Can Short Sprints During Moderate Intensity Exercise Reduce the Incidence of Exercise Mediated Hypoglycaemia in Individuals with Type 1 Diabetes?

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Abstract

Background: Short sprints have been shown to reduce exercise induced hypoglycaemia in controlled laboratory settings. This study tested the hypothesis that incorporating sprinting into moderate intensity exercise can reduce the incidence of exercise mediated hypoglycaemia in individuals with T1D in a free-living setting.

Methods: Individuals with T1D were recruited into a prospective randomised controlled cross over study. Participants completed three 14-day periods in random order. In one period participants undertook moderate intensity exercise for a minimum of 30 minutes, at least 3 times a week (control period). In the other periods, participants incorporated 10s (every 20 mins) or 4s sprints (every 2 mins) into the exercise regimen. The primary outcome was the incidence of hypoglycaemia, defined as sensor glucose readings <3.5mmol/L for ≥ 20 minutes over the 14-day period. Secondary outcome measures included the incidence of hypoglycaemia <3.1mmol/L and percentage time <3.1mmol/L and <3.5mmol/L.

Results: 24 participants completed the study. There was no difference in hypoglycaemic events (<3.5mmol/L) between the 4s and control period (p=0.28) or the 10s and control period (p=0.05). The 10s period was associated with fewer hypoglycaemia events <3.1mmol/L than the control period (p=0.04), with an incidence rate of 0.40 (95% CI 0.26-0.55), 0.33 (95% CI 0.21-0.45) and 0.28 (95% CI 0.17-0.38) events per day in control, 4s and 10s periods respectively. The 10s period was associated with a reduction in time spent <3.5mmol/L (3.1% vs. 2.1%, p=0.03) and time spent <3.1mmol/L (1.9% vs 1.2%, p= 0.03). There was no increase in nocturnal hypoglycaemia during the sprinting periods.

Conclusion: In a free-living setting, the inclusion of 10s sprints into moderate intensity exercise did not reduce hypoglycaemic events <3.5mmol/L but reduced hypoglycaemia <3.1mmol/l and the percentage time spent in hypoglycaemia. These observations may help active people with T1D to exercise more safely by reducing the risk of hypoglycaemia.

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Contribution of Others

The original research question was devised by Prof Tim Jones, Prof Elizabeth Davis and Professor Paul Fournier. Ray Davey contributed to the initial study design. Phillipa Eaton (honours student) performed a pilot study, with supervision from myself and Paul Fournier. I then developed and refined the study design with assistance from Prof Tim Jones, Prof Elizabeth Davis and Professor Paul Fournier. I finalised the study protocol and completed all regulatory approvals. I recruited subjects to the study with assistance from Julie Dart. VO_2 max testing was performed by Wayne Soon and Wade Brownlee. I managed and undertook the study visits with support from Julie Dart and Wade Brownlee. I collected and processed the study data with assistance from Heather Roby. Grant Smith provided support with power calculations and statistical analysis. I undertook the main analyses and was central to their interpretation. I will prepare and lead on the manuscripts arising from the study under the guidance of my supervisors.

List of abbreviations

ADP	Adenosine Diphosphate
ATP	Adenosine Triphosphate
CGM	Continuous Glucose Monitoring
CHO	Carbohydrate
CI	Confidence Interval
CI	Confidence Interval
CSII	Continuous Subcutaneous Insulin Infusion
DAFNE	Dose Adjustment for Normal Eating
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
EDIC	Epidemiology of Diabetes Interventions and Complications
FGM	Flash Glucose Monitoring
GI	Glycaemic Index
GLUT-4	Glucose transporter-4
GPS	Global Positioning Systems
HbA1c	Glycated Haemoglobin
LOPEH	Late Onset Post Exercise Hypoglycaemia
MARD	Mean absolute Relative Difference
MDI	Multiple Daily Injections
NICE	National Institute of Clinical Excellence
PACES	Physical Activity Enjoyment Scale
PCr	Phosphocreatine
Ra	Rate of glucose appearance
Rd	Rate of glucose disappearance
SD	Standard Deviation
SGL	Sensor Glucose Level
SMBG	Self-Monitoring of Blood Glucose
T1D	Type 1 Diabetes
VO_2 Max	Maximal rate of oxygen consumption

Contents

List of Tables

List of Figures

Chapter 1: Introduction

1.1 Glucose Homeostasis: Fasting and Fed States

Blood glucose is the key substrate for brain function (Zhang, Kuang et al. 2013). Normal fasting blood glucose levels are maintained within a narrow range (3.5-5.5mmol/L) in infants, children and adults (Guemes, Rahman et al. 2016). Studies using continuous glucose monitoring, show that blood glucose levels may transiently sit outside these limits especially after a meal, but quickly revert to within the normal range (Kaufman 2000). This narrow range of normal blood glucose levels is maintained by a complex interplay of hormones which control glucose production and glucose utilisation.

1.1.1 ***Post prandial state***

Ingestion of food causes blood glucose levels to increase and stimulates the enteroendocrine axis. The increase in the blood glucose level and production of gut derived hormones stimulates insulin secretion from the beta cells of the pancreas and supresses glucagon secretion from alpha pancreatic cells.

Peak concentrations of plasma glucose are reached around 30-60 minutes following food ingestion (Felber, Magnenat et al. 1977, Mitrakou, Kelley et al. 1990). Post prandial blood glucose levels are determined by the balance between glucose production and glucose removal. Insulin limits glucose production by suppressing hepatic glycogenolysis and gluconeogenesis and inhibits fat breakdown (lipolysis and ketogenesis) (Rizza, Mandarino et al. 1981). Insulin facilitates glucose uptake by the tissues (including the liver, brain, muscle, small intestine and adipose tissue) thereby removing glucose from the blood stream (Ferrannini, Bjorkman et al. 1985, Kelley, Mitrakou et al. 1988). It is the plasma insulin concentration that largely determines the amount of glucose uptake by the tissues, with the exception of the brain (Rizza, Mandarino et al. 1981). The uptake of glucose by the brain is independent of insulin levels and instead depends on plasma glucose concentrations (Zhang, Kuang et al. 2013).

Gut derived hormones, released in response to nutrient ingestion, play a key role in post prandial glucose homeostasis, including the stimulation of glucose dependent pancreatic insulin secretion (Holst, Gribble et al. 2016). Studies have shown that the ingestion of oral glucose is associated with larger amounts of insulin secretion compared to administration of

intravenous glucose (McIntyre, Holdsworth et al. 1964, Perley and Kipnis 1967). This phenomenon of postprandial enhancement of insulin secretion is known as the 'incretin effect' and is largely mediated by two main hormones: glucose dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) (Vilsboll, Krarup et al. 2003). GIP and GLP-1 are secreted from enteroendocrine cells in the gut epithelium in response to nutrient absorption. GIP is produced by K cells in the duodenum and proximal small intestine, GLP-1 secreting L cells are located more distally, and are found in the jejunum, ileum and colon (Sjolund, Sanden et al. 1983). In addition to reducing postprandial hyperglycaemia through insulinotropic effects, GLP-1 also supresses glucagon production (Hvidberg, Nielsen et al. 1994, Lund, Vilsboll et al. 2011) and slows gastric emptying (Wettergren, Schjoldager et al. 1993).

Preceding any post absorptive rise in blood glucose levels, a cephalic phase of insulin secretion has been described that occurs as an anticipatory response to the sight, smell and taste of food and is enhanced by chewing and swallowing for food (Teff, Levin et al. 1993). Cephalic insulin secretion occurs within 10 minutes of chewing food and is independent of the incretin response (Ahren and Holst 2001). This phase of insulin secretion is well described in animal models (Berthoud and Jeanrenaud 1982) (Siegel, Trimble et al. 1980) but findings are inconsistent in human studies where some describe a consistent cephalic response (Eliasson, Rawshani et al. 2017) and others do not (Veedfald, Plamboeck et al. 2016).

1.1.2 ***Post-absorptive state***

The post-absorptive state occurs 4-6 hours after a meal. During this phase glucose levels remain in a steady state as the rate of glucose utilisation is carefully matched by the rate of glucose production(Wasserman 2009). This balance is orchestrated by the effects of insulin and the counter regulatory hormones (glucagon, cortisol, growth hormone, adrenaline, noradrenaline). Glucagon promotes the release of hepatic stored glycogen from the liver (Exton and Park 1968, Robison, Butcher et al. 1968) . Insulin inhibits glycogenolysis in the liver, and stimulates fat and protein synthesis (Petersen, Laurent et al. 1998). Glucagon, adrenaline, cortisol and growth hormone promote gluconeogenesis and stimulate lipolysis, the breakdown of triglycerides into glycerol and free fatty acids (Bolli and Fanelli 1999). Increasing the supply of glycerol for gluconeogenesis, and free fatty acids for oxidation, reduces glucose consumption. In addition, cortisol and growth hormone play a role in

maintaining blood glucose levels by setting the insulin sensitivity of the peripheral tissues to glucagon and insulin (Moller, Jorgensen et al. 1990)

1.1.3 ***Fasted state***

As fasting continues tissue utilisation of free fatty acids and ketones increase while use of glucose decreases (Cahill, Herrera et al. 1966). There is a net reduction in glucose output from the liver with a decrease in glycogenolysis and an increase in gluconeogenesis (Rothman, Magnusson et al. 1991, Katz and Tayek 1998). This increase in gluconeogenesis is thought to be mediated by increased secretion of counter regulatory hormones including glucagon, and a reduction in insulin levels (Liljenquist, Mueller et al. 1977) . This hormonal milieu enables lipolysis and proteolysis (the breakdown of proteins into amino acids). The subsequent breakdown products of these processes provide the substrates (primarily amino acids and glycerol) for gluconeogenesis (Cahill, Herrera et al. 1966). Mitochondrial beta-oxidation of free fatty acids generates acetyl-coenzyme A that can be further oxidised in the Kreb's cycle or can be used in the biosynthesis of ketone bodies via the hydroxymethylglutaryl coenzyme A pathway (Houten and Wanders 2010).

1.1.4 ***Prolonged fasting***

As the fast becomes more prolonged, the tissues increasingly rely on free fatty acids and ketone bodies (acetoacetate and 3-beta-hydroxybutyrate) as a source of fuel. The brain is dependent solely on ketone bodies as an alternative fuel to glucose, as free fatty acids cannot cross the blood-brain barrier (Zhang, Kuang et al. 2013).

1.2 Counterregulatory Response to Hypoglycaemia

Blood glucose is the key substrate for brain function (Zhang, Kuang et al. 2013). Since the brain is permanently dependent on glucose, as plasma glucose levels fall (e.g during prolonged fasting) the healthy individual mounts a robust physiological neuroendocrine response to prevent hypoglycaemia (as described above). This neuroendocrine response is known as counterregulation, a system that prevents and corrects hypoglycaemia through the release of counterregulatory hormones (glucagon, adrenaline, noradrenaline, growth hormone and cortisol) (Bolli and Fanelli 1999). This is triggered when blood glucose levels decline below the lower end of the normal range and is preceded by suppression of endogenous insulin secretion. There is a hierarchy of glycaemia thresholds for activation of the counterregulatory hormones. Increased secretion of glucagon and adrenaline occurs at

blood glucose levels of approximately 3.8-3.9mmol/L, secretion of noradrenaline and growth hormone at approximately 3.6-3.7mmol/L and secretion of cortisol at around 3.0mmol/L (Mitrakou, Ryan et al. 1991). Glucagon and adrenaline are the most important hormones when considering the response to acute hypoglycaemia (Cryer 1993).

1.3 Definitions of Physical Activity and Exercise

The terms physical activity and exercise are often used interchangeably but describe different concepts. Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise is a subcategory of physical activity that is planned, structured and purposeful (Caspersen, Powell et al. 1985).

1.4 Physiology during Physical Activity and Exercise (Individual without T1D)

1.4.1 ***ATP generation during physical activity and exercise***

Performing any form of physical activity requires the transformation of chemical energy into mechanical energy (contraction of skeletal muscles). This chemical energy is obtained from hydrolysis of Adenosine Triphosphate (ATP). However, the amount of ATP that can be stored in the muscle is limited and would only enable a few seconds of muscle contraction (Gaitanos, Williams et al. 1993) . Therefore during physical activity ATP must be generated continuously to match demand.

There are three distinct energy systems to supply muscles with ATP to fuel muscle contraction (Fox, Robinson et al. 1969) The three systems have been described as working in a sequential manner with one then the next producing ATP as physical activity continues. However, although distinct, the systems are closely integrated and if activity is sustained (for longer than around a minute) all three systems will operate together contributing to a varying extent to energy production (Gastin 2001). The first two systems described are important at the beginning of any longer duration activity, and also if the intensity of the exercise is rapidly increased such as a sprint to the finish line (Colberg and Colberg 2009).

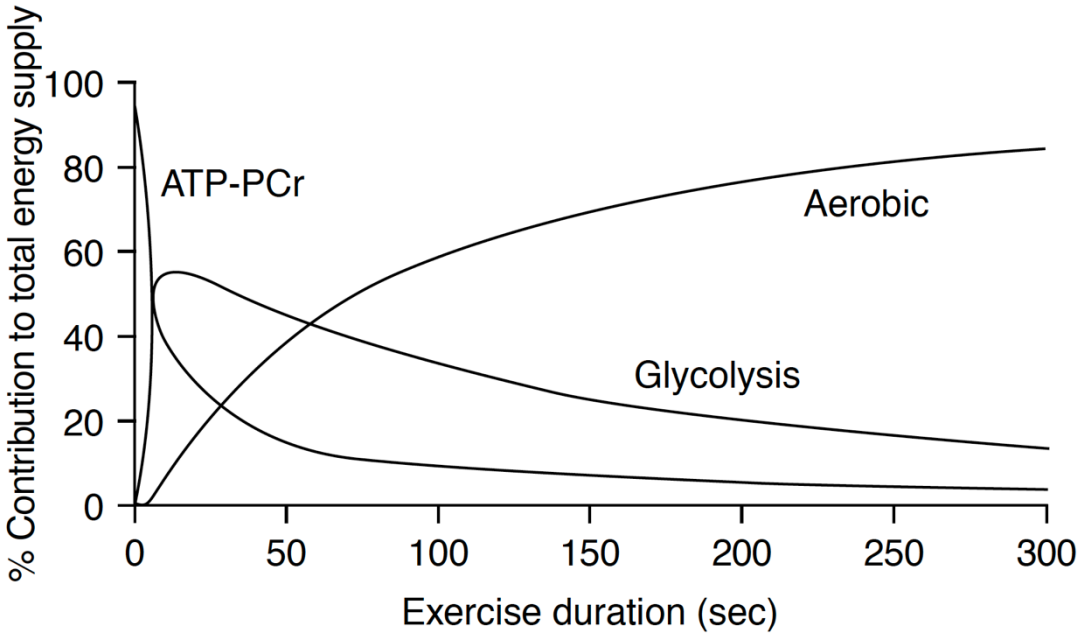

Figure 1: Relative energy system contribution to the total energy supply for any given duration of maximal exercise (Gastin 2001).

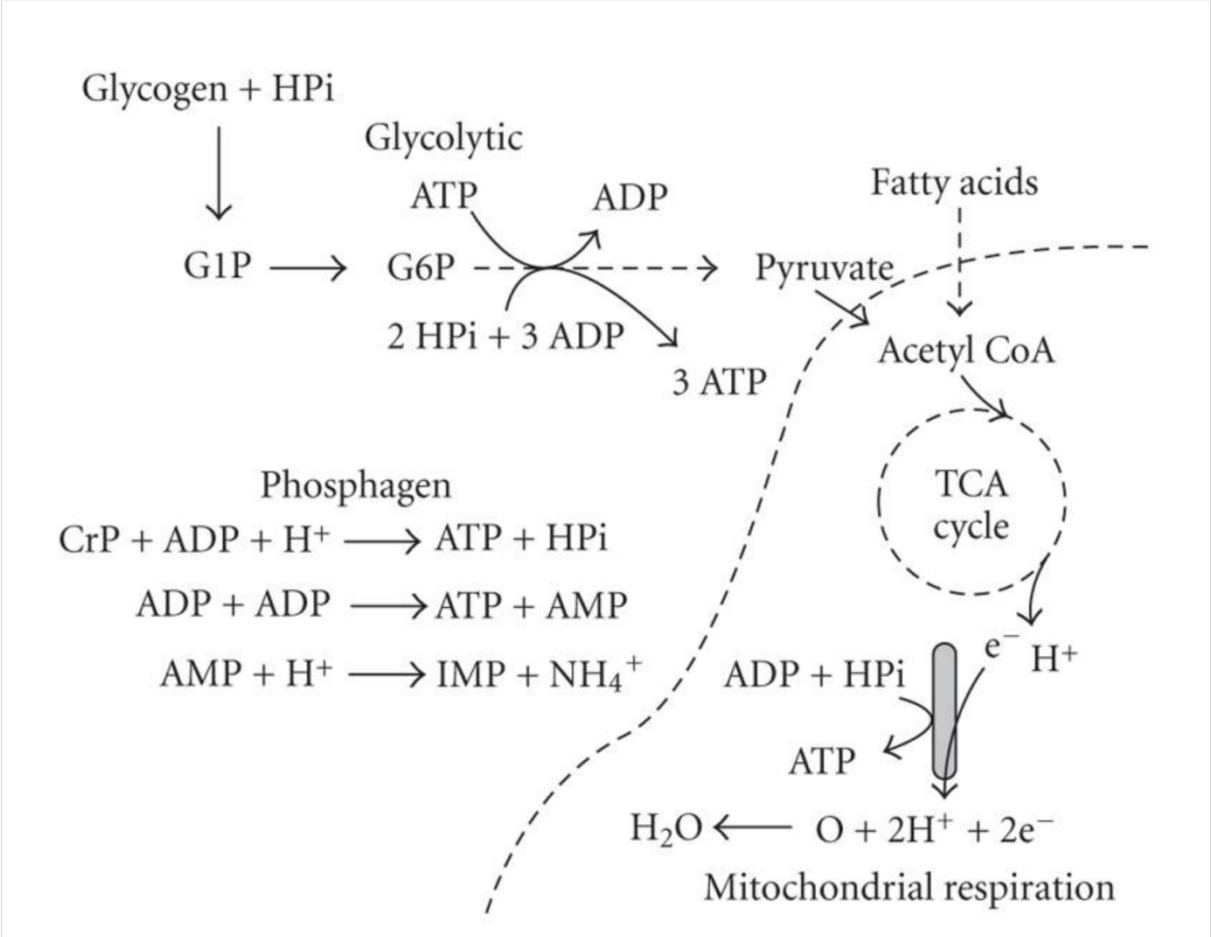

Figure 2: The three energy systems of muscle ATP generation (Baker, McCormick et al. 2010)

1.4.2 ***ATP- creatine phosphate system***

This process involves the splitting of phosphocreatine (PCr) to donate a phosphate group to Adenosine diphosphate (ADP) to form ATP. Together with the stored ATP in the muscle cell, this provides immediate energy in the initial stages of short and intense activities (Bogdanis, Nevill et al. 1996, Walter, Vandenborne et al. 1997). The PCr system can fuel an all-out effort for around a maximum of 10s before being depleted. This system does not require any oxygen for energy production, and is therefore anaerobic in nature.

1.4.3 ***Lactic acid system (glycolysis)***

The second system involves the anaerobic breakdown of carbohydrate via glycolysis and results in the production of lactic acid. This system supplies the additional energy for activities that last longer than 10 seconds (Gaitanos, Williams et al. 1993). This pathway is capable of generating ATP at high rates but is limited by the total amount of energy it can produce in a single bout of exercise (Colberg and Colberg 2009).

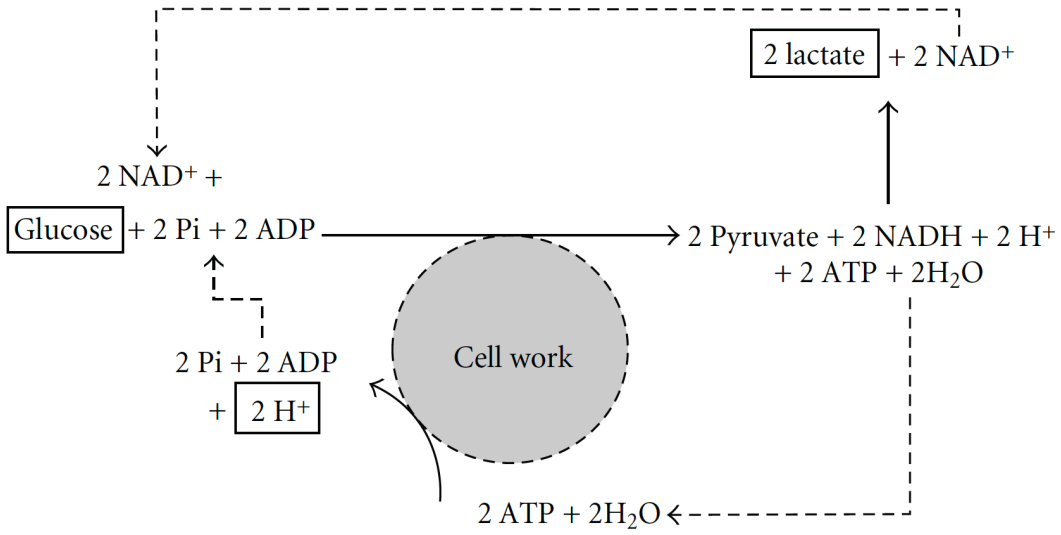

Figure 3: Glycolytic-lactate pathway (Baker, McCormick et al. 2010)

1.4.4 ***Aerobic system***

The aerobic energy system generates energy through the combustion of carbohydrates and fats in the presence of oxygen. This system is used in activities sustained for greater than 2 minutes. The main carbohydrate sources are muscle and liver glycogen, liver gluconeogenesis and ingested carbohydrates. The main fat sources are plasma free fatty

acids and intramuscular triglycerides. Protein can be used to fuel activity but it usually contributes less than 5% of the total energy used. In contrast to the anaerobic system the aerobic system has a larger capacity to produce energy, but takes longer to generate this energy (Gastin 2001).

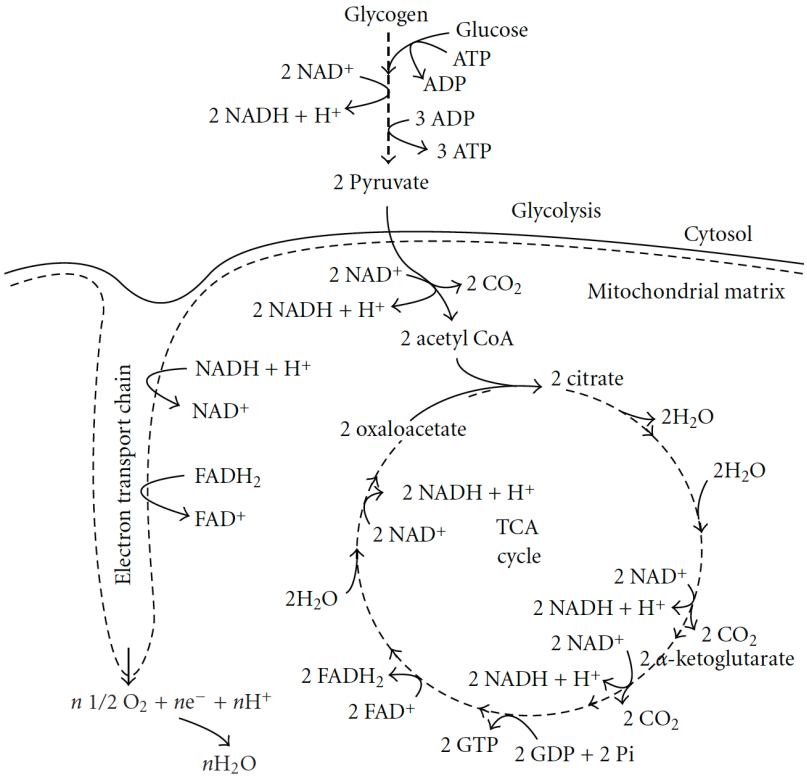

Figure 4: Anaerobic Respiration (Baker, McCormick et al. 2010)

1.4.5 ***Fuel utilisation during physical activity and exercise***

During the transition from rest to physical activity the muscle shift from using predominately free fatty acids to a complex mixture of circulating free fatty acids, intra muscular triglycerides and muscle and liver glycogen (Riddell and BA 2006). The pattern of substrate utilisation during physical activity changes with activity duration and intensity.

1.4.6 ***Fuel utilisation: duration of physical activity or exercise***

During the early stages of aerobic activity, muscle glycogen is the chief source of energy for muscle contraction, whereas circulating glucose and free fatty acids become more important with increasing exercise duration (Suh, Paik et al. 2007).

1.4.7 ***Fuel utilisation: intensity of physical activity or exercise***

Both muscle glycogen and blood glucose oxidation rates increase with increasing intensity of the activity (van Loon, Greenhaff et al. 2001). In contrast fat oxidation increases until around 60% of aerobic capacity is reached, then decreases thereafter (van Loon, Greenhaff et al. 2001) (Romijn, Coyle et al. 1993). Thus, fats provide the main fuel source for low-moderate intensity exercise (up to 60% $V0_2$ max) and carbohydrates are the main fuel source during high intensity exercise (see figure 1).

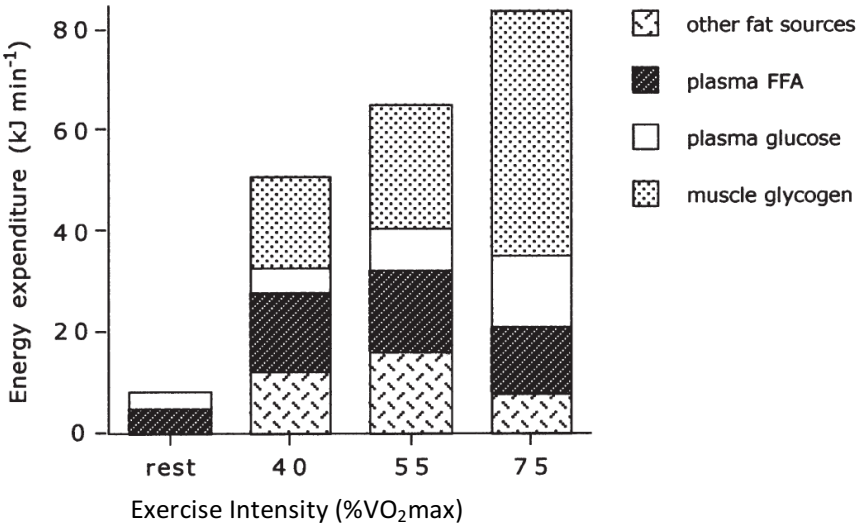

Figure 5: Energy expenditure and the contribution of different metabolic fuels during exercise of varying intensity in human (van Loon, Greenhaff et al. 2001)

During sustained activity of increasing intensity, a threshold will be reached above which carbohydrate fuel is being used at a greater rate than fat fuel sources. This threshold correlates with the threshold (or intensity of exercise) above which anaerobic mechanisms supplement aerobic mechanisms and is known as the "anaerobic threshold"(Connolly 2012).

1.4.8 ***Fuel utilisation: other factors***

In addition to intensity and duration other factors can affect the pattern of substrate utilisation during physical activity. These factors include training status, nutritional status and carbohydrate ingestion before and during activity (Gallen 2012). Endurance training has been shown to decrease carbohydrate utilisation and may enhance lipid use during mild to moderate exercise (Coggan, Kohrt et al. 1990). A carbohydrate rich diet may increase blood glucose utilisation during exercise in contrast to a low carbohydrate diet (Galbo, Holst et al. 1979). Carbohydrate ingestion just before or during exercise has been shown to suppress

hepatic glucose production and lipolysis (McConell, Fabris et al. 1994, Jeukendrup, Wagenmakers et al. 1999).

1.4.9 ***Glucose homeostasis during physical activity and exercise***

In the healthy individual blood glucose levels are normally maintained within a narrow physiological range during physical activity (Smith, Wilson et al. 2016). This is achieved in the face of increased energy demands by a complex neuroendocrine response starting at the onset of physical activity (Camacho, Galassetti et al. 2005, Coker and Kjaer 2005). As one of the main fuels for physical activity is carbohydrate, glucose utilisation by the working muscle must be equally matched by glucose production (predominately by the liver) or hypoglycaemia will occur (Gallen 2012). Indeed, hypoglycaemia can arise in healthy individuals when glucose production fails to match the rate of glucose utilisation, such as during prolonged activity (usually great than 3 hours) if additional carbohydrate is not consumed (Felig, Cherif et al. 1982).

During physical activity increased demand for glucose by skeletal muscle results in increased glucose uptake by the working muscle. This is mediated by an increase in the translocation of glucose transporter-4 (GLUT4) proteins to the plasma membrane (Thorell, Hirshman et al. 1999). Both insulin and muscle contraction increase GLUT4 expression and the affect is additive, indicating this is executed by two distinct mechanisms (Constable, Favier et al. 1988, Thorell, Hirshman et al. 1999).

Normal blood glucose levels are usually maintained during physical activity despite this increase in glucose uptake by the skeletal muscles. This is achieved through increased glucose production by the liver and by the mobilisation of other fuels that may serve as alternative energy sources (Coker and Kjaer 2005). This careful balance is orchestrated by complex neuroendocrine mechanisms as detailed below:

1.4.10 ***Hepatic glucose production during physical activity and exercise***

The liver plays a key role in maintaining blood glucose homeostasis by matching the increased demand for glucose by the skeletal muscle with an increased rate of hepatic glucose production (through augmented glycogenolysis and gluconeogenesis)(Wasserman 1995). In the early stages of moderate and high intensity activity, similar to fasting, increased glucose production is almost entirely attributable to accelerated hepatic glycogenolysis (Suh, Paik et al. 2007). As physical activity is prolonged and glycogen stores

are depleted, gluconeogenesis becomes increasingly important, generating glucose from glycerol, lactate and amino acids (Suh, Paik et al. 2007). In addition, the timing of activity in relation to food consumption influences the relative importance of gluconeogenesis in fuel provision during exercise. When physical activity occurs in fasting conditions increased hepatic glucose production is predominately from gluconeogenesis rather than glycogenolysis (Wahren, Efendic et al. 1977).

Hepatic regulation of glucose concentrations during exercise is mediated by both hormones and the autonomic nervous system. The typical hormone response to physical activity in a non-diabetic individual is characterised by a reduction in insulin levels (Hunter and Sukkar 1968) and an increase in glucagon, catecholamine (noradrenaline and adrenaline), cortisol and growth hormone levels (Coker and Kjaer 2005). The ratio of glucagon to insulin is the main regulator of glucose production during moderate exercise, with the counterregulatory hormones playing a supportive role (Wasserman, Lickley et al. 1984, Camacho, Galassetti et al. 2005). This decrease in insulin concentration occurs at the onset of activity and is a result of alpha- adrenergic stimulation of beta-pancreatic cells inhibiting insulin secretion (Hermansen, Pruett et al. 1970). The reduction in circulating insulin increases hepatic glucose production as insulin supresses both hepatic glycogenolysis and gluconeogenesis (Petersen, Laurent et al. 1998). In addition, a reduction in insulin levels facilitates an increase in supply of gluconeogenic precursors to the liver, as insulin suppresses lipolysis in adipose tissue (Edgerton, Ramnanan et al. 2009). Glucagon plays a major role in increasing glycogenolysis and to a lesser extent increases gluconeogenesis (Wasserman, Spalding et al. 1989).

1.4.11 ***Counterregulatory hormone production***

Both Glucagon and catecholamine secretion increase with physical activity intensity and duration (Adolfsson, Nilsson et al. 2012). During intense activity catecholamines increase glucose production by the liver (Sigal, Fisher et al. 1996, Kreisman, Halter et al. 2003). Increased glucose production is through both glycogenolysis and gluconeogenesis (Dufour, Lebon et al. 2009). Greater catecholamine secretion at higher activity intensities may be associated with hyperglycaemia if hepatic glucose production exceeds glucose utilisation. In healthy individuals, this is offset with a rise in insulin concentration above baseline in early recovery from high intensity interval training (Fahey, Paramalingam et al. 2012). However, the role of catecholamines in increasing glucose production by the liver during moderate

intensity exercise remains unclear. Studies investigating hepatic glucose output in adrenalectomised individuals (Howlett, Galbo et al. 1999), and in healthy individuals under alpha and beta blockade (Simonson, Koivisto et al. 1984) do not suggest that adrenergic mechanisms play an important role during moderate exercise. Furthermore, adrenaline has been shown to reduce glucose utilisation by inhibiting insulin-stimulated glucose uptake by skeletal muscle (Howlett, Galbo et al. 1999).

During short- term physical activity, growth hormone (secreted from the anterior pituitary gland) and cortisol (secreted from the adrenal cortex) appear to play only a minor role in glucose homeostasis (Gallen 2012). However, during prolonged activity growth hormone and cortisol increase lipolysis, generating a supply of free fatty acids for oxidation by the muscles and glycerol for hepatic gluconeogenesis (Hartley 1975, Bak, Moller et al. 1991). It should be noted that during prolonged physcial acivity when reliance on lipid as a primary fuel source is maximal, the body still has a requirement for carbohydrate provision and if this is not met either by gluconeogenesis or oral ingestion then hypoglycaemia will ensue (Dennis, Noakes et al. 1997).

1.5 Type 1 Diabetes

1.5.1 ***Prevalence and incidence***

Type 1 Diabetes (T1D) is a metabolic disorder characterised by an absolute deficiency of insulin secretion (Craig, Jefferies et al. 2014) . T1D accounts for approximately 10-15% of all diagnosed cases of diabetes, affecting over 16 million individuals worldwide (Onkamo, Vaananen et al. 1999) and accounts for over 90% of childhood and adolescent diabetes in most western countries. The incidence of Type 1 Diabetes is increasing in many countries; globally the overall annual increase is estimated at around 3% (Patterson, Guariguata et al. 2014). The global distribution of T1D demonstrates large area to area variation, both within and between countries and between different ethnic populations (Craig, Jefferies et al. 2014). For instance, Finland has the highest incidence worldwide at 57.6 per 100,000 population aged under 15 years, in contrast to countries such as China and India with a lower incidence of around of 0.1 per 100,000 (Patterson, Guariguata et al. 2014). This may reflect both different distributions of at risk genes and different distributions of environmental exposures as well as methodological challenges in epidemiological studies (Patterson, Guariguata et al. 2014). In Australia, the incidence of type 1 diabetes among 0-14 year olds is relatively high at 21.6 per 1000,000 (Catanzariti, Faulks et al. 2009).

1.5.2 ***Pathogenesis of Type 1 Diabetes***

TID is a permanent autoimmune disease caused by chronic immune- mediated destruction of pancreatic beta cells, resulting in a partial or more commonly an absolute insulin deficiency (Craig, Jefferies et al. 2014). The exact cause of T1D remains to be elucidated, although it is thought to result from a complex interaction between genetic and environmental risk factors.

1.5.3 ***Genetic component***

T1D is a polygenic disorder, with many different genes contributing to its development. Genome –wide association studies have identified more than 50 genetic regions that affect the risk of developing T1D (Storling and Pociot 2017). The major histocompatibility complex region encoding the Human Leukocyte Antigen on chromosome 6p21 contributes about 50% of the genetic risk of T1D (Pociot and Lernmark 2016). The remaining genes have small individual effects on disease risk and therefore cannot be used in isolation to predict disease development.

1.5.4 ***Environmental component***

Environmental triggers are implicated in the development of T1D. This is supported by evidence from identical twin studies that report that if one twin has T1D the second twin will only develop the disease in 30-50% of cases (Hemminki, Li et al. 2009, Nistico, Iafusco et al. 2012). Exact environmental triggers are yet to be confirmed. Factors of interest include: microbial and viral infections, dietary components, gut microbiome and vitamin D levels (Hershey, Perantie et al. 2005, Butalia, Kaplan et al. 2016).

1.5.5 ***Insulin deficiency***

T1D is characterised by an absolute insulin deficiency, thus individuals with T1D are completely dependent on exogenous delivery of insulin for survival. In a healthy individual, insulin is produced by the beta cells of the pancreas. Insulin is an anabolic hormone and plays an essential role in the regulation of carbohydrate, fat and protein metabolism, promoting the uptake of glucose from the blood stream into liver, fat and skeletal muscle cells. Insulin stimulates glycogen synthesis in the liver and muscle, inhibits glycogenolysis in the liver, and stimulates fat and protein synthesis (Rizza, Mandarino et al. 1981).

1.5.6 ***Symptoms and signs of Type 1 Diabetes***

In individuals with T1D when approximately 90% of pancreatic beta cells are destroyed, a lack of insulin will result in hyperglycaemia, and the individual will present with clinical signs of diabetes (Craig, Jefferies et al. 2014). When hyperglycaemia exceeds the renal threshold, glucose spills into the urine leading to an osmotic diuresis and polyuria which then drives a secondary polydipsia. Insulin deficiency results in a "catabolic state" causing lipolysis and the production of ketone bodies (3-beta- hydroxybutyrate and acetoacetate). The resultant high levels of ketones in the blood stream lower the pH of the blood and can result in life threatening coma due to diabetic ketoacidosis (DKA) (Alberti and Zimmet 1998).

1.5.7 ***Management of Type 1 Diabetes***

The management of T1D has been described as having three essential components- insulin, diet and exercise (Robertson, Riddell et al. 2014).

1.5.8 ***Insulin Treatment***

Since the discovery of insulin in 1922 by Banting and his colleagues, it has been possible to deliver life-preserving exogenous insulin to replace the lack of endogenous insulin production in individuals with T1D. Insulin treatment must be started as soon as possible after diagnosis to prevent metabolic decompensation and DKA (Danne, Bangstad et al. 2014). Insulin regimens aim to meet background (or basal) insulin requirements 24 hours a day with additional insulin to counteract glycaemic excursions associated with dietary intake.

1.5.9 ***Regular (soluble) insulin***

Bovine and porcine insulin extracts used in the past have been superseded by synthetic insulins. Biosynthetic human insulin (known as regular/soluble/ "short-acting" insulin) is manufactured using recombinant DNA technology and has an identical structure to human insulin.

1.5.10 ***Intermediate-acting insulin***

Complexing human insulin with protamine (known as NPH or isophane insulin) or zinc (lente insulin) results in results in intermediate insulins that have a longer duration of action than human insulin. Production of zinc-containing insulins has been stopped (Danne, Bangstad et al. 2014). The profile of NPH insulin make it suitable for twice daily regimens, however these regimens have little flexibility and often require dietary restrictions (Danne, Bangstad et al. 2014).

1.5.11 ***Insulin analogues***

Clinical limitations of older insulins including regular and intermediate forms have led to the development of current insulin analogues. Insulin analogues have a modified chemical structure compared to human insulin. Modifications enable the insulin to act faster than regular insulin in rapid-acting analogues, or slower than regular insulin in basal or long-acting analogues. Despite modern advances in insulin formulations unequivocal evidence for the benefit of newer insulins (analogues) remains to be established (Danne, Bangstad et al. 2014).

1.5.12 ***Rapid acting insulin analogues***

Rapid-acting analogues include aspart, glulisine and lispro, all have a similar onset and duration of action despite different chemical structures (Philotheou, Arslanian et al. 2011). Rapid acting analogues have been associated with a reduction in hypoglycaemia but not with a clear benefit in glycaemic control when compared to regular (soluble) insulins (Tupola, Komulainen et al. 2001, Holcombe, Zalani et al. 2002, Siebenhofer, Plank et al. 2006). When used in insulin pumps rapid-acting analogue insulins result in a small reduction in HbA1c compared with regular insulins (Colquitt, Royle et al. 2003). Fast acting insulin aspart, is a new rapid-acting insulin analogue with a faster onset of action than aspart insulin (Hovelmann, Heise et al. 2017). Fast acting insulin aspart, when used as part of an MDI regimen has been associated with a small reduction in HbA1c compared to insulin aspart, in adults with T1D (Mathieu, Bode et al. 2018).

1.5.13 ***Basal insulin analogues***

The basal insulin analogues such as glargine, detemir and degludec differ in structure, mode and duration of action. Basal insulin analogues have a more predictable profile with less within and between subject variability than NPH insulin (Lepore, Pampanelli et al. 2000). Basal analogues compared to NPH are associated with a reduction in hypoglycaemia; however, benefits in long-term glycaemic control remain controversial (Schober, Schoenle et al. 2002, Chase, Dixon et al. 2003, Vague, Selam et al. 2003, Porcellati, Rossetti et al. 2004, Robertson, Schoenle et al. 2007).

1.5.14 ***Insulin regimen***

Over the last decade the most notable trend in diabetes management has been a shift from twice daily regimens to intensive insulin treatment with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) (Danne, Bangstad et al. 2014). This paradigm

shift has been largely driven by conclusive evidence from the Diabetes Control and Complications Trial (DCCT) demonstrating that an improvement in long-term glycaemic control achieved with intensive management compared with conventional treatment (one or two injections per day) delays the onset and slows progression of diabetic complications (DCCT 1993, DCCT 1994). Subsequently intensive management has become the gold standard treatment for T1D in both adult and paediatric settings.

1.5.15 ***CSII versus MDI***

The MDI approach comprises injections of rapid-acting insulin analogues prior to meals and an injection of a long-acting (basal analogue) insulin usually at bedtime. CSII is achieved using an insulin pump consisting of a small portable external device containing rapid acting insulin connected by an infusion line to a subcutaneous cannula. Rapid acting insulin is infused at a basal rate 24 hours a day, with patient-activated boluses of insulin administered prior to the ingestion of food (Hanas and Adolfsson 2006, Pickup 2012). Given that basal rates changes can be programmed throughout the day, CSII has been described as a providing a more physiological pattern of insulin compared to MDI regimens.

As only short-acting insulin is used in CSII, there is a risk of hyperglycaemia and ketosis developing if insulin delivery is interrupted (Zisser 2008). Reassuringly, studies comparing MDI and CSII have not demonstrated an increase risk in DKA associated with pump use (Hanas and Adolfsson 2006).

CSII potentially allows more precise and flexible insulin dosing, with the opportunity to use up to hourly basal rates, give multiple boluses without extra injections and to utilise different ways of delivering the bolus dose. Furthermore, CSII has been shown to be safe and effective in all age groups (Ahern, Boland et al. 2002).

Despite these features, the impact of CSII on glycaemic control when compared to MDI treatment is still unclear. The majority of studies investigating CSII compare this means of insulin delivery to regimens that use NPH as the long acting insulin and report an improvement in hypoglycaemia and HbA1c (Boland, Grey et al. 1999, Pickup, Mattock et al. 2002). A study comparing CSII to MDI where glargine (a basal analogue) is used as the long acting insulin supports these findings (Bolli, Kerr et al. 2009). In contrast others have found no difference in glycaemic control between glargine based-MDI therapy and CSII, although CSII was associated with improved patient satisfaction (Skogsberg, Fors et al. 2008). A meta-

analysis of six paediatric randomised controlled trials including 165 patients demonstrated a 2.6mmol/mol (0.24% reduction) in HbA1c with CSII compared to MDI (where NPH was most commonly used as the basal insulin)(Pankowska, Blazik et al. 2009).

1.5.16 ***Continuous glucose monitoring***

Advances in technology are rapidly changing the landscape of diabetes management. Continuous glucose monitoring (CGM) and Flash Glucose Monitoring (FGM) consist of a subcutaneously inserted sensor that measures glucose levels in the interstitial fluid providing both a short and long-term view of glucose levels and trends. These devices are becoming increasingly accurate and user-friendly (Fonseca, Grunberger et al. 2016). CGM use has been shown to facilitate a modest improvement in glycaemic control in adults (JDRF 2010), adolescents and children (Lewis, McCrone et al. 2017).

1.5.17 ***Sensor augmented pump therapy: threshold suspend systems***

Sensor-augmented pump therapy integrates CSII with CGM. It consists of an insulin pump that uses a mathematical algorithm to automatically alter insulin delivery in response to sensor glucose levels. A low glucose suspend feature (where basal insulin is ceased for up to 2 hours when sensor glucose levels fall below a pre-set threshold) is associated with reduced rates of hypoglycaemia in individuals with T1D (Bergenstal, Klonoff et al. 2013, Ly, Nicholas et al. 2013). Furthermore, use of a predictive low glucose suspend feature (where basal insulin is stopped automatically if sensor glucose is predicted to fall below a threshold and re-starts at a predetermined level) has been shown to reduce hypoglycaemia in adults (Maahs, Calhoun et al. 2014) and children (Battelino, Nimri et al. 2017) with T1D.

1.5.18 ***Sensor augmented pump therapy: fully automated systems***

Research is in progress to develop a fully automated (closed loop) insulin delivery system to improve glycaemic control whilst reducing the burden of hypoglycaemia and diabetes self-care (Thabit and Hovorka 2016). Closed loop systems expand on the concept of threshold suspend, by using a control algorithm that continually increases or decreases insulin delivery in response to sensor glucose levels. Existing systems are described as “hybrid” as the delivery of basal insulin is fully automated but patients are still required to administer prandial insulin doses. Systems under investigation include dual hormone (insulin and glucagon) and single hormone (insulin only) pumps. Both systems have been found to be safe and effective in clinic (Haidar, Rabasa-Lhoret et al. 2016), outpatient/camp (Haidar, Messier et al. 2017) (Ly, Buckingham et al. 2016) and home settings (Thabit, Tauschmann et

al. 2015, Tauschmann, Allen et al. 2016, Garg, Weinzimer et al. 2017) in children, adolescents and adults with T1D. Further large multicentre randomised controlled trials are under way. The first commercial hybrid closed loop system was released in 2017 in the USA.

1.5.19 ***Diet***

In view of the impact of food on glycaemic control, nutritional management is fundamental to diabetes care and education. Dietary recommendations for children with diabetes are based on healthy eating recommendations suitable for all children and adults and therefore for the whole family (Smart, Annan et al. 2014). Goals of nutritional management in children should include maintenance of ideal body weight and optimal growth, as well as helping to prevent acute and chronic diabetes complications (Smart, Annan et al. 2014).

1.5.20 ***Carbohydrate counting***

Matching of insulin dose to carbohydrate intake to minimise postprandial glycaemic excursions has become a key component of diabetes management. This involves carbohydrate counting, a method of carbohydrate quantification that focuses on carbohydrate as a principal dietary component affecting postprandial glucose levels. Carbohydrate counting allows for flexibility of food choice and may improve glycaemic control (DAFNE 2003), although randomised controlled trials in children are lacking (Kawamura 2007).

1.5.21 ***Glycaemic control and risk of long-term complications***

T1D is associated with long-term microvascular complications including retinopathy, nephropathy, neuropathy and macrovascular disease including heart disease and stroke (Donaghue, Wadwa et al. 2014). The Diabetes Control and Complications Trial (DCCT), a multicentre randomised controlled clinical trial demonstrated that intensive diabetes and improved glycaemic control conferred a significant reduction in risk of microvascular complications compared with conventional treatment (DCCT 1993). Further follow-up of this study cohort in the Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that after 4 years there was no significant difference in glycaemic control between the former intensive and conventional groups (White, Sun et al. 2010). However, despite this, the positive effect in complication risk reduction was sustained in the former intensive treatment group (White, Cleary et al. 2001, Nathan, Cleary et al. 2005) This phenomenon has been described as a “memory effect” of improved glycaemic control (Donaghue, Wadwa et

al. 2014). This evidence underpins current clinical practice of striving to achieve optimal glycaemic control for each individual.

1.5.22 ***Monitoring glycaemic control***

Monitoring of glycaemic control includes immediate measures of glucose levels by self-monitoring of blood glucose (SMBG) or using continuous glucose monitoring devices (CGM), and periodic monitoring of overall glycaemia using glycated haemoglobin (HbA1c) (Rewers, Pillay et al. 2014). Glucose becomes irreversibly attached to the molecule of haemoglobin during the approximately 120-day life cycle of the circulating red blood cell forming glycated haemoglobin (Rewers, Pihoker et al. 2009). HbA1c reflects levels of glycaemia over the preceding 4-12 weeks, weighted toward the most recent 4 weeks (Tahara and Shima 1995). Elevated HbA1C predicts long-term microvascular and macrovascular complications (DCCT 1993). International guidelines recommend a target of <7.5% (58mmol/L) for all patients with T1D younger than 18 years of age (Rewers, Pillay et al. 2014) . More recently National Institute of Clinical Excellence (NICE) guidelines recommend that an HbA1C target level of 6.5% (48mmol/L) or lower is ideal in children or young people with T1D to minimise the risk of long-term complications (Beckles, Edge et al. 2016). More recently it has been suggested that CGM measures of glycaemic control will become more useful than HbA1c as average glucose levels, glycaemic variability and the proportion of time spent hypoglycaemic and hyperglycaemic can be accurately assessed (Danne, Nimri et al. 2017).

1.6 Hypoglycaemia in Type 1 Diabetes

1.6.1 ***Mechanisms underlying risk of hypoglycaemia in Type 1 Diabetes***

Insulin treated individuals with diabetes are at increased risk of hypoglycaemia and the mechanisms underlying this increased risk are multifactorial. The principle factor is the absence of natural feedback mechanisms, resulting in a failure to decrease insulin levels in response to falling blood glucose levels (Cryer 2008). This is because in the absence of endogenous insulin secretion, circulating insulin levels are principally a function of the absorption and clearance of injected insulin (Cryer 2013). Secondly, in individuals with T1D, glucagon secretion is impaired in response to hypoglycaemia (Cryer 2013). Glucagon is essential for preventing hypoglycaemia as it stimulates hepatic glucose production (through glycogenolysis and gluconeogenesis) and inhibits conversion of glucose to hepatic glycogen. This loss in the physiological glucagon response is related to the loss of insulin secretion and develops early in disease progression (Cryer 2013) (Cryer 2011). Evidence suggests that it is

the failure of a reduction in beta cell insulin secretion in response to hypoglycaemia that causes the lack of alpha cell glucagon secretion (Cryer 2011). Thirdly, in T1D, the normal increase in adrenaline levels in response to hypoglycaemia is attenuated, with a lower blood glucose threshold triggering adrenaline secretion (Cryer 2013). This combination of compromised defences to hypoglycaemia results in an increased risk of hypoglycaemia in the T1D population.

1.6.2 ***Definition of hypoglycaemia***

There is no internationally agreed numerical definition of hypoglycaemia in T1D. Guidelines recommend that hypoglycaemia is best defined as a fall of the blood glucose level that exposes the patient to potential harm (Ly, Maahs et al. 2014). In clinical practice, because of the risk of blood glucose levels falling further, a glucose level of 3.9mmol/L is used as a threshold value for initiating treatment for hypoglycaemia in T1D (Ly, Maahs et al. 2014). In the adult population hypoglycaemia is defined as severe when a hypoglycaemia event requires assistance from another person for treatment or resuscitative actions (Seaquist, Anderson et al. 2013). This includes events of hypoglycaemic seizures and coma. As children are often dependent on their caregiver to treat hypoglycaemia, the definition of severe hypoglycaemia is usually restricted to that resulting in seizure or convulsion (Ly, Maahs et al. 2014). Recently, there have been efforts to standardise hypoglycaemia definitions to allow consistent analyses over time and between cohorts and trials. Three levels of hypoglycaemia have been accepted by consensus: hypoglycaemia alert (blood glucose <3.9 mmol/l, significant biochemical hypoglycaemia (blood glucose <3.0 mmol/ l) and severe hypoglycaemia (a clinical event in which the person with diabetes requires external help because of hypoglycaemia induced cognitive dysfunction (IHSG 2017).

1.6.3 ***Incidence of hypoglycaemia in individuals with Type 1 Diabetes***

The incidence of mild or moderate hypoglycaemia is unknown. Clinical practice tells us that these events occur frequently in people with insulin treated T1D and that these events may be unreported or unrecognised. The incidence of severe hypoglycaemia has been reported in multiple studies; however, variations in definitions make studies difficult to compare (Ly, Maahs et al. 2014). The DCCT trial reported the incidence of coma or seizure was 27/100 patient-years in the intensively treated and 10/100 patient years in those conventionally treated, among the adolescents who participated in the study (DCCT 1993). More recent data suggests rates of severe hypoglycaemia may be decreasing (O'Connell, Cooper et al.

2011, Cengiz, Xing et al. 2013) and that the previously described inverse relationship between HbA1c and severe hypoglycaemia rates may no longer be the case (Haynes, Hermann et al. 2016, Gimenez, Tannen et al. 2018). It is postulated that this may be a consequence of changes in clinical practice including contemporary insulin regimens (Ly, Maahs et al. 2014). In support of this, evidence demonstrates that intensive glycaemic control with pump therapy can be achieved without increasing the risk of hypoglycaemia (Ahern, Boland et al. 2002).

1.6.4 ***Symptoms and signs of hypoglycaemia***

In a well individual, as the blood glucose levels fall, the symptoms and signs of hypoglycaemia occur in a hierarchical fashion (Mitrakou, Ryan et al. 1991). The initial symptoms (occurring at a blood glucose level of approximately 3.2-3.6mmol/L) result from activation of the autonomic nervous system and include shakiness, weakness, hunger, and sweating. As the blood glucose level falls, further symptoms result from glucose deprivation in the brain (neuroglycopenia) and include headache/difficulty concentrating, blurred vision, difficulty hearing, slurred speech, confusion, seizure, loss of consciousness and death (Ly, Maahs et al. 2014). In young children, behavioural changes such as irritability, agitation, quietness and tantrums may be the principal feature of hypoglycaemia, resulting from a combination of neuroglycopenic and autonomic responses (McCrimmon, Gold et al. 1995).

1.6.5 ***Impaired counterregulatory response in individuals with Type 1 Diabetes***

In an individual with T1D the counterregulatory response to hypoglycaemia is impaired with an inability to reduce exogenously administered insulin and a reduced or absent glucagon response (Cryer 2013). In this setting, the adrenomedullary secretion of adrenaline is of paramount importance as other early defences are compromised. However, as already described this very response may be attenuated in individuals with T1D (Cryer 2013). Consequently, the glucose threshold at which physiological responses occur and when symptoms of hypoglycaemia are perceived may be altered. Chronic hyperglycaemia may result in symptoms occurring at higher blood glucose levels. Repeated hypoglycaemia may cause symptoms to occur at lower blood glucose levels (Amiel, Sherwin et al. 1988) and this can result in impaired hypoglycaemia awareness, defined as the inability to perceive the onset of hypoglycaemia (Ly, Maahs et al. 2014). This is typically described when neuroglycopenic symptoms occur before the appearance of autonomic warning symptoms

Many factors can further blunt the already compromised counterregulatory response to hypoglycaemia in a person with T1D and thereby increase the risk of subsequent hypoglycaemia. A key factor is that hypoglycaemia attenuates defences against subsequent hypoglycaemia and this can result in a vicious cycle of recurrent low blood glucose levels (Dagogo-Jack, Craft et al. 1993). Other factors known to impair the counterregulatory response to hypoglycaemia include sleep and prior physical activity (Jones, Porter et al. 1998, Sandoval, Guy et al. 2004, Cryer 2013).

1.6.6 ***Short term consequences of hypoglycaemia***

Hypoglycaemia is associated with significant morbidity and mortality in people with T1D. In the short-term symptoms of hypoglycaemia can be unpleasant, embarrassing or potentially dangerous (Ly, Maahs et al. 2014). Severe prolonged hypoglycaemia can result in coma, seizures (Buckingham, Wilson et al. 2008) or even death (Tanenberg, Newton et al. 2010).

1.6.7 ***Long term consequences of hypoglycaemia***

Long term effects of hypoglycaemia, in particular in the context of a child's developing brain, remain controversial (Ly, Maahs et al. 2014). Several studies report that repeated severe hypoglycaemia can adversely affect cognitive function (Ryan, Vega et al. 1985, Wysocki, Harris et al. 2003). Furthermore, brain abnormalities, including mesial temporal sclerosis, have been described in the context of repeated episodes of hypoglycaemic seizures occurring in young children with early onset T1D (Ho, Weller et al. 2008). In contrast, other studies do not show an association between severe hypoglycaemia and impaired cognitive function. A case-control prospective follow up study of 33 young adults report no difference in intellectual ability, memory or emotional difficulties compared with matched controls (Ly, Anderson et al. 2011).

While the evidence is conflicting regarding hypoglycaemia and long-term effects on brain function, it is it clear that the risk of hypoglycaemia causes significant anxiety for people with T1D and their families. This fear of hypoglycaemia can act as a barrier to achieving optimal glycaemic control (Davis, Keating et al. 1998).

1.7 Physical Activity, Exercise and Type 1 Diabetes

1.7.1 ***Benefits of physical activity and exercise***

Exercise, was described by Joslin in the 1950's as the third essential component in diabetes management alongside diet and insulin (Robertson, Riddell et al. 2014). Physical exercise has

numerous well-established health benefits for individuals with T1D including improvement in glycaemic control (Herbst, Bachran et al. 2006, MacMillan, Kirk et al. 2014), increased cardiovascular function (Fuchsjager-Mayrl, Pleiner et al. 2002), and blood lipid profiles (Laaksonen, Atalay et al. 2000) as well as enhanced psychological wellbeing (Penedo and Dahn 2005, Martinez, Frazer et al. 2016).

1.7.2 ***Barriers to physical activity and exercise***

Despite these benefits, many individuals with T1D find participating in physical activity challenging (Riddell, Gallen et al. 2017). These challenges can act as barriers to exercise, preventing individuals from engaging in a physically active lifestyle (Dube, Valois et al. 2006). As a consequence, individuals with TID are on average less physically active and have lower fitness levels than non-diabetic individuals (Komatsu, Gabbay et al. 2005, Valerio, Spagnuolo et al. 2007, Williams, Guelfi et al. 2011).

Barriers to exercise include the difficulty of maintaining a stable blood glucose level during and after exercise (Lascar, Kennedy et al. 2014). This may involve hypoglycaemia, hyperglycaemia and/or the frustration of unpredictable blood glucose levels. In addition to overcoming the challenges of the effect of exercise on blood glucose levels, physically active young people with T1D may find that the blood glucose level itself impacts on their exercise performance (Kelly, Hamilton et al. 2010).

Many psychosocial factors may act as barriers to exercise. It is well recognised that the fear of both immediate and delayed hypoglycaemia can prevent individuals being physically active (Brazeau, Mircescu et al. 2012). The need for extra support from caregivers, teachers and coaches may also act as a barrier (Jabbour, Henderson et al. 2016). Inadequate knowledge around exercise management can be another obstacle in the course of engaging in an active lifestyle (Ryninks, Sutton et al. 2015). Furthermore, challenges not specific to individuals with T1D such as motivation, time, and resources may prevent young people from exercising (Lascar, Kennedy et al. 2014).

Barriers to exercise may be overcome with appropriate education and training (Colberg, Sigal et al. 2016, Riddell, Gallen et al. 2017). It is therefore of paramount importance that patients and health care professionals are empowered with knowledge to enable young people with T1D to engage in a physically active lifestyle.

1.8 Exercise Physiology in Individuals with Type 1 Diabetes

1.8.1 ***Physcial activity and exercise are risk factors for hypoglycaemia***

For individuals with insulin treated diabetes physical activity is associated with an increased risk of hypoglycaemia (Camacho, Galassetti et al. 2005). In the healthy individual blood glucose levels are normally maintained within a narrow physiological range during exercise regardless of the intensity or duration of the activity. As previously described, this is achieved despite increased energy demands by a complex neuroendocrine response. During sustained moderate intensity aerobic activity this is characterised by a decrease in insulin levels and an increase in glucagon levels at the onset of activity (Camacho, Galassetti et al. 2005) (Hunter and Sukkar 1968, Coker and Kjaer 2005).

1.8.2 ***Hypoglycaemia occurring during and shortly after physical activity and exercise***

An individual with T1D is at risk of hypoglycaemia during and after exercise. Exogenously administered insulin is not under regulation of the body's homeostatic mechanisms and insulin levels fail to fall at the onset of exercise, resulting in a relative hyperinsulinaemic state (Riddell and Perkins 2006, Chu, Hamilton et al. 2011). Therefore, during sustained aerobic exercise, blood glucose levels will fall in most individuals with T1D, unless additional carbohydrates are ingested (Tansey, Tsalikian et al. 2006). Moreover, contrary to normal physiological responses, it has been described that insulin concentrations may rise at the onset of exercise in individuals with T1D (Riddell, Gallen et al. 2017). This is thought be related to increased blood flow to the subcutaneous tissues during exercise (Frayn and Karpe 2014).

Relatively high insulin levels during exercise inhibit hepatic glucose production as insulin suppresses glycogenolysis and gluconeogenesis (Hunter and Sukkar 1968, Edgerton, Ramnanan et al. 2009). In addition, insulin suppresses lipolysis, thereby reducing both the availability of free fatty acids for oxidation by the muscles and reducing the supply of gluconeogenic precursors to the liver (Edgerton, Ramnanan et al. 2009). Insulin also increases glucose uptake by the skeletal muscles during and after physical activity. This is mediated by an increase in the translocation of glucose transpoter-4 (GLUT4) proteins to the plasma membrane (Thorell, Hirshman et al. 1999).

In summary, the failure to reduce insulin levels during and shortly after physical activity results in a mismatch between glucose production by the liver and increased glucose utilisation by the skeletal muscle, resulting in exercise mediated hypoglycaemia (Chu, Hamilton et al. 2011).

1.8.3 ***Late onset post exercise hypoglycaemia***

This risk of hypoglycaemia related to physical activity and exercise may be immediate, that is during or shortly after the activity or delayed by several hours after the activity. A study of 50 adolescents aged 11-17 years with T1D, reported twice as many hypoglycaemia events on the night following an exercise day compared with the night after a sedentary day (Tsalikian, Mauras et al. 2005).

Late onset post exercise hypoglycaemia (LOPEH) is multifactorial in origin. An important factor is increased glucose uptake by skeletal muscles, resulting in increased insulin sensitivity during and after exercise (MacDonald 1987, Peirce 1999). Increased glucose uptake by the skeletal muscles is mediated by both insulin dependent and insulin independent mechanisms. Both insulin and muscle contraction increase the translocation of glucose transpoter-4 (GLUT4) in skeletal muscle and these affects are additive (Thorell, Hirshman et al. 1999). Increased insulin sensitivity after exercise is related to replenishing muscle and liver glycogen stores after exercise. A study in 9 adolescents with T1D showed that glucose requirements to maintain euglycaemia after afternoon exercise with T1D increased in a biphasic manner: during and shortly after exercise and again from 7-11 hours after exercise (McMahon, Ferreira et al. 2007)(see Figure 2). In contrast, when exercise was performed earlier at midday, insulin sensitivity was increased throughout an 11 hour recovery period in adolescents with T1D, without a clear biphasic pattern in sensitivity(Davey, Howe et al. 2013).

Another factor to consider is that counter regulatory responses to hypoglycaemia may be impaired in T1D and this impairment can be exacerbated post activity (MacDonald 1987). Exercise in children often occurs in the afternoon, after school. This adds a further element of risk to this post exercise milieu, as late onset hypoglycaemia may occur overnight when counter regulatory responses to hypoglycaemia are impaired during sleep (Jones, Porter et al. 1998).

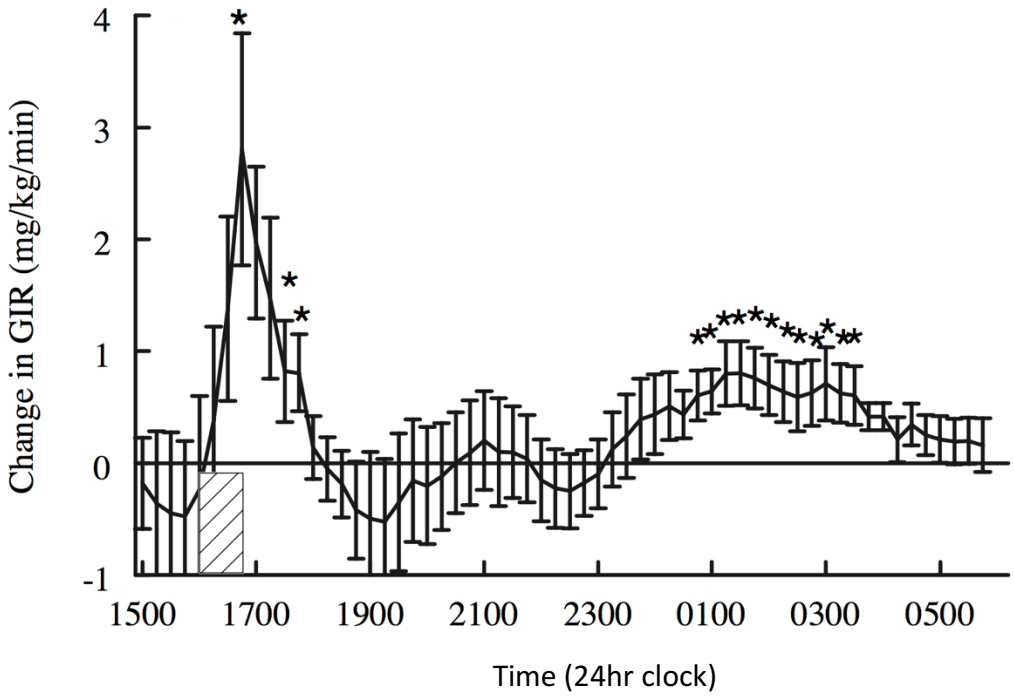

Figure 6: Difference in glucose infusion rate (GIR) between exercise and rest studies (mg/kg min) to maintain euglycaemia after afternoon exercise in adolescents with T1D. Hatched box, Exercise period, *P 0.05. (McMahon, Ferreira et al. 2007)

1.8.4 ***Exercise type and glycaemic responses***

In individuals with T1D the blood glucose response to exercise depends largely on the type of exercise performed, the duration of the activity and the amount of circulating insulin on board at the time of exercise (Riddell, Gallen et al. 2017).

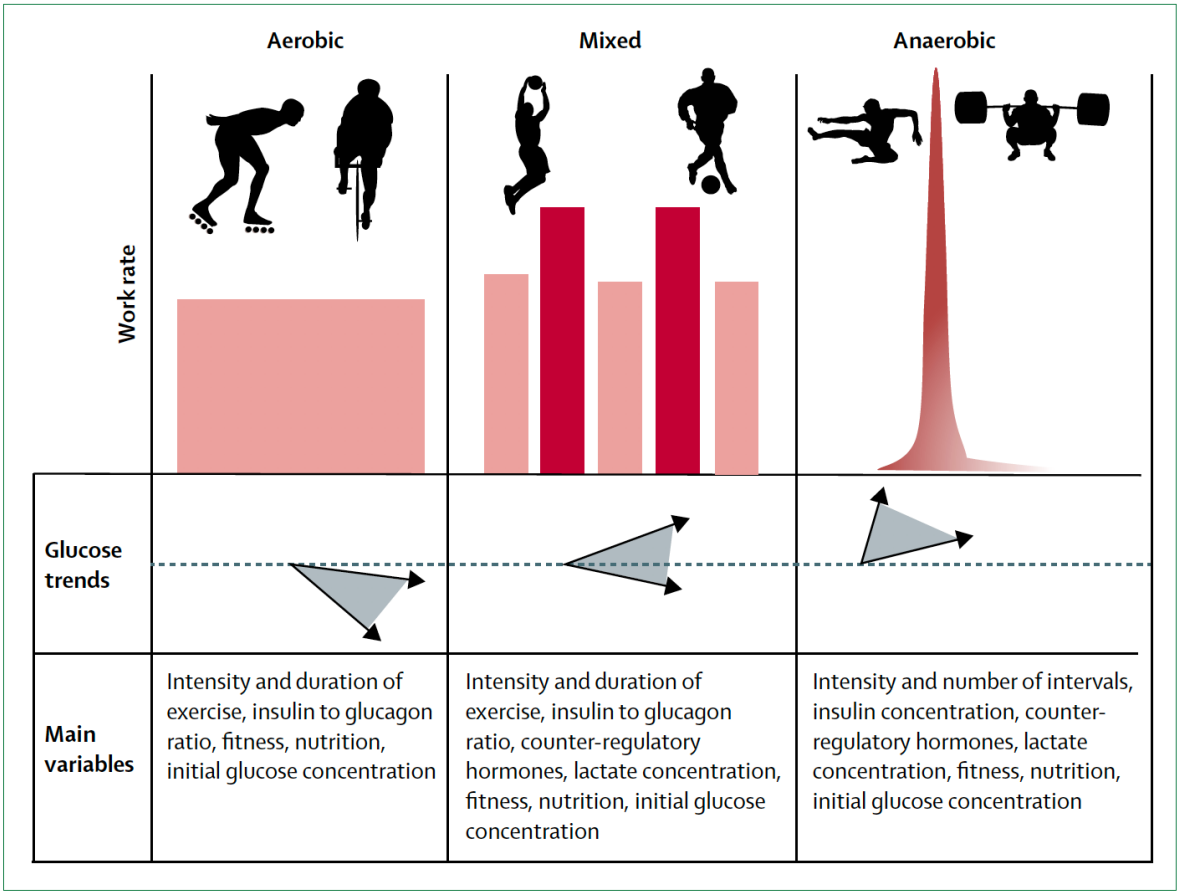

Figure 7: Variability in blood glucose response to different forms of exercise in people with type 1 diabetes (Riddell, Gallen et al. 2017)

1.8.5 ***Continuous moderate intensity exercise***

Moderate-Intensity exercise generally involves continuous aerobic activity between 40 and 59% of maximum oxygen uptake (VO_2 max) or 55-69% of maximal heart rate (Colberg, Sigal et al. 2016). Sustained moderate intensity aerobic exercise carries the greatest acute risk of hypoglycaemia for the reasons described above. Most individuals with T1D will develop hypoglycaemia within about 45 minutes of starting aerobic exercise if no additional carbohydrate is consumed (Tansey, Tsalikian et al. 2006, Garcia-Garcia, Kumareswaran et al. 2015). In individuals with T1D the pattern of substrate utilisation during exercise is largely similar to that described in healthy individuals and changes with exercise duration and intensity (Raguso, Coggan et al. 1995, Riddell, Bar-Or et al. 2000). One subtle alteration is that individuals with T1D who are under-insulinised have higher rates of lipid oxidation during exercise compared to controls (Wahren, Hagenfeldt et al. 1975).

1.8.6 ***High intensity exercise***

In contrast to continuous moderate intensity aerobic exercise, short but intense anaerobic activities such as sprinting typically result in a rise in blood glucose levels (Marliss and Vranic 2002). Similarly, resistance exercise (weight lifting) is associated with a more stable blood glucose profile than aerobic exercise and a lower risk of hypoglycaemia (Yardley, Kenny et al. 2012). Increased glucose levels in response to anaerobic exercise are thought to be mediated by a rise in catecholamine levels resulting in increased hepatic glucose production, and an increase in metabolites including lactate (Bally, Zueger et al. 2016) and glucose 6-phosphate (Fahey, Paramalingam et al. 2012) that may reduce glucose disposal.

The underlying mechanisms by which metabolites may affect glucose disposal in skeletal muscle remain unclear. It is thought that lactate may act by being a glucose competing substrate or by inducing peripheral insulin resistance. Increased blood lactate levels have been shown to be associated with increased lactate utilisation and decreased glucose oxidation in lactate clamp studies in healthy individuals performing moderate intensity exercise. Furthermore, animal studies report reduced glucose uptake by skeletal muscle when lactate levels are elevated (Vettor, Lombardi et al. 1997, Lombardi, Fabris et al. 1999, Choi, Kim et al. 2002). Glucose 6-phosphate has been postulated to play a role in the glycaemic excursion associated with a short sprint (Fahey, Paramalingam et al. 2012) . It is a metabolite associated with rapid glycogen breakdown and high levels can inhibit muscle glucose use via inhibition of hexokinase (Wasserman 1995).

This rise in glycaemia following high intensity exercise is also seen in non-diabetic individuals following intense anaerobic activity, but is brief and transient in nature (Marliss, Simantirakis et al. 1991). In the individual with T1D this glycaemic excursion is exaggerated because of a failed increase in insulin in response to the rise in glucose (Marliss and Vranic 2002).

1.9 Exercise Management in Type 1 Diabetes: The Classical Approach

For individuals with T1D maintaining stable blood glucose levels during and after exercise continues to be a challenge. This can act as a barrier, preventing people with T1D engaging in a physically active lifestyle despite the well-established benefits of exercise. Classical exercise management strategies involve monitoring blood glucose levels and tailoring carbohydrate intake and insulin adjustment to the type and duration of physical activity.

1.9.1 ***Patient goal***

The first step in formulating a patient's exercise management plan involves identifying the patients exercise goal, as this may influence subsequent management decisions. For example, if the goal is facilitating weight loss, it would be most appropriate to use an insulin sparing strategy rather than a carbohydrate supplementation approach to avoid hypoglycaemia (Riddell, Gallen et al. 2017). In contrast if the primary goal is exercise performance then nutritional guidance specific to the activity is required and insulin adjustment to match this additional carbohydrate intake should be considered (Riddell, Gallen et al. 2017).

1.9.2 ***Glucose monitoring***

Monitoring blood glucose and or sensor glucose levels is clearly important for managing glycaemia before, during and after exercise. Information gathered from glucose monitoring allows refinement of future exercise strategies. The blood glucose response to 60 minutes of intermittent moderate intensity exercise has been shown to be reproducible in an adolescent when the pre-exercise meal, timing of exercise and the amount of insulin were kept constant (Temple, Bar-Or et al. 1995). These findings suggest that glucose monitoring during and after exercise can help individuals learn how different factors and behaviours influence their glucose control. However, in contrast others report that an individual's blood glucose response to exercise may not be predictable on repeated exercise occasions (Biankin, Jenkins et al. 2003).

The blood glucose level at the time of starting exercise can be used to tailor glycaemic management strategies. A recent consensus statement suggests that 7-10mmol/l is an acceptable starting range for adult patients doing aerobic exercise for up to 60-minute duration (Riddell, Gallen et al. 2017).

1.9.3 ***Continuous glucose monitoring and flash glucose monitoring***

Continuous Glucose monitoring (CGM) and Flash Glucose Monitoring (FGM) can provide detailed information on glucose levels during and after exercise. Use of CGM in adolescents has shown that afternoon moderate-vigorous intensity exercise increases the risk of nocturnal and next day hypoglycaemia (Metcalf, Singhvi et al. 2014). CGM and FGM provide the opportunity to respond not only to sensor glucose levels but to directional arrows that indicate rates of change in glycaemia in real-time. An observational study in 25 adolescents in a camp-setting showed that use of a carbohydrate intake algorithm in response to sensor

glucose levels and trends prevents hypoglycaemia during exercise (Riddell and Milliken 2011).

CGM and FGM devices use electrochemical sensors to measure interstitial glucose concentration. It is well established that interstitial glucose levels may lag behind blood glucose levels, particularly at times of rapid glucose change (Davey, Low et al. 2010). This lag-time consists of the time for glucose to diffuse from blood to the interstitium, inherent electrochemical sensor delays due to the reaction process, and any signal processing delays (Keenan, Mastrototaro et al. 2009). Despite marked advances in sensor technology over the last decade with significant improvements in sensor accuracy, there are still concerns regarding the accuracy of CGM during exercise. Furthermore, reported mean absolute relative difference's (MARD's) from laboratory reference measures for commercially available sensors are usually in the setting of rest not exercise (Bailey, Chang et al. 2015). MARD is defined as the average of the absolute error between all CGM values and matched reference values; the smaller the difference, the closer the CGM reading is to the reference glucose value.

Exercise potentially poses challenges to sensor accuracy as it is associated with rapid changes in glucose concentration (Galassetti and Riddell 2013), body temperature and redistribution of body fluids including changes in subcutaneous tissue circulation (Jacobsson and Kjellmer 1964, Jacobsson and Kjellmer 1964). In addition, exercise may result in mechanical forces at the site where the sensor is placed. A number of studies have investigated the accuracy of CGM during exercise in non-T1D (Herrington, Gee et al. 2012) and T1D individuals (Kumareswaran, Elleri et al. 2013, Taleb, Emami et al. 2016, Biagi, Bertachi et al. 2018) and have reported lower CGM performance during exercise. In contrast, others have found comparable or improved CGM accuracy during exercise compared to rest (Yardley, Sigal et al. 2013, Bally, Zueger et al. 2016, Aberer, Hajnsek et al. 2017).

Evidence comparing the performance of different CGM systems during exercise is limited. Aberer et al compared the performance of 3 different commercially available sensors and reported improved sensor accuracy during exercise (15 minutes of continuous cycling at low intensity) compared to rest, with MARD's ($\pm$SD) of 8.7 $\pm$ 5.9%, 15.7 $\pm$14.6% and 19.4 $\pm$13.5% for Abott, Dexcom and Medronic systems respectively during exercise when comparing sensor glucose levels to earlobe capillary blood glucose levels.

As a consequence of the lag-time between blood glucose and sensor glucose levels, CGM may overestimate glucose levels when blood glucose levels are dropping, and underestimating glucose levels when blood glucose levels are quickly rising. However, some studies report CGM reading below plasma glucose levels during exercise (Yardley, Sigal et al. 2013, Bally, Zueger et al. 2016), while others report CGM over-reading during exercise (Moser, Yardley et al. 2018).

Given that high intensity intermittent exercise is known to be associated with metabolic changes including change in pH, increased lactate levels and changes in microcirculation it has been hypothesised that CGM accuracy may be influenced by exercise type. Studies to date comparing sensor performance in individuals with T1D during continuous exercise compared to intermittent high intensity exercise have shown comparable accuracy in both conditions (Yardley, Sigal et al. 2013, Bally, Zueger et al. 2016, Moser, Mader et al. 2016).

There is no current evidence to suggest that the duration of exercise influences the performance of CGM. Theoretically, dehydration from prolonged activity may affect the amount of fluid in the interstitial space and therefore influence sensor performance (Moser, Yardley et al. 2018). A study looking at CGM accuracy before, during and after exercise was associated with lower sensor performance during exercise compared to rest, but this returned to better than pre-exercise levels within 1 hour of exercise recovery (Biagi, Bertachi et al. 2018).

1.9.4 ***Carbohydrate intake***

Carbohydrate consumption before, during and after exercise can be used to prevent exercise -mediated hypoglycaemia (Dube, Lavoie et al. 2012). Several guidelines make recommendations for the amount of carbohydrate intake around exercise for children (Craig 2011, Robertson, Riddell et al. 2014) and adults (Colberg, Sigal et al. 2016, Riddell, Gallen et al. 2017) with T1D. The key factor to determine the amount of carbohydrate intake required for exercise is the timing of the last rapid acting insulin bolus. Other factors influencing the amount of carbohydrate required for exercise include body mass, exercise duration and intensity and the blood glucose level at the start of exercise.

1.9.5 ***Carbohydrate intake when circulating insulin levels are high (bolus conditions)***

The carbohydrate requirement to prevent exercise mediated hypoglycaemia increases with plasma insulin levels (Francescato, Geat et al. 2004). When insulin levels are high such as within 2-3 hours of a meal-time bolus (bolus conditions), International guidelines suggest consuming up to 1.0-1.5g of CHO per kilogram of body mass per hour of strenuous or longer duration exercise (Robertson, Riddell et al. 2014). Thus, carbohydrate intake is a particularly important strategy for unplanned activity occurring after a bolus of insulin, where insulin doses have not been reduced prior to exercise.

1.9.6 ***Carbohydrate intake when circulating insulin levels are low (basal conditions)***

When exercise is performed before breakfast, when insulin levels are low, the risk of hypoglycaemia is minimal (Ruegemer, Squires et al. 1990) and carbohydrate supplementation may not be required (Nathan, Madnek et al. 1985, Soo, Furler et al. 1996). International guidelines recommend 0.3g-0.5g of carbohydrate per kg of body mass per hour If the pre-meal bolus has been lowered or the exercise is performed several hours after administration of a bolus dose when insulin levels are low (basal conditions)(Robertson, Riddell et al. 2014).

1.9.7 ***Carbohydrate intake and exercise intensity***

Carbohydrate requirements to prevent blood glucose levels falling during exercise vary with the intensity and duration of exercise (Rabasa-Lhoret, Bourque et al. 2001). A study in young people with T1D reported that glucose requirements to maintain euglycaemia during exercise performed under basal insulin conditions increase with intensity up to 50% and 65% VO_2 max, but in contrast no glucose was required at 80% VO_2 max. This has been described as an “inverted U relationship” between exercise intensity and intravenous glucose requirement (Shetty, Fournier et al. 2016). Further studies are required to establish the relationship between intravenous and oral glucose requirements (Shetty, Fournier et al. 2016) and exercise intensity. Furthermore, it remains to be elucidated if this relationship is maintained when exercise is performed when insulin levels are high (bolus conditions).

The majority of existing guidelines regarding carbohydrate intake for exercise are limited as they do not take into account the intensity of the activity performed. A recent consensus statement provides recommendations on carbohydrate intake for adults with T1D tailored according to exercise intensity as well as insulin levels (Riddell, Gallen et al. 2017).

1.9.8 ***Glycaemic index of carbohydrate***

In addition to the amount of carbohydrate, the type and timing of carbohydrate ingestion should also be considered. Carbohydrates with a high glycaemic Index (GI) such as glucose liquid, tablets and gels, are digested and absorbed quickly resulting in a rapid rise in blood glucose levels. In contrast, low GI foods, including fruits, milk and wholemeal bread, are released more slowly causing a more gradual and sustained rise in glycaemia.

1.9.9 ***Low GI carbohydrates***

Low GI carbohydrate intake is important to optimise muscle glycogen stores up to 48 hours prior to activity and to replenish stores after exercise. A meal or snack, containing low GI carbohydrate is recommended 1-4 hours prior to exercise to increase hepatic glycogen stores (West, Morton et al. 2011, Bracken, Page et al. 2012) and provide sustained carbohydrate release during exercise. The addition of protein to the pre- exercise meal may have some further benefits in preventing exercise mediated hypoglycaemia (Dube, Lavoie et al. 2012). Furthermore, consumption of bedtime snacks containing low GI carbohydrate (Kaufman, Halvorson et al. 1997), protein (Kalergis, Schiffrin et al. 2003) and or fat (including whole milk)(Hernandez, Moccia et al. 2000) may help reduce the risk of late onset post exercise hypoglycaemia.

1.9.10 ***High GI carbohydrates***

High GI carbohydrates are preferable immediately prior to and during prolonged exercise (greater than 60 minutes duration)(Grimm, Ybarra et al. 2004). Ideally the amount of carbohydrate ingested should match the carbohydrate utilised during activity and should be consumed in divided doses (every 15-20 minutes) (Riddell, Bar-Or et al. 1999). However recommendations should be modified to an individual's gut toleration of carbohydrate (Perrone, Laitano et al. 2005). Furthermore, a high GI snack should be consumed early in recovery (1-2 hours post exercise) to aid glycogen restoration.

1.9.11 ***Carbohydrate intake for exercise performance***

Carbohydrate intake requirements for optimal exercise performance may differ from recommendations based solely on hypoglycaemia prevention (Riddell, Gallen et al. 2017). Given that high carbohydrate intake is often recommended for healthy individuals during prolonged exercise to optimise performance, this strategy has been explored in T1D (Adolfsson, Mattsson et al. 2015). The author's report that increased carbohydrate supplementation, matched with increased insulin doses is safe and allows maintenance of

glycaemic control during prolonged aerobic activity (Adolfsson, Mattsson et al. 2015). Indeed, excessive carbohydrate supplementation without matched insulin may result in hyperglycaemia (Francescato, Stel et al. 2015). Although anecdotal evidence suggests hyperglycaemia may adversely affect exercise performance, studies have failed to demonstrate a difference in sports skill performance during acute hyperglycaemia compared to normoglycaemia (Stettler, Jenni et al. 2006, Kelly, Hamilton et al. 2010). Therefore, it remains unclear if there is an optimal blood glucose target range for exercise performance.

1.9.12 ***Insulin adjustment***

Insulin adjustment is a key tool for achieving stable blood glucose levels during and after exercise (Robertson, Riddell et al. 2014, Colberg, Sigal et al. 2016, Riddell, Gallen et al. 2017). The degree to which blood glucose levels fall during moderate intensity exercise is dependent on plasma insulin levels (Francescato, Geat et al. 2004). It is therefore important to establish the timing of exercise in relation to the last bolus dose of rapid acting insulin.

1.9.13 ***Bolus insulin dose adjustments***

Reductions in rapid-acting insulin bolus doses are recommended if exercise is occurring within 2-3 hours of bolus insulin administration (Robertson, Adolfsson et al. 2009, Colberg, Sigal et al. 2016, Riddell, Gallen et al. 2017). If exercise is performed within 2-3 hours of a meal-time insulin bolus then a bolus dose reduction of 25-75% should be considered. The extent of this rapid acting insulin dose reduction should be proportional to both the intensity and duration of the physical activity (Riddell, Gallen et al. 2017).

1.9.14 ***Basal insulin dose adjustments***

Exercise performed in the late postprandial period (> 3 hours) after a rapid acting insulin bolus (i.e under basal conditions) is less likely to result in hypoglycaemia as circulating insulin levels are typically low. Despite relatively low insulin levels, basal insulin adjustment may still be required (Tsalikian, Kollman et al. 2006) to prevent exercise mediated hypoglycaemia. Prolonged moderate intensity exercise performed 4 hours after lunch by adolescents with T1D has been shown to result in a consistent fall in blood glucose levels (Tansey, Tsalikian et al. 2006).

Insulin pumps allow greater flexibility in adjusting basal rates than multi-dose injection regimens. Furthermore, less post exercise hyperglycaemia has been reported with insulin pump therapy compared to MDI regimens in physically active adults (Yardley, Iscoe et al.

2013). For those on insulin pumps, guidelines suggest use of a temporary basal rate reduction of 50-80% commenced 60-90 minutes prior to the onset of activity, lasting until the end of the activity (Robertson, Riddell et al. 2014, Colberg, Sigal et al. 2016, Riddell, Gallen et al. 2017). In reality, individuals may opt to completely suspend basal insulin delivery at the start of exercise. This approach has been shown to be more effective in reducing a fall in blood glucose levels during intermittent high intensity activity compared to continuous aerobic activity (Zaharieva, Yavelberg et al. 2017).

A basal insulin reduction of 20% for 6 hours (21:00 to 3am) has been shown to reduce the incidence of post afternoon exercise nocturnal hypoglycaemia (Taplin, Cobry et al. 2010). Reduction in basal insulin for those on MDI may result in hyperglycaemia and is only appropriate for those engaging in more activity than usual such as sports camps (Riddell, Gallen et al. 2017).

Advances in pump technology may provide further strategies for basal rate adjustment to avoid exercise mediated hypoglycaemia. Studies investigating low glucose suspend (a feature where basal insulin is discontinued when a low sensor glucose level is detected) and predictive low glucose suspend technology (where basal insulin is turned off when hypoglycaemia is predicted to occur within a set time by an algorithm) during exercise are encouraging (Brazg, Bailey et al. 2011, Abraham, Davey et al. 2016). Future technological goals include the development of a fully automated insulin delivery system for exercise (Colberg, Laan et al. 2015, de Bock, Dart et al. 2016).

1.10 Exercise Strategies to Prevent Exercise Mediated Hypoglycaemia

1.10.1 ***High intensity exercise and the prevention of exercise mediated hypoglycaemia***

Not all forms of exercise result in hypoglycaemia in individuals with T1D with, as previously described, different forms of exercise resulting in different glycaemic responses (Riddell and Perkins 2006). In particular, exercise performed at high intensity (>80% maximal aerobic capacity) for approximately 10-15 minutes results in a rise in blood glucose levels during and after exercise in both non-diabetic (Hermansen, Pruett et al. 1970, Brooks, Nevill et al. 1990) and T1D individuals (Mitchell, Abraham et al. 1988, Sigal, Purdon et al. 1994, Sigal, Fisher et al. 1999). One difference in this response is that the rise in blood glucose levels is sustained for several hours in individuals with T1DM, in contrast to non-diabetic individuals, where

blood glucose levels return to baseline within an hour (Mitchell, Abraham et al. 1988, Marliss and Vranic 2002).

1.10.2 ***Role of catecholamine's in the glycaemic response to high intensity exercise***

This high intensity exercise induced rise in blood glucose levels is mediated, in part, by a rise in catecholamine levels causing a disproportionate rise in hepatic glucose production relative to the rise in the rate of muscle glucose (Mitchell, Abraham et al. 1988, Marliss and Vranic 2002, Kreisman, Halter et al. 2003). When adrenaline and noradrenaline are infused during moderate intensity exercise to mimic the levels seen in high intensity exercise there is an increase in hepatic glucose production and blood glucose levels similar to that observed during high intensity exercise (Kreisman, Halter et al. 2003). In contrast, findings from a recent study investigating hormonal responses to high intensity exercise, suggest decreased glucose uptake rather than increased hepatic glucose production is the cause of lower glucose requirements during high intensity exercise (Bally, Zueger et al. 2016). Furthermore, it is known that catecholamines inhibit insulin-mediated glucose uptake in skeletal muscle at rest (Nonogaki 2000, Guy, Sandoval et al. 2005) and during exercise (Howlett, Galbo et al. 1999, Watt and Hargreaves 2002).

1.10.3 ***Role of insulin in the glycaemic response to high intensity exercise***

The sustained rise in glycaemia seen in individuals with T1D is thought to be a result of a failure to increase insulin levels in response to elevated blood glucose levels (Marliss and Vranic 2002). Insulin is required to supress hepatic glucose production and to provide a stimulus for insulin-induced glucose uptake by the skeletal muscle (Riddell and Perkins 2006). Supporting this mechanism, infusion of physiological levels of insulin following high intensity exercise accelerates the return of blood glucose levels to pre-exercise levels in individuals with T1D (Sigal, Purdon et al. 1994).

1.10.4 ***Role of cortisol and growth hormone in the glycaemic response to high intensity exercise***

Growth hormone and cortisol are not principal factors in producing the rise in glucose levels associated with high intensity exercise (Marliss and Vranic 2002). The change in these hormone levels is minimal during a bout of intense exercise, with levels only rising later in recovery (Marliss and Vranic 2002). In addition infusion of octreotide to inhibit insulin, glucagon and growth hormone secretion, with simultaneous replacement of insulin and

glucagon by basal-rate infusions, has no effect on the increase in glucose production during intense exercise (Marliss and Vranic 2002).

1.10.5 ***Feasibility of high intensity exercise as a strategy to prevent exercise mediated hypoglycaemia***

The glycaemia increasing effect of a sustained bout of intense exercise raises the possibility that this type of exercise may be beneficial in the prevention of exercise medicated hypoglycaemia in individuals with T1D. However, 10-15 minutes of sustained exercise at high intensity is unlikely to be well tolerated by most individuals with T1D, thereby limiting the translation of this strategy into a free-living setting. This has led to the investigation of the glucoregulatory responses to short (up to 10s) sprints, potentially a more clinically applicable strategy.

1.10.6 ***The 10s maximal sprint***

The effect of a 10s maximal sprint on blood glucose levels in T1DM individuals has been investigated by a series of clinic based studies by Professor Tim Jones and the diabetes research team in Perth, Western Australia (Bussau, Ferreira et al. 2006, Bussau, Ferreira et al. 2007, Fahey, Paramalingam et al. 2012, Davey, Bussau et al. 2013).

1.10.7 ***The 10s maximal sprint performed under basal conditions***

It has been shown that a single maximal 10s sprint effort performed under basal insulinaemic conditions results in a sustained post exercise rise in blood glucose levels (1.2 ± 0.2mmol/L)(Fahey, Paramalingam et al. 2012). This pattern of increased blood glucose levels in recovery are similar to the patterns associated with prolonged high intensity exercise (Fahey, Paramalingam et al. 2012).

1.10.8 ***The 10s maximal sprint performed under bolus conditions***

Furthermore, a 10s sprint performed under bolus conditions, immediately before or after moderate intensity exercise stabilises an exercise induced fall in blood glucose levels for up to 2 hours post exercise in individuals with T1D (Bussau, Ferreira et al. 2006, Bussau, Ferreira et al. 2007) (see figure 3). This glycaemia increasing effect is not impaired by antecedent hypoglycaemia (Davey, Paramalingam et al. 2014).

1.10.9 ***Hormonal response to the 10s maximal sprint***

The reduced rate of fall in blood glucose levels in response to a 10s sprint is associated with a marked rise in the levels of counterregulatory hormones including catecholamine, growth

hormone and cortisol in recovery (peak levels at onset, 15 minutes, and 30 minutes of recovery respectively)(Bussau, Ferreira et al. 2006). Glucagon levels increased in the early recovery period in the control group (moderate intensity exercise only) but did not change significantly in the sprint group (Bussau, Ferreira et al. 2006, Bussau, Ferreira et al. 2007). Insulin levels remained relatively stable throughout exercise and recovery in both groups. (Bussau, Ferreira et al. 2006, Bussau, Ferreira et al. 2007). This pattern of hormonal response suggests that the marked rise in catecholamine levels at the onset of recovery underpins the mechanism by which a sprint counters an exercise mediated fall in glycaemia, as the levels of the other counterregulatory hormones did not change significantly in early recovery. Lactate may also contribute to stabilisation of blood glucose levels in early recovery, as lactate levels were elevated immediately after exercise in the sprint group. It is thought this may be due to lactate providing gluconeogenic precursors for hepatic glucose production and by increasing peripheral resistance (Bussau, Ferreira et al. 2007).

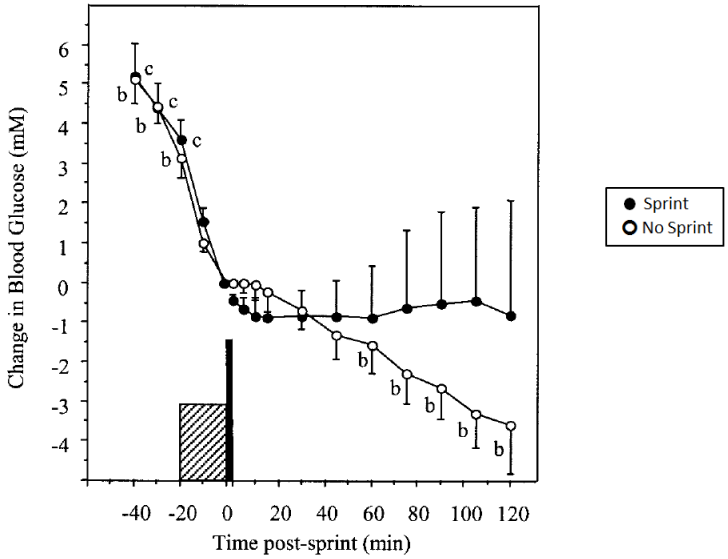

Figure 8: Effect of a 10s sprint on blood glucose after moderate-intensity exercise. The moderate-intensity exercise commenced at time point -20. Blood glucose levels are expressed relative to those immediately after the moderate-intensity exercise (time point 0). Vertical bar=sprint, hatched box=exercise. (Bussau, Ferreira et al. 2006).

1.10.10 ***Glycaemic response to a 10s sprint: glucose kinetics***

Interestingly, the blood glucose rise in response to a 10s sprint has been shown to result from a transient decline in rate of glucose disappearance (Rd) in the presence of a stable rate of glucose appearance (Ra) (Fahey, Paramalingam et al. 2012). This is contrast to the marked rise in Ra relative to Rd reported in both healthy and diabetic individuals following

high intensity exercise (Marliss and Vranic 2002) but consistent with more recent data showing a decrease in Rd in response to high intensity exercise (Bally, Zueger et al. 2016)in individuals with T1DM. This pattern of glucose kinetics is further supported by findings from animal models. A short bout of high intensity exercise has been shown to cause a post exercise transient fall in the rate of glucose utilisation by the skeletal muscles in streptozotocin-induced diabetic rats (Ferreira, Xu et al. 2005).

1.10.11 ***Mechanism underlying decline in rate of glucose disappearance***

The mechanism explaining how a 10s sprint inhibits Rd during early recovery remains to be elucidated. One proposed mechanism is that catecholamines mediate this effect (Fahey, Paramalingam et al. 2012), as they increase early in recovery and there is evidence to suggest they inhibit muscle glucose uptake. However others have reported that catecholamine infusion during exercise has little effect on Rd and may in fact enhance rather than inhibit glucose uptake (Howlett, Febbraio et al. 1999). Growth hormone may also play a role as high levels of growth hormone are associated with a reduction in peripheral glucose uptake (Moller, Jorgensen et al. 1990).

Another potential explanation for the lower Rd in high intensity exercise may be related to competing substrates, such as lactate, being used by the working muscle (Bally, Zueger et al. 2016). Indeed, increased lactate utilisation has been associated with decreased glucose disappearance during moderate intensity exercise (Miller, Fattor et al. 2002). Alternatively, lactate may exert an effect on Rd by reducing glucose uptake in the muscle as described in animal models (Vettor, Lombardi et al. 1997, Lombardi, Fabris et al. 1999). Another factor postulated to play a role in reducing Rd is Glucose 6-phosphate, a metabolite associated with rapid glycogen breakdown (Fahey, Paramalingam et al. 2012) as high levels of this metabolite can inhibit muscle glucose use via inhibition of hexokinase (Wasserman 1995).

1.10.12 ***Repeated 4s maximal sprints***

Most team sports and patterns of spontaneous play in children are characterised by low-moderate intensity exercise or rest interspersed with 3-4 s sprints and therefore repeated short sprints may more closely mimic real-life activity patterns in children (Guelfi, Jones et al. 2005). This has led to interest in understanding the blood glucose response to intermittent sprinting. Additionally, given that sprinting before or after moderate intensity exercise prevents blood glucose levels falling during recovery, has led to the question “can repeated short sprints performed during exercise prevent blood glucose levels falling during exercise

as well as recovery". This question has been addressed by a series of clinic based studies by diabetes research team in Perth, Western Australia. It has been shown that the addition of repeated short sprints (4s sprints every 2 minutes) significantly reduced the decline in glycaemia during exercise and early recovery compared with continuous moderate intensity exercise in individuals with T1D (Guelfi, Jones et al. 2005, Guelfi, Jones et al. 2005)(see Figure 4).

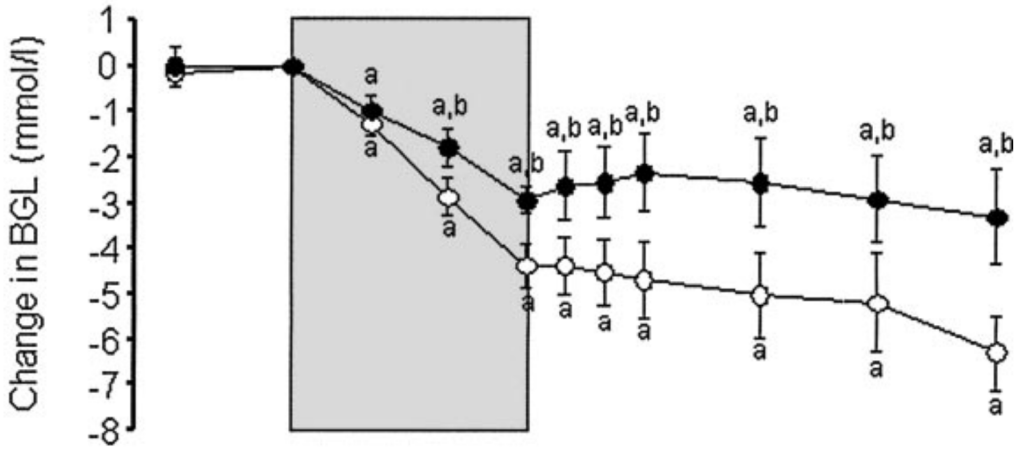

Figure 9: Effect of 30 min (represented by box) of intermittent high intensity exercise (4s sprints every 2 minutes) (•) or continuous moderate intensity exercise (○) on blood glucose levels. Results are expressed as means ± SE. [a]Statistically significant difference (P 0.05) from resting. [b]Statistically significant difference (P 0.05) between IHE and MOD. (Guelfi, Jones et al. 2005)

1.10.13 ***Mechanism underlying glycaemia rising effect of repeated 4s sprints***

The stabilisation in blood glucose levels in response to repeated 4 s sprints is associated with elevated lactate, catecholamine and growth hormone levels (Guelfi, Jones et al. 2005, Guelfi, Jones et al. 2005). Investigation of the glucose kinetics to explain this, suggest the glycaemia stabilising effect of repeated 4s sprints may be attributed to a greater increase in Ra during exercise and a marked decrease in Rd during exercise and early recovery(Guelfi, Ratnam et al. 2007).

1.10.14 ***Short sprints during exercise and risk of late onset post exercise hypoglycaemia***

Although short sprints during exercise may protect against exercise mediated hypoglycaemia during exercise and up to 2 hours of recovery, evidence on how this pattern of exercise impacts on late onset post exercise hypoglycaemia is conflicting. In one study, intermittent high intensity exercise (5s sprints every 2 minutes during moderate intensity exercise) was

associated with an increased risk of nocturnal hypoglycaemia when compared with continuous moderate intensity exercise alone in non-trained individuals with T1D (Maran, Pavan et al. 2010). In contrast, another study found that intermittent high intensity exercise (15s sprints spaced 5 minutes apart during moderate intensity exercise) was associated with less late onset post exercise hypoglycaemia than moderate intensity exercise alone in trained athletes with T1D (Iscoe and Riddell 2011). The explanation for the discrepancy in these studies findings is unclear. However, it should be noted that the main difference between the study populations was the training status of the participants. Overall these findings indicate that it is still unclear whether the incorporation of short sprints during exercise can reduce the incidence of late onset post exercise hypoglycaemia

1.10.15 ***Feasibility of short sprints during exercise to prevent exercise mediated hypoglycaemia***

The practical logistics and feasibility of incorporating short sprints into exercise should also be considered when investigating the effectiveness of sprinting to prevent exercise mediated hypoglycaemia. High intensity exercise regimens (including different work-to-recovery ratios) have been found to be safe, and well tolerated in a healthy adult population (Tucker, Sawyer et al. 2015). It should be noted that most studies investigating high intensity exercise and or sprinting are in physically active individuals. To perform a maximal sprint requires a degree of physical fitness and this is clearly not going to be an achievable strategy for all.

Given that most team sports and spontaneous play in children are characterised by short repeated bouts of intense activity, there may be limited gain in adding sprints to this already intermittent high intensity exercise. Furthermore, it may not be practical to suggest adding short sprints in this setting. In contrast, the decline in blood glucose levels associated with light or moderate intensity running or cycling may be reduced if interspersed with short sprints and this may be a workable strategy translatable to a real-word setting. A further advantage of this approach is it potentially provides a carbohydrate sparing approach to unplanned activity.

1.11 Summary of Findings from Literature Review

It is clear from the literature review presented that maintaining stable blood glucose levels around physical activity remains a major challenge for individuals with T1D. In particular,

physical activity is associated with an increased risk of hypoglycaemia for insulin treated individuals with diabetes.

Not all forms of exercise result in a decline in blood glucose levels. High intensity exercise and sprinting can be associated with a rise in blood glucose levels. This has led to the investigation of sprints as a possible strategy to prevent exercise mediated hypoglycaemia in individuals with T1D.

Clinical guidelines suggest that exercise management strategies should be individualised and tailored to the person's exercise goal as well as the type, duration and intensity of the activity. Sprinting, may provide another clinical tool, in addition to the classical approaches of carbohydrate intake and insulin adjustment in the diabetes exercise management 'tool box'. Given that insulin adjustment strategies require forward planning and carbohydrate intake strategies result in additional calorie consumption, sprinting may be a useful carbohydrate sparing in option the setting of unplanned exercise.

1.12 Hypothesis

This study tests the hypothesis that incorporating short sprints into periods of sustained moderate intensity exercise can reduce the incidence of exercise mediated hypoglycaemia in a free-living setting in adolescents and young people with T1D.

1.13 Thesis Rationale and Aim

Previous clinic based studies have shown that short sprints performed before, during or after exercise during can help prevent an exercise mediated decline in blood glucose levels. Before advocating the use of sprinting as a method for reducing the risk of exercise-mediated hypoglycaemia in individuals with T1D, it is important to determine whether findings in the laboratory are also applicable in a practical, free-living setting.

This thesis describes a clinical study that aims to address the question "can the incorporation of short sprints into periods of sustained moderate intensity exercise decrease the risk of exercise mediated hypoglycaemia in individuals with T1D in a free-living setting?".

1.14 Objectives

In order to achieve this aim, I will conduct a randomised controlled study to determine if sprinting during moderate intensity exercise:

- Reduces the incidence of hypoglycaemic events
- Reduces the average time spent in hypoglycaemia
- Increases the incidence of nocturnal hypoglycaemia
- Increases the time spent in hyperglycaemia
- Influences carbohydrate dosing and insulin dosing around exercise
- Is feasible in a free-living setting
- Is perceived to be enjoyable by participants

Chapter 2: Methodology

2.1. Participants

2.1.1 ***Eligibility criteria***

Eligible patients were individuals aged 14-35 years with T1D receiving insulin pump therapy or multiple daily injections, having been diagnosed with diabetes for at least a year, with a mean glycated haemoglobin level of 9.0% or lower over the last 12 months, free from any clinical evidence of diabetes complications and having awareness of hypoglycaemia. Hypoglycaemia awareness was determined with the modified Clarke questionnaire (Clarke, Cox et al. 1995) with a score of less than 4 being suggestive of hypoglycaemia awareness (see appendix A).

Participants were required to have an HbA1c of 75mmol/mol (9.0%) or lower to be eligible to take part in the study. Exercise may precipitate ketosis when glycaemic control is poor and pre-exercise blood glucose levels are high with low circulating insulin levels(Wahren, Felig et al. 1978). Therefore, to minimise this potential safety concern, individuals with HbA1C > 75mmol/mol (9.0%) were not eligible to participate in the study.

Exclusion criteria included musculoskeletal injuries and other medical conditions where exercise is contraindicated.

Inclusion Criteria	Exclusion Criteria
• Diagnosis of T1D for > or equal to 1 year • Age 14-35 years • Mean HbA1c < or equal to 75mmol/mol (9.0%) • Free from diabetes complications • Hypoglycaemia aware (defined as Clarke's score of <4)	• Musculoskeletal injuries • Medical conditions where exercise is contraindicated

Table 1: Inclusion and exclusion criteria

2.1.2 ***Recruitment***

Participants were recruited from the general population in Perth Western Australia, and from patients attending the Princess Margaret Hospital, Sir Charles Gairdner Hospital and Fiona Stanley Hospital and Royal Perth Hospital Diabetes Clinics.

2.1.3 ***Ethical approval and informed consent***

The protocol was approved by the Princess Margaret Hospital for Children Human Research Ethics Committee on 4.12.15.

Informed written consent was obtained from parents and participants prior to inclusion in the study (see appendix B). Assent was obtained from participants aged less than 16 years old.

2.2. Overview of Study Design

This study was a prospective randomised cross over trial (see figure 5). On three occasions participants wore a blinded continuous glucose monitoring (CGM) device for 14 days under free-living conditions. On one occasion, they were asked to follow their usual blood glucose management during periods of activity (control). In the alternate conditions the participants followed their usual blood glucose management and incorporated 10s or 4 s sprints to periods of physical activity. A sprint was defined as running or cycling as fast as the individual was able to, for the defined time period. Participants completed all three experimental conditions (control, 10s and 4s sprint protocols) in a random order, separated by a one to two-week wash-out period where the individual resumed their usual pattern of activities and refrained from sprinting.

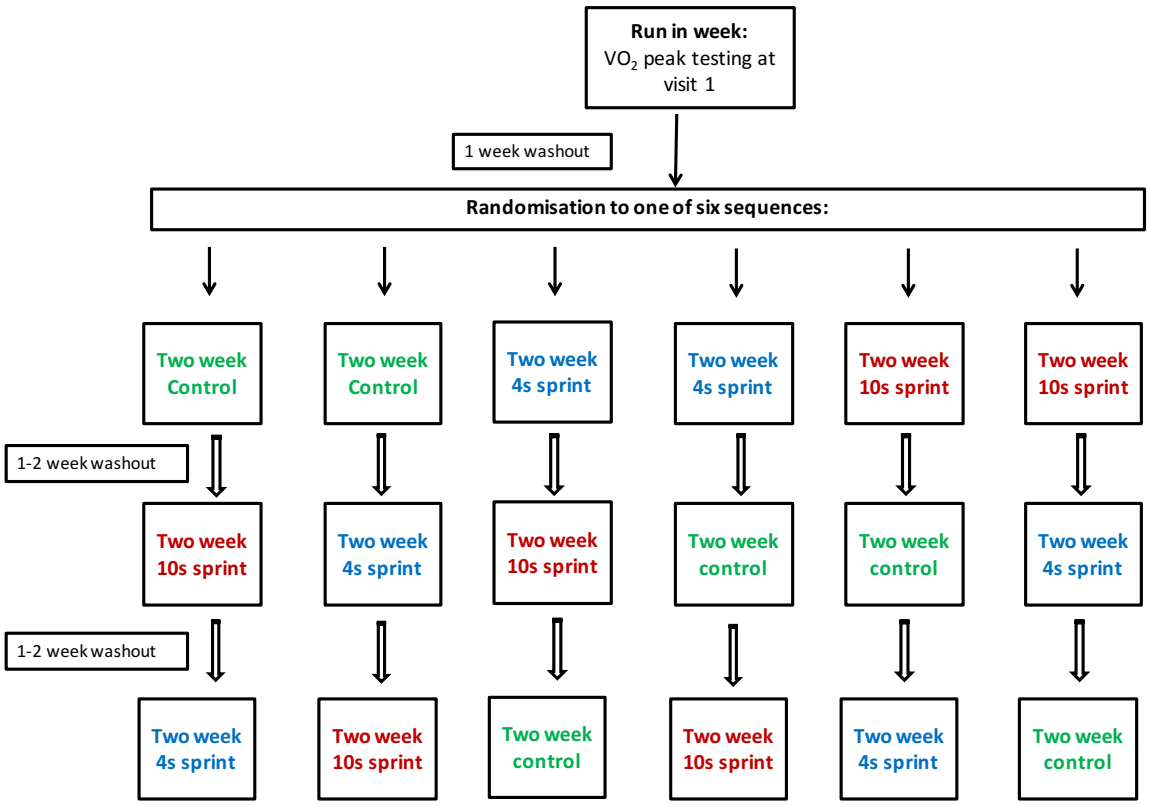

Figure 10: Flow diagram of study design

2.3. Justification of Study Design

A prospective randomised controlled trial is the gold standard study design to investigate the effectiveness of an intervention. Thus, to address the question "can the incorporation of short sprints into moderate intensity exercise reduce the risk of exercise mediated hypoglycaemia?" a randomised, prospective controlled trial was conducted. Both parallel and cross-over study designs were considered.

2.1.4 ***Advantages of a cross-over design***

The primary advantage of a cross-over study design over a parallel design in the context of this free-living study, is that all participants serve as their own controls, thereby reducing the influence of confounding co-variates. Many factors are known to influence an individual's glycaemic response to exercise including the intensity and duration of the activity, insulin dosing and carbohydrate intake before, during and after exercise. In a cross-over design all participants complete all conditions, therefore reducing the impact of these covariates. Furthermore, a cross-over design is more efficient, requiring fewer participants than a parallel design.

2.1.5 ***Disadvantages of a cross-over design***

Potential disadvantages of a cross-over design include the possibility that the order conditions are completed may affect the outcome. For example, will the participants get fatigued and be less compliant with sprinting in the final arm of the study? To balance any order effects, we randomised participants using a counterbalanced design in which participants were allocated to one of six "sequences" based on the order in which they were to receive conditions (see figure 5).

Another problem associated with a cross-over study design is the potential for 'carry over' between arms. This means that the effects of one condition may influence the outcome of subsequent conditions. We have addressed this problem by including a 1-2-week washout period between study arms, where participants resume their normal activity patterns and do not engage in sprinting.

2.2 Overview of Study Visit Schedule

Participants attended a total of 8 study visits over a 10- 12-week period (see figure 6). All study visits took place at the Children's Clinical Research Facility at Princess Margaret Hospital, Perth, Western Australia.

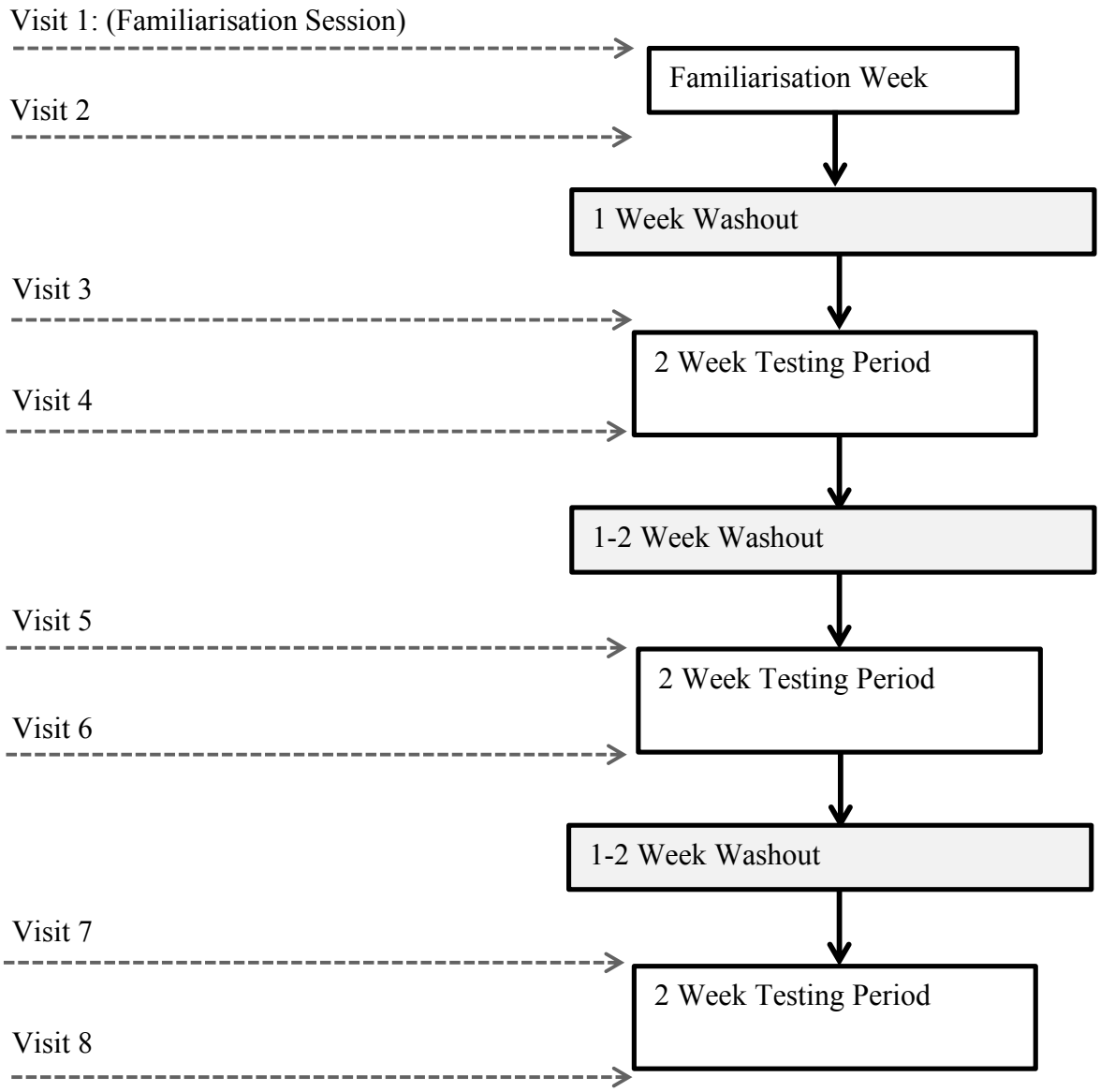

Figure 11: Study visit schedule

2.3 Familiarisation Week

Prior to randomisation participants completed a familiarisation 'run-in' week. During this week participants were asked to perform moderate intensity exercise at least 3 times a week and to try out the different exercise protocols. The purpose of the familiarisation week was twofold; firstly, to familiarise participants with study equipment and protocols, and secondly to determine if participants were able to follow the protocols and comply with study instructions.

2.3.1 ***Familiarisation session (visit 1)***

At the start of the familiarisation week, participants attended the Children's Clinical Research Facility at Princess Margaret Hospital. During this visit, eligibility for the study was confirmed including screening for hypoglycaemia awareness, baseline characteristics were collected and all participants completed a maximal rate of oxygen consumption test to assess their aerobic fitness levels. Participants were familiarised with the use of the CGM device (Dexcom G4 Platinum), exercise watch (Suunto Ambit 3), participant diary and sprinting protocols before returning home to complete a 7-day familiarisation week.

The following variables were measured during the familiarisation session, and will be discussed in turn:

- Hypoglycaemia awareness
- Baseline characteristics
- VO_2 Max

2.4 Hypoglycaemia Awareness

2.4.1 ***Why was hypoglycaemia awareness assessed prior to study start?***

Participants were required to be assessed as aware of hypoglycaemia to be eligible to take part in the study. This was deemed necessary as previous studies demonstrating the glycaemia rising effect of short sprints have done so in a population of people with T1D who are aware of hypoglycaemia. Theoretically, as the mechanism causing blood glucose levels to rise following a sprint may be due to counter regulatory hormone production, attenuations in this response associated with impaired hypoglycaemia awareness may affect the glycaemic effect of sprinting. Furthermore, impaired hypoglycaemia awareness is a risk factor for severe hypoglycaemia and therefore individuals with impaired hypoglycaemia awareness were excluded from a safety perspective.

2.4.2 ***Method of hypoglycaemia awareness assessment***

Awareness of hypoglycaemia was assessed using Clarke's hypoglycaemia awareness questionnaire (see appendix A). Clarke's hypoglycaemia awareness questionnaire is a validated survey encompassing 8 questions concerning personal experiences with hypoglycaemia (Clarke, Cox et al. 1995). These questions quantify episodes of mild, moderate and severe hypoglycaemia and the respondent's ability to recognise symptoms

associated with low blood glucose levels. Participants had to be aware of hypoglycaemia to be eligible for the study, defined as a Clarke's score of equal or less than 4.

2.4.3 ***Justification for method of hypoglycaemia awareness assessment***

There are three established questionnaire based methods to assess awareness of hypoglycaemia in individuals with T1D. These include the methods proposed by Clarke et al (Clarke, Cox et al. 1995), Gold et al (Gold, MacLeod et al. 1994), and Pedersen-Bjergaard et al (Pedersen-Bjergaard, Agerholm-Larsen et al. 2001).

The Clarke's method, as previously described comprises 8 questions characterising the individuals experience of moderate and severe hypoglycaemia and explores the glycaemic threshold for symptoms of hypoglycaemia. A score of more than four implies impaired hypoglycaemia awareness.

The Gold method asks the question "do you know when your hypos are commencing?" The respondent completes a 7 point Likert scale, with 1 representing "always aware" and 7 representing "never aware". A score of greater or equal to 4 implies impaired hypoglycaemia awareness.

The Pedersen-Bjergaard method poses the question "can you feel when you are low? The participant then selects an answer from the following options- "always", "usually", "sometimes" or "never". Participants who answer always are classified as hypoglycaemia aware, all other options imply impaired awareness of hypoglycaemia.

All of the above questionnaires were considered for use in our study. The Clarke's and Gold questionnaires have been demonstrated to strongly correlate with one another in an adult cohort (Geddes, Wright et al. 2007), and to detect an incidence of impaired hypoglycaemia awareness consistent to population surveys (Hepburn, Patrick et al. 1990, Muhlhauser, Heinemann et al. 1991, Pramming, Thorsteinsson et al. 1991). The Pedersen-Bjergaard method has been criticised for potentially overestimating the prevalence of impaired hypoglycaemia (Geddes, Wright et al. 2007).

The Clarke's questionnaire has been reported to be more effective than the Gold questionnaire at identifying those with impaired hypoglycaemia awareness in a paediatric setting (Graveling, Noyes et al. 2014). Furthermore, our centre has extensive experience of using the Clarke's questionnaire in children and adolescents (Ly, Gallego et al. 2009,

Johnson, Cooper et al. 2013, Ly, Nicholas et al. 2013, Abraham, Gallego et al. 2016). Therefore, the Clarke's questionnaire was chosen for this study.

2.5 Baseline Characteristics

Baseline Characteristics including anthropometric and clinical data were collected. Anthropometric data included standing height and body mass. Clinical data included; age, mean HbA1c over last 12 months, duration of diagnosis of T1D, insulin regimen, total daily insulin dose and total daily basal insulin dose. Participants were then interviewed about their usual exercise routine and their diabetes management strategies to avoid hypoglycaemia before, during and after exercise.

2.6 Maximal Rate of Oxygen Consumption Test (VO_2 Max)

2.6.1 ***Why was a VO_2 max test performed prior to study start?***

Participants completed a maximal rate of oxygen consumption (VO_2 max) to assess their aerobic fitness levels prior to starting the study. Predictors of VO_2 max in adult population include: age, gender and body weight (Myers, Kaminsky et al. 2017). Adolescents with T1D diabetes have been shown to have a reduced maximal oxygen consumption compared to adolescents without diabetes (Komatsu, Gabbay et al. 2005), although in contrast other studies do not support this finding (Adolfsson, Nilsson et al. 2012).

The VO_2 max test was performed for two reasons. Firstly, training status of participants has previously been postulated to influence the risk of hypoglycaemia on nights following high intensity exercise (Maran, Pavan et al. 2010, Iscoe and Riddell 2011). Secondly, it was felt that baseline fitness levels would be pivotal information when interpreting the generalisability of our findings.

2.6.2 ***Method of VO_2 max test***

Participants completed a VO_2 max test on a cycle ergometer (Lode Corival) (see figure 7). Initial workload was set at 25 W and subsequently increased by 25 W every 3 minutes until volitional exhaustion. During exercise, respiratory gases were sampled and analysed at 15s intervals by a computerised metabolic cart (Parvomedics TrueOne®2400 Metabolic Measurement System) (see figure 7), which was calibrated prior to each exercise test. Calibration of the gas analysers was performed against room air and a sample gas mixture of known composition. Calibration of the flow meter involved a five-stroke calibration using a

3L Hans Rudolph Syringe and different flow rates for each stroke. Heart rate was continuously recorded during the test using a Polar heart rate chest strap. VO_2 max was the highest rate of oxygen consumption reached in the incremental test using the 60 second epochs.

2.6.3 ***Justification of method for VO_2 max assessment***

Maximal oxygen uptake using ventilator gas exchange techniques is recognised as the gold standard measure of cardiorespiratory fitness (Ross 2003). Gas exchange measurements are highly reproducible within a given subject if testing methods are consistent (Crouter, Antczak et al. 2006). The computerised metabolic cart used in this study uses a mixing chamber system (see figure 8) connected to a measurement module which contains a paramagnetic oxygen analyser and an infrared, single beam, single wave length carbon dioxide analyser to measure gas exchange. This system has been demonstrated to provide accurate and reliable results for the measurement of gas exchange variables in healthy young men (Crouter, Antczak et al. 2006, Cooper, Watras et al. 2009, Macfarlane and Wu 2013).

Figure 12: Parvomedics TrueOne® 2400 metabolic measurement system and Lode Corival Cycle Ergometer

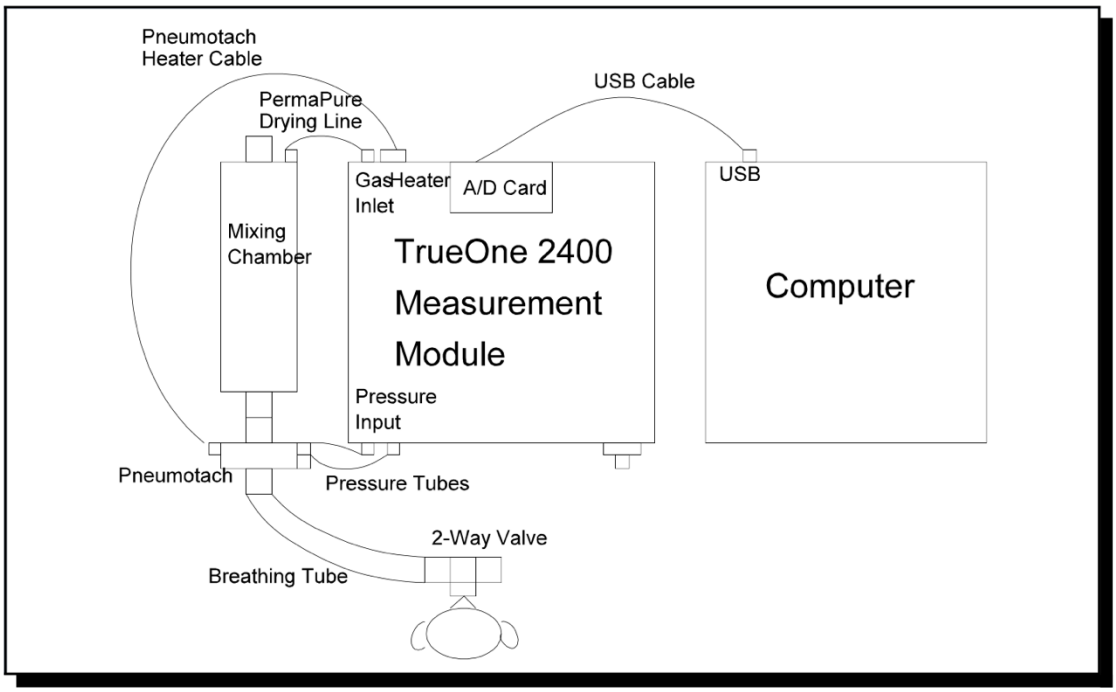

Figure 13: Parvomedics TrueOne® 400 system connections

2.7 Testing Periods

Following completion of the familiarisation week, participants completed three 14-day testing periods in random order, during which time they adhered to the control, 10s or 4s sprinting protocol during exercise. Participants attended study visits at the Children's Clinical Research Facility at Princess Margaret Hospital, Perth, Western Australia, at the beginning and end of each testing period, a total of 6 visits over an 8-10 week period.

2.7.1 ***Study visit at start of testing period***

Prior to the commencement of each 14-day testing period, participants attended a study visit to have their glucose sensor inserted and to be given the exercise watch and study diaries. Participants were shown how to insert and calibrate the sensor and were instructed to change the sensor on day 7 of the testing period. Participants were given verbal and written instructions for their assigned protocol. The study diary was re-visited and participants were asked to record carbohydrate intake and insulin administration on exercise days.

2.7.2 ***Study visit at completion of testing period***

After completing the 2-week study period participants met briefly with the study team to return equipment, at that time data were uploaded from devices. Participants completed a Physical Activity Enjoyment Scale (PACES) to assess their enjoyment of exercise, a validated questionnaire consisting of 16 statements with 7-point Likert-type scale (see appendix C). Participants were then given a 1 to 2-week washout period before undertaking the next study period.

2.7.3 ***Wash-out period***

Each 2-week study period was separated by a one to two-week wash-out period where usual activities were resumed. The purpose of the wash-out period was to prevent any potential carry-over effect of the control/intervention.

2.7.4 ***Justification for duration of testing period***

The duration of the testing period was required to be sufficiently long enough to capture repeated bouts of exercise, thereby for the first time investigating the effect of repeated bouts of sprinting. We considered a one week duration- but decided that if an exercise session was missed then there would likely be inadequate exercise occurring to demonstrate an effect of sprinting. A 14-day period was a pragmatic approach to optimise the duration of

data capture, while still trying to minimise the burden of study engagement for the participant.

2.8 Exercise Protocols

During each 14-day study period participants were asked to perform continuous moderate intensity exercise (running or cycling) at least 3 times per week for a minimum of 30 minutes and to wear an exercise watch during activity.

Moderate intensity exercise was described to participants as being able to talk comfortably during exercise (Quinn and Coons 2011). Participants were instructed to apply a 10s sprint (intervention 1), 4 s sprint (intervention 2) or control (no sprint) protocol to physical activity during each 14-day testing period in a random order. A sprint was defined as running or cycling as fast as the individual was able to, for the defined time period.

2.8.1 ***10s sprint protocol***

The 10s-sprint protocol involved a maximal 10 s sprint at the start of activity, every 20 minutes during the activity and at the end of the activity (see figure 9).

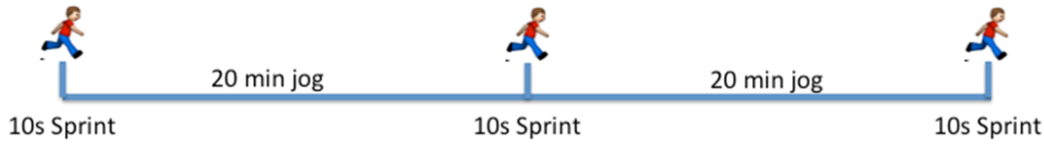

Figure 14: 10s sprint protocol

2.8.2 ***4s sprint protocol***

The 4s sprint involved a 4s sprint every 2 minutes during the activity, followed by a 10s maximal sprint at the end of the activity (see figure 10).

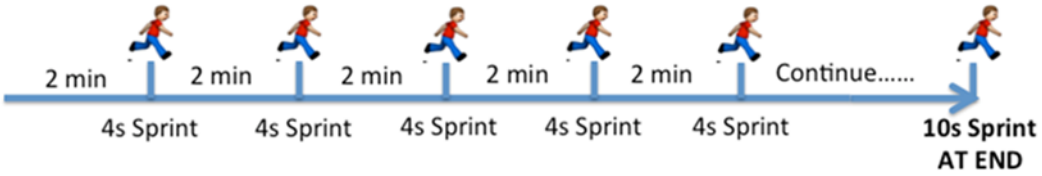

Figure 15: 4s sprint protocol

2.8.3 ***Control protocol***

The control protocol was a continuous moderate intensity run or cycle without sprints.

2.9 Summary of Variables Measured

During each 2-week study period the same outcome variables were measured (see table 2). Sensor glucose levels were measured continuously during the 2-week period. On each exercise day, the following additional variables were collected: carbohydrate intake, insulin administration and participants speed during exercise. At the completion of each 2-week study period, participants completed a Physical Activity Enjoyment Scale (PACES) questionnaire and were interviewed about their study experiences.

The following variables will be described:

- Sensor glucose levels
- Insulin dosing on exercise days
- Carbohydrate intake on exercise days
- Symptomatic hypoglycaemia
- Enjoyment of physical activity
- Participants speed during exercise and adherence with exercise protocols

Variable	How Measured (units)	When Collected	Description
Aerobic fitness	VO_2 max (ml/kg/min)	Visit 1	Stepwise incremental exercise test
Interstitial (sensor) glucose levels	Dexcom G4 Platinum (mmol/L)	14-day study period	Sensor glucose levels generated every 5 minutes
Insulin dosing on exercise days	Prospective diary- and insulin pump uploads (U/kg)	On exercise days only	Insulin dosing analysed in relation to timing of exercise
CHO intake on exercise days	Prospective diary (grams)	On exercise days only	Carbohydrate intake analysed in relation to timing of exercise
Symptomatic hypoglycaemia	Prospective diary (number of events)	14-day study period	Participant asked to document date, time and symptoms of hypoglycaemia
Enjoyment of physical activity	Physical Activity Enjoyment Scale Questionnaire	At completion of each 14-day study period	Validated questionnaire consisting of 16 statements with 7-point Likert-type scale.
Compliance with sprinting protocol	Speed (GPS generated) on exercise watch (Suunto Ambit 3)	During exercise bouts	Graphs of speed against time during exercise assessed to determine compliance with sprinting protocols.

Table 2: Variables measured

2.10 Sensor Glucose Levels

Participants wore a blinded continuous glucose monitoring (CGM) system (Dexcom G4 Platinum) for the duration of each 14-day study period (see figure 11).

Figure 16:Dexcom G4 transmitter and receiver

2.10.1 ***Justification for the CGM device chosen***

The Dexcom G4 Platinum system was chosen because at the time of study commencement it was reported to be the most accurate commercially available CGM system able to be blinded. The Dexcom G4 Platinum system has a reported mean absolute relative difference (MARD) from laboratory reference blood glucose measurements of 11.3% (Bailey, Chang et al. 2015). MARD is defined as the average of the absolute error between all CGM values and matched reference values; the smaller the difference, the closer the CGM reading is to the reference glucose value. However, the MARD may be larger at times of rapid blood glucose change.

2.10.2 ***Blinded CGM***

This blinded CGM system differs from standard CGM in that the participant received no feedback from the device- the screen of the handset (receiver) was masked (sensor glucose levels were not displayed) and there were no alarms to warn of hypoglycaemia or hypoglycaemia (see figure 12). Therefore, this system provided data for retrospective analysis only.

Figure 17: Dexcom G4 receiver in "blinded" mode and transmitter

2.10.3 ***Method of sensor glucose measurement***

The CGM system consists of a 7-day transcutaneous sensor, a transmitter and a receiver. The sensor uses glucose oxidase sensor technology to generate interstitial glucose at 5 minute intervals. The transmitter sends an electrical signal to the receiver, where it is processed by a mathematical algorithm into a glucose value and adjusted based on calibration using self-monitoring of blood glucose levels.

2.10.4 ***Calibration***

Participants were instructed to calibrate the sensor glucose levels 2 hours post insertion to their blood glucose level by entering two separate glucometer blood glucose readings into the CGM receiver. Thereafter the participant was instructed to calibrate the CGM system a minimum of every 12 hours. Sensor glucose data was uploaded after each of 14-day testing periods.

2.10.5 ***Advantages of CGM***

CGM is currently the only tool available to measure glucose variability throughout the day in an ambulatory setting. Advancement in CGM technology means devices are increasingly accurate, especially in the hypoglycaemic range. Improvement in accuracy has led to increasing use of CGM to assess glycaemic outcomes in clinical trials. A meta-analysis including data from six CGM studies on people with T1D found that CGM has high concordance with blood glucose measurements and can be a meaningful primary outcome in the appropriate setting (Beck, Calhoun et al. 2012).

2.10.6 ***Disadvantages of CGM***

Despite advancements in technology limitations of CGM systems still exist. In particular it is well established that there is a lag time between blood glucose and interstitial glucose levels when glucose levels are changing rapidly, such as during exercise (Davey, Low et al. 2010, Taleb, Emami et al. 2016). To account for this lag symptomatic hypoglycaemia was included in addition to sensor glucose levels in the primary outcome, and the primary outcome was collected over the entire two-week study period, not just times of physical activity.

2.11 Insulin Dosing on Exercise Days

Participants using MDI regimens were instructed to record the time, dose and type of insulin administered on exercise days in their participant diary. For participants using insulin pumps, pumps were uploaded at the final study visit to capture insulin dosing data for exercise days during each of the 14-day study periods. Therefore, those on insulin pumps were not required to record insulin administration in the participant diary.

2.12 Carbohydrate Intake on Exercise Days

On days when exercise was performed, participants were instructed to record the time, amount and describe any carbohydrate consumed in their participant diary. Participants were not required to record carbohydrate intake on non-exercise days. A pilot study where participants were instructed to record carbohydrate intake on all study days demonstrated that food diary data was incomplete and participants feedback suggested that this was related to the burden of collecting the data. It was therefore decided to collect data only on exercise days in an attempt to reduce the study burden for participants with an aim to improve the overall quality of data collected.

2.13 Symptomatic Hypoglycaemia and 'Other' Events

Participants were asked to record the time and details of episodes of symptomatic hypoglycaemia and to give descriptions of any 'other' events including events including sickness and ketosis in their participant diary.

2.14 Enjoyment of Physical Activity

Participants' perceived enjoyment of exercise was assessed at the completion of each 14-day testing by completing the Physical Activity Enjoyment Scale Questionnaire (PACES) (see appendix C). PACES is a validated scale to assess enjoyment of physical activity across

exercise modalities and has been shown to have acceptable internal consistency and test-retest reliability in children, adolescents and adults (Kendzierski and DeCarlo 1991, Motl, Dishman et al. 2001, Moore, Yin et al. 2009). It consists of 16 statements on a 7-point continuum (I enjoyed it- I hated it) which are summed to produce a total score.

In addition to completion of the PACES questionnaire participants were interviewed at their final study visit regarding their preferred protocol and experiences throughout the trial.

2.15 Participant's Speed During Exercise and Adherence with Sprinting Protocols

Participants wore an exercise watch (Suunto Ambit 3 Sport) (see figure 13) during bouts of physical activity. The exercise watch used Global Positioning Systems (GPS) to calculate and record the participants speed during exercise. This device was chosen as it measures speed in 1 s epochs enabling the detection of short duration (4-10s) sprinting.

Figure 18: Suunto Ambit 3 Sport

Participants were instructed to switch on the watch to start recording GPS data at the onset of exercise, and to switch off the GPS recording at the end of exercise. Alarms were programmed on the watch to remind the participant to sprint during exercise in accordance with the relevant protocol. During the 10s sprint protocol an alarm was programmed to beep for 10s every 20 minutes during exercise, during the 4s arm an alarm beeped for 4s every 2 minutes during exercise.

Data from the exercise were then used to determine the extent to which participants complied with the experimental sprinting protocol. A graph was generated of participant speed over time (see figures 14 and 15) for each exercise session and assessed independently by one of 2 researchers for the presence of sprints at the expected time points for the given protocol.

Exercise sessions during the control (no sprints arm) were classified as compliant if greater or equal to 25 minutes in duration. Exercise bouts during sprinting arms were classified as adherent if they met the following criteria (1) greater or equal to 25 minutes in duration and (2) presence of greater or equal to 60% of the expected sprints. GPS data was only generated when participants exercised outdoors, therefore indoor activity could not be assessed for adherence to sprinting protocols.

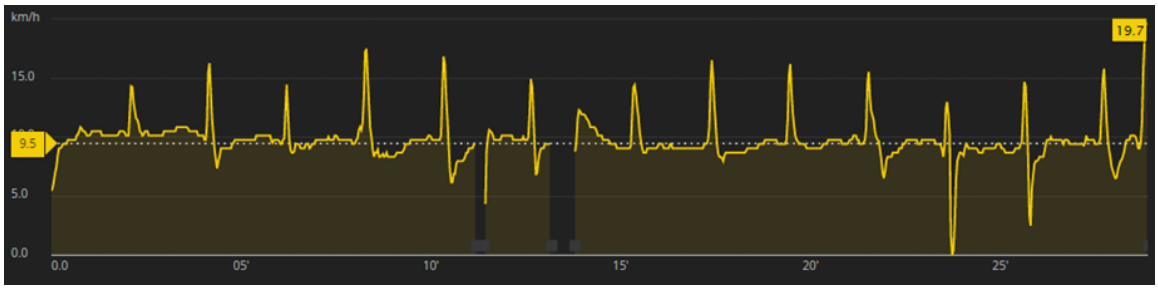

Figure 19: Exercise watch trace for 4s sprint

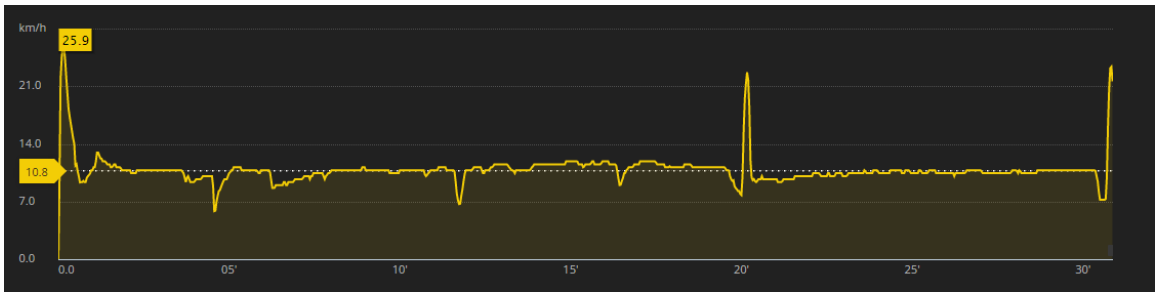

Figure 20: Exercise watch trace for 10 s sprint

2.16 Enjoyment of Physical Activity

Participants' perceived enjoyment of exercise was assessed at the completion of each 14-day testing by completing the Physical Activity Enjoyment Scale Questionnaire (PACES) (see appendix C). PACES is a validated scale to assess enjoyment of physical activity across exercise modalities and has been shown to have acceptable internal consistency and test-retest reliability in children, adolescents and adults (Kendzierski and DeCarlo 1991, Motl, Dishman et al. 2001, Moore, Yin et al. 2009). It consists of 16 statements on a 7-point continuum (I enjoyed it- I hated it) which are summed to produce a total score.

In addition to completion of the PACES questionnaire participants were interviewed at their final study visit regarding their preferred protocol and experiences throughout the trial.

2.17 Primary and Secondary Outcomes

The primary outcome of the study was the incidence of hypoglycaemia (defined as glucose sensor readings <3.5mmol/L for greater than or equal to 20 minutes); and or treated symptomatic hypoglycaemia.

Secondary glycaemic outcomes included:

- The incidence of hypoglycaemic events defined as:
    - sensor glucose levels <3.9mmol/L for greater or equal to 20 minutes
    - sensor glucose levels <3.1mmol/L for greater or equal to 20 minutes
- Average percent of time spent in various glycaemic ranges including:
    - sensor glucose levels less than 3.1mmol/L
    - sensor glucose levels less than 3.5mmol/L
    - sensor glucose levels less than 3.9mmol/L
    - sensor glucose levels between 3.5- <8mmol/L
    - sensor glucose levels between 8.0 and 10.0mmol/L
    - sensor glucose levels > 10.0mmol/L
- Glycaemic outcomes (as above) for day- time (06:00hr-22:00hrs) and night- time periods (2200hrs-0600hrs)

Other secondary outcomes included:

- Compliance with the sprinting protocols
- Carbohydrate intake before, during and after exercise

- Insulin (fast acting) bolus dose before, during and after exercise
- Participant enjoyment of exercise as determined by PACES questionnaire

2.17.1 ***Justification of primary outcome***

We chose to use hypoglycaemic events, defined as: sensor glucose levels of <3.5mmol/L for greater or equal to 20 minutes, as our primary outcome. Readings with sensor values of less than 3.5mmol/L were flagged, each group of consecutive readings were identified. The total time represented by each instance of consecutive flagged readings was calculated and a hypoglycaemic event was counted if the period of time was greater or equal to 20 minutes duration. A level of <3.5mmol/L was used, as this represents a level of clinically important hypoglycaemia, approximately the onset of physiological responses to hypoglycaemia in a non-diabetic population (Mitrakou, Ryan et al. 1991).

A minimum duration of 20 minutes was used as numbers of events are subject to distortion by fluctuations across a threshold. International guidelines published subsequent to the study starting suggest that for this reason an 'event' should have a minimum duration of 15 minutes to be counted (Danne, Nimri et al. 2017, Schnell, Barnard et al. 2017).

Our primary outcome was defined as hypoglycaemic events, instead of the average time spent in a hypoglycaemic range. Hypoglycaemic events may provide a more accurate representation of burden to the patient than time spent low (Maahs, Buckingham et al. 2016). In addition, we attempted to capture episodes of symptomatic hypoglycaemia- again a representation of burden to the patient.

2.17.2 ***Justification of secondary glycaemic outcomes***

In addition to the primary outcome we also analysed the incidence of hypoglycaemic events defined by a cut off level of 3.9mmol/L. The level of 3.9 was chosen as it is a clinically relevant threshold representing an alert level at which point treatment should be instigated to prevent a further decline in glycaemia (Ly, Maahs et al. 2014).

Reporting the average time spent in hypoglycaemic, in target and hyperglycaemic ranges is well established in studies using CGM based outcomes (Maahs, Buckingham et al. 2016, Danne, Nimri et al. 2017), therefore these measures were included in our secondary analysis. Average percent of time spent in various glycaemic ranges was calculated as a function of the number of readings in the defined range over the total number of 5-minute sensor glucose levels.

Subsequent to the onset of our study International guidelines on reporting CGM based outcomes in clinical trials suggest using a hypoglycaemia cut-offs of 3.1mmol/l (Schnell, Barnard et al. 2017). We therefore included the cut-off of 3.1mmol/L (for hypoglycaemia events and the average time spent hypoglycaemic) in our secondary analysis in response to this new guidance.

It remains controversial whether sprinting increases the risk of nocturnal hypoglycaemia, as previous studies have conflicting findings (Maran, Pavan et al. 2010, Iscoe and Riddell 2011, Bally, Zueger et al. 2016). To address this question glycaemic outcomes were explored for day and night-time periods in addition to the whole study period.

2.18 Randomisation, Sample Size and Statistical Analysis

2.18.1 ***Randomisation***

All participants completed all three experimental conditions (control, 4s and 10s sprint) in a random order, following a crossover study design. Randomisation was computer generated used a counterbalanced design in which participants were allocated to one of six 'Sequences' based on the order in which they receive the conditions. Minimisation randomisation was used and randomisation was stratified by 2 age groups (14-17, 18-35), gender and sequence.

Participants were evenly distributed across the 'Sequences' to balance any potential order effect. It was also postulated that age and HbA1c could be potential co-founding factors and therefore these variables were also distributed evenly across the sequences.

2.18.2 ***Sample size***

We have previously shown, using a similar experimental design, an average of 1.4 low glucose events (sensor glucose readings ≤3.5mmol/L) per day in free-living individuals with T1D with a standard deviation of 1.0 in free-living individuals with T1D. Since a 30% reduction in this incident rate to 1.0 event per day would represent a statistically significant change with an alpha set at 0.05, we have calculated that a sample size of 45 participants will provide us with enough statistical power ($\beta = 0.85$) to test our hypothesis.

We aimed to recruit 50 participants to account for an approximate 10% loss to follow-up based on previous studies of this nature.

2.18.3 ***Statistical analysis***

To address the primary aim of the study, each of the sprinting exercise protocols (10 second; and 4 second) were compared to the control condition with regard to number of hypoglycaemic events over the study period. Generalized linear mixed models with a negative binomial distribution and log link were used to determine whether, compared to the control condition, each of the sprinting exercise protocols reduced the incidence of hypoglycaemic episodes associated with physical activity (both during physical activity and at other times of the day). Compliance with protocols was evaluated using exercise activity watch data. Finally, average sensor glucose levels were analysed as a secondary outcome to compare the extent to which glycaemic control is affected by the guidelines. Linear mixed models were used to examine the effect of the exercise protocols on sensor glucose levels. A p value of <0.05 was considered significant.

Chapter 3: Results

3.1 Participants

3.1.1 ***Enrolment and randomisation***

39 individuals enrolled in the study (see figure 16). Of the 39 who attended visit 1, 31 were randomised to exercise protocol sequence order. 8 subjects declined to participate prior to randomisation because following visit 1 they felt unable to commit to the study protocol and associated hospital visits. Of the 31 randomised, 4 withdrew consent prior to starting the study for the following reasons: 1 participant was pregnant, 1 participant sustained a knee injury at work and could no longer participate in regular exercise, and 2 participants decided they were too busy to commit to the study schedule.

3.1.2 ***Participants excluded from data analysis***

All 27 participants who started the study completed all three study arms. Three participants were excluded from data analysis; 1 for equipment failure and 2 for breach of study protocol as detailed below. 24 participants were therefore included in the data analysis.

One participant was excluded due to equipment failure; as despite wearing the CGM device for all 2-week study periods, no sensor glucose levels were recorded during the 4s study arm. As stated in our initial protocol the remaining data were not used in analysis.

Two participants were excluded from the analysis due to significant breaches in study protocol. On inspection of insulin pump data, it became apparent that 1 participant had worn a real-time (unblinded) CGM device in addition to the blinded study CGM device during their second (4s) and third (10s) study arms. Furthermore, this device was linked to their insulin pump and was enabling use of a predictive low glucose suspend feature. A predictive low glucose suspend feature stops basal insulin automatically if the sensor glucose level is predicted to fall below a pre-set threshold and re-starts at a predetermined level. Given that this feature is known to prevent hypoglycaemia (Battelino, Nimri et al. 2017), this participants data were excluded from analysis. A further patient was excluded from data analysis as CGM traces were clinically consistent with inappropriate and excessive insulin dosing. Pump data were missing despite the study team uploading the device on multiple occasions, therefore it was not possible to assess insulin administration and hence to

determine if the pump had been used to deliver excessive insulin. The clinical team were alerted to these concerns and appropriate clinical and psychological support were arranged.

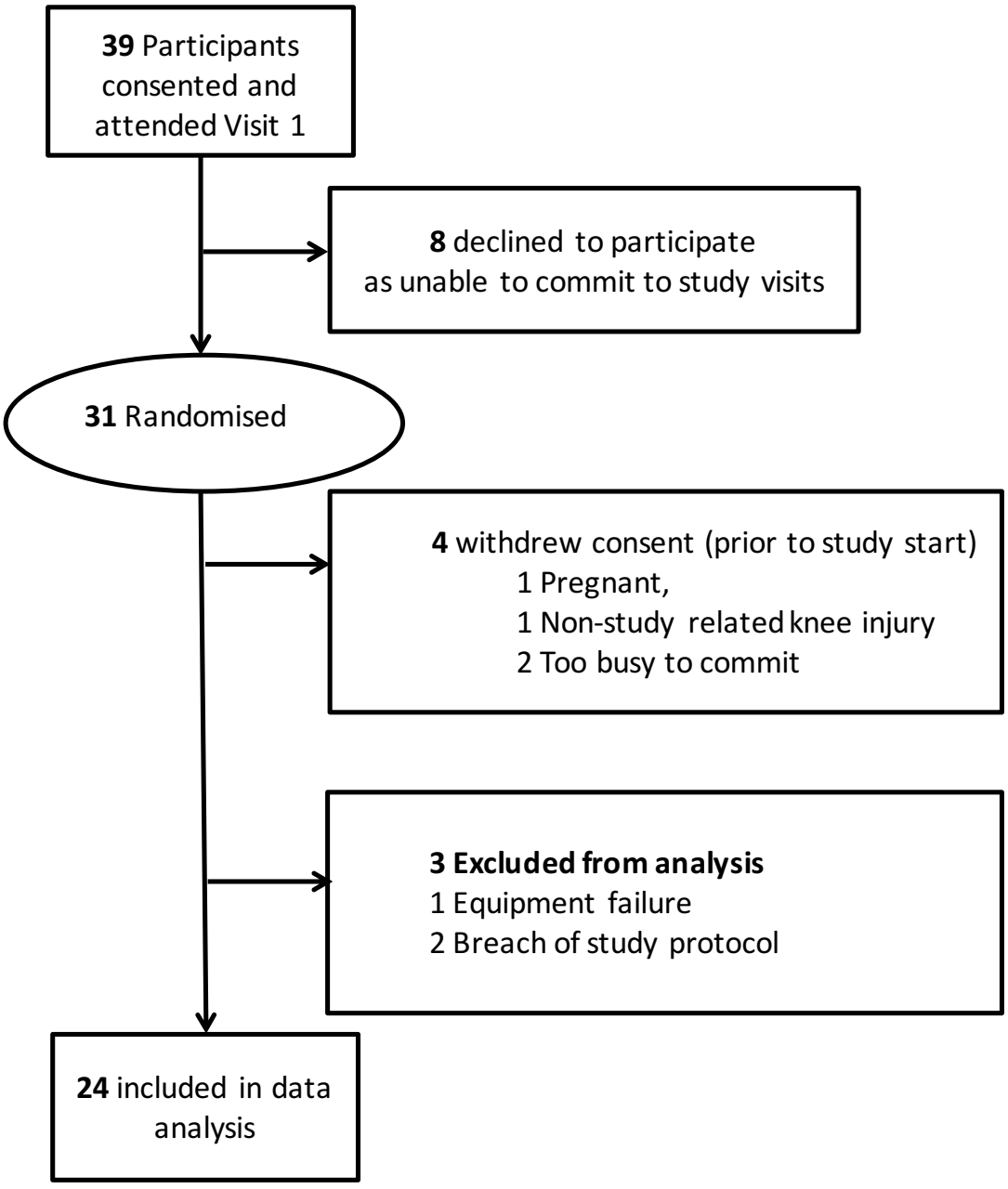

Figure 21: Study enrolment and randomisation

3.2 Baseline Characteristics

3.2.1 ***Description of study cohort***

Twenty-four individuals (14 female, 10 male) with T1D aged 19.7 ± SD 5.4 years (11 participants aged 14-17 years and 13 participants aged 18-35 years); BMI 23.8 ± SD 4.2 kg/m^2 were included in the study (see Table 3). The participants had a mean Hba1c over the last 12 months of 58 ± SD 7.7mmol/mol (7.5 ± SD 0.7%) and a mean duration of diagnosis of diabetes of 9.1 ± SD 6.3 years. All participants were free from complications of diabetes and hypoglycaemia aware (defined as a Clarke's sore of equal or less than 4) with a mean Clarke's score of 0.2 ± SD 0.5.

3.2.2 ***Insulin regimen***

The average total daily insulin dose prior to starting the study was 0.7 ± SD 0.2units/kg/day. 16 participants were treated with insulin pumps and 8 with multiple daily injection (MDI) insulin regimens. For those on insulin pumps, the mean duration of pump use was 5.1 (range 0.2- 12.3) years. Of the 8 participants using MDI regimens, 7 were using Glargine (once daily, in the evening), and 1 was using Detemir (twice daily) as long-acting insulin.

3.2.3 ***Engagement in planned exercise and VO_2 max test***

Participant reported time spent engaging in planned exercise prior to commencement of the study was 2.0 ± SD 1.3 hours per week. All participants completed a maximal rate of oxygen consumption (VO_2 max) test, the mean VO_2 max was 32.7 ± SD 7.1ml/kg/min.

Female	14
Age, mean (SD) [range], years	19.7 (5.4) [14.0-32.8]
Age group, years	
14-17	11
18-35	13
BMI, mean (SD) [range], kg/m^2	23.8 (4.2) [15.4-31.1]
Mean HbA1c over last 12 months (SD) [range], mmol/mol	58 (8) [46-73]
Mean HbA1c over last 12 months (SD) [range], %	7.5(0.7)[6.4-8.8]
Insulin regimen:	
Multiple daily injections	8
Insulin pump	16
Physical activity prior to study, mean (SD) [range], hours per week	2.0 (1.3) [0-6]
Duration of diabetes, mean (SD) [range], years	9.1 (6.3) [1.0-23.4]
Average Total Daily Insulin, mean (SD) [range], U/kg	0.7 (0.2) [0.4-1.1]
Hypoglycaemia unawareness score, mean (SD) [range]	0.2 (0.5) [0-2]
VO_2 max, mean (SD) [range], ml/kg/min	32.7 (7.1) [22.3-45.9]

Table 3: Baseline characteristics of study participants (n=24)

3.3 CGM Adherence and Accuracy

Glycaemic outcomes were calculated from sensor glucose levels (SGL) obtained from continuous glucose monitoring over the three 14-day study periods. The mean sensor use during each 14-day study period was 88% (± SD 14.0%) in the control arm, 89% (± SD 9.0%) in the 4s arm and 90% (± SD 8.0%) in the 10s arm.

The mean absolute relative difference (MARD) between blood glucose levels and sensor glucose levels (based on sensor glucose levels taken within 10 minutes prior to blood glucose meter readings) was 14.7 (± SD 14.0) % using all blood glucose readings (n=1864). The MARD for blood glucose levels less than 3.5, 3.5-8.0, 8.0-10.0 and greater than 10mmol/L was 34.0 (± SD 31.0) %, 15.9 (± SD 14.8) %, 13.0 (± SD 11.9) % and 12.6 (± SD 10.4) % respectively.

3.4 Primary Outcome

The primary outcome was defined as sensor glucose readings <3.5mmol/L for greater or equal to 20 minutes *and* symptomatic treated hypoglycaemia. Data capture of self-reported symptomatic treated hypoglycaemia from participant food diaries was incomplete and therefore an unreliable field. The decision was made to include only the reliable and complete data. Therefore, hypoglycaemic events were defined using the measure of CGM-derived hypoglycaemia events alone.

Readings with sensor values of less than 3.5mmol/L were flagged, each group of consecutive readings were identified. The total time represented by each instance of consecutive flagged readings was calculated and a hypoglycaemic event was counted if the period of time was greater or equal to 20 minutes duration.

The total number of hypoglycaemic events (defined as sensor glucose readings of readings <3.5mmol/L for greater or equal to 20 minutes) was 193 in the control arm, compared to 170 and 154 events in the 4s and 10s arms respectively. The hypoglycaemia incidence rate was 0.63 (95% CI 0.46-0.80) events per day in the control arm, 0.55 (95% CI 0.40-0.70) events per day in the 4s arm and 0.49 (95% CI 0.36-0.63) events per day in the 10s arm (see figure 17). A negative binomial mixed model was used to compare the incidence rate of hypoglycaemic events in the control arm versus the 4s and 10s sprinting arms. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.88 (95% CI 0.69-1.11; p= 0.28). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.78 (95% CI 0.61-1.00; p= 0.05).

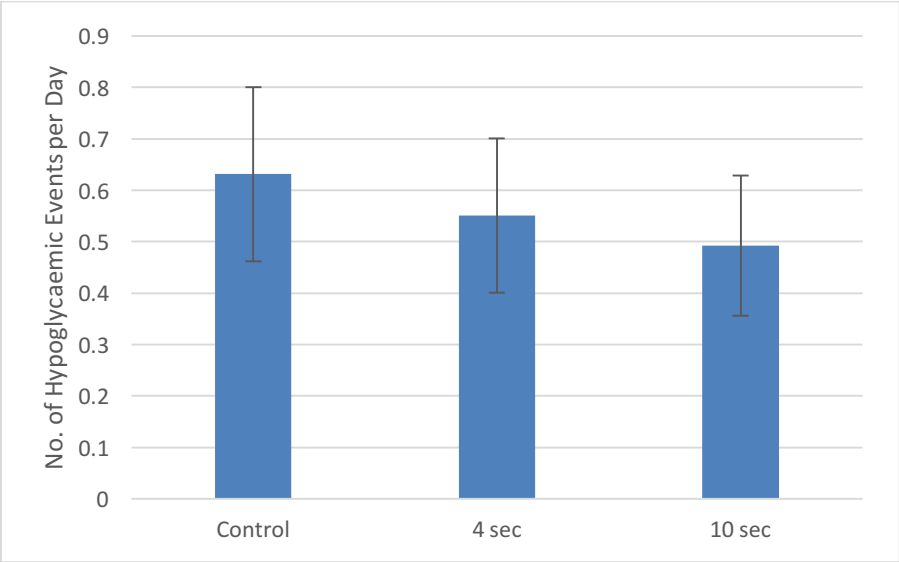

Figure 22: Incidence of hypoglycaemia: SG<3.5mmol/L for ≥ 20mins Error bars represent 95% CI

3.5 Secondary Outcomes

3.5.1 ***Summary of secondary outcomes***

The following glycaemic outcomes (see table 4) will be reported for each study arm. The sprinting arms of the study (4s and 10s) were compared to the control arm.

Hypoglycaemic events:
Sensor glucose levels <3.1mmol/L for ≥ 20 mins
Sensor glucose levels <3.9mmol/L for ≥ 20 mins
Average percent of time spent with sensor glucose levels*:
<3.1mmol/l
<3.5mmol/l
<3.9mmol/l
3.5-<8.0mmol/L
8.0-10.0mmol/L
>10.0mmol/L

Table 4: Secondary outcomes: based on sensor glucose levels *Average percent of time spent in various glycaemic ranges was calculated as a function of the number of readings in the defined range over the total number of 5-minute sensor glucose levels.

Other secondary outcomes will subsequently be reported including:

- Glycaemic outcomes including hypoglycaemic events and average time spent in hypoglycaemic, in-target and hyperglycaemic range for day time (06:00-22:00hrs) and night-time (22:00hrs06:00hrs) periods
- Total daily insulin dose
- Insulin dosing before, during and after exercise
- Carbohydrate intake before, during and after exercise
- Adverse events

3.5.2 ***Hypoglycaemic events: defined as sensor glucose levels of <3.1mmol/L for greater or equal to 20 minutes***

The total number of hypoglycaemic events (defined as glucose sensor readings of readings <3.1mmol/L for greater or equal to 20 minutes) was 124 in the control arm, compared to 102 and 87 events in the 4s and 10s arms respectively. The hypoglycaemia incidence rate was 0.4 (95% CI 0.3-0.6) events per day in the control arm, 0.3 (95% CI 0.2-0.5) events per day in the 4s arm and 0.3 (95% CI 0.2-0.4) events per day in the 10s arm (see figure 18). When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.81 (95% CI 0.56-1.18; p= 0.27). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.68 (95% CI 0.46-0.98; p= 0.04), favouring the 10s arm.

3.5.3 ***Hypoglycaemic events: defined as sensor glucose levels of <3.9 mmol/L for greater or equal to 20 minutes***

The total number of hypoglycaemic events (defined as glucose sensor readings of readings <3.9mmol/L for greater or equal to 20 minutes) was 307 in the control arm, compared to 258 and 273 events in the 4s and 10s arms respectively. The hypoglycaemia incidence rate was 1.0 (95% CI 0.8-1.2) events per day in the control arm, 0.8 (95% CI 0.6-1.0) events per day in the 4s arm and 0.9 (95% CI 0.7-1.1) events per day in the 10s arm (see figure 18). When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.82 (95% CI 0.66-1.04; p= 0.10). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.87 (95% CI 0.69-1.09; p= 0.21).

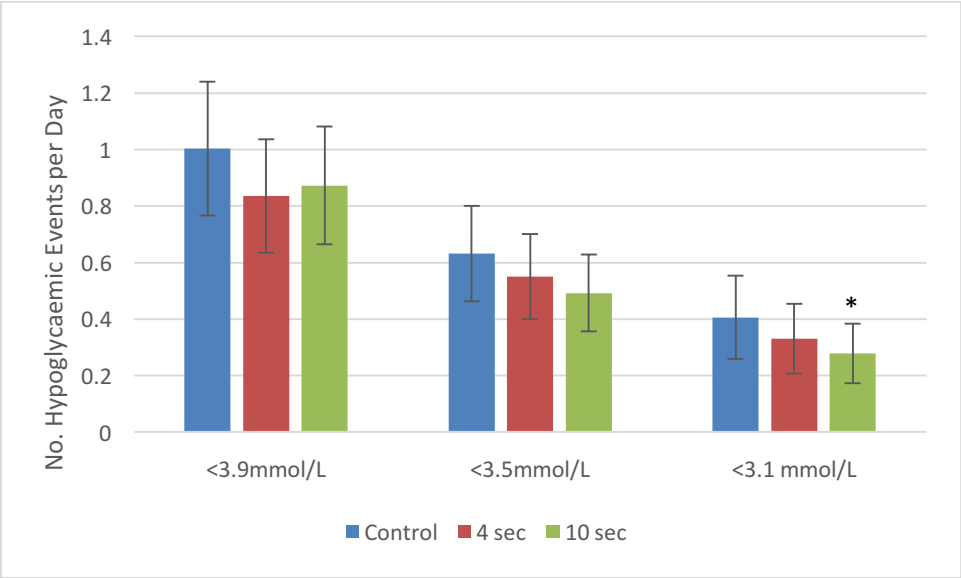

Figure 23: Incidence of hypoglycaemic events
****p= 0.04, comparing 10s to control arm using a negative binomial mixed model***
Error bars represent 95% CI

3.5.4 ***Percentage of time spent with sensor glucose levels < 3.1mmol/L***

The average percent of time spent in the hypoglycaemic range, defined as sensor glucose levels of < 3.1mmol/l, was 1.9 (± SD 1.8) % in the control arm, 1.4 (± SD 1.5) % in the 4s arm and 1.2 (± SD 1.1) % in the 10s arm (see figure 19). A mixed model was used to compare the time spent with sensor glucose levels less than 3.1mmol/l in the sprinting arms (4s and 10s) to the control arm. Significantly less time was spent less than 3.1 in the 10s-arm compared to the control (95% CI -1.4- -0.1%, p=0.03) arm. There was no significant difference between the 4s and control arms (95% CI -1.2- 0.2%, p=0.13).

3.5.5 ***Percentage of time spent with sensor glucose levels < 3.5mmol/L***

The average percent of time spent in the hypoglycaemic range, defined as sensor glucose levels of < 3.5mmol/l, was 3.1% (± SD 2.5) % in the control arm, 2.5% (± SD 2.1) % in the 4s arm and 2.1 (± SD 1.5) % in the 10s arm (see figure 19). A mixed model was used to compare the time spent with sensor glucose levels less than 3.5mmol/l in the sprinting arms (4s and 10s) to the control arm. Significantly less time was spent less than 3.5 in the 10s arm compared to the control (95% CI -1.8- -0.1%, p=0.03) arm. There was no significant difference between the 4s and control arms (95% CI -1.5- 0.3%, p=0.18).

3.5.6 ***Percentage of time spent with sensor glucose levels < 3.9mmol/L***

The average percent of time spent in the hypoglycaemic range, defined as sensor glucose levels of < 3.9mmol/l, was 5.0 (± SD 3.3) % in the control arm, 4.0 (± SD 2.8) % in the 4s arm and 3.9 (± SD 2.1) % in the 10s arm (see figure 19). A mixed model was used to compare the time spent with sensor glucose levels less than 3.9mmol/l in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -2.3- 0.04%, p=0.06) or the 4s and control arms (95% CI -2.2- 0.1%, p=0.08).

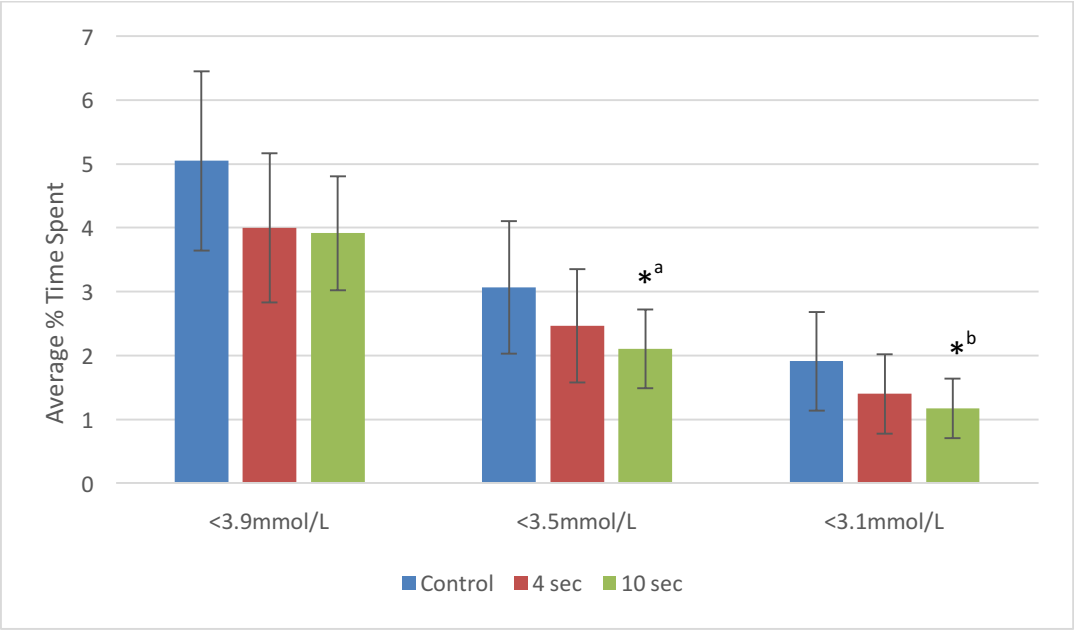

Figure 24: Average percent of time spent in hypoglycaemia
[a] p=0.03, comparing 10s to control arm using a linear mixed model
[b] p=0.03, comparing 10s to control arm using a linear mixed model
Error bars represent 95% CI

3.5.7 ***Percentage of time spent with sensor glucose levels 3.5- <8.0mmol/L***

The average percent of time spent in the in-target range, defined as sensor glucose levels of 3.5- <8.0mmol was 38.0 (± SD 14.9) % in the control arm, 37.4 (± SD 17.3) % in the 4s arm and 36.0 (± SD 15.9) % in the 10s arm (see figure 20) A mixed model was used to compare the time spent with sensor glucose between 3.5 and 8mmol/l in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -6.0- 2.0%, p=0.33) or the 4s and control arms (95% CI-4.6- 3.4% p=0.77).

3.5.8 ***Percentage of time spent with sensor glucose levels 8.0- 10.0mmol/L***

The average percent of time spent in the hyperglycaemic range, defined as sensor glucose levels of 8.0-10.0mmol was 17.0 (± SD 3.6) % in the control arm, 17.3 (± SD 3.7) % in the 4s arm and 16.8 (± SD 4.7) % in the 10s arm (see figure 20). A mixed model was used to compare the time spent with sensor glucose between 8.0 and 10mmol/l in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -1.8- 1.3%, p=0.77) or the 4s and control arms (95% CI -1.4- 1.8% p=0.79).

3.5.9 ***Percentage of time spent with sensor glucose levels greater than 10.0mmol/L***

The average percent of time spent in the hyperglycaemic range, defined as sensor glucose levels of greater than 10.0mmol/L was 41.9 (± SD 17.6) % in the control arm, 42.9 (± SD 19.4) % in the 4s arm and 45.1 (± SD 19.4) % in the 10s arm (see figure 20). A mixed model was used to compare the time spent with sensor glucose greater than 10mmol/l in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -1.7- 8.1%, p=0.21) or the 4s and control arms (95% CI -4.0- 5.9%, p=0.70).

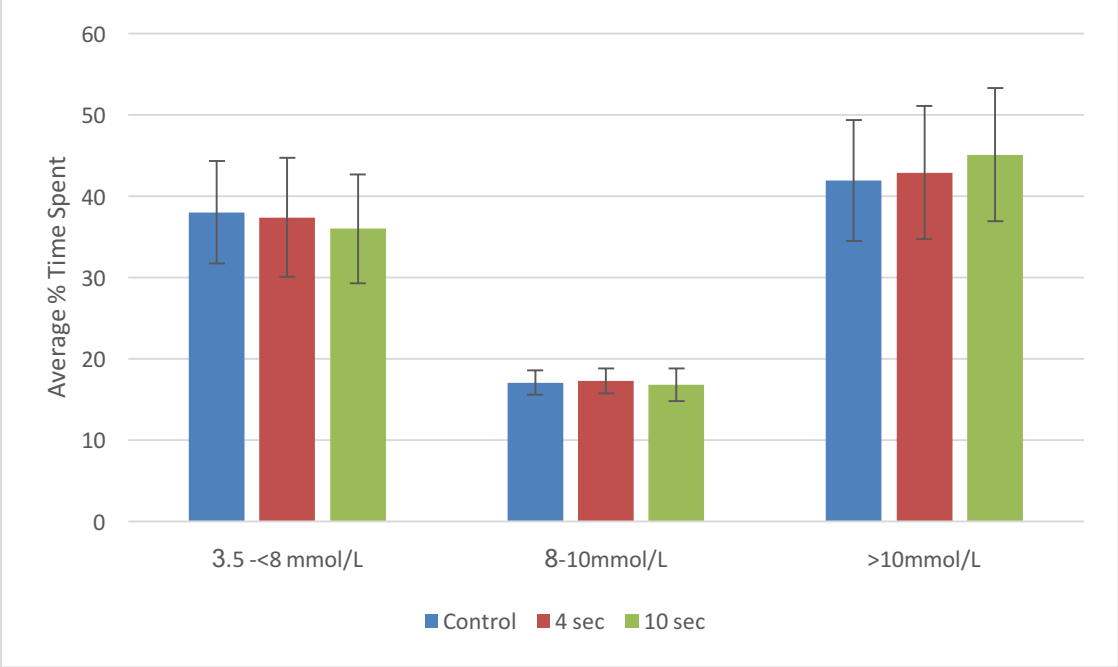

Figure 25: Average percent of time spent in target range and in hyperglycaemia Error bars represent 95% CI

3.5.10 ***Total daily insulin dose***

The total daily insulin dose did not differ significantly between study arms. The mean total daily insulin dose in the control arm was 0.65 (± SD 0.23) units/kg/day in the control arm, 0.66 (± SD 0.22) units/kg/day in the 4s arm and 0.69 (± SD 0.25) units/kg/day in the 10s arm (see table 10). A mixed model comparing 4s and 10s arms to the control arm showed no significant difference between the groups (control vs 10s: 95% CI 0.00- 0.06, p=0.05, control versus 4s: 95% CI -0.02- 0.03 p=0.87).

3.5.11 ***Insulin bolus doses during and prior to exercise***

No insulin boluses were administered during exercise in the 4s, 10s, or control study arms.

Insulin bolus doses administered less than or equal to 60, 180 or 360 minutes prior to starting exercise did not differ significantly between the study arms (control, 10s and 4s) (see table 10).

The mean insulin bolus dose administered less than or equal to 60 minutes prior to exercise was 1.2 (± SD 2.5) units in the control arm, 0.8 (± SD 1.6) units in the 4s arm and 1.1 (± SD 2.2) units in the 10s arm. A mixed model was used to compare the mean insulin bolus dose administered within 60 minutes prior to exercise in the control group compared to the sprinting (4s and 10s) arms and did not find a significant difference between the groups (control vs 10s: 95% CI -0.8- 0.5, p=0.74, control versus 4s: 95% CI -1.0- 0.3, p=0.24).

The mean insulin bolus dose administered less than or equal to 180 minutes prior to exercise was 3.1 (± SD 4.1) units in the control arm, 4.1 (± SD 5.0) units in the 4s arm and 3.6 (± SD 3.7) units in the 10s arm. A mixed model was used to compare the mean insulin bolus dose administered within 60 minutes prior to exercise in the control group compared to the sprinting (4s and 10s) arms and did not find a significant difference between the groups (control vs 10s: 95% CI -0.8- 1.7, p=0.44, control versus 4s: 95% CI -0.5- 1.9, p=0.27).

The mean insulin bolus dose administered less than or equal to 360 minutes prior to exercise was 6.7 (± SD 5.7) units in the control arm, 7.6 (± SD 6.6) units in the 4s arm and 7.3 (± SD 5.4) units in the 10s arm. A mixed model was used to compare the mean insulin bolus dose administered within 360 minutes prior to exercise in the control group compared to the sprinting (4s and 10s) arms and did not find a significant difference between the groups (control vs 10s: 95% CI -1.0- 2.4, p=0.40, control versus 4s: 95% CI -1.0- 2.3, p=0.41).

3.5.12 ***Insulin bolus doses after exercise***

Insulin bolus doses administered less than or equal to 60, 180 or 360 minutes after finishing exercise did not differ significantly between the study arms (control, 10s and 4s) (see table 10).

The mean insulin bolus dose administered less than or equal to 60 minutes after exercise was 2.8 (± SD 4.4) units in the control arm, 2.2 (± SD 3.6) units in the 4s arm and 2.4 (± SD 3.7) units in the 10s arm. A mixed model was used to compare the mean insulin bolus dose

administered within 60 minutes after exercise in the control group compared to the sprinting (4s and 10s) arms and did not find a significant difference between the groups (control vs 10s: 95% CI -1.3- 0.6 p=0.46, control versus 4s: 95% CI -1.3 -0.6, p=0.47).

The mean insulin bolus dose administered less than or equal to 180 minutes after exercise was 6.0 (± SD 7.5) units in the control arm, 5.0 (± SD 5.3) units in the 4s arm and 6.5 (± SD 5.7) units in the 10s arm. A mixed model was used to compare the mean insulin bolus dose administered within 180 minutes after exercise in the control group compared to the sprinting (4s and 10s) arms and did not find a significant difference between the groups (control vs 10s: 95% CI -0.6- 2.2, p=0.25, control versus 4s: 95% CI -1.6- 1.1, p=0.68).

The mean insulin bolus dose administered less than or equal to 360 minutes after exercise was 8.7 (± SD 8.6) units in the control arm, 7.2 (± SD 5.9) units in the 4s arm and 9.1 (± SD 7.4) units in the 10s arm. A mixed model was used to compare the mean insulin bolus dose administered within 360 minutes after exercise in the control group compared to the sprinting (4s and 10s) arms and did not find a significant difference between the groups (control vs 10s: 95% CI –1.0- 2.4, p=0.43, control versus 4s: 95% CI -2.2- 1.1, p=0.52).

3.5.13 ***Carbohydrate intake prior to exercise***

Carbohydrate intake prior to exercise (ingested less than or equal to 60, 180 or 360 minutes prior to starting exercise) did not differ significantly between the study arms (control, 10s and 4s) (see table 10).

The mean amount of carbohydrate ingested less than or equal to 60 minutes prior to starting exercise was 8.5 (± SD 8.4) g in the control arm 6.7 (± SD 7.5) g in the 4s arm and 7.9 (± SD 6.6) g in the 10s arm. A mixed model was used to compare the mean carbohydrate intake within 60 minutes prior to exercise in the control group compared to the sprinting arms and did not find a significant difference between the groups (control vs 10s: 95% CI –5.0- 3.1, p=0.65, control versus 4s: 95% CI -6.0 -1.8, p=0.30).

The mean amount of carbohydrate ingested less than or equal to 180 minutes prior to starting exercise was 24.9 (± SD 18.6) g in the control arm 26.0 (± SD 16.9) g in the 4s arm and 29.3 (± SD 21.2) g in the 10s arm. A mixed model was used to compare the mean carbohydrate intake within 180 minutes prior to exercise in the control group compared to the sprinting arms and did not find a significant difference between the groups (control vs 10s: 95% CI -5.3- 11.6, p=0.46, control versus 4s: 95% CI -7.5- 8.9, p=0.87).

The mean amount of carbohydrate ingested less than or equal to 360 minutes prior to starting exercise was 55.4 (± SD 28.5) g in the control arm 59.1 (± SD 31.3) g in the 4s arm and 59.5 (± SD 31.5) g in the 10s arm. A mixed model was used to compare the mean carbohydrate intake within 360 minutes prior to exercise in the control group compared to the sprinting arms and did not find a significant difference between the groups (control vs 10s: 95% CI -10.1- 10.2, p=0.99, control versus 4s: 95% CI -8.5- 11.2, p=0.79).

3.5.14 ***Carbohydrate intake during exercise***

The proportion of exercise bouts with carbohydrate intake (exercise bouts with carbohydrate intake/exercise bouts without CHO intake) was compared between groups instead of total grams of carbohydrate consumed during exercise as the distribution of carbohydrate intake during a bout of exercise was not normally distributed and it was therefore more meaningful to analyse from a dichotomous perspective.

Carbohydrate was consumed during exercise in 13.3% of the total number of exercise bouts in the control arm, 14.5% in the 4s arm and in 4.7% in the 10s arm. A mixed logistic regression was used to compare the proportion of exercise bouts with carbohydrate intake during exercise in the control and sprinting arms (see figure 21).

There was a significantly lower proportion of exercise bouts with carbohydrate intake in the 10s compared to the control arm (95% CI 0.09- 0.81, p=0.02) with an odds ratio of 0.27. There was no difference between the 4s compared to the control arm (95% CI 0.50-2.42, p=0.81) with an odds ratio of 1.10.

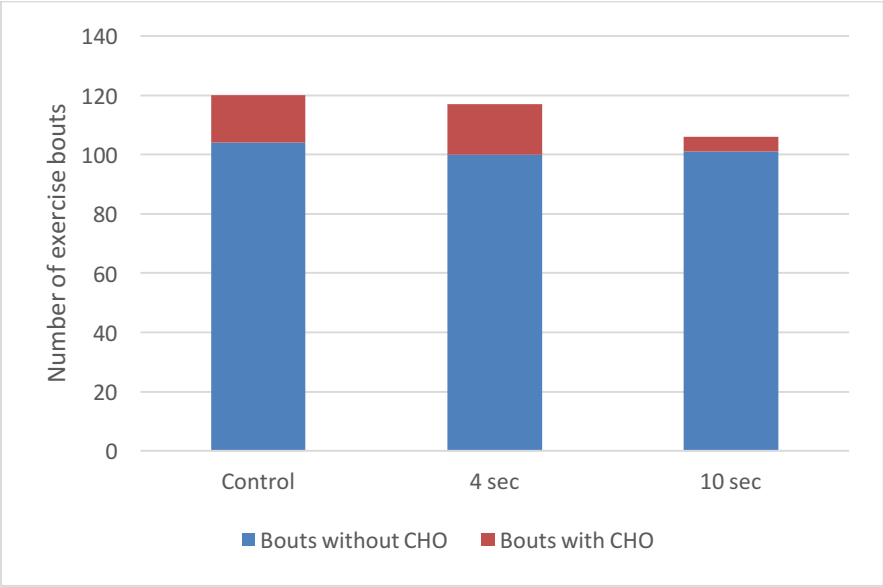

Figure 26: Proportion of exercise bouts with carbohydrate intake during exercise

3.5.15 ***Carbohydrate intake after exercise***

Carbohydrate intake after exercise (ingested less than or equal to 60, 180 and 360 minutes after finishing exercise) did not differ significantly between the study arms (control, 10s and 4s) (see table 10).

The mean amount of carbohydrate ingested less than or equal to 60 minutes after finishing exercise was 15.6 (± SD 17.5) g in the control arm, 12.2 (± SD 12.6) g in the 4s arm and 12.6 (± SD 11.2) g in the 10s arm. A mixed model was used to compare the mean carbohydrate intake within 60 minutes after exercise in the control group compared to the sprinting arms and did not find a significant difference between the groups (control vs 10s: 95% CI –9.4- 3.4, p=0.36, control versus 4s: 95% CI -9.5- 2.9, p=0.30).

The mean amount of carbohydrate ingested less than or equal to 180 minutes after finishing exercise was 44.1 (± SD 25.8) g in the control arm, 45.7 (± SD 22.4) g in the 4s arm and 45.9 (± SD 21.3) g in the 10s arm. A mixed model was used to compare the mean carbohydrate intake within 180 minutes after exercise in the control group compared to the sprinting arms and did not find a significant difference between the groups (control vs 10s: 95% CI –6.8- 10.2, p=0.70, control versus 4s: 95% CI -5.6- 10.8, p=0.53).

The mean amount of carbohydrate ingested less than or equal to 360 minutes after finishing exercise was 60.6 (± SD 32.8) g in the control arm, 66.0 (± SD 34.2) g in the 4s arm and 73.4 (± SD 32.0) g in the 10s arm. A mixed model was used to compare the mean carbohydrate

intake within 360 minutes after exercise in the control group compared to the sprinting arms and did not find a significant difference between the groups (control vs 10s: 95% CI –1.6- 24.7, p=0.09, control versus 4s: 95% CI -6.7- 18.8 p=0.35).

3.5.16 ***Adverse events***

No adverse events including moderate (requiring assistance) and severe hypoglycaemia (coma or convulsion) occurred during the study.

3.6 Glycaemic Outcomes for Day and Night

3.6.1 ***Summary of glycaemic outcomes for day and night***

Glycaemic outcomes including hypoglycaemic events and the average time spent in hypoglycaemic, in-target and hyperglycaemic ranges were examined during day and night time periods (see Table 5). Day-time was defined as 06:00-22:00 hrs, night-time was defined as 22:00-06:00 hrs.

Day (0600-22:00 hrs)	**Night** (22:00-0600 hrs)
Hypoglycaemic events:	**Hypoglycaemic events:**
SGLs <3.1mmol/L for ≥ 20 mins	SGLs <3.1mmol/L for ≥ 20 mins
SGLs <3.5mmol/L for ≥ 20 mins	SGLs <3.5mmol/L for ≥ 20 mins
SGLs <3.9mmol/L for ≥ 20 mins	SGLs <3.9mmol/L for ≥ 20 mins
Average percent of time spent with SGLs:	**Average percent of time spent with SGLs:**
<3.1mmol/l	<3.1mmol/l
<3.5mmol/l	<3.5mmol/l
<3.9mmol/l	<3.9mmol/l
3.5-<8.0mmol/L	3.5-<8.0mmol/L
8.0- 10.0mmol/L	8.0-10.0mmol/L
>10.0mmol	>10.0mmol/L

Table 5: Glycaemic outcomes for day and night

3.6.2 ***Day-time hypoglycaemic events: defined as sensor glucose levels of <3.1mmol/L for greater or equal to 20 minutes***

There were no between group differences in day-time hypoglycaemic events defined as sensor glucose levels of <3.1 for greater or equal to 20 minutes (see figure 22). The total number of hypoglycaemic events (defined as glucose sensor readings of readings <3.1mmol/L for greater or equal to 20 minutes) during the day (06:00-22:00) was 71 in the control arm, compared to 64 and 66 events in the 4s and 10s arms respectively. The hypoglycaemia incidence rate was 0.4 (95% CI 0.2- 0.5) events per day, in the control arm, 0.3 (95% CI 0.2- 0.5) events per day in the 4s arm and 0.3 (95% CI 0.2- 0.5) events per day in the 10s arm. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.85 (95% CI 0.57- 1.27; p= 0.43). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.87 (95% CI 0.59- 1.29; p= 0.50).

3.6.3 ***Daytime hypoglycaemic events: defined as sensor glucose Levels of <3.5mmol/L for greater or equal to 20 minutes***

There were no between group differences in day-time hypoglycaemic events defined as sensor glucose levels of <3.5 for greater or equal to 20 minutes. The total number of hypoglycaemic events (defined as glucose sensor readings of readings <3.5mmol/L for greater or equal to 20 minutes) during the day (06:00-22:00) was 132 in the control arm, compared to 111 and 116 events in the 4s and 10s arms respectively. The hypoglycaemia incidence rate was 0.7 (95% CI 0.5-0.9) events per day in the control arm, 0.6 (95% CI 0.4-0.7) events per day in the 4s arm and 0.6 (95% CI 0.4- 0.7) events per day in the 10s arm. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.11 (95% CI 0.61- 1.04; p= 0.10). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.83 (95% CI 0.64- 1.09; p= 0.17).

3.6.4 ***Day-time hypoglycaemic events: defined as sensor glucose levels of <3.9mmol/L for greater or equal to 20 minutes***

There were no between group differences in day-time hypoglycaemic events defined as sensor glucose levels of <3.9 for greater or equal to 20 minutes (see figure 22). The total number of hypoglycaemic events (defined as glucose sensor readings of readings <3.9mmol/L for greater or equal to 20 minutes) during the day (06:00-22:00) was 215 in the control arm, compared to 184 and 209 events in the 4s and 10s arms respectively. The hypoglycaemia incidence rate was 1.1 (95% CI 0.8- 1.4) events per day in the control arm, 0.9 (95% CI 0.7-1.2) events per day in the 4s arm and 1.0 (95% CI 0.8-1.3) events per day in the 10s arm. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.82 (95% CI 0.64- 1.04; p= 0.10). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.93 (95% CI 0.73-1.17; p= 0.53).

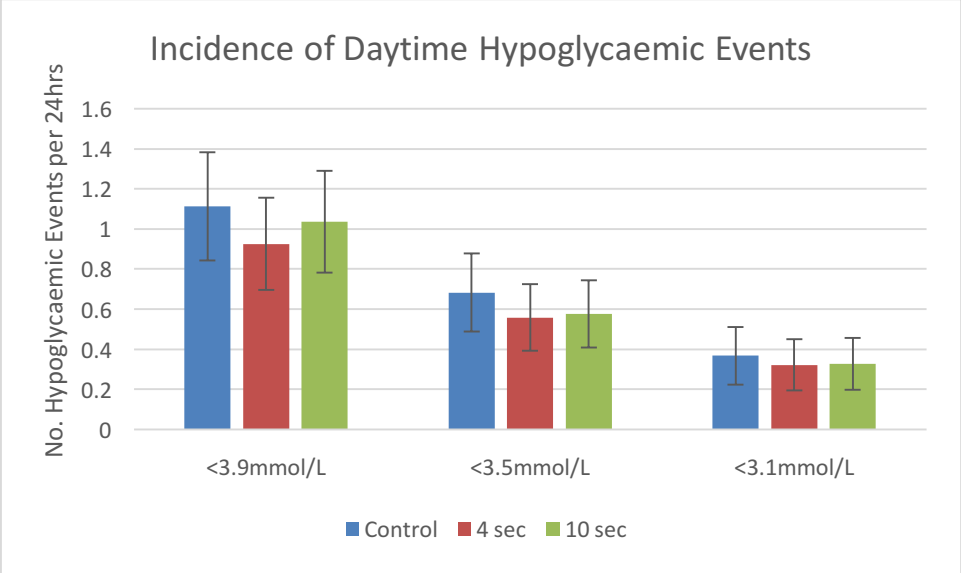

Figure 27: Incidence of daytime hypoglycaemia
Error bars represent 95% CI

3.6.5 ***Night- time hypoglycaemic events: defined as sensor glucose Levels of <3.1mmol/L for greater or equal to 20 minutes***

There were less night-time hypoglycaemic events defined as sensor glucose levels of <3.1 for greater or equal to 20 minutes in the 10s-arm compared to the control arm (see figure 23). The total number of hypoglycaemic events (defined as glucose sensor readings of readings

<3.1mmol/L for greater or equal to 20 minutes) during the night (22:00-06:00) was 47 in the control arm, compared to 40 and 26 events in the 4s and 10s arms respectively. The hypoglycaemia incidence rate was 0.5 (95% CI 0.3-0.7) events per day in the control arm, 0.4 events per day (95% CI 0.2- 0.6) in the 4s arm and 0.2 events per day (95% CI 0.1-0.4) in the 10s arm. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.81 (95% CI 0.45- 1.44; p= 0.47). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.51 (95% CI 0.27- 0.96; p= 0.04), favouring the 10s arm.

3.6.6 ***Night-time hypoglycaemic events: defined as sensor glucose levels of <3.5mmol/L for greater or equal to 20 minutes***

There were no between group differences in night-time hypoglycaemic events defined as sensor glucose levels of <3.5 for greater or equal to 20 minutes (see figure 23). The total number of hypoglycaemic events (defined as glucose sensor readings of readings <3.5mmol/L for greater or equal to 20 minutes) during the night (22:00-06:00) was 61 in the control arm, compared to 58 and 43 events in the 4s and 10s arms respectively. The hypoglycaemia incidence rate was 0.6 (95% CI 0.4- 0.9) events per day in the control arm, 0.6 events per day (95% CI 0.3-0.8) in the 4s arm and 0.4 (95% CI 0.2-0.6) events per day in the 10s arm. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.93 (95% CI 0.58- 1.5; p= 0.78). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.68 (95% CI 0.41- 1.12; p= 0.13).

3.6.7 ***Night-time hypoglycaemic events: defined as sensor glucose levels of <3.9mmol/L for greater or equal to 20 minutes***

There were no between group differences in night-time hypoglycaemic events defined as sensor glucose levels of <3.9 for greater or equal to 20 minutes (see figure 23). The total number of hypoglycaemic events (defined as glucose sensor readings of readings <3.9mmol/L for greater or equal to 20 minutes) during the night (22:00-06:00) was 92 in the control arm, compared to 84 and 73 events in the 4s and 10s arms respectively. The hypoglycaemia incidence rate was 0.9 (95% CI 0.6-1.2) events per day in the control arm, 0.8 (95% CI 0.5-1.1) events per day in the 4s arm and 0.7 (95% CI 0.4 -0.9) events per day in the 10s arm. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.88 (95% CI 0.60- 1.29, p= 0.50). Comparing the 10s

arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.75 (95% CI 0.51- 1.11; p= 0.15).

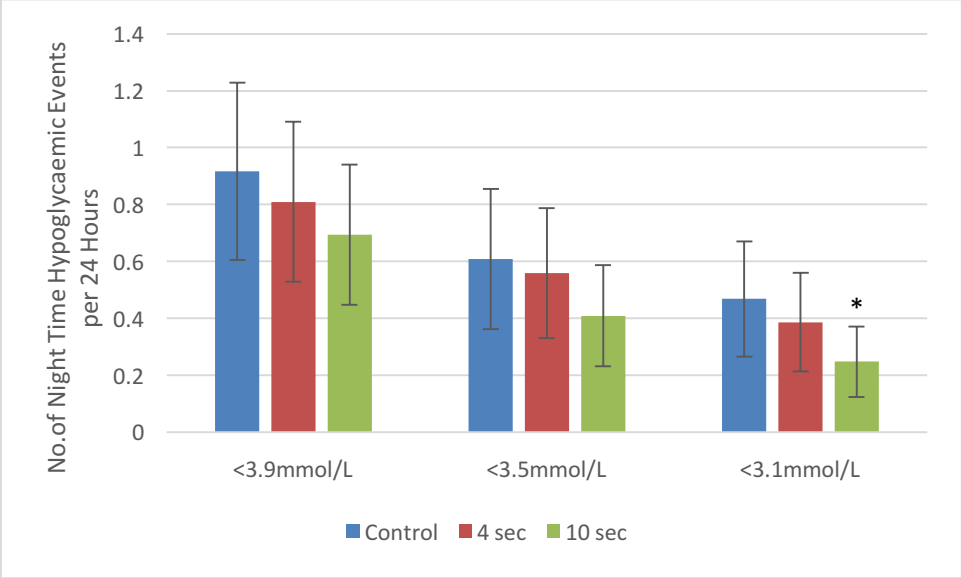

Figure 28: Incidence of night-time hypoglycaemia
****p=0.04, comparing 10s to control arm using a negative binomial mixed model***
Error bars represent 95% CI

3.6.8 ***Percent of day-time spent with sensor glucose levels< 3.1mmol/L***

The average percent of day-time spent in the hypoglycaemic range, defined as sensor glucose levels of < 3.1mmol/l, was 1.9 (± SD 2.0) % in the control arm, 1.2 (± SD 1.2) % in the 4s arm and 1.1 (± SD 0.9) % in the 10s arm (see figure 24). A mixed model was used to compare the time spent with sensor glucose levels less than 3.1mmol/l in the sprinting arms (4s and 10s) to the control arm. Significantly less time was spent less than 3.1mmol/l during the daytime in sprinting arms compared to control (10s arm compared to the control, 95% CI -1.4- -0.2%, p=0.01, 4s arm compared to control, 95% CI -1.3- -0.2%, p=0.01).

3.6.9 ***Percent of day-time spent with sensor glucose levels< 3.5mmol/L***

The average percent of day-time spent in the hypoglycaemic range, defined as sensor glucose levels of < 3.5mmol/l, was 3.0 (± SD 2.6) in the control arm, 2.1 (± SD 1.8) % in the 4s arm and 2.0 (± SD 1.5) in the 10s arm (see figure 24). A mixed model was used to compare the time spent with sensor glucose levels less than 3.5mmol/l in the sprinting arms (4s and 10s) to the control arm. Significantly less time was spent less than 3.5mmol/l during the daytime in sprinting arms compared to control (10s arm compared to the control, 95% CI -1.8- -0.2%, p=0.01, 4s arm compared to control, 95% CI -1.7- -0.2%, p=0.02).

3.6.10 ***Percent of day-time spent with sensor glucose levels< 3.9mmol/L***

The average percent of day-time spent in the hypoglycaemic range, defined as sensor glucose levels of < 3.9mmol/l, was 5.0 (± SD 3.3) % in the control arm, 3.5 (± SD 2.5) % in the 4s arm and 3.8 (± SD 2.3) % in the 10s arm (see figure 24). A mixed model was used to compare the time spent with sensor glucose levels less than 3.5mmol/l in the sprinting arms (4s and 10s) to the control arm. Significantly less time was spent less than 3.9mmol/l during the daytime in sprinting arms compared to control (10s arm compared to the control, 95% CI -2.3- -0.1%, p=0.03, 4s arm compared to control, 95% CI -2.6- -0.4, p=0.01).

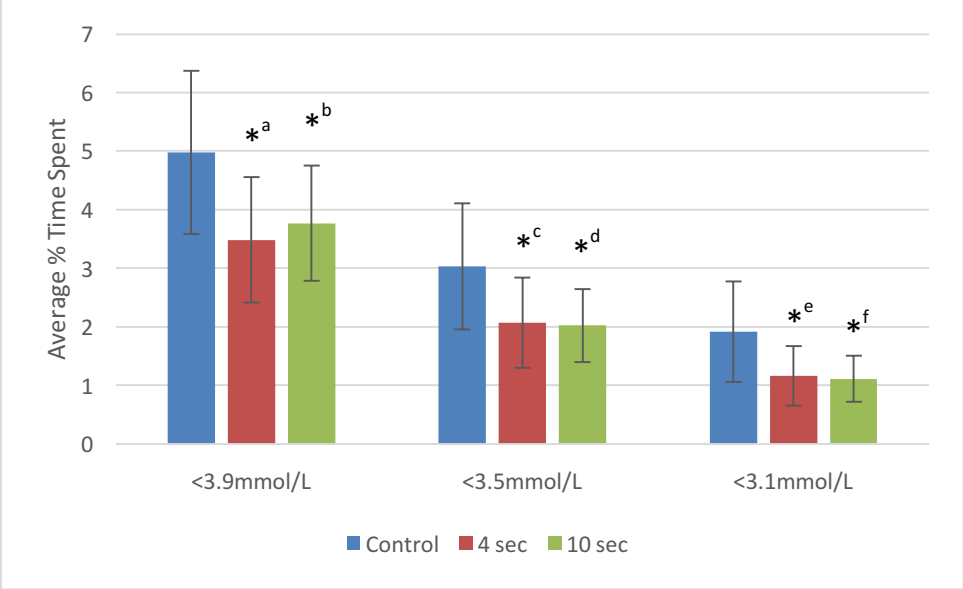

Figure 29: Average percent of daytime spent in hypoglycaemia
****a p=0.01, comparing 4s to control arm using a linear mixed model***
****b p=0.01 comparing 10s to control arm using a linear mixed model***
****c p=0.01, comparing 4s to control arm using a linear mixed model***
****d p=0.01, comparing 10s to control arm using a linear mixed model***
****e p=0.01, comparing 4s to control arm using a linear mixed model***
****f p=0.03, comparing 10s to control arm using a linear mixed model***
Error bars represent 95% CI

3.6.11 ***Percent of day-time spent with sensor glucose levels 3.5-<8.0mmol/L***

The average percent of day-time spent in target range, defined as sensor glucose levels of between 3.5-<8.0mmol/l, was 38.3 (± SD 14.6) % in the control arm, 37.4 (± SD 16.6) % in the 4s arm and 36.8 (± SD 16.1) % in the 10s arm (see table 12). A mixed model was used to compare the day-time spent with sensor glucose levels in the range 3.5- <8mmol in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between

the 10s and control arms (95% CI -5.5- 2.6, p=0.48) or the 4s and control arms (95% CI -5.0- 3.2, p=0.68).

3.6.12 ***Percent of day-time spent with sensor glucose levels 8.0-10.0mmol/L***

The average percent of day-time spent in the hyperglycaemic range defined as sensor glucose levels of between 8 -10mmol/l, was 16.8 (± SD 4.1) % in the control arm, 17.4 (± SD 4.1) % in the 4s arm and 17.0 (± SD 5.0) % in the 10s arm (see table 12). A mixed model was used to compare the day-time spent with sensor glucose levels in the range 8mmol-10mmol/L in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -1.5- 1.9%, p=0.84) or the 4s and control arms (95% CI -1.1- 2.3%, p=0.47).

3.6.13 ***Percent of day-time spent with sensor glucose levels greater than 10.0mmol/L***

The average percent of day-time spent in the hyperglycaemic range defined as sensor glucose levels greater than 10mmol/l, was 41.9 (± SD 18.1) % in the control arm, 43.1(± SD 19.0) % in the 4s arm and 44.2 (± SD 19.8) % in the 10s arm (see table 12). A mixed model was used to compare the day-time spent with sensor glucose levels in the range 8mmol-10mmol/L in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -2.3- 6.9, p =0.32) or the 4s and control arms (95% CI -3.4- 5.8%, p=0.61).

3.6.14 ***Percent of night-time spent with sensor glucose levels< 3.1mmol/L***

The average percent of night-time spent in the hypoglycaemic range, defined as sensor glucose levels of < 3.1mmol/l, was 1.9 (± SD 2.2) % in the control arm, 1.8 (± SD 2.7) % in the 4s arm and 1.3 (± SD 2.0) % in the 10s arm (see figure 25). A mixed model was used to compare the night-time spent with sensor glucose levels less than 3.1mmol/l in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -1.9- 0.7%, p=0.35) or the 4s and control arms (95% CI -1.4- 1.2, p=0.90).

3.6.15 ***Percent of night-time spent with sensor glucose levels< 3.5mmol/L***

The average percent of night-time spent in the hypoglycaemic range, defined as sensor glucose levels of < 3.5mmol/l, was 3.2 (± SD 3.2) % in the control arm, 3.2 (± SD 3.5) % in the 4s arm and 2.3 (± SD 2.7) % in the 10s arm (see figure 25). A mixed model was used to

compare the night-time spent with sensor glucose levels less than 3.5mmol/l in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -2.5- 0.8%, p=0.31) or the 4s and control arms (95% CI -1.6- 1.7%, p=0.97).

3.6.16 ***Percent of night-time spent with sensor glucose levels< 3.9mmol/L***

The average percent of night-time spent in the hypoglycaemic range, defined as sensor glucose levels of < 3.9mmol/l, was 5.2 (± SD 4.6) % in the control arm, 5.0 (± SD 4.4) % in the 4s arm and 4.2 (± SD 3.4) % in the 10s arm (see figure 25). A mixed model was used to compare the night-time spent with sensor glucose levels less than 3.9mmol/l in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -3.1- 1.1%, p=0.37) or the 4s and control arms (95% CI -2.3- 1.9%, p=0.82).

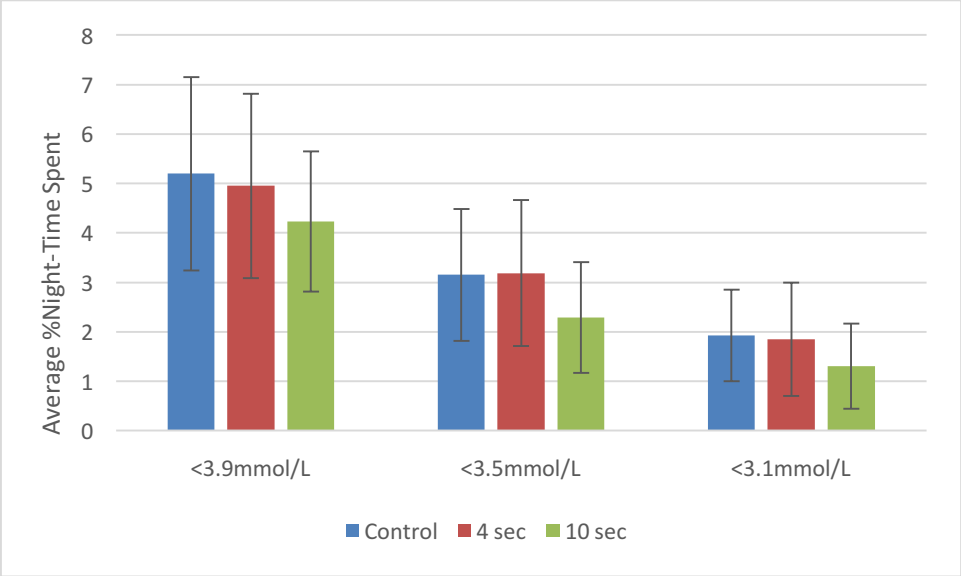

Figure 30: Average percent of night-time spent in hypoglycaemia
Error bars represent 95% CI

3.6.17 ***Percent of night-time spent with sensor glucose levels 3.5-<8.0mmol/L***

The average percent of night-time spent in target range, defined as sensor glucose levels of between 3.5-<8.0mmol/l, was 37.3 (± SD 18.1) % in the control arm, 37.3 (± SD 22.4) % in the 4s arm and 34.4 (± SD 20.1) % in the 10s arm (see table 12). A mixed model was used to compare the night-time spent with sensor glucose levels in the range 3.5- 8mmol in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between

the 10s and control arms (95% CI -8.6- 2.8%, p=0.32) or the 4s and control arms (95% CI -5.7- 5.7%, p=1.0).

3.6.18 ***Percent of night-time spent with sensor glucose levels 8.0-10.0mmol/L***

The average percent of night-time spent in the hyperglycaemic range defined as sensor glucose levels of between 8.0 -10.0mmol/l, was 17.3 (± SD 6.2) % in the control arm, 16.9 (± SD 5.5) % in the 4s arm and 16.4 (± SD 7.4) % in the 10s arm (see table 12). A mixed model was used to compare the night-time spent with sensor glucose levels in the range 8 mmol-10mmol/L in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -4.1- 2.2%, p=0.56) or the 4s and control arms (95% CI -3.6- 2.7%, p=0.78).

3.6.19 ***Percent of night-time spent with sensor glucose levels greater than 10.0mmol/L***

The average percent of night-time spent in the hyperglycaemic range defined as sensor glucose levels greater than 10.0mmol/l, was 42.2 (± SD 19.7) % in the control arm, 42.6 (± SD 23.4) % in the 4s arm and 46.9 (± SD 23.6) % in the 10s arm (see table 12). A mixed model was used to compare the night-time spent with sensor glucose levels in the range 8mmol-10mmol/L in the sprinting arms (4s and 10s) to the control arm. There was no significant difference between the 10s and control arms (95% CI -2.3- 11.7%, p=0.19) or the 4s and control arms (95% CI -6.6- 7.4%, p=0.91).

3.7 Adherence to Exercise Protocols

A total of 420 episodes of exercise occurred during the study, including 144, 138 and 138 sessions in the control, 4s and 10s arms respectively. The average number of exercise sessions during the 2-week study period were similar between the study arms 5.9 (± SD 1.0) in the control, 5.5 (± SD 1.3) in the 4s and 5.7 (± SD 1.0) in the 10s arm. Exercise watch data were only available for exercise occurring outdoors (not indoors), including 69/144, 75/138 and 67/138 total sessions in the control, 10s and 4s arms respectively. Adherence with exercise protocols were assessed using watch data and episodes were categorised as "adherent" or "non-adherent" based on pre-determined criteria outlined in the methods section. Exercise sessions were classified as adherent in 69/69 (100%), 66/75 (88%) and 65/67 (97%) of sessions in the control, 4s and 10s arms respectively.

3.8 Enjoyment of Physical Activity

The PACES questionnaire was completed by 23/24, 24/24, 24/24 participants in the control, 4s and 10s arms respectively. The mean paces score was 82.3 (± SD 11.6) for the control group, 79.5 (± SD 16.3) for the 4s 86.0 (± SD 10.7) for the 10s arms (see table 13). There was no significant difference between the 10s arm and control arms (95% CI -2.1- 8.6, p=0.23) or the 4s and control arms (95% CI -8.6- 2.1, p=0.23). However, there was statistically significant difference between the 4s and 10s arms (difference 6.5, p=0.02), with participants scoring the 10s arm as more enjoyable than the 4s arm.

3.9 Hypoglycaemia after Exercise

An exploratory analyses of hypoglycaemia outcomes in time blocks after exercise was performed post hoc. The incidence of hypoglycaemic events (defined as the number of sensor glucose readings <3.5mmol/L) and the percentage of sensor glucose readings spent in hypoglycaemic ranges (defined as number of SG readings less than 3.5mmol/l divided by the total number of SG readings) were analysed in time blocks in relation to exercise. Time blocks included; from the onset of exercise until 6 hours, 12 hours and 24 hours post exercise.

3.9.1 ***Analysis of hypoglycaemic events after exercise***

In the post exercise analyses, hypoglycaemic events were defined as a single time-point less than the defined hypoglycaemic range, and this SGL did not need to be sustained for greater or equal to 20 minutes. It was decided that counting a single time point as an event was more meaningful in view of fewer measurements in the shorter time frame of analyses, resulting in a large number of zero values when events were defined as a minimum of 20 minutes duration. Analysis was only performed for hypoglycaemic events as defined by our primary outcome, as SG levels of less than 3.5mmol/L due to the small number of events recorded in this time frame.

3.9.2 ***Analysis of percentage of sensor readings spent in hypoglycaemic ranges after exercise***

In the previously described secondary analyses, time spent in various hypoglycaemic ranges was calculated as a function of the number of readings over the total number of 5-minute sensor glucose levels. This was treated as a continuous measure and analysed using a linear

mixed model. This approach of using sensor glucose readings as a continuous variable is well established in the literature.

The post exercise analysis differs, as each reading in the defined hypoglycaemic range is treated as a count, expressed as a proportion of the total number of sensor glucose readings in the defined period. This 'count' data is analysed using a negative binomial model. This approach is used as there are far fewer measurements in this smaller time frame and if we were to treat sensor glucose levels as a continuous variable (i.e percentage time spent low) the resultant measure would be more volatile with a larger standard deviation.

3.9.3 ***Hypoglycaemic events (SGL< 3.5mmol/L) occurring up to 6 hours post exercise***

There was no difference in the incidence of hypoglycaemic events in the time period from the onset of exercise to 6 hours post exercise. The total number of hypoglycaemic events (defined as glucose sensor readings of readings <3.5mmol/L) during this period, was 27 in the control arm, compared to 26 and 28 events in the 4s and 10s arms respectively. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.98 (95% CI 0.57- 1.68; p= 0.94). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 1.05 (95% CI 0.62- 1.79, p= 0.85).

3.9.4 ***Hypoglycaemic events (SGL <3.5mmol/L) occurring up to 12 hours post exercise***

There was no difference between the arms in the incidence of hypoglycaemic events in the time period from the onset of exercise to 12 hours post exercise. The total number of hypoglycaemic events (defined as glucose sensor readings of readings <3.5mmol/L) during this period, was 54 in the control arm, compared to 41 and 45 events in the 4s and 10s arms respectively. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.78 (95% CI 0.52-1.18; p= 0.24). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.83 (95% CI 0.56- 1.25, p= 0.37).

3.9.5 ***Hypoglycaemic events (SGL <3.5mmol/L) occurring up to 24 hours post exercise***

There was no difference between the arms in the incidence of hypoglycaemic events in the time period from the onset of exercise to 24 hours post exercise. The total number of

hypoglycaemic events (defined as glucose sensor readings of readings <3.5mmol/L) during this period, was 88 in the control arm, compared to 75 and 80 events in the 4s and 10s arms respectively. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.87 (95% CI 0.62- 1.23; p= 0.43). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.89 (95% CI 0.64- 1.26, p= 0.52).

3.9.6 ***Percentage of sensor glucose levels < 3.5mmol/L up to 6 hours post exercise***

There was no difference between the arms in the percentage of sensor glucose levels less than 3.5mmol/l in the time period from the onset of exercise to 6 hours post exercise. The percentage of SGLs less than 3.5mmol/L was 2.6 (95% CI 1.7-3.6) % in the control arm, 2.6 (95% CI 1.7-3.5) % in the 4s arm and 2.6 (95% CI 1.5-3.7) % in the 10s arm. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.98 (95% CI 0.48- 2.0; p= 0.95). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 1.00 (95% CI 0.49- 2.0, p= 0.99).

3.9.7 ***Percentage of sensor glucose levels < 3.5mmol/L up to 12 hours post exercise***

There was no difference in the percentage of sensor glucose levels less than 3.5mmol/ in the time period from the onset of exercise to 12 hours post exercise. The percentage of SGLs less than 3.5mmol/L was 3.9 (95% CI 2.5-5.3) % in the control arm, 2.7 (95% CI 1.5-3.8) % in the 4s arm and 2.5 (95% CI 1.5- 3.6) % in the 10s arm. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.63 (95% CI 0.32- 1.26; p= 0.19). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.61 (95% CI 0.31-1.19, p= 0.15).

3.9.8 ***Percentage of sensor glucose levels < 3.5mmol/L up to 24 hours post exercise***

There was no difference in the proportion of sensor glucose levels less than 3.5mmol/ in the time period from the onset of exercise to 24 hours post exercise. The percentage of SGLs less than 3.5mmol/L was 3.4 (95% CI 2.3- 4.4) % in the control arm, 2.6 (95% CI 1.7- 3.5) % in the 4s arm and 2.2 (95% CI 1.5- 2.9) % in the 10s arm. When comparing the 4s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.72 (95% CI 0.42- 1.24 p= 0.24). Comparing the 10s arm to the control arm, the adjusted incidence rate ratio using the negative binomial model was 0.64 (95% CI 0.38- 1.09, p= 0.10).

3.10 Sensor Glucose Levels During Exercise

An exploratory analyses of sensor glucose levels during exercise was performed post hoc.

3.10.1 ***Sensor glucose levels at the start of exercise***

There was no difference in sensor glucose levels (SGL) at the start of exercise between the study arms. The mean SGL at the onset of exercise was 9.7 (95% CI 9.0-10.4), 9.1 (95% CI 8.4-9.7) and 9.2 (95% CI 8.6-9.8) mmol/L for the control, 4s and 10s arms respectively. A linear mixed model approach was used to compare the sprinting arms to the control arm. There was no significant difference between the 10s and control arms (95% CI -1.2- 0.5mmol/L, p=0.37) or the 4s and control arms (95% CI -1.5- 0.2mmol/L, p=0.14).

3.10.2 ***Change in sensor glucose levels during exercise***

No significant difference in the change in SGL (SGL at onset exercise- SGL at end of exercise) was demonstrated between the sprinting and control study arms. The mean change in SGL during exercise was -1.6mmol/l (95% CI -1.9- -1.3) in the control arm, -1.3 (95% CI -1.5- -1.0) in the 4s arm and -1.3 (95% CI -1.6- -1.0) mmol/l in the 10s arm. A linear mixed model comparing the sprinting arms to the control arm showed no significant differences between the groups (10s arm compared to the control, 95% CI -0.1- 0.6, p=0.2, 4s arm compared to control, 95% CI -0.1- 0.7, p=0.13).

3.10.3 ***Percentage of sensor glucose levels < 3.5mmol/L during exercise***

The percentage of SGL in the hypoglycaemic range <3.5mmol/L during exercise did not differ between the arms. Due to the short duration of exercise, there were insufficient readings to calculate percentage time spent less than 3.5mmol/L. Instead as previously described, each time point with a reading of <3.5 was counted as a single 'count', and this was divided by the total number of readings to generate the percentage of sensor glucose levels spent in hypoglycaemia. During exercise, the percentage of SGLs less than 3.5mmol/L was 3.9 (95% CI 1.3- 6.5) % in the control arm, 3.0 (95% CI 1.1- 5.0) % in the 4s arm and 3.7 (95% CI 1.4- 6.0) % in the 10s arm.

A mixed negative binomial model for the 'events' was used to compare the sprinting arms to the control arm, and found no significant difference between the arms. When comparing the 4s arm to the control arm, the adjusted incident rate ratio using the negative binomial model

was 0.82 (95% CI 0.24- 2.79, p 0.75). Comparing the 10s arm to the control arm, the adjusted incident rate ratio was 0.98 (95% CI 0.29- 3.33, p=0.98)

3.11 Subgroup Analysis

A subgroup analysis was performed to evaluate the effect of sprinting on the incidence of hypoglycaemia (defined as our primary outcome: sensor glucose readings of readings <3.5mmol/L for greater or equal to 20 minutes) in the following subgroups of participants:

- Gender (male vs female)
- Age group (aged 14-17 years vs 18-33 years)
- HbA1c category (<58mmol/mol (7.5%) vs ≥58mmol/mol (7.5%))
- VO_2 max category (<30 vs ≥ 30 ml/kg/min)
- Regimen (pump vs MDI)

No differences were identified between the sprinting arms and control arms in any of the subgroups.

Subgroup	p [¶]
Gender (Male vs female)	0.12
Age group (aged 14-17 years vs 18-33 years)	0.49
HbA1c category (<58mmol/mol (7.5%) vs ≥ 58mmol/mol (7.5%))	0.86
VO_2 max category (<30 vs ≥ 30 ml/kg/min)	0.30
Regimen (pump vs MDI)	0.12

Table 6: Subgroup analysis.
[¶]Chi^2 used to compare interaction of subgroup with study arm

3.12 Summary of Key Findings

3.12.1 ***Glycaemic outcomes***

A pattern of reduction in hypoglycaemia in the sprinting arms compared to the control arms was demonstrated across all hypoglycaemic outcomes. This pattern was seen in both 10s and 4s sprinting arms and was most marked in the 10s arm. This did not reach statistical significance in our primary outcome, but did for other established hypoglycaemia definitions (see Table 7).

A summary of key glycaemic outcomes follows:

- No significant difference was demonstrated in hypoglycaemic events as defined by our primary outcome (glucose sensor readings of readings <3.5mmol/L for greater or equal to 20 minutes) in the sprinting arms compared to the control arms. A trend of a reduction in hypoglycaemic events, most marked in the 10s arm was shown, but this did not reach statistical significance.
- There was a significant reduction in hypoglycaemic events in the 10s arm, compared to the control arm when events were defined as sensor glucose levels <3.1mmol/L for greater or equal to 20 minutes.
- The 10s sprint arm was associated with a significant reduction in time spent <3.5 and time spent <3.1mmol/L compared to the control arm.
- A reduction in night time hypoglycamic events (defined as sensor glucose levels less than 3.1mmol/ was demonstrated in the 10s arm compared to the control arm.
- No increased risk of nocturnal hypoglycaemia was found in the sprinting arms compared to the control arms.
- Both the 4s and 10s sprinting arms were associated with a significant reduction in time spent in hypoglycaemic ranges (<3.1, <3.5 and <3.9mmol/L) during the day compared to the control arm.
- There was no difference in time spent in hyperglycaemic ranges in the sprinting arms compared to the control arms

Hypoglycaemia Outcomes	Control	4s	p	10s	p
Events: SG<3.5mmol/L for ≥20 mins, incidence rate per 24 hrs	0.6	0.6	0.28	0.5	0.05
Events: SG<3.1mmol/L for ≥20 mins/24 hrs	0.4	0.3	0.27	0.3*	0.04a
% Time (hours) spent SG <3.5mmol/L	3.1	2.5	0.18	2.1*	0.03[b]
% Time (hours) spent SG <3.1mmol/L	1.9	1.4	0.13	1.2*	0.03[b]
Night events (22:00-06:00): SG<3.1mmol/L for ≥20 mins/24 hrs	0.5	0.4	0.47	0.2*	0.04[a]
% Day time (06:00-22:00) spent SG <3.1mmol/L	1.9	1.2*	0.01[c]	1.1*	0.01[b]
% Day time (06:00-22:00) spent SG <3.5mmol/L	3.0	2.1*	0.02[c]	2.0*	0.01[b]
% Day time (06:00-22:00) spent SG <3.9mmol/L	5.0	3.5*	0.01[c]	3.8*	0.03[b]

Table 7: Summary of key hypoglycaemic outcomes

[a] Comparing 10s to control arm using a negative binomial mixed model

[b] Comparing 10s to control arm using a linear mixed model

[c] Comparing 4s to control arm using a linear mixed model

****Statistically significant finding, where p value <0.05***

3.12.2 ***Insulin dosing and carbohydrate intake around exercise***

A summary of key insulin and carbohydrate outcomes follows:

- Insulin dosing before, during and after exercise did not differ between the study arms.
- Carbohydrate intake before and after exercise did not differ between the study arms
- Fewer carbohydrate intake episodes occurred during the 10 s sprint exercise sessions compared to the control exercise sessions

3.12.3 ***Enjoyment of physical activity***

Key findings:

- There was no difference in participants enjoyment of exercise (as determined by the PACES questionnaire) in the 10s arm compared to the control arm.
- Participants rated the 10s-sprint exercise as significantly more enjoyable than the 4s sprint exercise using the PACES scale.

3.13 Results Tables

	Control	4s	p[a]	10s	p[b]
SG<3.5mmol/L for ≥20 mins, incidence rate per 24 hrs (95% CI)	0.6 (0.5-0.8)	0.6 (0.4-0.7)	0.28	0.5 (0.4-0.6)	0.05
SG<3.1mmol/L for ≥20 mins, incidence rate per 24 hrs (95% CI)	0.4 (0.-03.6)	0.3 (0.2-0.5)	0.27	0.3 (0.2-0.4)	0.04*
SG<3.9mmol/L for ≥20 mins, incidence rate per 24 hrs (95% CI)	1.0 (0.8-1.2)	0.8 (0.6-1.0)	0.10	0.9 (0.7-1.1)	0.21

Table 8: Hypoglycaemic events

[a] Comparing 4s to control arm using a negative binomial mixed model

[b] Comparing 10s to control arm using a negative binomial mixed model

**** Statistically significant finding, where p value <0.05***

Mean %Time Spent	Control	4s	p[a]	10s	p[b]
Mean % time spent SG <3.1mmol/L (SD)	1.9 (1.8)	1.4 (1.5)	0.13	1.2* (1.1)	0.03
Mean % time spent SG <3.5mmol/L (SD)	3.1 (2.5)	2.5 (2.1)	0.18	2.1* (1.5)	0.03
Mean % time spent SG <3.9mmol/L (SD)	5.0 (3.3)	4.0 (2.8)	0.08	3.9 (2.1)	0.06
Mean % time spent SG 3.5-<8.0 mmol/L (SD)	38.0 (14.9)	37.4 (17.3)	0.77	36.0 (15.9)	0.33
Mean % time spent SG 8.0-10.0 mmol/L (SD)	17.0 (3.6)	17.3 (3.7)	0.79	16. 8 (4.7)	0.77
Mean % time spent SG >10.0 mmol/L (SD)	41.9 (17.6)	42.9 (19.4)	0.70	45.1 (19.4)	0.21

Table 9: Average percent of time spent in defined glycaemic ranges

[a] Comparing 4s to control arm using a linear mixed model

[b] Comparing 10s to control arm using a linear mixed model

	Control	4s	p[a]	10s	p[b]
Mean total daily insulin dose, (SD) U/kg/day	0.65 (0.23)	0.66 (0.22)	0.87	0.69 (0.25)	0.05
Insulin bolus doses prior to exercise:					
Insulin bolus dose ≤ 60 mins prior to exercise (SD), U	1.2 (2.5)	0.8 (1.6)	0.24	1.1 (2.2)	0.74
Insulin bolus dose ≤ 180 mins prior to exercise (SD), U	3.1 (4.1)	4.1 (5.0)	0.27	3.6 (3.7)	0.44
Insulin bolus dose ≤ 360 mins prior to exercise (SD), U	6.7 (5.7)	7.6 (6.6)	0.41	7.3 (5.4)	0.40
Insulin bolus does after exercise:					
Insulin bolus dose ≤ 60 mins after exercise (SD), U/kg	2.8 (4.4)	2.2 (3.6)	0.47	2.4 (3.7)	0.46
Insulin bolus dose ≤ 180 mins after exercise (SD), U	6.0 (7.5)	5.0 (5.3)	0.68	6.5 (5.7)	0.25
Insulin bolus dose ≤ 360 mins after exercise (SD), U	8.7 (8.6)	7.2 (5.9)	0.52	9.1 (7.4)	0.43
CHO intake prior to exercise:					
CHO intake ≤ 60 mins prior to exercise, (SD) g	8.5 (8.4)	6.7 (7.5)	0.30	7.9 (6.6)	0.65
CHO intake ≤ 180 mins prior to exercise, (SD) g	24.9 (18.6)	26.0 (16.9)	0.87	29.3 (21.2)	0.46
CHO intake ≤ 360 mins prior to exercise (SD), g	55.4 (28.5)	59.1 (31.3)	0.79	59.5 (31.5)	0.99
CHO intake during exercise:					
Proportion of exercise bouts with CHO intake during exercise, % of total exercise bouts per arm	13.3	14.5	0.81	4.7*	0.02
CHO intake after exercise:					
CHO intake ≤ 60 mins after exercise, (SD) g	15.6 (17.5)	12.2 (12.6)	0.30	12.6 (11.2)	0.36
CHO intake ≤ 180 mins after exercise, (SD) g	44.1 (25.8)	45.7 (22.4)	0.53	45.9 (21.3)	0.70
CHO intake ≤ 360 mins after exercise (SD), g	60.6 (32.8)	66.0 (34.2)	0.35	73.4 (32.0)	0.09

Table 10: Insulin dosing and carbohydrate (CHO) intake before, during and after exercise

[a] Comparing 4s to control arm using a linear mixed model

[b] Comparing 10s to control arm using a linear mixed model

	Control	4s	p[a]	10	p[b]
Daytime (06:00-22:00) events:					
SG<3.1mmol/L for ≥20 mins, incidence rate per 24 hrs (95% CI)	0.4 (0.2-0.5)	0.3 (0.2-0.5)	0.43	0.3 (0.2-0.5)	0.50
SG<3.5mmol/L for ≥20 mins, incidence rate per 24 hrs (95% CI)	0.7 (0.5-0.9)	0.6 (0.4-0.7)	0.10	o.6 (0.4-0.7)	0.17
SG<3.9mmol/L for ≥20 mins, incidence rate per 24 hrs (95% CI)	1.1 (0.8-1.4)	0.9 (0.7-1.2)	0.10	1.0 (0.8-1.3)	0.53
Night-time (22:00-06:00) events:					
SG<3.1mmol/L for ≥20 mins, incidence rate per 24 hrs (95% CI)	0.5 (0.3-0.7)	0.4 (0.2-0.6)	0.47	0.2* (0.1-0.4)	0.04
SG<3.5mmol/L for ≥20 mins, incidence rate per 24 hrs (95% CI)	0.6 (0.4-0.9)	0.6 (0.3-0.8)	0.78	0.4 (0.2-0.6)	0.13
SG<3.9mmol/L for ≥20 mins, incidence rate per 24 hrs (95% CI)	0.9 (0.6-1.2)	0.8 (0.5-1.1)	0.50	0.7 (0.4-0.9)	0.15

Table 11: Daytime and night-time hypoglycaemic events

[a] Comparing 4s to control arm using a negative binomial mixed model

[b] Comparing 10s to control arm using a negative binomial mixed model

[*] Statistically significant finding, where p value <0.05

	Control	4s	p[a]	10s	p[b]
Average percent of daytime spent:					
Mean % daytime spent SG <3.1mmol/L (SD)	1.9 (2.0)	1.2* (1.2)	0.01	1.1* (0.9)	0.01
Mean % daytime spent SG <3.5mmol/L (SD)	3.0 (2.6)	2.1* (1.8)	0.02	2.0* (1.5)	0.01
Mean % daytime spent SG <3.9mmol/L (SD)	5.0 (3.3)	3.5* (2.5)	0.01	3.8* (2.3)	0.03
Mean % daytime spent SG 3.5-8mmol/L (SD)	38.3 (14.6)	37.4 (16.6)	0.68	36.8 (16.1)	0.48
Mean % daytime spent SG 8.0-10.0mmol/L (SD)	16.8 (4.1)	17.4 (4.1)	0.47	17.0 (5.0)	0.84
Mean % day time spent SG >10mmol/L	41.9 (18.1)	43.1 (19.0)	0.61	44.2 (19.8)	0.32
Average percent of night time spent:					
Mean % night-time spent SG <3.1mmol/L (SD)	1.9 (2.2)	1.8 (2.7)	0.90	1.3 (2.0)	0.35
Mean % night-time spent SG <3.5mmol/L (SD)	3.2 (3.2)	3.2 (3.5)	0.97	2.3 (2.7)	0.31
Mean % night-time spent SG <3.9mmol/L (SD)	5.2 (4.6)	5.0 (4.4)	0.82	4.2 (3.4)	0.37
Mean % night-time spent SG 3.5-8.0mmol/L (SD)	37.3 (18.1)	37.3 (22.4)	1.00	34.4 (20.1)	0.32
Mean % night-time spent SG 8-10.0mmol/L (SD)	17.3 (6.2)	16.9 (5.5)	0.78	16.4 (7.4)	0.56
Mean % night- time spent SG >10.0mmol/L (SD)	42.2 (19.7)	42.6 (23.4)	0.91	46.9 (23.6)	0.19

Table 12: Average percent of day time and night-time spent in defined glycaemic ranges

[a] Comparing 4s to control arm using a linear mixed model

[b] Comparing 10s to control arm using a linear mixed model

	Control	4s	10	p[a]	p[b]	p[c]
Mean PACES score[¶] (SD) [n]	82.3 (11.6) [23]	79.5 (16.3) [24]	86.0* (10.7) [24]	0.23	0.23	0.02

Table 13: Physical activity enjoyment scale questionnaire score

[¶] 16 statements scored 1-7 (1 least enjoyable, 7 most enjoyable) and summed

[a]Comparing 4s to control using a mixed model

[b]Comparing 10s to control using a mixed model

[c]Comparing 10s to 4s using a mixed model

Chapter 4: Discussion

4.1 Purpose of the Study

Maintaining stable blood glucose levels around exercise remains a major challenge for individuals with T1D. In particular, physical activity is associated with an increased risk of hypoglycaemia for insulin treated individuals with diabetes (Camacho, Galassetti et al. 2005, Galassetti and Riddell 2013). The resulting fear of hypoglycaemia is often perceived by people with T1D as the most significant barrier to adopting a physically active lifestyle (Brazeau, Rabasa-Lhoret et al. 2008), despite the well-established health benefits of regular exercise.

Not all forms of exercise result in a decline in blood glucose levels. It is well known that high intensity exercise and sprinting can be associated with a rise in blood glucose concentrations (Mitchell, Abraham et al. 1988, Marliss, Simantirakis et al. 1991, Sigal, Fisher et al. 2000). This has led to the investigation of sprinting as a possible strategy to prevent exercise mediated hypoglycaemia in individuals with T1D (Guelfi, Jones et al. 2005, Bussau, Ferreira et al. 2006, Bussau, Ferreira et al. 2007, Guelfi, Ratnam et al. 2007). Classical exercise management strategies involve adjustment of carbohydrate intake or insulin dosing. As insulin adjustment requires a degree of forward planning, sprinting may be a useful carbohydrate sparing tool in the setting of unplanned exercise.

Previous studies have demonstrated that a 10s-sprint performed before or after 20 minutes of moderate-intensity exercise can prevent blood glucose levels from falling for up to two hours post-exercise (Bussau, Ferreira et al. 2006, Bussau, Ferreira et al. 2007). It has also been shown that engaging in repeated maximal 4-s sprints every 2 min during a 30-minute bout of moderate intensity exercise compared to continuous moderate intensity exercise reduces the rate of fall in blood glucose levels both during and up to 90 minutes after exercise in individuals with T1D (Guelfi, Jones et al. 2005). All studies to date have investigated the glycaemic effects of sprinting in a clinic-based setting under controlled laboratory conditions.

Before advocating the use of sprinting as a method for reducing the risk of exercise-mediated hypoglycaemia in individuals with T1D, it is important to determine whether findings in the laboratory are also applicable in a practical, free-living setting. This is an essential step in translating laboratory findings into clinical practice. Therefore, the specific

aim of this study was to determine the effectiveness of incorporating short sprints into moderate intensity exercise for hypoglycaemia prevention during exercise in individuals with T1D in a free-living setting.

4.2 Summary of Main Findings

In this study, we found that incorporating sprinting into moderate intensity exercise did not reduce the rate of hypoglycaemic events, as defined in our primary outcome (sensor glucose levels of less than 3.5mmol/L for greater or equal to 20 minutes). However, when hypoglycaemic events were defined, in concordance with recently published guidelines (Schnell, Barnard et al. 2017) as <3.1mmol/l, we demonstrated a reduction in hypoglycaemic events over the 2-week study period in the 10s-arm compared to the control arm. The 10s arm, was also shown to be associated with a significant reduction in the time spent in a hypoglycaemic range (<3.1 and <3.5mmol/l). In addition, carbohydrate intake during exercise occurred less frequently during the 10s-sprint condition, and may represent reduced symptomatic hypoglycaemia during exercise. There was no increase in nocturnal hypoglycaemic events in the sprinting compared to the control arms. The 10s-sprint arm was associated with a reduction in hypoglycaemic events <3.1mmol/l overnight. There was no difference in time spent in hyperglycaemic ranges between sprinting and control study arms. Enjoyment of exercise sessions, as determined by the PACES questionnaire was similar for the 10s and control arms. Participants scored exercise in the 10s arm as more enjoyable than the 4s arm.

In summary, the incorporation of short sprints into periods of sustained moderate intensity exercise did not reduce the incidence of exercise mediated hypoglycaemia when hypoglycaemia was defined as sensor glucose levels of < 3.5mmol/l for greater or equal to 20 minutes. However, the 10s-sprint arm was associated with fewer hypoglycaemia events <3.1mmol/L and a reduction in the average time spent <3.5mmol/L and <3.1mmol/L than the control period. Furthermore, the 10s arm was associated with a reduction in hypoglycaemic events <3.1mmol/L overnight.

Data from this study suggest that incorporating 10s sprints into continuous moderate intensity exercise may reduce the incidence of hypoglycaemic events and the average time spent in a hypoglycaemic range over a 2-week period, without increasing the incidence of nocturnal hypoglycaemia or time spent in hyperglycaemia. These findings suggest that

sprinting can be incorporated into exercise management plans for individuals with T1D and may reduce the risk of exercise mediated hypoglycaemia.

4.3 Results in Relation to Previous Studies

Our results are consistent with laboratory based studies that report that a 10s-sprint performed before or after 20 minutes of moderate intensity exercise can prevent a decline in blood glucose levels in recovery (Bussau, Ferreira et al. 2006, Bussau, Ferreira et al. 2007). In contrast to previous studies (Guelfi, Jones et al. 2005), no significant difference in hypoglycaemia was demonstrated between the 4s sprint and control arms of the study. However, although no statistical difference was demonstrated between the 4s and control study arms, a pattern of a graded reduction in hypoglycaemia greatest in the 10s arm, followed by the 4s arm, was evident across hypoglycaemia outcomes and may represent a dose-like effect of sprinting in reducing hypoglycaemia. Furthermore, participant adherence and perceived enjoyment of exercise was lowest in the 4s condition compared to 10s or control conditions. These findings may imply that participants found the 4s sprint protocol difficult to perform in a free-living setting, raising questions about the practical feasibility of translating the 4s sprint protocol from the laboratory into the real-world. Consequently, the lack of glycaemic outcome difference between the 4s and control arms may in part be related to insufficient sprinting during the 4s protocol because of difficulties with protocol adherence.

4.4 Potential Concerns about Sprinting

4.4.1 ***Sprinting and risk of late onset post exercise hypoglycaemia***

In contrast to some reports in the literature, our study did not demonstrate any increased risk of nocturnal hypoglycaemia associated with sprinting. Maran et al, found that intermittent high intensity exercise (5s sprints every 2 minutes during moderate intensity exercise) was associated with an increased risk of nocturnal hypoglycaemia when compared with continuous moderate intensity exercise alone in non-trained individuals with T1D (Maran, Pavan et al. 2010). Similar to our findings, other studies do not demonstrate an increased risk of delayed onset post exercise hypoglycaemia with intermittent high intensity exercise (Iscoe and Riddell 2011, Davey, Bussau et al. 2013, Campbell, West et al. 2015, Moser, Tschakert et al. 2015, Bally, Zueger et al. 2016).

The reasons for conflicting findings in the literature remain unclear. Iscoe et al suggest that the discrepancy in findings between their study and Maran's study may in part be related to differences in the training status of the study populations. Iscoe et al postulate that their finding of a reduction in nocturnal hypoglycaemia following high intensity exercise, may be related to the highly trained nature of their participants who had a mean VO_2 max of 42.4 $\pm$ 1.6 (Iscoe and Riddell 2011), higher than the participants in Maran's study who had a mean VO2 max of 33 $\pm$ 6.1ml/kg/min (Maran, Pavan et al. 2010). Our findings do not support this hypothesis as our study population were not highly trained and no increased risk of late onset post exercise hypoglycaemia was demonstrated. Our study population had a mean VO_2 max of 32.7 $\pm$ 7.1 ml/kg/min, lower than reported by Iscoe et al. Our VO_2 findings are also lower than data reported from a study population of individuals with T1D aged between 9 and 20 years, who were exercising not more than twice a week and had a mean VO_2 max of 41.6 $\pm$ 7.7 (Komatsu, Gabbay et al. 2005). Our VO_2 data are similar to normative data derived from an adult population of healthy, untrained individuals where females had a mean VO_2 max of 27.5ml/kg/min and males had a mean VO_2 max of 37.9ml/kg/min (Myers, Kaminsky et al. 2017).

4.4.2 ***Effect of antecedent hypoglycaemia and exercise on the glycaemia rising effect of sprinting***

The glycaemic effects of sprinting in a free-living setting, in-contrast to the laboratory, may be influenced by other factors such as antecedent hypoglycaemia and exercise. Antecedent hypoglycaemia has been shown to increase the risk of exercise induced hypoglycaemia in subsequent moderate intensity exercise by blunting the counter regulatory response to hypoglycaemia (Galassetti, Tate et al. 2003). There is evidence to suggest that this is not the case following a 10s sprint, as the glycaemia increasing effect of a 10s sprint is not diminished following hypoglycaemia (Davey, Paramalingam et al. 2014).

Antecedent exercise has also been shown to increase the risk of hypoglycaemia in subsequent moderate intensity exercise. There are no studies to date examining the effect of frequent bouts of high intensity exercise on the glycaemic response to sprinting. Our findings of a small reduction in the incidence of hypoglycaemia over a 2-week period, suggest that antecedent exercise or hypoglycaemia does not completely diminish the protective effect of sprinting.

4.4.3 ***Effect of sprinting on hypoglycaemia awareness***

The study was not designed to test the effect of sprinting on hypoglycaemia awareness. The fact that a positive effect was seen in hypoglycaemia reduction during the study period is reassuring as it suggests that any reduction in hypoglycaemia awareness was not large enough to result in increased hypoglycaemia events. Furthermore, there were no episodes of moderate or severe hypoglycaemia during the study. All participants had to be hypoglycaemia aware (defined as a Clarke's score of equal or less than 4) to be eligible to take part in the study. There is some evidence that in individuals with T1D who are hypoglycaemia aware, high intensity intermittent training may reduce awareness of subsequent hypoglycaemia (Rooijackers, Wiegers et al. 2017). Interestingly, in the same study symptoms of hypoglycaemia were not reduced in individuals with T1D with known impaired awareness of hypoglycaemia. In addition, high intensity exercise has recently been shown to restore the counter regulatory response in recurrently hypoglycaemic rodents (McNeilly, Gallagher et al. 2017).

4.4.4 ***Feasibility of sprinting***

Findings from this study show that sprinting during exercise is feasible in a free-living setting. Sprinting did not adversely impact on the enjoyment of exercise compared to sustained moderate intensity exercise. Participants scored the 10s-sprint exercise as more enjoyable than the 4s sprint exercise using the PACES questionnaire. Based on outdoor exercise sessions (as only outdoor exercise could be assessed for protocol adherence), 97% 10s sprint exercise sessions were classified as adherent compared to 88% of 4s sprint exercise sessions. These findings suggest that the 10s protocol was more enjoyable and potentially more feasible in a free-living setting compared to the 4s sprint protocol.

4.5 Potential Confounding Factors

We set out to test the hypothesis that incorporating short sprints into moderate intensity exercise can reduce the incidence of exercise mediated hypoglycaemia in individuals with T1D. Our findings suggest that incorporating 10s sprints into moderate intensity exercise may reduce the incidence of hypoglycaemia over a 2-week period during which exercise is performed at least 3 times a week.

Results are in keeping with laboratory studies that demonstrate a glycaemia rising effect of short sprints. Nevertheless, we should consider if our positive findings could be a result of a confounding factor and not directly attributable to sprinting per se.

Our study design and secondary analysis (including insulin dosing and carbohydrate intake on exercise days and sensor glucose levels at the start of exercise) suggest our findings are likely to be caused by the presence of sprinting during exercise and not due to a confounding factor.

4.5.1 ***Study design and minimisation of confounding factors***

The cross over design of the study means that all participants completed all three study conditions (control, 10s and 4s sprint protocols), thereby acting as their own controls. This reduces the likelihood of confounding factors such as differences in fitness levels, gender, glycaemic control, exercise management strategies including carbohydrate intake and insulin adjustment. To balance any effect of the order of conditions on study findings, participants were randomised to one of six 'sequences' based on the order in which they were to receive conditions.

4.5.2 ***Insulin dosing and carbohydrate intake on exercise days***

Analysis of insulin dosing and carbohydrate intake in time bands before and after exercise shows no differences between sprinting and control arms. Investigation of carbohydrate intake during exercise shows a reduction in carbohydrate intake during exercise in the 10s compared to the control arm. This suggests that there may be fewer episodes of symptomatic hypoglycaemia during exercise in the 10s arm.

4.5.3 ***Sensor glucose levels at the start of exercise***

Another potential confounding factor is the sensor glucose level at the start of exercise and we have shown that this did not differ significantly between conditions.

4.6 Mechanism of Glycaemia Rising Effect of Sprinting and Timing of Effect

This home-based study was not designed to assess the mechanisms underpinning the glycaemic effects of sprinting or to investigate the timing of these effects in relation to exercise. Previous laboratory based studies show that a 10s-sprint performed before or after 20 minutes of moderate intensity exercise can oppose a decline in glycaemia seen with moderate intensity exercise (without sprints) for up to 120 minutes post exercise.

Furthermore, engaging in repeated maximal 4-s sprints every 2 min during a 30-minute bout of moderate intensity exercise compared to continuous moderate intensity exercise has been shown to reduce the rate of fall in blood glucose levels both during and up to 90 minutes after exercise.

4.6.1 ***Glycaemic outcomes after exercise***

To ascertain when the sprint was exerting its glycaemia raising effect we performed an exploratory analysis to look at hypoglycaemic outcomes in time blocks (6 hours, 12 hours and 24hrs) after exercise. Unexpectedly, this did not show any differences between the groups.

This negative finding may relate to the study being underpowered to detect a difference in this shorter timeframe. A further explanation may be that if sprinting is associated with a small reduction in hypoglycaemia following exercise that we have been underpowered to detect, then this positive effect may have ongoing continued benefit in hypoglycaemia reduction on subsequent non-exercise days. It is well established that lows beget lows- and a single episode of afternoon hypoglycaemia has been shown to impair physiological defences to hypoglycaemia the following morning (Dagogo-Jack, Craft et al. 1993). Thus, a small reduction in hypoglycaemia on exercise days may confer a larger benefit when outcomes are measure over a longer (i.e 2 week) time frame.

This study occurring in a free-living setting was designed to address the question: “can sprinting during exercise help prevent exercise mediated hypoglycaemia.” Our findings suggest that sprinting for 10s at 20 minute intervals may offer a small reduction in hypoglycaemia over a 2 -week period, the mechanism of exactly how and when this positive effect is occurring is beyond the scope of this study.

4.6.2 ***Glycaemic outcomes and carbohydrate intake during exercise***

We looked at the change in sensor glucose level from the start of exercise to the end of exercise and showed no statistical difference between the sprinting and control study arms. However, we found that there was a significantly lower proportion of exercise bouts with carbohydrate intake in the 10s compared to the control arm. During the 10s arm the participants were 2.7 times less likely to consume carbohydrate during exercise than in the control arm. This may be clinically relevant as carbohydrate intake during exercise is likely to represent treated symptomatic hypoglycaemia.

4.6.3 ***Influence of other factors (age, fitness, HbA1c, gender and adherence with study protocol)***

Glycaemic responses to sprinting may vary based upon factors such as age, gender, glycaemic control and fitness levels. We performed a post hoc subgroup analysis to explore if specific factors influenced the effect of sprinting in our study population. We did not demonstrate any difference in hypoglycaemic outcomes when outcomes were analysed by HbA1c, gender, insulin regimen, baseline VO_2 max score or compliance with exercise protocols. It should be noted that the study was not powered for subgroup analysis and negative findings may represent inadequate power to detect a difference between the groups.

4.7 Limitations of the Study

4.7.1 ***Sample size and study power***

The sample size achieved for the study was lower than estimated in the original power calculation. A total of 24 participants were included in analyses, compared to a recommended sample size of 50. This smaller sample size means the study may not have been sufficiently powered to detect a difference between the groups. This may explain the failure to demonstrate a difference in our primary outcome (defined as sensor glucose readings of readings <3.5mmol/L for greater or equal to 20 minutes). However, a statistically significant difference was seen in our secondary analysis, when hypoglycaemic events were defined as <3.1mmol/L, and when the average time spent in various hypoglycaemic ranges were explored. Furthermore, consistent with these positive findings, a dose-like effect pattern of a graded reduction in hypoglycaemia greatest in the 10s arm, followed by the 4s arm (although not statistically significant), was evident across hypoglycaemia outcomes.

4.7.2 ***Recruitment, retention and exclusion of participants.***

The main factors contributing to this suboptimal sample size were difficulties with recruitment and retention of participants. Recruitment was indeed challenging. Verbal feedback form patients who declined to participate included concerns about committing to a 10-12-week study period, having to exercise at least 3 times a week, attending up to 8 hospital visits, and wearing blinded CGM. Recruitment became even more challenging in April 2017, when the Australian government announced that they would provide fully subsidised CGM to eligible children and young people aged under 21 years with T1D. Subsequently an increased accessibility to “real-time” CGM meant that many individuals

were no longer interested in participating in a study where only “blinded” CGM could be used during the study period. Therefore, a decision was made to stop recruitment in May 2017.

In terms of retention of participants, a total of 39 participants consented and attended visit 1. Eight participants then declined to participate prior to randomisation as on second thoughts they decided they were unable to commit to the study visits. 31 individuals were randomised to study protocol. Following this a further 4 participants withdrew consent (1 pregnant, 1 non-study related knee injury, 2 decided they were too busy to commit to the study visits). It is important to note that all participants who withdrew consent did so before formally starting the study period and therefore is unlikely to reflect feasibility issues with the sprinting protocols.

A further 3 participants were excluded from analysis (as detailed in the results section). This included 1 participant who despite wearing his CGM device for all 2-week study periods, no sensor glucose levels were recorded during his 4s arm. Multiple attempts were made to retrieve this data, including liaising with the CGM company directly. Unfortunately, there was no evidence of this data on the device. In line with our study protocol, data from the remaining study arms were not included in our final analysis.

2 participants were excluded from the analysis on a basis of significant breaches of study protocol. On exploration of insulin pump data, it became apparent that one participant had been wearing his own “real-time CGM device, with the predictive low suspend feature enabled, during 2 out of this 3 study periods. As this system is known to reduce hypoglycaemia this participant’s data had to be excluded from analyses. This case has important learning points for future research studies, as it demonstrates the changing landscape of technology in diabetes management, with real-time CGM and augmented insulin pump use becoming a standard of care for some individuals. This change in clinical practice may need to be reflected in future study protocols.

A further participant was excluded from data analysis as their CGM traces were clinically suggestive of inappropriate and excessive insulin dosing. This could not be corroborated by insulin pump data as unusually pump data was not able to be retrieved from the pump despite multiple attempts to upload the pump by the study team. Of note, this participant did not have any evidence of adverse events including moderate or severe hypoglycaemia.

Psychological issues were subsequently explored by the clinical team and support arranged. There was no evidence to suggest that underlying psychological issues were in anyway related to participation in the study. It was recommended to exclude this participant's data from the final data analysis following review of CGM traces by an independent diabetes researcher who was not a member of the sprint study team.

4.7.3 ***Accuracy of CGM***

CGM is the only tool that can measure glycaemic outcomes throughout the day and night in an ambulatory setting (Heinemann 2009) and has been shown to provide feasible and meaningful outcome measures in clinical trials (Beck, Calhoun et al. 2012, Schnell, Barnard et al. 2017). Although advancement in CGM technology means devices are increasingly accurate, particularly in hypo and hyperglycaemic ranges, there are still ongoing concerns regarding the accuracy of CGM systems. It is well-established that there is a lag time between blood glucose and interstitial glucose levels when glucose levels are changing rapidly, such as during exercise (Davey, Low et al. 2010, Taleb, Emami et al. 2016). Consequently, this may result in CGM over estimating glucose levels when blood glucose levels are dropping, and underestimating glucose levels when blood glucose levels are quickly rising (Riddell, Gallen et al. 2017).

To address this issue of accuracy, our study used the most accurate CGM device (Dexcom G4 platinum) available on the market at the time of study commencement. The Dexcom G4 Platinum system has a reported mean absolute relative difference (MARD) from SMBG measurements of 11.3% (Bailey, Chang et al. 2015). MARD is defined as the average of the absolute error between all CGM values and matched reference values; the smaller the difference, the closer the CGM reading is to the reference glucose value. However, the MARD may be larger at times of rapid blood glucose change.

The MARD calculated from our data at 14.7% is higher than previously reported. However, it should be noted that this study was not designed to determine the MARD and therefore several factors may be influencing this finding.

Firstly, MARD is usually measured by comparing the sensor reading to the meter reading when both readings are taken *concurrently*. We do not have concurrent SGL for all BGL's entered into the CGM device. We have taken the closet SGL reading occurring within 10

minutes prior to the BGL, as SGL readings post the BGL will be influenced by the BGL as part of the calibration process.

Secondly, the BGL readings are not being taken at random times; the participant determined when these were taken. There are likely to be some behavioural determinants such as “it’s been a long time I’ve been wearing the sensor, I should calibrate”, and “my sensor says X, but I feel different”. Given the non-random nature of sampling, there is therefore the potential for bias with testing at times when the sensor and the meter are most discordant.

Finally, we did not standardise the procedure for blood glucose measurement during the study. Studies designed to assess the accuracy of glucose measuring devices, compare glucose levels to a ‘gold standard’ laboratory reference blood glucose measurement. In our study participants used their own blood glucose meters and were asked to follow standard clinical recommendations for blood glucose monitoring. It is known that the MARDs of point-of care- blood glucose meters vary widely between devices. When 17 different commercially available blood glucose meters were assessed against a laboratory reference (YSI 2300) the MARD of the meters ranged from 5.6-20.8% (Ekhlaspour, Mondesir et al. 2017). Therefore, differences in the accuracy of blood glucose meters would have further impacted on the MARD in our study.

Nonetheless, our reported MARD should be considered as a limitation to our glycaemic outcomes. Furthermore, discordance between SGL and BG levels was even more pronounced in the hypoglycaemic range. To minimise the potential issue of underreporting hypoglycaemia during times of rapid change such as exercise we measured glycaemic outcomes throughout the 2-week period, not just during exercise. In addition, we attempted to prospectively capture episodes of symptomatic hypoglycaemia in the study diary, as these may represent episodes of hypoglycaemia not captured on CGM due to rapidly changing blood glucose levels. Indeed, we have shown that there were less episodes of carbohydrate intake during exercise in the 10s-sprint arm, likely to reflecting fewer episodes of symptomatic hypoglycaemia when the 10s sprint is incorporated into exercise compared to moderate intensity exercise alone.

4.7.4 ***Adherence to CGM wear and calibration***

As our primary outcome, and secondary glycaemic outcomes are based on sensor glucose levels, adherence to CGM use is central to the validity of our findings. Mean sensor wear was 89%, 90% and 91% of the 14-day period for the control 4s, and 10s arms respectively.

Mean sensor use was therefore similar between the study arms and cannot account for our study findings.

Twice daily calibration is required to maintain the accuracy of the sensor glucose recordings. Furthermore, the precision with which the blood glucose measurement is performed has an impact on the quality of the sensor glucose data (Heinemann 2009). Our study population calibrated on average 1.8 times per day. This is less than recommended practice of twice per day and may have adversely impacted on the accuracy of sensor glucose readings. It should also be acknowledged that we did not standardise the procedure for blood glucose measurement during the study. Participants used their own blood glucose meters and were asked to follow standard clinical recommendations for blood glucose monitoring.

4.7.5 ***Blinding of CGM***

Our study utilised masked or blinded CGM. This differs from real-time CGM in that the participant received no feedback from the device- the screen of the handset (receiver) was masked (sensor glucose levels were not displayed) and there were no alarms to warn of hypoglycaemia or hypoglycaemia. Thus, CGM data was only available for retrospective analyses, thereby removing any investigator or participator bias. The blinded nature of the CGM used in the study presented a barrier to recruitment as real-time CGM became increasingly accessible and was perceived by many as a key standard of care.

4.7.6 ***CGM endpoint selection***

CGM can potentially provide meaningful primary outcomes in clinical trials (Schnell, Barnard et al. 2017) and has been used in a number of studies as an outcome evaluation method including investigation of glucose excursions associated with diet and exercise (Riddell and Milliken 2011, Adolfsson, Mattsson et al. 2015, Paterson, Smart et al. 2016), closed-loop systems (Maahs, Buckingham et al. 2016) and glucose lowering medications (Baek, Jin et al. 2015, Holst, Buse et al. 2015, Bergenstal, Bailey et al. 2017).

One of the key issues in CGM trials is which glycaemic end point should be used. We chose to use hypoglycaemic events, defined as: sensor glucose levels of <3.5mmol/L for greater or

equal to 20 minutes, as our primary outcome. A level of <3.5mmol/L was used, as this was felt to represent a level of clinically important hypoglycaemia, approximately the onset of physiological responses to hypoglycaemia in a non-diabetic population (Mitrakou, Ryan et al. 1991). We used the traditional alert level of <3.9mmol/l in our secondary analysis.

Subsequent to the onset of our study the International Hypoglycaemia Study group recommended that glucose concentrations of less than 3.0mmol/L should be reported in clinical trials (IHSG 2017). Following this, in May 2017, recommendations on reporting CGM based outcomes in clinical trials were published and suggest hypoglycaemia cut-offs of <3.9mmol/l and <3.1mmol/l (Schnell, Barnard et al. 2017). We have therefore, included the cut-off of 3.1mmol/L in our secondary analysis in response to this new guidance. Most recently, an international consensus on use of CGM, recommends reporting hypoglycaemia outcomes in clinical trials as the percentage of CGM values that are below 3.9 or 3.0mmol/L, or the number of minutes or hours below these thresholds (Danne, Nimri et al. 2017).

Our primary outcome was defined as hypoglycaemic events, instead of the average time spent in a hypoglycaemic range. Hypoglycaemic events may provide a more accurate representation of burden to the patient than time spent low (Maahs, Buckingham et al. 2016). In addition, we attempted to capture episodes of symptomatic hypoglycaemia- again a representation of burden to the patient. Despite our best efforts to prospectively collect self-reported events of symptomatic hypoglycaemia it is apparent that this was most likely under reported. Reliable capture of symptomatic hypoglycaemia is a well-known challenge in clinical trials and hypoglycaemic event rates is an established alternative (Maahs, Buckingham et al. 2016).

4.7.7 ***Adherence with exercise protocols***

Assessment of adherence with exercise protocols was limited to exercise occurring outdoors. Evaluation of adherence involved assessment of a GPS watch generated speed trace for overall duration and presence of acceleration suggestive of sprinting. GPS information was only available for exercise episodes occurring outdoors. Thus, indoor exercise could not be assessed for adherence with exercise protocols.

4.7.8 ***Assessment of exercise intensity***

A further limitation of the study is that we did not formally measure the intensity of the exercise performed by participants. Laboratory based studies demonstrating the glycaemia

raising effects of sprinting incorporated into moderate intensity exercise define moderate intensity exercise as 40% of the VO_2 max. This intensity is justified as representing the type of activity pattern performed by the general population when exercising in "real-life" conditions.

Clearly, it is not possible to set the exercise intensity as a proportion of VO_2 max in an ambulatory setting. An established alternative to quantify exercise intensity is to measure the percentage of maximal heart rate. We explored use of a heart rate monitor during protocol development. As wrist worn heart rate monitors are prone to inaccuracy we trialled the use of an 'actiheart' device- a combined accelerometer/heart rate monitor (Actiheart, Cambridge Neurotechnology Ltd, Papworth, UK). However, this device was poorly tolerated by participants, who fed-back that it was uncomfortable leading to poor adherence with wearing the device. Moreover, data capture was unreliable with multiple periods of missing data due to signal loss, and it was difficult to identify sprints based on accelerometry data. The decision was made to not collect heart rate data in an attempt to minimise participant burden and maximise compliance with data collection of other variables.

In an attempt to set exercise at moderate intensity (40-59% VO_2 max), we asked our participants to exercise (when not sprinting) at a level where they could still maintain a conversation comfortably. This recommendation was based on the "talk test", a subjective measure of exercise intensity (Persinger, Foster et al. 2004). In a laboratory based setting the talk test involves a participant reading a passage at a particular point in exercise and then being asked if he or she can talk comfortably. The last point at which participants could comfortably respond to conversation during a period of continuous exercise has been shown to represent approximately 60% VO_2 max and 81% of maximal heart rate (Quinn and Coons 2011).

In summary, we did not objectively measure the intensity of the exercise performed in the study. This means we cannot determine if exercise intensity varied throughout the exercise episode, or indeed between episodes. However, the fact that the study exercise is performed in "free-living" conditions make our findings relevant to people exercising in the real world.

4.8 Significance of Findings

This is the first study to investigate the use of short sprints during exercise to prevent exercise mediated hypoglycaemia in individuals with T1D in a real-world setting. This is a key step in translating laboratory based findings into practical recommendations for patients. Studies to date have evaluated the glycaemic effect of sprinting in early recovery from exercise and up to 24 hours after exercise. This study, for the first time, investigates the effect of sprinting over a longer time frame (2 weeks). Moreover, this study is novel as it looks at the effect of repeated bouts of sprinting exercise during this timeframe.

Investigating how regular sprinting impacts on glycaemia over a 2-week period is important as concerns have been raised regarding potential sequelae from sprinting such as an increased risk of nocturnal hypoglycaemia and reduced awareness of hypoglycaemia. No evidence of adverse effects of sprinting have been demonstrated in this study, suggesting that sprinting could be incorporated into exercise recommendations. Findings from this study will inform the development of exercise guidelines for young people with T1D.

It should be acknowledged that the statistically significant reduction in hypoglycaemic events (<3.1mmol/L) and percentage time spent low (<3.1 and <3.5mmol/L) associated with the 10s sprint period is modest and raises questions regarding the clinical significance of these findings. An event rate of 0.4 events per day in the control period versus 0.3 events per day in the 10s period equates to an absolute reduction of 1.4 events per week. The reduction in time spent less than 3.1mmol/L from 1.9% to 1.2% equates to a reduction from 6.3 hours to 4.0 hours spent less than 3.1mmol/L over a 2 week period. Although these effect sizes are small the fact that sprinting is an easy to use, carbohydrate free strategy, which in contrast to insulin adjustment does not require prior planning makes it an attractive management option and with no burden associated with technology or any demonstrated adverse sequelae such as nocturnal hypoglycaemia, perhaps any conferred benefit is clinically relevant. Furthermore, it remains to be determined if the glycaemic benefits of sprinting are augmented when used in conjunction with other exercise strategies such as reduction in basal insulin delivery or in the setting of automated insulin delivery.

4.9 Generalisability of Results

The finding from this free-living study are generalisable to other young people with T1D participating in exercise. Our study population were not highly trained as reflected in a VO_2 max of 32.7ml/kg/min and had a suboptimal mean HbA1c of 58mmol/mol (7.5%) and thus are representative of the general T1D population.

It should be noted that we have not assessed the benefits of sprinting in a very young population. Furthermore, as patterns of spontaneous play in young children are typically characterised by short repeated bouts of activity separated by periods of moderate intensity activity or rest- akin to intermittent high intensity exercise, the role of sprinting as a tool to prevent hypoglycaemia in this young population my not be relevant. Neither have we assessed the role of sprinting in an older, sedentary population- and in this context sprinting may not be feasible.

We have only assessed the benefits of incorporating sprinting into continuous moderate intensity exercise, including running and cycling. The glycaemic effects of sprinting during other exercise types such as swimming remain to be elucidated.

Diabetes technology is rapidly evolving and is changing the landscape of diabetes management. Increasing accessibility to diabetes technology including real-time CGM and automated insulin delivery, directly impacted on the recruitment and retention of participants in this trial. The benefits of sprinting to prevent exercise mediated hypoglycaemia in the setting of automated insulin delivery such as predictive low glucose suspend and closed loop insulin delivery remains to be determined. On one hand, automated insulin adjustment may in itself prevent exercise mediated hypoglycaemia thereby making other strategies such as sprinting less useful. On the other hand, automated insulin delivery may reduce the basal percentage of the total daily dose, and this reduction in basal insulin may potentially allow the glycaemic effect of sprinting to be more pronounced.

It should be acknowledged many individuals with T1D are cared for in healthcare systems with limited resources and diabetes technology may not be accessible (Acerini, Craig et al. 2014). Access to healthcare uninterrupted supplies of insulin remains problematic in some settings. (Beran and Yudkin 2010). Furthermore, even when technology such as insulin pump therapy and automated insulin delivery systems are available, some individuals may choose alternative management strategies because of patient or parent perceived barriers

to technology uptake (Commissariat, Boyle et al. 2017). Consequently, despite technological advances, simple strategies such as sprinting may have a role to play in exercise management in both resource limited and technology accessible settings.

4.10 Clinical Implications of the Study

We have demonstrated that, in a free-living setting, the inclusion of 10s sprints into regular moderate intensity exercise can reduce the incidence of hypoglycaemia over a 2-week period, without increasing the risk of nocturnal hypoglycaemia. Conventional strategies for the prevention of exercise mediated hypoglycaemia include carbohydrate intake and insulin adjustment, thus sprinting offers a third dynamic strategy. Potential benefits of sprinting include that it is a carbohydrate free strategy (and does not carry the risk of weight gain associated with carbohydrate intake) and does not require any prior planning. Our findings are of a very practical nature and will directly inform guidelines to help young people with T1D to exercise more safely.

4.11 Directions for Future Research

In order to translate these findings into improved patient care we first need to address how to effectively educate healthcare professionals and patients about integrating sprinting as a strategy to prevent exercise mediated hypoglycaemia into exercise management plans. Furthermore, it remains to be assessed how well sprinting as a strategy is adopted by individuals with T1D in the real-world out-with a study setting.

Further work is required to determine the glycaemic impact of sprinting in different exercise modalities. The effect of sprinting during prolonged or endurance exercise remains to be determined. Sprinting may be a limited tool in this setting when glycogen stores are depleted. Furthermore, the effect of sprinting in a wider range of exercise types such as swimming remains unknown.

We acknowledge that our study population is limited to adolescents and young adults who were of average fitness levels with HbA1C levels of <75mmol/mol (9%). Further studies are needed to assess the effectiveness of sprinting to reduce exercise mediated hypoglycaemia in wider patient groups. Moreover, in clinical practice, health care professionals strive to provide patients with individualised exercise management plans. For this reason, it would be helpful to understand if sprinting is more effective in some people/situations than others-

such as gender, glycaemic control, the amount of insulin on board or evidence of impaired hypoglycaemia awareness. Further research is required to address these specific questions

Physical activity and exercise remains one of the challenges to automated insulin delivery systems. Given technological advances and increased accessibility to technology it would be pertinent to evaluate sprinting as an adjunctive exercise management tool in the setting of automated insulin delivery.

To address these questions incorporation of short sprints during exercise should be integrated with other exercise strategies and evaluated on a wider scale. Future research directions include formulation of an exercise management tool such as an app or calculator to provide patient goal directed management recommendations including use of short sprints during exercise. This tool should be developed with direct engagement from patients and families to ensure the content and presentation of information is patent led and user friendly. This exercise management tool should be evaluated in a randomised controlled trial and findings translated into clinical practice.

Appendices

Appendix A: Clarkes Hypoglycaemia Awareness Questionnaire

Hypoglycaemia Awareness Questionnaire

Name: _____ Date _____

Please answer all questions by placing a tick in one box

1. Tick the box that best describes you? (tick only one)

A0 ❒ I always have signs when my BGL is low
R1 ❒ I sometimes have signs when my BGL is low
R2 ❒ I never have signs when my BGL is low
R2 ❒ I no longer have signs when my BGL is low

2. Have you lost some of the signs and symptoms that used to occur when your BGL was low?

R2 ❒ Yes
A0 ❒ No

3. In the past 6 months how many times have you had a hypo episode where you have been confused, disorientated or lethargic, and needed help to treat your hypo?

A0 ❒ Never
R1 ❒ One or twice
R1 ❒ Every other month
R1 ❒ Once a month
R2 ❒ More than once a month

4. In the past year how often have you had a severe hypo episode, where you were unconscious or had a seizure?

A0 ❒ Never
R1 ❒ 1 to 11 times
U2 ❒ 12 times or more

5. In the last month how many times have you had a blood glucose level (BGL) of less than 3.9 mmol, with symptoms?

❒ Never
❒ 1 to 3 times in the month
❒ Once a week
❒ 2 to 3 times a week
❒ More than 3 times a week
❒ Almost every day

6. In the last month how many times have you had a blood glucose level (BGL) of less than 3.9 mmol, without any symptoms?

0	❒ Never
1	❒ 1 to 3 times in the month
1	❒ Once a week
2	❒ 2 to 3 times a week
2	❒ More than 3 times a week
2	❒ Almost every day

7. How low does your BGL fall before you notice any signs?

R2	❒ Less than 2.2
R1	❒ 2.2 – 2.7
A0	❒ 2.8 – 3.3
A0	❒ Greater than 3.3

8. Can you tell your BGL is low by certain signs or behaviour?

R2	❒ Never
R2	❒ Rarely
R1	❒ Sometimes
A1	❒ Often
A0	❒ Always

THANK YOU!

Scoring Explanation:

Calculation of the Clarke's Score

- A score of 1 was given each time an 'R' response was selected
- An additional R score of '1' was given if the answer to question 6 was greater than the answer to question 5.
- The total 'R' score was summed.

Interpretation of the Clarke's score

- Hypoglycaemia aware was defined as a total score of 4 or less
- Impaired hypoglycaemia awareness was defined as a score of more than 4.

FORM 3A

Government of Western Australia
Department of Health
Child and Adolescent Health Service

TELETHON KIDS INSTITUTE
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THE UNIVERSITY OF WESTERN AUSTRALIA
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PARTICIPANT INFORMATION SHEET

The benefits of sprinting for improving blood glucose management in individuals with type 1 diabetes mellitus

Why are we doing the study?
The aim of this study is to find out whether adding short sprints to exercise in real-life improves blood glucose management in people with type 1 diabetes. To determine this we are asking people with diabetes to try adding 4 and 10 second sprints to their exercise.

Who is carrying out the study?
The Diabetes and Obesity Research Team at Princess Margaret Hospital (PMH) and the Telethon Kids Institute, together with the School of Sports Science, Exercise and Health at the University of Western Australia, will be running the study.

What will the study tell us?
The study will tell us whether adding short sprints to a period of exercise will help to minimise changes in blood glucose levels in people with type 1 diabetes.

Do you have to take part?
No. You do not have to take part in this study. If you decide to take part and then change your mind, you can stop at any time.

What will you be asked to do if you decide to take part in this study?
You will be asked to visit PMH 8 times. We will ask you to test three different types of activity in two week blocks. These are doing what you normally do (control), adding a 4 second sprint to your exercise, or adding 10 second sprint to your exercise.

Visit 1 –
On your first visit, you will meet the study team and be able to ask any questions about the study. You will then be fitted with a Continuous Glucose Monitoring System (CGMS) to monitor your blood glucose levels. This device includes a small sensor that will be placed just under your skin using a small needle and an insertion tool. The sensor will send glucose readings to a monitor the size of an insulin pump that you will carry in your pocket or clipped to your belt. You will also be given an exercise activity watch to wear during exercise to monitor your physical activity levels. You will then spend the next week at home getting use to the equipment and practicing the sprints.

Visit 2 -
One week later, you will come back to PMH to return the CGMS, and exercise activity watch. You will then be sent home to continue your usual activity for one week without any monitoring.

Visit 3 –
Seven (7) days later you will visit the research unit again and we will re-fit a CGMS, and give you the exercise activity watch to wear during exercise. You will also be given instructions for adding a 4 second or 10 second sprint to your exercise or completing your normal routine. For the next 2 weeks, you will follow these instructions every time you exercise. You will also have to write down when and for how long you exercise, when you have a hypo and what you eat after exercise. During the study, you will change your glucose sensor at home after 7 days.

Visit 4 –
After the two weeks is up, you will come back to PMH to return the CGMS, and exercise activity watch. You will then be sent home to continue your usual activity for one week without any monitoring.

Visit 5 & 7–
Are the same as visit 3, however you will try a different type of activity.

Visit 6 & 8 –
Are the same as visit 4.

What do you need to do to be in the study?
Please contact Tarini or Niru (contact details below), who will make an appointment for your first visit. To be part of the study you must be between 14 and 35 years old, physically active at least 3 times per week, with an HbA1c of less than 9%, and aware of your hypos. We will work out if you're aware of your hypos by asking you to answer a questionnaire. You will have to wear a CGMS continuously during the study. During exercise you will need to wear an exercise watch and follow the instructions given to you. If you have an injury or any health conditions (other than type 1 diabetes), please let us know as you may not be able to participate in the study.

Is there likely to be a benefit to me?
Yes. You will benefit by learning about how to manage your blood glucose levels during exercise. You will also be given continuous glucose readings that can be used to help improve your blood glucose management, if necessary.

Is there likely to be a benefit to other people in the future?
Yes. The outcomes of this study will help to work out the benefit of including short sprints into periods of exercise for minimising changes in blood glucose levels in people with type 1 diabetes. This will help to improve guidelines for people with type 1 diabetes to exercise without the worry of hypos.

What are the possible risks and/or side effects?
There is a risk of hypos when you exercise. But, this will be small since you will mostly do what you normally do and we will give you the most up-to-date recommendations for keeping this risk small.

There is also a small risk of infection with the CGMS sensor. But, this risk is small and we will follow correct instructions to keep it that way. We have used these devices in lots of other studies and generally they are very well tolerated.

What are the possible discomforts and/or inconveniences?
You may find that wearing the CGMS all the time is a bit of a bother, but most people tolerate this device very well.

Where is my information kept?
All information collected during the study will be kept in a secure office and on computer files that need a password at PMH.

What about my privacy?
Your identity will be kept private by using codes to label data sheets and blood samples..

Who has approved the study?
The study has been approved by the Princess Margaret Hospital Human Research Ethics Committee.

Who to contact for more information about this study:
If you would like more information about this study, please do not hesitate to contact a member of the research team. We are very happy to answer your questions.

Dr Tarini Chetty, Fellow on 6229 3322 or Tarini.Chetty@health.wa.gov.au

Ms Niru Paramalingam, Clinical Research Coordinator and Research Nurse on 9340 8671 or nirubasini.paramalingam@telethonkids.org.au

Who to contact if you have any concerns about the organisation or running of the study?
If you have any concerns or complaints regarding the conduct of this study, you can contact the Director of Medical Services at PMH (Telephone No: (08) 9340 8222). Your concerns will be reviewed by the Ethics Committee who is monitoring the study.

What to do next if you would like to take part in this research:
If you would like to take part in this study, please contact Dr. Chetty on 6229 3322 Niru Paramalingam on 9340 8671.

THANK YOU FOR YOUR TIME

Government of **Western Australia**
Department of **Health**
Child and Adolescent Health Service

FORM OF CONSENT
(For Adult)

PLEASE NOTE THAT PARTICIPATION IN RESEARCH STUDIES IS VOLUNTARY AND SUBJECTS CAN WITHDRAW AT ANY TIME WITH NO IMPACT ON CURRENT OR FUTURE CARE.

I ..... have read
Given Names Surname

the information explaining the study entitled

The benefits of sprinting for improving blood glucose management in individuals with type 1 diabetes mellitus

I have read and understood the information given to me. Any questions I have asked have been answered to my satisfaction.

I understand that I may withdraw from the study at any stage and withdrawal will not impact on routine care.

I agree that research data gathered from this study may be published, provided that names are not used.

Dated ..... day of ..... 20 .....

Signature .....

I, ... have explained the above to the
(Investigator's full name)

signatory who stated that he/she understood the same.

Signature .....

Appendix C. Physical Activity Enjoyment Scale (PACES)

Please rate how you feel **at the moment** about the exercise you have been doing.

I enjoyed it	**1**	**2**	**3**	**4**	**5**	**6**	**7**	I hated it
I felt bored	**1**	**2**	**3**	**4**	**5**	**6**	**7**	I felt interested
I disliked it	**1**	**2**	**3**	**4**	**5**	**6**	**7**	I liked it
It was pleasurable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It was not pleasurable
It was no fun at all	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It was lots of fun
It gave me energy	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It was tiring
It made me depressed	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It made me happy
It was very unpleasant	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It was very pleasant
My body felt good	**1**	**2**	**3**	**4**	**5**	**6**	**7**	My body felt bad
I got something out of it	**1**	**2**	**3**	**4**	**5**	**6**	**7**	I got nothing out of it
It was very exciting	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It was not at all exciting
It frustrated me	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It didn’t frustrate me
It was not at all interesting	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It was very interesting
It gave me strong feelings of success	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It didn’t give me feelings of success
It felt good	**1**	**2**	**3**	**4**	**5**	**6**	**7**	It felt bad
I would rather be doing something else	**1**	**2**	**3**	**4**	**5**	**6**	**7**	There is nothing else I would rather be doing

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