The effects of thermal stress on glucoregulation during exercise in participants with Type 1 Diabetes Mellitus

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Dedication

To Dad, Mom & Holly, without you, none of this would have been possible. Your dedication, time and love during this process made all of this possible. Thank you.

Abstract

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease that destroys pancreatic beta cells, affecting glucose homeostasis. In T1DM, glucoregulation and carbohydrate oxidation may be altered in different ambient temperatures; however, current literature has yet to explore these mechanisms. This study examines the effects of 30 minutes of exercise at 65% VO_{2max} in 5ºC, 20ºC and 35ºC in individuals with T1DM. No significant differences were observed for blood glucose across the 3 conditions ($p = 0.442$), but significance was found for core temperature, heat storage, and sweat rate ($p < 0.01$). Blood glucose was also shown to vary greatly between individuals among conditions. The mechanisms behind the differences in blood glucose may be due to the lack of significant glucagon production among conditions. These findings suggest that T1DM individuals may exercise submaximally for 30 minutes in different ambient temperatures without significant differences in glucoregulation.

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List of Abbreviations

Adenosine monophosphate	AMP
Adenosine monophosphate kinase	AMPK
Analysis of variance	ANOVA
Arteriovenous	A-V
Body mass index	BMI
Body surface area	A_D
Calcium	Ca^{2+}
Carbohydrate	CHO
Coefficient of convective heat exchange	h_c
Coefficient of radiative heat exchange	h_f
Conductive heat transfer	K
Convective heat loss transfer respiration	C_{res}
Convective heat transfer	C
Evaporative heat transfer via respiration	E_{res}
Evaporative heat transfer via skin	E_{sk}
Glucose transporter	GLUT
Heat storage	S
Hemoglobin A_{1c}	HbA_{1c}
Hyperosmolar hyperglycemic nonketotic syndrome	HHNS
Maximal oxygen uptake	VO_{2max}
Metabolic heat production	M
Preoptic anterior hypothalamus	PO/AH

Radiative heat transfer	R
Ratings of perceived exertion	RPE
Respiration rate	RR
Skin temperature	T_{sk}
Standard deviation	SD
Sweat rate	SR
Sympathetic Nervous System	SNS
Thermal comfort	TC
Thermal resistance	TR
Thermal Sensation	TS
Type 1 Diabetes Mellitus	T1DM
Type 2 Diabetes Mellitus	T2DM
Work	W

Introduction

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease of unknown etiology, characterized by hyperglycemia, and is often diagnosed in childhood, although it is not uncommon for diagnosis in later adulthood. The disease renders the beta cells of the pancreas unable to produce insulin, and as such, impacts the glucose dynamics of the individuals affected. It is estimated that over 200,000 Canadians currently suffer from T1DM (StatsCan, Sanmartin & Gilmore, 2009). T1DM is managed with regular monitoring of blood glucose, insulin injections, and exercise. Complications associated with poor blood glucose management include retinopathy, nephropathy, and possible amputation, ultimately leading to a lower quality of life, increased mortality, and a greater financial health cost. Exercise in individuals with Type 1 diabetes can help maintain good general health, prevent obesity, control diabetic symptoms and reduce the risks for other complications, such as high cholesterol and high blood pressure (American Diabetes Association, 2008).

In non-diabetic subjects, the rate of glucose production is increased in proportion with glucose uptake for a given exercise intensity, but in subjects with moderately controlled T1DM, the rate of glucose production is sharply increased, and could be accredited to the rate of gluconeogenesis during exercise (Petersen, Price & Bergeron, 2004). In order to maintain stable blood glucose during exercise, there is a concomitant decrease in insulin secretion from the beta cells, and an increase in glucose production from the liver in people not affected by type 1 diabetes. However, in people affected by T1DM, insulin is administered via insulin pump, or bolus injection, and if adjustments are

not made, hypoglycemia will occur. Numerous studies (Peirce, 1999; Corigliano et al., 2006; Guelfi, et al., 2005; Perrone, et al., 2005) have demonstrated a decrease in the blood glucose of exercising individuals with T1DM. With moderate exercise in individuals with T1DM, if it is only 20-30 minutes in duration and less than 70% VO_{2max}, minimal insulin adjustments may need to be made (Peirce, 1999). However, West, Morton, Bain, Stephens & Bracken (2010), showed that a 75% reduction in pre-exercise insulin best preserves blood glucose responses for 24 hours following 45 minutes of running at 70% VO_{2peak}.

Differing environments have also been shown to impact the body during exercise. When the environment is warmer than the skin, the body gains heat through dry heat exchange that increases the requirements for sweating and circulatory responses, such as vasodilation, increasing blood flow to the skin (Kenny, et al., 2010). In non-diabetic individuals, exercise in the heat to the point of hyperthermia has been shown to alter the body's metabolism, with alterations in carbohydrate metabolism including: increased gluconeogenesis, depressed glycogenesis, glucose intolerance and insulin resistance (Mizock, 1995). Likewise, during exercise in a cold environment in non-diabetic persons, there is an increase in carbohydrate utilization. Prolonged/strenuous exercise and alterations in diet have important effects on the quantity and the quality of metabolic fuel reserves that are available for shivering, and of all metabolic fuels, CHO reserves are the most affected by such changes in exercise and diet regimen (Haman, 2006). This increased CHO oxidation may often result in hypoglycemia. Plasma glucose and muscle glycogen have been shown to play significant roles in heat production during cold exposure (Jacobs, Martineau & Vallerand, 1994), but a more recent study by Haman et

al., (2002) showed that even though plasma glucose oxidation was strongly stimulated during low-intensity shivering, it only contributed a minor role (10%) to heat production. Prolonged/strenuous exercise and alterations in diet have important effects on the quantity and the quality of metabolic fuel reserves that are available for shivering, and of all metabolic fuels, CHO reserves are the most affected by such changes in exercise and diet regimen (Haman, 2006). Shivering has also been shown to use more CHO and less lipids than exercise (Weber & Haman, 2005). Hypothetical explanations for this include hormonal differences (i.e. catecholamines), or different neural control of shivering and exercise (Mentel, Duch, Stypa, Wegener, Müller & Pfluger, 2003). However, free fatty acid and glycerol levels are not higher, but may be lower during exercise in cold air or water when compared to corresponding warmer conditions (Doubt, 1991). Individuals with T1DM are at increased risk for hypoglycemia during exercise. Passias et al., (1996) found that hypoglycemia reduces, but does not eliminate, hypothermia-induced heat production and the reduction is achieved by decreasing the core temperature threshold for shivering thermogenesis by approximately 0.6ºC and the magnitude of heat production by approximately 20% compared to euglycemia. This decrease in the threshold for shivering is believed to be due to the decreased blood glucose perfusing tissue in the preoptic anterior hypothalamus (PO/AH), exciting warm-sensitive neurons, and inhibiting cold-sensitive neurons (Passias, et al., 1996). Therefore, hypoglycemia causes a greater cooling of the core by inhibiting heat production. Currently, there is a limited literature pertaining to exercise in different temperatures and the effects on individuals living with T1DM.

This thesis will examine the effects of different thermal stress on glucoregulation during exercise in participants with Type 1 Diabetes Mellitus. Current literature involving both thermal and metabolic responses during exercise in individuals with T1DM is limited. Previous studies involving individuals with T1DM have shown significant rises in core temperature and diminished sweat rates when passively exposed to hot conditions (Petrofsky, et al., 2006), and have shown significant differences in blood glucose decrease during non-continuous, aerobic exercise in 10°C and 30ºC (Rönnemaa & Koivisto, 1988). The aim of the current study is to examine the effects of 5°C, 20°C, and 35°C during exercise at 65% VO_{2max} on core temperature, sweat rate, heat storage, blood glucose, insulin and glucagon in participants with T1DM.

Literature Review

Diabetes

a) What is Diabetes?

It is estimated that over 200,000 Canadians currently live with Type 1 Diabetes Mellitus (StatsCan, Sanmartin & Gilmore, 2009). There are two kinds of diabetes: Type 1 Diabetes Mellitus (T1DM), comprising 5% to 10% of the total diabetic population (Salsali & Nathan, 2006), is characterized by insulin injections and is regularly diagnosed in childhood. T1DM is one of the most common chronic conditions of adolescence and young adulthood, and is the leading cause of medically related disabilities, including blindness, amputation, and renal failure, in the United States (Salsali & Nathan, 2006). Type 1 Diabetes is an autoimmune disease of unknown etiology. The disease affects the pancreas, rendering it unable to produce insulin. The pancreas has both exocrine and endocrine functions. The endocrine portion of the pancreas is composed of three types of specialized cells known as alpha cells, beta cells, and delta cells, which make up the islets of Langerhans; however, T1DM affects only the beta cells on the islets of Langerhans, leaving them unable to produce insulin.

Type 2 diabetes mellitus (T2DM) is frequently diagnosed in later adulthood and is most often associated with overweight, sedentary individuals and is accompanied by insulin resistance. Accompanying the insulin resistance in T2DM is low-grade systemic inflammation, causing an increase in the release of TNF-alpha, which has direct inhibitory effects on insulin signaling and has been proposed to cause insulin resistance

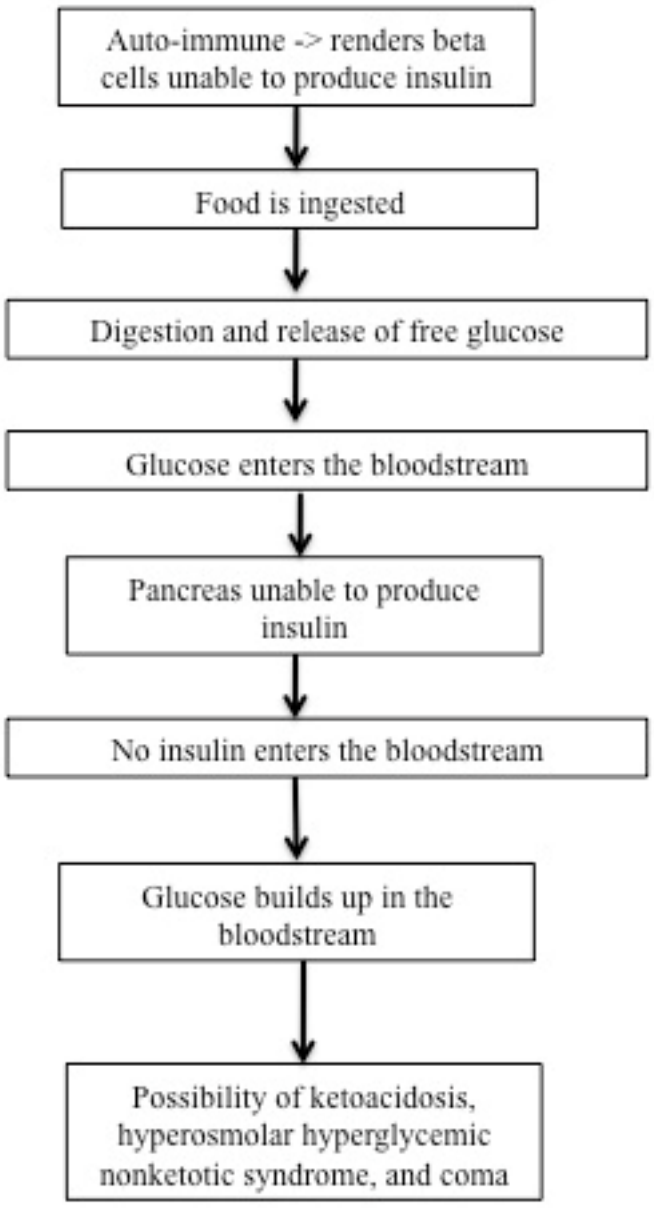
by releasing free fatty acids from adipose tissue (Petersen & Pedersen, 2005). However, TNF-alpha is not the only mechanism by which insulin signaling is affected. Individuals affected by Type 1 or 2 diabetes must engage in continual self-care actions such as healthy eating and exercise if they are to minimize their risks of developing long-term diabetic complications (Balfe, 2007).

b) Glucose Dynamics and Insulin Physiology

The blood glucose of a non-diabetic individual is typically below 6.1 mmol/L (Diabeteshome, 2004), which is indicative of a functional pancreas that maintains homeostatic blood glucose levels. The target blood glucose for an individual with T1DM is meant to mimic that of a non-diabetic individual, and is maintained through regular blood glucose readings, and the administration of insulin injections, or the use of an insulin pump. Figure 1 illustrates the glucose dynamics in individuals with T1DM. Individuals with T1DM frequently meet with an endocrinologist to discuss blood glucose levels, insulin dosage, and HbA_{1c} values. The typical lifespan of a red blood cell (RBC) is 90 days, and during this time, plasma glucose becomes glycosylated and attaches to the RBC, HbA_{1c} values are representative of the 3-month average of blood glucose and are a measure of the long-term control of blood glucose. Poor blood glucose control results in excess glucose that binds to red blood cells, and therefore results in a higher HbA_{1C}. Normal values are between 5-7%, and are indicative of well- controlled T1DM. T1DM individuals must also meet with a dietician to discuss an insulin-carbohydrate ratio, in which a unit of insulin is given for a certain number of carbohydrate grams ingested. Exercise is important for individuals with T1DM for many reasons, including achieving

better blood glucose control and improving insulin sensitivity, thereby making it easier for the body to transfer sugar from the blood stream into the cells, and improving regulation of glucose by increasing the muscle-to-fat ratio and attainment of a longer life (Waden et al., 2005 & Kolatkar, 2006).

Figure 1: Glucose-Insulin dynamics in T1DM individuals.

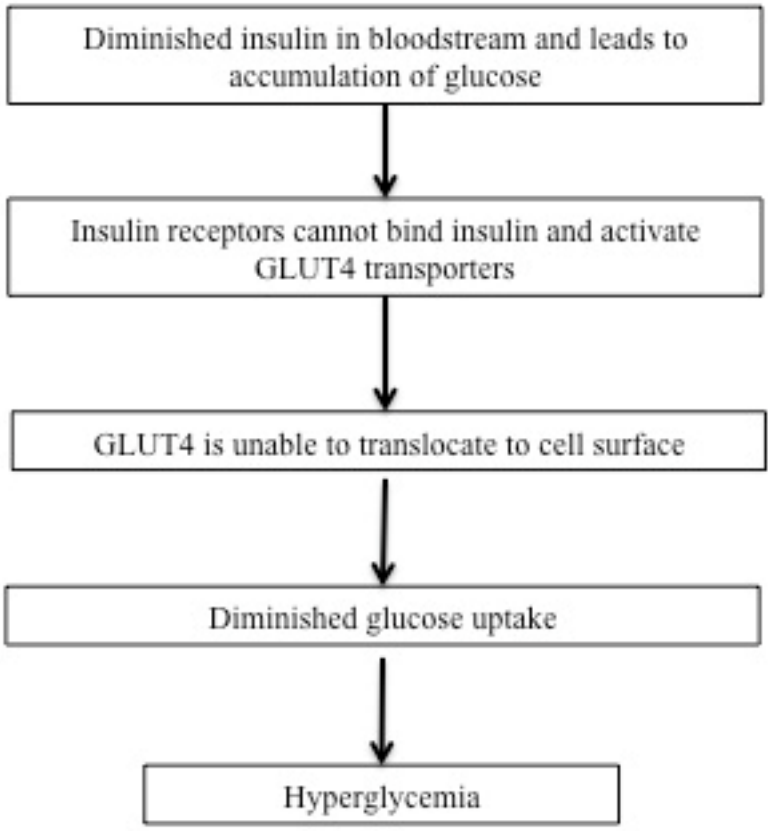


Insulin has profound effects on both carbohydrate (CHO) and lipid metabolism (Bowen, 2007). Glucose enters the blood stream after CHO is broken down in the small intestine. Insulin then acts on the cells throughout the body to stimulate uptake of glucose into the tissues. However, it should be noted that the brain and liver are two organs that do not require insulin for glucose uptake because they do not use GLUT4 for transporting glucose. The role of GLUT4 transport and insulin signaling will be discussed in a subsequent section. Insulin does stimulate glycogen synthesis in the liver by activating the hexokinase enzyme, phosphorylating glucose and keeping it in the cell as well as by activating glycogen synthase. In relation to lipid metabolism, insulin promotes de-novo fatty acid synthesis in the liver and adipose tissue, inhibiting the breakdown of triglycerides in adipose tissue by hindering intracellular lipases and directly stimulating fat accumulation in adipose tissue (Bowen, 2007).

T1DM is a chronic medical disease characterized by potentially significant perturbations in blood glucose levels as a result of disrupted insulin homeostasis, namely hyperglycemia and hypoglycemia. Hyperglycemia is portrayed by elevated glucose (above 13.9 mM) in the blood stream, and has short-term consequences that include ketoacidosis, hyperosmolar hyperglycemic nonketotic syndrome (HHNS) and coma (Kolatkar, 2006). Impaired peripheral glucose uptake leads to hyperglycemia, hyperosmolarity, glycosuria and osmotic diuresis. The inability of the tissues to utilize glucose causes lipolysis and increased reliance on fat, causing the production of ketones in the liver that are responsible for metabolic acidosis (Sivanandan, et al., 2010). The role of the adrenergic response to stress hyperglycemia is based on interference with feedback mechanisms of hyperglycemia in beta and alpha cell function, ultimately leading to

increased glucagon secretions and decreased insulin (Halter, Beard & Porte, 1984). The consequences of long-term hyperglycemia include: kidney damage leading to diabetic nephropathy, neuropathy, retinopathy, and cardiovascular complications (angiopathy, heart attack and stroke). The fastest and most efficient way to combat hyperglycemia is by administering insulin, which should be administered based on the level of hyperglycemia. Figure 2 denotes hyperglycemia in the blood stream.

Figure 2: Hyperglycemia in T1DM



(Adapted from Kitabchi, et al., 2009)

Conversely, hypoglycemia results when serum blood glucose levels drops below 3.9 mM. Hypoglycemia that results during exercise is caused by enhanced insulin sensitivity combined with reduced glycogen stores as a consequence of increased energy

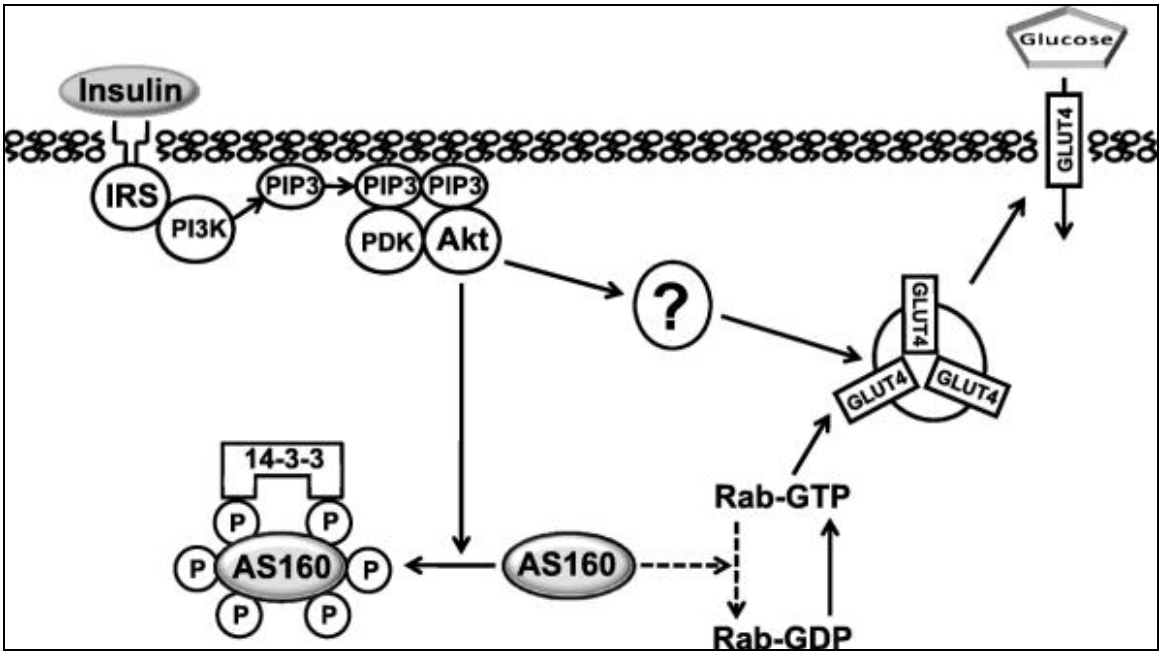
expenditure (Corigliano, et al., 2006). The relative increase in the ratio of insulin to carbohydrate in the blood stream may be a result of glucose being taken into the cell during exercise, or by administration of too much insulin following a meal. Hypoglycemia evokes changes in autonomic activity such as sweating, nausea, warmth, anxiety, tremulousness, palpitations, and paresthesia. Insufficient blood glucose also affects the brain and results in headache, blurred or double vision, confusion, difficulty speaking, seizures and possibly coma (Merck Manual Index, 2007). When blood glucose reaches the point of hypoglycemia, it is treated by the ingestion of glucose or, in extreme cases, by the administration of a glucagon bolus to stimulate liver glucose output. Hypoglycemia has short-term consequences including insulin shock and diabetic coma (Kolatkar, 2006), and if untreated, will lead to death.

c) Insulin Signaling

In order to maintain postprandial euglycemia, carbohydrates must be taken into the cells. This is accomplished by a number of pathways; however, this section will focus on insulin stimulation and muscle contraction. Insulin concentration must be low enough to allow hepatic glucose output necessary to maintain energy supply to vital organs like the brain and liver during a fasted state, yet high enough to suppress the excess formation of ketoacids (Riddell & Perkins, 2006). Because glucose is not able to passively diffuse into a cell, it must be transported through the cell membrane via glucose transporters (GLUTs). The major glucose transporter isoform expressed in skeletal muscle is GLUT4, and it has a large capacity to increase glucose transport across the cell membrane by facilitated diffusion (Merry & McConell, 2009). GLUT4 is internalized from the plasma

membrane in the absence of insulin, and resides in intracellular tubulovesicular elements associated with the trans-Golgi reticulum (James & Piper, 1994). Insulin primarily promotes GLUT4 vesicle exocytosis (Klip, 2009); however, insulin also decreases the rate of GLUT4 vesicle endocytosis approximately 2-3 fold (Watson & Pessin, 2001). In the basal state, GLUT4 cycles between the plasma membrane and intracellular compartments, but when the insulin receptor is activated, this causes an increase in the rate of GLUT4 vesicle exocytosis, resulting in a net increase of GLUT4 on the cell surface, therefore, increasing the rate of glucose uptake (Watson & Pessin, 2001). Both exercise, (pertaining to muscle) and insulin (with respect to muscle and fat) cause a rapid and pronounced increase in cell surface levels of GLUT4 following recruitment from intracellular stores (James & Piper, 2004). Insulin initiates a signaling pathway that includes phosphatidylinositol kinase (PI3K), and the kinase known as Akt (Cartee & Funai, 2009). Figure 3, taken from Cartee & Funai (2009), demonstrates the detailed insulin-signaling pathway, resulting in translocation of GLUT4 to the cell surface.

Figure 3: Insulin pathway to activate GLUT4

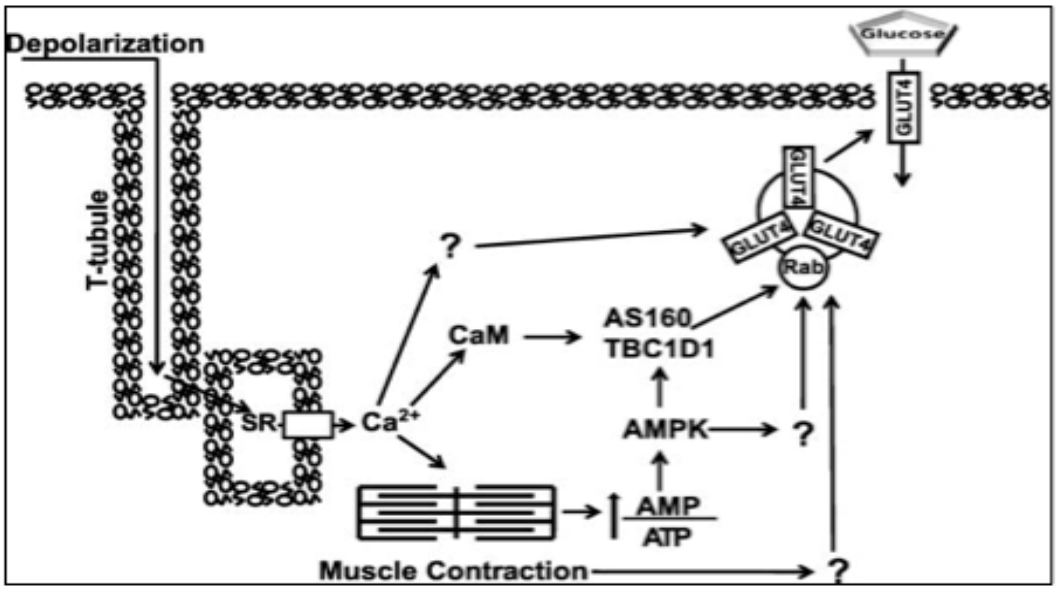


(Cartee & Funai, 2009)

Exercise (skeletal muscle contraction) can also affect glucose uptake using a different pathway than insulin. Muscle contraction, depolarization, and mitochondrial uncoupling can each increase the density of GLUT4 units at the muscle membrane and elevate the rate of glucose uptake (Klip, 2009). Membrane depolarization that triggers muscle contraction involves a rise in myocytoplasmic Ca^{2+}, and is required for contraction-induced stimulation of glucose uptake (Klip, 2009). Exercise relies on the cumulative effects of multiple inputs with adenosine monophosphate (AMP)-activated protein kinase (AMPK) and increased Ca^{2+} are considered as likely to be major factors, as a great deal of evidence suggests that increased cytosolic Ca^{2+} is important for a portion of the contraction-stimulated increase in glucose transport (Cartee & Funai, 2009). Figure 4, taken from Cartee & Funai (2009), shows the pathway of translocation of

GLUT4 to the cell surface during exercise. Note, that this pathway is independent of the insulin pathway.

Figure 4: GLUT4 activation by skeletal muscle contraction



(Cartee & Funai, 2009)

The pathway that glucose takes to get into the cell during exercise differs from the insulin pathway, and it has been suggested that this results (at least in part) from the activation of adenosine monophosphate (AMP)-dependent protein kinase (Watson & Pessin, 2001). Activation of AMPK via 5-aminoimidazole-4-carboxamide-riboside (AICAR) reduces GLUT4 endocytosis provides proof of concept that the enzyme is able to regulate this aspect of GLUT4 traffic (Klip, 2009).

Metabolism During Exercise

a) Non-Diabetic

The liver is responsible for blood glucose homeostasis in the body under varying conditions. During exercise in the non-diabetic body, the glucose production of the liver is increased. Glycogenolysis is the process that breaks down liver glycogen into glucose, whereas gluconeogenesis is the process that synthesizes glucose from gluconeogenic precursors (lactate, alanine, glycerol and pyruvate), circulating in the blood stream. When exercise is short-term with extensive exertion, hepatic glycogenolysis is the primary source of extra glucose for skeletal muscle. Increased pre-exercise muscle glycogen availability increases muscle glycogenolysis during exercise; conversely, reduced muscle glycogen levels result in a lower rate or muscle glycogen breakdown during exercise (Hargreaves, McConell & Proietto, 1995). However, during prolonged exercise, hepatic gluconeogenesis becomes gradually more important as a result of falling insulin and rising glucagon levels (Wahren & Ekberg, 2007).

b) Type 1 Diabetes

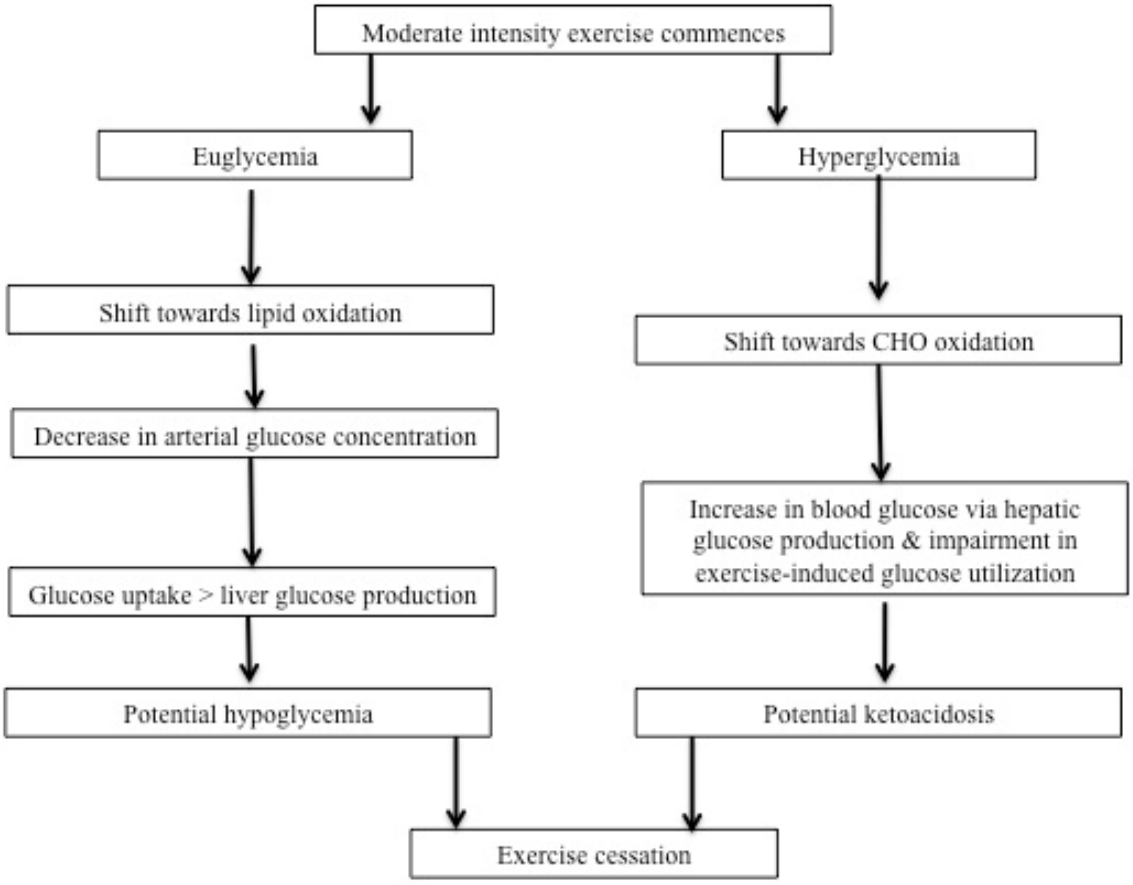
Both T1DM and T2DM have effects on metabolism during exercise. The following will compare metabolic properties in both T1DM and T2DM. In a T1DM individual, it has been shown that during moderate-intensity exercise with euglycemia (blood glucose equal to that of a non-diabetic) the body mimics that of a non-diabetic individual by making a substrate oxidation shift towards lipid oxidation; however, when exercise is undertaken during hyperglycemia, fuel metabolism is dominated by carbohydrate oxidation (Jenni et al., 2008). Upon cessation of exercise, the liver's glycogen reservoir

waits to be replenished following the postprandial period, which is accomplished by three factors (Radziuk & Pye, 2001):

1. an increment in the hepatic glucose uptake from the liver,
2. metabolic and hormonal signals in the portal vein,
3. an increment in the gluconeogenic flux (gluconeogenesis).

The response to exercise is also dependent upon the intensity of exercise undertaken. At the onset of light exercise, there is a tendency towards increased arterial glucose concentration due to the increase in liver glucose output induced by exercise. During recovery from submaximal exercise, muscle glycogen content increases at similar rates in both diabetic, and non-diabetic individuals, with the most pronounced increase in the first four hours of recovery (Maehlum, HØstmark & Hermansen, 1977). Glycogen synthesis following prolonged heavy exercise has been shown to proceed at a similar rate in the muscles of people affected by T1DM as in muscles of non-diabetics when individuals with T1DM take their insulin and carbohydrates given per os (Maehlum, HØstmark & Hermansen, 1977). If these intensities are not prolonged, they will not cause hypoglycemia. Figure 5 shows the hormonal response to exercise in individuals with T1DM.

Figure 5: T1DM response to exercise



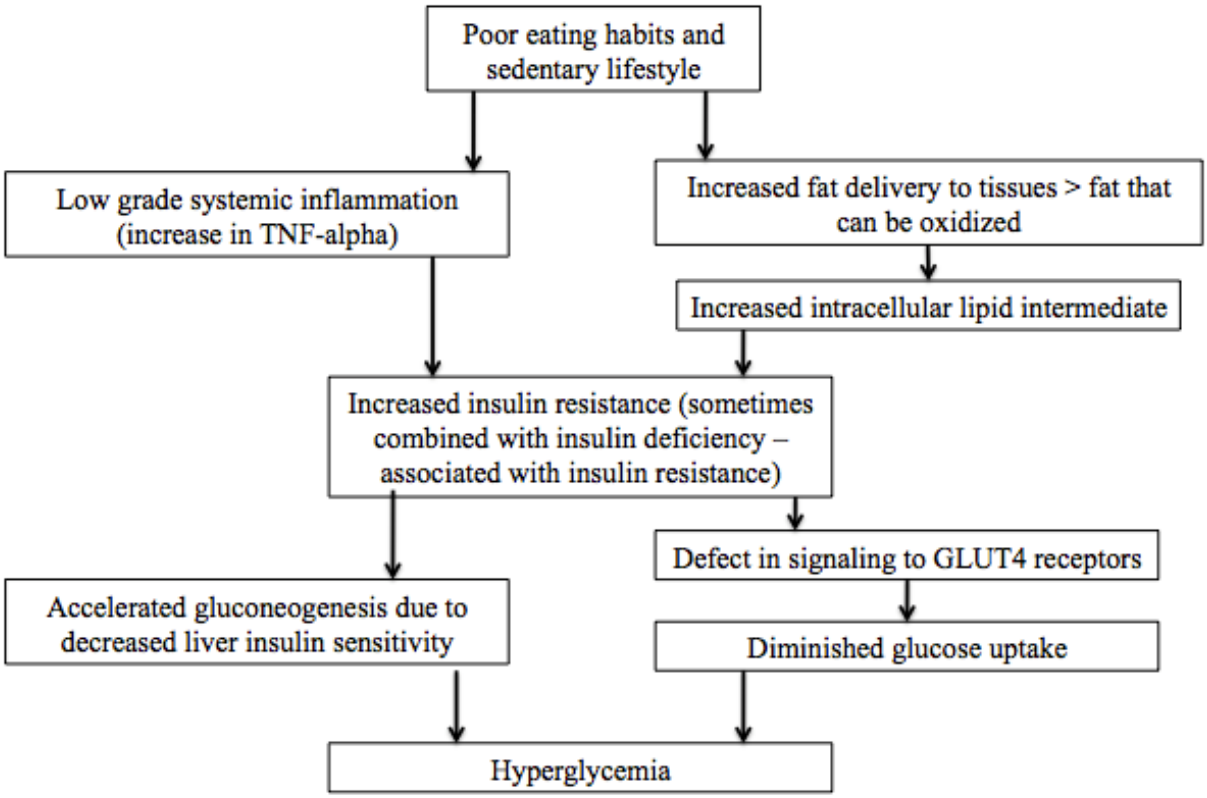
(Adapted from Jenni, et al., 2008)

c) Type 2 Diabetes

Exercise is one of the main prescriptions for individuals with T2DM, as its effects have shown to markedly improve the consequences that accompany the disease (Wahren & Ekberg, 2007; Bordenave et al., 2008; Wang, Simar & Singh, 2009).

T2DM is diagnosed by insulin resistance, and is sometimes combined with relative insulin deficiency. While T1DM patients have diminished hepatic glycogen stores, augmented gluconeogenesis, and an increase in basal hepatic glucose (Wahren & Ekberg, 2007). Conversely, the hyperglycemia of T2DM is partly caused by glucose overproduction from the liver, secondary to accelerated gluconeogenesis due to decreased liver insulin sensitivity, which would normally decrease gluconeogenesis (Wahren & Ekberg, 2007). A single bout of aerobic exercise at moderate intensity has been shown to aid in the effects of T2DM by increasing insulin sensitivity, indicating that the acute effects of exercise on insulin receptiveness are qualitatively important in the interpretation of training-related insulin sensitivity (Bordenave, et al., 2008). Such effects are also seen with lipid metabolism after aerobic exercise and include decreases in intramuscular triglyceride concentration and enhanced insulin sensitivity (Wang, et al., 2009). Figure 6 demonstrates insulin resistance in T2DM. Exercise has been shown to increase insulin sensitivity and increase GLUT4 transport via 2 independent mechanisms. Increased glucose uptake is the result of contraction-mediated GLUT4 translocation to the surface of the cell, (insulin-independent), while chronic exercise or training, thereby causes increased insulin sensitivity.

Figure 6: Type 2 Diabetes Mellitus



(Adapted from review by Wang, et al., 2009)

c) Individual Variability in T1DM

In individuals with T1DM, and non-diabetic individuals alike, there is a degree of variability associated with metabolism, and responses to thermal stress that are dependent on numerous factors. Baldi, Cassuto, Foxx-Luppo, Wheatley & Snyder (2010) found lower resting cardiac output and a higher systemic vascular resistance in T1DM individuals with a higher HbA_{1C} (7.8 ± 0.4%) when compared to a low-HbA_{1C} group (6.5 ± 0.3%) during maximal incremental cycle ergometry. The main findings of the study were that despite similar training volumes, subjects with higher HbA_{1C} had lower peak workload, VO_{2peak}, and peak cardiac output than those with lower HbA_{1C}. The study also

found that pulmonary function measures were lower with the higher HbA_{1C} group during peak exercise, and suggests that cardiopulmonary training adaptations are greater in individuals with T1DM when good glycemic control is maintained. The authors commented that the further research is needed to elucidate mechanism through which poor glycemic control influences both cardiac and pulmonary responses to maximal exercise, but postulated that autonomic dysfunction may have influenced the hemodynamic exercise response in the high-HbA1c group (Baldi, et al., 2010).

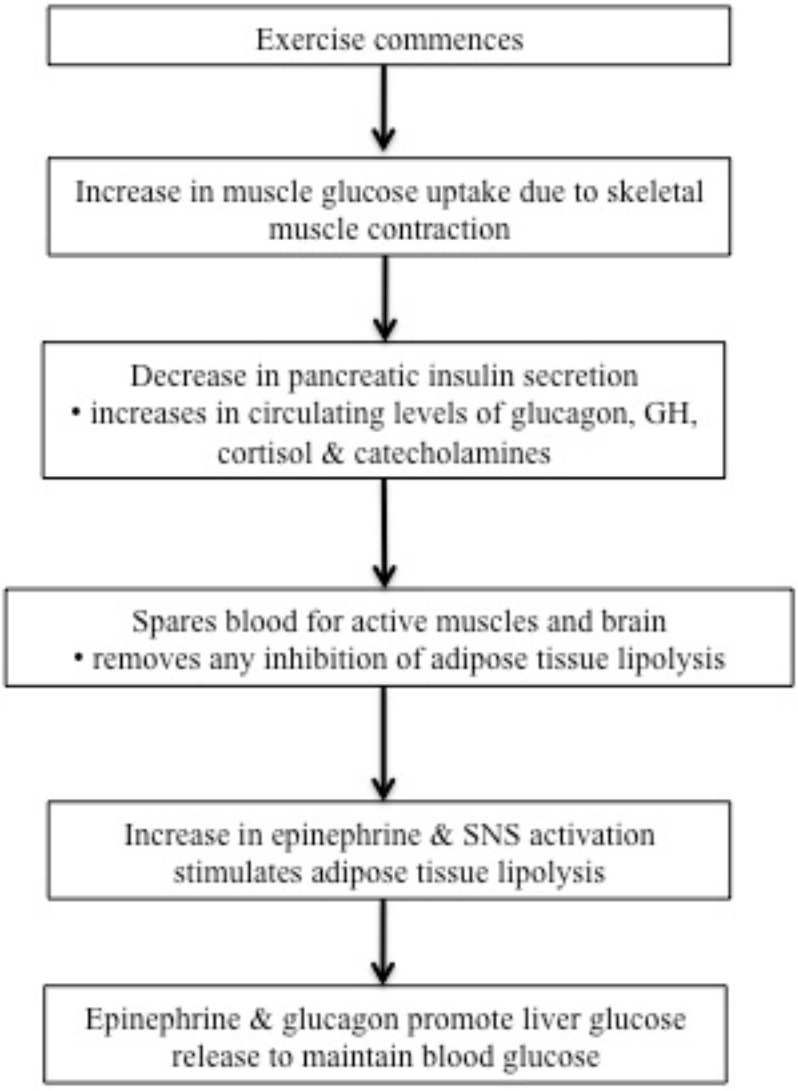
When comparing the metabolic control and lipid utilization (via insulin and glycemic clamp) in sedentary individuals and athletes with T1DM, Ebeling, Tuominen, Bourey, Koranyi & Koivisto (1995) determined that in athletes with T1DM, when competitive exercise is performed at variable schedules and intensities, it leads to a decrease in required insulin dose, impairment of metabolic control, and increase in lipid utilization. Further, there is no enhancement of insulin sensitivity, and glucose A-V (arteriovenous) difference, not blood flow, is the major determinant of body sensitivity to insulin. The study also found that glycemic control, as estimated by HbA_{1C} level, was worse and insulin dose requirements were less for the athletes than their sedentary counterparts, and the energy expenditure was higher in the athletes than in the sedentary patients both between 50 and 80 min and between 130 and 160 min. At the end of insulin infusion, the metabolic rate had increased significantly in the control patients but remained unchanged in the athletes (Ebeling, et al, 1995). The main findings of the study were that the only difference between the athletes and sedentary patients regarding cellular mechanisms of glucose metabolism was increased muscle glycogen synthase activity in the diabetic athletes in the basal state, as has been previously reported

(Ebeling, et al., 1993 & Taylor et al., 1972) in healthy athletes. The mechanism behind this finding could be explained by the increased muscle contraction seen in athletes when compared to sedentary individuals; however, it has been shown that in healthy athletes, the non-oxidative glucose disposal rate is greater than in the sedentary subjects (Ebeling et al., 1992), but this was not observed between diabetic athletes and sedentary patients. Therefore, it is possible that athletes affected by T1DM demonstrate a reduced stimulatory effect of insulin on the utilization of glucose (Ebeling, et al., 1995).

Exercise

Exercise is an important tool in maintaining the health of an individual, and there are many physiological mechanisms behind the benefits of exercise. The following will outline the effect and role of exercise in non-diabetic individuals to provide a framework for how the body is meant to function in the absence of T1DM. Figure 7 shows the non-diabetic hormonal response to exercise. In a non-diabetic body, exercise can reduce the risk of hypertension, T2DM, coronary heart disease, stroke, and mild anxiety and depression.

Figure 7: Non-diabetic hormonal response to exercise



(Adapted from Sigal, et al., 1999)

Exercise can also increase stamina, and the capacity for work, ameliorate the effects of aging and muscle disease, and help prevent osteoporosis. During exercise, there is a decrease in insulin release from the pancreas and an increase in glucagon secretion by the liver due to increased sympathetic activity. Plasma glucose concentration is tightly regulated in exercise at 60% VO_{2max} or less, with muscle glucose uptake being matched

by hepatic glucose production, and is regulated by the increase in the portal vein glucagon-to-insulin ratio (Shili, Wasserman & Vranic, 1996). Afferent signals for the increase in glucagon and decrease in insulin arise from the exercising muscle, consisting of a feedback mechanism (Shili, Wasserman, & Vranic, 1996). The decreased plasma insulin concentration during exercise is followed by a marked augmentation at the end of exhaustive exercise, lasting until 60 minutes of recovery and is linked with sustained hyperinsulinemia (Sigal et al., 1999). This hyperinsulinemia prevents hyperglycemia following exercise because of the increased glucose production during exercise, and promotes muscle and liver glycogen synthesis during recovery. During exercise in a non-diabetic individual, plasma glucose concentration remains stable, and muscle glucose uptake is matched by hepatic glucose production. This response is due to the increase in the portal vein glucagon to insulin ratio (Shili, Wasserman & Vranic, 1996).

Carbohydrates are the primary, but not the only, source for providing energy during strenuous exercise, with the body relying more on fat as a source of energy during prolonged moderate intensity exercise. Timing of ingestion of carbohydrates is just as important as the type of food being ingested. In cycling endurance performance at 70% of maximal oxygen uptake (VO_{2max}), time to exhaustion is 44, 32, and 17% longer (201 min, $p > 0.05$) for CHO feedings before and during exercise, CHO feedings during exercise, and pre-exercise CHO feedings, respectively, than for the same exercise without CHO ingestion (Wright, Sherman, & Dernbach, 1991). When exercise intensity is between 65% and 85% of VO_{2max}, the body's CHO reserves influence performance capacity; for example, low muscle glycogen or blood glucose concentrations result in a reduction in work capacity (Coyle, & Coggan, 1984).

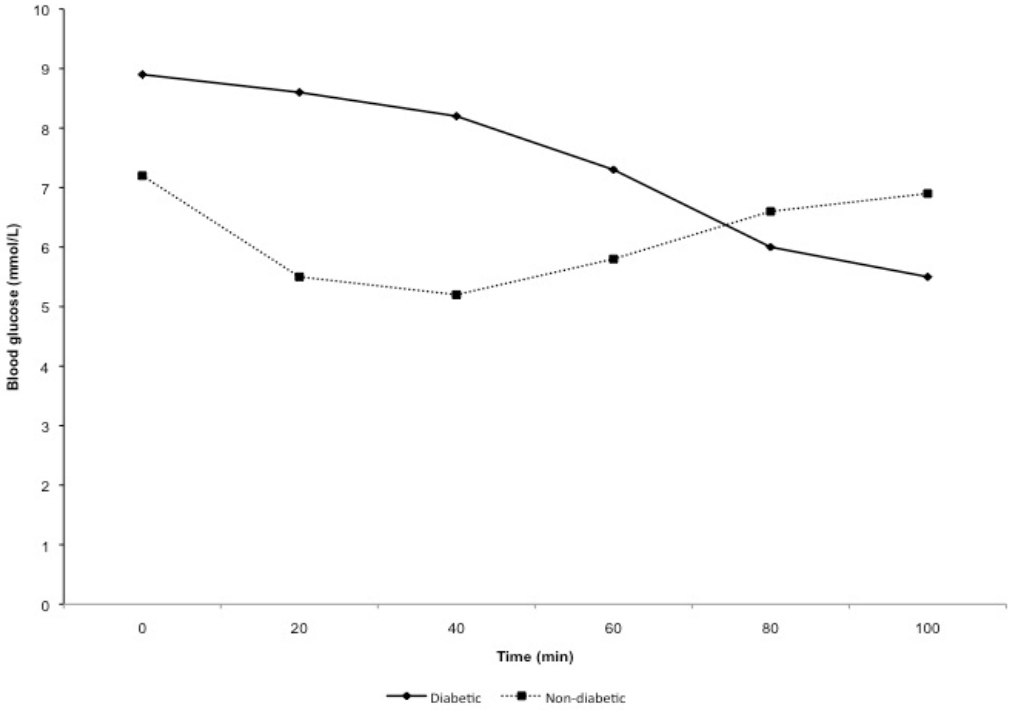
a) Exercise and Diabetes

The effects of exercise on the body of an individual with T1DM differ from the effects of exercise on the body of a non-diabetic individual. If exercise is undertaken with high insulin concentration, hepatic glucose output is inhibited and glucose disposal into active muscle causes hypoglycemia; on the other hand, if insulin levels are low or counter-regulatory hormone (adrenaline, glucagon, cortisol, and growth hormone) release is excessive when exercise is started, hepatic glucose output (and ketone production) will be excessive, leading to hyperglycemia (Riddell & Perkins, 2006). With regards to aerobic fitness, glycemic control and body composition in T1DM, there is a negative correlation between aerobic capacity and HbA_{1c} (Wallymahmed, et al., 2007); however, this correlation does not necessarily reflect a cause and effect relationship. This does mean that the higher the aerobic capacity of an individual, the more HbA_{1c} resembles that of a non-diabetic, healthy individual, and therefore, increased physical activity often translates into the T1DM individual being in better overall physical health due to better long term glucose regulation.

Regular physical activity is encouraged in people with Type 1 diabetes as exercise can help maintain good general health, prevent obesity, control diabetic symptoms and reduce the risks for other complications, such as high cholesterol and high blood pressure (American Diabetes Association, 2008). In order to maintain stable blood glucose levels, it is important to exercise and adjust insulin injections according to the type and intensity of exercise being performed. With respect to moderate exercise, if it is only 20-30 minutes in duration and less than 70% VO_{2max}, minimal reductions in insulin administration may need to be made (Peirce, 1999), noting that carbohydrates are the

dominant substrate oxidized at 60-70% VO_{2max}, in 30 to 60 minutes of exercise (Corigliano, et al., 2006). However, West, Morton, Bain, Stephens & Bracken (2010), showed that a 75% reduction in pre-exercise insulin best preserves blood glucose responses for 24 hours following 45 minutes of running at 70% VO_{2peak}. The balance between carbohydrate and lipid oxidation is determined by the intensity of exercise expressed in relation to aerobic capacity (Weber & Haman, 2005). As previously stated, the blood glucose of a non-diabetic individual is typically below 6.1 mM, and signifies the range in which an individual with T1DM should aim to have their blood glucose concentration. Prolonged blood glucose of more than 7-8 mM may compromise long-term control, although levels below 10-12 mM will allow safe exercise; however, levels below 6 mM may increase the risk of hypoglycemia even if the exercise intensity is between 50-70% (Peirce, 1999). Figure 8 depicts the blood glucose response to prolonged endurance exercise in both diabetic and non-diabetic individuals at 50-70% of VO_{2max} (moderate intensity) without carbohydrate supplementation.

Figure 8: Diabetic and non-diabetic blood glucose response to endurance exercise



(Adapted from Riddell & Perkins, 2009)

It should be noted that figure 8 shows the theoretical blood glucose response to prolonged endurance exercise in an individual with T1DM, without CHO ingestion.

In adolescents, it has been published that the effect of acute physical activity on children with T1DM probably depends on the type of activity, and not its intensity or the metabolic control. The type of exercise being performed will determine the effect, if any, on blood glucose. Endurance (aerobic) exercise has demonstrated to have a greater impact on reductions in average self-monitored blood glucose levels, when compared to resistance exercise; however, HbA_{1C} was increased with aerobic training (Ramalho et al., 2006). Glucose disposal during aerobic exercise causes an immediate requirement for increased hepatic glucose output, and if insulin levels are not changed to accommodate

for exercise, insulin levels will be high, inhibiting hepatic glucose output (Perkins & Riddell, 2006). With high-intensity, anaerobic exercise, the counter-regulatory hormone response (which may antagonize the effects of insulin at non-working muscles, permitting more available glucose for working muscles) frequently causes a dramatic exercise-induced ketoacidosis because anaerobic energy production relies on intracellular stores of muscle glycogen, while aerobic energy production relies more heavily on glucose uptake (Perkins & Riddell, 2006).

Post-exercise, the body of a T1DM individual enters a fasted state in which glycogen stores in muscle and liver are low and hepatic glucose production is accelerated. During any instance in which a T1DM individual is physically active, the risk of experiencing hypoglycemia is present.

b) Exercise Intensity and Hypoglycemia

When hypoglycemia occurs, subsequent exercise sessions undertaken within 24 hours will result in acute counter-regulatory failure of proportionally greater magnitude. This may be induced in a dose dependent fashion by differing depths of prior hypoglycemia in patients with T1DM (Galasetti et al., 2006). This translates into hypoglycemia being reached earlier in similar intensity exercise following a previous hypoglycemic episode. Post-exercise hypoglycemia and delayed onset hypoglycemia in individuals with T1DM can occur up to 4 and 24 hours after exercise, respectively (Peirce, 1999). Increased insulin sensitivity (due to the acute bout of exercise) and depleted glycogen stores combine to produce profound hypoglycemia that is most commonly nocturnal (Peirce, 1999).

During exercise, the glycemic response, or effect of different foods on blood glucose may be combated with carbohydrate ingestion. Ingesting a 6% carbohydrate drink during 60 minutes of moderate exercise and 30 minutes of recovery has been shown to increase blood glucose concentration by 1.17 mM in T1DM subjects (Perrone, et al., 2005). The type and intensity of exercise also has a role in hypoglycemia. Blood glucose levels are found to be lower in individuals with T1DM following moderate intensity exercise than with moderate intensity exercise interspersed with high-intensity bouts (Guelfi, et al., 2005). It is assumed that similar intensities of exercise have the same effects on blood glucose among individuals with T1DM (whether they are well controlled or not, as determined by HbA_{1c} values). In the past, studies concerned with T1DM have used individuals with "moderately controlled" blood glucose. It is presumed that individuals with moderately controlled T1DM were used because they were most willing to take part in the study. However, it is possible that these results may not translate equally well to uncontrolled type 1 diabetics.

c) Glucose Regulation During Exercise

As previously discussed, glycogen content of the muscles and liver are decreased when exercising and hepatic glucose production is accelerated (Peirce, 1999). During exercise in a non-diabetic individual, plasma glucose concentration remains stable, and muscle glucose uptake is matched by hepatic glucose production, with the response caused by the increase in the portal vein glucagon to insulin ratio (Shili, Wasserman & Vranic, 1996). However, in individuals with T1DM who are hyperglycemic at the onset of exercise, plasma glucose levels did not change significantly during moderate intensity

exercise, but decreased approximately 40% when exercise intensity was 70% of VO_{2max} (Petersen, Price & Bergeron, 2004). In non-diabetic subjects, the rate of liver glucose production is proportionally increased with exercise intensity, but the rate of glucose production is distinctly increased in subjects with moderately controlled Type 1 Diabetes and could be accredited largely to the rate of gluconeogenesis (rather than hepatic glycogenolysis) during exercise (Petersen, Price & Bergeron, 2004).

d) Thermoregulation & Diabetes

Currently, there is a lack of literature concerning the effects of ambient temperature on individuals with T1DM. However, one study (Rönnemaa & Koivisto, 1988) examined the effects of rest and exercise on the absorption of insulin and blood glucose in 10°C and 30°C in individuals with T1DM. These authors (Rönnemaa & Koivisto, 1988) found that insulin absorption (unbound circulating insulin) was 3- to 5-fold higher at 30°C than at 10°C, regardless of exercise. The study failed to examine heat storage, blood lactate, and sweat rate, as well as blood glucose at significant intervals. Their experimental protocol was performed on a cycle ergometer in three 15-minute periods with 5-minute rest intervals between periods. This protocol does not reflect the normal exercise undertaken by individuals with Type 1 Diabetes. A follow up study by Rönnemaa, et al., (1991) repeated the protocol of the previous study (1988), but examined the hormonal response at 10°C and 30°C. It was found that during the 55-minute exercise period at the 10°C, blood glucose was 3.4 mM lower than at rest and the corresponding difference at 30°C was 5.0 mM lower. Plasma lactate and norepinephrine concentrations from the pre-exercise to the end of exercise were greater at 30°C than at 10°C. A later

study found that in diabetic subjects at rest, heat tolerance is poor, resulting in a central body temperature of 1˚C higher and a clear correlation between abnormal rises in skin temperatures and rising core temperature when compared to control subjects (Petrofsky, et al., 2006). This experiment also showed that when compared with non-diabetic counterparts, individuals with T1DM were found to sweat at least 2 times less during exposure to external temperatures of 42ºC with core temperature and sweat rate increasingly proportionally in non-diabetic participants. However, sweat rate seemingly reached a plateau irrespective of the rise in core temperature seen in subjects with diabetes. Current data concerning T1DM and sweating (Petrofsky, et al., 2006) shows nonselective general damage to all areas of the body associated with diabetes, and did not appear to correlate with the duration or type of diabetes.

Temperature

a) Thermoregulation

The body's thermoregulatory system is vital to the maintenance of a homeostatic structure, and is regulated by the hypothalamus and thermoreceptors located in different parts of the body. Hammel's neuronal model suggests four types of hypothalamic neurons that control set-point thermoregulation, and include: warm-sensitive and temperature-insensitive neurons, heat loss and heat production effector neurons (Blount, 1996). The warm-sensitive neurons integrate core and peripheral thermal information; temperature-insensitive neurons are important in determining thermoregulatory set points; and, heat loss effector neurons are excited by warm-sensitive neurons and inhibit heat production effector neurons (Blount, 1996). The body reacts to both extreme heat, and extreme cold

in a manner that preserves the body's central organs. Humans produce 40-60 kilocalories of heat per square metre of body surface while at rest. These kilocalories are generated by cellular metabolism in the liver and heart (Edelstein, Li, Silverberg & Decker, 2007). Adverse effects can also be seen with a decreased body temperature. At temperatures below 34˚C, cellular metabolism slows, causing unconsciousness and cardiac arrhythmias (Brooks, Fahey & Baldwin, 2005).

Exertional heat illness has classically been defined by 3 categories: heat cramps, heat exhaustion, and heat stroke, but a more complete definition includes heat syncope and exertional hyponatremia (Binkley, et al., 2002). Hyperthermia is a condition in which the body takes on heat faster than it is able to dissipate it, causing the core temperature of an individual to rise considerably above the normal 37˚C. Exertional heat stroke is an elevated core temperature that is usually above 40ºC, associated with signs of organ system failure. Exertional heat stroke is due to the overheating of organ tissues that may cause break down of the temperature-control centre in the brain, with signs and symptoms including tachycardia, hypotension, sweating, hyperventilation, altered mental state, vomiting, diarrhea, seizures and coma (Binkley, et al., 2002). There are various effects on the body while in a hyperthermic state, evoking a stress response on the body. Hyperthermia alters carbohydrate metabolism through increased gluconeogenesis, depressed glycogenesis, glucose intolerance and insulin resistance (Mizock, 1995). The effect of increasing core temperature resulting in increased hepatic glycogen release and higher blood glucose is examined in studies by Valerio, et al., 2001, Mizock, 1995, and Halter, Beard & Porte, 1984, for review. Not surprisingly then, plasma glucose levels have been found to be significantly higher in hyperthermic patients (core temperature >

39°C) (Valerio, et al., 2001). Specific effects of hyperthermia (effects on glucagon production, sweat rate, and heat storage) on individuals with T1DM has yet to be examined; however, a pilot study demonstrated that increased body temperature during exercise causes an increase in blood glucose values following 30 minutes of cycling at 60% of VO_{2max} in a person with T1DM (see appendix, page 108). The study aimed to examine the effect of an increase in core temperature on glucoregulation during submaximal exercise; however, blood samples were not taken during the study, and the cause for the increase in blood glucose was not determined.

Exposure to a cold environment may result in hypothermia, and results in numerous physiological changes. Vasoconstriction, which retards heat loss and helps defend core temperature, starts when skin temperature drops below approximately 35ºC, and becomes maximal when skin temperature is 31ºC or less (Young & Castellani, 2000). Hypothermia is a condition in which a greater amount of heat leaves the body than the body is able to produce, causing the core temperature of an individual to fall below the normal 37˚C. Bradycardia (decreased heart rate, usually below 60 beats per minute), caused by decreased depolarization of cardiac pacemaker cells, is a result of hypothermia (Edelstein, et al., 2007). Hypothermia also affects metabolism of lipids and carbohydrates. Shivering has been shown to use more CHO and less lipids than exercise (Weber & Haman, 2005). Hypothetical explanations for this include hormonal differences (i.e. catecholamines), or different neural control of shivering and exercise (Mentel, Duch, Stypa, Wegener, Müller & Pfluger, 2003). Prolonged/strenuous exercise and alterations in diet have important effects on the quantity and the quality of metabolic fuel reserves that are available for shivering, and of all metabolic fuels, CHO reserves are the most affected

by such changes in exercise and diet regimen (Haman, 2006). However, plasma free fatty acid and glycerol levels are not higher, but may be lower during exercise in cold air or water when compared to corresponding warmer conditions (Doubt, 1991). Hypoglycemia has been shown to decrease body temperature during cold exposure by inhibiting heat production by approximately 20%, thereby inhibiting shivering thermogenesis (Passias, et al., 1996). However, this inhibition of shivering thermogenesis appears to be centrally mediated, rather than a limitation to peripheral energy metabolism (Young & Castellani, 2000). Previous studies have shown that plasma glucose and muscle glycogen have been shown to play significant roles in heat production during cold exposure (Jacobs, et al., 1994), yet a more recent study showed that even though plasma glucose oxidation was strongly stimulated during low-intensity shivering, it only contributed a minor role (10%) to heat production (Haman, et al., 2002). Even if blood glucose only plays a minor role in low-intensity shivering, this reliance on blood glucose may result in hypoglycemia in individuals with T1DM.

b) Exercise and Temperature

The body's natural response to exercise in a warm environment is to use evaporative heat loss through sweating and vasodilation in order to maintain a stable, but elevated core temperature. In instances where the body is not able to dissipate this heat fast enough, a rise in core temperature and skin temperature is witnessed. However, following the onset of exercise there is a rise core temperature and temporal dissociation (time taken to balance the differential rates of heat production and heat loss) resulting in a higher rate of heat storage (Kenny, et al., 2010). With regard to the effect of heat on

thermoregulation and performance, when body temperature rises, the gradient core to skin is decreased and the cutaneous blood flow necessary to maintain thermal balance is reduced. A more rapid rise in core temperature will occur if a reduction in the rate of heat loss, or the addition of an external heat load occurs as soon as the environmental temperature exceeds the skin temperature (Maughan, et al., 2007). An increase in body temperature is well acknowledged as one of the limiting, physiological factors for prolonged exercise performance (González-Alonso, et al., 1999). Physiologic responses to cold exposure depend on factors such as; subcutaneous fat, metabolic rate, temperature of the surrounding environment, and initial body temperature. Individuals with excess body fat are better able to insulate heat when blood is diverted to the internal organs during exposure to cold stress. As metabolic heat production rises with increasing exercise intensity, both skin and core temperatures are maintained warmer and the afferent stimulus experienced in a cold environment, decreases (Young & Castellani, 2000). It has been shown that oxygen consumption of a man with a healthy Body Mass Index (BMI; 18.5-24.9) is significantly higher than the oxygen consumption of a man with an obese BMI (>30) between 17˚C and 8˚C; however, at 5˚C, the oxygen consumption of the two men was not significantly different (Wyndham, Williams, & Loots, 1968). The differences in oxygen consumption are different because the man with the larger BMI has greater insulation, and therefore, prevents greater heat loss than the man with lower BMI. This relates to the current study because individuals with a higher BMI may have a better insulation, and therefore a greater reliance on fat than CHO in the cold, having less of an impact on blood glucose. Many physiological factors are different when comparing and individual with a healthy BMI to an obese individual when dealing

with cold exposure. A healthy man increases his metabolic rate sharply when ambient temperatures fall below 20˚C, while an obese man in the same circumstances does not alter his metabolism until the ambient temperature falls below 10˚C, suggesting that the insulation against heat flow is less in the healthy man, than in the obese man (Wyndham, Williams, & Loots, 1968).

Knowledge Gaps

Currently, the majority of literature regarding T1DM and exercise simply investigates different intensities (Guelfi et al., 2005), two different temperatures (Rönnemaa & Koivisto, 1988; Rönnemaa et al., 1990), modes of exercise (Ramalho et al, 2006) and their effects on blood glucose and other blood markers. There is a large gap in the literature pertaining to T1DM in terms of understanding heat storage, core temperature and sweat rate during continuous aerobic exercise at different temperatures. Because North America, and many places like it in the northern hemisphere are affected by all 4 seasons, it is not unusual to see a large variation in ambient temperature. Exercise in the heat and exercise in the cold both affect the non-diabetic body. However, the effect of different ambient temperatures has yet to be thoroughly investigated in individuals with T1DM. Although, it is beneficial for individuals with T1DM to exercise, it must be recognized that (in many countries) they are subject to the varying temperatures of the 4 seasons. However, there is little information on the effects of these varying temperatures on thermal, metabolic and perceived responses in individuals with Type 1 Diabetics. During exercise in non-diabetic subjects, the rate of glucose production is proportionally increased with exercise intensity, but the rate of glucose production is distinctly increased

in subjects with moderately controlled Type 1 Diabetes and could be accredited to the rate of gluconeogenesis during exercise (Petersen, Price & Bergeron, 2004), but whether this is altered with different ambient temperatures has yet to be examined. The investigation of the effects of different ambient temperatures in individuals with T1DM is important in order to enhance the understanding of these individuals with respect monitoring their blood glucose and ingesting CHO when exercising in different ambient environments. To date, a study has yet to examine the effects of continuous aerobic exercise at 5°C, 20°, and 35C° on blood glucose, sweat rate, blood flow, heat storage and insulin and glucagon concentrations. The information obtained from this study will provide important information for the scientific community versed in Type 1 Diabetes, and millions of individuals living with T1DM.

Summary and Statement of Problem

Currently, there is a lack of literature concerning glucose dynamics, heat storage, blood flow, and sweat rate during exercise under varying ambient temperatures in individuals diagnosed with T1DM. Early studies by Rönnemaa & Koivisto, (1988) & Rönnemaa et al., (1991) suggest that blood glucose is lower with exercise in hot (30ºC), than cold (10ºC) temperatures. However, current literature (Jacobs, Martineau & Vallerand, 1994; Haman, 2002) and a case study conducted in 2008 (see appendix), in which blood glucose rose post-exercise in an increased body temperature condition, suggest otherwise. The primary aim of the present study is to investigate the effect(s) of different ambient temperatures during exercise in subjects with T1DM. Subjects exercised in 35˚C (H), 20˚C (T) and 5˚C (C) at 65% of their VO_{2max} for 30 minutes.

Blood glucose, blood lactate, insulin, glucagon, heart rate, heat storage, sweat rate, blood flow and core temperature were all measured during each exercise condition. Blood glucose was monitored every 10 minutes for 60 minutes post-exercise, and at 6, 12, and 24 hours post-exercise.

Hypotheses

We evaluated the hypothesis that upon cessation of exercise in the hot condition, blood glucose will rise acutely because of increased gluconeogenesis (Hagreaves et al, 1996) before beginning to fall in the post-exercise period. During the cold condition, we anticipated a significant drop in blood glucose because alterations in diet have important effects on the quantity and the quality of metabolic fuel reserves that are available for shivering, and of all metabolic fuels, CHO reserves are the most affected by such changes in exercise and diet regimen (Haman, 2006). It was expected that CHO oxidation would dominate in the cold environment with exercise at 65% VO_{2max} because respiratory exchange ratios of between 0.8 and 0.9 (indicative of a mix of CHO and lipid metabolism, with a higher reliance on CHO) have been measured for exercise intensities of 60% to 75% of VO_{2max} (Gray, Kolterman, & Cutler, 1990; Muojo, Leddy, Horvath, Awad, & Pendergast, 1994); and exposure to cold conditions has been shown to decrease reliance on lipid oxidation, and increase CHO oxidation (Weber & Haman, 2005). As a result of increased gluconeogensis, we expected glucagon to be significantly higher in the hot condition, and no significant differences would be apparent between conditions with respect to insulin. With respect to perceived responses, we hypothesized that participants

would be more uncomfortable in the hot and cold conditions, and would also have a higher rating of perceived exertion in these conditions than in the neutral condition.

Methods

Participants

The experimental protocol and instrumentation conformed to the standards set by the Declaration of Helsinki and approved by the Research Ethics Board of Brock University (REB 09-005). Inclusion/exclusion criteria are outlined in Table 1. Eight participants with an activity level greater than or approximately equal to recreationally active (5 males, 3 females) were recruited from the University community and the Niagara region. Mean (±SD) age, height, body mass, relative body fat, A_{1C}, and predicted VO_{2max} of all participants are presented in Table 2. Four of the subjects took regular bolus insulin injections (2 males, 2 females), while the remaining four subjects were on an insulin pump (3 males, 1 female). Participants were instructed to follow the same diet the day prior to, the day of, and the day after each experimental condition.

Table 1: Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Activity level ≤ recreationally active	Pre-existing heart condition
Living with diagnosed diabetes for a minimum of 5 years	Pain in the chest while exercising
Receiving insulin therapy (bolus or pump)	Deemed to be obese (body fat percentage above 32%)
Able to recognize hypoglycemic symptoms (hypoglycemia aware)	Diagnosed with hypertension
Physician permission	Pregnant
	Severe peripheral neuropathy or active proliferative retinopathy, unstable cardiac or pulmonary disease, disabling stroke, or severe arthritis

Table 2: Individual Participant Characteristics

Participant	Gender	Relative Body Fat % (sum of 7)	Predicted VO_{2max} ($ml \bullet kg \bullet min^{-1}$)	Years with T1DM	HbA_{1C}	Type of insulin therapy
1	Male	10.7	55	23	8.3	Bolus
2	Male	14	53	10	6.3	Bolus
3	Male	7.6	64	16	6.0	Pump
4	Female	28.6	42	9	7.3	Pump
5	Male	20.7	39	21	6.8	Pump
6	Female	23.6	61	35	8.4	Bolus
7	Female	30.3	36	23	6.6	Bolus
8	Female	8.9	48	23	7.2	Pump

Screening Visit (Anthropometrics and Predictive Maximal Oxygen Consumption)

Participants had their height and body mass measured. Skin fold thickness were measured with a caliper at seven sites (chest, triceps, mid axillary, subscapular, suprailiac, abdominal and thigh) and relative body fat was calculated using the equations of Jackson and Pollock (1978) seen below.

Jackson & Pollock 7-site body fat calculation for men:

Body Density = 1.112 - (0.00043499 * SUM7) + (0.00000055 * SUM7²) - (0.00028826 * Age)

Body Fat Percentage: [(4.95/Bone Density) - 4.5] 100

Jackson & Pollock 7-site body fat calculation for women:

Body Density = 1.097 - (0.00046971 * SUM7) + (0.00000056 * SUM7²) - (0.00012828 * Age)

Body Fat Percentage: [(4.95/Bone Density) - 4.5] 100

Participants were excluded if they were deemed to be obese (body fat percentage above 32%), had hypertension diagnosed by their physician, had T1DM for less than 5 years, or had an HbA_{1C} of above 9.0 $mmol \bullet mol^{-1}$. Predicted Maximal Oxygen

Consumption (VO_{2max}) was determined on a cycle ergometer (Lode R.V. Medical Technology, Groningen, Netherlands). Participants were outfitted with a telemetric heart rate monitor (RS800CX, Polar Electro, Kempele, Finland), and performed an Astrand-Rhyming (1954) cycle ergometry test as a predictive measure of VO_{2max}. Participants cycled at 60 rpm at a wattage that elicited a heart rate between 130-160 beats per minute. If the participant's heart rate was not in the target range of 130-160 beats per minute, then the wattage was increased to reach the desired heart rate. After 6 minutes, the participant ceased cycling, and final wattage and heart rate were recorded to determine predictive VO_{2max}.

Following the Astrand-Rhyming test, participants were hooked up to a metabolic cart (Moxus, AEI Technologies, Naperville, Illinois) and cycled in 4-minute incremental stages until they reached 65% of their VO_{2max}. One day prior, and 3 days following Session 1, participants were asked to keep a diet log. This diet log provided baseline measurements of the typical CHO ingestion, and participants were instructed to follow their typical (baseline) eating habits prior to, and following each exercise session.

Experimental Protocol

All conditions were identical in instrumentation and protocol; the only difference between the three conditions was the application of ambient temperature in a randomized fashion: 1) temperature of 5˚C (C, cool); 2) temperature of 20˚C (N, neutral); and 3) temperature of 35˚C (H, hot). In all conditions, humidity was set at 40%. Prior to exercise, participants rested in the chamber for 5 minutes while baseline values were collected. This 5-minute baseline period provided measurements to which all exercise and

post-exercise values were compared. Participants then cycled for 30 minutes at 65% of their predicted VO_{2max} on a cycle ergometer (Lode R.V. Medical Technology, Groningen, Netherlands) in the environmental chamber, with a relative humidity of 40%, and wind speed between 0.4-0.8 m/s (Kestrel Air Flow meter, Niche Retail, Sylvan Lake, MI). After exercise, the chamber was turned off, and the participants remained seated for 60 minutes in an ambient temperature of approximately 22ºC.

Participants were asked to refrain from strenuous physical exercise, caffeine, and alcohol for 24 hours prior to each session. Participants were also informed to follow their regular diet, and insulin administration. All studies were begun between the hours of 0800 and 1000 h to avoid potential confounding effects from circadian rhythm in temperature. Experimental sessions were conducted at least 2 days apart to ensure adequate recovery. One hour prior to entering the laboratory, participants were instructed to take a blood glucose reading using Accu-Chek Compact Plus blood glucose monitors (Roche Diagnostics, Laval, Québec). These monitors were used for all blood glucose measurements, to ensure participant safety and blood glucose reliability. If blood glucose was at the level of, or below 4.0 mM, participants were instructed to ingest sufficient CHO to raise their blood glucose by 3.5-4.0 mM before entering the lab. Conversely, if hyperglycemia was present (blood glucose > 13.9 mM), the exercise trial was rescheduled to a later time in order to standardize blood glucose values. All trials were conducted in a controlled environmental chamber capable of temperature control. Blood glucose, blood lactate (Akray, Lactate Pro, Shiga, Japan), thermal sensation, thermal comfort and rating of perceived exertion were measured every 10 minutes from the onset of exercise until 60 minutes post-exercise. If hypoglycemia occurred at any time during exercise, or post-

exercise, participants were given 500 mL of Gatorade™ and remained in the chamber with all instrumentation attached. All bouts of hypoglycemia were noted and analyzed accordingly. To normalize blood glucose levels when Gatorade™ was administered, the average increase caused by Gatorade™ was subtracted from blood glucose for each time point. For example, in the 2 instances where hypoglycemia occurred in the cold condition, the average increase as from 20 to 30 minutes post-exercise as a result of Gatorade™ consumption was 0.9 $mmol \bullet mol^{-1}$ (one increase was 1.6 $mmol \bullet mol^{-1}$, and the other was 0.3 $mmol \bullet mol^{-1}$). Therefore, 0.9 was subtracted from blood glucose values at 30 minutes post-exercise for the 2 values where hypoglycemia occurred. Throughout the experiment, indirect calorimetric analysis of oxygen uptake was performed (Moxus, AEI Technologies, Naperville, Illinois). Participants were required to stay for 60 minutes post-exercise with blood glucose taken every 10 minutes. Rating of perceived exertion (RPE) (Borg, 1982) was also taken every 10 minutes during exercise. The Borg scale, ranging from 6-20, is indicative of the level of exertion felt by the participant, the greater the exertion, the greater the number reported. The Borg scale also provides a fairly good estimate of the participant's heart rate.

Upon leaving the laboratory, participants were given Dex-4™, and Gatorade™ to be taken in any instance in which hypoglycemia occurred. Participants were instructed to measure blood glucose every 6 hours for 24 hours post-exercise. Follow up phone calls were made to each participant at 6, 12, and 24 hours post-exercise to ensure participant safety, and for blood glucose reports. Participants also kept a diet log, indicating what foods were ingested, including quantity of food. Insulin and blood glucose levels were also recorded for each instance in which food was ingested. Participants were asked to

follow the same diet following each exercise session, and noted when hypoglycemia occurred. In instances were hypoglycemia did occur, sufficient CHO was ingested to counter hypoglycemia, and was different for each participant.

Blood Collection

Blood was drawn from the antecubital vein prior to exercise, upon cessation, and 60-minutes post-exercise. Blood was centrifuged at 2500 rpm for 10 minutes at 4ºC, and plasma was then pipetted into cryovials to be frozen for analysis. Insulin and glucagon were analyzed using Milliplex Human Endocrine Panel 2-plex for Insulin and Glucagon (Millipore, Billerica, MA). Blood analysis was performed at the University of Western Ontario.

Instrumentation

Upon arrival at the laboratory, participants changed into a t-shirt and shorts and had their height (cm) and weight (kg) measured prior to each session using standard laboratory equipment. Euhydration, defined as urine specific gravity of 1.02 or less (Dirckx, 2001), was assessed with a refractometer (Atago, PAL-10S, USA). Participants inserted a flexible core temperature thermistor (Mon-A-Therm Core, Mallinkrodt Medical, St Louis, MO) to a depth of 15 cm beyond the anal sphincter to measure rectal temperature. Participants were instrumented with a heart rate monitor strap (RS800CX, Polar Electro, Kempele, Finland) across the chest for telemetric recording of heart rate (HR).

Distribution of SkBF was quantified using Laser Doppler skin blood flow probes (PeriFlux System 5000, PeriMed, Järfälla, Sweden), placed on the lateral aspect of the forehead and the upper trapezium. Skin blood flow velocity was averaged over 5 min of

baseline and taken as 100%. Further measurements were averaged over the ensuing 5 min intervals (0-90 min) and recorded as a percentage change in flow velocity, relative to baseline.

A ventilated sweat capsule (13.19 cm^2) was firmly attached over the medial inferior aspect of the trapezius. Anhydrous air of known, constant volume flowed through the sweat capsule at a rate of 0.24 $l \cdot min^{-1}$ (Brooks 5850, mass flow controller, Emerson electric, Hetfield, PA). SR was defined as the product of the difference in vapour density between effluent and influent air with the flow rate adjusted for skin surface area under the capsule (mg·min-1·cm^{-2}). The temperature and relative humidity difference between air entering and exiting the capsule was determined by a temperature and humidity sensor (Omega HX93, Omega Engineering, Stanford, CT). Consistent airflow measured the amount of sweat produced and was determined by DasyLab 10 (Measurement Computing, Norton, MA). Partitional calorimetry was used to measure residual body heat storage, and mean skin temperature was calculated using a seven point weighted averages equation, as described by Hardy and DuBois (1938).

Heat flux, skin temperature/heat flow were quantified using heat flow transducers (Concept Engineering, Old Saybrook, Connecticut) placed on the forehead, abdomen, forearm, hand, quadriceps, shin, and foot surfaces (Hardy and Dubois, 1938). Humidity at the surface of the skin was measured using small humidity probes (HMP50 RH/T, Vaisala Inc., Vantaa, Finland), taped parallel to the surface of the skin of the upper back, abdomen and upper thigh. Metabolic data was collected using open-circuit spirometry (Moxus, AEI Technologies, Naperville, Illinois) to determine oxygen uptake and ventilation data during exercise.

Thermal comfort was assessed on a 5-point scale, increasing by increments of 0.5, (1- comfortable, 1.5, 2 – slightly uncomfortable, 2.5, 3 – uncomfortable, 3.5, 4 – very uncomfortable, 4.5, 5 – extremely uncomfortable) (Gagge, Stolwijk, & Hardy,1967). Thermal sensation was assessed on an 11-point scale, increasing by increments of 1 (0 – unbearably cold, 1 – very cold, 2 – cold, 3 – cool, 4 – slightly cool, 5 – neutral, 6 slightly warm, 7 – warm, 8 – hot, 9 – very hot, 10 – unbearably hot) (Gagge, Stolwijk & Hardy, 1967).

Heat Storage Measurements and Calculations

The dynamic equilibrium of core body temperature, or the rate of heat storage (S), was calculated using the following heat balance equation:

$$S = M \pm W \pm E_{res} \pm C_{res} \pm E_{sk} \pm K \pm C \pm R$$

where *M* represents the heat created by metabolism, specifically the transport of oxygen throughout the body, and was calculated using the following equation :

$$M = 352(0.23 \cdot RQ + 0.77)(VO_2 \cdot A_D^{-1})$$

where RQ represents the respiratory quotient, and A_D is the body surface area, which was calculated by:

$$A_D = 0.007184\, Weight^{0.425} \cdot Height^{0.725}$$

W is the release of heat though the mechanical work of the human body. E_{res} represents the transfer of heat though evaporative process of respiration and C_{res} represents the transfer of heat through convective processes of respiration, and was modeled by the following equations, respectively:

$$E_{res} = 0.0023 \cdot M \cdot (6.51 - P_a)$$

$$C_{res} = 0.0014 \cdot M \cdot \left(37 - T_a\right)$$

Evaporative heat loss through the skin, as indicated by E_{sk}, was modeled by the following equation:

$$E = (P_{sk} - P_a) \bullet v^{0.5} \bullet 124$$

in which E is evaporative heat loss in $W \bullet m^{-2}$, P_{sk} the saturated water vapour pressure at skin temperature in kPa, P_a the ambient water vapour pressure in kPa, v the air velocity moving over the participant in $m \bullet s^{-1}$, 124 the evaporative coefficient for heat exchange in $W \bullet m^{-2}$ kPa $v^{0.5}$ (Dennis & Noakes, 1999). In still air, as was seen in the recovery period, air velocity was used as 0.75 $km \bullet h^{-1}$ (0.2 $m \bullet s^{-1}$) (Adams, et al., 1992). The partial pressure of water vapour can be calculated by Antoine's equation as follows:

$$P_{sa} = \exp\left(18.956 - \frac{4030.18}{t + 235}\right)$$

Convective heat loss in still air (during recovery) was calculated using:

$$C = 6(T_{sk} - T_{db})$$

Where C is convective heat loss in $W \bullet m^{-2}$, 6 the heat transfer coefficient in $W \bullet m^{-2}$ °C, T_{sk} the average skin temperature in °C, and T_{db} the dry bulb temperature in °C (Adams, et al., 1992). In moving air, present during baseline and the exercise protocol, the formula:

$$C = 8.3 \bullet v^{0.6} \bullet (T_{sk} - T_{db})$$

was used. Where 8.3 is the convective coefficient for heat exchange in $W \bullet m^{-2}$ °C, v is the velocity of moving air over the body in $m \bullet s^{-1}$ (Kenney, 1998).

Thermal resistance is represented by *R* and is modeled by the following equation:

$$R = \frac{1}{h} = \frac{1}{h_r + h_c}$$

where h_r represents the radiative heat transfer coefficient, and h_c represents the convective heat transfer coefficient. Heat transfer coefficients were recently determined by Kurazumi et al., (2008) using thermal manikins, and are listed below for convection and radiation, respectively:

$$h_c = 1.175\Delta T^{0.351}$$

$$h_r = 3.871$$

Data Analysis

Data was analyzed using a repeated measures analysis of variance (ANOVA) in SPSS 18 (IBM, Somers, NY). All measurements were compared under each environmental condition as a 2-way ANOVA (condition x time) with a Bonferroni adjustment for pairwise comparisons and controlling familywise Type 1 error. If Mauchly's Test of Sphericity was significant, Greenhouse-Geisser values were used for significance. In instances where Mauchly's Test of Sphericity was insignificant, values for Sphericity Assumed were used. Mauchly's test of Sphericity was used to validate the repeated measures ANOVA, as it relates to the equality of the variances of the differences between levels of the repeated measures factor. If significance for condition x time was found, a one-way ANOVA was performed to determine at which time points significant differences could be found. For each condition, the onset blood glucose served as the baseline measurement to which all other values were compared. For all other measures, the first 5 minutes (baseline), served as the value to which all other time points were measured against. Where appropriate, Tukey post hoc tests for conditions were performed

to permit less conservative pairwise comparisons. Diet logs were analyzed using Diet Analysis Plus version 7.0 (Thomson-Wadsworth, 2006).

Results

Diet Logs

Participants were instructed to follow the same diet the day prior to, the day of, and the day after each experimental condition. Mean and standard deviation values for every participant are presented in Table 3 for the day prior to, the day of, and the day after experimental trials. Outlined in Table 4, are the lunch and dinnertime insulin injections for the day prior to, the day of, and the day after experimental sessions. Five participants experienced nocturnal low blood sugars on the day of, or the day after experimental trials. In 3 of the 5 participants, the low nighttime blood sugars occurred in the nights following experimental conditions and occurred a total of 4 times (twice in one participant). Low blood sugars were also observed in 3 subjects (a total of 4 times) on the day of an experimental session. Of these participants, only 1 also experienced low blood glucose the day after an experimental session. In instances where low blood sugar occurred on the day of an experimental session, 2 were in the hot condition, 1 was in the neutral condition, and 1 was in the cold condition.

Table 3: Average Individual Diet Information for 3 Conditions

			Day Before				Day Of				Day After			
Subject	Sex	Body Weight (kg)	Pro (g)	CHO (g)	Fat (g)	Kcal	Pro (g)	CHO (g)	Fat (g)	Kcal	Pro (g)	CHO (g)	Fat (g)	Kcal
1	M	74	99	237	35	1631	70	192	40	1365	102	224	23	1481
2	M	85	60	255	62	1774	52	750	91	3819	61	307	56	1927
3	M	91	69	366	90	2490	76	592	61	3029	82	263	59	1872
4	F	79	37	164	23	986	31	156	17	895	29	157	25	936
5	M	89	35	178	23	1009	42	201	24	1152	43	178	31	1119
6	F	59	54	142	46	1157	55	121	49	1129	48	129	57	1159
7	F	71	46	200	48	1386	55	178	50	1366	58	205	45	1432
8	M	89	77	163	54	1417	62	179	60	1461	65	164	47	1315

Table 4: Average Individual Insulin Dosages for 3 Conditions

	Subject							
	1	2	3	4	5	6	7	8
Breakfast								
Day Before	3.3±0	5.7±0	5.2±1.2	4.4±2.7	6.1±1.7	8±1.2	6.4±1	4.6±0.7
Day of	2.0±0	4.7±0.6	4.1±0.1	2.4±0.3	5±0	7.3±1.2	4.3±0.6	2.5±0
Day After	4.0±0	6.3±0.6	5.7±0.1	7.3±0.3	6.3±1.5	8.0±0	9.0±1.7	5.6±0.3
Lunch								
Day Before	5.6±0.6	10.3±1.5	6.4±0	8.5±1.1	9.3±2.3	0.0±0	7.3±2.3	4.0±0
Day Of	5.3±0.6	10.0±2	5.8±0	9.1±2.4	8.7±0.6	0.0±0	7.7±0.6	4.0±0
Day After	5.3±0.6	8.0±2	6.1±0	7.1±1.9	7±1.7	0.0±0	5.7±0.6	4.0±0
Dinner								
Day Before	5.0±1	7.7±1.2	7.2±0	3.7±0.4	10±1.7	8.0±0	8.7±3	6.0±0
Day Of	5.6±0.6	10.7±1.2	6.8±0	7.7±1.2	9.3±1.5	8.0±0	7.0±1	7.1±0
Day After	5.3±0.6	9.7±0.6	6.8±0	7.4±0.9	8.7±1.2	8.0±0	8.0±0	5.0±0

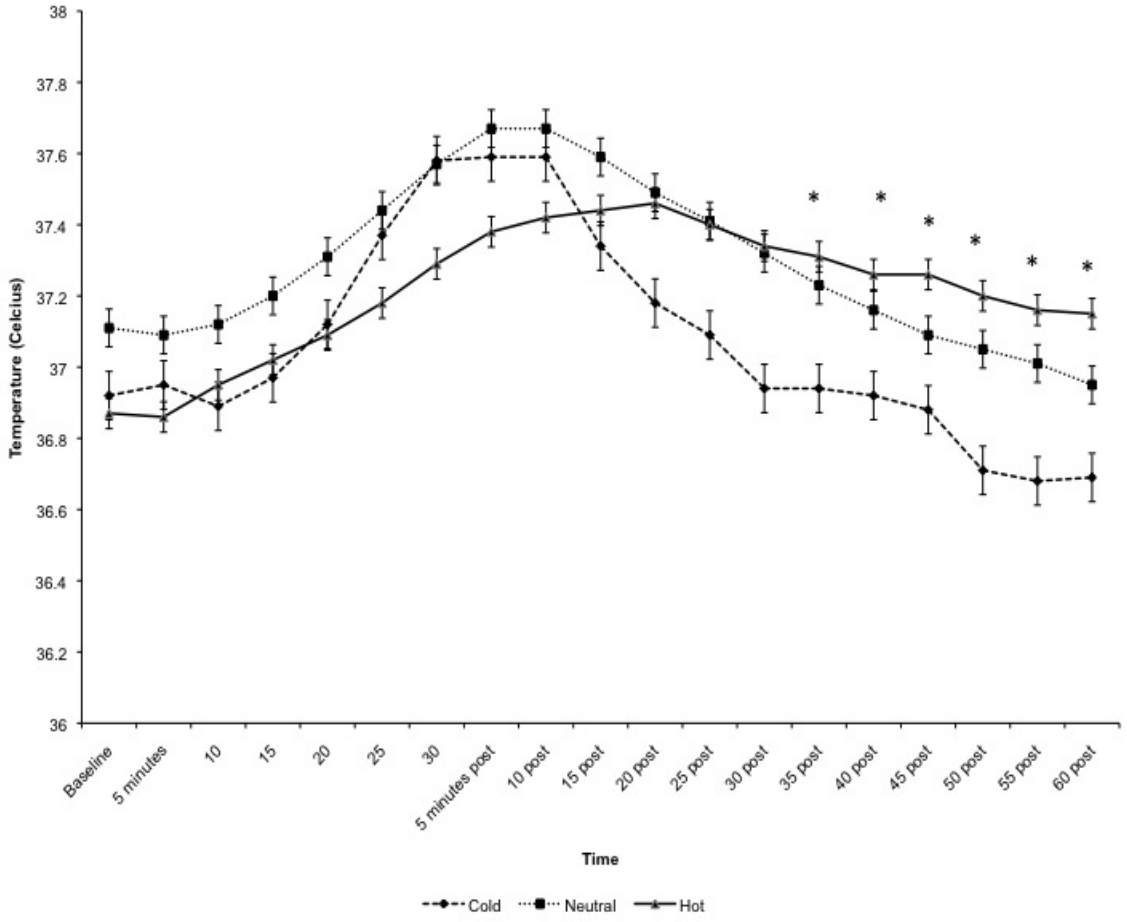
Thermal Responses

Core Temperature

A significant difference was observed for time ($p<0.01$), and for condition x time ($p<0.01$). Core temperature in the hot condition was significantly different from the cold condition from 35 to 60 minutes post-exercise. In the cold condition, core temperature increased 0.66 ± 0.27ºC from the onset of exercise to the cessation of exercise and dropped down to 0.23 ± 0.25ºC lower than baseline by 60 minutes post-exercise. Core temperature in the neutral condition increased 0.46 ± 0.27ºC from onset to cessation of exercise, and was 0.15 ± 0.27ºC lower than onset at 60 minutes post-exercise. In the hot

condition, core temperature increased 0.42 ± 0.44ºC from the onset of exercise to the cessation of exercise, and was 0.28 ±0.29ºC higher than the onset of exercise at 60 minutes post-exercise. Core temperature reached a maximum of 0.59ºC higher than baseline at 20 minutes post-exercise in the hot condition. Figure 9 shows core temperature from baseline to 60 minutes post-exercise.

Figure 9: Core Temperature



* - indicates significant differences between cold and hot conditions ($p \leq 0.05$)

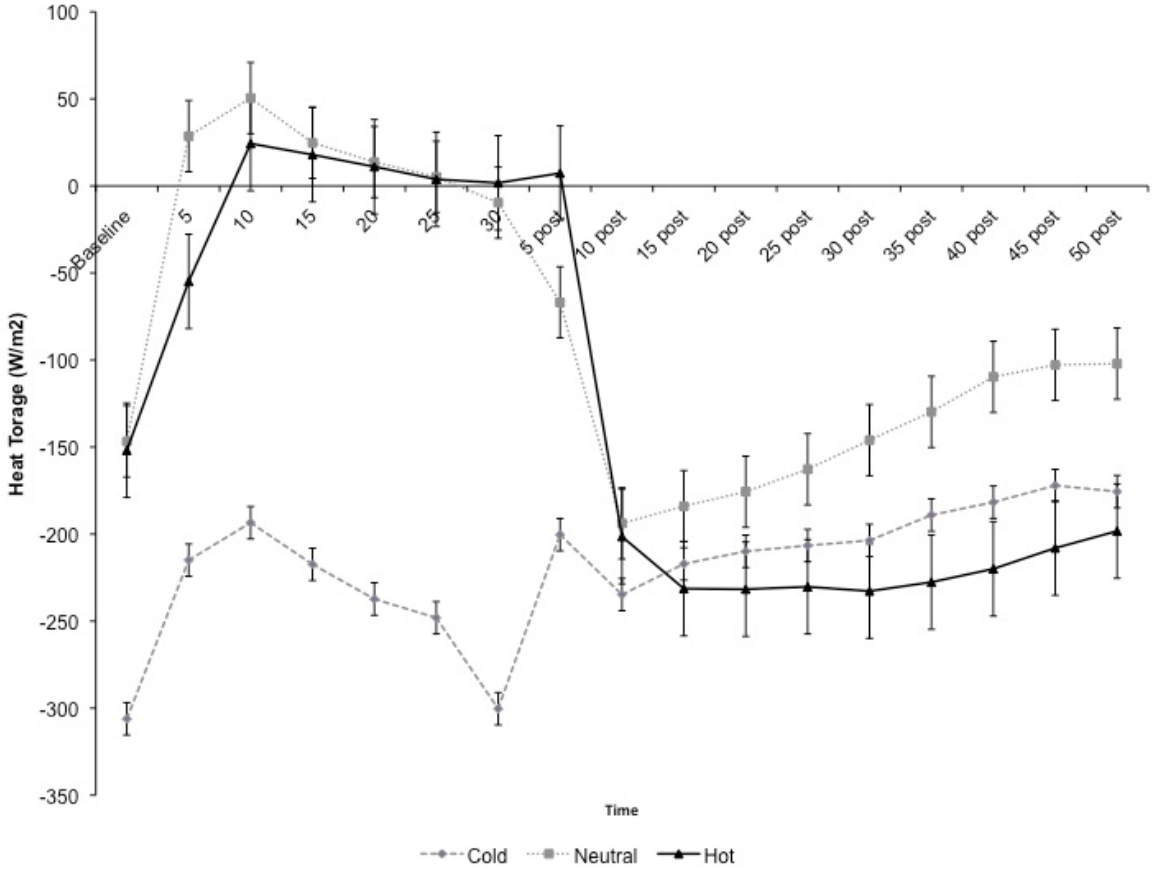
Skin blood flow

With Laser Doppler sensors placed on the forehead and upper trapezium, no significant differences were observed for time ($p = 0.557$), or condition x time ($p = 0.887$). Although mean forehead and trapezium skin blood flow were higher than baseline for all time points during the 30 minutes of exercise in all conditions, the increase was not statistically significant. No significant differences were observed between the forehead and upper trapezium sensor placements ($p = 0.493$).

Heat Storage

Heat storage was attained using partitional calorimetry by attaching 7 heat flow transducers and 3 humidity sensors placed on the surface of the skin. Heat storage values up to 50 minutes post-exercise are displayed due to missing values in several trials for 55 and 60 minutes post-exercise; however, heat storage had already reached a plateau prior to 50 minutes post-exercise. Significant differences were observed for both time ($p<0.01$) and condition x time ($p<0.01$). Heat storage increased from baseline to 30 minutes of exercise in all conditions. Heat storage increased 3.46 $W \bullet m^{-2}$ from baseline to 30 minutes of exercise in the cold condition, 70.01 $W \bullet m^{-2}$ in the neutral condition, and 77.27 $W \bullet m^{-2}$ in the hot condition.. Figure 10 displays heat storage values for each condition, up to 50 minutes post-exercise.

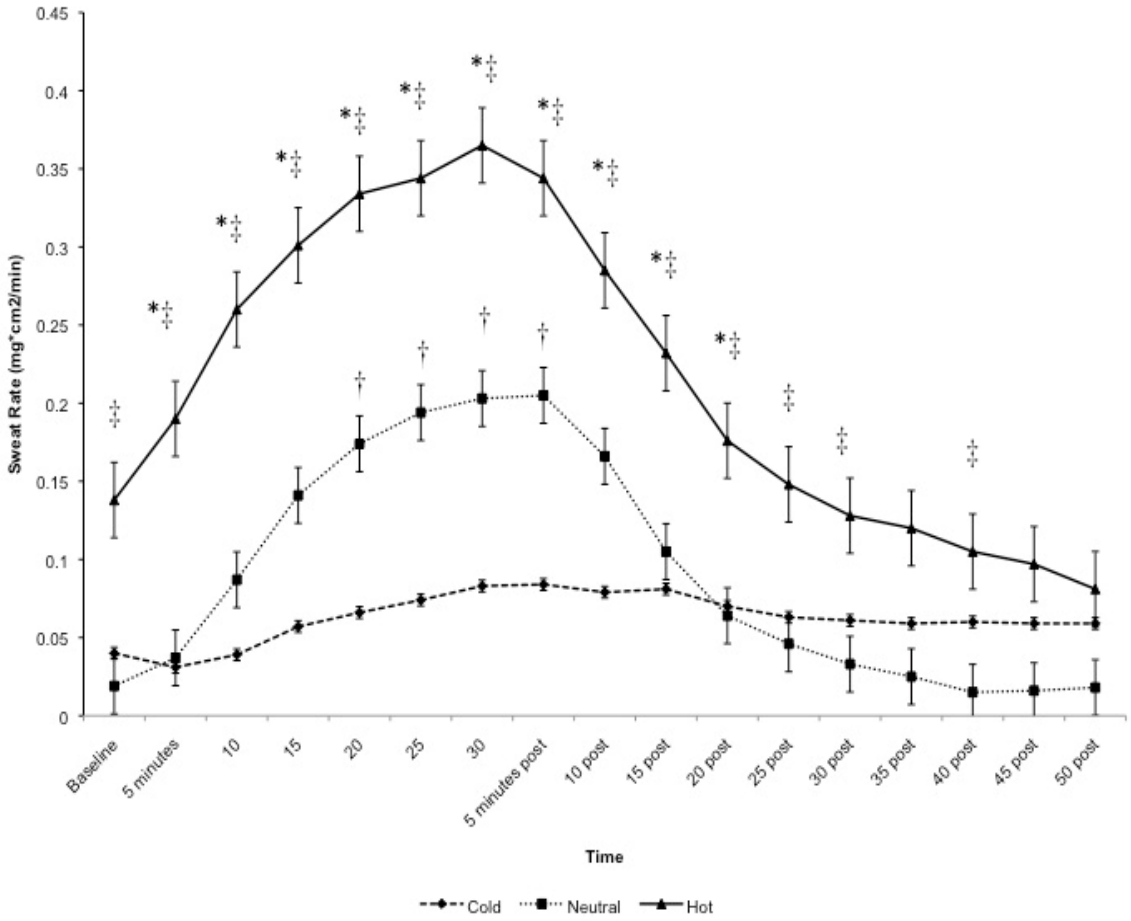
Figure 10: Heat Storage



Sweat Rate

Significant differences were found for both time ($p<0.01$), and condition x time ($p<0.01$). Significant differences were observed from the onset of exercise to 30 minutes post-exercise, and again at 40 minutes post-exercise. Significant differences were apparent between cold vs. hot, and neutral vs. hot ($p < 0.01$ and $p = 0.02$, respectively), but not for cold vs. neutral ($p = 0.617$). When exercise commenced, significant differences in sweat rate were observed for all exercise time points up to exercise cessation (5-25 minutes of exercise, p values<0.05). In the cold condition, sweat rate increased 0.043 $mg \bullet cm^{2} \bullet \min^{-1}$ from baseline, to 30 minutes of exercise. Likewise, sweat rate increased 0.184 $mg \bullet cm^{2} \bullet \min^{-1}$ in the neutral condition from baseline, to 30 minutes of exercise. Finally, in the hot condition, sweat rate increased 0.227 $mg \bullet cm^{2} \bullet \min^{-1}$ from baseline, to 30 minutes of exercise. Like heat storage, sweat rate values to 50 minutes post-exercise are displayed due to missing values in several trials for 55 and 60 minutes; however, with the exception of the hot condition, sweat rate had reached a plateau in all conditions. A post hoc test revealed significance between conditions for cold vs. hot ($p<0.01$) and neutral vs. hot ($p = 0.002$), but not for cold vs. neutral ($p = 0.644$). Figure 11 shows sweat rate for cold, neutral, and hot conditions.

Figure 11: Sweat Rate



* - indicates significant differences between cold and hot conditions ($p \leq 0.05$)
† - indicates significant differences between cold and neutral conditions ($p \leq 0.05$)
‡ - indicates significant differences between neutral and hot conditions ($p \leq 0.05$)

Metabolic Responses

Blood Glucose

Blood glucose was taken every 10 minutes from the onset of exercise, to the completion of the 60-minute recovery period. Blood glucose began at 13.0 ± 2.9 mM, 12 ± 2.6 mM and 12.1 ± 2.5 mM, and dropped by 5.2 ± 2.3 mM, 3.3 ± 2.2 mM, and 2.7 ± 1.6 mM during exercise in the cold, neutral, and hot conditions ($p<0.01$), respectively. From onset, to 60-minutes post-exercise blood glucose fell 3.0 ± 0.75 mM, 3.5 ± 0.37 mM, and 3.4 ± 0.037 mM in the cold, neutral, and hot conditions respectively. There was no significant difference between condition x time ($p = 0.442$).

Hypoglycemia occurred in 5 of the experimental trials (2 cold, 2 neutral, and 1 hot) in 5 different participants, 2 of which received insulin pump therapy, and 3 received bolus insulin therapy. With respect to the cold condition, both cases of hypoglycemia took place within 20 minutes of exercise cessation (at 30 minutes of exercise, and 20 minutes post-exercise), the neutral condition had hypoglycemia at 20 and 60 minutes post-exercise, and the incidence of hypoglycemia in the hot condition took place at 40 minutes post-exercise. In instances where hypoglycemia occurred, 500 mL of Gatorade™ was given. To normalize blood glucose levels when Gatorade™ was administered, the average increase caused by Gatorade™ was subtracted from blood glucose for each time point. Figure 12 shows the blood glucose response both during exercise, and post-exercise. Also of note, a rise in blood glucose (insignificant) occurred at 6 hours post-exercise; however, this was due to 2 outlying values (15.0 mM and 20.0 mM), because of insufficient insulin for the amount of carbohydrate ingested.

Individual blood glucose responses for the cold, neutral and hot conditions are presented in Figures 13, 14 and 15, respectively.

Figure 12: Blood Glucose Response to Exercise in Different Ambient Temperatures

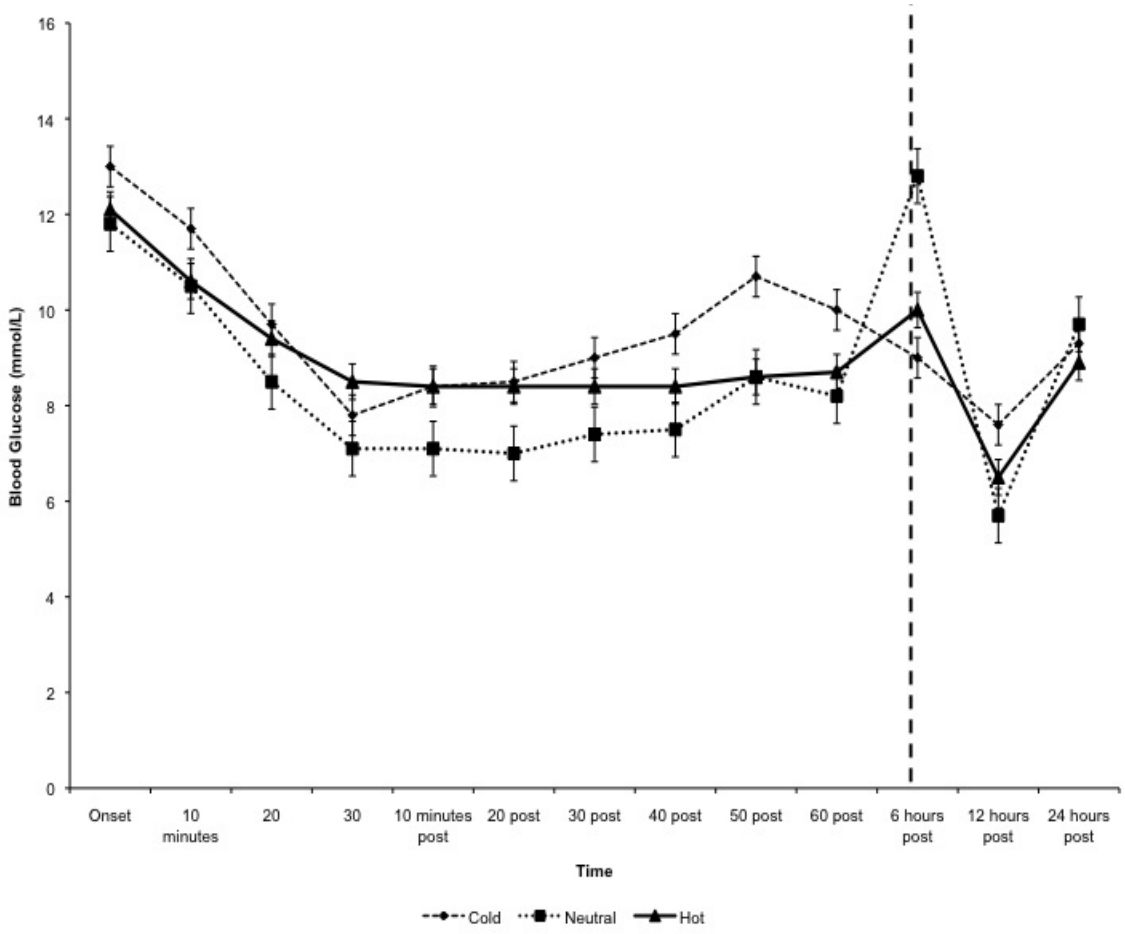


Figure 13: Individual Blood Glucose Responses to Cold Condition

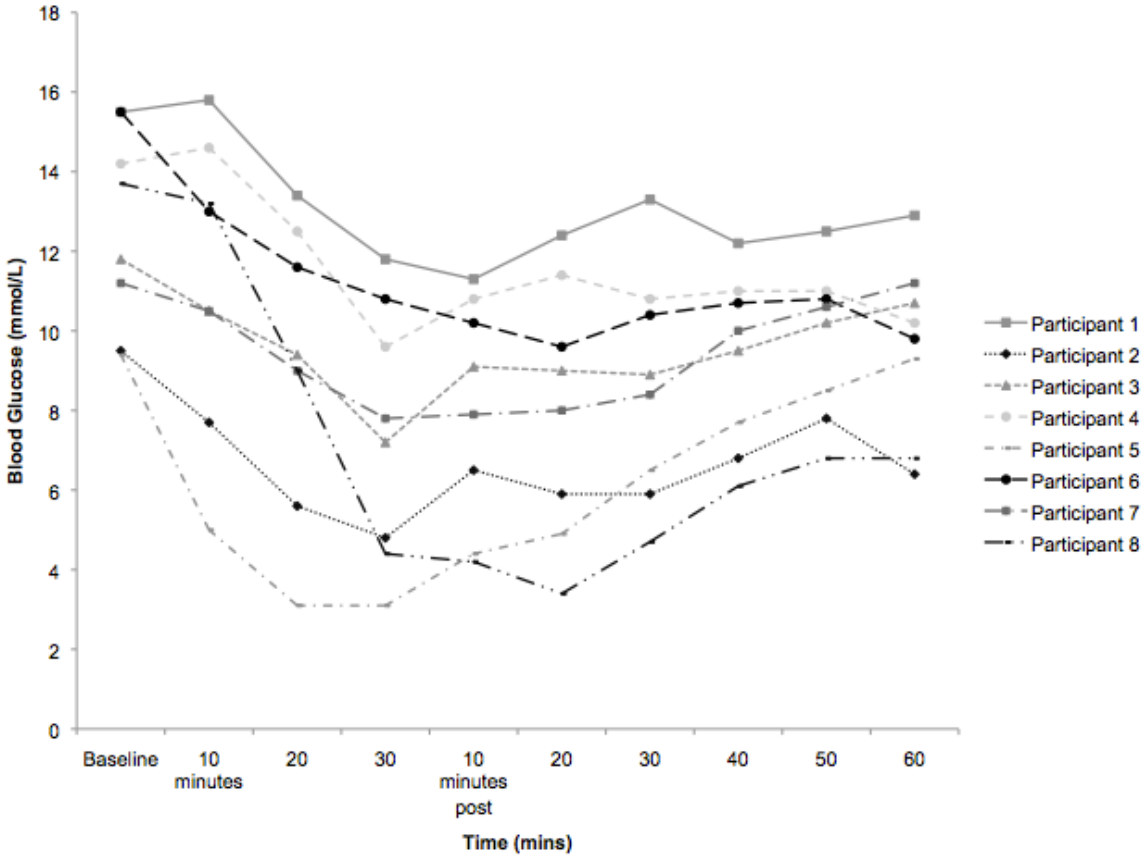


Figure 14: Individual Blood Glucose Responses to Neutral Condition

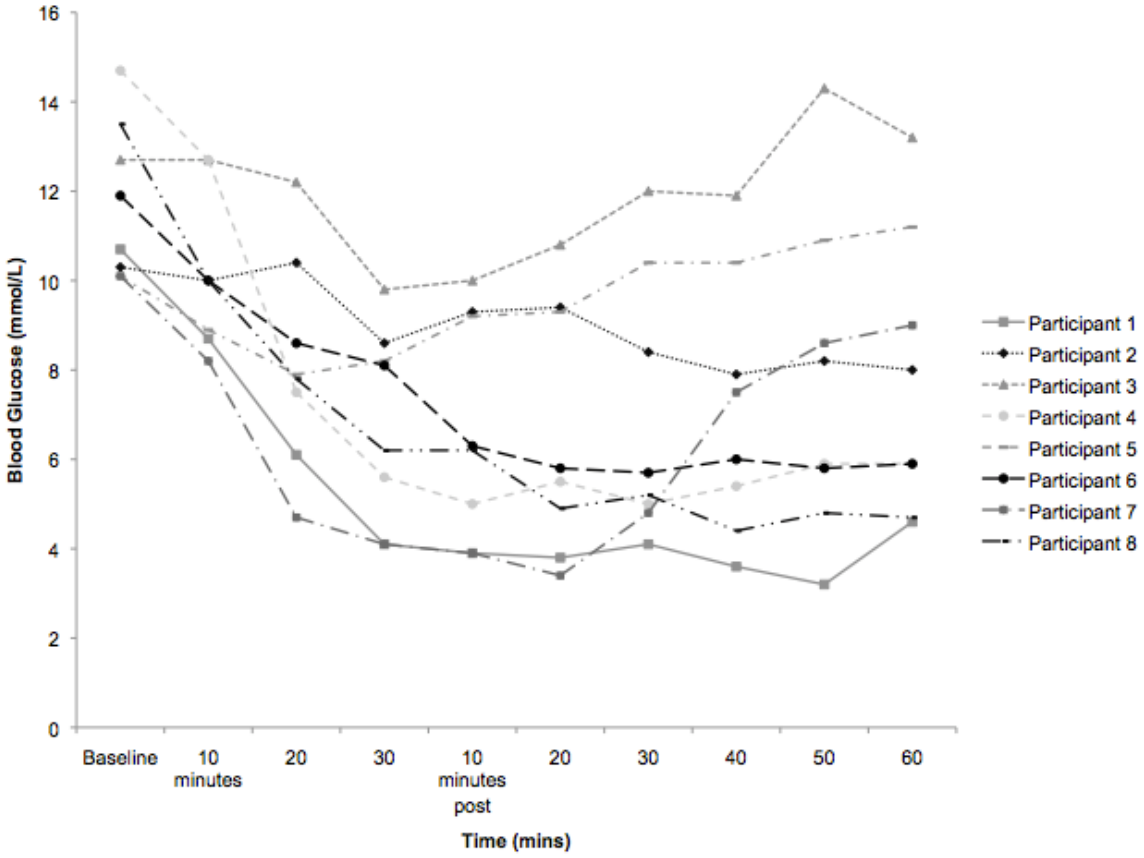
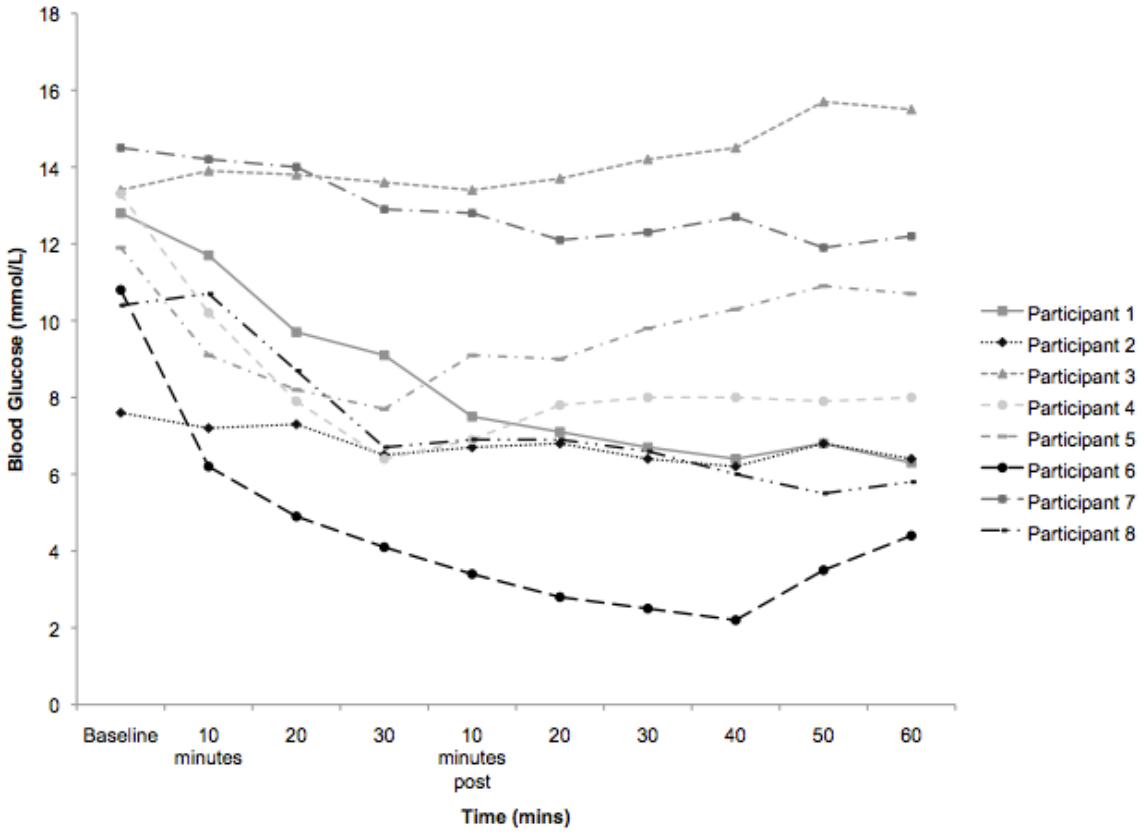


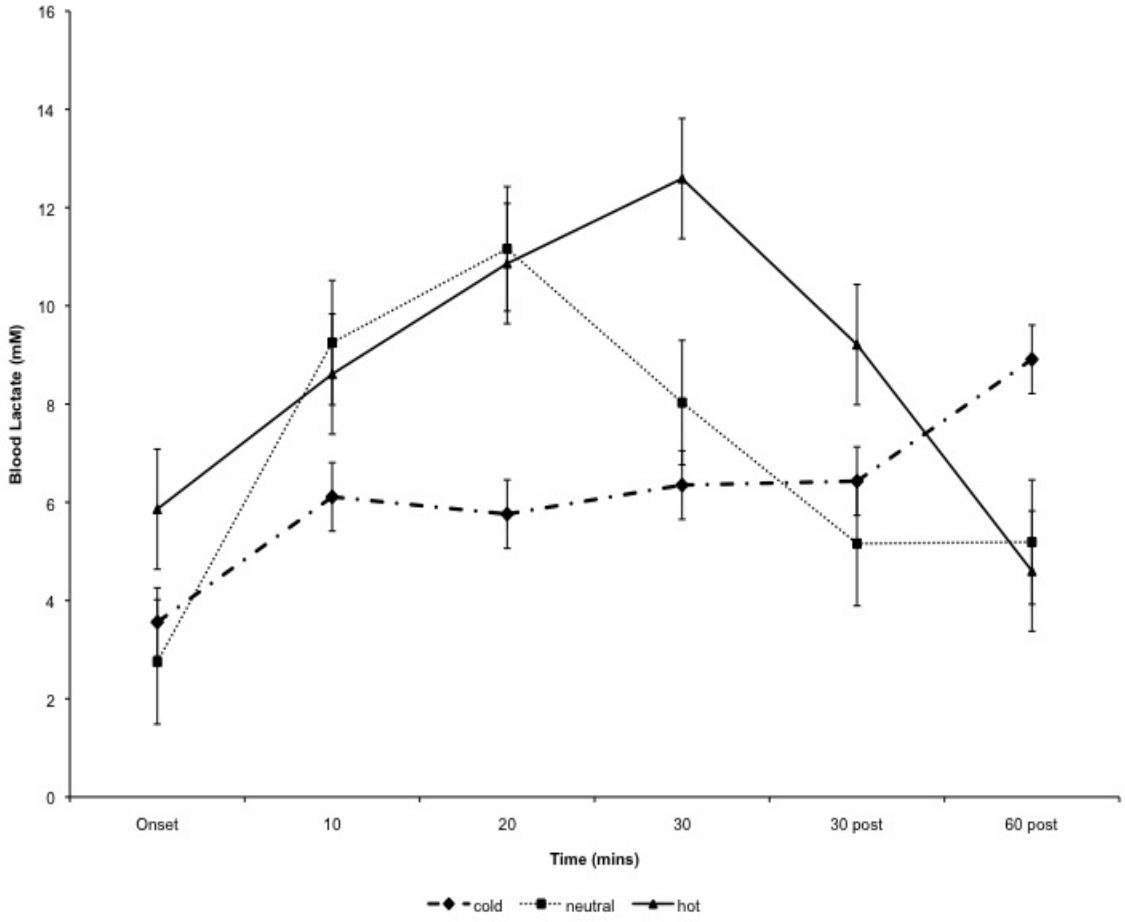
Figure 15: Individual Blood Glucose Responses to Hot Condition



Blood Lactate

Blood lactate was taken using a Lactate Pro blood lactate test meter, and was measured every 10 minutes from the onset of exercise until cessation, and again at 30 and 60 minutes post-exercise. A significant difference was found for both time ($p < 0.01$), and for condition x time ($p = 0.01$). From the onset to cessation of exercise, blood lactate increased 2.9 ± 1.3 mM in the cold condition, and continued to rise up to 60 minutes post-exercise, where it reached its apex. In the neutral condition, blood lactate increased 8.4 ± 4.4 mM from onset up to 20 minutes of exercise, before beginning to decline at 30 and 60 minutes post-exercise. In the hot condition, blood lactate increased 6.7 ± 2.9 mM from the onset of exercise until 30 minutes of exercise, and decreased at 30 and 60 minutes post-exercise. Blood lactate values are shown in Figure 16.

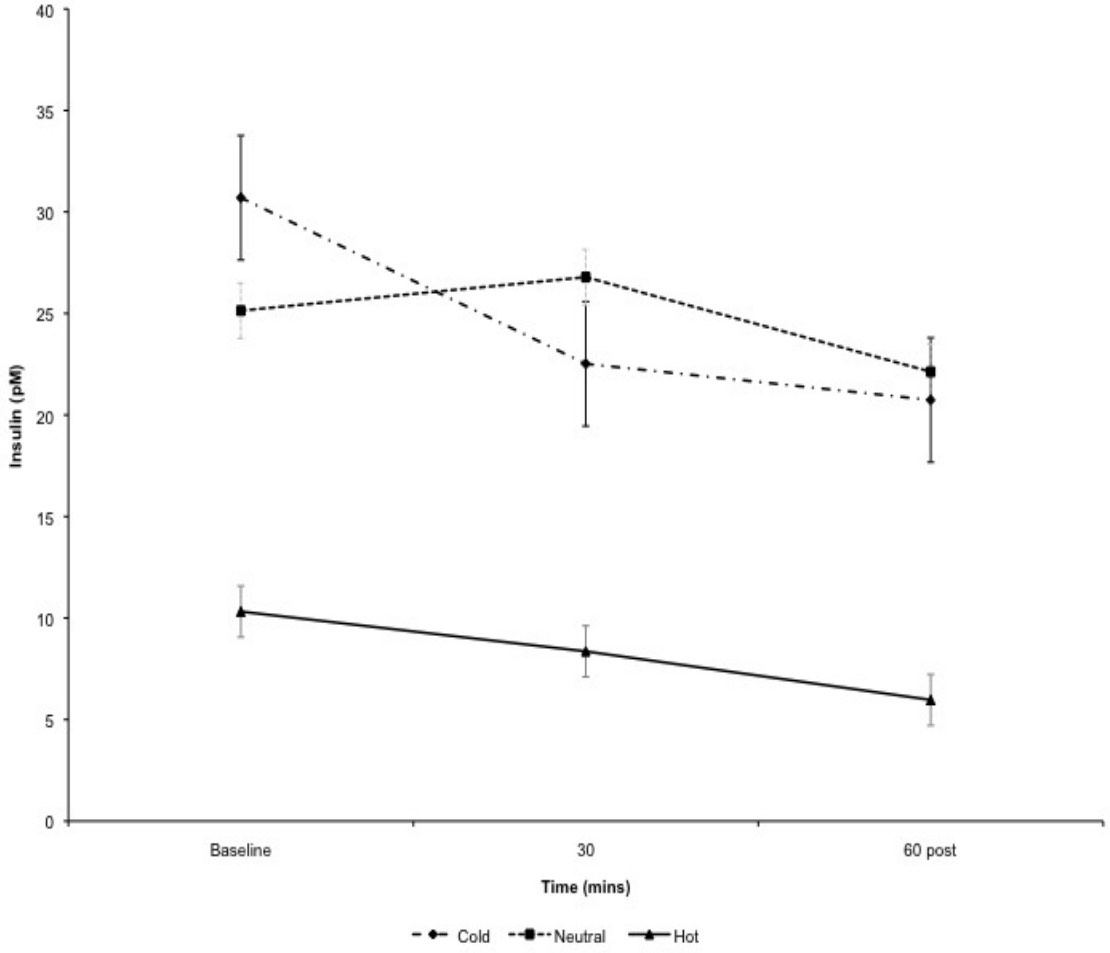
Figure 16: Blood Lactate



Insulin

Insulin was obtained via blood samples from the antecubital vein at baseline, 30 minutes of exercise, and 60 minutes post-exercise. Insulin was analyzed for the 4 participants that received bolus insulin injections because the assayed insulin levels for the participants on insulin pump therapy were out of range, or not detectable. There was no significant difference for time ($p = 0.072$), or for condition x time ($p = 0.288$). Insulin levels dropped (statistically insignificant) from baseline, to 30 minutes of exercise, to 60 minutes post-exercise in both the cold and hot conditions. In the neutral condition, insulin levels saw only slight fluctuations between time points. In the hot condition, insulin levels continuously dropped, although the decrease was statistically insignificant. Insulin values are displayed in Figure 17.

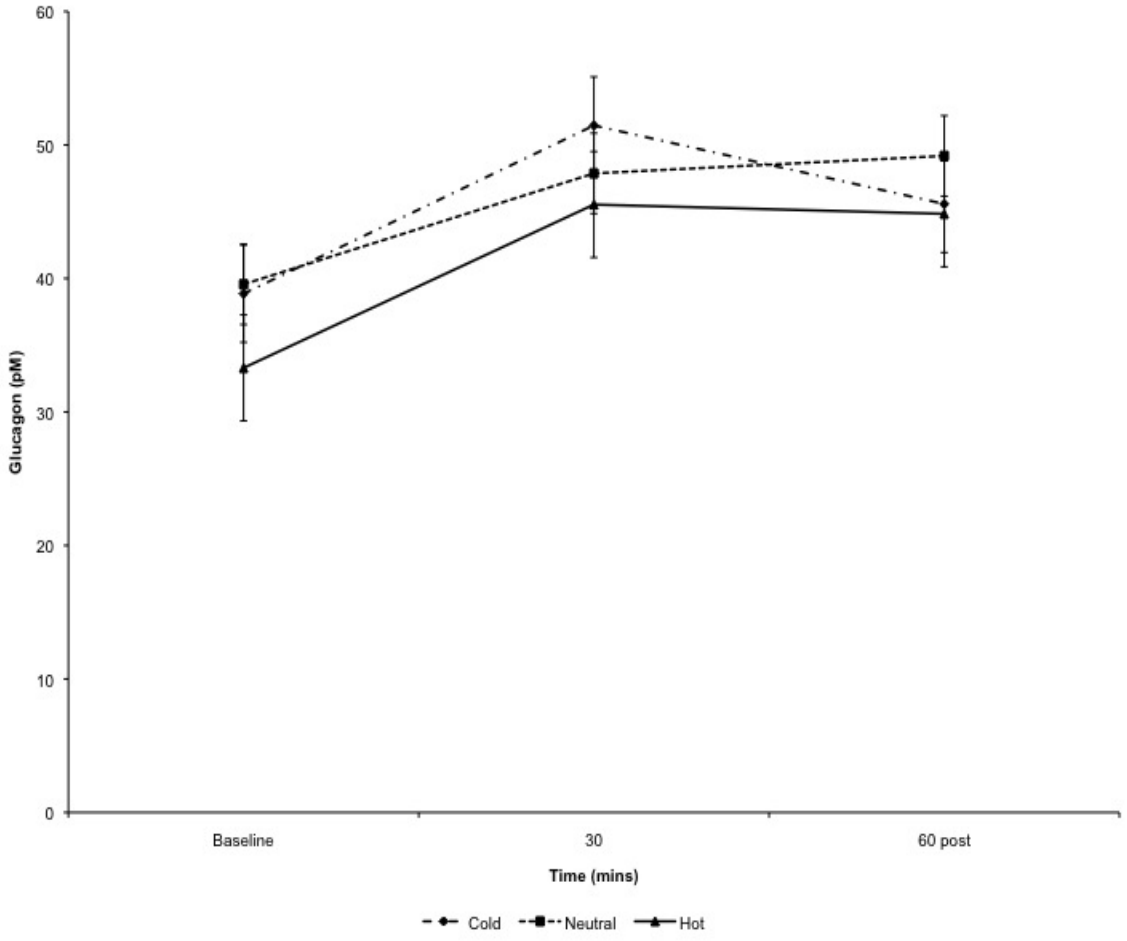
Figure 17: Insulin



Glucagon

Glucagon was obtained via blood samples from the antecubital vein at baseline, 30 minutes of exercise, and 60 minutes post-exercise. Glucagon was analyzed for the 4 participants that received bolus insulin injections because the assayed glucagon levels for the participants on insulin pump therapy were out of range, or not detectable. A significant difference was observed for time ($p = 0.01$), but not for condition x time ($p = 0.542$). Glucagon levels increased from baseline to 30 minutes of exercise in all conditions, and then decreased from 30 minutes of exercise, to levels that were above baseline by 60 minutes post-exercise. Glucagon values are shown in Figure 18.

Figure 18: Glucagon



Perceived Responses

Ratings of Perceived Exertion

Ratings of perceived exertion (RPE) were determined using the Borg Scale (Borg, 1983) at 10, 20 and 30 minutes of exercise. There were significant differences observed for time ($p < 0.01$), but not for condition x time ($p = 0.466$). There was also a significant main effect of condition ($p = 0.012$). Significant differences were found with cold vs. hot, and neutral vs. hot conditions ($p = 0.021$ and $p = 0.034$, respectively), but not for cold vs. neutral conditions ($p = 1.00$). RPE was 11 (fairly light) at 10 minutes of exercise in the neutral condition, was 12 (between fairly light and somewhat hard) in the cold condition, and 13 (somewhat hard) in the hot condition at the same time point. By 30 minutes of exercise, RPE had increased to 12 in the neutral condition, and had increased to 14 (between somewhat hard and hard) in the hot condition. A post hoc test confirmed significance for conditions ($p = 0.019$, and $p = 0.029$) for cold vs. hot, and neutral vs. hot respectively, and a non-significant value for cold vs. neutral ($p = 0.980$). Mean and S.D. values for RPE are presented in Table 5.

Thermal Comfort

Thermal comfort was taken every 10 minutes from the onset of exercise until the completion of the 60-minute recovery period. There was a significant finding with both time ($p<0.01$) and condition x time ($p<0.01$). There was also a significant main effect of condition ($p = 0.02$). A significant difference existed for the neutral vs. hot condition ($p = .024$), but no other significant differences existed between conditions ($p = 0.094$ for cold

vs. neutral, and p = 1.00 for cold vs. hot). At the onset of exercise, the average value for the thermal comfort was 3 (uncomfortable) in the cold condition, 1.5 (between comfortable and slightly uncomfortable) in the neutral condition, and 2 (slightly uncomfortable) in the hot condition. There were no significant differences between the onset of exercise, and three exercise time points, but significance was attained between the onset, and all post-exercise time points. At 30 minutes of exercise, participants had become more comfortable in the cold condition, with the average response decreasing from 3, to 2. Thermal comfort level increased from 1.5, to 2 and 2 to 3 from the onset of exercise to 30 minutes of exercise, in the neutral, and hot conditions, respectively. Mean and S.D. values for Thermal Comfort are presented in Table 5.

Thermal Sensation

Thermal sensation was taken every 10 minutes from the onset of exercise until the completion of the 60-minute recovery period. Significant differences existed for both time ($p<0.01$), and condition x time ($p <0.01$). There was also a significant main effect of condition ($p < 0.01$). There were significant differences for all condition comparisons ($p<0.01$). Significant differences were apparent between baseline and all exercise time points ($p<0.01$). At the onset of exercise, the average response for thermal sensation was 1 (very cold) in the cold condition, 4 (slightly cool) in the neutral condition, and 7 (warm) in the hot condition. By 30 minutes of exercise, thermal sensation values had increased to 4 in the cold condition, 7 in the neutral condition, and 8 (hot) in the hot condition. Mean and S.D. values for Thermal Sensation are presented in Table 5.

Table 5: Values for Perceived Responses

		Ratings of Perceived Exertion (RPE)	Thermal Sensation (TS)	Thermal Comfort (TC)
Cold Condition	10 minutes	11.6 ± 0.52	3.0 ± 0.76*	1.9 ± 0.23
	20 minutes	11.9 ± 0.35*	3.6 ± 0.52*	1.9 ± 0.42
	30 minutes	12.0 ± 0.53*	3.9 ± 0.64*	1.8 ± 0.46*
Neutral Condition	10 minutes	11.4 ± 0.92	5.4 ± 0.74‡	1.2 ± 0.37‡
	20 minutes	12.1 ± 1.13	6.0 ± 0.53‡	1.6 ± 0.35‡
	30 minutes	12.3 ± 0.89	6.5 ± 0.53	1.7 ± 0.37‡
Hot Condition	10 minutes	12.5 ± 0.76	7.4 ± 0.92	2.3 ± 0.89
	20 minutes	13.3 ± 1.04	8.0 ± 0.76	2.8 ± 0.93
	30 minutes	13.5 ± 1.69	8.0 ± 0.76	3.0 ± 1.07

* - indicates significant differences between cold and hot conditions ($p \leq 0.05$)

‡ - indicates significant differences between neutral and hot conditions ($p \leq 0.05$)

Discussion

The main findings of the current study were the lack of significant differences in blood glucose and glucagon concentrations among the three conditions, and significant differences observed for condition x time with core temperature, heat storage and sweat rate. However, due to the limited sample size and probability of a great deal of individual variability, these results are not surprising.

Thermal Responses

In examining core temperature and sweat rates for the current study, sweat rate was highest in the hot condition, whereas core temperature was highest in the neutral condition. Recent literature (Petrofsky et al., 2005 & 2006) would indicate that both passive heat exposure and isometric contraction in the heat, results in elevated core temperature, and sweat rates that were significantly lower in patients with diabetes when compared to non-diabetic individuals. The current study demonstrated similar sweating results in participants with T1DM (0.227 $mg \bullet cm^{2} \bullet \min^{-1}$) during exercise in 35ºC when compared to passive heat exposure of 42ºC (0.23 $mg \bullet cm^{2} \bullet \min^{-1}$) in subjects with diabetes (Petrofsky et al., 2006); however, core temperature was increased 0.59ºC as a result of exercise and exposure to 35ºC in the current study, in contrast to the 1ºC increase in core temperature as seen with Petrofsky et al., (2006). These differences may be attributed to the 7ºC difference in ambient temperature between the two studies. An abstract published in the Canadian Society for Exercise Physiology (McGarr, et al., 2010) found sweat rates of 0.33 ±0.08 $mg \bullet cm^{2} \bullet \min^{-1}$ during 30 minutes of in cycling in 35ºC

at 65% VO_{2max} in non-diabetic participants. The sweat rates observed by McGarr, et al. (2010), may indeed be higher than the current study because of diminished sweating ability in people with T1DM, but also may be due to the increased exercise time. McGarr et al., (2010) also showed core temperature values of 37.78±0.30°C and 37.83±0.30°C (different training protocols) with 60 minutes of cycling at 65% VO_{2max}, which are similar to the core temperature values attained in the hot condition in the current study (37.61 ± 0.54ºC). Therefore, the current study does not support the findings of Petrofsky et al., (2005 & 2006) where individuals with diabetes showed significant elevations in core temperature, and elicited diminished sweat rates when compared to non-diabetic counterparts; however, future studies must compare diabetics and non-diabetics in the context of the current study in order to draw definitive conclusions.

Core temperature values at the cessation of exercise fell into safe ranges in all conditions (all core temperature values were well below the point of hyperthermia or exertional heat illness); (Armstrong, et al., 2007), indicating that 30 minutes of exercise at 65% VO_{2max} in participants with T1DM can be undertaken without risk of heat illness. The potential mechanism behind a lower core temperature in the hot condition than in the neutral condition may be attributed to the significantly higher sweat rate in the hot condition. The increased sweat rate would facilitate a higher heat loss, and would explain the lower core temperature seen in the hot condition. Previous studies have shown that T1DM patients have thinner skin, reduced skin blood flow (Petrofsky, et al., 2008; Forst, et al., 2006), increased core temperature, and increased heat storage, which could contribute to heat illness (Kenny, et al., 2010). However, if exercise is prolonged, this rise in core temperature may be greater, and put individuals with T1DM more at risk for heat

illness. Core temperature was only significantly different between conditions in the post-exercise period. The mechanism behind this lack of significant increase may be explained by looking at the sweat rates attained during exercise. The higher sweat rates achieved are a mechanism of cooling for the body. This evaporation of sweat from the body aids in the rise in core temperature. The higher sweat rates seen from baseline, through to 25 minutes post-exercise are believed to be the reason for the lack of significant increase in core temperature that would have been expected in the hot condition. These findings indicate that exercise for 30 minutes at a submaximal intensity in participants with T1DM may be safe in 5ºC, 20ºC, and 35ºC.

To date, this is the first study to examine the effects of heat storage during exercise in different ambient temperatures in participants with T1DM. Observed differences in residual body heat storage and peak heat storage were an expected result of the respective ambient temperatures in which subjects exercised. The rapidly decreasing heat storage following cessation of exercise, reaching a plateau at 15 minutes post-exercise in the hot and cold conditions, at 40 minutes post-exercise in the neutral condition, is likely attributed to the ambient temperature being approximately 22ºC for the 60-minute post-exercise period. Because participants remained in the chamber at 22ºC for the 60-minute post-exercise period when exercise had stopped after each of the 3 conditions, the participants were in an environment that did not favour heat storage (i.e. not exercising), ultimately leading to the plateau in heat storage. Currently, comparable heat storage data in individuals with T1DM only exists with skin temperature as a measurement. This ambient temperature and the lack of activity during the 60-minute post-exercise period are the reason for decrease in heat storage in all conditions.

Rönnemaa et al., (1991) found that during exercise at 30ºC, skin temperature decreased on average to a level lower (by 1.5ºC) than the pre-exercise value; whereas during exercise in the 10ºC condition, skin temperature increased on average by 3.0ºC from the level prior to the start of exercise and remained at the higher level for 30 minutes post-exercise. Rönnemaa & Koivisto (1988) attribute this to constriction of skin veins and decrease in skin blood flow during exercise in a warm temperature.

The current study saw no significant differences in heat storage between any of the three conditions, and significant differences in sweat rate in all conditions. When the environment is warmer than the skin, the body gains heat through dry heat exchange that increases the requirements for sweating and circulatory responses, such as vasodilation, increasing blood flow to the skin (Kenny, et al., 2010). This means that blood vessels must dilate, and sweat rate must increase in order to dissipate heat. Petrofsky et al., (2006) found that during passive exposure to different ambient temperatures (22ºC and 42ºC), significant differences existed in both core temperature and sweat rate between control subjects, and subjects with T1DM. Compared to controls, after 30 minutes of heat exposure, subjects with T1DM demonstrated higher core temperature increases (1.0ºC vs. 0.2ºC), and also attained a sweat rate that was half that of control participants (0.44 vs. 0.81 $mg \bullet cm^{2} \bullet \min^{-1}$). This means that control subjects were able to sweat at least twice the rate of subjects with diabetes (Petrofsky et al., 2006) even though their core temperature increase was lower. In T1DM, lack of circulation (Fealey, et al., 1989) and neuropathy (Kihara, Opfer-Gehrking, & Low, 1993) can result in damage to the sweat glands that innervate the skin resulting in lower sweat rates when compared to non-diabetics. These findings would explain the lower sweat rates during exercise in 35ºC at

65% VO_{2max} in participants with T1DM, as seen in the current study, when compared to 60 minutes of exercise in 35ºC in non-diabetics (McGarr, et al., 2010).

The lack of circulation and diabetic neuropathy is believed to lead to decreases in skin blood flow, which ultimately cause a reduction in sweat rate. During thermal stress, skin blood flow can increase to 6 – 8 L/min as a result of vasodilation, which represents a vital aspect of normal thermoregulation in humans (Charkoudian, 2003). In both T1DM and T2DM, the body's ability to dilate blood vessels may be impaired, which could decrease the amount of blood being brought to the skin's surface to dissipate heat. In comparing skin blood flow responses to non-diabetic individuals, vascular reactivity was decreased during 5 minutes of heat exposure in diabetics (Stansberry, Hill, Shapiro, et al., 1997). This inability to sufficiently dilate blood vessels, leads to potential heat illness as a result of increased core temperature, and heat storage when exposed to hot environments. In people with diabetes, there appears to be no apparent reduction in the vasoconstriction ability of smooth muscle, whereas a reduction in principally nitric oxide release or the sensitivity of nitric oxide receptors in smooth muscle reduces the ability to vasodilate (Petrofsky, et al., 2008). Therefore, potential problems for individuals with T1DM would be more apparent in the heat, rather than in the cold. On exposure to cold environments, skin blood flow decreases via cutaneous vasoconstriction, and results in a decrease in heat dissipation from the skin surface and less convective heat transfer from the core to the surface (Charkoudian, 2003). In the current study, the largest changes in skin blood flow were seen in the cold condition, when compared to baseline. This indicates significant vasoconstriction during baseline, and greater vasodilation during exercise; however, there were no significant differences in skin blood flow between conditions.

The current study showed similar skin blood flow changes (although, with much higher standard deviation) to cycling at 65% VO_{2max} in 35ºC when compared to non-diabetic individuals. McGarr, et al, (2010) demonstrated a 329 ± 112% change from baseline with 60 minutes of exercise at 35º compared to 429 ± 858%, as seen with the current study. However, future studies must directly compare diabetic, and non-diabetics under these conditions in order to draw definitive conclusions.

No significant differences were observed with skin blood flow between the forehead, and upper trapezium locations, indicating that if there is damage to the sweat glands, the damage does not differ between the two locations. The relative thickness of skin and subcutaneous fat may explain lower skin blood flow values, and higher core temperature. Petrofsky, et al., (2008) examined the thickness of subcutaneous fat layer and skin thickness and the response to continuous heat stress on the lower back in non-diabetic, and diabetic individuals. In the current study, all participants fell within the mean ± standard deviation for their sex and age range for tricep, subscapular, and suprailiac measurements according to Durnin & Womersley (1974). Associated with skinfold measurements is the risk of human error; however, experienced individuals performed all skinfold measurements and error is believed to have been minimal. It was found that core temperature dropped slower, skin temperature increased more rapidly, and blood flow was significantly lower in diabetic subjects, compared to non-diabetics when exposed to heat stress (Petrofsky, et al., 2008). In diabetics, skin thickness was found to be one-third as thick as their non-diabetic counterparts (Petrofsky, et al., 2008). It has also been found that individuals with T1DM demonstrate both significantly reduced skin thickness, as well as, significantly reduced microvascular blood flow when

compared to non-diabetic individuals (Forst, et al., 2006). Since skin thickness correlates with blood flow as a result of reduced microvascular flow, this may be caused by less blood flow attainable with thermal stress. If part of the reduction in skin blood flow is due to a lower number of capillaries, then irrespective of the mechanism of change in blood flow, there would be less blood flow attainable with thermal stress because there are fewer arterioles to dilate (Petrofsky, et al., 2008). However, the current study only used skinfold measurements to determine body fat percentage, as outlined by Jackson & Pollock (1978), and in order to draw more definitive conclusions on skinfold thickness, a control group would be needed for comparison, and measurements must be done in nonglaborous skin, as was seen in Forst, et al. (2006).

Metabolic Responses

One of the main findings of the current study is the lack of significance in the decrease of blood glucose among the three conditions. Like Rönnemaa & Koivisto (1988), blood glucose decreased significantly during exercise, but no significant differences were present among the different conditions in the current study like those seen with Rönnemaa & Koivisto (1988). The potential mechanism behind the differences in the current study, and Rönnemaa & Koivisto (1988) could be the methodology of exercise. Rönnemaa & Koivisto (1988) had participants exercise in three 15-minute bouts, increasing in the first, second and third minute, until 65% VO_{2max} for the final 12-minutes of exercise, with 5 minute intervals between each bout. The current study was largely driven by the findings of a case study (see appendix) in which blood glucose began to rise post-exercise in an increased body temperature condition. The case study

participant (Participant 1 in the current study) did not demonstrate similar results in the current study. The potential mechanism behind this lack of similar responses could be the result of core temperature not reaching a level as high in the current study. With the case study, tympanic measurements of core temperature were as high as 38.9°C, which may have lead to an increase in gluconeogenesis, and therefore, an increase in blood glucose post-exercise. Figure 15 shows the individual blood glucose response in the hot condition. The blood glucose of Participant 1 continuously drops throughout exercise, and reaches a plateau in the post-exercise period. Blood glucose decreased in all conditions, both during, and post-exercise (despite a spike at 30 minutes post-exercise in the cold condition). Again, the possible mechanism behind the lack of increase in blood glucose post-exercise in the current study may be due to the lack of increased core temperature to the point where it was high enough to increase gluconeogensis, and therefore, blood glucose. In non-diabetic individuals, exercise in the heat to the point of hyperthermia has been shown to alter the body's metabolism, with alterations in carbohydrate metabolism including: increased gluconeogenesis, depressed glycogenesis, glucose intolerance and insulin resistance (Mizock, 1995); however, this has yet to be examined in individuals with T1DM. Because glucagon levels were only detectable for 4 of 8 subjects in the current study, further studies are needed to elicit the effects of increased ambient temperature, and at what core temperature an increase in glucagon secretion elicits a response.

There was a large amount of individual variability with respect to blood glucose both during exercise, and post-exercise in all conditions. In the cold condition, hypoglycemia occurred in participants 5 and 8, and was treated with Gatorade™. In

participants 1-4, blood glucose remained relatively stable post-exercise, but contained small (insignificant) increases. In participants 6 and 7, blood glucose plateaued and remained stable post-exercise. In the neutral condition, participants 1 and 7 became hypoglycemic, and Gatorade™ was administered. Blood glucose in participants 2, 4, 6, and 8 decreased slightly in the post-exercise period, and in participants 3 and 5, blood glucose increased. In the hot condition, hypoglycemia occurred in participant 6, and again, was treated with Gatorade™. Blood glucose decreased in participants 1, 2, and 8, and showed slight increases in participants 3, 4, 5, and 7. All of these instances show the large variability in the response to exercise in different ambient temperatures in individuals with T1DM, and may be due to HbA_{1C} (Baldi, et al., 2010), fitness (Ebeling, et al., 1995), and/or muscle glycogen synthase relating to glucose metabolism (Ebeling, et al., 1993; Taylor, et al., 1972).

Apart from major cardiovascular and thermoregulatory responses that occur as a result of acute exercise and heat exposure, a number of metabolic alterations associated with T1DM may reduce heat tolerance and affect exercise performance in the heat (Kenny, et al., 2010). Mizock (1995) showed that in non-diabetic individuals, when core temperature is elevated to the point of hyperthermia, it resulted in altered metabolism, with changes in carbohydrate metabolism including increased gluconeogenesis, depressed glycogenesis, glucose intolerance and insulin resistance. The effect of increasing core temperature results in increased hepatic glycogen release and higher blood glucose (Valerio, et al., 2001; Mizock, 1995; Halter, Beard & Porte, 1984). Despite the fact that these studies examined non-diabetic individuals, we hypothesized that there would be a significant rise in blood glucose in the hot condition because insulin, and not

glucose production, are affected in individuals with T1DM; however, this was not the case.

One potential mechanism for the lack of significant increase in blood glucose in the hot condition may be that core temperature did not reach the point of hyperthermia to increase gluconeogenesis, and therefore, blood glucose. This finding suggests that the increase in blood glucose during exercise in hot conditions, therefore, may be the result of a critical core temperature leading to increased gluconeogenesis. Because core temperature in the present study increased to a maximum of only 0.59ºC above baseline during exercise in the hot condition, this could have been the reason that no significant increase in blood glucose was observed. The increase in core temperature in participants in the current study potentially could have been higher, however, the mechanism preventing this increase could involve the participant's capacity to dissipate heat being high enough to offset large rises in core temperature. Comparitively, in non-diabetics during exercise in the heat, it has been found that plasma glucose levels were higher after 40 minutes of exercise at 65% VO_{2peak} in 40ºC than at 20ºC as a result of higher hepatic glucose production during the last 30 minutes of exercise (Hargreaves, et al., 1996). These investigators (Hargreaves, et al., 1996) also found that plasma insulin levels were not different between the trials in these non-diabetic subjects, and therefore, this did not appear to account for the differences in liver glucose output. Although, glucagon, cortisol, and growth hormone did not play a significant role in stimulating liver glucose output in the Hargreaves et al., (1996) study, their increased plasma levels of these hormones in the 40ºC trial, may have contributed to greater liver glucose output.

In the cold, we hypothesized that there would be a more significant decrease in blood glucose during exercise than in any other condition because shivering has been shown to utilize more CHO, and less lipids than exercise alone (Weber & Haman, 2005). Again, despite the majority of studies examining non-diabetic individuals, because only insulin production is affected in T1DM, we believed that the increased reliance on CHO utilization would lead to a decrease in blood glucose. We then inferred that exercise in the cold would lead to more CHO oxidation, and therefore, lower blood glucose. In examining exercise in non-diabetics in -10ºC, 0ºC, 10ºC and 20ºC, Layden, et al., (2002) found that the lower blood glucose concentrations during exercise in the -10ºC, compared to the 20ºC, might imply that glucose utilization was increased in the cold. This finding suggests that there may be an effect of ambient temperature on blood glucose during exercise, but the current study did not reach this threshold. Passias, et al. (1996), found that hypoglycemia reduces, but does not eliminate, hypothermia-induced heat production and the reduction is achieved by decreasing the core temperature threshold for shivering thermogenesis by approximately 0.6ºC and the magnitude of heat production by approximately 20% compared to euglycemia. From this finding, hypoglycemia, as seen in 2 instances in the cold condition, would significantly be expected to affect heat production. However, hypothermic core temperature values (below 35ºC) were never attained in the current study, heat production during the cold condition, therefore, is not believed to have been altered.

In order to obtain results applicable to clinical practice, participants were told to follow the same insulin administration protocol they normally would prior to exercise for all conditions, as it was advised that insulin be individually tailored depending on fitness

level, and medical condition (Admon, et al., 2005). Participants on the pump were also instructed to follow protocol they would normally undertake prior to, and during exercise (2 participants - no change in basal rate, 1 participant– 50% decrease in basal rate for exercise, 1 participant – pump turned off for exercise). With respect to moderate exercise, as seen in the present study, if exercise is only 20-30 minutes in duration and less than 70% VO_{2max}, minimal insulin adjustments may need to be made (Peirce, 1999). Previously, no significant difference was found during prolonged exercise in adolescents with an insulin pump at 50% of regular basal rate, and with the pump turned off (Admon, et al., 2005).

Hypoglycemia occurred in 5 experimental sessions; two times in the cold condition, two times in the neutral condition, and once in the hot condition, in 5 separate participants. Of the 5 instances of hypoglycemia, 2 were in participants receiving insulin pump therapy, and the other 3 instances were in participants receiving bolus insulin therapy. To normalize blood glucose levels when Gatorade™ was administered in cases where hypoglycemia occurred, the average increase caused by Gatorade™ was subtracted from blood glucose for each time point. In a high heat loss environment, hypoglycemia has been shown to induce a greater cooling of the core, which appears to be mediated by a reduction in heat production rather than an enhancement of heat loss (Passias, et al., 1996). In a non-diabetic body, responses to hypoglycemia include inhibition of insulin release, activation of glucagon, epinephrine secretion, as well as other neuroendocrine release (Briscoe, et al., 2007). The inhibition of insulin release is obtained by increased α-adrenergic activity, and the lower insulin then sensitizes the liver to basal levels of glucagon and epinephrine, de-inhibiting glycogenolysis and gluconeogenesis (Schneider

et al., 1991). However, this is not the case in individuals with T1DM. As the ability to inhibit insulin secretion is lost; therefore, there is persistent absorption of exogenous insulin despite falling glucose levels (Briscoe, et al., 2007). Hypoglycemia was, therefore, not an unexpected result, except that it would have been predicted to be more prevalent in the cold condition if ambient temperature was a factor. Instances of hypoglycemia were seen almost equally in each condition, supporting the lack of significance of ambient temperature during exercise on blood glucose. Five participants experienced nocturnal low blood sugars on the day of, or the day after experimental trials. In 3 of the 5 participants, the low nighttime blood sugars occurred in the nights following experimental conditions and occurred a total of 4 times (twice in one participant). Hypoglycemia has been shown to occur up to 24 hours post-exercise (Peirce, 1999), but in these cases, the low blood sugars were experienced more than 24 hours post-exercise, and therefore, these low blood sugars are believed to have been caused by too much insulin administered for the amount of CHO ingested, and not because of experimental exercise sessions. Low blood sugars were also observed in 3 subjects (a total of 4 times) on the day of an experimental session. Of these participants, only 1 also experienced low blood glucose the day after an experimental session. In instances where low blood sugar occurred on the day of an experimental session, 2 were in the hot condition, 1 was in the neutral condition, and 1 was in the cold condition. All of these instances were addressed before reaching the point of hypoglycemia, and were corrected with CHO ingestion. Again, because instances of low nighttime blood glucose were witnessed almost equally across the 3 conditions, this supports the notion that exercise in different ambient temperatures does not significantly differ with respect to blood glucose.

Respiratory exchange ratios (RER) during exercise were 0.87 ± 0.02, 0.86 ± 0.03, and 0.84 ± 0.03 (data no shown), for the cold, neutral, and hot conditions, respectively. High values for RER indicate that CHO are the predominate substrate oxidized, whereas a low RER is indicative of primarily lipid oxidation (Simonson & DeFronzo, 1990; review by Pendergast, Leddy, & Venkatraman, 2000). Respiratory exchange ratios of between 0.8 and 0.9 have been measured for exercise intensities of 60% to 75% of VO_{2max} (Gray, Kolterman, & Cutler, 1990; Muojo, Leddy, Horvath, Awad, & Pendergast, 1994). The current study contained RER values that are indicative of both CHO, and lipid oxidation. The balance between CHO and lipid oxidation is determined by exercise intensity and not by exercise time and intramuscular stores of CHO and lipids determine the maximal endurance exercise time at a given VO_{2max} percentage (review by Pendergast, Leddy, & Venkatraman, 2000). Post-exercise, RER values were 0.74 ± 0.06, 0.73 ± 0.08, and 0.72 ± 0.06 for the cold, neutral and hot conditions, respectively. These lower values (lower than exercise) demonstrate an increased reliance on lipid utilization as a fuel source.

Diet

Dietary intake was assessed via self-reported food logs (see appendix). The average daily intake for calories for Canadian men aged 18-30 years and 31-50 years are 2,729 and 2,500 kcal respectively; for Canadian women in the same age ranges the daily calorie intakes are 1,899 and 1,846 kcal respectively (Garriguet, 2007). In the current study, the average caloric consumption for participants on the day prior to, the day of, and the day after experimental trials were considerably lower than the average value for

men and women in the same age ranges. Although we believe that participants in the current study were honest with self-reporting food consumption, there may have been instances in which foods were not reported, leading to a hypocaloric diet report. Maurer et al. (2006), identified 9 possible categories for energy misreporting, including demographics, diet, eating behaviour, social desirability, dieting/weight history, body image, psychology, life status, and physical activity. This misreporting, specifically underreporting, is likely the result of one or a combination of incomplete record keeping on the part of the participant as a result of one or many established factors, conscious misreporting, the recording process itself causing a person to temporarily change their eating behaviour, and/or training and quality control (Maurer, et al., 2006). With respect to the current study, misreporting may have been present, but it is the belief of the investigators that if there was misreporting, it did not negatively impact the results of the study. However, if the diets of the participants were indeed hypocaloric, adjustments in insulin (decreased dosages of fast acting insulin) would be needed in order to avoid hypoglycemia. When comparing high CHO (>500g/day) to a mixed diet (<200g CHO/day), Schwellnus, Gordon, van Zeyl, et al., (1990) showed that although RER was significantly higher in the high CHO fed group during 150 minute cycle ergometer test (indicating a higher reliance on CHO oxidation), there were no significant differences in rectal or esophageal temperatures, sweating, and plasma volume between the high CHO, and mixed diet groups. It was concluded that an increased contribution of CHO to muscle metabolism because of a high CHO diet did not evoke any deleterious thermoregulatory consequences during prolonged exercise (Schwellnus, et al., 1990). When looking at prolonged exercise, Ainslie et al., (2003) examined the effects of a high-energy intake

(~3,019 kcal) compared with a low-energy intake (~616 kcal) on the time to complete at 21 km hill walk. A clear trend of lowered rectal temperature was observed for the low-energy intake group, but did not reach statistical significance at any time point (Ainslie et al., 2003). From these studies, we can infer that despite the participants in the current study consuming hypocaloric diets, there was no significant impact on the thermal responses to exercise in the 3 conditions.

Not surprisingly, exercise caused a decrease in blood glucose in all conditions and verifies previous research (Peirce, 1999; Corigliano et al., 2006; Perrone, et al., 2005; Guelfi, et al., 2005). The current study required the participants to cycle at 65% of VO_{2max} in cold, neutral, and hot conditions for 30 minutes, and the decline in blood glucose was likely caused by a mechanism involving an increase energy demand during contraction. In T1DM individuals, the body enters a situation that mimics a 'fasted' state post-exercise, in which glycogen stores in muscle and liver are low and hepatic glucose production is accelerated. The counter-regulatory hormone levels (adrenaline, glucagon, cortisol, and growth hormone) may remain elevated for some considerable time and there is a concomitant hyperglycemic and hyperinsulinemic response.

Insulin and Glucagon

Insulin levels are dependent on the binding capacity of circulating antibodies and insulin dose, with values ranging from 0-717 pM (Esoterix, 2010). During exercise in a non-diabetic, insulin release is inhibited, but this is not the case in people with diabetes. In order to mimic the actions of the pancreas, insulin pumps deliver a basal rate of insulin, and when food is ingested, it is up to the individual to administer bolus insulin. In

the current study, the 4 participants on insulin pump therapy differed in their insulin administration. Regardless, this resulted in insulin values that were not detectable by the human endocrine panel assay. However, for the participants receiving bolus insulin injection therapy, all values fell within 0.90 – 70.45 pM. As a result, a continuous decrease in blood glucose was observed. As stated previously, plasma insulin levels were not different between exercise trials at 20ºC and 35ºC, and therefore, do not appear to account for differences in liver glucose output (Hargreaves, et al., 1996).

Regarding glucagon, individuals with T1DM have been shown to have a 55% higher fasting glucagon level than non-diabetic counterparts (Alford et al., 1977). In the presence of decreased insulin-effect, this glucagon elevation in diabetics may be biologically important and contribute to fasting hyperglycemia (Alford et al., 1977). The glucagon values obtained in the current study ranged from 3.25 pM at baseline, to as high as 83.06 pM at 30 minutes of exercise. When compared to non-diabetics, acute disappearance time for glucagon was significantly prolonged in diabetics, indicating that the kinetics of the overall in vivo metabolism of pancreatic glucagon are different in diabetic, compared to non-diabetic individuals (Alford et al., 1976). In the current study, no significant difference was observed in glucagon between any of the conditions. Based on these findings (Alford et al., 1976), it would be expected that glucagon levels would be higher in the hot condition; however, this was not the case. A study by Schneider et al., (1991) looked at 60 minutes of exercise at 60-65% VO_{2max} in both individuals with T1DM, and non-diabetics, and found small, insignificant increases in glucagon in both groups. Previous studies (Tuttle, et al., 1988; Bjorkman, et al., 1981) have suggested that increments in glucagon may not be of major importance for glucose during homeostasis

in non-diabetics (Schneider, et al., 1991). With respect to the current study, the lack of significant difference in glucagon concentration between conditions may be the result of core temperature not reaching the point of hyperthermia that could increase gluconeogenesis, in the hot condition. Future studies will need to examine both the rate of appearance, and the rate of disappearance of glucagon in such conditions in order to draw definitive conclusions.

Conclusions

The current study found no significant difference in blood glucose between conditions for exercise at 65% VO_{2max} in participants with T1DM; however, future studies should examine the effects of prolonged exercise in the different ambient temperatures, as more significant rises in core temperature may occur, leading to increased heat storage, and increase the risk of heat illness. The rise in core temperature for each condition fell within a safe range, and indicates that it is safe for individuals with T1DM to undertake submaximal exercise in 5ºC, 20ºC, and 35ºC.

Future Directions

Future studies may also examine the effects of passive exposure to different ambient temperatures, as prolonged exposure to a cold condition would lead to shivering thermogenesis, an increased reliance on CHO metabolism, and therefore, a decrease in blood glucose. A cold environment has been shown to cause an increase in the rate of substrate oxidation to fuel shivering, utilizing more CHO, and less lipids (Weber & Haman, 2005). This increased CHO oxidation may often result in hypoglycemia in persons with T1DM. Finally, sport specific training, such as running, cycling, and

swimming, would represent another potential direction for research with regards to exercise in different ambient temperatures in people with T1DM because of the potential for different substrate utilization with differing intensities and muscle activation. Such information would be beneficial for events like triathlons, and Olympic oriented events.

Clinical Application and Recommendations

Previous research (Petrofsky et al., 2005, 2006, 2008; Fealey, 1989; Kenny et al., 2010) has provided evidence for lower sweat rates, skin blood flow, and higher core temperature in varying situations in individuals with T1DM when compared to non-diabetic individuals. This evidence suggests that individuals with T1DM may be at much greater risk for heat illness with exercise in the heat. However, the current study found similar sweat rates when compared to Petrofsky et al., (2006); but, core temperature only increased to a maximum of 0.59ºC higher than baseline during exercise in 35ºC, which still falls within a safe range to avoid possible heat illness. However, due to reduced skin blood flow, sweat rate, and inappropriate rises in core temperature, it would be prudent to advise caution to T1DM individuals when exercising in the heat for prolonged periods, as this may result in heat illness and homeostasic disruption. However, future work would be needed to confirm this fact.

With respect to blood glucose, although no significant differences were found between conditions as a result of exercise, blood glucose did decrease, and validates previous research (Peirce, 1999: Corigliano, et al., 2006; Rönnemaa & Koivisto, 1988). Just as with exercise in the heat, individuals with T1DM may be at risk with prolonged exercise in the cold, because plasma glucose oxidation is strongly stimulated during low-

intensity shivering, it only contributes a minor role (10%) to heat production (Haman, et al., 2002). Hypoglycemia reduces, but does not eliminate, hypothermia-induced heat production and the reduction is achieved by decreasing the core temperature threshold for shivering thermogenesis by approximately 0.6ºC and the magnitude of heat production by approximately 20% compared to euglycemia (Passias et al., 2006). Therefore, in instances where individuals with T1DM may be exercising in various ambient temperatures, it is recommended that caution still be taken, and blood glucose be monitored regularly in order to avoid hypoglycemia.

Limitations

The current study used Accu-Chek Compact Plus blood glucose monitors in order to obtain blood glucose values throughout the experimental conditions, and for 24 hours post-exercise. Because blood glucose was taken at pre-determined intervals, potential changes between each interval could not be observed. Continuous blood glucose monitoring systems would have permitted a more complete view on the effects of different ambient temperatures during exercise, both during the exercise period, and for the 24 hours post-exercise. The Astrand-Rhyming submaximal ergometer test (1954) for predictive measurements of VO_{2max} is a limitation of the current study. Ideally, a maximal VO_{2max} test would have allowed an exact measurement of maximal oxygen consumption; however, use of the submaximal, Astrand-Rhyming (1954) test, permitted participants to undergo preliminary testing, without increased exertion, and potential withdrawal from the study. The use of a relative workload (65% VO_{2max}), as seen in the current study, results in different metabolic and thermal outcomes, when compared to absolute

workloads. In comparing 1 hour of cycling exercise at relative (70 ± 4% VO_{2max}) and absolute (140 W) in 22.5ºC, Greenhaff (1989) found that during exercise at a relative workload, sweat loss (932±383 g; 341-1410g) was equal to 1.3±0.5 per cent of pre-exercise body weight, and was related to body weight , body surface area, absolute exercise workload and $V0_{2max}$. While exercise at an absolute workload (140 W), sweat loss (468±123 g; range 349-702 g) was equal to 0.7±0.1 percent of pre-exercise body weight and was related only to V02 max (Greenhaff, 1989). These results suggest that when exercise is undertaken at the same absolute workload, the sweat loss of an individual is not related to body weight or body surface area, and indicates that the greater sweat loss observed in fitter individuals during the absolute workload exercise, was not the result of body weight influencing their metabolic rate (Greenhaff, 1989). With respect to core temperature, during exercise at an absolute workload, core temperature increased gradually throughout exercise, whereas during exercise at a relative workload, there was no increase until after 5 minutes of exercise. Absolute workload was shown to be inversely related to VO_{2max} and was positively related to the relative exercise intensity (%VO_{2max}) at which exercise was performed. However, this was not the case during the relative workload intensity; rectal temperature recorded during the final minute of exercise was related only to resting pre-exercise heart rate (Greenhaff, 1989). The strong relationship between relative exercise intensity and core temperature supports previous research (Saltin & Hermansen, 1966) showing that during, exercise, rectal temperature is closely related to the (relative workload performed, and as would be expected, the results suggest that $V0_{2max}$ will significantly influence core temperature during exercise; accounting for 74 per cent of the variability in core

temperature measured during the final minute of exercise during absolute intensity exercise (Greenhaff, 1989). When examining relative and absolute workloads in different environments, Havenith, Coenen, Kistemaker & Kenney (1998) revealed that during absolute exercise intensities, "heat production is equal for all individuals, and the higher heat loss efficiency of subjects with high VO_{2max}, will then result in lower core temperature." However, at relative exercise intensities, "the higher heat productions of subjects with high VO_{2max} will be balanced by the higher heat loss efficiency, resulting in the absence of a net VO_{2max} effect, as seen in Astrand, 1960; Saltin and Hermansen, 1966." Therefore, in instances where heat loss is limited by the climate, as was the case in the hot condition in the present study, "the balance will even go the opposite way in these relative conditions. The higher heat production of subjects with high VO_{2max} will result directly in higher core temperature." With regard to the current study, the use of a relative intensity instead of an absolute workload may have resulted in a higher sweat rate. Core temperature was shown to be related to VO_{2max} (Greenhaff, 1989); therefore, each individual's core temperature would be affected by fitness. The relative intensity of exercise for the current study was chosen because it was believed to be the intensity undertaken by the general T1DM population (the pace of a brisk walk), and would therefore, be most clinically applicable. Although, participants did ingest similar servings of carbohydrates prior to and following experimental conditions, ideally, participants would have been given the same meals, as pre-determined by the experimenters. With respect to insulin and glucagon results, because there were only values that were detectable, or in range for 4 participants, definitive conclusions are unable to be drawn. Ideally, a larger number of participants would have been utilized, and a greater number

blood samples could be analyzed. A larger sample size may have revealed significant differences between conditions. Applying an a priori statistical Power analysis to the repeated measures ANOVA, within factors test assuming moderate effect size f (0.2), α = 0.05, nonsphericity correction (ε) =1, and set for (1-β) error probability = 0.8 the total sample size was determined to be 16. Post hoc testing with determined effect size f set at 0.15 determined that (1-β) error probability = 0.7910317 would have required a sample size of n=20 for α =0.05. Finally, the use of a control group may have provided more appropriate comparisons between diabetic, and non-diabetic individuals; however, it was the specific goal of this study to examine the effects of different ambient temperatures during exercise in participants with Type 1 Diabetes Mellitus, and not the effects on non-diabetic individuals.

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Appendix

The Effects of Increased Body Temperature During Exercise on a Subject with Type 1 Diabetes Mellitus: A Case Study

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Abstract

Type 1 Diabetes Mellitus (T1DM) is a disease that renders the beta cells of the pancreas unable to produce insulin. T1DM is treated with insulin, diet, and exercise. The purpose of this study is to determine if blood glucose decreases more rapidly during exercise in an increased body temperature condition than in a control condition. The investigation consists of a single subject case study. The subject is a healthy, 22 year old male with T1DM. The subject cycled at 60% VO_{2max} for 30 minutes in a control and increased body temperature condition on non-consecutive days. Measures include blood glucose, tympanic core temperature, and heart rate. Results show that blood glucose decreased during exercise to the same extent in the control and increased body temperature conditions (P=0.52). In the control condition, blood glucose continued to decrease post-exercise. However, upon cessation of exercise in the increased body temperature condition, blood glucose began to rise. The results agree with current literature regarding decrease in blood glucose during exercise in subjects with T1DM. The findings also suggest that in an increased body temperature condition, the body will respond in the same manner as in a febrile state. Because the study only utilizes a single subject, additional research into the area is required to validate results. More research into the effects of thermoregulation and exercise in subjects with T1DM is needed.

Introduction

Diabetes is a chronic disease characterized by hyperglycaemia. It is the leading cause of medically related disabilities, including blindness, amputation, and renal failure, in the United States (Salsali & Nathan, 2006). It is estimated that over thirteen million people in the U.S. are living with diabetes. Salsali & Nathan (2006), state that the number of people with diabetes worldwide is projected to double to more than 366 million by 2030. Exercise is important for individuals with Type 1 Diabetes Mellitus (T1DM) to help control blood glucose and promote blood circulation in the extremities.

When discussing the effects of exercise on the diabetic body, Peirce (1999) says that at the end of exercise, the body enters a fasted state in which glycogen stores in muscle and liver are low and hepatic glucose production is accelerated. The counter-regulatory hormone levels may remain elevated for some considerable time and there is a concomitant hyperglycaemic and hyperinsulinemic response. With respect to moderate exercise, if it is only 20-30 minutes in duration and less than 70% VO_{2max}, minimal insulin adjustments may need to be made (Peirce, 1999). Peirce (1999) states that increases in blood glucose of more than 7-8 mmol/L may compromise long term control, although levels below 10-12 mmol/L will allow safe exercise. However, levels below 6 mmol/L may increase the risk of hypoglycaemia even if the exercise intensity is between 50-70% VO_{2max}.

Galassetti et al. (2006), investigated the effect of differing antecedent hypoglycemia on counter-regulatory responses to exercise in T1DM. The study set out to determine if prior levels of hypoglycemia induce acute counter-regulatory failure of

proportionally greater magnitude during subsequent exercise in individuals with T1DM. Twenty-two individuals with T1DM (11 males and 11 females), a Hemoglobin A1C of no higher than 8.4% and a mean age of 30 +/- 2, took part in the study. The study found that acute counter-regulatory failure prolonged by moderate-intensity exercise may be induced in a dose-dependent fashion by differing depths of antecedent hypoglycemia starting at only 3.9mmol/L in patients with T1DM. This shows that if hypoglycaemia occurs on a given day, an individual must carryout the physical activity under extreme caution.

A study by Tsalikian et al. (2005) found that overnight hypoglycemia after exercise is common in children with T1DM and supports the importance of modifying diabetes management post-afternoon exercise to reduce the risk of hypoglycaemia. These findings must be considered when all individuals with T1DM are exercising, as the implications, if not carefully taken into account, can be fatal. Balfe (2007) states that modern management of diabetes is not just based on avoiding sugar and injecting insulin; it is based on a healthy diet and exercise.

The current study examines the effect of increased body temperature on blood glucose during exercise. An article by Petrofsky, Besonis, Rivera, Schwab & Lee (2006) investigated heat tolerance in patients with Type 1 and Type 2 diabetes. The study involved subjecting control subjects, individuals with Type 1 diabetes and individuals with Type 2 diabetes to an environmental temperature of 42˚C while at rest. The finding of the experiment showed that for all diabetic subjects, heat tolerance was poor, resulting in a central body temperature of 1˚C higher than control subjects (Petrofsky, Besonis, Rivera, Schwab & Lee, 2006). The study also showed a clear correlation between

abnormal noncompensatory rises in skin temperatures with inappropriate rising of core temperature in subjects with diabetes (Petrofsky, Besonis, Rivera, Schwab & Lee, 2006).

Valerio, Franzese, Carlin, Pecile, Perini & Tenore (2001) examined the increased prevalence of stress hyperglycaemia in children with febrile seizures and traumatic injuries. The study found that plasma glucose levels were significantly higher in patients exposed to stress (Valerio, Franzese, Carlin, Pecile, Perini & Tenore, 2001). Presence of fever (body temperature > 38˚C), seizures and pain made up the stress conditions. Mizock (1995) quotes, "*a number of alterations in carbohydrate metabolism have been described, including increased gluconeogenesis, depressed glycogenesis, glucose intolerance and insulin resistance as a consequence of decreased skeletal muscle*."

At this time, there is a significant gap in the literature concerning thermoregulation and exercise with regards to individuals with T1DM. The aim of the current study was to determine the relationship between increased body temperature and blood glucose during exercise in a subject with T1DM. It was hypothesized that a more rapid decline in blood glucose would occur in the increased body temperature condition than when riding in the control condition.

Methods

Subject

The subject, also the author of this paper is a healthy, 22 year-old male with T1DM (height, 170 cm; body weight, 73 kg; body mass index, 25.3 kg/m^2; body fat percentage, 14.1%: HbA_{1C}, 8.21%). At the time of the study, the subject had been living

with T1DM for 20 years. The subject is active on a regular basis, taking part in resistance or aerobic training 5 days a week.

Protocol

The study occurred over 10 non-consecutive exercise days in two conditions: control, and increased body temperature. Each condition was completed a total of 5 times, alternating between the control condition and increased body temperature condition on given testing days. Blood glucose was tested a total of 8 times in a span of 2 hours on testing days. All testing was performed on a Monark ErgoMedic 828E cycle ergometer. The subject first took part in an Astrand submaximal test to obtain a predicted VO_{2max}. The subject then refrained from physical activity 24 hours prior to each test condition. Blood glucose was taken using a OneTouch UltraSmart glucometer, OneTouch UltraSoft lancet and OneTouch Ultra test strips. Each site was sterilized with an alcohol swab before attaining the blood glucose sample. Because the subject is also the author of this paper, approval from the School of Health and Human Performance at Dalhousie University was not required.

The subject recorded blood glucose 1 hour prior to every experimental trial to avoid increased risk of hypoglycaemia while cycling. If the blood glucose reading was below 7 mmol/L, the subject consumed 30g of carbohydrate. If the blood glucose reading was below 4 mmol/L, the subject consumed 60g of carbohydrate. All trials were conducted on non-consecutive days to prevent the effects of counter-regulatory hypoglycaemia (Galassetti et al., 2006)

Control Condition

The control condition consisted of a 30-minute bicycle ride at 60% of predicted VO_{2max} with the subject wearing shorts and a t-shirt. Blood glucose, body temperature and heart rate were recorded at the onset of exercise, at 10 minutes, 20 minutes, upon completion, 10 minutes post, 20 minutes post and 30 minutes post-exercise. Body temperature was recorded from tympanic measurements using a ThermoScan thermometer. If at any point blood glucose was below 3.5 mmol/L, or the subject reported symptoms of hypoglycaemia, cycling was immediately stopped and Gatorade® was administered.

Increased Body Temperature Condition

The increased body temperature condition consisted of a 30-minute bicycle ride at 60% of predicted VO_{2max} with the subject wearing shorts and a t-shirt, underneath a non-permeable rain suit. Blood glucose, body temperature and heart rate were recorded at on-set of exercise, at 10 minutes, 20 minutes, completion 10 minutes post, 20 minutes post and 30 minutes post-exercise. Body temperature was recorded from tympanic measurements using a ThermoScan thermometer. If at any point blood glucose was below 3.5 mmol/L, or the subject reported symptoms of hypoglycaemia, cycling was immediately stopped and Gatorade® was administered.

Statistical Analysis

The data were analyzed using SPSS 13.0, and treated as a single-subject design. The data was evaluated using a univariate mixed ANOVA. Thermal condition was analyzed as a between-subjects fixed effect, and time of testing was analyzed as a within-

subjects fixed effect. The five repeated trials of each condition were treated as random effects.

Results

The analysis of blood glucose levels showed a significant main effect of interval ($F = 18.36$, $P < 0.05$). This indicates that blood glucose levels were lower at the end of exercise (mean value of 4.4) than initial values (mean value of 10.6) in both the control and increased body temperature conditions. The results (Figure 1) show no interaction between the thermal condition, and time of the blood glucose measure ($P = 0.52$). These values indicate there is no significant difference in the decrease of blood glucose when comparing the control and increased body temperature conditions.

To be noted, the blood glucose values for 20 and 30 minutes post-exercise could not be included in the ANOVA analysis due to missing data points. The values were not included because hypoglycaemia occurred in 2 trials of the control condition and 1 trial of the increased body temperature. As a result, 591 mL of Gatorade® was administered and no blood glucose values were recorded for experimental purposes post-hypoglycaemia. However, when blood glucose did not reach a state of hypoglycaemia, results show a continued decrease in the blood glucose during the control condition, but not in the increased body temperature condition. In each control condition, blood glucose values continued to decrease from the completion to 30-minute post-exercise interval (Table 1). In the increased body temperature condition, each trial, with the exception of trial 3, resulted in an increase in blood glucose from completion to 30 minutes post-exercise (Table 2). Although the mean values in Table 1 indicate a small increase in blood glucose

from completion to 30 minutes post-exercise in the control condition, in each trial, blood glucose values decreased when compared to the value at cessation of exercise.

Core temperature and heart rate were measured at each interval of exercise and 30 minutes post-exercise. Mean values for heart rate and core temperature were 127 beats per minute and 37˚C and 135 beats per minute and 37.5˚C for control and increased body temperature conditions from onset of exercise to 30 minutes post, respectively. The highest body temperature and heart rate reached during either condition was 38.9˚C, and 189 beats per minute, respectively. Both were attained in the increased body temperature condition.

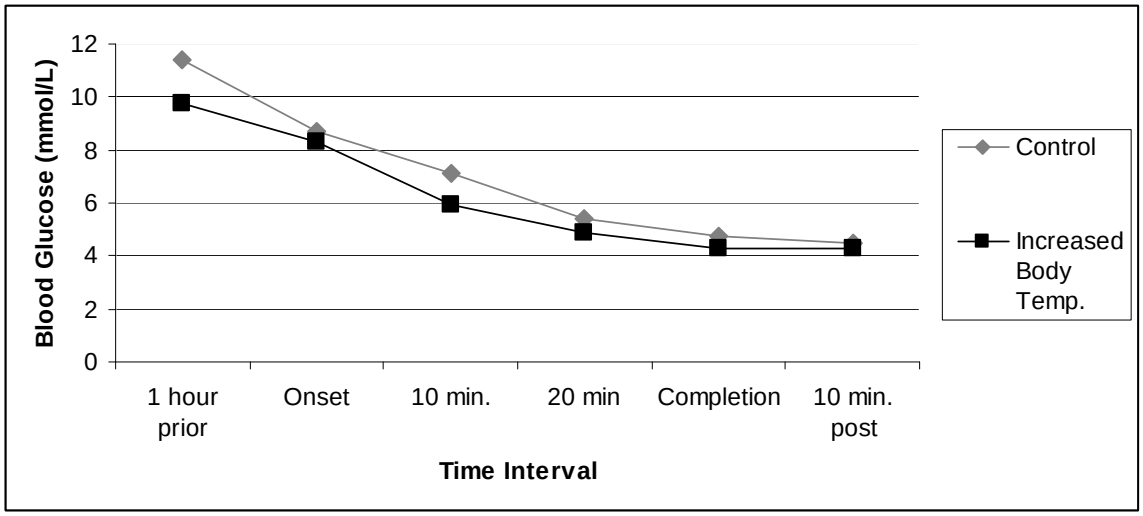

Figure 1: Results of blood glucose values for both control and increased body temperature conditions. Time includes from 1 hour prior to 10 minutes post-exercise.

Table 1: Blood glucose values from completion to 30 minutes post-exercise for the control condition. Areas that do not contain blood glucose values were not recorded due to hypoglycaemia. Although the mean value for 30 minutes post is greater than completion, in each trial blood glucose is lower than at completion.

	Control			
	Completion	10 min. post	20 min. post	30 min. post
	4.9	4.6	4.4	4.3
	3.4	3.3	3	
	3.5	3.1		
	6.1	6	5.9	5.8
	5.7	5.4	5.2	4.9
MEAN	4.72	4.48	4.625	5
STD DEV	1.24	1.27	1.24	0.755

Table 2: Blood glucose values from completion to 30 minutes post-exercise for the increased body temperature condition. The area that does not contain blood glucose values was not recorded due to hypoglycaemia. In each trial, blood glucose is higher at 30 minutes post-exercise than at completion.

	Increased Body Temperature			
	Completion	10 min. post	20 min. post	30 min. post
	3.6	3.5	4.1	5.2
	6	5.1	5.6	6.1
	3.4	3.9	3.3	
	3.5	3.5	4.6	4.9
	5	5.4	5.8	5.7
MEAN	4.3	4.28	4.68	5.475
STD DEV	1.15	0.906	1.04	0.532

Discussion

The results of this study show that blood glucose decreases during exercise in a subject with T1DM. This result concurs with the findings of Peirce (1999) who examined exercise and diabetes, finding that hypoglycaemia can occur post-exercise up to 24 hours after cessation of exercise due to increased insulin sensitivity and depleted glycogen stores. Although profound hypoglycaemia did not occur, it should be noted that in 2 of

the 5 trials of the control condition, hypoglycaemia was evident. The results also correspond to data collected by Corigliano, Iazzetta, Corigliano, & Strollo (2006), who examine blood glucose changes in diabetics during common sports activity. One of the main findings of the 2006 study by Corigliano, Iazzetta, Corigliano, & Strollo was that hypoglycemia is due to enhanced insulin sensitivity combined with reduced glycogen stores as a consequence of increased energy expenditure. The current study required the subject to cycle at 60% of VO_{2max} for 30 minutes, resulting in a greater glycogen demand by the muscles causing an increase in energy expenditure and, therefore, a decline in blood glucose.

Another result of the present was that the decrease in blood glucose during exercise was not significantly different between the control and increased body temperature conditions, despite the 8 beats more per minute and 0.5˚C higher core temperature in the increased body temperature condition. This discovery relates to findings by Cheung (2007) who found that thermal strain is usually accompanied by high levels of cardiovascular strain, and an impairment of blood pressure or critical levels of blood flow to the brain and the splanchnic tissues that may accelerate fatigue and precipitate exhaustion. These outcomes would suggest that the increased body temperature condition would result in a much higher heart rate than the control condition. However, the difference in heart rate between the control and increased body temperature conditions, as stated above, was only 8 beats per minute. The minimal difference may be due to the slight difference in body temperature in exercise conditions, 37˚C and 37.5˚C, for the control and increased body temperature conditions, respectively. Cheung & McLellan (1998) found that moderately fit individuals reached the point of voluntary

exhaustion at a consistent rectal temperature of ~38.7˚C in an uncompensable heat stress environment irrespective of hydration and acclimation status. One clear benefit of aerobic fitness is the ability to tolerate a higher rectal temperature at the point of voluntary fatigue, with highly fit individuals having a lower initial rectal temperature (by ~0.2˚C) coupled with a higher final rectal temperature (an increase of ~0.7˚C). Because the subject is healthy and is classified in the above average VO_{2max} category for his age, this may explain the slight differences in core temperature and heart rate between the increased body temperature and control conditions. As stated by Petrofsky, Besonis, Rivera, Schwab & Lee (2006), heat tolerance is poor in diabetic subjects and their study resulted in diabetic subjects having a higher central body temperature of 1˚C. In subjects with T1DM, the study also demonstrated a relationship between abnormal non-compensatory rises in skin temperatures with inappropriate rising of core temperature. Although Petrofsky, Besonis, Rivera, Schwab & Lee (2006) did not inquire into the effects of increased temperature during exercise, it can be suggested that in the current study, body temperature may have been elevated because of the subject's poor heat tolerance and inappropriate rise in core temperature.

The interesting finding of this study is the increase in blood glucose upon cessation of exercise in the increased body temperature condition. One would assume that because there was no significant decrease in the rate of decline of blood glucose between the control and increased body temperature conditions, that the post-exercise values would be the same. A study of the high prevalence of stress hyperglycaemia was examined by Valerio, Franzese, Carlin, Pecile, Perini & Tenore in 2001. In relation to the present study, Valerio, Franzese, Carlin, Pecile, Perini & Tenore (2001) find that blood

glucose levels were notably higher in patients subjected to stress. The subject in the current study was exposed to heat stress and, therefore, would exhibit the same response to stress as an individual in a febrile state. Mizock (1995) notes that in a febrile state there are changes in carbohydrate metabolism including increased gluconeogenesis, depressed glycogenesis, glucose intolerance and insulin resistance. The intriguing aspect related to this field suggests that in an individual with T1DM exercising at an increased body temperature will exhibit an increase in blood glucose post-exercise because of increased gluconeogenesis and, therefore, increased levels of blood glucose.

Conclusion

The main findings of this study are; the lack of difference in decrease of blood glucose when comparing control and increased body temperature conditions, and; the increase in blood glucose upon cessation of exercise in an increased body temperature condition. Type 1 Diabetes is a field that is heavily understudied with regards to exercise. The reasoning behind this is most likely because individuals with T1DM make up only 10% of the diabetic population. Future research into thermoregulation and its effects on T1DM and exercise is greatly needed due to the fact that exercise is an important factor in maintaining a healthy lifestyle for people with T1DM.

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Informed Consent: EEL-057

Project Title: The Effects of Different Ambient Temperatures during Exercise in Subjects with Type 1 Diabetes Mellitus (EEL-057)

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INVITATION

You are invited to participate in a study that involves research. The purpose of this study is to test the effects that exercise has under different temperatures. These measurements will give us information on the effects that different temperatures have on people with Type 1 Diabetes Mellitus (T1DM) during and after exercise. You will be required to have the accompanying screening form signed by your physician to take part in the study. Your care provided at McMaster will not be affected by decision to participate or not.

WHAT'S INVOLVED

There will be a total of four sessions that will require you to come to the lab. In the first session you will have your physical characteristics measured, report H_bA_{1C}, and perform a cycle ergometer test to determine your fitness. In sessions 2-4, you will exercise on the cycle ergometer for 30 minutes at a moderate pace in 5, 20, or 35˚C. Time commitment will be approximately 10.5 hours over the five sessions, spaced out over approximately five weeks. Prior to each session, you will be asked to refrain from alcohol and/or heavy exercise for 24 hours prior to the trial and caffeine on the day of the trial. In all five sessions, you will change into your own exercise shirt and shorts. Appropriate change rooms will be provided for you to change into the required clothing. You will have free access to water throughout all sessions. When you come to the lab, you will be given a parking pass to permit parking in the Brock, Lot S lot.

At your convenience, prior to beginning the study (Session 0), you will meet with the Principal Student Investigator to receive all consent material and will be informed of the measures and purpose of the study.

In the first session (Session 1), you will have your height, weight, and the amount of body fat in your body measured. Body fat testing will be performed using skinfold calipers, which might cause a slight pinching sensation, and will be taken by someone of the same sex in a private room. You will also cycle on an ergometer to determine your predicted Maximal Oxygen Consumption (VO_{2max}). You will perform an Astrand submaximal cycle ergometer test to determine your VO_{2max}. Based on your age, and fitness level, you will be instructed to cycle at 60 revolutions per minute (rpm) for 6 minutes. Heart rate will be monitored throughout the test using a telemetric heart rate monitor (s810i, Polar Electro Oy, Finland). Your heart rate will be measured every minute, and should be between 130-160 beats per minute (bpm)You're your heart rate is not in the 130-160 bpm range, the wattage will be increased or decreased accordingly, until your heart rate falls in the desired range. With the heart rate and wattage from your final minute, the Astrand-Ryhming Nomogran will be used to predict your maximal oxygen uptake, giving us an idea of your fitness level. One day prior, and 3 days after Session 1, you will be asked to keep a diet log. This diet log will provide baseline measurements of your typical carbohydrate ingestion, and you will be instructed to follow your typical (baseline) eating habits prior to, and following each exercise session. Before leaving the laboratory, you will be asked to find a 'partner' that will be able to monitor you for 24h post-exercise, and their contact information will be required upon your next visit. Before leaving the lab, you will be given an Accu-Chek Compact Plus blood glucose monitor and strips to be used throughout the study. The contact information for your chosen 'partner' will also be recorded. Time commitment for this session will be approximately 2h.

In the experimental sessions (sessions 2-4), all conditions will be identical in instrumentation and protocol; the only difference between the three conditions will be the application of the chamber's temperature in a randomized fashion: 1) temperature of 5˚C (C, cool); 2) temperature of 20˚C (T, thermoneutral); and 3) temperature of 35˚C (H, hot). In the incident that you have had a hypoglycemic incident in the 48 hours leading up to the exercise session, you will be required to inform the PSI, and the exercise session will be rescheduled, as prior hypoglycemic events can increase the risk of another hypoglycemic episode. Conversely, if hyperglycemia is present (blood glucose > 13.9 mmol/L), you will be required to take an additional finger stick for a meter test of blood ketones. Should ketones be present, you will be instructed to inject a correction bolus of insulin, and exercise will be postponed until blood glucose levels drop below 13.9 mmol/L. If no ketones are present, you will need to wait 30 minutes before testing again, and exercise will commence when blood glucose is below 13.9 mmol/L. If hyperglycemia is present (blood glucose > 13.9 mmol/L) and blood glucose is not decreasing, the exercise trial will be rescheduled to a later time in order to standardize blood glucose values. If blood glucose levels are low (i.e. near 5 mmol/L and showing a decreasing trend, or below 5 mmol/L) you will be provided with glucose in tablet form (around 16 g). You will be asked to check your blood glucose after 20 and 40 minutes to ensure that levels are greater than 5 mmol/L and stable before starting exercise. Should the correct range not be reached within 90 minutes, the exercise session will be terminated and the exercise trial will be rescheduled to a later time in order to standardize blood glucose values One hour prior to entering the laboratory, you will be need to take a blood glucose

reading to ensure your safety. If your blood glucose is at the level of hypoglycemia (below 4.0 mmol/L), you will be instructed to ingest sufficient CHO to raise your blood glucose 2.5-4.0 mmol/L before resuming the trial. Upon arrival at the laboratory, you will change into a t-shirt and shorts and insert the rectal probe to a depth of 15 cm beyond the anal sphincter. You will have your baseline body mass measured and provide a small urine sample so that we can measure your hydration level. You will then be instrumented with a heart rate monitor strap (s810i, Polar Electro Oy, Finland) across the chest for telemetric recording of heart rate (HR). Skin temperature sensors will be taped onto the body surface at the following sites: chest, upper arm, front thigh, calf, which will be used to calculate a mean skin temperature. Prior to the commencement of the first exercise session, you will have a catheter inserted into your antecubital vein (at the elbow) for blood analysis prior to exercise, at 15 minutes during exercise, and 60 minutes post-exercise. Throughout the experiment, you will breathe through a soft silicone mask and have your expired air collected and analyzed to measure oxygen uptake. Every 10 min throughout the experiment, you will have your blood glucose measured, to monitor changes to exercise and ambient temperature. You will then begin exercise at 65% of your predetermined VO_{2max} on a cycle ergometer. Exercise time will last 30 minutes. At times 0, 10, 20 and 30 min, you will have a small blood sample taken via finger prick, for analysis of blood lactate. You will have a blood sample, taken via the blood draw for analysis prior to starting exercise, and upon completion of exercise. In the case of severe hypoglycemia, an injection of glucagon will be administered. Glucagon will be kept in the fridge in the Environmental Ergonomics Laboratory. Glucagon will be drawn into a needle, and given via bolus injection into the right posterior (gluteus maximus) and emergency services will immediately be called, as well as your partner. Immediately following the exercise period, you will be seated outside the chamber in the laboratory, and will be required to stay for 60 minutes post-exercise with blood glucose taken every 10 minutes. Upon leaving the laboratory, you will be given Dextrosol ® of Glucosol ® to be taken in any instance in which hypoglycemia may occur. You will be instructed to measure blood glucose every 6 hours for 24 hours post-exercise. A follow up phone call will be made to you at approximately 6, 12, 18, and 24 hours post-exercise to ensure your safety, and for blood glucose reports. These phone calls are for research purposes and you may need to address your glucose readings more regularly. You are responsible for your maintaining the monitoring of your own health status and consulting your physician as needed. If you should feel hypoglycemic at any point, take the required steps to ensure that your blood glucose returns to normal values.
Time commitment for each experimental session will be approximately 2.5 h.

POTENTIAL BENEFITS AND RISKS

Possible benefits of participation include knowing your maximal fitness levels through the Maximal Oxygen Consumption (VO_{2max}) test. You will also receive an Accu-Chek Compact Plus blood glucose monitor that you are free to keep following the study.

There may be risks associated with participation. The Bruce submaximal protocol test may leave your legs feeling sore (calf muscles), possibly causing discomfort. There is also the risk of hypoglycaemia associated with Sessions 3-5 up to 24h after exercise. There is also a very remote risk of heart attack or stroke when exercising to exhaustion, but this is minimized with the use of the health screening questionnaire. With the blood draws, there is a risk of bruising, and a risk that infection may develop at the site of insertion. The risk of heart disease is greater in individuals with Type 1 Diabetes Mellitus, even if you are physically active. You should consult with your physician about whether an ECG analysis is advisable prior to taking part in the study. There will be at least two investigators trained in First Aid and CPR present for each experiment. The investigators will contact you at regular intervals following each session to check on your health status, and your 'partner' will be asked to check on you regularly also.

Experimental sessions will be terminated if:
1. Rectal temperature increases beyond 39.5^{o}C.
2. Blood glucose reaches 4.0 mmol/L or below
3. Subject experiences hypoglycemic signs and/or symptoms
4. Heart rate has risen above 95% of its predicted maximum (220-age) for 3 min.
5. Dizziness or nausea precludes further experimentation.
6. Subject decides, for any reason, to end the experiment.
7. The investigators determine that the subject is unable/unfit to continue.

Insertion of the flexible rectal probe may cause slight discomfort. You will be given instruction about how to prepare the probe, and will self-insert the probe in a private room. You will be provided with water-based lubricant if necessary, and will secure the probe with a soft gauze "sumo sling" harness which will keep it in place during exercise. There is a slight but real risk of perforation of the bowel from the insertion of the rectal probe, though the investigators are unaware of this ever occurring in a research setting. There is also a chance that surface electrodes or electrode tape may cause some skin irritation.

Because of the duration of the exercise test (30 min), you can expect to experience fatigue and some degree of sweating or mild rise in body temperature. Some of the symptoms that may be experienced with an elevated body temperature include: discomfort, sweating, flushing and redness in the face and body, thirst, loss of fine motor coordination due to sweating, minor mental confusion, dizziness or nausea. These symptoms commonly disappear almost immediately upon return to normal body temperature. You will be able to drink water during and after the test. If you experience any unusual symptoms after completing a testing session, you should immediately seek medical attention and inform Dr. Cheung. The investigators will also contact you the evening of your participation to ensure that you are in a healthy state. Depending on your health status, you may be asked to consult with a physician.

RECTAL PROBE

When performed in a healthcare setting, insertion of the rectal probe is a controlled act as set out in the Regulated Health Professions Act. While this act does not extend to research outside of a healthcare setting, you should be aware of the following potential risks:

- Insertion of the rectal probe can stimulate the vagus nerve which can cause slowing of the heart rate which may lead to fainting. This is more likely to happen if you have a low resting heart rate.
- Perforation of the bowel can lead to peritonitis, a serious infection of the abdominal cavity.
- You should not participate in this research if you are pregnant, are under the influence of alcohol or other sedating substances (tranquilizers, sleeping pills, street drugs) or have any history of fainting or heart disease.

CONFIDENTIALITY

Access to this data will be restricted to Dr. Cheung and the principal student investigator, Mr. Matthew Smith. Other members of Dr. Cheung's lab may be assisting with the study, and therefore will have some access to data. Your participation will remain confidential. The data collected from this investigation will be kept secured on the premises of the Department of Physical Education and Kinesiology (PEKN) at Brock University in Dr. Cheung's office or laboratory, and will not be accessed by anyone other than the listed investigators. The data (paper and electronic) will be destroyed five years after the publication of the results of the study. Blood draws will be stored in a freezer at -80ºC in the PEKN Department, and will only be accessible by the PI and PSI for research purposes. Blood analyses will be done upon completion of data collection from all subjects, and then will be appropriately disposed in biohazardous waste disposal bins. Investigators will require disclosure of your name and contact information (phone, email), and therefore your participation is not anonymous during the conduct of the research. All participants will have their names removed from any data. The master list matching participants to data will be kept by Dr. Cheung and Mr. Smith, and will be destroyed following the publication of data.

All information you provide is considered confidential; your name will not be included or, in any other way, associated with the data collected in the study. Furthermore, because our interest is in the average responses of the entire group of participants, you will not be identified individually in any way in written reports of this research.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. If you wish, you may decline to answer any questions or participate in any component of the study. Further, you may decide to withdraw from this study at any time and may do so without any penalty or loss of benefits to which you are entitled. Participation, non-participation, or withdrawal from the study will not affect your standing at Brock University.

PUBLICATION OF RESULTS

Results of this study may be published in professional journals and presented at conferences, but your personal information and participation will remain confidential. Approximately one month after we finish testing all participants, we will provide you with a summary of your own results and also the overall group results. Feedback about this study will be available from Dr. Stephen Cheung (stephen.cheung@brocku.ca, 905-688-5550x5662).

CONTACT INFORMATION AND ETHICS CLEARANCE

If you have any questions about this study or require further information, please contact Dr. Cheung or Mr. Smith using the contact information provided above. This study has been reviewed and received ethics clearance through the Research Ethics Board at Brock University (REB 09-005). If you have any comments or concerns about your rights as a research participant, please contact the Research Ethics Office at (905) 688-5550 Ext. 3035, reb@brocku.ca.

CONSENT FORM

I agree to participate in this study described above. I have made this decision based on the information I have read in the Information-Consent Letter. I have had the opportunity to receive any additional details I wanted about the study and understand that I may ask questions in the future. I understand that I may withdraw this consent at any time. My participation, non-participation, or withdrawal from the study will not affect my standing at Brock University.

Participant:

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

Name Signature Date

Person obtaining consent:

I have discussed this study in detail with the participant. I believe the participant understands what is involved in this study.

Name, Role in Study Signature Date

Investigator:

In my judgment, this participant has the capacity to give consent, and has done so voluntarily.

Name, MD Signature Date

The Effects of Different Ambient Temperatures During Exercise in Subjects with Type 1 Diabetes Mellitus (EEL-057)

Environmental Ergonomics Laboratory Fitness Screening Form

Please read over the questions below*. They are to assist in assessing whether you are fit to participate in this study. Please ask the investigators if you have any queries before you begin filling out the form. **THIS FORM DOES NOT REPLACE YOUR RIGHT TO CONSULT YOUR DOCTOR AT ANY TIME, and you should bring this and the informed consent document to review with your doctor prior to participation.**

Screening Questions*	**YES**	**NO**
1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?		
2. Do you feel pain in your chest when you do physical activity?		
3. In the past month, have you had chest pain when you were not doing physical activity?		
4. Do you lose your balance because of dizziness or do you ever lose consciousness?		
5. 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?		
6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?		
7. Do you know of any other reason why you should not do physical activity?		
8. Current pregnancy or menstrual irregularities (e.g., loss of cycle) in females?		
9. Do you have any bowel or prostate problems (e.g. colitis, irritable bowel syndrome, prostate problems)?		
10. Neuromuscular (e.g., epilepsy, Multiple Sclerosis, Cerebral Palsy) or skeletal (e.g., inflammatory or degenerative arthritis) disorders?		
11. Do you have a tendency for, or ever been diagnosed with, claustrophobia (a very strong fear of confined spaces)?		
12. Are you unable to detect the symptoms of a low blood sugar (ie. Sweating, shaking/trembling, rapid pulse, etc.)?		
13. Has it been less than 5 years since you were diagnosed with Type 1 Diabetes and began to receive insulin therapy?		
14. Do you smoke?		
15. Have you had a severe hypoglycemic episode in the last 3 months that required assistance from another person?		
16. Is your HbA1c greater than 9%? (as determined by your physician/endocrinologist)		

17. Do you have frequent, unpredictable hypoglycemia and/or hyperglycemia?		
18. Do you have intermittent cramping pains in your periphery? Do you have severe peripheral neuropathy or active proliferative retinopathy, unstable cardiac or pulmonary disease, disabling stroke, or severe arthritis?		
19. Do you have known or suspected clinically significant gastroparesis? (as diagnosed by your physician) – symptoms include chronic nausea, vomiting (of undigested food), heartburn, weight loss, abdominal bloating, erratic blood glucose levels or lack of appetite?		
20. Do you have an expected requirement within the subsequent 6 months for medications (other than insulin) that will affect your glucose metabolism (e.g. corticosteroids)?		

Name: _____

Signature_____ Date**_____

I have discussed the project with the above signed individual, and deem them physically capable to participate in the above mentioned study

Name of physician: _____

Signature_____ Date**_____

Thermal Comfort Scale

1 Comfortable

1.5

2 Slightly uncomfortable

2.5

3 Uncomfortable

3.5

4 Very uncomfortable

4.5

5 Extremely uncomfortable

Thermal Sensation Scale

0	Unbearably cold
1	Very cold
2	Cold
3	Cool
4	Slightly cool
5	Neutral
6	Slightly warm
7	Warm
8	Hot
9	Very hot
10	Unbearably hot

The ratings of perceived exertion (RPE) takes into account all that you are perceiving in terms of fatigue, including psychological, musculoskeletal, and environmental factors. This level of perceived physical effort is assigned a rating from the scale below:

RPE

6	
7	very, very light
8	
9	very light
10	
11	fairly light
12	
13	somewhat hard
14	
15	hard
16	
17	very hard
18	
19	very, very hard
20	

On this scale, an RPE of 12 to 13 corresponds to approximately 60 to 79 percent of maximal heart rate. An RPE of 16 would correspond to about 90 percent of maximal heart rate. Thus, as a rule, most folks would exercise between 12 and 16 on this scale.