly higher insulin dose prior to the RA session (0.1 and 3U respectively) and two had a slightly higher insulin dose prior to the AR session (0.2 and 2U respectively).

Total daily insulin doses (Table 4) did not differ significantly between conditions on the first two days, or between the first and second day. On the day after the exercise

testing session insulin intake was lower after the **AR** session (**AR**=36.1±16.3 U, **RA**=38.8±18.5 U, P=0.028). Carbohydrate intake was similar between conditions for all three days (Table 4). Ten out of twelve participants experienced sufficiently low blood glucose to require supplementation during the **AR** exercise session, as compared to only 6 out of 12 during the **RA** session. Of those requiring supplementation, 7 involved exercise interruptions during the **AR** session (average delay of 24 minutes per interruption) while only 3 participants required a break from exercise for supplementation (average break time of 9 minutes) during the **RA** session.

#### **CGM:**

In the **RA** condition, average maximum nocturnal glucose levels were significantly lower after exercise than the previous (non-exercise) night (pre-exercise= 9.5±3.0 mmol/l, post-exercise maximum=8.8±4.0 mmol/l; P=0.04). Within the **AR** condition there was a trend towards greater AUC post-exercise for nocturnal hypoglycemia (P=0.06). While the frequency of nocturnal hypoglycemic events did not differ between the two exercise sessions the lows experienced tended to be longer and more severe after the **AR** exercise session (Table 5).

## **DISCUSSION/CONCLUSIONS**

This study evaluated the effects of a combined resistance and aerobic exercise session, as well as the effects of exercise order, on blood glucose levels in individuals with type 1 diabetes. As we had anticipated, performing resistance exercise prior to aerobic exercise rather than the reverse resulted in reduced declines in glucose throughout exercise

in individuals with type 1 diabetes, and less need for carbohydrate supplementation. Post-exercise CGM data also showed that the duration and severity of hypoglycemic events was reduced when resistance exercise was performed prior to aerobic exercise.

Resistance exercise is a primarily anaerobic activity. Other types of high intensity exercise involving a contribution of anaerobic metabolism (e.g. exhaustive cycling at greater than 85% of  $\dot{V}O_{2\text{peak}}$ ) have been shown to increase the rate of glucose appearance to a greater extent than the rate of glucose utilization (seven and four times respectively) during exercise in type 1 diabetes [16]. This can result in glucose levels increasing during exercise to the point of producing post-exercise hyperglycemia if very intense exercise is sustained for 12 or more minutes [17]. Much shorter bouts of anaerobic activity (either in the form of intermittent 4-s sprints, or 10-s sprints prior to or post-moderate aerobic exercise) have been shown to attenuate declines in blood glucose both during and after exercise when combined with low intensity (40%  $\dot{V}O_{2\text{peak}}$ ) cycling [6-8]. Elevated glucose production from very high-intensity exercise is generally attributed to increased levels of circulating epinephrine (known to triple with short sprints [6, 8, 9] and increase up to 14 times its resting value [16] after 12 minutes of exhaustive cycling) augmenting glycogenolysis throughout exercise and the first 20 minutes of recovery [16, 17].

While our laboratory facilities were not equipped to measure catecholamine responses in our participants during the testing sessions, responses to high intensity exercise are known to be comparable [16, 18, 19] or slightly attenuated [17, 20] in individuals with type 1 diabetes when compared to their non-diabetic counterparts. Increases in catecholamines to three to four times resting values are known to occur during moderate-intensity resistance exercise in individuals without diabetes [21, 22] with

responses increasing in proportion to the exercise intensity [23]. It is probable that resistance exercise in our study produced increases in catecholamine secretion which could have persisted post-exercise for up to 20 minutes for epinephrine [7, 17] and 40 minutes for norepinephrine [7, 17]. This may have contributed to the attenuated rate of decline in blood glucose during the first 15 minutes of aerobic exercise in the **RA** condition, and to the increase in glucose seen during resistance exercise in the **AR** condition (Figure 1). The latter should be interpreted with caution, however, as most participants needed glucose supplements to prevent hypoglycemia during aerobic exercise in this session.

Of the hormones that we measured in this study, the most substantial differences between conditions occurred in GH. GH secretion was attenuated in our participants during the second 45 minutes of exercise in the **AR** condition. Similar attenuated GH secretion was found by Goto *et al.*[14] in non-diabetic individuals: an exercise protocol consisting of endurance exercise (one hour of cycling at 50%  $\dot{V}O_{2peak}$ ) followed by resistance exercise (4 sets of 10 repetitions with 90 seconds between sets) produced GH concentrations that were roughly one third of those produced by resistance exercise alone. The authors of the study surmise that the elevated NEFA levels produced by the aerobic activity may have played a role in suppressing GH secretion during resistance exercise. This would also be consistent with our results, where elevated levels of NEFA were found during the resistance exercise portion of the **AR** condition.

In our study, elevated GH could have contributed to the attenuated decline in blood glucose during the first 15 minutes of aerobic exercise in the **RA** condition, as higher levels of GH have been shown to decrease muscle glucose uptake and increase fat oxidation rates in individuals without diabetes [24]. This is also supported by a separate

study by Goto *et al.* [13] showing that prior resistance exercise resulted in lipid oxidation contributing almost twice as much to energy production during the first 30 minutes of subsequent submaximal ( $50\% \dot{V}O_{2\text{peak}}$ ) aerobic exercise compared to aerobic exercise alone. The authors surmised that the elevated epinephrine and GH levels produced by resistance exercise could have enhanced lipolysis through modification of the beta adrenergic pathway [13].

High intensity cycle ergometer exercise has been shown to increase blood lactate levels both during and up to 40 minutes post-exercise in individuals with type 1 diabetes [6, 7, 9, 16, 17, 25]. We are unaware of published data describing lactate responses to resistance exercise in this population. Resistance exercise protocols similar to the one used in our study have resulted in lactate concentrations up to four times those measured at rest, with levels remaining significantly higher than baseline until at least 30 minutes post-exercise in non-diabetic individuals [26]. As elevated lactate could serve to increase gluconeogenesis [7] it could have also been a contributing factor in the attenuated decline in glucose during the first 15 minutes of aerobic exercise in the **RA** condition, as well as the increases in post-exercise glucose in **AR**.

Previous studies have suggested that high intensity exercise may be associated with a greater frequency of nocturnal hypoglycemia in individuals with type 1 diabetes [10, 11]. Nocturnal hypoglycemia in our participants occurred with the same frequency post-exercise as it did on non-exercise nights. As nocturnal hypoglycemia has been identified as a risk inherent with intensive insulin therapy [27], it is possible that overnight hypoglycemia in our study was more related to insulin therapy than to exercise. It is noteworthy that hypoglycemic events occurring after the **AR** session tended to be longer

and more severe than those experienced in the **RA** session as demonstrated by a greater AUC. Studies using glucose clamp techniques have found that counter-regulatory responses to subsequent hypoglycemia can be blunted after exercise, even in the absence of significant changes in glucose during exercise [28, 29]. In addition, in nondiabetic individuals, hypoglycemia as mild as 3.9 mmol/l is sufficient to elicit a counter-regulatory response which can blunt neuroendocrine responses to subsequent hypoglycemia occurring within 24 hours [30]. As decreases in blood glucose were greater during the **AR** sessions (reaching a mean of  $5.5 \pm 2.4$  mmol/l as compared to  $6.9 \pm 3.1$  mmol/l in **RA**), it is plausible that subsequent responses to declining blood glucose could have been subject to a certain level of impairment post-exercise.

While having participants stay in the hospital overnight prior to the testing and providing standardized meals may have led to less variability in the data, we chose instead to use a study design that was more reflective of real-life conditions. Participants had complete control over their meals and insulin, but were asked to eat the same breakfast, lunch and dinner at the same time for every day of sensor wear and to match their insulin intake as closely as possible. Exercise took place at 1700 h when many individuals who work during the day opt to exercise, unlike several other studies where mid-morning exercise was performed [6-9, 16, 17].

The results of this study could have been strengthened by having a larger and/or more homogeneous sample. Due to both inter and intra-individual variability within our sample, it was difficult to find statistically significant differences where they may have otherwise existed. The ability to measure glucagon, catecholamines and lactate would have also been an asset, as they would have been useful in explaining some of the changes in

plasma glucose observed. Finally, as our participants were mostly male (10 out of 12) and all regularly active, the conclusions pulled from this study may not apply to women and inactive individuals with type 1 diabetes.

Our results nonetheless support the need to examine the role of resistance exercise in blood glucose management in type 1 diabetes more closely. Glucose responses may have been different if participants had performed the exercise at a different time of day as both hormone and exogenous insulin concentrations are likely to be different. In addition, participants in this study were fit, habitual exercisers with well-controlled diabetes. The effect of aerobic exercise may be less pronounced in unfit individuals exercising at the same relative intensity, as the activity would be at a lower absolute intensity. In non-diabetic subjects running at very high relative intensity, glucose production and catecholamine concentrations increase more in athletes than in physically-untrained individuals, resulting in hyperglycemia after exercise in the athletes, because glucose production does not fall as quickly as glucose utilization when exercise ends [31]. Further research on different subpopulations of individuals with type 1 diabetes, including those with lower levels of fitness and poorer glycemic control is warranted.

In summary, our findings suggest that individuals with type 1 diabetes who perform both resistance and aerobic exercise should consider performing their resistance exercise first, as doing so may attenuate declines in glucose during subsequent aerobic exercise. This order of exercise could lead to less of a reliance on glucose supplementation during exercise, and may also decrease the severity of potential nocturnal hypoglycemia. As responses to exercise depend on many factors, and can vary greatly both between and

within individuals, careful monitoring of blood glucose levels before, during and post-exercise should always be recommended.

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## **Tables and Figures<sup>3</sup>**

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<sup>3</sup> Tables 2 and 3 may be submitted as online appendices

**Table 1.** Participant characteristics

N	12 (10 male, 2 female)
Age (yrs)	31.8 ± 15.3
Height (m)	1.77 ± 0.07
Weight (kg)	79.2 ± 10.4
BMI (kg/m <sup>2</sup> )	25.3 ± 3.0
$\dot{V} O_{2\text{peak}}$ (mLO <sub>2</sub> ·kg <sup>-1</sup> ·min <sup>-1</sup> )	51.2 ± 10.8
HbA <sub>1c</sub> (%)	7.1 ± 1.1
Diabetes duration (yrs)	12.5 ± 10.0
Insulin delivery	Multiple Daily Injection = 5, Insulin pump = 7

Data are presented as mean ± SD. BMI, body mass index.  $\dot{V} O_{2\text{peak}}$ , peak oxygen consumption

**Table 2.** Changes in glucose, non-esterified fatty acids (NEFA), cortisol, insulin and growth hormone (GH) throughout exercise.

<b>Glucose (mmol/l)</b>	<b>Aerobic then Resistance (AR)</b>	<b>P (change from baseline in AR)</b>	<b>Resistance then Aerobic (RA)</b>	<b>P (change from baseline in RA)</b>	<b>P (AR vs RA)</b>
Baseline	9.1 ± 2.4		9.7 ± 3.9		0.655
5 min	8.5 ± 2.6	0.088	9.8 ± 4.1	0.765	0.399
10 min	7.8 ± 2.9	0.023	9.5 ± 4.0	0.554	0.213
15 min	7.2 ± 3.1	0.013	9.6 ± 4.0	0.838	0.091
30 min	5.9 ± 3.2	0.002*	9.2 ± 3.9	0.287	0.019
45 min	5.5 ± 2.4	<0.001*	9.2 ± 4.0	0.244	0.006
50 min	6.9 ± 1.7	<0.001*	9.5 ± 3.7	0.590	0.017
55 min	7.0 ± 2.0	0.009	9.6 ± 3.5	0.719	0.005
60 min	7.2 ± 2.0	0.011	9.4 ± 3.7	0.461	0.014
75 min	7.4 ± 2.4	0.040	8.0 ± 3.4	0.044	0.345
90 min	7.5 ± 2.6	0.068	6.9 ± 3.1	0.018	0.436
<b>NEFA (µmol/l)</b>					
Baseline	520 ± 298		407 ± 171		0.303
5 min	399 ± 220	0.025	380 ± 155	0.231	0.823
10 min	434 ± 272	0.111	341 ± 142	0.068	0.355
15 min	493 ± 335	0.682	340 ± 143	0.104	0.210
30 min	519 ± 370	0.986	378 ± 151	0.556	0.313
45 min	507 ± 290	0.827	328 ± 139	0.151	0.134
50 min	709 ± 446	0.213	290 ± 145	0.017	0.024
55 min	579 ± 271	0.577	317 ± 178	0.070	0.010
60 min	482 ± 187	0.666	361 ± 213	0.273	0.054
75 min	606 ± 187	0.748	391 ± 214	0.700	0.003*
90 min	531 ± 269	0.929	418 ± 164	0.782	0.106
<b>Cortisol (nmol/l)</b>					
Baseline	367.69 ± 117.36		403.46 ± 105.34		0.140
5 min	327.67 ± 102.82	0.009	388.19 ± 110.07	0.007	0.052
10 min	325.79 ± 99.14	0.027	364.99 ± 106.83	0.008	0.039
15 min	332.86 ± 61.62	0.504	351.70 ± 110.40	0.002*	0.716
30 min	383.50 ± 209.63	0.901	344.04 ± 131.00	0.053	0.772
45 min	333.54 ± 117.31	0.675	317.97 ± 139.22	0.041	0.879
50 min	375.13 ± 123.23	0.929	313.09 ± 153.10	0.089	0.585
55 min	369.10 ± 159.98	0.988	333.82 ± 201.03	0.377	0.805
60 min	369.56 ± 141.95	0.983	376.47 ± 251.68	0.793	0.964
75 min	343.05 ± 109.73	0.700	424.46 ± 281.55	0.870	0.552
90 min	365.24 ± 119.39	0.974	522.12 ± 380.07	0.522	0.298
<b>Insulin (µmol/l)</b>					
Baseline	60.96 ± 23.98		65.49 ± 12.91		0.670
5 min	66.74 ± 35.21	0.338	71.08 ± 15.36	0.093	0.771
10 min	75.31 ± 48.35	0.273	64.07 ± 12.16	0.712	0.624
15 min	69.67 ± 37.88	0.282	69.34 ± 13.83	0.272	0.980
30 min	77.02 ± 51.73	0.290	61.11 ± 11.32	0.433	0.521
45 min	59.06 ± 17.63	0.734	61.72 ± 10.06	0.337	0.811
50 min	53.49 ± 15.28	0.178	60.12 ± 7.90	0.167	0.449
55 min	53.54 ± 11.56	0.300	64.34 ± 11.51	0.780	0.222
60 min	52.41 ± 13.49	0.229	73.92 ± 24.44	0.517	0.120
75 min	48.18 ± 9.73	0.187	75.61 ± 31.20	0.538	0.109
90 min	47.32 ± 7.91	0.196	69.79 ± 24.88	0.745	0.094

<b>GH</b>	<b>(nmol/l)</b>				
Baseline	2.48 ± 1.85		3.10 ± 5.84		0.834
5 min	2.17 ± 1.76	0.436	6.96 ± 15.62	0.380	0.503
10 min	2.37 ± 2.18	0.816	4.82 ± 10.31	0.393	0.615
15 min	3.17 ± 2.38	0.309	5.19 ± 10.80	0.353	0.678
30 min	9.70 ± 9.05	0.101	5.93 ± 8.69	0.091	0.430
45 min	13.44 ± 10.81	0.069	12.07 ± 13.54	0.054	0.766
50 min	8.66 ± 8.10	0.155	11.34 ± 9.07	0.030	0.120
55 min	7.74 ± 7.45	0.195	12.50 ± 9.98	0.022	0.076
60 min	6.48 ± 5.73	0.211	13.28 ± 10.62	0.016	0.043
75 min	4.49 ± 4.33	0.381	16.25 ± 14.08	0.022	0.034
90 min	4.49 ± 4.47	0.397	15.12 ± 13.96	0.031	0.044

Data are presented as mean ± SD. \* denotes statistical significance after Holm-Bonferroni adjustment. Glucose: n=11. Non-esterified fatty acids (NEFA), insulin and growth hormone (GH): n=6. Cortisol: n=5.

**Table 3.** Changes in glucose, non-esterified fatty acids (NEFA), cortisol, insulin and growth hormone (GH) throughout recovery.

Glucose (mmol/l)	Aerobic then Resistance (AR)	P (AR change from baseline)	P (AR change from end-exercise)	Resistance then Aerobic (RA)	P (RA change from baseline)	P (RA change from end-exercise)	P (AR vs RA)
95 min	7.6±2.6	0.082	0.233	7.3±2.9	0.045	0.100	0.693
100 min	7.7±2.7	0.177	0.105	7.2±3.0	0.047	0.145	0.613
105 min	7.8±2.9	0.159	0.015	7.4±2.9	0.063	0.097	0.665
110 min	8.0±3.0	0.253	0.018	7.5±3.0	0.093	0.113	0.662
120 min	8.5±3.0	0.486	0.006*	7.7±3.3	0.138	0.130	0.527
130 min	8.9±3.0	0.792	0.004*	7.9±3.6	0.197	0.125	0.441
140 min	9.1±3.0	0.993	0.008*	8.0±3.6	0.219	0.142	0.357
150 min	9.1±2.9	0.962	0.014	7.9±3.5	0.232	0.264	0.375
<b>NEFA (µmol/l)</b>							
95 min	737±422	0.229	0.027	937±564	0.047	0.032	0.190
100 min	848±539	0.164	0.040	955±653	0.069	0.054	0.543
105 min	954±589	0.110	0.025	959±647	0.074	0.058	0.980
110 min	973±389	0.048	0.008	951±703	0.103	0.085	0.917
120 min	1217±533	0.034	0.012	940±796	0.164	0.149	0.264
130 min	1246 ±600	0.056	0.027	810±632	0.189	0.172	0.054
140 min	1229±647	0.078	0.042	705±540	0.268	0.253	0.043
150 min	1122±595	0.088	0.060	652±414	0.263	0.254	0.085
<b>Cortisol (nmol/l)</b>							
95 min	362.91±137.91	0.955	0.844	570.24±381.08	0.377	0.110	0.158
100 min	454.25±225.00	0.523	0.175	578.50±354.43	0.334	0.189	0.265
105 min	477.28±298.45	0.527	0.275	671.07±362.80	0.186	0.042	0.103
110 min	442.55±250.65	0.609	0.305	673.01±353.64	0.174	0.049	0.048
120 min	392.23±226.78	0.853	0.648	582.66±263.30	0.209	0.443	0.060
130 min	350.62±114.81	0.834	0.303	555.41±270.28	0.258	0.642	0.060
140 min	337.16±138.03	0.719	0.052	494.75±239.76	0.433	0.717	0.099
150 min	316.42±122.36	0.513	0.000*	467.61±231.03	0.536	0.537	0.109
<b>Insulin (pmol/l)</b>							
95 min	46.46±7.56	0.205	0.413	62.63±17.12	0.772	0.085	0.083
100 min	45.28±7.17	0.182	0.105	57.67±12.52	0.360	0.081	0.103
105 min	44.09±6.25	0.157	0.036	59.40±16.65	0.554	0.030	0.092
110 min	43.24±6.68	0.181	0.133	54.80±12.73	0.254	0.060	0.115
120 min	47.27±9.15	0.268	0.983	51.10±8.08	0.133	0.076	0.467
130 min	49.31±16.52	0.409	0.720	48.44±7.87	0.123	0.057	0.908
140 min	50.60±22.96	0.552	0.721	49.13±8.14	0.127	0.067	0.886
150 min	47.50±15.55	0.380	0.976	50.04±9.07	0.129	0.085	0.770
<b>GH (nmol/l)</b>							
95 min	4.22±4.47	0.464	0.089	14.92±14.49	0.034	0.799	0.049
100 min	4.23±4.94	0.490	0.484	12.14±11.40	0.032	0.064	0.032
105 min	3.38±3.91	0.663	0.017	9.61±9.63	0.044	0.036	0.047
110 min	2.80±3.19	0.855	0.031	7.88±7.55	0.086	0.053	0.041
120 min	2.09±2.49	0.801	0.037	5.71±5.94	0.173	0.038	0.054
130 min	1.22±1.29	0.283	0.055	3.77±3.61	0.673	0.044	0.047
140 min	0.77±0.72	0.111	0.060	3.05±3.04	0.976	0.044	0.063
150 min	0.63±0.67	0.087	0.057	2.56±2.64	0.810	0.048	0.079

Data are presented as mean ± SD. \* denotes statistical significance after Holm-Bonferroni adjustment. Glucose: n=11. Non-esterified fatty acids (NEFA), insulin and growth hormone (GH): n=6. Cortisol: n=5.

**Table 4** – Carbohydrate intake and total daily insulin doses.

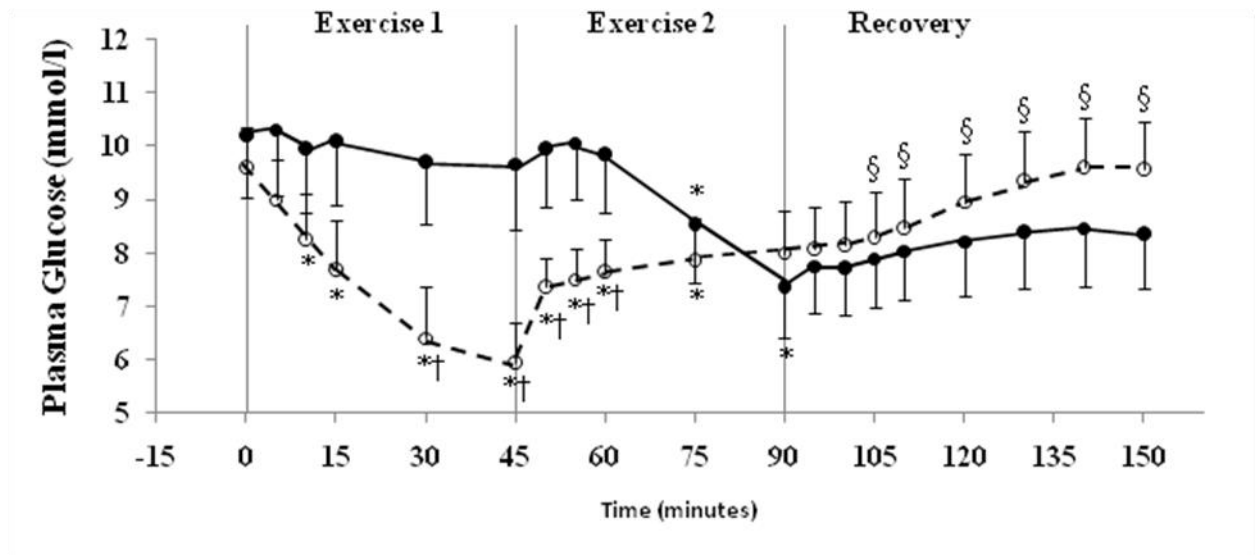
	<b>Aerobic then Resistance (AR)</b>			<b>Resistance then Aerobic (RA)</b>		
	<b>Day 1</b>	<b>Day 2</b> Exercise	<b>Day 3</b>	<b>Day 1</b>	<b>Day 2</b> Exercise	<b>Day 3</b>
<b>Mean carbohydrate intake (grams)</b>	267±97	304±106	156±48	276±108	308±110	165±63
<b>Mean daily insulin intake (U)</b>	48±19	49±21	36±16	50±19	48±21	39±18*

Data were from detailed food and insulin diaries, and are presented as mean ± SD (n=12). Exercise sessions were performed on day 2 starting at 1700h. Day 3 does not include the evening meal. \* denotes statistically significant difference (P<0.05) when AR is compared to RA for the same day.

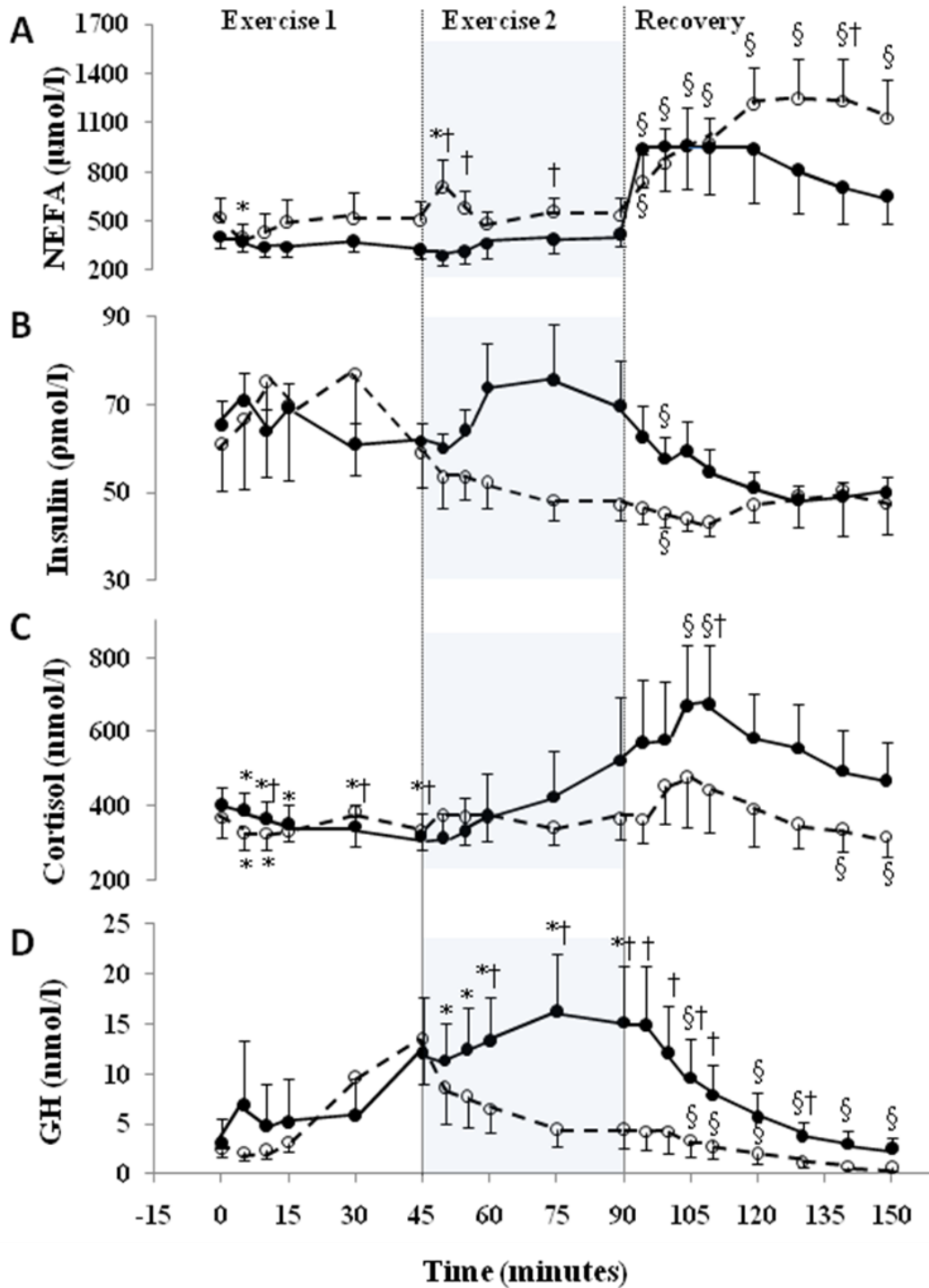
**Table 5** – Summary of overnight continuous glucose monitoring data for the night after exercise

	Aerobic then Resistance	Resistance then Aerobic
Number of participants experiencing nocturnal hypoglycemia (< 3.5 mmol/l)	3/12 (25%)	4/12 (30%)
Total number of hypoglycemic episodes	5	6
Mean duration of hypoglycemia per episode (minutes)	105±116	48.0±68
Mean area under the curve for hypoglycemia (glucose < 3.5 mmol/l) per episode (mmol·min)	112±145	70.9±110
Mean overnight glucose (mmol/l)	6.3±2.4	6.7±3.1

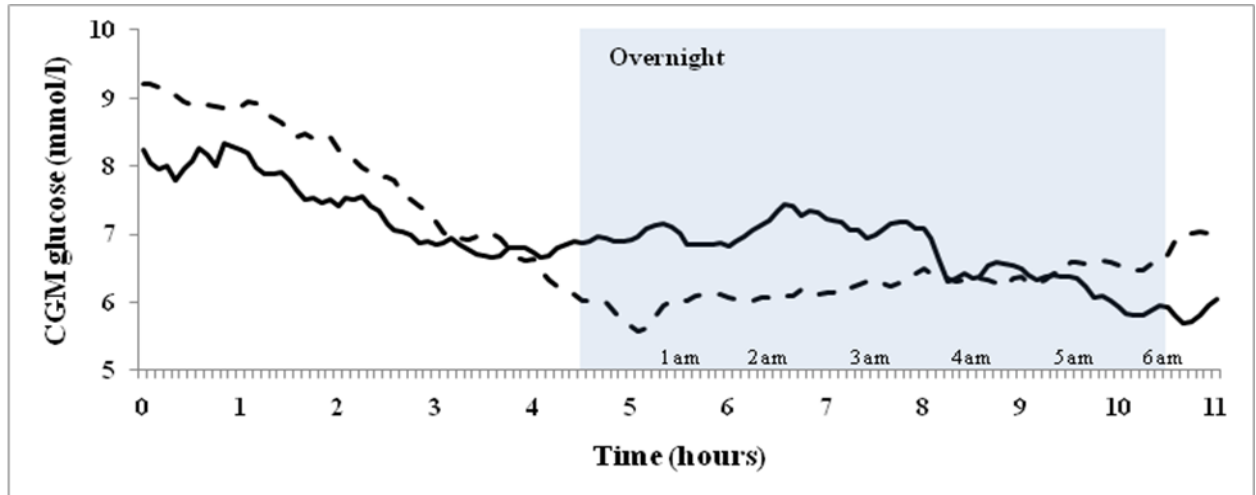
n=12. Data are presented as mean ± SD



**Figure 1** – Plasma glucose during exercise and recovery for aerobic exercise performed before resistance exercise (**AR** – dashed line with open symbols  $\circ$ ) and resistance exercise performed before aerobic exercise (**RA** – solid line with closed symbols  $\bullet$ ). Data are presented as means and error bars represent SE. (n=11). \* denotes difference from baseline during exercise where  $P < 0.05$ . § denotes change throughout recovery from end-exercise level where  $P < 0.05$ . † denotes difference between conditions where  $P < 0.05$ . Data are presented as mean  $\pm$  SE.



**Figure 2** – Effect of 90 minutes of exercise on (A) non-esterified fatty acids (NEFA) (n=6), (B) growth hormone (GH) (n=6), (C) insulin (n=6) and (D) cortisol (n=5) levels when aerobic exercise is performed before (AR – dashed line with open symbols ○) or after (RA – solid line with closed symbols ●) resistance exercise. Results are expressed as means ± SE. \* denotes difference from baseline during exercise where p < 0.05. § denotes difference from end-exercise level where p < 0.05. † denotes difference between conditions where p < 0.05.



**Figure 3** - Mean glucose (n=12) as measured by continuous glucose monitoring from 1 to 12 hours post-exercise following aerobic exercise performed before resistance exercise (solid line, **AR**) and resistance exercise performed before aerobic exercise (dashed line, **RA**).

## **6.0 GENERAL DISCUSSION AND CONCLUSIONS**

## 6.1 Discussion

When compared to aerobic exercise, resistance exercise on its own is associated with lesser declines in blood glucose during exercise. The lower amount of glucose supplementation needed during the resistance exercise protocol, along with the less pronounced counter-regulatory responses, also led to less of an increase in blood glucose post-exercise as compared to the aerobic exercise trial where hyperglycemia was found in the 3<sup>rd</sup> to 6<sup>th</sup> hours post-exercise. For individuals who partake in physical activity on an almost daily basis, higher than desirable glucose levels for 3 to 4 hours per day would probably have a negative impact on HbA<sub>1c</sub> levels. The information gleaned from this research program may, in part, explain why exercise interventions involving resistance exercise have had beneficial effects on blood glucose control in type 1 diabetes while aerobic exercise interventions generally have not.

Differences in blood glucose response during the single modality exercise sessions were probably not due to any of the hormones or metabolites that we measured (NEFA, insulin, cortisol, growth hormone) as no significant differences among the conditions were found with respect these biological or metabolic markers. Based on findings from past research, we can infer that increases in catecholamines and blood lactate, which were most likely greater with resistance exercise than aerobic exercise, probably assisted in decreasing fluctuations in blood glucose during and after resistance exercise when compared to aerobic exercise. Nocturnal hypoglycemia was more frequent after resistance exercise, probably due to a need to replenish glycogen stores, but episodes were brief and mild in comparison to those that occurred after aerobic exercise, as demonstrated by mean AUC being lower (albeit not statistically significant) after the resistance exercise trial.

If resistance exercise is performed prior to aerobic exercise (rather than aerobic exercise being performed on its own), blood glucose levels decline less quickly during aerobic activity, leading once again to a lower need for glucose supplementation. Slightly greater levels of growth hormone may be partly responsible for the lesser decline in blood glucose, due to a greater reliance on lipid oxidation to fuel activity. While we did not have the opportunity to measure them in this study, higher levels of catecholamines and lactate resulting from resistance exercise could have also been responsible for the attenuated declines in blood glucose during aerobic activity when it was performed subsequent to resistance exercise. In spite of greater amounts of work being performed when resistance exercise preceded aerobic exercise, there was no increase in post-exercise nocturnal hypoglycemia.

If both exercise modalities are to be combined in a single exercise session, our data would indicate that performing resistance exercise first has several benefits. Glucose levels during exercise have a tendency to stay in a safer range and not drop as quickly if resistance exercise is performed prior to aerobic exercise rather than performing aerobic exercise first. Similar to the situation when aerobic exercise is performed on its own, performing aerobic exercise first led to a greater need for glucose supplementation during exercise, and again, a trend towards higher post-exercise blood glucose.

Where aerobic exercise was performed first, the resulting higher NEFA levels may have suppressed growth hormone release. As a result, higher growth hormone levels were present during aerobic activity when it followed resistance activity, which probably led to a greater reliance on lipids to fuel the exercise, resulting in smaller decreases in blood glucose. Post-exercise nocturnal hypoglycemia, while occurring with a similar frequency

after both exercise conditions, tended to be of greater duration and severity when aerobic exercise was performed before resistance exercise. This may be due to the greater declines in blood glucose occurring during this exercise condition causing blunted responses to late post-exercise hypoglycemia, or to a greater reliance on carbohydrate as a fuel source during exercise leading to an increased need to replenish stores.

In spite of our findings that resistance exercise not only results in less of a decline in blood glucose during exercise but might also have a protective effect against hypoglycemia during aerobic exercise in regularly active individuals with type 1 diabetes, there are several other well-documented approaches to preventing dangerous declines in blood glucose levels during exercise. When exercise is planned in advance, decreases in insulin intake (either as a reduced basal rate for those using CSII (60, 72), a decrease in long or intermediate acting insulin injection, or a smaller insulin bolus with any snack or meal consumed within the hours pre-exercise (58)) can help decrease the risk of hypoglycemia. The consumption of a carbohydrate snack or supplement before, during, or after activity has also been shown to decrease the risk of hypoglycemia (74-78). Regardless of the approach adopted, individuals with type 1 diabetes taking part in physical activity should monitor their blood glucose levels frequently in order to ensure that a safe and healthy level is maintained.

## **6.2 Limitations**

Due to the difficulty of finding willing participants who met all of the inclusion and exclusion criteria, the sample for this study was relatively heterogeneous. The ages of the participants ranged from 17 years to 62 years, which would have affected cortisol, growth

hormone, and catecholamine responses to exercise. While our participants were all regularly physically active, there was a broad range of fitness levels with aerobic capacity varying from  $33.1 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in our oldest participant to  $65.1 \text{ ml}\cdot\text{kg}^{-1} \text{ min}^{-1}$  in one of the youngest. We also had both males and females, HbA<sub>1c</sub> levels varying from 5.5 % to 9.0%, and a mix of insulin pump and multiple daily injection users. In many instances, especially with respect to our blood analyses, there were fairly clear trends but we failed to find statistically significant differences, due to the large amount of both intra- and inter-individual variability in the data.

As only two females took part in the research program, it is difficult to say whether or not the results of this research can be generalized to physically active women with type 1 diabetes. There is evidence from individuals without type 1 diabetes, that hormonal responses to exercise might be very different in females, with catecholamine response to both aerobic (142), and resistance exercise (44) as well as lactate response to resistance exercise being lower in females when compared to males (44). As catecholamines release and lactate accumulation may help in providing a protective effect against hypoglycemia both during and after exercise, it is possible that females with type 1 diabetes will be at a higher risk of exercise-induced hypoglycemia both during and after activity. However, using euglycemic clamp techniques Glassetti et al. (143) found that, in spite of lower neuroendocrine responses and higher lipolytic response to aerobic exercise in females compared to males with type 1 diabetes, no differences in endogenous glucose production or glucose infusion rates to maintain euglycemia existed between the sexes. This may indicate that the risk of hypoglycemia during aerobic exercise may not differ between males and females with type 1 diabetes. Further research will be required in order to

examine this question more fully, especially with respect to resistance exercise where there is currently an almost complete lack of information.

It is also difficult to determine from our data whether the age of the individual will affect their risk of hypoglycemia during exercise. Growth hormone responses to exercise are known to decrease with increasing age (41), as are catecholamine responses to anaerobic exercise (44) in nondiabetic individuals. This may lead to less lipolysis during submaximal exercise and a lower rate of endogenous glucose production with higher intensity activity. Meanwhile, decreases in physical fitness, muscle mass and overall metabolic rate that occur with age (129) will lead to lower overall energy requirements to fuel exercise and consequently less of a reliance on plasma glucose. The effect of age on counterregulatory responses to both aerobic and resistance exercise in individuals with type 1 diabetes will need to be examined in more detail before this question can be answered adequately.

The fitness level of individuals with type 1 diabetes may also impact their risk of hypoglycemia both during and after exercise. In individuals without type 1 diabetes, higher aerobic fitness is associated with a greater reliance on lipids as a fuel source during submaximal aerobic exercise due to lower catecholamine responses, increases in blood flow (and consequently oxygen delivery), a greater number of mitochondria within the muscles, as well as an overall increase in oxidative enzymes (30). With less of a reliance on carbohydrate as a fuel source during submaximal exercise, it seems plausible that fitter individuals with type 1 diabetes would have a lower risk of exercise-induced hypoglycemia. A study by Ebeling et al (144), however, found that athletes with type 1 diabetes, while having lower insulin requirements than their non-athletic counterparts, had

similar rates of glucose uptake and oxidation during exercise, possibly indicating that the risk of hypoglycemia during exercise may be the same for both fit and unfit individuals with type 1 diabetes. Energy expenditure will also be higher in fitter individuals during the same relative intensity exercise session, which could potentially lead to a similar, if not higher, absolute amount of carbohydrate oxidized, and consequently a greater risk for low blood glucose levels.

Where higher intensity exercise or resistance exercise is concerned, trained individuals without diabetes tend to have a greater catecholamine response during these activities leading to greater rates of hepatic glucose production during exercise (36). In theory, this may have a greater protective effect during exercise for individuals with type 1 diabetes as glycogenolysis would be increased. It could, however, also lead to a greater risk of late post-exercise hypoglycemia when glycogen stores need to be replenished. Whether or not catecholamine responses are increased to the same extent in fit versus unfit individuals with type 1 diabetes remains to be examined, and the question as to whether or not the fitness level of individuals with type 1 diabetes affects their risk of exercise-related hypoglycemia with high intensity exercise (both during and after the exercise session) should be explored further. As the participants in this research program were regularly physically active and, for the most part, very fit, the applicability of the outcomes to less fit individuals with type 1 diabetes may be limited.

It was also not possible for us to measure catecholamine and glucagon levels during the study. While we had intended to measure glucagon and took all the steps necessary in handling (treating with aprotinin) and storing the blood samples, the assay kits selected for the analysis either could not detect any glucagon in our samples, or yielded highly

inconsistent results. We therefore did not have adequate data to include these results in our statistical analyses. With respect to catecholamines, we unfortunately had neither the laboratory equipment nor the funding available to perform the necessary tests. This information would have been helpful in trying to explain some of the changes in glucose that were observed, as these hormones have important counter-regulatory functions with respect to hypoglycemia. They also both play an important role in glucose metabolism during exercise.

Continuous glucose monitors are useful tools, but are nonetheless not without their imperfections. These systems are limited to reading values between 2.2 and 22.2 mmol/l. On a few occasions the sensor values hit high or low plateaus for a stretch of time. The full severity of these hypoglycemic and hyperglycemic events would then have been underestimated. We also had three instances of sensor and/or monitor failure, where no valid data was collected. In addition, there is a certain amount of variability in the delays in sensor measurement, but these would not have overly impacted our outcomes, as we were generally examining fairly large (minimum 6 hours) windows of time.

While we requested that participants provide us with as much detail as possible, the quality of the food diaries varied greatly. Some participants measured and weighed their foods precisely, while others were less detailed about their intake, in spite of being encouraged to be more accurate and precise. With any type of self-report there is always the possibility of participants failing to report events that might be seen as undesirable. In the case of this study, this would probably be in the form of either additional carbohydrate intake or eating different foods than those called for. This may have resulted in

statistically significant differences between conditions with respect to insulin and carbohydrate intake where we have currently only found trends.

### **6.3 Relevance to Population Health**

An inequity seems to exist with respect to the distribution of the incidence of type 1 diabetes, with less wealthy areas demonstrating higher rates of onset (145-148). While the exact cause of the auto-immune disorder that leads to type 1 diabetes is currently unknown, various infectious diseases and environmental factors have been proposed as instigators (145, 147, 149-151). It is generally accepted that type 1 diabetes has a genetic component (150, 152), however the distribution of the gene thought to be responsible does not differ from areas of higher and lower incidence of the disease (145, 147, 149-152). This would indicate that external factors such as lifestyle and environment are equally important in its onset. In addition, morbidity and mortality rates in patients with type 1 diabetes tend to vary by socio-economic status and ethnicity, with failures in blood glucose management often being attributed to social and economic deprivation (153-156).

With these factors considered, it is important to make all of the tools and treatments for the management of blood glucose in type 1 diabetes mellitus accessible to all individuals. Exercise, which is related to lower rates of both macro- and microvascular complications (84-89) as well as increased longevity (4) in individuals with type 1 diabetes, can be a relatively inexpensive tool in blood glucose management. Unfortunately, individuals with type 1 diabetes list the fear of hypoglycemia as the biggest barrier to undertaking an exercise training regimen (5). The outcomes of this research program provide information that should assist in alleviating some of the fear related to

exercise-induced hypoglycemia by suggesting that resistance-type activities are associated with lesser declines in blood glucose during resistance exercise, and also during subsequent aerobic exercise, when both exercise types are performed in sequence.

The finding that resistance exercise is relatively safe to perform in terms of maintaining healthy blood glucose has important clinical implications for individuals with type 1 diabetes. Resistance exercise has been shown to increase muscular strength (21), improve lipid profiles (21), lower insulin requirements (21, 22) and decrease self-monitored blood glucose levels (21, 22) in individuals with type 1 diabetes. While there is currently limited data involving individuals with type 1 diabetes, resistance exercise is known to increase insulin sensitivity, increase bone mineral density and improve cardiovascular function in non-diabetic individuals (157). As type 1 diabetes is accompanied by a higher risk of myopathy (158) and complications associated with insulin resistance (158, 159), the benefits of resistance exercise to maintaining a healthy muscle mass and metabolism could be substantial.

#### **6.4 Future Research Consideration**

This research program examined the acute effects of aerobic and resistance exercise, both alone and in combination, on blood glucose levels in moderately to well-controlled, physically active individuals with type 1 diabetes. As it was discussed above, it is possible that these exercise sessions will have a different impact on women, older individuals, those who are not habitually active and/or physically fit or those who do not have good control of their blood glucose levels. At least two of the exercise interventions showing a positive effect of resistance exercise, alone or combined with aerobic exercise,

involved sedentary individuals or individuals with poor glucose control (22, 24). An examination of the acute effects of resistance exercise, alone or combined with aerobic exercise, in subgroups of different physical fitness or with different levels of pre-existing blood glucose control is warranted. In addition, interpreting any changes that might occur as a result of training in these individuals would be assisted by providing an examination of changes in glucose concentration during and after exercise both before and after an exercise training intervention.

In our testing sessions, aerobic and resistance exercise was performed in 45 minute blocks. Whether or not changes in blood glucose would be similar if these were broken into smaller time frames and alternated (i.e. circuit training) has yet to be examined. Intervention studies where this type of approach to training has been employed have been successful in lowering Hb<sub>A1c</sub> in individuals with type 1 diabetes (24, 160). An examination of the acute effects of circuit training in individuals with type 1 diabetes would be helpful in elucidating the mechanisms for these improvements.

The resistance exercise portions of this study involved a very general resistance exercise protocol (3 sets of 8 repetitions). A great deal more research can be done to examine the effects of other types of resistance exercise training protocols on blood glucose levels in individuals with type 1 diabetes. A resistance exercise training program designed to improve muscular endurance (involving a larger number of repetitions, lighter weight, and shorter rest periods) may involve participants using oxidative metabolism frequently throughout their workout. Conversely, programs designed for gaining strength and power will involve short, powerful, sets with very heavy weight where the main source of fuel will come from the glycolytic system. As these two types of resistance exercise

training differ substantially in the stress that they place on the body, it is likely that blood glucose responses to these exercise programs in individuals with type 1 diabetes will also differ. Examining both the acute and chronic effects of a greater array of resistance exercise training protocols, whether alone or combined with aerobic exercise, in individuals with type 1 diabetes would be a worthwhile endeavor.

Finally, it would also be useful to examine whether the method of insulin delivery affects the risk of hypoglycemia both during and after the different types of exercise sessions. While we had a mix of CSII and MDI users in this study, neither the study design nor the sample size would permit an adequate analysis as to whether or not the risks of exercise-induced hypoglycemia were affected by the insulin delivery system. As developments in synthetic insulin preparations and insulin delivery systems continue, it will be important to understand how these affect an individual's ability to manage blood glucose levels during exercise.

## **6.5 Summary and Recommendations**

In habitually-active, complication-free individuals with type 1 diabetes having good to moderate glycemic control:

- 1) Resistance exercise is associated with a lower risk of hypoglycemia during exercise than aerobic exercise
- 2) Rapid decreases in blood glucose levels during aerobic exercise necessitate a greater amount of carbohydrate intake both before and during exercise as compared to resistance exercise or no exercise
- 3) Post-exercise blood glucose levels are higher after aerobic exercise as compared to

resistance exercise or no exercise, likely due to glucose demands decreasing more quickly than counter-regulatory responses

- 4) While hypoglycemic events were more frequent after resistance exercise, they were more severe after aerobic exercise
- 5) Performing resistance exercise before aerobic exercise decreases the risk of exercise-induced hypoglycemia during aerobic exercise as compared to aerobic exercise alone
- 6) When resistance exercise is performed prior to aerobic exercise (rather than performing aerobic exercise first) there is a decreased need for carbohydrate supplementation during exercise
- 7) Attenuated declines in blood glucose levels and the lower need for glucose supplementation seen during aerobic exercise when it is preceded by resistance exercise are probably due to the presence of higher levels of epinephrine, lactate and growth hormone after resistance exercise, which would serve to decrease the reliance on carbohydrates as a fuel source during the subsequent aerobic activity
- 8) Performing resistance exercise prior to aerobic exercise (in comparison to performing aerobic exercise first) decreases the risk of hypoglycemia both during exercise and overnight following exercise
- 9) The elevated risk of hypoglycemia during exercise and after exercise when aerobic exercise precedes resistance exercise may be related to growth hormone suppression both during and post-exercise, leading to a greater reliance on carbohydrate as a fuel source during exercise and recovery

## **6.6 Conclusions**

With the above taken into consideration, it seems reasonable to recommend a combination of resistance and aerobic exercise for complication-free individuals with type 1 diabetes. For habitually active individuals, performing resistance exercise prior to aerobic exercise will reduce the risk of exercise-induced hypoglycemia both during and after exercise. This does not decrease the need for frequent self-monitoring of blood glucose levels during exercise, as it is impossible to account for all factors that could potentially cause large increases or decreases in glucose levels during exercise.

## **7.0 STATEMENT OF CONTRIBUTIONS OF COLLABORATORS AND CO-AUTHORS**

## **Laboratory Assistance**

Dr. Heather Wright, Ms. Nadia Balaa, Ms. Ghazal Bandeh-Bahman, and Ms. Jerilee Barnett provided assistance with blood collection and separation during testing sessions.

Dr. Heather Wright and Ms Nadia Balaa also assisted with laboratory analysis of blood samples. Dr. Pierre Boulay provided services in electrocardiogram monitoring and interpretation during  $\dot{V} O_{2\text{peak}}$  tests on participants.

## **Article 1**

G.K., B.P., M.R., and R.S. contributed to the conception and design of the project, provided guidance on the data analysis and reviewed/edited the manuscript. G.K. and R.S. oversaw the data collection and assisted in the data analysis. N.B. assisted in the data collection and analysis. F.K. provided guidance on statistical analyses. J.Y. contributed to the conception and design of the project, collected and analyzed the data, and drafted, reviewed and edited the manuscript.

## **Article 2**

G.K., B.P., M.R., and R.S. contributed to the conception and design of the project, provided guidance on the data analysis and reviewed/edited the manuscript. G.K. and R.S. oversaw the data collection and assisted in the data analysis. F.K. provided guidance on all statistical analyses. J.Y. contributed to the conception and design of the project, collected and analyzed the data, and drafted, reviewed and edited the manuscript.

### **Article 3**

G.K., B.P., M.R., and R.S. contributed to the conception and design of the project, provided guidance on the data analysis and reviewed/edited the manuscript. G.K. and R.S. oversaw the data collection and assisted in the data analysis. F.K. provided expert advice on statistical procedures. J.Y. contributed to the conception and design of the project, collected and analyzed the data, and drafted, reviewed and edited the manuscript.

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## **9.0 APPENDICES**

## **APPENDIX A – SUMMARY DATA TABLES**

**Table A-1.** Plasma glucose (mmol/l) during exercise and recovery for each experimental condition

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
<b>Exercise</b>					
0 min	8.4 ± 3.5	9.2 ± 3.4	8.4 ± 2.7	9.1 ± 2.4	9.7 ± 3.9
5 min	8.5 ± 3.5	8.9 ± 3.7	8.3 ± 2.7	8.5 ± 2.6	9.8 ± 4.1
10 min	8.6 ± 3.5	8.1 ± 3.6	7.8 ± 2.6	7.8 ± 2.9	9.5 ± 4.0
15 min	8.8 ± 3.6	7.6 ± 3.3	7.8 ± 2.6	7.2 ± 3.1	9.6 ± 4.0
30 min	8.8 ± 3.8	6.1 ± 2.7	7.3 ± 2.6	5.9 ± 3.2	9.2 ± 3.9
45 min	8.6 ± 3.8	5.8 ± 2.0	6.8 ± 2.3	5.5 ± 2.4	9.2 ± 4.0
50 min				6.9 ± 1.7	9.5 ± 3.7
55 min				7.0 ± 2.0	9.6 ± 3.5
60 min				7.2 ± 2.0	9.4 ± 3.7
75 min				7.4 ± 2.4	8.0 ± 3.4
90 min				7.5 ± 2.6	6.9 ± 3.1
<b>Recovery</b>					
0 min	8.6 ± 3.8	5.8 ± 2.0	6.8 ± 2.3	7.5 ± 2.6	6.9 ± 3.1
5 min	8.9 ± 4.1	6.4 ± 2.0	6.8 ± 2.4	7.6 ± 2.6	7.3 ± 2.9
10 min	8.6 ± 3.9	6.4 ± 2.1	6.7 ± 2.5	7.7 ± 2.7	7.2 ± 3.0
15 min	8.6 ± 3.9	6.5 ± 2.1	6.8 ± 2.5	7.8 ± 2.9	7.4 ± 2.9
20 min	8.6 ± 4.0	6.5 ± 2.2	6.7 ± 2.6	8.0 ± 3.0	7.5 ± 3.0
30 min	8.5 ± 3.6	7.0 ± 2.5	6.7 ± 2.7	8.5 ± 3.0	7.7 ± 3.3
40 min	8.5 ± 3.3	7.6 ± 2.3	6.8 ± 2.7	8.9 ± 3.0	7.9 ± 3.6
50 min	8.3 ± 3.2	7.9 ± 2.0	6.6 ± 2.7	9.1 ± 3.0	8.0 ± 3.6
60 min	8.1 ± 3.1	8.0 ± 2.4	6.6 ± 2.7	9.1 ± 2.9	7.9 ± 3.5

Data are presented as means (±SD)

**Table A-2.** Non-esterified fatty acid (NEFA) concentration ( $\mu\text{mol/l}$ ) during exercise and recovery for each experimental session

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
<b>Exercise</b>					
0 min	193 $\pm$ 57	211 $\pm$ 70	264 $\pm$ 97	520 $\pm$ 298	407 $\pm$ 171
15 min	202 $\pm$ 60	190 $\pm$ 52	263 $\pm$ 144	399 $\pm$ 220	380 $\pm$ 155
10 min	205 $\pm$ 67	223 $\pm$ 93	256 $\pm$ 127	434 $\pm$ 272	341 $\pm$ 142
15 min	220 $\pm$ 101	251 $\pm$ 130	254 $\pm$ 132	493 $\pm$ 335	340 $\pm$ 143
30 min	206 $\pm$ 112	267 $\pm$ 187	268 $\pm$ 142	519 $\pm$ 370	378 $\pm$ 151
45 min	204 $\pm$ 122	260 $\pm$ 200	194 $\pm$ 91	507 $\pm$ 290	328 $\pm$ 139
50 min				709 $\pm$ 446	290 $\pm$ 145
55 min				579 $\pm$ 271	317 $\pm$ 178
60 min				482 $\pm$ 187	361 $\pm$ 213
75 min				606 $\pm$ 187	391 $\pm$ 214
90 min				531 $\pm$ 269	418 $\pm$ 164
<b>Recovery</b>					
0 min	204 $\pm$ 122	260 $\pm$ 200	194 $\pm$ 91	531 $\pm$ 269	418 $\pm$ 164
5 min	215 $\pm$ 118	474 $\pm$ 259	232 $\pm$ 112	737 $\pm$ 422	937 $\pm$ 564
10 min	195 $\pm$ 93	543 $\pm$ 418	237 $\pm$ 128	848 $\pm$ 539	955 $\pm$ 653
15 min	192 $\pm$ 90	501 $\pm$ 346	250 $\pm$ 138	954 $\pm$ 589	959 $\pm$ 647
20 min	202 $\pm$ 81	484 $\pm$ 320	223 $\pm$ 115	973 $\pm$ 389	951 $\pm$ 703
30 min	210 $\pm$ 82	488 $\pm$ 307	250 $\pm$ 135	1217 $\pm$ 533	940 $\pm$ 796
40 min	217 $\pm$ 73	549 $\pm$ 446	349 $\pm$ 218	1246 $\pm$ 600	810 $\pm$ 632
50 min	239 $\pm$ 102	614 $\pm$ 538	419 $\pm$ 272	1229 $\pm$ 647	705 $\pm$ 540
60 min	263 $\pm$ 103	575 $\pm$ 367	534 $\pm$ 309	1122 $\pm$ 595	652 $\pm$ 414

Data are presented as means ( $\pm$ SD)

**Table A-3.** Insulin concentrations (pmol/l) during exercise and recovery for each experimental session

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
<b>Exercise</b>					
0 min	98.90 ± 28.66	62.88 ± 9.88	77.52 ± 22.01	60.96 ± 23.98	65.49 ± 12.91
5 min	112.08 ± 46.79	73.16 ± 13.58	86.54 ± 28.64	66.74 ± 35.21	71.08 ± 15.36
10 min	99.08 ± 33.75	80.68 ± 21.63	81.11 ± 26.14	75.31 ± 48.35	64.07 ± 12.16
15 min	99.90 ± 39.59	80.61 ± 27.33	89.22 ± 27.34	69.67 ± 37.88	69.34 ± 13.83
30 min	86.88 ± 30.32	90.48 ± 44.77	78.34 ± 29.98	77.02 ± 51.73	61.11 ± 11.32
45 min	76.23 ± 22.94	81.28 ± 37.90	76.80 ± 28.41	59.06 ± 17.63	61.72 ± 10.06
50 min				53.49 ± 15.28	60.12 ± 7.90
55 min				53.54 ± 11.56	64.34 ± 11.51
60 min				52.41 ± 13.49	73.92 ± 24.44
75 min				48.18 ± 9.73	75.61 ± 31.20
90 min				47.32 ± 7.91	69.79 ± 24.88
<b>Recovery</b>					
0 min	76.23 ± 22.94	81.28 ± 37.90	76.80 ± 28.41	47.32 ± 7.91	69.79 ± 24.88
5 min	75.72 ± 18.11	65.60 ± 14.06	74.17 ± 24.63	46.46 ± 7.56	62.63 ± 17.12
10 min	72.92 ± 19.70	56.62 ± 7.32	68.87 ± 18.96	45.28 ± 7.17	57.67 ± 12.52
15 min	69.70 ± 14.15	54.25 ± 7.70	67.82 ± 20.93	44.09 ± 6.25	59.40 ± 16.65
20 min	71.33 ± 17.69	53.50 ± 6.13	64.73 ± 19.99	43.24 ± 6.68	54.80 ± 12.73
30 min	71.22 ± 11.81	49.86 ± 6.87	62.38 ± 17.75	47.27 ± 9.15	51.10 ± 8.08
40 min	68.18 ± 8.60	47.38 ± 6.94	70.04 ± 24.77	49.31 ± 16.52	48.44 ± 7.87
50 min	68.34 ± 8.74	47.74 ± 5.07	76.35 ± 38.63	50.60 ± 22.96	49.13 ± 8.14
60 min	68.62 ± 6.04	48.76 ± 7.12	74.01 ± 34.80	47.50 ± 15.55	50.04 ± 9.07

Data are presented as means (±SD)

**Table A-4.** Cortisol levels ( $\eta\text{mol/l}$ ) during exercise and recovery for each experimental session

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
<b>Exercise</b>					
0 min	343.29 $\pm$ 102.53	364.48 $\pm$ 174.32	382.80 $\pm$ 165.42	367.69 $\pm$ 117.36	403.46 $\pm$ 105.34
5 min	329.62 $\pm$ 95.73	327.38 $\pm$ 151.08	353.62 $\pm$ 149.74	327.67 $\pm$ 102.82	388.19 $\pm$ 110.07
10 min	335.85 $\pm$ 114.59	309.41 $\pm$ 136.86	333.12 $\pm$ 131.85	325.79 $\pm$ 99.14	364.99 $\pm$ 106.83
15 min	320.03 $\pm$ 104.55	306.92 $\pm$ 114.95	310.45 $\pm$ 114.83	332.86 $\pm$ 61.62	351.70 $\pm$ 110.40
30 min	300.96 $\pm$ 110.8	300.62 $\pm$ 113.96	277.38 $\pm$ 93.65	383.50 $\pm$ 209.63	344.04 $\pm$ 131.00
45 min	272.68 $\pm$ 96.72	323.74 $\pm$ 216.33	260.83 $\pm$ 105.11	333.54 $\pm$ 117.31	317.97 $\pm$ 139.22
50 min				375.13 $\pm$ 123.23	313.09 $\pm$ 153.10
55 min				369.10 $\pm$ 159.98	333.82 $\pm$ 201.03
60 min				369.56 $\pm$ 141.95	376.47 $\pm$ 251.68
75 min				343.05 $\pm$ 109.73	424.46 $\pm$ 281.55
90 min				365.24 $\pm$ 119.39	522.12 $\pm$ 380.07
<b>Recovery</b>					
0 min	272.68 $\pm$ 96.72	323.74 $\pm$ 216.33	260.83 $\pm$ 105.11	365.24 $\pm$ 119.39	522.12 $\pm$ 380.07
5 min	274.94 $\pm$ 104.71	347.86 $\pm$ 286.68	265.71 $\pm$ 91.25	362.91 $\pm$ 137.91	570.24 $\pm$ 381.08
10 min	275.09 $\pm$ 91.60	369.36 $\pm$ 337.00	275.28 $\pm$ 82.28	454.25 $\pm$ 225.00	578.50 $\pm$ 354.43
15 min	279.04 $\pm$ 80.44	392.04 $\pm$ 367.60	275.04 $\pm$ 65.35	477.28 $\pm$ 298.45	671.07 $\pm$ 362.80
20 min	300.18 $\pm$ 96.17	409.63 $\pm$ 389.98	264.60 $\pm$ 68.85	442.55 $\pm$ 250.65	673.01 $\pm$ 353.64
30 min	277.27 $\pm$ 80.27	345.71 $\pm$ 289.70	234.92 $\pm$ 83.21	392.23 $\pm$ 226.78	582.66 $\pm$ 263.30
40 min	281.12 $\pm$ 111.73	364.78 $\pm$ 313.35	239.40 $\pm$ 86.55	350.62 $\pm$ 114.81	555.41 $\pm$ 270.28
50 min	273.13 $\pm$ 98.70	364.35 $\pm$ 288.52	232.82 $\pm$ 84.44	337.16 $\pm$ 138.03	494.75 $\pm$ 239.76
60 min	262.42 $\pm$ 105.98	354.32 $\pm$ 291.20	213.73 $\pm$ 82.61	316.42 $\pm$ 122.36	467.61 $\pm$ 231.03

Data are presented as means ( $\pm$ SD)

**Table A-5.** Growth hormone ( $\eta$ mol/l) concentration during exercise and recovery for each experimental session

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
<b>Exercise</b>					
0 min	1.26 $\pm$ 0.72	0.74 $\pm$ 0.97	8.52 $\pm$ 8.90	2.48 $\pm$ 1.85	3.10 $\pm$ 5.84
5 min	0.96 $\pm$ 0.53	0.82 $\pm$ 0.96	9.32 $\pm$ 11.67	2.17 $\pm$ 1.76	6.96 $\pm$ 15.62
10 min	1.11 $\pm$ 0.85	0.96 $\pm$ 0.98	6.51 $\pm$ 7.91	2.37 $\pm$ 2.18	4.82 $\pm$ 10.31
15 min	1.24 $\pm$ 1.04	2.19 $\pm$ 2.35	5.95 $\pm$ 6.96	3.17 $\pm$ 2.38	5.19 $\pm$ 10.80
30 min	1.72 $\pm$ 1.80	6.58 $\pm$ 4.51	5.27 $\pm$ 4.56	9.70 $\pm$ 9.05	5.93 $\pm$ 8.69
45 min	1.88 $\pm$ 2.13	9.83 $\pm$ 5.96	10.16 $\pm$ 8.41	13.44 $\pm$ 10.81	12.07 $\pm$ 13.54
50 min				8.66 $\pm$ 8.10	11.34 $\pm$ 9.07
55 min				7.74 $\pm$ 7.45	12.50 $\pm$ 9.98
60 min				6.48 $\pm$ 5.73	13.28 $\pm$ 10.62
75 min				4.49 $\pm$ 4.33	16.25 $\pm$ 14.08
90 min				4.49 $\pm$ 4.47	15.12 $\pm$ 13.96
<b>Recovery</b>					
0 min	1.88 $\pm$ 2.13	9.83 $\pm$ 5.96	10.16 $\pm$ 8.41	4.49 $\pm$ 4.47	15.12 $\pm$ 13.96
5 min	1.56 $\pm$ 1.72	9.49 $\pm$ 5.72	9.27 $\pm$ 7.07	4.22 $\pm$ 4.47	14.92 $\pm$ 14.49
10 min	1.27 $\pm$ 1.47	7.79 $\pm$ 3.73	8.64 $\pm$ 6.14	4.23 $\pm$ 4.94	12.14 $\pm$ 11.40
15 min	1.04 $\pm$ 1.10	6.78 $\pm$ 3.85	6.92 $\pm$ 4.46	3.38 $\pm$ 3.91	9.61 $\pm$ 9.63
20 min	0.86 $\pm$ 0.82	5.59 $\pm$ 3.41	6.78 $\pm$ 4.53	2.80 $\pm$ 3.19	7.88 $\pm$ 7.55
30 min	0.58 $\pm$ 0.26	4.33 $\pm$ 2.94	6.69 $\pm$ 3.48	2.09 $\pm$ 2.49	5.71 $\pm$ 5.94
40 min	0.46 $\pm$ 0.25	2.82 $\pm$ 1.89	5.95 $\pm$ 4.26	1.22 $\pm$ 1.29	3.77 $\pm$ 3.61
50 min	0.46 $\pm$ 0.22	1.85 $\pm$ 1.08	4.57 $\pm$ 3.62	0.77 $\pm$ 0.72	3.05 $\pm$ 3.04
60 min	0.55 $\pm$ 0.53	1.25 $\pm$ 0.72	3.71 $\pm$ 2.96	0.63 $\pm$ 0.67	2.56 $\pm$ 2.64

Data are presented as means ( $\pm$ SD)

**Table A-6.** Summary of carbohydrate and insulin intake over the three days of continuous glucose monitoring

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
<b>Carbohydrate intake (g)</b>					
Day 1	268 ± 78	272 ± 92	271 ± 107	267 ± 97	276 ± 108
Day 2	284 ± 97	311 ± 109	276 ± 109	305 ± 106	308 ± 110
Day 3*	157 ± 40	157 ± 60	163 ± 61	155 ± 48	165 ± 63
<b>Insulin intake (U)</b>					
Day 1	46 ± 17	48 ± 19	51 ± 21	48 ± 19	50 ± 19
Day 2	47 ± 20	49 ± 20	47 ± 20	49 ± 21	48 ± 21
Day 3*	37 ± 17	39 ± 16	38 ± 18	36 ± 16	39 ± 18

Data are presented as means (±SD). \* Day 3 does not include the evening meal.

**Table A-7.** Carbohydrate supplementation and glucose means for each experimental session

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
Number of participants requiring supplements	2 (16.6%)	9 (75%)	3 (25.0%)	10 (83.3%)	6 (50%)
Total carbohydrate provided per session (g)	41	290	56	320	224
Minimum mean ( $\pm$ SD) plasma glucose during testing (mmol/l)	8.1 $\pm$ 3.1	5.8 $\pm$ 2.0	6.6 $\pm$ 2.6	5.5 $\pm$ 2.4	6.9 $\pm$ 3.1
Maximum mean plasma glucose during testing (mmol/l) ( $\pm$ SD)	8.9 $\pm$ 4.2	9.2 $\pm$ 3.4	8.4 $\pm$ 2.7	9.1 $\pm$ 2.4	9.8 $\pm$ 4.1

**Table A-8.** Summary of continuous glucose monitoring data for 24 hours prior to each exercise session

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
Number of participants experiencing hypoglycemia	8/11 (73%)	6/10 (60%)	11/12 (92%)	8/12 (67%)	8/11 (73%)
Number of hypoglycemic events	17	14	21	20	20
Mean duration of hypoglycemia (minutes)	127 ± 46	81 ± 41	153 ± 53	114 ± 41	111 ± 36
Mean AUC for hypoglycemia	137 ± 51	97 ± 52	182 ± 73	120 ± 45	109 ± 39
Number of participants experiencing hyperglycemia	8/11 (73%)	4/10 (40%)	10/12 (83%)	8/12 (67%)	10/11 (91%)
Number of hyperglycemic events	16	14	25	20	22
Mean time spent in hyperglycemia	236 ± 98	267 ± 114	119 ± 35	141 ± 48	193 ± 72
Mean AUC for hyperglycemia	598 ± 346	922 ± 472	155 ± 65	359 ± 177	270 ± 142
Average maximum CGM glucose (mmol/l)	13.7 ± 1.1	14.2 ± 1.4	13.5 ± 0.8	13.3 ± 1.1	12.7 ± 0.5
Average minimum CGM glucose (mmol/l)	3.2 ± 0.3	3.4 ± 0.3	2.9 ± 0.2	3.0 ± 0.2	2. ± 0.3
Mean CGM glucose	7.6 ± 0.7	7.9 ± 0.8	6.9 ± 0.4	6.9 ± 0.4	7.2 ± 0.5
Proportion of time spent in hypoglycemia (%)	8.8 ± 3.2	5.6 ± 2.7	10.6 ± 3.8	10.1 ± 3.0	7.7 ± 2.5
Proportion of time spent in hyperglycemia (%)	16.4 ± 6.8	18.5 ± 7.5	8.3 ± 2.5	9.8 ± 3.7	13.4 ± 5.0
Proportion of time spent in euglycemia (%)	74.7 ± 5.9	75.7 ± 6.7	81.1 ± 4.4	81.5 ± 4.4	78.9 ± 4.4

Data are presented as means (±SE)

**Table A-9.** Summary of nocturnal (2400 to 0600h) continuous glucose monitoring data the night prior to each exercise session

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
Number of participants experiencing hypoglycemia	6/11 (55%)	3/11 (27%)	8/12 (67%)	4/12 (33%)	6/11 (55%)
Number of hypoglycemic events	8	5	12	4	7
Mean duration of hypoglycemia (minutes)	69 ± 33	39 ± 21	78 ± 31	33 ± 19	30 ± 12
Mean AUC for hypoglycemia	80 ± 42	51 ± 27	92 ± 40	37 ± 22	27 ± 12
Number of participants experiencing hyperglycemia	4/11 (36%)	4/11 (36%)	1/12 (8%)	4/12 (33%)	3/11 (27%)
Number of hyperglycemic events	6	4	1	7	4
Mean time spent in hyperglycemia	80 ± 39	86 ± 42	27 ± 27	47 ± 29	40 ± 33
Mean AUC for hyperglycemia	312 ± 238	245 ± 171	54 ± 54	136 ± 116	73 ± 67
Average maximum CGM glucose (mmol/l)	10.2 ± 1.6	10.0 ± 1.3	8.1 ± 0.7	9.4 ± 1.0	9.5 ± 0.9
Average minimum CGM glucose (mmol/l)	5.4 ± 1.2	5.8 ± 1.1	4.2 ± 0.7	4.2 ± 0.6	4.6 ± 0.9
Mean CGM glucose	7.7 ± 1.4	7.9 ± 1.2	6.1 ± 0.8	6.7 ± 0.9	6.9 ± 0.8
Proportion of time spent in hypoglycemia (%)	19.1 ± 9.1	10.9 ± 5.8	21.8 ± 8.8	9.0 ± 5.5	8.3 ± 3.4
Proportion of time spent in hyperglycemia (%)	22.2 ± 10.9	23.9 ± 11.6	7.4 ± 7.7	13.0 ± 8.5	11.1 ± 9.0
Proportion of time spent in euglycemia (%)	58.7 ± 10.8	65.3 ± 10.7	70.8 ± 10.3	78.0 ± 8.9	80.6 ± 8.8

Data are presented as means (±SE)

**Table A-10.** Summary of continuous glucose monitoring data 1 to 6 hours post-exercise for each testing condition

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
Number of participants experiencing hypoglycemia	6/11 (55%)	3/10 (30%)	7/12 (58%)	3/12 (25%)	4/12 (33%)
Number of hypoglycemic events	8	6	9	3	8
Mean duration of hypoglycemia (minutes)	39 ± 17	20 ± 12	19 ± 6	10 ± 6	24 ± 13
Mean AUC for hypoglycemia	47 ± 21	18 ± 12	13 ± 5	10 ± 7	27 ± 16
Number of participants experiencing hyperglycemia	3/11 (27%)	3/10 (30%)	4/12 (33%)	5/12 (42%)	8/12 (67%)
Number of hyperglycemic events	7	5	4	5	9
Mean time spent in hyperglycemia	29 ± 18	35 ± 20	11 ± 6	52 ± 27	33 ± 14
Mean AUC for hyperglycemia	47 ± 33	56 ± 41	8 ± 5	109 ± 66	75 ± 51
Average maximum CGM glucose (mmol/l)	9.9 ± 1.0	10 ± 0.9	9.8 ± 0.7	10.5 ± 0.9	10.9 ± 1.3
Average minimum CGM glucose (mmol/l)	4.1 ± 0.6	4.9 ± 0.6	3.8 ± 0.2	4.8 ± 0.6	5.2 ± 0.8
Mean CGM glucose	6.6 ± 0.8	7.3 ± 0.8	6.5 ± 0.4	7.7 ± 0.7	7.3 ± 0.8
Proportion of time spent in hypoglycemia (%)	14.2 ± 5.7	7.1 ± 4.1	6.3 ± 2.2	3.3 ± 2.1	8.1 ± 4.4
Proportion of time spent in hyperglycemia (%)	10.5 ± 6.1	12.6 ± 6.9	3.6 ± 2.1	17.2 ± 9.4	11.1 ± 4.8
Proportion of time spent in euglycemia (%)	75.3 ± 6.3	71.2 ± 9.7	90.1 ± 3.3	79.4 ± 9.5	80.8 ± 5.1

Data are presented as means (±SE)

**Table A-11.** Summary of post-exercise nocturnal (2400 to 0600h) continuous glucose monitoring data for each testing condition

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
Number of participants experiencing hypoglycemia	4/11 (36%)	2/10 (20%)	6/12 (50%)	3/12 (25%)	4/12 (33%)
Number of hypoglycemic events	4	4	9	5	6
Mean duration of hypoglycemia (minutes)	15 ± 6.2	21 ± 18	30 ± 13	45 ± 27	24 ± 16
Mean AUC for hypoglycemia	34 ± 13	54 ± 89	31 ± 26	47 ± 31	30 ± 23
Number of participants experiencing hyperglycemia	3/11 (27%)	2/10 (20%)	4/12 (33%)	3/12 (25%)	2/12 (17%)
Number of hyperglycemic events	3	2	8	4	3
Mean time spent in hyperglycemia	45 ± 30	45 ± 30	46 ± 23	27 ± 20	39 ± 31
Mean AUC for hyperglycemia	74 ± 49	59 ± 44	37 ± 22	24 ± 21	151 ± 124
Average maximum CGM glucose (mmol/l)	9.9 ± 0.8	8.3 ± 1.0	8.5 ± 0.9	8.2 ± 0.8	8.8 ± 1.2
Average minimum CGM glucose (mmol/l)	4.5 ± 0.6	5.4 ± 0.7	4.6 ± 0.5	4.6 ± 0.5	4.7 ± 0.8
Mean CGM glucose	7.2 ± 0.6	7.0 ± 0.9	6.8 ± 0.7	6.3 ± 0.7	6.7 ± 0.9
Proportion of time spent in hypoglycemia (%)	4.0 ± 1.7	5.8 ± 5.1	8.3 ± 3.7	12.6 ± 7.5	6.7 ± 4.3
Proportion of time spent in hyperglycemia (%)	12.4 ± 8.4	12.4 ± 8.3	12.8 ± 6.5	7.4 ± 5.6	10.9 ± 8.5
Proportion of time spent in euglycemia (%)	83.6 ± 8.2	81.8 ± 8.8	78.8 ± 6.6	80 ± 8.7	82 ± 8.8

Data are presented as means (±SE)

**Table A-12.** Summary of continuous glucose monitoring data over 24 hours post-exercise for each testing condition

	<b>Control</b>	<b>Aerobic</b>	<b>Resistance</b>	<b>Aerobic then Resistance</b>	<b>Resistance then Aerobic</b>
Number of participants experiencing hypoglycemia	8/11 (73%)	8/10 (80%)	9/12 (75%)	8/12 (67%)	7/12 (58%)
Number of hypoglycemic Events	15	19	21	19	22
Mean duration of hypoglycemia (minutes)	98 ± 32	133 ± 63	93 ± 26	110 ± 48	111 ± 50
Mean AUC for hypoglycemia	98 ± 31	141 ± 74	71 ± 22	118 ± 51	131 ± 60
Number of participants experiencing hyperglycemia	8/11 (73%)	8/10 (80%)	11/12 (92%)	9/12 (75%)	10/12 (83%)
Number of hyperglycemic Events	18	17	32	14	22
Mean time spent in Hyperglycemia	261 ± 91	160 ± 64	202 ± 49	232 ± 93	211 ± 61
Mean AUC for hyperglycemia	541 ± 212	289 ± 127	431 ± 149	611 ± 311	629 ± 204
Average maximum CGM glucose (mmol/l)	13.5 ± 0.9	12.7 ± 0.9	14.4 ± 0.9	13.5 ± 1.1	14.7 ± 1.2
Average minimum CGM glucose (mmol/l)	3.2 ± 0.3	3.1 ± 0.3	3.4 ± 0.3	3.0 ± 0.2	3.4 ± 0.3
Mean CGM glucose	7.7 ± 0.6	7.1 ± 0.6	7.4 ± 0.5	7.4 ± 0.6	7.4 ± 0.5
Proportion of time spent in hypoglycemia (%)	6.8 ± 2.2	9.2 ± 4.4	6.4 ± 1.8	7.7 ± 3.3	7.7 ± 3.5
Proportion of time spent in hyperglycemia (%)	18.1 ± 6.3	11.1 ± 4.5	14.1 ± 3.5	16.1 ± 6.4	14.9 ± 4.2
Proportion of time spent in euglycemia (%)	75.1 ± 5.3	79.7 ± 4.6	79.5 ± 3.3	76.2 ± 7.0	77.4 ± 4.3

Data are presented as means (±SE)

**Table A-13.** Summary of continuous glucose monitoring data for the control session

	<b>24 hours pre- exercise</b>	<b>Overnight pre- exercise</b>	<b>1 to 6 hours post- exercise</b>	<b>Overnight post- exercise</b>	<b>24 hours post- exercise</b>
Number of participants experiencing hypoglycemia	8/11 (73%)	6/11 (55%)	6/11 (55%)	4/11 (36%)	8/11 (73%)
Number of hypoglycemic events	17	8	8	4	15
Mean duration of hypoglycemia (minutes)	127 ± 46	69 ± 33	43 ± 17	15 ± 6.2	98 ± 32
Mean AUC for hypoglycemia	126 ± 51	80 ± 42	51 ± 22	13 ± 6	98 ± 31
Number of participants experiencing hyperglycemia	8/11 (73%)	4/11 (36%)	3/11 (27%)	3/11 (27%)	8/11 (73%)
Number of hyperglycemic events	16	6	6	3	18
Mean time spent in hyperglycemia	236 ± 98	80 ± 39	31 ± 18	45 ± 30	261 ± 91
Mean AUC for hyperglycemia	598 ± 346	312 ± 238	52 ± 34	74 ± 49	541 ± 212
Average maximum CGM glucose (mmol/l)	13.7 ± 1.1	10.2 ± 1.6	9.9 ± 1.0	9.9 ± 0.8	13.5 ± 0.9
Average minimum CGM glucose (mmol/l)	3.2 ± 0.3	5.4 ± 1.2	4.1 ± 0.6	4.5 ± 0.6	3.2 ± 0.3
Mean CGM glucose	7.6 ± 0.7	7.7 ± 1.4	6.6 ± 0.8	7.2 ± 0.6	7.7 ± 0.6
Proportion of time spent in hypoglycemia (%)	8.8 ± 3.2	19.1 ± 9.1	14.2 ± 5.7	4.0 ± 1.7	6.8 ± 2.2
Proportion of time spent in hyperglycemia (%)	16.4 ± 6.8	22.2 ± 10.9	10.5 ± 6.1	12.4 ± 8.4	18.1 ± 6.3
Proportion of time spent in euglycemia (%)	74.7 ± 5.9	58.7 ± 10.8	75.3 ± 6.3	83.6 ± 8.2	75.1 ± 5.3

Data are presented as means (±SE)

**Table A-14.** Summary of continuous glucose monitoring data for the aerobic exercise session

	<b>24 hours pre- exercise</b>	<b>Overnight pre- exercise</b>	<b>1 to 6 hours post- exercise</b>	<b>Overnight post- exercise</b>	<b>24 hours post- exercise</b>
Number of participants experiencing hypoglycemia	6/10 (60%)	3/11 (27%)	3/10 (30%)	2/10 (20%)	8/10 (80%)
Number of hypoglycemic events	14	5	6	4	19
Mean duration of hypoglycemia (minutes)	81 ± 41	39 ± 21	20 ± 12	21 ± 18	133 ± 63
Mean AUC for hypoglycemia	97 ± 52	51 ± 27	18 ± 12	20 ± 19	141 ± 74
Number of participants experiencing hyperglycemia	4/10 (40%)	4/11 (36%)	3/10 (30%)	2/10 (20%)	8/10 (80%)
Number of hyperglycemic events	14	4	5	2	17
Mean time spent in hyperglycemia	267 ± 114	86 ± 42	35 ± 20	45 ± 30	160 ± 64
Mean AUC for hyperglycemia	922 ± 472	245 ± 171	56 ± 41	59 ± 44	289 ± 127
Average maximum CGM glucose (mmol/l)	14.2 ± 1.4	10.0 ± 1.3	10 ± 0.9	8.3 ± 1.0	12.7 ± 0.9
Average minimum CGM glucose (mmol/l)	3.4 ± 0.3	5.8 ± 1.1	4.9 ± 0.6	5.4 ± 0.7	3.1 ± 0.3
Mean CGM glucose	7.9 ± 0.8	7.9 ± 1.2	7.3 ± 0.8	7.0 ± 0.9	7.1 ± 0.6
Proportion of time spent in hypoglycemia (%)	5.6 ± 2.7	10.9 ± 5.8	7.1 ± 4.1	5.8 ± 5.1	9.2 ± 4.4
Proportion of time spent in hyperglycemia (%)	18.5 ± 7.5	23.9 ± 11.6	12.6 ± 6.9	12.4 ± 8.3	11.1 ± 4.5
Proportion of time spent in euglycemia (%)	75.7 ± 6.7	65.3 ± 10.7	71.2 ± 9.7	81.8 ± 8.8	79.7 ± 4.6

Data are presented as means (±SE)

**Table A-15.** Summary of continuous glucose monitoring data for the resistance exercise session

	<b>24 hours pre- exercise</b>	<b>Overnight pre- exercise</b>	<b>1 to 6 hours post- exercise</b>	<b>Overnight post- exercise</b>	<b>24 hours post- exercise</b>
Number of participants experiencing hypoglycemia	11/12 (92%)	8/12 (67%)	7/12 (58%)	6/12 (50%)	9/12 (75%)
Number of hypoglycemic events	21	12	9	9	21
Mean duration of hypoglycemia (minutes)	153 ± 53	78 ± 31	19 ± 6	30 ± 13	93 ± 26
Mean AUC for hypoglycemia	182 ± 73	92 ± 40	13 ± 5	23 ± 11	71 ± 22
Number of participants experiencing hyperglycemia	10/12 (83%)	1/12 (8%)	4/12 (33%)	4/12 (33%)	11/12 (92%)
Number of hyperglycemic events	25	1	4	8	32
Mean time spent in hyperglycemia	119 ± 35	27 ± 27	11 ± 6	46 ± 23	202 ± 49
Mean AUC for hyperglycemia	155 ± 65	54 ± 54	8 ± 5	37 ± 22	431 ± 149
Average maximum CGM glucose (mmol/l)	13.5 ± 0.8	8.1 ± 0.7	9.8 ± 0.7	8.5 ± 0.9	14.4 ± 0.9
Average minimum CGM glucose (mmol/l)	2.9 ± 0.2	4.2 ± 0.7	3.8 ± 0.2	4.6 ± 0.5	3.4 ± 0.3
Mean CGM glucose	6.9 ± 0.4	6.1 ± 0.8	6.5 ± 0.4	6.8 ± 0.7	7.4 ± 0.5
Proportion of time spent in hypoglycemia (%)	10.6 ± 3.8	21.8 ± 8.8	6.3 ± 2.2	8.3 ± 3.7	6.4 ± 1.8
Proportion of time spent in hyperglycemia (%)	8.3 ± 2.5	7.4 ± 7.7	3.6 ± 2.1	12.8 ± 6.5	14.1 ± 3.5
Proportion of time spent in euglycemia (%)	81.1 ± 4.4	70.8 ± 10.3	90.1 ± 3.3	78.8 ± 6.6	79.5 ± 3.3

Data are presented as means (±SE)

**Table A-16.** Summary of continuous glucose monitoring data for the aerobic then resistance session

	<b>24 hours pre- exercise</b>	<b>Overnight pre- exercise</b>	<b>1 to 6 hours post- exercise</b>	<b>Overnight post-exercise</b>	<b>24 hours post- exercise</b>
Number of participants experiencing hypoglycemia	8/12 (67%)	4/12 (33%)	3/12 (25%)	3/12 (25%)	8/12 (67%)
Number of hypoglycemic events	20	4	3	5	19
Mean duration of hypoglycemia (minutes)	114 ± 41	33 ± 19	10 ± 6	45 ± 27	110 ± 48
Mean AUC for hypoglycemia	120 ± 45	37 ± 22	10 ± 7	47 ± 31	118 ± 51
Number of participants experiencing hyperglycemia	8/12 (67%)	4/12 (33%)	5/12 (42%)	3/12 (25%)	9/12 (75%)
Number of hyperglycemic events	20	7	5	4	14
Mean time spent in hyperglycemia	141 ± 48	47 ± 29	52 ± 27	27 ± 20	232 ± 93
Mean AUC for hyperglycemia	359 ± 177	136 ± 116	109 ± 66	24 ± 21	611 ± 311
Average maximum CGM glucose (mmol/l)	13.3 ± 1.1	9.4 ± 1.0	10.5 ± 0.9	8.2 ± 0.8	13.5 ± 1.1
Average minimum CGM glucose (mmol/l)	3.0 ± 0.2	4.2 ± 0.6	4.8 ± 0.6	4.6 ± 0.5	3.0 ± 0.2
Mean CGM glucose	6.9 ± 0.4	6.7 ± 0.9	7.7 ± 0.7	6.3 ± 0.7	7.4 ± 0.6
Proportion of time spent in hypoglycemia (%)	10.1 ± 3.0	9.0 ± 5.5	3.3 ± 2.1	12.6 ± 7.5	7.7 ± 3.3
Proportion of time spent in hyperglycemia (%)	9.8 ± 3.7	13.0 ± 8.5	17.2 ± 9.4	7.4 ± 5.6	16.1 ± 6.4
Proportion of time spent in euglycemia (%)	81.5 ± 4.4	78.0 ± 8.9	79.4 ± 9.5	80 ± 8.7	76.2 ± 7.0

Data are presented as means (±SE)

**Table A-17.** Summary of continuous glucose monitoring data for the resistance then aerobic session

	<b>24 hours pre- exercise</b>	<b>Overnight pre- exercise</b>	<b>1 to 6 hours post- exercise</b>	<b>Overnight post- exercise</b>	<b>24 hours post- exercise</b>
Number of participants experiencing hypoglycemia	8/11 (73%)	6/11 (55%)	4/12 (58%)	4/12 (33%)	7/12 (58%)
Number of hypoglycemic events	20	7	8	5	22
Mean duration of hypoglycemia (minutes)	111 ± 36	30 ± 12	24 ± 13	24 ± 15	111 ± 50
Mean AUC for hypoglycemia	109 ± 39	27 ± 12	27 ± 16	30 ± 23	131 ± 60
Number of participants experiencing hyperglycemia	10/11 (91%)	3/11 (27%)	8/12 (67%)	2/12 (17%)	10/12 (83%)
Number of hyperglycemic events	22	4	9	3	22
Mean time spent in hyperglycemia	193 ± 72	40 ± 33	33 ± 14	39 ± 31	211 ± 61
Mean AUC for hyperglycemia	270 ± 142	73 ± 67	75 ± 51	151 ± 124	629 ± 204
Average maximum CGM glucose (mmol/l)	12.7 ± 0.5	9.5 ± 0.9	10.9 ± 1.3	8.8 ± 1.2	14.7 ± 1.2
Average minimum CGM glucose (mmol/l)	2.9 ± 0.3	4.6 ± 0.9	5.2 ± 0.8	4.7 ± 0.8	3.4 ± 0.3
Mean CGM glucose	7.2 ± 0.5	6.9 ± 0.8	7.3 ± 0.8	6.7 ± 0.9	7.4 ± 0.5
Proportion of time spent in hypoglycemia (%)	7.7 ± 2.5	8.3 ± 3.4	8.1 ± 4.4	6.7 ± 4.3	7.7 ± 3.5
Proportion of time spent in hyperglycemia (%)	13.4 ± 5.0	11.1 ± 9.0	11.1 ± 4.8	10.9 ± 8.5	14.9 ± 4.2
Proportion of time spent in euglycemia (%)	78.9 ± 4.4	80.6 ± 8.8	80.8 ± 5.1	82 ± 8.8	77.4 ± 4.3

Data are presented as means (±SE)

## **APPENDIX B – RESEARCH ETHICS APPROVALS**



**Université d'Ottawa University of Ottawa**

Service de subventions de recherche et déontologie Research Grants and Ethics Services

### **HEALTH SCIENCES AND SCIENCE RESEARCH ETHICS BOARD**

#### **CERTIFICATE OF ETHICAL APPROVAL**

This is to certify that the University of Ottawa Health Sciences and Science Research Ethics Board has examined the application for ethical approval of the research project entitled **The Acute Effects of Aerobic and Resistance Exercise on Blood Glucose Levels and Whole Body Fuel Selection in Type 1 Diabetes (H 06-07-01)** submitted by Glen Kenny of the School of Human Kinetics of the University of Ottawa and Ron Sigal of the University of Calgary. Jane Yardley will also be working on this project for her Ph.D. thesis. The REB found that this research project met appropriate ethical standards as outlined in the Tri-Council Policy Statement and in the Procedures of the University of Ottawa Research Ethics Boards, and accordingly gave it a Category 1a (approval). This certification is valid one year from the date indicated below.

\_\_\_\_\_  
Catherine Paquet  
Protocol Officer for Ethics in Research  
For Daniel Lagarec, Chair of the  
Health Sciences and Science REB

August 30, 2007  
Date



**HEALTH SCIENCES AND SCIENCES RESEARCH ETHICS BOARD**  
**CERTIFICATION OF ETHICAL APPROVAL**

This is to certify that the University of Ottawa Health Sciences and Science Research Ethics Board (REB) examined the application for extension of ethics approval for the research project **The Acute Effects of Aerobic and Resistance Exercise on Blood Glucose Levels and Whole Body Fuel Selection in Type 1 Diabetes (File # H06-07-01)** submitted by Glen Kenny and Jane Yardley of the Department of Human Kinetics of the University of Ottawa. This project received initial ethics approval on August 30, 2007 by the REB as meeting appropriate ethical standards set out in the Tri-Council Policy Statement and in the Procedures of the University of Ottawa Research Ethics Boards. The University of Ottawa REB members are accordingly granting it a one-year extension of ethics approval. This extension is valid one year from the date indicated below.

\_\_\_\_\_  
Germain Zongo  
Protocol Officer for Ethics in Research  
For Daniel Lagarec, Chair of the  
Health Sciences and Sciences REB

August 30, 2008  
Date



**Ethics Approval Notice**  
**Health Sciences and Science REB**

**Principal Investigator / Supervisor / Co-investigator(s) / Student(s)**

<u>First Name</u>	<u>Last Name</u>	<u>Affiliation</u>	<u>Role</u>
Glen	Kenny	Health Sciences / Human Kinetics	Principal Investigator
Pierre	Boulay	Others / Others	Co-investigator
Jane	Yardley	Health Sciences / Others	Research Assistant

**File Number:** H06-07-01

**Type of Project:** Professor

**Title:** The Acute Effects of Aerobic and Resistance Exercise on Blood Glucose Levels and Whole Body Fuel Selection in Type 1 Diabetes

<b>Renewal Date (mm/dd/yyyy)</b>	<b>Expiry Date (mm/dd/yyyy)</b>	<b>Approval Type</b>
08/30/2009	08/29/2010	Ia

(Ia: Approval, Ib: Approval for initial stage only)

**Special Conditions / Comments:**  
N/A



**Ethics Approval Notice**  
**Health Sciences and Science REB**

**Principal Investigator / Supervisor / Co-investigator(s) / Student(s)**

<u>First Name</u>	<u>Last Name</u>	<u>Affiliation</u>	<u>Role</u>
Glen	Kenny	Health Sciences / Human Kinetics	Principal Investigator
Pierre	Boulay	Others / Others	Co-investigator
Jane	Yardley	Health Sciences / Others	Research Assistant

**File Number:** H06-07-01

**Type of Project:** Professor

**Title:** The Acute Effects of Aerobic and Resistance Exercise on Blood Glucose Levels and Whole Body Fuel Selection in Type 1 Diabetes

<b>Renewal Date (mm/dd/yyyy)</b>	<b>Expiry Date (mm/dd/yyyy)</b>	<b>Approval Type</b>
08/30/2010	08/29/2011	Ia

(Ia: Approval, Ib: Approval for initial stage only)

**Special Conditions / Comments:**

N/A



Le 13 décembre 2007

Dr Glen Kenny  
Université d'Ottawa  
School of Human Kinetics

**Objet : Approbation des projets de recherche en diabète**

Docteur,

La présente est pour vous informer de la décision du Comité de recherche de l'Hôpital Montfort d'accepter les deux projets de recherche suivants :

**«The Acute effects of resistance and aerobic exercise on blood levels and whole body fuel selection in trained type 1 diabetic subjects »;**

**«Effects of type 2 diabetes on body heat storage during physical work».**

Le Comité de recherche a consulté le Comité d'éthique avant de prendre la décision.

Vous pouvez discuter les modalités de fonctionnement avec Monsieur Brian Malcolmson de la Direction des affaires académiques au ( ) Vous devrez nous fournir un rapport d'étape et un sommaire des résultats de vos projets de recherche.

Nous vous remercions de l'intérêt que vous portez à la recherche au sein de l'Hôpital Montfort et nous vous souhaitons du succès dans votre étude.

Veillez agréer, ~~Docteur~~, l'assurance de nos meilleurs sentiments.

Dr Harvey Barkun  
Président du Comité de recherche

c.c Dr Pierre Boulay, gestionnaire, service de santé cardiovasculaire/clinique de diabète  
Mme Lucille Perreault, vice-présidente, direction des services cliniques  
Mme Diane Poirier, directrice par intérim, informations cliniques et support décisionnel  
M. Brian Malcolmson, vice-président associé, affaires académiques  
Dr André Bilodeau, vice-président, affaires académiques

Un hôpital d'enseignement affilié à l'Université d'Ottawa.



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Wednesday, September 24, 2008

Dr. Janine Malcolm  
The Ottawa Hospital - Riverside Campus  
Division of Endocrinology & Metabolism

Dear Dr. Malcolm:

**Re: Protocol # 2008454-01H The Acute Effects of Aerobic and Resistance Exercise on Blood Glucose Levels and Whole Body Fuel Section in Type 1 Diabetes**

**Protocol approval valid until - Monday, November 24, 2008**

Thank you for the letter from Ms. J. Richardson dated September 17, 2008. I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved for two months to start recruiting English-speaking participants. No changes, amendments or addenda may be made to the protocol or the consent form without the OHREB's review and approval.

Approval is for the following documentation:

Research Proposal received February 25, 2008

English Physical Activity Questionnaire (PAR-Q & YOU)

English AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire

English Medtronic System Gold Continuous Glucose Monitoring System Instructions

English Food and Insulin Diary

English and French Posters

English Information Letter and Consent Form (Pilot Testing Only) received September 19, 2008

English Information Letter and Consent Form received September 19, 2008

Upon receipt and review of the French AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire and the French Medtronic System Gold Continuous Glucose Monitoring System Instructions, the protocol may be extended to September 23, 2009 (one year from the initial approval date), and the recruitment of French-speaking participants may commence.

When submitting the French documentation to the OHREB, confirm that it has been translated or approved by Eric Lepine.

The validation date should be indicated on the bottom of all consent forms and information sheets (see copy attached).

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.



**Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches**

Monday, November 09, 2009

Dr. Janine Malcolm  
The Ottawa Hospital - Riverside Campus  
Division of Endocrinology & Metabolism

Dear Dr. Malcolm:

**RE: Protocol# - 2008454-01H The Acute Effects of Aerobic and Resistance Exercise on Blood Glucose Levels and Whole Body Fuel Section in Type 1 Diabetes**

**Renewal Expiry Date - Monday, November 08, 2010**

Thank you for the letter of October 23, 2009 from Colleen Gilchrist. I am pleased to inform you that your Annual Renewal Request (listed above) and the Revised English and French Information Letter and Consent Form, version dated October 02, 2009, were reviewed by the Ottawa Hospital Research Ethics Board (OHREB) and are approved. No changes, amendments or addenda may be made in the protocol or the consent form without the OHREB's review and approval.

Renewal is valid for a period of one year. The validation date should be indicated on the bottom of all consent forms and information sheets (see attached copy). Approximately one month prior to that time, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. As well, you must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

Raphael Saginur, M.D.  
Chairman  
Ottawa Hospital Research Ethics Board

Encl.

/km



FACULTY OF | UNIVERSITY OF  
MEDICINE | CALGARY

July 24, 2008

OFFICE OF MEDICAL BIOETHICS

Dr. Ronald J. Sigal  
Department of Medicine  
Alberta Children's Hospital  
Calgary, Alberta

Dear Dr. Sigal:

Re: **Type 1 Diabetes Aerobic and Resistance Exercise (T1-DARE)**

Ethics ID: 20806

Your request to modify the above-named protocol and consent form has been reviewed and approved.

I am pleased to advise you that it is permissible for you to modify the above-noted clinical trial by adding a substudy entitled, "A Substudy of the T1-DARE Study: The Acute Effects of Aerobic and Resistance Exercise on Blood Glucose Levels and Whole Body Fuel Selection in Type 1 Diabetes", based on the information contained in your correspondence dated June 5, 2008.

I am pleased to advise you that it is permissible for you to use the following documents, which you have provided for the above-named protocol in your correspondence dated June 5, 2008:

- Thesis committee approval form (University of Ottawa, Defense held on: November 19, 2007)
- University of Ottawa Ethics committee approval form (dated August 30, 2007)
- Monfort Hospital Research Ethics committee approval form (dated December 13, 2007)
- Consent Form (Version 1.0, dated June 5, 2008)
- Description of the rationale and protocol of the substudy

A progress report concerning this study is required annually, from the date of the original approval (2007-05-17). The report should contain information concerning:

- (i) the number of subjects recruited;
- (ii) a description of any protocol modification;
- (iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
- (iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
- (v) a copy of the current informed consent form;
- (vi) the expected date of termination of this project;

Thank you for the attention which I know you will bring to these matters.

Yours sincerely,

Stacey A. Page, PhD  
Acting Chair, Conjoint Health Research Ethics Board

SAP/cw

c.c. Ms. Diana Mitchell

## APPENDIX C – HEALTH QUESTIONNAIRES

Physical Activity Readiness  
Questionnaire - PAR-Q  
(revised 2002)

# PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
<input type="checkbox"/>	<input type="checkbox"/>	1. <b>Has your doctor ever said that you have a heart condition <u>and</u> that you should only do physical activity recommended by a doctor?</b>
<input type="checkbox"/>	<input type="checkbox"/>	2. <b>Do you feel pain in your chest when you do physical activity?</b>
<input type="checkbox"/>	<input type="checkbox"/>	3. <b>In the past month, have you had chest pain when you were not doing physical activity?</b>
<input type="checkbox"/>	<input type="checkbox"/>	4. <b>Do you lose your balance because of dizziness or do you ever lose consciousness?</b>
<input type="checkbox"/>	<input type="checkbox"/>	5. <b>Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?</b>
<input type="checkbox"/>	<input type="checkbox"/>	6. <b>Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?</b>
<input type="checkbox"/>	<input type="checkbox"/>	7. <b>Do you know of <u>any other reason</u> why you should not do physical activity?</b>

If  
you  
answered

### YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

### NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active — begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal — this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

### DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever — wait until you feel better; or
- if you are or may be pregnant — talk to your doctor before you start becoming more active.

**PLEASE NOTE:** If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

**Informed Use of the PAR-Q:** The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

**No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.**

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME \_\_\_\_\_

SIGNATURE \_\_\_\_\_

DATE \_\_\_\_\_

SIGNATURE OF PARENT  
or GUARDIAN (for participants under the age of majority) \_\_\_\_\_

WITNESS \_\_\_\_\_

**Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.**



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continued on other side...

# Q-AAP et VOUS

(Un questionnaire pour les gens de 15 à 69 ans)

L'exercice physique pratiqué d'une façon régulière constitue une occupation de loisir saine et agréable. D'ailleurs, de plus en plus de gens pratiquent une activité physique de façon régulière. Règle générale, augmenter la pratique sportive n'entraîne pas de risques de santé majeurs. Dans certains cas, il est cependant conseillé de passer un examen médical avant d'entreprendre un programme régulier d'activités physiques. Le Q-AAP (questionnaire sur l'aptitude à l'activité physique) vise à mieux cerner les personnes pour qui un examen médical est recommandé.

Si vous prévoyez modifier vos habitudes de vie pour devenir un peu plus actif(ve), commencez par répondre aux 7 questions qui suivent. Si vous êtes âgé(e) de 15 à 69 ans, le Q-AAP vous indiquera si vous devez ou non consulter un médecin avant d'entreprendre votre nouveau programme d'activités. Si vous avez plus de 69 ans et ne participez pas d'une façon régulière à des activités physiques exigeantes, vous devriez consulter votre médecin avant d'entreprendre ces activités.

Lisez attentivement et répondez honnêtement à chacune des questions suivantes. Le simple bon sens sera votre meilleur guide pour répondre correctement à ces questions. Cochez OUI ou NON.

OUI	NON	
<input type="checkbox"/>	<input type="checkbox"/>	1. Votre médecin vous a-t-il déjà dit que vous souffriez d'un problème cardiaque <u>et</u> que vous ne deviez participer qu'aux activités physiques prescrites et approuvées par un médecin?
<input type="checkbox"/>	<input type="checkbox"/>	2. Ressentez-vous une douleur à la poitrine lorsque vous faites de l'activité physique?
<input type="checkbox"/>	<input type="checkbox"/>	3. Au cours du dernier mois, avez-vous ressenti des douleurs à la poitrine lors de périodes autres que celles où vous participiez à une activité physique?
<input type="checkbox"/>	<input type="checkbox"/>	4. Éprouvez-vous des problèmes d'équilibre reliés à un étourdissement ou vous arrive-t-il de perdre connaissance?
<input type="checkbox"/>	<input type="checkbox"/>	5. Avez-vous des problèmes osseux ou articulaires (par exemple, au dos, au genou ou à la hanche) qui pourraient s'aggraver par une modification de votre niveau de participation à une activité physique?
<input type="checkbox"/>	<input type="checkbox"/>	6. Des médicaments vous sont-ils actuellement prescrits pour contrôler votre tension artérielle ou un problème cardiaque (par exemple, des diurétiques)?
<input type="checkbox"/>	<input type="checkbox"/>	7. Connaissez-vous <u>une autre raison</u> pour laquelle vous ne devriez pas faire de l'activité physique?

Si vous  
avez  
répondu

## OUI à une ou plusieurs questions

Consultez votre médecin AVANT d'augmenter votre niveau de participation à une activité physique et AVANT de faire évaluer votre condition physique. Dites à votre médecin que vous avez complété le questionnaire sur l'aptitude à l'activité physique et expliquez-lui précisément à quelles questions vous avez répondu «OUI».

- Il se peut que vous n'ayez aucune contre-indication à l'activité physique dans la mesure où vous y allez lentement et progressivement. Par ailleurs, il est possible que vous ne puissiez faire que certains types d'efforts adaptés à votre état de santé. Indiquez à votre médecin le type d'activité physique que vous comptez faire et suivez ses recommandations.
- Informez-vous quant aux programmes d'activités spécialisés les mieux adaptés à vos besoins, offerts dans votre localité.

## NON à toutes ces questions

Si, en toute honnêteté, vous avez répondu «NON» à toutes les questions du Q-AAP, vous êtes dans une certaine mesure, assuré(e) que:

- vous pouvez augmenter votre pratique régulière d'activités physiques en commençant lentement et en augmentant progressivement l'intensité des activités pratiquées. C'est le moyen le plus simple et le plus sécuritaire d'y arriver.
- vous pouvez faire évaluer votre condition physique. C'est le meilleur moyen de connaître votre niveau de condition physique de base afin de mieux planifier votre participation à un programme d'activités physiques.

## REMETTRE À PLUS TARD L'AUGMENTATION DE VOTRE PARTICIPATION ACTIVE :

- si vous souffrez présentement de fièvre, d'une grippe ou d'une autre affection passagère, attendez d'être remis(e); ou
- si vous êtes enceinte ou croyez l'être, consultez votre médecin avant de modifier votre niveau de pratique sportive régulière.

**Veillez noter** que si votre état de santé se trouve modifié de sorte que vous deviez répondre «OUI» à l'une ou l'autre des questions précédentes, consultez un professionnel de la santé ou de la condition physique, afin de déterminer s'il vous faut modifier votre programme d'activités.

**Formule de consentement du Q-AAP:** La Société canadienne de physiologie de l'exercice, Santé Canada et ses représentants n'assument aucune responsabilité vis-à-vis des accidents qui pourraient survenir lors de l'activité physique. Si, après avoir complété le questionnaire ci-dessus, un doute persiste quant à votre aptitude à faire une activité physique, consultez votre médecin avant de vous y engager.

**Toute modification est interdite. Nous vous encourageons à copier le Q-AAP dans sa totalité.**

Dans la mesure où le Q-AAP est administré avant que la personne ne s'engage dans un programme d'activités ou qu'elle fasse évaluer sa condition physique, la section suivante constitue un document ayant une valeur légale et administrative.

«Je soussigné(e) affirme avoir lu, compris et complété le questionnaire et avoir reçu une réponse satisfaisante à chacune de mes questions.»

NOM \_\_\_\_\_

SIGNATURE \_\_\_\_\_

DATE \_\_\_\_\_

SIGNATURE D'UN PARENT  
or TUTEUR (pour les mineurs) \_\_\_\_\_

TÉMOIN \_\_\_\_\_

**N.B. – Cette autorisation de faire de l'activité physique est valide pour une période maximale de 12 mois à compter du moment où le questionnaire est rempli. Elle n'est plus valide si votre état de santé change de telle sorte que vous répondiez «OUI» à l'une des sept questions.**



© Société canadienne de physiologie de l'exercice

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suite au verso...

**Table 2. AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire**

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Assess your health needs by marking all true statements.

History

You have had:

- a heart attack
- heart surgery
- cardiac catheterization
- coronary angioplasty (PTCA)
- pacemaker/implantable cardiac defibrillator/rhythm disturbance
- heart valve disease
- heart failure
- heart transplantation
- congenital heart disease

If you marked any of the statements in this section, consult your healthcare provider before engaging in exercise. You may need to use a facility with a medically qualified staff.

Symptoms

- You experience chest discomfort with exertion.
- You experience unreasonable breathlessness.
- You experience dizziness, fainting, blackouts.
- You take heart medications.

Other health issues:

- You have musculoskeletal problems.
- You have concerns about the safety of exercise.
- You take prescription medication(s).
- You are pregnant.

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Cardiovascular risk factors

- You are a man older than 45 years.
- You are a woman older than 55 years or you have had a hysterectomy or you are postmenopausal.
- You smoke.
- Your blood pressure is >140/90.
- You don't know your blood pressure.
- You take blood pressure medication.
- Your blood cholesterol level is >240 mg/dL.
- You don't know your cholesterol level.
- You have a close blood relative who had a heart attack before age 55 (father or brother) or age 65 (mother or sister).
- You are diabetic or take medicine to control your blood sugar.
- You are physically inactive (ie, you get <30 minutes of physical activity on at least 3 days per week).

If you marked 2 or more of the statements in this section, consult your healthcare provider before engaging in exercise. You might benefit by using a facility with a professionally qualified exercise staff to guide your exercise program.

\_\_\_\_\_ You are >20 pounds overweight.

None of the above is true.

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You should be able to exercise safely without consulting your healthcare provider in almost any facility that meets your exercise program needs.

## Tableau 2. Questionnaire de l'AHA/ACSM à l'intention des centres de santé et de conditionnement physique en vue du dépistage préparatoire

Évaluez vos besoins de santé en cochant tous les énoncés qui s'appliquent :

Antécédents médicaux :

Vous avez déjà eu :

- une crise cardiaque
- une chirurgie cardiaque
- un cathétérisme cardiaque
- une angioplastie coronaire
- un stimulateur cardiaque/défibrillateur implantable cardiaque/des troubles de rythme cardiaque
- une maladie de valvule cardiaque
- une insuffisance cardiaque
- une greffe du cœur
- une cardiopathie congénitale

Si vous avez coché un des énoncés dans cette section, veuillez consulter votre médecin avant d'entreprendre tout programme d'activités physiques. Il est possible que vous ayez à faire appel à des installations employant du personnel avec des compétences médicales.

Symptômes

Autres problèmes de santé :

- Vous souffrez de douleurs au niveau de la poitrine quand vous faites des efforts physiques.
- Vous souffrez d'essoufflements excessifs.
- Vous avez connu sensations vertigineuses ou des évanouissements
- Vous prenez des médicaments pour votre cœur.

- Vous souffrez de troubles musculosquelettiques.
- La pratique d'activités physiques vous inquiète.
- Vous faites appel à de(s) médicament(s) sous ordonnance.
- Vous êtes enceinte.

Critères de risque cardiovasculaire :

- Vous êtes un homme âgé de 45 ans ou plus.
- Vous êtes femme âgée de 55 ans ou plus ou vous avez subi une hystérectomie ou vous êtes ménopausée.
- Vous êtes fumeur.
- Votre tension artérielle est >140/90.
- Vous ne connaissez pas votre tension artérielle.
- Vous prenez des médicaments

Si vous avez coché deux ou plus des énoncés dans cette section, consultez votre médecin avant d'entreprendre tout programme d'activités physiques. Il serait préférable de faire appel à des installations employant du personnel ayant des compétences médicales qui saura diriger votre programme d'exercices.

pour votre tension artérielle.

— Votre taux de cholestérol sanguin est >240 mg/dL.

— Vous ne connaissez pas votre taux de cholestérol.

— Un membre de votre famille immédiate a souffert d'une crise cardiaque avant l'âge de 55 ans (père ou frère) ou 65 ans (mère ou sœur)

— Vous êtes diabétique ou vous prenez des médicaments pour le contrôle de votre taux de glycémie.

— Vous êtes inactif (c.-à-d., vous vous adonnez à <30 minutes d'activités physiques au moins trois fois par semaine).

— Vous avez 20 livres en trop.

— Aucun des énoncés précédents ne s'applique.

Vous devriez être en mesure d'entreprendre un programme d'activités physiques en toute sécurité sans devoir consulter votre médecin. La plupart des installations sportives sauront répondre à vos besoins.

## **APPENDIX D –INFORMATION LETTERS AND CONSENT FORMS**

### **Information Letter and Consent Form**

#### **The acute effects of resistance and aerobic exercise on blood glucose levels and whole body fuel selection in type 1 diabetes**

##### **Investigators:**

Dr. Glen Kenny (Ph.D.), Professor  
University of Ottawa, School of Human Kinetics

Dr. Ron Sigal (MD), Associate Professor  
University of Calgary  
Departments of Medicine / Cardiac Sciences / Community Health Sciences / Kinesiology

Jane Yardley, Ph.D. Student  
University of Ottawa, Institute of Population Health

Dr. Pierre Boulay, Manager  
Clarence Rockland Family Health Team

Dr. Janine Malcolm, Assistant Professor  
Division of Endocrinology, Dept. of Medicine, University of Ottawa

## **Background**

Exercise is strongly recommended for type 1 diabetic patients in order to reduce the risk of diabetes-related complications. Aerobic activity, while providing many health benefits, may not improve glycemic control in type 1 diabetes, and actually increases the risk of hypoglycemia. When added to aerobic exercise, anaerobic activity, such as sprinting, causes an increase in blood glucose and provides more stable glucose profiles in the immediate hours after exercise. It is possible that resistance exercise may have the same effect, but this remains unexplored. Examining fuel selection (where the primary source of fuel (carbohydrate, protein, or lipid) being used by the body is determined by measuring gas exchange) alongside blood glucose will provide information on the mechanism by which these activities affect blood glucose levels.

## **Purpose**

The primary aim of this study is to determine the acute effects of resistance exercise on blood glucose control and fuel selection in type 1 diabetes and to compare these to the effects of aerobic exercise. We will also determine the effects of combining these two types of exercise into a single training session, and explore how the order in which the exercise modalities are performed affects blood glucose during and after exercise.

Your participation in this study will help us increase our understanding of the acute effects of resistance and aerobic exercise (whether performed individually or combined) on blood glucose levels and fuel selection in type 1 diabetes. This will aid in eventually providing type 1 diabetic patients with the safest and most beneficial exercise prescriptions possible. Funding for this research is provided by the Canadian Diabetes Association. This research study is also part of Drs Kenny and Sigal's CIHR funded Resistance Exercise in Already-active Type 1 Diabetic Individuals (READI) and Type 1 Diabetes Aerobic and Resistance Exercise (T1-DARE) studies. Portions of the data collected will be used by Ms. Jane Yardley in the preparation of her PhD thesis dissertation.

## **Preliminary session**

The preliminary session and the test sessions will take place at the University of Ottawa in the Human Bioenergetics and Environmental Physiology Laboratory or at the Cardiovascular Health Service Clinic of the Montfort Hospital. The preliminary session will take approximately 45 minutes to an hour. During this session we will review with you all of the procedures, equipment and measuring devices that will be used throughout the experimental sessions.

During this session you will also be asked to fill out the following questionnaires: Physical Activity Readiness Questionnaire (PAR-Q) and American Heart Association/American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire (AHA/ACSM HFFPSQ). These are standard questionnaires that will allow us to evaluate your general physical health, level of physical activity, and readiness to perform exercise.

At the end of the familiarization session, you will be given the opportunity to read the Background and Informed Consent document, approved by the University of Ottawa Ethics Board, in its entirety. If you are still willing to take part in the study, we will ask you to sign the informed consent below.

After the preliminary session, but prior to the first experimental session, you will be asked to present yourself either at the Gamma-Dynacare laboratory at the University of Ottawa Health Services Clinic or at the Cardiovascular Health Service Clinic of the Montfort Hospital. Blood will be drawn and tested for blood glucose. You will be asked to take a capillary reading with your home testing kit immediately after the venipuncture so that the accuracy of your home meter can be assessed. Once the analysis has been performed, blood samples will be properly destroyed and discarded by the respective laboratories.

If you were not part of the T1-DARE or READI studies you will also be required to schedule a blood test at the Gamma-Dynacare laboratory at the University of Ottawa Health Services Clinic or at the Cardiovascular Health Service Clinic of the Montfort Hospital to ensure that your HbA1c is less than 9%. You will also be required to schedule a strength test (8RM) and a maximal aerobic capacity test at the Montfort Hospital or at the University of Ottawa. The 8RM strength test will determine the maximum weight you can safely lift 8 times on each of the six weight machines being used during the resistance exercise tests (see exercise description below).

### **Experimental test sessions**

Experimental sessions will be conducted by Ms. Jane Yardley of the Institute of Population Health, under the supervision of Dr. Glen Kenny and will last approximately 4 hours. You will be scheduled to attend 5 separate testing sessions, a minimum of 5 days apart.

On the day prior to each experimental session, you will be asked to insert the sensor of the continuous glucose monitoring system under your skin. We will train you on how to do this and assist you in the process. The sensors are designed to be worn 72 hours and will remain inserted until the day after the exercise test where you will be able to remove it yourself. You will also be asked to test your capillary glucose 4 times per day using a glucose meter, and use these values to calibrate the continuous glucose monitor. In addition to the verbal and physical instruction on sensor and monitor usage provided during the preliminary session, you will also be provided with an instruction manual for the product. At the same time you will be provided with a pedometer (step counter) which we will ask you to use to track your background physical activity levels. You will be asked to wear the pedometer at all times while you are awake, except when you are showering, bathing or swimming.

Before each testing session, you will be asked to refrain from intense physical activity for a period of 48 hours prior to the insertion of the sensor, and to avoid caffeine and alcohol for a 24 hour period before the testing session. In addition, you will be asked to keep a detailed diary of food intake and insulin administration for 36 hours before the first test. Over the three day test period we will ask you to eat the same breakfast, lunch, dinner and snacks at as close as possible to the same times as you did on the first day. You will then be asked to repeat this pattern as closely as possible for the rest of your visits.

It will also be necessary to make a small adjustment to your insulin intake on the exercise testing days. As per the guideline provided with the READI and T1-DARE studies, if you are taking insulin three times or more a day you will be asked to reduce your morning dose by 10%. If you are using an insulin pump you will be asked to decrease your basal rate by 50% one hour before exercise and maintain it at this level until 1 hour after exercise. Further needs will be assessed on an individual basis, based on capillary glucose readings throughout the experimental sessions.

On test days, you will be asked to consume a standardized snack (which we will have provided you with) at 4pm before coming to the laboratory. We will ask you to arrive at the laboratory at 4pm in exercise clothing (shorts, t-shirt, running shoes). Over the following hour, we will ask you to perform three finger stick tests to ensure that you have both stable and safe blood glucose levels (between 5 and 13.9 mmol/L) prior to the onset of exercise. The first of these will take place as soon as you arrive, the second 30 minutes later, and the final one immediately before beginning exercise. If your blood glucose is high (>14 mmol/L) we will ask you to perform an additional finger stick for a meter test of blood ketones. If no or minimal ketones are present and blood glucose is below 20 mmol/L you will be asked to wait until your blood glucose levels decrease. If, however, blood glucose is greater than 20 mmol/L subjects you will be asked to inject 30% of your usual correction bolus, and wait until your glucose levels are lower before beginning exercise. Should ketones be present in moderate to large quantities, you will be asked to inject a correction bolus of insulin, and the testing session will be postponed to another date.

If blood glucose levels are low (i.e. near 4.5 mmol/L and showing a decreasing trend, or below 4.5 mmol/L) you will be provided with 32g of glucose in tablet form. You will then be asked to check your capillary glucose levels after 15 minutes to ensure that levels are increasing. If a blood glucose level of at least 5.7 mmol/L is not achieved, these steps will be repeated.

If initial blood glucose is between 4.5 and 5.6 mmol/L, you will be provided with 16g of glucose in tablet form. You will then be asked to check your capillary glucose levels after 15 minutes, and exercise will be permitted when a level of at least 5.7 mmol/L is achieved. Should the correct range not be reached within 90 minutes, the exercise session will be rescheduled. You will also perform a finger stick test after 45 minutes of exercise, and/or upon completion of exercise, with the necessary insulin and glucose adjustments (same as above) being made where necessary

We will be taking notes on all measurements taken (including height, weight, and blood pressure) and all actions taken throughout the testing session. For the final 20 minutes before exercise, during exercise and for 20 minutes after exercise you will be asked to wear a portable gas analysis system (Oxycon Mobile, Jaeger; Hoechberg, Germany). You will be asked to lie down while wearing this system for the measurement of pre and post-exercise values.

The following five exercise sessions (one per visit) will be performed in a random order (similar to being drawn out of a hat):

- 1) Aerobic exercise session: You will be asked to run on a treadmill at a moderate pace (60% VO<sub>2</sub>max) for a period of 45 minutes.
- 2) Resistance exercise session: You will be asked to perform three sets of eight repetitions of supine bench press, leg press, shoulder press, abdominal crunches, lat pulldown, leg curl and seated cable row. A rest period of 60 seconds will be provided between sets. This will take approximately 45 minutes.
- 3) Aerobic-Resistance exercise session: This exercise session will combine the exercises from both the aerobic and resistance exercise sessions, with the aerobic exercises being performed before the resistance exercises. This will take approximately 85 to 90 minutes.
- 4) Resistance-Aerobic exercise session: This exercise session will be the same as 3) above, except that the resistance exercise will take place before the aerobic exercise.
- 5) Resting (control) session: You will spend 45 minutes in the laboratory resting in a sitting or supine position.

Before you start exercising, either a registered nurse or research staff delegated by the study physician will insert a catheter in your arm so that we may take blood samples from you throughout exercise. These will be used to determine the levels of certain chemical compounds (hormones, catecholamines etc.) in your blood. We will take samples of your blood just before starting exercise, 5, 10, 15, 30, and 45 minutes into each type of exercise (aerobic/resistance), at the end of exercise, and 5, 10, 15, 20, 30, 45 and 60 minutes post-exercise. We will be freezing these samples for analyses that will be performed at the end of the study, and will continue to store the samples for additional, later testing unless you ask us to destroy them. At that point, samples would be disposed of through the biohazard waste systems in place at the University of Ottawa and the Montfort Hospital. You will be asked to measure blood glucose by finger prick at baseline, mid-exercise and at the end of exercise. Oxygen consumption will be measured during all activities for the purpose of calculating energy expenditure and determining fuel consumption. On the day after the test the continuous glucose monitoring system will be retrieved by the investigators so that blood glucose profiles before, during and after exercise may be downloaded and examined.

All of the exercise listed above will take place in the Human Bioenergetics and Environmental Physiology Laboratory (room 308-309 of the Montpetit Building) or at the Cardiovascular Health Service Clinic of the Montfort Hospital. Tests for female subjects will be scheduled so that they take place in the same phase of the menstrual cycle (either follicular or luteal). To determine oestrogen and progesterone levels, blood samples will be taken by a trained individual at the Gamma-Dynacare laboratory at the University of Ottawa Health Services Clinic or at the Cardiovascular Health Service Clinic of the Montfort Hospital. Once the analysis has been performed, blood samples will be properly destroyed and discarded by the respective laboratories.

### **Experimental Procedures**

**Continuous Glucose Monitoring System:** On the morning of the day prior to testing, you will be asked to insert a sensor under your skin in the gluteal region (the back of your hip, just below the waist) with the assistance of a "Sensarter" device designed for this purpose. All sensors, Sensarters, and continuous glucose monitoring systems will be provided by the investigators, as well as instruction for their proper insertion and calibration. You will also be provided with written instructions, trouble-shooting guides, and emergency contacts should you encounter any difficulties.

**Capillary blood glucose test:** You will already be very familiar with this test (a.k.a finger stick test) as it is already part of daily blood glucose self-management for type 1 diabetic individuals. The test, which will be performed once prior to, once during, and once after exercise, involves pricking the end of a finger with a sterilized spring-loaded lancing device so that the resulting blood droplet may be placed on a test strip inserted

in a blood glucose meter. You will be asked to bring your regular blood glucose testing kit to the lab with you, and will perform the test yourself, as you would regularly do at home.

Oxygen consumption: Oxygen consumption will be measured either by use of an automated metabolic cart (MOXUS system) or a portable gas exchange system (Jaeger System). You will be wearing a breathing valve (mask) connected to either the MOXUS or Jaeger systems for the majority of the study. During this time, you will also be required to wear a nose plug.

Heart rate: A strap will be placed around your chest in order to measure your heart rate during exercise (Polar Vantage heart rate monitor).

Pedometer: You will be asked to wear a pedometer (step counter) at or near your waist while you are wearing the continuous glucose monitoring system. Each day you will be asked to record the number of steps taken on the line provided at the top of the food diary forms. This will allow us to assess your background day-to-day physical activity levels.

Electrocardiogram (ECG): During the maximal aerobic capacity test, a qualified technician will perform an electrocardiogram to screen for cardiac abnormalities. This will allow us to exclude individuals with cardiac abnormalities and reduce the risk of a cardiac event during the trials. Although the test does not pose any risk to you, the placement of the electrodes may require that areas of your chest be shaved. There is also a small chance that the removal of the adhesive used to hold the electrodes in place might cause some skin irritation or discomfort.

### **Risks**

While the risks associated with physical activity are minimal for healthy and well-controlled type 1 diabetic individuals performing submaximal exercise, maximal exercise tests can sometimes be associated with chest pain, nausea, abnormal blood pressure, dizziness, fainting, leg cramps and fatal injury. The incidence of cardiac arrest during such tests is approximately 1 in 10 000 tests. In order to minimize these risks, the conditions for human exercise experiments as described by the Canadian Society for Exercise Physiology and the American College of Sports Medicine will be met. There will be at least one researcher present for all testing sessions, who will be well-practiced in CPR and First Aid. You may stop at any time during either the maximal exercise test, or the submaximal exercise sessions.

Subcutaneous (under the skin) blood glucose sensors as well as the adhesives that hold them in place can cause both mild sensitivity and skin irritation in the insertion areas. Although rare, there is also a possibility of infection at the sensor insertion site. This risk can be minimized by properly cleaning all necessary skin surfaces (including your hands) and equipment prior to the insertion of the sensor.

The possibility of muscle, bone or joint injury exists in any setting where physical activity is being performed. Performing a light warm-up prior to exercise, the use of proper lifting and breathing techniques, as well as the use of pre-determined submaximal resistance will minimize these risks. You will also be supervised throughout the exercise sessions and may discontinue at any time should you experience any unusual sensations or injury-related discomfort.

There is a risk of infection, bruising and discomfort during and following a venipuncture to sample blood. Venipunctures associated with blood sampling will be performed by a trained individual at Gamma-Dynacare laboratory (University of Ottawa Health Services Clinic) or at the Montfort Hospital and will follow standard care procedures. The affected area will be prepared by treatment with isopropyl alcohol and/or hydrogen peroxide applied by sterile gauze pads. Once analysis has been completed, both laboratories immediately discard and properly destroy all blood samples.

There is a risk of infection, bruising and discomfort during and following the insertion of an intravenous (iv) catheter for blood sampling. Catheters will be inserted by a registered nurse or trained research staff delegated by the study physicians. Standard care procedures will be followed in order to minimize all risks of infection. There is also a slight risk that the catheter might be disturbed during exercise. To minimize this risk tubes will be taped firmly to your body, and monitored carefully by the researchers while you are exercising.

Physical activity is associated with an increased risk of hypoglycemia (low blood sugar) in type 1 diabetic individuals. In order to avoid hypoglycemia during exercise, you will not be permitted to begin exercise unless your blood glucose levels, as measured by a pre-exercise finger stick test, are within a safe range (5 to 13.9 mmol/L). If your blood glucose is excessively high (>14 mmol/L) we will test for the presence of ketones. If no or minimal ketones are present and blood glucose is below 20 mmol/L you will be asked to wait until your blood glucose levels decrease. If, however, blood glucose is greater than 20 mmol/L subjects you will be asked to inject 30% of your usual correction bolus, and wait until your glucose levels are lower before beginning exercise. Should ketones be present in moderate to large quantities, your will be asked to inject a correction bolus of insulin, and the testing session will be postponed to another date.

If blood glucose levels are low (i.e. near 4.5 mmol/L and showing a decreasing trend, or below 4.5 mmol/L) you will be provided with 32g of glucose in tablet form. You will then be asked to check your capillary glucose levels after 15 minutes to ensure that levels are increasing. If a blood glucose level of at least 5.7 mmol/L is not achieved, these steps will be repeated.

Finally, if initial blood glucose is between 4.5 and 5.6 mmol/L, you will be provided with 16g of glucose in tablet form. You will then be asked to check your capillary glucose levels after 15 minutes, and exercise will be permitted when a level of at least 5.7 mmol/L is achieved. Should the correct range not be reached within 90 minutes, the exercise session will be rescheduled. You will also perform a finger stick test after 45 minutes of exercise, and/or upon completion of exercise, with the necessary insulin and glucose adjustments (same as above) being made where necessary

Should a health-related emergency occur, all lab personnel at the University and the Hospital are trained in CPR and first aid. Phones are located both in the weight room and the laboratory at the University of Ottawa so that the University emergency response (University Protection Office) may be immediately contacted ensuring that prompt medical attention is provided. Emergency services are available at the Montfort Hospital.

#### **Anonymity and Confidentiality**

Your anonymity is ensured throughout all aspects of this research study. All data collected in this study will be stored on a password-protected computer using a coding system. As such, no one will be able to identify you as your name will not appear on these files. All data and records, both in electronic and paper format, will be kept in a locked office, which is accessible only to the investigators. Only the research team will have access to your data. All data collected over the course of the study will be kept for a period of 15 years following the completion date of the study, at which point it will be destroyed accordingly.

The data collected in this study will be submitted for publication in scientific journals and will be used by Ms. Jane Yardley as part of her PhD thesis work.

No records bearing your name will leave the institution. You will not be identified by name in any reports or publications. You are encouraged to request and discuss the results of the experimental trials at any time.

The Ottawa Hospital Research Ethics Board, the Ottawa Health Research Institute, the Sisters of Charity Research Ethics Board and the Montfort Hospital Research Ethics Board may review your relevant study records under the supervision of Dr. Janine Malcolm's staff for audit purposes.

**For the entire duration of the study, it is fully understood that you may refuse to participate or withdraw from the study at any time.**

## **INFORMED CONSENT OF THE PARTICIPANT**

Research involving human subjects requires written consent of the participants.

I, \_\_\_\_\_, hereby volunteer to participate as a subject in the study entitled “**The acute effects of resistance and aerobic exercise on blood glucose levels and fuel selection in type 1 diabetes**”. The experiment has been clearly described to me, I have read the information presented in this 9-page document and I have had the opportunity to ask questions to the investigators.

I understand that there are 5 experimental test sessions, that they each take approximately 4 hours, and that I will be compensated for my time and expenses to a maximum of \$50 per experimental session.

Income earned as a result of your participation in this study, which is not for reimbursement of study expenses, will be considered taxable income by Revenue Canada. In order to receive payment for your participation in this study, it will be necessary to provide the investigator or their delegate with your Social Insurance Number. The Ottawa Hospital will then issue a T4A for any amount over \$500.00, by the end of February of the following year.

I recognize that as a participant, I will be exposed to some risks associated with exercise, hypoglycaemia, and the experimental equipment. I also acknowledge that by participating in this study I may be exposed to certain risks that are currently unforeseen.

I am aware that I am free to refuse to participate and if I consent to participate, I may withdraw my consent at any time. I know that I can ask questions before, during or after the various tests. I recognize that the only benefits that I will receive from this study are a free VO<sub>2</sub> max test and printed copies of my 72-hour blood glucose profiles for each experimental session.

Please choose and initial one of the following:

- If I withdraw from the study, the researchers may continue to use my data for the purposes of this study. \_\_\_\_\_
- If I withdraw from the study, I wish for the data gathered from me until the time of my withdrawal to be destroyed and not used. \_\_\_\_\_

I am aware and accept that the data collected may be used in future analyses and publications.

I recognize that the University of Ottawa Research Ethics Board, the Ottawa Hospital Research Ethics Board, the Ottawa Health Research Institute, and the Montfort Hospital Research Ethics Board may audit study records.

**I understand that if I have any questions regarding the conduct of this study, I may contact Ms. Jane Yardley or Dr. Glen Kenny.**

If I have any questions with regards to the ethical conduct of the study, I may contact the Protocol Officer for Ethics in Research any of the following institutions: the University of Ottawa, the Montfort Hospital, or the Ottawa Hospital.

I have been given a copy of this consent form, as well as the background information sheet for me to keep. A copy of this signed document will be provided to the study physician.

Signature of Participant: \_\_\_\_\_ Date: \_\_\_\_\_

Printed Name of Witness: \_\_\_\_\_

Signature of Witness: \_\_\_\_\_ Date: \_\_\_\_\_

Printed Name of Researcher: \_\_\_\_\_

Signature of Researcher: \_\_\_\_\_ Date: \_\_\_\_\_

## **INFORMED CONSENT OF THE PARTICIPANT**

Research involving human subjects requires written consent of the participants.

I, \_\_\_\_\_, hereby volunteer to participate as a subject in the study entitled “**The acute effects of resistance and aerobic exercise on blood glucose levels and fuel selection in type 1 diabetes**”. The experiment has been clearly described to me, I have read the information presented in this 9-page document and I have had the opportunity to ask questions to the investigators.

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Please choose and initial one of the following:

- If I withdraw from the study, the researchers may continue to use my data for the purposes of this study. \_\_\_\_\_
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I have been given a copy of this consent form, as well as the background information sheet for me to keep. A copy of this signed document will be provided to the study physician.

Signature of Participant: \_\_\_\_\_ Date: \_\_\_\_\_

Printed Name of Witness: \_\_\_\_\_

Signature of Witness: \_\_\_\_\_ Date: \_\_\_\_\_

Printed Name of Researcher: \_\_\_\_\_

Signature of Researcher: \_\_\_\_\_ Date: \_\_\_\_\_

**Lettre d'information et formulaire de consentement**

**Les effets aigus de l'exercice en résistance et d'aérobie sur les niveaux de glycémie et l'utilisation des substrats énergétiques dans le diabète de type 1**

**Chercheurs:**

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D<sup>r</sup> Ron Sigal, Professeur associé  
Université de Calgary  
Départements de Médecine/Sciences cardiaques/Sciences de Santé communautaire/Sciences de l'activité physique

Jane Yardley, Étudiante au doctorat  
Université d'Ottawa, Institut de recherche de la santé des populations

D<sup>r</sup> Pierre Boulay, Gestionnaire  
Équipe de Santé Familiale de Clarence-Rockland

D<sup>r</sup> Janine Malcolm, Professeure Assistante  
Division d'endocrinologie, Dép. de Médecine, Université d'Ottawa

### **Antécédents**

L'exercice est vivement recommandé pour les patients avec le diabète de type 1 afin de réduire le risque de complications qui y sont reliées. L'activité aérobique, tout en fournissant plusieurs bénéfices médicaux, n'améliore pas nécessairement le contrôle glycémique et peut même augmenter le risque d'hypoglycémie. L'activité anaérobique ajoutée à l'exercice aérobique, par exemple la course (le sprint), peut causer une augmentation de la glycémie et fournir des profils plus stables immédiatement après l'exercice. Il est possible que l'exercice de résistance puisse avoir le même effet, mais ceci reste encore inconnu. Examiner le choix des substrats énergétiques (lorsque la source principale d'énergie [hydrate de carbone, protéine et lipides] est déterminée en mesurant la consommation d'oxygène) en même temps que la glycémie nous fournira des informations sur le mécanisme par lequel ces activités affectent les niveaux de glycémie dans le sang.

### **But de l'étude**

Le but principal de cette étude est de déterminer les effets aigus de l'exercice de résistance sur le contrôle de la glycémie et le choix des substrats énergétiques sur le diabète de type 1 et ainsi comparer ces derniers aux effets de l'exercice aérobique. Nous déterminerons également les effets d'une combinaison de ces deux types d'exercices dans une seule session d'entraînement et explorerons de quelle façon l'ordre dans lequel les modalités d'exercice sont exécutées affectera la glycémie pendant et après l'exercice.

Votre participation à cette étude nous aidera à augmenter notre compréhension des effets aigus de l'exercice de résistance et de l'exercice aérobique (exécutés individuellement ou ensemble) sur les niveaux de la glycémie et sur le choix des substrats énergétiques chez les individus touchés par le diabète de type 1. Ceci nous aidera à fournir éventuellement aux patients diabétiques de type 1 les prescriptions d'exercice les plus sûres et les plus bénéfiques possible. Cette étude est subventionnée par l'Association Canadienne du Diabète. Elle fait aussi partie des projets de recherche des Drs. Kenny et Sigal subventionnées par les IRSC: «Exercice de résistance chez les individus déjà actifs souffrant du diabète de type 1 (READI)» et «l'Étude de l'exercice aérobique et de l'exercice de résistance sur le diabète de type I (T1-DARE)». Certaines parties des données recueillies seront utilisées par Mme Jane Yardley pour la préparation de sa thèse de doctorat.

### **Session préliminaire**

La session préliminaire ainsi que les sessions d'examen se dérouleront au laboratoire de Bioénergétiques Humaine et de Physiologie Environnementale de l'Université d'Ottawa ou à la clinique Santé cardiovasculaire à l'Hôpital Montfort. La session préliminaire prendra environ 45 minutes à une heure. Durant cette session, nous réviserons avec vous les procédures qui seront utilisées tout au long des sessions expérimentales.

Pendant cette session vous serez également invité à remplir les questionnaires suivants: Questionnaire sur l'aptitude à l'activité physique (Q-AAP) et la *Health/Fitness Facility Pre-participation Screening Questionnaire (AHA/CSM HFFPSQ)* de l'Association Américaine du Coeur/Collège de la médecine sportive. Ces questionnaires nous permettront d'évaluer votre santé physique générale, votre niveau d'activité physique et votre aptitude à exécuter de l'exercice.

À la fin de la session, vous pourrez prendre connaissance en totalité de la lettre d'information et du consentement éclairé approuvé par le Conseil d'éthique de l'Université d'Ottawa. Si vous désirez toujours participer à l'étude, nous vous demanderons alors de signer le formulaire de consentement.

Après la session préliminaire, mais avant le premier essai expérimental, nous vous demanderons de vous présenter soit au Laboratoire Gamma-Dynacare à la clinique du service de santé de l'Université d'Ottawa ou à la clinique Santé cardiovasculaire à l'Hôpital Montfort. Une prise de sang sera faite afin de vérifier votre taux de glycémie. Immédiatement après la prise de sang, nous vous demanderons de mesurer votre glycémie capillaire afin que nous puissions vérifier la précision de votre appareil de mesure que vous utilisez à la maison. Une fois l'analyse terminée, les échantillons de sang seront convenablement détruits par les laboratoires en question.

Si vous n'avez pas fait partie des études T1-DARE ou READI, vous devrez également vous présenter pour une prise de sang au laboratoire de Gamma-Dynacare à la Clinique du service de santé de l'Université d'Ottawa ou à la clinique Santé cardiovasculaire à l'Hôpital Montfort afin de vérifier que votre HbA1c est moins de 9%. Vous devrez également vous présenter pour un essai de capacité aérobique maximale et un test de force 8RM à

l'Hôpital Montfort ou à l'Université d'Ottawa. Le test de force déterminera le poids maximal que vous pouvez soulever 8 fois (utilisant une bonne technique) pour chacun des six exercices requis par l'étude (voir ci-dessous).

### **Sessions d'essais expérimentales**

Mme Jane Yardley, de l'Institut de recherche sur la santé des populations, sera responsable des sessions expérimentales, sous la supervision de M. Glen Kenny. Les sessions auront une durée d'environ quatre heures. Nous veillerons à ce que vous assistiez à cinq sessions expérimentales avec au moins cinq jours d'intervalle entre les sessions.

La journée avant chaque session expérimentale, nous vous demanderons d'insérer sous la peau une sonde du système de surveillance continue pour la glycémie. Nous vous fournirons la formation nécessaire à cette tâche. La sonde est conçue pour être portée pendant 72 heures et restera insérée jusqu'au jour suivant l'essai d'exercice, lorsque vous pourrez l'enlever vous-même. Pour assurer l'étalonnage du système de surveillance continu pour la glycémie, on vous demandera d'exécuter au moins quatre tests de glycémie capillaire par jour à l'aide d'un glucomètre. En plus des instructions verbales et des démonstrations physiques sur l'utilisation des sondes et du moniteur fournis pendant la session préliminaire, nous vous donnerons un manuel d'instructions pour le produit. Pendant les jours où vous utilisez le moniteur, nous vous demanderons aussi de porter un podomètre *Yamax Digiwalker* (*Yamax Corporation*, Tokyo, Japon) pour déterminer votre taux d'activité physique journalier. Nous vous demanderons de porter le podomètre en tout temps pendant la journée à l'exception des heures de sommeil, de douche ou de baignade.

Avant chaque session expérimentale, nous vous demanderons de vous abstenir de faire de l'activité physique intense pendant une période de 48 heures avant l'insertion de la sonde et d'éviter la caféine et l'alcool pour une période de 24 heures avant la séance d'exercice. Aussi, vous serez invité à garder un journal détaillé d'ingestion de nourriture et des doses d'insuline pendant 36 heures avant le premier essai. Pour toutes les visites subséquentes, nous vous demanderons de suivre la même procédure aussi attentivement que possible, en mangeant les mêmes repas et collations aux mêmes heures chaque jour..

Il sera aussi nécessaire de faire de petits changements à vos doses d'insuline pendant les journées d'exercice. Conformément aux instructions fournies par les études READI et T1-DARE, si vous prenez de l'insuline trois fois ou plus par jour, nous vous demanderons de réduire votre dose matinale de 10%. Si vous utilisez une pompe à insuline, votre taux de base sera réduit par 50% une heure avant le début de la séance d'exercice, et restera à ce niveau pour une heure après la séance. Des changements additionnels seront envisagés individuellement selon les résultats des tests de taux de glycémie.

Les jours d'examens, nous vous fournirons une collation que vous devrez manger à 15 h. Vous devrez ensuite vous présenter au laboratoire à 16 h, vêtu de vos vêtements d'exercice (culotte, t-shirt, chaussures de course). Pendant la prochaine heure, nous vous demanderons de faire 3 tests de sang sur le doigt afin de nous assurer que votre taux de glycémie est stable et sécuritaire (entre 5 et 13,9 mmol/L) avant le début de l'exercice. Le premier test sera fait dès votre arrivée au laboratoire, le deuxième, 30 minutes plus tard et le dernier, juste avant de débiter vos exercices. Si votre taux de glycémie est élevé (>14 mmol/L), vous devrez faire un test de sang additionnel pour mesurer les corps cétoniques. S'il y a peu ou pas de corps cétoniques présents et que votre glycémie est moins de 20 mmol/L, vous devrez attendre que votre glycémie diminue. Si toutefois votre glycémie est plus de 20 mmol/L, vous devrez vous injecter une dose corrective de 30% de votre dose habituelle d'insuline et attendre que votre glycémie soit moins élevée avant de débiter vos exercices. Si les corps cétoniques sont présents en moyennes ou grandes quantités, vous devrez vous injecter une dose corrective d'insuline et la session sera remise à une date ultérieure.

Si votre taux de glycémie est bas (c.-à-d. près de 4,5 mmol/L et démontre une tendance décroissante ou inférieur à 4,5 mmol/L) nous vous donnerons 32g de glucose sous forme de comprimés. Après 15 minutes, vous devrez alors vérifier à nouveau votre taux de glycémie pour vous assurer qu'il augmente. Si le niveau voulu de 5,7 mmol/L n'est pas atteint, ces étapes seront répétées.

Si, initialement, votre taux de glycémie est entre 4,5 et 5,6 mmol/L, nous vous donnerons 16g de glucose sous forme de comprimés. Vous devrez alors vérifier votre glycémie capillaire après 15 minutes. Vous pourrez débiter vos exercices lorsque votre taux aura atteint au moins 5,7 mmol/L. Si le niveau réglementaire n'est pas atteint dans un délai de 90 minutes, la session d'exercice sera remise à plus tard. Vous devrez faire un test de glycémie 45 minutes après et/ou au moment où vous terminerez vos exercices et faire l'ajustement (voir ci-dessus) de l'insuline et de votre glucose si nécessaire.

Avant l'exercice, nous mesurerons et prendrons en note votre taille (grandeur), votre poids, votre tour de taille ainsi que votre tension artérielle ainsi que toutes les interventions effectuées lors de la session.. Votre consommation d'oxygène sera mesurée pendant 20 minutes avant le début des exercices, pendant l'exercice, et pour 20 minutes après que l'exercice soit fini à l'aide d'un système portable d'analyse (Oxycon Mobile, Jaeger; Hoehberg, Allemagne). Vous serez couché pour toutes mesures de consommation d'oxygène prises avant et après l'exercice. Les cinq sessions d'exercices suivantes (une par visite) seront exécutées dans un ordre aléatoire (au hasard, comme tiré à pile ou face):

- 1) Session d'exercice aérobique: Vous serez invité à courir sur un tapis roulant à un niveau d'intensité modéré (60% V02max) pendant une période de 45 minutes.
- 2) Session d'exercice de résistance: Vous devrez exécuter trois séries de 8 répétitions de développé- couché, développé des jambes, développé des épaules, demi-redressement assis, tirage-poitrine à la poulie haute, flexion des jambes et rameur assis. Il y aura une période de repos de 60 secondes entre les séries. Cette session prendra approximativement 45 minutes à compléter.
- 3) Session d'exercice aérobique-résistance: Cette session combinera les exercices d'aérobie et de résistance. Les exercices aérobique seront exécutés avant les exercices de résistance. Cette session prendra approximativement 85 à 90 minutes à compléter.
- 4) Session d'exercice résistance-aérobique: Cette session d'exercice sera identique à la session précédente, sauf que l'exercice de résistance aura lieu avant l'exercice aérobique.
- 5) Session de repos (contrôlée): Vous aurez une période de 45 minutes de repos dans le laboratoire dans une position assise ou couchée.

Avant d'entreprendre l'exercice, une infirmière ou un membre de l'équipe de recherche délégué par le médecin assigné à cette étude insérera un cathéter dans votre bras pour l'échantillonnage de sang pendant la session. Ces échantillons seront utilisés pour déterminer le taux de certains composés chimiques (hormones, catécholamines, etc.) dans votre sang. Nous allons prendre des échantillons de sang avant le début de l'exercice et à 5, 10, 15, 30 et 45 minutes de durée pour chaque type d'exercice (résistance ou aérobique). Nous prendrons également des échantillons dès que l'exercice sera terminé et 5, 10, 15, 20, 30, 40, 50 et 60 minutes après la conclusion de l'exercice. Les échantillons seront congelés pour des analyses qui seront effectuées à la fin de l'étude. Les échantillons seront ensuite gardés pour des analyses futures à moins que vous n'insistiez qu'ils soient détruits immédiatement. Le cas échéant, les échantillons seront détruits utilisant le système de vidange biohazard en place à l'hôpital Montfort et à l'Université d'Ottawa. Vous serez invité à mesurer votre glycémie au début, à mi-exercice et à la fin de l'exercice. La consommation d'oxygène sera mesurée pendant toutes les activités afin de calculer votre dépense énergétique et de déterminer la consommation des substrats énergétiques. Le jour après l'essai, vous ramènerez le système de surveillance continu de la glycémie aux chercheurs qui téléchargeront et examineront les données afin d'établir le profil de votre glycémie avant, pendant et après l'exercice.

Tous les exercices énumérés se feront dans le Laboratoire de Bioénergétiques humaines et de physiologie environnementale ou à la clinique Santé cardiovasculaire de l'Hôpital Montfort.

Si vous êtes une femme, vos séances seront programmées de façon à s'assurer que vous serez dans la même phase de votre cycle menstruel (première ou deuxième phase) pour chaque test. Pour déterminer les niveaux d'œstrogène et de progestérone, un individu qualifié au laboratoire de Gamma-Dynacare à la clinique du service de santé de l'Université d'Ottawa ou à la clinique Santé cardiovasculaire de l'Hôpital Montfort exécutera une prise de sang. Une fois que l'analyse du sang aura été faite, les échantillons seront convenablement détruits par les laboratoires en question.

## Procédures expérimentales

Système de surveillance continue de la glycémie: Le matin précédant le jour de l'essai, nous vous demanderons d'insérer une sonde sous-cutanée dans la région fessière avec l'aide d'un dispositif «Senserter» conçu pour ceci. Toutes les sondes, Senserters et systèmes de surveillance continue de glycémie seront fournis par les chercheurs, ainsi que les instructions pour leur insertion et leur étalonnage. Vous recevrez également une copie des instructions, un guide de dépannage, et le nom des personnes avec qui vous pourrez communiquer si vous rencontrez des difficultés.

Test de glycémie (capillaire): Ce test (test sur le bout du doigt) devrait déjà faire partie de la gestion quotidienne de votre glycémie. Ce test, qui sera fait avant, pendant et après l'exercice, consiste à piquer l'extrémité du doigt avec un dispositif auto-piqueur stérilisé afin d'obtenir une gouttelette de sang qui pourra être déposée sur une bandelette et insérée dans un glucomètre. Nous vous demanderons d'apporter votre lecteur de glycémie au laboratoire, et de faire votre test vous-même comme à la maison.

Consommation d'oxygène: La consommation d'oxygène sera mesurée au moyen d'un système automatisé (système MOXUS) ou d'un système d'échange gazeux portatif (système Jaeger). Vous porterez un masque d'oxygène relié au MOXUS ou au système Jaeger pour la majorité de l'étude. Pendant ce temps, vous devrez aussi porter un pince-nez.

Fréquence cardiaque : Une courroie sera placée autour de votre thorax afin de mesurer la fréquence cardiaque pendant l'exercice (moniteur cardiaque *Polar Vantage*).

Podomètre: Nous vous demanderons de porter un pedomètre près de votre taille pendant que vous portez le système de surveillance continue de la glycémie. Chaque jour, vous devrez noter le nombre de pas pris dans l'espace prévu du Journal de Nutrition. Ceci nous permettra de déterminer votre taux approximatif d'activité physique journalier.

Électrocardiogramme (ECG): Pendant l'essai de capacité maximal d'aérobie, un technicien qualifié effectuera un électrocardiogramme pour détecter toute anomalie cardiaque. Ceci nous permettra d'exclure les individus avec des anomalies cardiaques et de réduire le risque d'un incident cardiaque pendant les épreuves. Bien que l'essai ne pose aucun risque pour vous, l'application d'électrodes sur votre thorax peut exiger le rasage de certains endroits. Il se pourrait également que le ruban adhésif retenant les électrodes puisse causer un peu de douleur et une irritation de la peau lorsque qu'il sera retiré.

## Risques

Les risques liés à l'activité physique pour l'individu en santé avec un diabète de type 1 bien contrôlé et pratiquant de l'exercice sous le niveau maximal, sont minimes. On peut parfois associer différents problèmes dont douleur thoracique, les nausées, la tension artérielle anormale, les étourdissements, la perte de conscience, les crampes dans les jambes et même les blessures mortelles aux tests de capacité aérobie maximale. La possibilité d'un arrêt cardiaque durant un tel test est d'environ 1 sur 10,000. Afin de réduire au minimum les risques potentiels, nous respecterons les normes pour des expériences d'exercices avec des sujets humains tels que décrites par la Société canadienne de physiologie d'exercice et la *American College of Sports Medicine* seront respectées. Il y aura au moins un chercheur présent pour toutes les sessions d'essai, entraîné pour pratiquer la RCR ainsi que pour donner les premiers soins. Vous pouvez vous arrêter en tout moment pendant les essais d'exercices.

Les sondes sous-cutanées (sous la peau) pour la glycémie ainsi que les rubans adhésifs qui les retiennent en place peuvent causer une légère sensibilité et une irritation de la peau aux endroits d'insertion. Bien que rare, il y a également une possibilité d'infection à l'endroit d'insertion de la sonde. Ce risque peut être réduit au minimum en nettoyant correctement toutes les surfaces nécessaires de la peau (y compris vos mains) et l'équipement avant l'insertion de la sonde.

La possibilité de blessures aux muscles, os et articulations existe toujours lors de la pratique d'activité physique. Afin de minimiser ces risques, nous suggérons une période d'échauffement avant de débiter les exercices. Des

levées et des techniques de respirations adéquates, ainsi que l'utilisation de résistance sous-maximale prédéterminée minimiseront ces risques. Tout au long de la session d'exercice, vous serez supervisé et si vous éprouvez certains malaises ou inconforts reliés à l'exercice, vous pourrez cesser en tout temps.

Il y a un risque d'infection, d'ecchymose et de douleur pendant un prélèvement de sang par intraveineuse. Un individu autorisé au laboratoire Gamma Dynacare (Clinique du service de santé de l'Université d'Ottawa) ou à l'hôpital Montfort fera toutes les prises de sang selon les procédures recommandées. Afin de réduire au minimum les risques d'infection, la région affectée sera nettoyée adéquatement avec des tampons stériles d'alcool isopropylique et/ou de peroxyde d'hydrogène. Les deux laboratoires détruisent tous les échantillons de sang une fois l'analyse terminée.

Il y a un risque de douleur, d'ecchymose et d'infection associé à l'insertion d'un cathéter intraveineux pour l'échantillonnage du sang. Les cathéters seront insérés par un(e) infirmier(e) ou par un chercheur formé et autorisé par les médecins assignés à l'étude. Toutes les procédures recommandées seront respectées pour minimiser les risques d'infection et de douleur. Il y a aussi le risque que le cathéter soit perturbé pendant l'activité physique. Pour éviter ceci, les tubes seront attachés à votre corps avec du ruban adhésif, et seront surveillés attentivement par les chercheurs pendant que vous êtes actif.

L'activité physique est associée à un plus grand risque d'hypoglycémie (taux de glycémie bas) chez les individus souffrant de diabète de type 1. Afin d'éviter l'hypoglycémie pendant l'exercice, vous ne serez pas autorisé à débiter l'exercice sans avoir préalablement effectué le test pour votre taux de glycémie et que le résultat soit sécuritaire (entre 5 et 13,9 mmol/L). Si votre glycémie est trop élevée (>14 mmol/L) vous devrez refaire un test afin de vérifier la présence des corps cétoniques à l'aide d'un appareil de mesure. Si aucun ou peu de corps cétoniques sont présents et que votre glucose est moins que 20 mmol/L, nous vous demanderons d'attendre qu'il redescende. Si, par contre, votre glucose est plus élevé que 20 mmol/L vous devrez vous injecter une dose corrective de 30% de votre dose habituelle d'insuline, et attendre que votre glycémie diminue avant d'entreprendre vos exercices. S'il y a présence modérée ou élevée de corps cétonique, vous devrez vous injecter une dose corrective d'insuline et la session sera remise à une autre date.

Si votre glycémie est basse (c.-à-d. près de 4,5 mmol/L et démontre une tendance à baisser ou est en dessous de 4,5 mmol/L) nous vous donnerons 32g de glucose sous forme de comprimés. Vous devrez vérifier votre glycémie 15 minutes plus tard pour vous assurer que les niveaux ont augmenté. Si un niveau de glucose de 5,7 mmol/L n'est pas atteint, ces étapes seront répétées.

Si le taux initial de votre glucose est entre 4,5 et 5,6 mmol/L, nous vous donnerons 16g de glucose sous forme de comprimés. Après 15 minutes, vous devrez alors faire un test de glycémie capillaire et vous pourrez débiter vos exercices lorsque le taux de glucose atteindra 5,7mmol/L. Si vous ne réussissez pas à atteindre un taux désiré en dedans de 90 minutes, la session d'exercice sera remise à plus tard. Un test de sang sera fait 45 minutes après et/ou lorsque vous aurez terminé vos exercices et des ajustements d'insuline et de glucose (voir ci-haut) seront faits si nécessaire.

Si une urgence devait survenir, tout le personnel du laboratoire à l'université est formé pour la réanimation cardio-respiratoire (RCR) et pour offrir les premiers soins. Des téléphones sont situés dans la salle de musculation et dans le laboratoire de sorte que le Service de la protection de l'Université puisse immédiatement être appelé. Des services d'urgence sont disponibles à l'Hôpital Montfort.

### **Anonymat et la confidentialité**

Votre anonymat sera assuré au cours de toutes les étapes de cette étude. Tous les résultats seront conservés en mémoire dans un ordinateur (sous mot de passe) selon un code alphanumérique. Personne ne pourra vous identifier car votre nom n'apparaîtra pas sur les dossiers. Toutes les données et l'information, sous forme électronique ou papier, seront conservées dans un bureau sous clef accessible seulement aux chercheurs. Seulement les investigateurs auront accès aux données recueillies. Toutes les données rassemblées au cours de l'étude seront gardées pendant une période de 15 ans suivant la fin de l'étude et seront ensuite totalement détruites.

Les données recueillies au cours de cette étude seront soumises pour publication dans des revues scientifiques et seront utilisées par Mme Jane Yardley en tant qu'élément de son travail de thèse de doctorat.

Aucun document portant votre nom ne quittera l'établissement. Vous ne serez pas identifié par votre nom dans les publications ou les rapports provenant de cette recherche. Vous êtes encouragé à poser des questions et à discuter des résultats expérimentaux en tout temps.

Dans le cas d'une vérification, les conseils d'éthique en recherches de l'Hôpital d'Ottawa, des Sœurs de la Charité et de l'Hôpital Montfort, ainsi que l'Institut de recherche en santé d'Ottawa pourraient réviser toute information liée à cette étude, sous la supervision du bureau de la D<sup>re</sup> Janine Malcolm.

**Pour la durée entière de l'étude, il est entendu que vous avez le droit de refuser de participer ou de vous retirer de l'étude en tout temps.**

## CONSENTEMENT ÉCLAIRÉ DU PARTICIPANT

Une recherche impliquant des sujets humains doit avoir le consentement écrit des participants.

Par la présente, je soussigné(e), \_\_\_\_\_, consens de mon propre gré à participer au projet d'étude intitulé **“Les effets aigus de l'exercice de résistance et d'aérobic sur les niveaux de glycémie et l'utilisation des substrats énergétiques dans le diabète de type 1”**. Le projet d'étude m'a été clairement expliqué, j'ai pris connaissance de l'information présentée dans la lettre d'information de 9 pages et j'ai eu l'occasion de poser des questions aux chercheurs.

Je reconnais qu'il y aura cinq sessions expérimentales, chacune d'une durée d'environ quatre heures et que je serai rémunéré pour ma participation et mes dépenses, à concurrence de 50 \$ par session, seront remboursées.

Tout argent gagné qui excède le remboursement de dépenses résultant de ma participation à l'étude sera considéré comme revenu imposable par l'Agence du revenu du Canada. Pour recevoir le paiement pour ma participation, je devrai fournir mon numéro d'assurance social aux chercheurs ou à leur délégué. L'Hôpital d'Ottawa me fournira un T4A pour tout revenu excédant 500 \$ avant la fin du mois de février de l'année suivante.

Je reconnais qu'en tant que participant(e), je serai exposé(e) à des risques reliés à l'exercice, l'hypoglycémie et à l'équipement expérimental. Je reconnais aussi qu'en tant que participant(e) à cette étude je pourrais être exposé à certains risques présentement imprévus.

Je reconnais également que je suis libre de refuser et que si je consens à participer, je peux me retirer en tout temps. Je reconnais que je peux poser des questions avant, durant et après les nombreux tests. Je reconnais que les seuls bénéfices que je retirerai de ma participation sont un test de capacité aérobique maximale et l'information sur mes taux de glycémie fournis par les sondes sous-cutanés.

Veillez choisir une des réponses suivantes en y apposant vos initiales:

- Si je me retire de l'étude, les chercheurs pourront continuer d'utiliser les données recueillies sur moi pour les besoins de l'étude. \_\_\_\_\_
- Si je me retire de l'étude, je désire que les données recueillies sur moi depuis le début ne soient pas utilisées et qu'elles soient détruites. \_\_\_\_\_

Je reconnais que les données de cette étude pourront être utilisées par les chercheurs pour des analyses subséquentes et/ou dans des publications.

Je suis conscient(e) du fait que l'Institut de recherche en santé d'Ottawa ainsi que les conseils d'éthique en recherches de l'Université d'Ottawa, de l'Hôpital Montfort, et de l'Hôpital d'Ottawa peuvent vérifier toute documentation reliée à cette étude.

**Je comprends que pour toute question concernant la présente étude je peux communiquer avec Mme Jane Yardley ou avec Dr. Glen Kenny.**

Pour toute question concernant les aspects éthiques de ce projet de recherche, je peux m'adresser à un agent du conseil d'éthique en recherches des établissements suivants: l'Université d'Ottawa, L'Hôpital d'Ottawa ou l'Hôpital Montfort.

Une copie de cette lettre d'information et formulaire de consentement m'a été remise. Une copie du document signé sera remise au médecin assigné à l'étude.

Signature du participant(e): \_\_\_\_\_ Date: \_\_\_\_\_

Nom du témoin \_\_\_\_\_  
(en caractères d'imprimerie)

Signature du témoin: \_\_\_\_\_ Date: \_\_\_\_\_

Nom du chercheur \_\_\_\_\_  
(en caractères d'imprimerie)

Signature du chercheur: \_\_\_\_\_ Date: \_\_\_\_\_

## CONSENTEMENT ÉCLAIRÉ DU PARTICIPANT

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Veillez choisir une des réponses suivantes en y apposant vos initiales:

- Si je me retire de l'étude, les chercheurs pourront continuer d'utiliser les données recueillies sur moi pour les besoins de l'étude. \_\_\_\_\_
- Si je me retire de l'étude, je désire que les données recueillies sur moi depuis le début ne soient pas utilisées et qu'elles soient détruites. \_\_\_\_\_

Je reconnais que les données de cette étude pourront être utilisées par les chercheurs pour des analyses subséquentes et/ou dans des publications.

Je suis conscient(e) du fait que l'Institut de recherche en santé d'Ottawa ainsi que les conseils d'éthique en recherches de l'Université d'Ottawa, de l'Hôpital Montfort, et de l'Hôpital d'Ottawa peuvent vérifier toute documentation reliée à cette étude.

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Signature du participant(e): \_\_\_\_\_ Date: \_\_\_\_\_

Nom du témoin \_\_\_\_\_  
(en caractères d'imprimerie)

Signature du témoin: \_\_\_\_\_ Date: \_\_\_\_\_

Nom du chercheur \_\_\_\_\_  
(en caractères d'imprimerie)

Signature du chercheur: \_\_\_\_\_ Date: \_\_\_\_\_

















## **APPENDIX F – PARTICIPANT CGMS INSTRUCTIONS**

### **Medtronic System Gold™ Continuous Glucose Monitoring System Instructions**

#### **Practical Tips: Orienting Patient to Monitor**

Orientation to the monitor includes:

- Buttons
- Cable
- Battery compartment
- Sensor and Insertion site

Teaching checklist:

- The monitor may not be disconnected at any time during the length of the study.
- The monitor must not be turned off until the end of the study.
- It must be protected from dampness / wet. Please use the provided shower bag.
- The cable must not be wound tightly or kinked as it will break the wire inside it.
- BG values should be entered at least 4 times per day. At least one of these tests should be a post meal glucose value. Important to enter 3 by midnight the first day.
- BG must be entered in mmol/L. Provide conversion chart and demonstration.
- Event “1” should be entered for each meal of the day. Do not enter “1” for snacks.
- If monitor alarms, clear it by pressing SEL / ACT x 2 then wait 15 minutes and enter another BG value.
- If 3 subsequent alarms, call the 1-800 number on the back of the monitor and/or pull the sensor.
- Battery: Uses two AAA batteries. If alarms “lo batt” during sensor study, please change the batteries (we will reimburse you). New batteries must be in place within 5 minutes of old batteries being removed.
- You will have 8 hours of warning “lo batt” before monitor will run out of power.
- You must remove the belt clip to change the batteries.
- At the end of the study, enter a BG, wait 10 minutes then remove the sensor.
- Gently loosen the tape around the sensor before you pull it out.
- Shut off the monitor by pressing and holding (briefly) the red button. Confirm your action by pressing ACT.
- Leave the sensor in place on the cable. Place the end of the cable in a ziplock (plastic) bag. Do not disconnect the sensor from the cable.
- Return the monitor to the “Off” setting. The study memory will not be lost.

## Practical Tips: Sensor Insertion

- Clear the monitor. SEL x 3 to setup, SEL to CLEAR press ACT and confirm
- Enter Patient ID. SEL x 3 to set up, SEL to Patient, 000 0000 Press ACT and set number.
- If monitor is on for more than 5 minutes but not connected, it will alarm DISCONN (disconnect) Clear alarm by pressing SEL ACT x2

- Check expiry date and quality assurance of sensor on package.
- Load the sensor into the Sen – Serter.
- Remove the front tab of tape and the needle guard.
- Prepare the site. Use alcohol only. Choose an area away from the beltline where irritation by clothing can occur. Upper outer buttock, side of abdomen.
- Stretch the skin slightly between the “feet” of the sen-serter.
- Verify placement and angle. Should be 45 degrees.
- Fire the sensor. Slide the sen-serter off the sensor laterally (not away from the body)
- Remove the needle. Pull the back tab tape off. Keep two fingers on the front of the tape while you are doing this.
- Keep a hold of the sensor site until it is fully taped in place.
- Hook up the cable making sure you hear the clicks.
- Use Tegaderm. One horizontally over the sensor, the other vertically.
- Pinch the cable along the occlusive dressing to make sure it is sealed
- The cable should emerge from the occlusive dressing 1 or 2 inches from the sensor. This will help hold the sensor in place.
- You may use an extra piece of tape to secure a loop of cable a few inches from the site though this is not mandatory.
- Any moisture entering the system will affect the quality of the study. It may cut the study short.

## Practical Tips: Sensor Initialization

- Full initialization of a sensor can only be done once per sensor.
- Wait 1-2 minutes with the patient hooked up to the sensor before you initialize.
- Initialize the sensor if the ISIG is greater than 10. (range between 10 – 100) Still may get a good study if over this range when initializing.

- Go to the signals screen SEL x 3 –setup, ACT, Signals ACT.
- VCTR stands for Voltage Counter.
- ISIG stands for Input Signal. You can toggle between these by pressing SEL while in the

Signals screen.

- Watch the fluctuations for about 2 minutes.
- Exit and re:enter the Setup screen, this time SEL to the last screen "INIT" for initialization
- Initialize and Confirm by pressing ACT.
- "60" minutes should appear on the screen. No buttons should be pressed during this time. This is very important!
- The unit counts down to 0 minutes, beeps "enter BG" then goes back to the time of day screen.
- Enter a BG sometime after the enter BG reminder beep. It is not imperative to catch that screen but do it as soon as possible as this begins the line on the study.

### ***Practical Tips: Entering Events and BG Values***

- Only event "1" will be recognized as a meal marker.
- Other events may be entered at the recommendation of the clinician.
- Patient should be instructed on keeping an activity log as well during the study.
- Monitor will alarm "CAL ERROR" if there is too much of a discrepancy between BG value entered and value being sensed. Stands for calibration error.
- Clear alarm, wait 15 minutes and re-enter a NEW value.
- Sensor study will last 24-72 hours.

- Enter finger stick BG values into the monitor as soon as possible after the test. Waiting even 5 minutes can affect the acceptance of that value. (CAL ERROR) may occur within 5 minutes of BG entry.
- Enter value by pressing SEL ACT, then scroll up or down with your arrow keys, press ACT when you reach the appropriate number, then confirm to the question "CAL YES?" by pressing ACT a second time.
- Enter meal marker when start eating. Always enter "event 1" SEL x 2 ACT
- Enter at least 4 BG values per day. Try to include one, 2 hour post meal BG.
- If the BG is outside of the range of 2.2 – 22mmol Treat your diabetes first. Do not enter a value in the monitor as it will result in a calibration error.
- When BG is back within the range, enter another BG value into the monitor.
- Maintain a log which includes: Meals, hypoglycemia, exercise (type, time, duration), type of diabetes medication, amount and time taken.

## Instructions relatives au Système de surveillance du glucose en continu Medtronic System Gold<sup>™</sup>

### Conseils pratiques: Introduction au système de surveillance à l'intention du patient

L'introduction au système:

- Les touches
- Le câble
- Le compartiment pour piles
- La sonde et le site d'insertion

Liste de contrôle:

- Le dispositif de contrôle ne devrait être débranché à aucun moment pendant l'étude.
- Le dispositif de contrôle ne devrait pas être mis hors tension jusqu'à la fin de l'étude.
- Il devrait être protégé de l'eau et de l'humidité. Veuillez utiliser les sacs fournis pour la douche.
- Le câble ne devrait pas être plié ou enroulé, au risque sinon de briser le fil à l'intérieur.
- Les taux de glycémie devraient être notés aux moins 4 fois par jour. Au minimum, un de ces tests devrait être effectué suivant un repas. Il est important d'inscrire au moins 3 valeurs avant minuit pour la première journée.
- Les taux de glycémie devraient être inscrits en mmol/L. Un tableau de conversion et de démonstration sera fourni.
- Évènement «1» devrait signifier un repas. Vous ne devez pas inscrire «1» pour les collations.
- Si le dispositif de contrôle sonne une alarme, vous pouvez l'arrêter en appuyant SEL / ACT x 2. Attendez 15 minutes et inscrivez un autre taux de glycémie.
- Si vous entendez trois alarmes de suite, appeler le numéro 1-800 inscrit sur le dispositif de contrôle et/ou enlever la sonde.
- Les piles: Le dispositif de contrôle utilise deux piles AAA. Si l'alarme «lo batt» sonne pendant l'étude, veuillez changer les piles (nous vous rembourserons). De nouvelles piles devraient être installées dans les 5 minutes après que les vieilles piles ont enlevé.
- Vous recevrez 8 heures d'avertissement «lo batt» avant que le dispositif de contrôle s'éteigne.
- Vous devrez enlever la pince à ceinture pour changer les piles.
- À la fin de l'étude, inscrivez un taux de glycémie, et attendez 10 minutes avant d'enlever la sonde.
- Dégagez doucement la bande adhésive avant d'enlever la sonde.
- Éteignez le dispositif de contrôle en appuyant la touche rouge pendant quelques secondes. Confirmer cette action en appuyant sur la touche ACT.

- Laissez la sonde attachée au câble. Mettez le bout du câble dans un sac Ziplock (plastique). Ne débranchez pas la sonde du câble.
- Laissez le dispositif de contrôle éteint. Les données de l'étude seront conservées.

### **Conseils pratiques: L'insertion de la sonde**

- Videz la mémoire du dispositif de contrôle. SEL x 3 (setup), SEL pour l'option CLEAR, appuyer la touche ACT pour confirmer.
- Entrez le numéro d'identification du patient. SEL x 3 (set up), SEL pour l'option PATIENT, 000 0000 Appuyez ACT pour déterminer le numéro.
- Si le dispositif de contrôle est en marche pour plus de 5 minutes sans être branché, l'alarme DISCONN sonnera. Enlevez l'alarme en appuyant SEL ACT x2

- Vérifiez la date d'échéance et assurez-vous de la qualité de la sonde.
- Chargez le Sen – Serter avec la sonde.
- Enlevez la languette de ruban adhésif et la gaine de l'aiguille.
- Préparez le site d'insertion. Utilisez seulement de l'alcool. Choisissez un endroit sur le côté de l'abdomen ou des fesses, loin de la ligne de ceinture où les vêtements peuvent causer de l'irritation.
- Étirez la peau doucement entre les «pieds» du Sen-Serter.
- Vérifiez l'angle de l'emplacement, qui devrait être de 45 degrés.
- Insérez la sonde. Enlevez Sen-Serter en le glissant latéralement au corps
- Enlevez l'aiguille et la languette postérieure, tout en gardant deux doigts sur le ruban adhésif antérieur.
- Tenez bien la sonde jusqu'à ce qu'elle soit fixée en place avec une bande adhésive.
- Branchez le câble, en vous assurant qu'il soit bien en place (vous entendrez un «clic»).
- Utilisez du Tegaderm. Un horizontalement sur la sonde, l'autre verticalement.
- Pincez le câble en dessous du Tegaderm en vous assurant qu'il soit bien scellé.
- Le Tegaderm devrait couvrir le câble jusqu'à 1 ou 2 pouces de la sonde, ce qui permettra d'assurer qu'il reste bien en place.
- Vous pouvez également utiliser du ruban adhésif pour faire une boucle avec le câble afin de prévenir le débranchement, mais cela n'est pas absolument nécessaire.
- La qualité des données pourrait être compromise et l'étude alors interrompue si de l'humidité devait pénétrer à l'intérieur du système.

## Conseils pratiques: Initialisation de la sonde

- L'initialisation d'une sonde ne peut être effectuée qu'une seule fois.
- Attendez 1-2 minutes avec la sonde insérée et branchée avant d'initialiser.
- Initialisez la sonde si le ISIG est entre 10 et 100. Il se peut que les données soient toujours bonnes si le ISIG est plus de 100 au moment de l'initialisation.

- Procédez à l'écran SIGNAL - SEL x 3 –setup, ACT, Signals ACT.
- VCTR signifie «Voltage Counter».
- ISIG signifie «Input Signal». Vous pouvez changer entre les deux en appuyant SEL pendant que vous vous trouvez à l'écran «Signals».
- Observez les fluctuations pendant 2 minutes.
- Quittez et revenez à l'écran «Setup». Appuyer SEL jusqu'à l'écran «INIT» pour l'initialisation
- Initialisez et confirmez en appuyant la touche ACT.
- «60» min devrait apparaître à l'écran. Il est important de ne pas appuyer sur aucune touche pendant cette période. Ceci est TRÈS important!
- Le dispositif comptera à rebours jusqu'à «0», après quoi il sonnera «enter BG» et retournera à l'écran indiquant l'heure.
- Inscrivez un taux de glycémie après cette étape. Il n'est pas essentiel de le faire immédiatement, mais le plus tôt ce sera fait, le plus tôt la collecte des données pourra commencer.

### ***Conseils pratiques: Signaler des événements et les taux de glycémie***

- Seul événement «1» sera reconnu comme un repas.
- Les autres événements pourraient être indiqués selon les instructions du clinicien.
- Le patient devrait également maintenir un journal d'activité physique pendant l'étude.
- L'alarme «CAL ERROR» (erreur de calibration) sonnera si la différence entre le taux de glycémie inscrit et le taux détecté par le système est trop grande.
- Enlevez l'alarme, attendez 15 minutes et inscrivez un nouveau taux de glycémie.
- L'étude aura une durée de 24 à 72 heures.

- Inscrivez le taux de glycémie d'un test de capillaire dans le dispositif de contrôle aussitôt que possible après le test. Un délai de seulement quelques minutes peut produire une erreur de calibration (CAL ERROR) et une alarme sonnera.
- Pour inscrire le taux de glycémie, appuyez SEL ACT. Utilisez les flèches pour arriver au bon numéro. Appuyez sur la touche «ACT». Pour confirmer, appuyez ACT une deuxième fois quand les mots «CAL YES?» apparaissent.
- Indication de repas devrait être inscrite au début du repas. «Événement 1» SEL x 2 ACT
- Inscrivez des valeurs de test de glycémie capillaire au moins 4 fois par jour. Essayez d'inclure au moins un test 2 heures après un repas.
- Si votre taux de glycémie ne se situe pas entre 2.2 et 22 mmol, prenez soin de votre diabète en premier. N'inscrivez pas cette valeur dans le dispositif de contrôle, car ceci produira une erreur de calibration.
- Quand votre taux de glycémie est de retour entre 2.2 et 22 mmol, inscrivez une nouvelle valeur.
- Maintenez un journal qui inclut vos repas, tout événement d'hypoglycémie, votre activité physique (durée, type, temps de la journée), et tout médicament pris pendant l'étude.