The influence of high and low glycaemic index meals on the glycaemic, metabolic and performance responses to running in type 1 diabetes.

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THE INFLUENCE OF HIGH AND LOW GLYCAEMIC INDEX MEALS ON THE GLYCAEMIC, METABOLIC AND PERFORMANCE RESPONSES TO RUNNING IN TYPE 1 DIABETES

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ABSTRACT

RATIONALE: Carbohydrate (CHO) ingestion is a recommended strategy to reduce the risk of hypoglycaemia during and after exercise in people with type 1 diabetes (T1DM). Emerging research has shown that pre-exercise consumption of the low glycaemic index (GI) CHO isomaltulose increases blood glucose (BG) concentrations less and still protects against hypoglycaemia. However, glycaemic and performance benefits have been under-researched in T1DM following ingestion of CHO with differing GIs. This study compared the metabolic and performance responses to running following ingestion of a low- and high- GI CHO in T1DM.

METHODS: With ethical approval, seven individuals (34±5 years, 70±2 kg, HbA_{1c}: 76.6±6.5 $mmol \cdot mol^{-1}$) attended the laboratory twice following preliminary testing. Participants were provided with either 0.6 $g \cdot kg^{-1}$ BM of either dextrose (DEX) or isomaltulose (ISO) immediately after a 50% reduced rapid-acting insulin dose. After 2-h rest participants completed a discontinuous incremental treadmill protocol (4-min running: 90 s rest at 31±1, 41±2, 53±2, 69±3 and 80±2% $\dot{V}O_{2\ PEAK}$) before a 10 min performance run. Blood samples were obtained throughout and analysed immediately for BG, lactate and other variables. Data are expressed as mean±SEM and analysed using repeated measures ANOVA with statistical significance ($P<0.05$).

RESULTS: BG peak during the 2-h rest was lower after ingestion of ISO (ISO +5.6±0.4 vs. DEX +10.3±0.7 $mmol \cdot L^{-1}$, $P<0.05$). BG reductions throughout the submaximal exercise were similar (ISO -1.9±0.5 vs. DEX -1.0±0.5 $mmol \cdot L^{-1}$, $P>0.05$) as were changes following the performance bout (ISO +0.7±0.4 vs. DEX +0.7±0.3 $mmol \cdot L^{-1}$, $P>0.05$). Lactate was higher in the 2-h rest period in ISO ($P<0.05$), although there were no differences once exercise began. Distance covered during the performance bout was comparable (ISO 1.14±0.09 vs. DEX 1.15±0.09 km, $P>0.05$).

CONCLUSION: Pre-exercise consumption of ISO is an effective CHO for those exercising T1DM individuals wishing to improve glycaemic control without loss of exercise performance.

DECLARATION AND STATEMENTS

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed .. .. (candidate)

Date ..... 22/12/2011 .....

STATEMENT 1

This thesis is the result of my own investigations, except where otherwise stated.

Other sources are acknowledged by giving explicit references. A bibliography is appended.

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I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

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PUBLICATIONS ARISING FROM THIS THESIS

PEER-REVIEWED PUBLICATIONS

R.M. Bracken, R. Page, B. Gray, L.P. Kilduff, D.J. West, J.W. Stephens, S.C. Bain (In Press) Isomaltulose improves glycaemia and maintains run performance in type 1 diabetes *Medicine & Science in Sports & Exercise* DOI: 10.1249/MSS.0b013e31823f6557

CONFERENCE PROCEEDINGS

B.J. Gray, R. Page, J.W. Stephens, S.C. Bain, RM. Bracken. (2011). Glycaemic responses following ingestion of carbohydrates with reported novel properties. *Welsh Endocrine and Diabetes Society*. May 19th Celtic Manor, Cardiff

R. Page. B.J. Gray. J.W. Stephens. S.C. Bain, R.M. Bracken. (2011). Ingestion of pre-exercise high and low molecular mass carbohydrates influences fuel combustion and blood glucose to a similar degree during aerobic running. *Welsh Endocrine and Diabetes Society*. May 19th Celtic Manor, Cardiff

R.M. Bracken, B. Gray, R. Page, D.J. West, J.W. Stephens, S.C. Bain. (2011) Isomaltulose tightens pre-exercise glycaemia and produces similar run performance in type 1 diabetes. *European Association for the Study of Diabetes*. Lisbon, Portugal 12th - 16th September 2011, Diabetologia, 54 (suppl 1), S253

1.0 INTRODUCTION

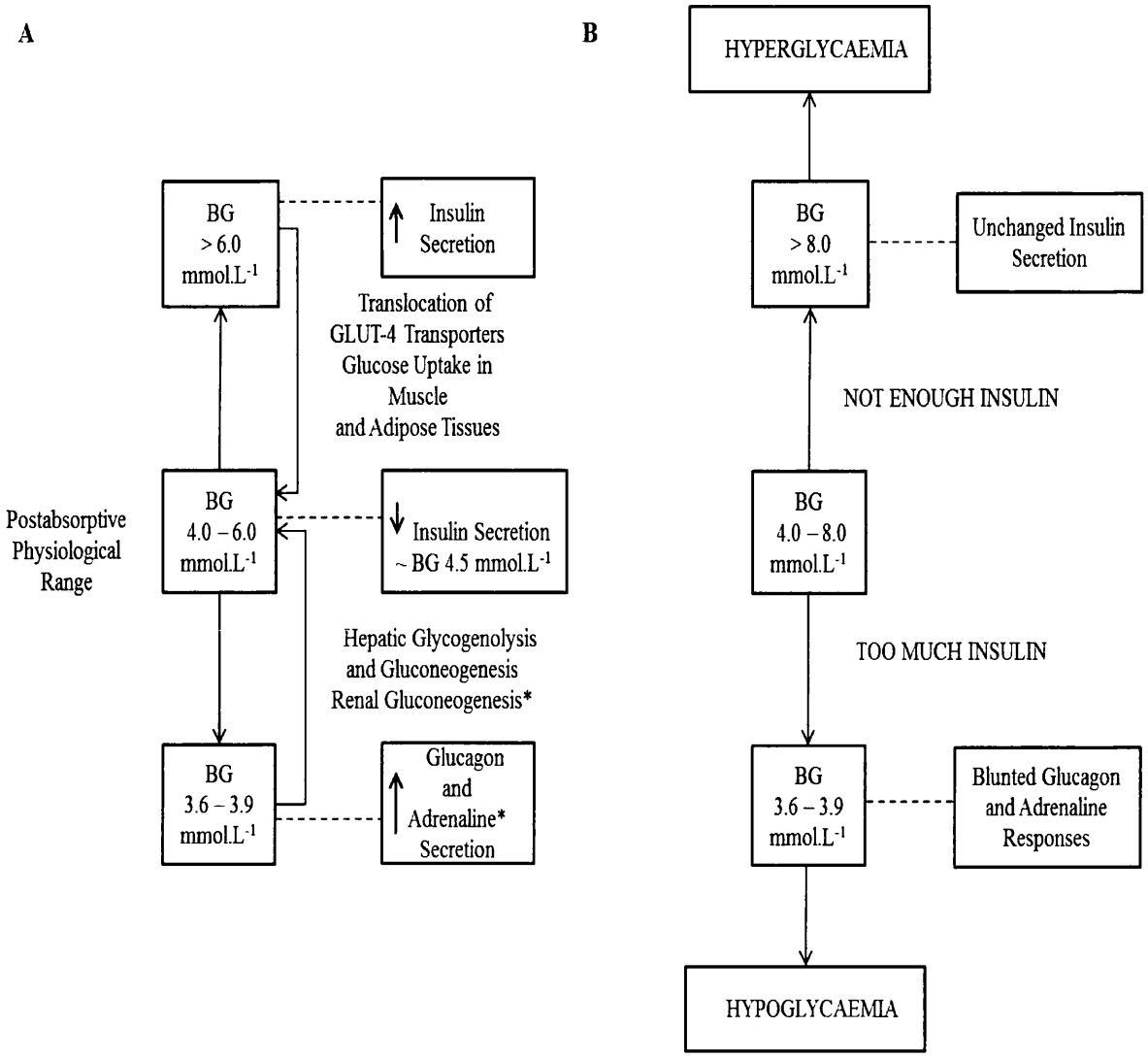

Figure 1.1 Glucoregulatory processes in non-diabetic and T1DM individuals (A) illustrates the hormonal secretions and associated glycaemic responses, (B) illustrates the difficulties of glucoregulation in T1DM and the dangers of too much or too little insulin administration, compiled using data from Cryer, Davis & Shamoon (2003); Khan & Pessin (2002).

Latest figures (Diabetes UK, 2009) report that between 140,000 – 420,000 individuals are currently diagnosed with type 1 diabetes mellitus (T1DM) in the UK. T1DM is a condition that is autoimmune in nature that selectively targets and destroys the insulin producing β-cells of the Islets of Langerhans located in the pancreas (Devendra, Liu & Eisenbarth, 2004). Insulin, alongside glucagon and catecholamines (especially adrenaline), are key regulators in levels of blood glucose (Figure 1.1A) and without these hormones and associated responses

individuals with T1DM are prone to episodes of either hypo- or hyperglycaemia (Figure 1.1B). The principal treatment in T1DM is the exogenous administration of insulin. Insulin is injected subcutaneously usually by a series of injections, these regimens range from two (conventional) to four (multi daily or basal bolus) administrations of insulin per day (Stephens & Riddle, 2003). The exogenous administration of insulin can sometimes be difficult to regulate which may lead to an individual experiencing either hypo- (if too much insulin is administered) or hyperglycaemia (if too little insulin is administered) (Figure 1.1B). However, developments in technology now offer individuals the option to be intensely treated with a battery operated insulin pump that regularly administers doses of insulin (Stephens & Riddle, 2003).

Diet and exercise alongside insulin administration are important components in the treatment of T1DM (Diabetes UK, 2011). Individuals with T1DM are actively encouraged to exercise as much as their healthy counterparts on the basis that they are in good glycaemic control and have no cardiovascular complications (Zinman, Ruderman, Campaigne, Devlin & Schneider, 2004). Regular participation in physical activity and/or exercise has been shown to have a number of benefits for individuals with T1DM; increased levels of cardiorespiratory fitness have been widely reported (Lehmann, Kaplan, Bingisser, Bloch & Spinas, 1997; Laaksonen et al., 2000; D'hooge et al., 2011) as have cardiovascular health and specific benefits to individuals with T1DM. Insulin sensitivity has been shown to be improved by 23 ± 5% after completion of a 12 week aerobic exercise intervention (Landt, Campaigne, James & Sperling, 1985), whist glycaemic control has also documented to be improved (Mosher, Nash, Perry, LaPerriere & Goldberg, 1998; Stratton, Wilson, Endres & Goldstein 1987). In addition to cardiovascular and metabolic benefits, regular engagement of exercise in persons with long standing T1DM has been proven to increase feelings of health related quality of life (Wiesinger et al., 2001). However, even with all the evident benefits ~ 60% of the adult T1DM population report sedentary behaviour (Thomas, Alder & Leese, 2004; Plotnikoff et al., 2006). The greatest barrier to exercise in T1DM is the fear of experiencing hypoglycaemia (Brazeau, Rabasa-Lhoret, Strychar & Mircescu, 2008). Hypoglycaemia is the result of too much insulin, not enough food or a combination of these two factors.

Current guidelines to reduce the incidence of hypoglycaemia during exercise recommend the reduction of pre-exercise insulin doses and/or the consumption of carbohydrate (CHO) prior to exercise (Riddell & Perkins, 2006; Lumb & Gallen, 2009; Perry & Gallen, 2009). The need to reduce pre-exercise insulin doses was first documented by Lawrence (1926) to lower the risk of hyperinsulinemia in the exercising individual. As insulin is exogenously administered in T1DM, circulating levels of the hormone do not decrease at the onset of exercise as they would in non-diabetic individuals. No decrease in circulating insulin combined with an insufficient glucagon response results in an unchanged insulin to glucagon ratio, which in turn increases the risk that hepatic glucose production will not increase to match the increased fuel requirement of exercise (Lumb & Gallen, 2009). Higher than normal insulin levels can also result in the translocation of GLUT-4 transporters resulting in glucose uptake in the muscle and adipose tissues (Khan & Pessin, 2002). To counteract these declines in blood glucose, carbohydrate consumption is recommended prior to and/or during exercise (De Feo et al., 2006; Lumb & Gallen, 2009). However, there is a lack of research pertaining to the type of CHO to be ingested in these individuals as it is an important consideration that not all CHO are the same and can be classified by their glycaemic index (GI).

The GI was a concept first introduced in 1981 by Jenkins and colleagues categorised on postprandial blood glucose responses after ingestion of foodstuff in direct comparison to the responses after ingestion of an identical amount of a reference food usually either white bread or glucose. The GI of foodstuff is an important consideration in T1DM individuals. Incorporating low GI foods into daily diets of T1DM individuals as opposed to higher GI foodstuff has shown to reduce peak blood glucose and daytime mean blood glucose values with no difference in nadir or nocturnal blood glucose levels. These lesser excursions can benefit glycaemic control and enhance quality of life in T1DM (Gilbertson et al., 2001; Nansel, Gellar & McGill, 2008). Moreover, selecting low GI foodstuff as an alternative to conventional meals has a small but clinical benefit similar to that of pharmacological therapies that combat postprandial hyperglycaemia (Brand-Miller, Hayne, Petocz & Colagiuri, 2003). Low GI diets can also increase feelings of satiety, decreasing hunger ratings after meals (Stephenson, Williams & Nute, 2005) and reduce energy intake at lunch when low GI foodstuff are ingested for breakfast (Warren, Henry & Simonite, 2003) which can be potentially beneficial for weight loss/control (Ball et al., 2003).

Recent literature (West et al., 2011b) has shown that pre-exercise ingestion of the low GI CHO isomaltulose (Palatinose®) can protect against hypoglycaemia equally well as a high GI CHO following 45 minutes of continuous moderate intensity exercise in T1DM. Lesser reliance on carbohydrate oxidation and higher combustion rates of lipids during exercise after isomaltulose consumption were attributed to this finding. Ingestion of isomaltulose also results in lesser excursions in levels of blood glucose prior to exercise than a high GI CHO which is an important consideration in regards to glycaemic control in this clinical population.

There is currently no research directly examining exercise performance in T1DM after manipulation of pre-exercise CHO and the associated glycaemic responses before, during and post-exercise. Performance testing involves high intensity exercise which increases the possibility of hyperglycaemia during and after exercise in T1DM even in those individuals that have good glycaemic control (Mitchell, Abraham, Schiffen, Leiter & Marliss, 1988). Regular hyperglycaemic episodes can have both acute and long term complications, which include increased risk of cardiovascular disease, hypertension, sudden death and reduced exercise capacity (Peirce, 1999). Whilst it is established that low GI CHO supplementation can equally reduce incidence of hypoglycaemia as high GI CHO supplementation (West et al., 2011b) the lower blood glucose excursions witnessed warrants further investigation. This study will therefore examine the blood glucose responses following ingestion of high and low GI CHO supplementation and whether the lower excursions previously reported (West et al, 2011b) limit the incidences of negative hyperglycaemia in T1DM at high intensity running. Exercise performance will also be evaluated to investigate whether the better glycaemia and more reliance on lipid oxidation witnessed in previous literature after isomaltulose ingestion (West et al., 2011b) may impact upon subsequent performance testing.

2.0 REVIEW OF LITERATURE

2.1 Type 1 Diabetes Mellitus Overview

Latest figures (Diabetes UK, 2009) report that 2.8 million people have been diagnosed with diabetes in the UK, with type 1 diabetes mellitus (T1DM) accounting for 5 – 15% of these cases.

T1DM is a condition, autoimmune in nature, which selectively targets and destroys the β-cells of the Islets of Langerhans in the pancreas and inhibits the production of insulin, (Devendra, Liu & Eisenbarth, 2004) an important hormone responsible for regulating levels of blood glucose. Glucagon and catecholamines are also both key principle glucoregulators (Figure 2.1) and secretions of these hormones can also become blunted in T1DM (Cryer, Davis & Shamoon, 2003). Therefore, individuals with T1DM are prone to either elevated (hyperglycaemia) or low (hypoglycaemia) levels of blood glucose (Figure 1.1B). Suffering from an episode of either hypo- or hyperglycaemia can be at the very least an unpleasant experience for the individual concerned (Cryer et al., 2003; Warren, Deary & Frier, 2003).

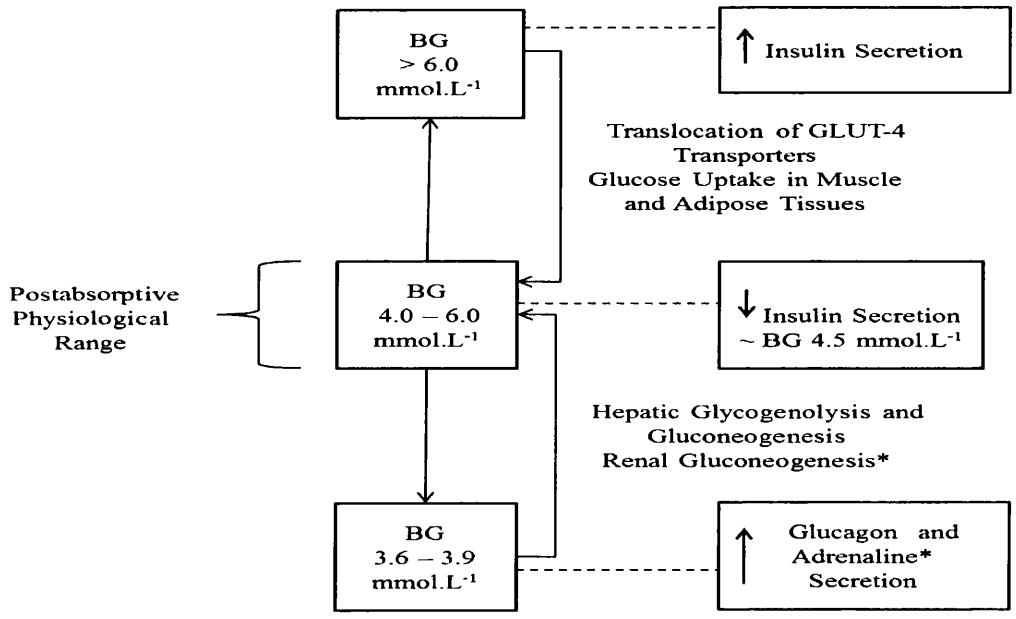

Figure 2.1 The process of glucoregulation and influences of counter-regulatory hormones in healthy individuals, compiled using data from Cryer et al. (2003); Khan & Pessin (2002).

Individuals with T1DM are predisposed to a number of risk factors for a range of illnesses and life expectancy is said to be on average 11.6 – 19.0 years shorter than their healthy counterparts dependent on age of diagnosis (Venkat Narayan, Boyle, Thompson, Sorensen & Williamson, 2003). In addition, there is a reported 10-fold increased chance of developing cardiovascular disease in T1DM with risk factors including diabetic or autonomic neuropathy, hypertension, dyslipidaemia and more specific microvascular cardiac disease (Daneman, 2006).

To counteract the body's inability to naturally produce insulin, individuals with T1DM are treated with exogenously administered insulin. Insulin is typically injected subcutaneously 2 – 4 times per day dependent on treatment regimen. Conventional treatment involves two injections per day usually at breakfast and dinner of a combination of short and an intermediate acting dosage. Individuals can also choose to adopt a more intensive approach and inject themselves four times per day. This method of treatment involves one injection of long acting analogue prior to sleep or first thing in the morning and three further administrations at mealtimes of rapid acting insulin. This treatment is referred to as multiple daily injections or basal-bolus regimen (Stephens & Riddle, 2003). Recent developments now allow for an additional option in intensive treatment which involves the use of an insulin pump. Insulin pumps are battery operated and provide rapid-acting insulin, usually insulin aspart at frequent intervals through a catheter administered subcutaneously in the abdomen with the bolus of insulin adjusted during meals to more precisely replicate the natural pattern of insulin secretion (Stephens & Riddle, 2003).

In addition to insulin therapy, a healthy lifestyle is also a key component in diabetes treatment, incorporating a balanced diet and regular exercise are strongly encouraged in people with T1DM (Diabetes UK, 2011).

2.2 Benefits of exercise for individuals with T1DM

The latest position statement encourages individuals with T1DM to partake in physical activity and exercise at any level on the basis that they have good glycaemic control and no other cardiovascular or diabetic complications apart from mild background nonproliferative retinopathy (Zinman, Ruderman, Campaigne, Devlin & Schneider, 2004). Regular

participation in physical activity and/or exercise has been shown to have a number of benefits for individuals with T1DM; increased levels of cardiorespiratory fitness have been widely reported (Lehmann, Kaplan, Bingisser, Bloch & Spinas, 1997; Laaksonen et al., 2000; D'hooge et al., 2011) as have cardiovascular health and specific benefits to individuals with T1DM. However, functional aerobic capacity in T1DM is reportedly lower than non-diabetic controls as characterised in levels of maximal oxygen consumption (Komatsu et al., 2005) and in time to exhaustion assessments (Komatsu et al., 2005; Ramires et al., 1997).

Insulin sensitivity has been shown to be improved by 23 ± 5% after completion of a 12-week aerobic exercise intervention when compared to a control group (Landt, Campaigne, James & Sperling, 1985). Improvement in glycaemic control following exercise interventions has also been documented. Stratton, Wilson, Endres & Goldstein (1987) reported better glycaemic control after an 8-week supervised training program as reflected in glycosylated serum albumin and blood glucose values. Completion of a 12-week circuit training intervention comprising both aerobic and resistance activities benefits glycaemic control further, with reported reductions of .96% point in HbA_{1c} scores (Mosher, Nash, Perry, LaPerriere & Goldberg, 1998). Mosher et al. also found that levels of low density lipoprotein (LDL) cholesterol had fallen as a result of the exercise intervention. Similar reductions in LDL cholesterol levels were also demonstrated after a 12 – 16 week moderate intensity exercise intervention (Laaksonen et al., 2000). Fuchsjäger – Mayrl et al. (2002) further demonstrated that participation in a four month training program of stationary cycling at 60 – 70% maximum heart rate improved vascular endothelial function in T1DM individuals, especially in flow-mediated dilation of the brachial artery with an increase from 6.5 ± 1.1 to 9.8 ± 1.1% reported. This finding may be of some importance as recent literature (Giménez et al., 2011) concluded that repeated episodes of hypoglycaemia aggravated preclinical atherosclerosis, more specifically in observing lower percentages of maximal flow-mediated brachial dilation and higher carotid and femoral intima-media thickness.

Apart from evident cardiovascular and metabolic benefits, regular engagement of exercise in persons with long standing T1DM has been proven to increase feelings of health related quality of life, particularly in social functioning and vitality scores (Wiesinger et al., 2001).

2.3 Barriers to exercise for individuals with T1DM

Although benefits of regular physical activity and exercise are well documented and described previously (Chapter 2.2), for one reason or another not every individual with T1DM partakes in some type of exercise regularly with ~60% of T1DM adults reporting sedentary behaviour (Thomas, Alder & Leese, 2004; Plotnikoff et al., 2006).

Barriers to exercise were reported to be work schedule, low fitness level, loss of control over diabetes, with the strongest barrier to exercise being the fear of hypoglycaemia (Brazeau, Rabasa-Lhoret, Strychar & Mircescu, 2008). Brazeau et al. further commented that factors which influenced such responses were based around lack of basic knowledge in regards to insulin pharmacokinetics and strategies to implement prior to exercise to prevent hypoglycaemia. The same authors also discovered that those individuals that reported greater perceived barriers to exercise had poorer levels of glycaemic control as measured by HbA_{1c}.

2.4 Hypoglycaemia and Hyperglycaemia

2.4.1 Definition, symptoms and causes of hypoglycaemia

Although quality of life in T1DM individuals has been enhanced through increased flexibility of timing in regards to exercise and meals with basal-bolus insulin treatments, the occurrence of hypoglycaemia is still a frequent experience (Shalitin & Phillip, 2008). Hypoglycaemia is defined as a blood glucose concentration below 3.5 $mmol \cdot L^{-1}$ and categorised further as severe hypoglycaemia if the individual requires assistance from another person (Rabasa-Lhoret, Bourque, Ducros & Chiasson, 2001).

Symptoms of hypoglycaemia can be classified as either autonomic, neuroglycopenic or general malaise. Autonomic symptoms are regulated by the autonomic nervous system, whilst neuroglycopenic symptoms result directly from low blood glucose concentrations on the brain (McAuley, Deary & Frier, 2001). Common autonomic responses to hypoglycaemia include sweating, palpitations, shaking and hunger, frequently experienced neuroglycopenic symptoms were confusion, drowsiness, odd behaviour, speech difficulty and incoordination, with headaches and nausea reported as general malaise symptoms (Deary, Hepburn, MacLeod & Frier, 1993).

Hypoglycaemia can be caused by exogenous insulin excess which results in levels of plasma glucose declining to low levels in T1DM. The fall in plasma glucose is not accompanied by a decrease in levels of insulin, simply as these levels are unregulated and the result of passive absorption of administered insulin and the individual pharmacokinetics of the treatment. Due to this factor the first defence against hypoglycaemia is lost in established T1DM (Cryer et al., 2003). Decreasing levels of plasma glucose is usually associated with increased glucagon secretion, which promotes hepatic glycogenolysis and gluconeogenesis and in turn raises plasma glucose concentrations (Cryer et al., 2003). In established T1DM this response is not present (Gerich, Langlois, Noacco, Karam & Forsham, 1973; Bolli et al., 1983), the absent response to glucose levels appears to be a signalling defect as glucagon secretory responses are present in relation to other stimuli (Cryer et al., 2003). It is currently unknown as to the mechanism to which inhibits the glucagon secretion, however there is a suggestion the absent response is related to endogenous insulin deficiency (Banarer, McGregor & Cryer, 2002).

Directly beneath glucagon in the hierarchy of counter-regulatory hormones in the defence against hypoglycaemia are catecholamines, more specifically the secretion and response of adrenaline. Catecholamines raise blood glucose concentrations through the combination of decreased glucose utilisation and increased rate of hepatic glucose production (Sherwin et al., 1980). In T1DM this secretion has also been reported to be attenuated (Bolli et al., 1983; Amiel, Sherwin, Simonson & Tamborlane, 1988; Dagogo-Jack, Craft & Cryer, 1993), with secretions reported at lower plasma glucose concentrations in those individuals with strict glycaemic control (Amiel et al., 1988) and impaired further following previous episodes of hypoglycaemia (Dagogo-Jack et al., 1993). Apart from the blunted counter-regulatory response observed in T1DM (Cryer, 2002) one of the major contributors to hypoglycaemia is missed meals (Davis, Keating, Byrne, Russell & Jones, 1997; Boyle & Zrebiec, 2007), leading to decreased exogenous glucose delivery and therefore excess circulating insulin (Cryer et al., 2003).

Evening alcohol consumption can also impair morning glucose levels with hypoglycaemia a more frequent occurrence after individuals drank wine compared to water. Evening and overnight glycaemia was comparable with a decreased nocturnal secretion of growth hormone offering an explanation to the observed morning episodes of hypoglycaemia (Turner, Jenkins, Kerr, Sherwin & Cavan, 2001). Unfortunately, glycaemic control does not aid in preventing low blood glucose concentrations with a higher proportion of individuals

with strict glycaemic control more likely to experience an episode of severe hypoglycaemia (Taverna et al., 2000).

Simplistically, hypoglycaemia may be caused by too much insulin and associated impaired counter-regulatory response, not enough food or a combination of both. An additional cause of hypoglycaemia is exercise which has its own associated risks.

2.4.2 Definition, symptoms and causes of hyperglycaemia

On the other end of the glycaemic spectrum are elevated levels of blood glucose known as hyperglycaemia. Hyperglycaemia is generally classified as a level of blood glucose above euglycaemia (4 – 8 $mmol \cdot L^{-1}$), and can be defined as higher than 11 $mmol \cdot L^{-1}$ in experimental induced scenarios where blood glucose is manipulated by the use of hyperglycaemic clamps or when blood glucose values are self-reported (Cox et al., 2005; Jenni et al., 2008; Stettler et al., 2006).

The symptoms of hyperglycaemia can be categorised into four groups; agitation, osmotic, neurological and malaise. Agitation symptoms include feeling tense, restlessness and poor concentration, whilst thirst, dry mouth, need to urinate and a sweet taste sensation are classified as osmotic symptoms, dizziness, light-headedness and blurred vision are defined as neurological symptoms and feelings of malaise include headache and nausea (Warren et al., 2003). Furthermore, hyperglycaemic blood glucose levels over a prolonged period of time can cause either acute or long term complications. Elevated blood glucose levels are an independent and clinically significant risk factor for cardiovascular disease (Gerich, 2003) and given that coronary artery disease is the leading cause of death in T1DM strict glycaemic control is of great importance and consideration (Conway, Costacou & Orchard, 2009). Further complications related to sustained levels of hyperglycaemia include hypertension, sudden death, reduced exercise capacity, neuropathy, nephropathy, retinopathy and even blindness, all of which are further worsened with poor glycaemic control (Peirce, 1999) and increase both an individual's morbidity and mortality (Conway et al., 2009; Khan & Pessin, 2002)

Insulin, as previously discussed is a key player in glucoregulation and is an essential component in the postprandial state. In healthy individuals, as blood glucose levels start to

rise, insulin is released by the pancreas which in turn promotes glucose uptake into adipose and muscle for storage as intracellular triglycerides and glycogen (Khan & Pessin, 2002). Glucose uptake in adipose and muscle tissues is insulin-stimulated through a complex pathway proceeding through the insulin receptor tyrosine kinase, where the main effect is to promote the movement of GLUT-4 receptors from intracellular storage sites to the plasma membrane (Khan & Pessin, 2002). In addition to stimulated glucose uptake, insulin also inhibits the production and release of glucose from the liver (Khan & Pessin, 2002). Therefore, this fine equilibrium of inhibition and stimulated glucose uptake is lost in T1DM individuals as with insulin being exogenously administered, circulating insulin levels do not change and individuals can be susceptible to elevated levels of blood glucose, especially in the postprandial state.

Hyperglycaemia simplistically is a result of too little insulin, too much food (especially carbohydrate) or a combination of both and as with hypoglycaemia, exercise is also a risk factor for hyperglycaemia.

2.4.3 Glycaemic responses and risks associated with exercise

Engaging in exercise can have impacts on levels of glycaemia either lowering blood glucose and increasing the risk of hypoglycaemia or elevating levels of blood glucose and raising the possibility of hyperglycaemia.

Risks of hypoglycaemia associated with exercise following exogenous insulin administration have always been apparent and were first documented by Lawrence (1926). Lawrence discovered that the effects of insulin on blood glucose were increased when an individual engaged in exercise over a 2 hour 30 minute period in comparison to no exercise taking place. The insulin effects were so greatly increased that blood glucose fell to levels of hypoglycaemia in the studied individual. Hypoglycaemia in exercise is generally attributed to insulin being exogenously administered, due to this administration it does not decrease at the beginning of exercise as it would in healthy individuals. No decrease in circulating insulin combined with an insufficient glucagon response results in an unchanged insulin to glucagon ratio, which in turn increases the risk that hepatic glucose production will not increase to match the increased fuel requirement of exercise (Lumb & Gallen, 2009). In addition there is a reversal of the usual portal to systematic insulin ratio and a relatively higher insulin

concentration in the periphery ensues (Lumb & Gallen, 2009), this concentration promotes peripheral muscle glucose uptake, further reducing levels of glycaemia and increasing the chances of hypoglycaemia (Goodyear & Kahn, 1998).

Associated risks can be completed further as different types of exercise result in different glycaemic responses. It is generally documented that participation in moderate intensity aerobic exercise results in a decline in blood glucose levels (Tsalikian et al., 2005; Tansey et al., 2006; West, Morton, Bain, Stephens & Bracken, 2010) with individuals more susceptible to hypoglycaemia 20 – 60 minutes after the onset of exercise (Riddell, Bar-Or, Ayub, Calvert & Heigenhauser, 1999). In comparison to continuous moderate intensity aerobic exercise, the drop in blood glucose has been found to be less after completion of high intensity intermittent exercise (Guelfi, Jones & Fournier, 2005). The decline in blood glucose after 30 minutes of high intensity intermittent exercise was 2.9 ± 0.8 mmol·L^{-1}, whilst blood glucose fell 4.4 ± 1.2 mmol·L^{-1} after completion of 30 minutes of continuous exercise. In a later publication (Guelfi, Ratnam, Smythe, Jones & Fournier, 2007), the authors suggested that the lesser declines previously reported could be credited to a greater increase in endogenous glucose production and attenuated glucose utilisation during exercise with the attenuation of glucose utilisation persisting through to stages of early recovery.

Performing a 10 second maximal sprint after a bout of moderate intensity exercise has been proven to prevent the continuing fall in glycaemia for a 120 minute recovery period (Bussau, Ferreira, Jones & Fournier, 2006). The observed stability of blood glucose levels was accompanied with increased levels of catecholamines, growth hormone and cortisol (Bussau et al., 2006). Carrying out the same maximal sprint method prior to engaging in moderate exercise does not prevent the continuous fall in glycaemia, however for 45 minutes after cessation of exercise glycaemia remained stable (Bussau, Ferreira, Jones & Fournier, 2007). In this instance the glycaemic stability was attributed to elevated blood lactate and noradrenaline levels (Bussau et al., 2007). However, exercising at high intensity raises the possibility of hyperglycaemia during and after exercise even in those individuals that have good glycaemic control (Mitchell, Abraham, Schiffrin, Leiter & Marliss, 1988). Hyperglycaemia during exercise results from an increased release of catecholamines, leading to the rise in hepatic blood glucose production that exceeds the rate of utilisation (Mitchell et al., 1988). Unlike their healthy counterparts, insulin levels do not increase following exercise leading to the occurrence of post-exercise hyperglycaemia (Lumb & Gallen, 2009) and there

has been some suggestion that administering corrective units of insulin following high intensity exercise may mimic the insulin responses in non-diabetic individuals (Riddell & Perkins, 2009). Adaptations to a sprint training program over 7 weeks have been shown to reduce both glycolytic rate and metabolic destabilisation in T1DM individuals suggesting increased muscle oxidative metabolism (Harmer et al., 2008), which in turn may help to decrease the possibility of developing hyperglycaemia. Even the stress and/or anticipation of competition can increase the potential of hyperglycaemia (Riddell & Perkins, 2009).

Glucose levels need to be monitored following exercise due to the possible risk of late onset post exercise hypoglycaemia (LOPEH) that has been documented, usually occurring at night and 6 - 15 hours after cessation of exercise (MacDonald, 1987). Sustained increase of insulin sensitivity in the tissues and the need of the body to replenish muscle glycogen stores offer an explanation for LOPEH (Grimm, 2005). Muscle glycogen storage is attributed to GLUT-4 transporters which have been shown to be increased in expression for at least 3 hours following exercise, regardless of the exercise intensity performed (Kraniou, Cameron-Smith & Hargreaves, 2006). A further complication is that counter-regulatory responses to hypoglycaemia are blunted rapidly following exercise (Sandoval, Aftab Guy, Antoinette Richardson, Ertl & Davis, 2006) with this impairment potentially lasting for up to 24 hours (Sandoval, Aftab Guy, Antoinette Richardson, Ertl & Davis, 2004). As a result of the blunted counter-regulatory responses there has also been a suggestion of a vicious cycle between regular exercise and episodes of hypoglycaemia (Ertl & Davis, 2004). Another complication is that warning indications associated with the early stages of hypoglycaemia such as sweating, dizziness and tiredness have the possibility of being masked by the physiological responses of engaging in exercise (Lumb & Gallen, 2009; Riddell & Perkins, 2009).

Limited research has been performed in regards to glycaemic responses after completing a bout of progressive, incremental, submaximal exercise in T1DM individuals. Incremental exercise would incorporate all exercise intensities, beginning at a low intensity and finishing at a high, but not maximal exercise intensity. Theoretically, all blood glucose responses described previously could be observed in such an exercise protocol.

2.5 Strategies to reduce incidences of hypoglycaemia during and after exercise

Current strategies to reduce hypoglycaemic incidences during and post exercise are to reduce the pre-exercise insulin doses and/or ingest simple carbohydrates prior to engaging in exercise (Riddell & Perkins, 2006; Lumb & Gallen, 2009; Perry & Gallen, 2009). Periodically testing blood glucose levels every 30 minutes of exercise is also recommended with 20 – 60 g simple carbohydrate supplementation if necessary (De Feo et al., 2006). A limitation to these recommendations could be the lack of focus on limiting hyperglycaemia which can be as equally detrimental to the health of individuals and potentially even more so long-term as hypoglycaemic episodes. However, there are no specified recommendations in regards to insulin dosage or amount of carbohydrate to be consumed and the main strategy should be on the individual to monitor their own blood glucose and familiarise themselves with their own responses to exercise (Perry & Gallen, 2009). The next few chapters discuss the current literature surrounding which strategies to adopt in T1DM individuals.

2.5.1 Manipulation of pre-exercise insulin doses

Lawrence (1926) first suggested that insulin administered prior to exercise should be reduced, in turn lowering the risk of hyperinsulinemia in the exercising individual with observed decreases in glycaemia theoretically being similar to those levels if the individual had not engaged in exercise but administered their normal insulin dose. Many studies have investigated the optimum pre-exercise reduction in insulin that effectively regulates blood glucose. Strategies adopted ranged from 10 – 30% (Grimm, Ybarra, Berné, Muchnick & Golay, 2004), 10 - 40% (De Feo et al., 2006), 50 – 75% (Rabasa-Lhoret, Bourque, Ducros & Chiasson, 2001) to 50-90% decreases (Mauvais-Jarvis et al., 2003) in insulin doses. However a recent publication by West et al. (2010) concluded that a 75% reduction in rapid-acting pre-exercise insulin improved blood glucose responses for up to 24 hours after exercise compared to an administered full, 25% or 50% reduced dose. Suspending basal insulin infusion completely at the start of exercise has also been shown to reduce the incidence of hypoglycaemia during exercise (Tsalikian et al., 2006). Reasons for strategic variations adopted in the literature can be influenced by a number of factors including insulin regimen, insulin pharmacokinetics and intensity of exercise, furthermore the timing of the administered insulin dosage is also worthy of consideration.

Table 2.1 Existing insulin reduction strategies and associated glycaemic responses

Research (Author, Year)	**Insulin Strategy**	**Insulin Regimen**	**Blood Glucose Responses**
Grimm et al., 2004	Reduction of daily insulin dose by more than 10% with or without CHO provision	2x NPH Injections and 3x Pre-prandial rapid acting insulin doses	CHO and Insulin reduction strategies were more protective than either no CHO and insulin adaptations or insulin reduction alone
Mauvais-Jarvis et al., 2003	Either 50% reduction (2x injections) OR 90% reduction (3x injections)	Either 2x Regular Insulin injections and 1x Mixed Reg/NPH injection OR 2x (30% Reg/70% NPH) injections	In reduction trials BG was maintained to near euglycaemic levels. In trials where no reductions took place 66% of participants suffered hypoglycaemia
Rabasa-Lhoret et al., 2001	Either Full dose, 50% or 75% reduction of bolus insulin and 600 kcal breakfast meal (75 g CHO)	Basal-bolus regimen. 1x Ultralente (basal) injection and 3x lispro (bolus) injections	Full dose increased risk of hypoglycaemia at all exercise intensities in comparison to reductions. 75% reduction resulted in increased blood glucose from baseline following exercise
West et al., 2010	Either Full dose, 25%, 50% or 75% reduction of bolus insulin and 1.12 mJ meal (60 g CHO)	Basal-bolus regimen. 1x glargine (basal) injection and either 3x lispro OR 3x aspart injections	Pre-exercise blood glucose values increased as insulin doses decreased Blood glucose declined in all conditions following 45 min run at 70% $\dot{V}O_{2\,PEAK}$. Full dose – 6.1; 75% Dose – 4.3; 50% Dose – 5.5; 25% Dose – 3.2 $mmol \cdot L^{-1}$. 21 hour blood glucose area under the curve greater after 50% and 75% reductions.

Suggested reductions (Table 2.1) were either to reduce regular or rapid-acting doses (De Feo et al., 2006), reduce both rapid acting and intermediate neutral protamine Hagedorn (NPH) analogues (Grimm et al., 2004), manipulation of either an injection of regular insulin or

combined insulin (30% regular/ 70% NPH) dose (Mauvais-Jarvis et al., 2003) or reduced doses of bolus injections in basal-bolus regimens treated intensively with either insulins ultralente as basal and lispro (Rabasa-Lhoret et al., 2001) or insulin glargine as basal and insulin lispro or insulin aspart (West et al., 2010). The reasoning behind insulin reductions is predominately two-fold, firstly to prevent the potential for over-insulinisation during exercise and secondly to elevate blood glucose levels to compensate for any exercise-induced falls in glycaemia. Therefore, the larger the reductions in pre-exercise insulin dosage, the higher the blood glucose values are prior to the onset of exercise (West et al., 2010). Nevertheless it is worth considering that reducing pre-exercise basal insulin can cause pre-exercise and late post-exercise hyperglycaemia, whilst reducing basal doses are unsuitable for late postprandial activities (Lumb & Gallen, 2009).

Moreover, the dynamics and pharmacokinetics of insulins aspart and lispro are considered similar with both equally effective at controlling postprandial blood glucose excursions (Plank et al., 2002), and also the metabolic influences on correcting fat and carbohydrate abnormalities are indistinguishable between insulins (Homko, Deluzio, Jimenez, Kolaczynski & Boden, 2003). Aspart and lispro both differ from human insulin, with a single substitution of proline with aspartic acid in position B28 and the substitution of proline with lysine in position 28 and vice-versa in position 29 of the B chain in aspart and lispro respectively. These alterations increase the rate of absorption as the analogues are less likely to convert into dimmers and hexamers (Homko et al., 2003). Insulin pump therapy aside, basal-bolus regimens are generally recommended for exercising individuals with T1DM (Gallen, 2005; Grimm, 2005).

Duration and intensity of exercise performed must also be taken into account when manipulating insulin doses, as discussed previously (Chapter 2.4.2) different exercise intensities result in different glycaemic responses. The larger 75 – 90% insulin reductions (Rabasa-Lhoret et al., 2001; Mauvais-Jarvis et al., 2003; West et al., 2010) were administered prior to engaging in continuously aerobic exercise, intensities ranging from 25 – 75% $\dot{V}O_{2\ MAX}$ and lasting between 30 – 60 minutes in duration. Grimm et al., (2004) suggested to only reduce insulin doses if exercising for over 20 minutes at a higher intensity (> 75% maximum heart rate (MHR)) or for prolonged periods (> 60 minutes) of moderate intensity exercise (60 – 75% MHR), no alterations in insulin doses was recommended for lower

intensity exercise (< 60% MHR). The recommendations by Grimm et al. (2004) were largely based around carbohydrate consumption alongside insulin reductions for the different exercise intensities.

Insulin administration and timing of subsequent exercise is of important consideration. Time to peak serum insulin levels are quicker in newer rapid-acting analogues, reaching peak values at 30 – 45 minutes following administration (Plank et al., 2002). Exercise should therefore be performed when insulin action is on the decline with current suggestions being 3 – 4 hours following regular insulin administration and 2 hours after rapid-acting injections (De Feo et al., 2006). Allowing this sufficient time before exercise diminishes the risk of over over-insulinisation of the active musculature during exercise (De Feo et al., 2006; Perry & Gallen, 2009). Conversely, most recent literature has established that administration of low doses of rapid-acting insulin combined with carbohydrate ingestion 30 minutes prior to exercise can reduce incidences of hypoglycaemic episodes rather than increase the risk of developing exercise-induced hypoglycaemia (West et al., 2011a).

With a number of recommendations (Grimm et al., 2004; West et al., 2010; West et al., 2011a) also accounting for carbohydrate consumption it appears that a combined management strategy of insulin reduction together with carbohydrate intake is a more sensible and viable option.

2.5.2 Carbohydrate ingestion

2.5.2.1 Amount of carbohydrate

Unfortunately the risk of hypoglycaemia cannot be simply resolved by ingestion of carbohydrate to significantly elevate levels of blood glucose. Increased amounts of carbohydrate ingestion in combination with lowered insulin doses can lead to hyperglycaemia which as discussed previously prolonged durations of elevated blood glucose have their own risks for the exercising individual (Chapter 2.4.2).

In reference to the amount of carbohydrate needed to fuel exercise and prevent hypoglycaemia, the information supplied in the guidelines is limited. With blood glucose responses to exercise being individualised, this is reflected somewhat in the current

guidelines, as carbohydrate is recommended to be consumed as required (Zinman et al, 2004). Suggested amounts of carbohydrate to be consumed prior to exercise range from 20 – 60 g (De Feo et al., 2006), 30 g (Grimm et al., 2004), 40 g (Dubé, Weisnagel, Prud'homme & Lavoie, 2005), 75 g (West et al., 2011a; West et al., 2011b) up to 1 $g \cdot kg^{-1} \cdot BM \cdot h^{-1}$ (Hernandez, Moccia, Fluckey, Ulbrecht & Farrell, 2000). Matching the amount of carbohydrate ingested with the carbohydrate utilised during exercise has also be shown to attenuate hypoglycaemia (Riddell et al., 1999) and this method has also been remarked as the most important pre-exercise prevision to safeguard against hypoglycaemia (Grimm et al., 2004). Considering exercise duration and intensity, Kordi and Rabbani (2007) composed a table from the data collected by a number of authors, (Moriarity, 1997; Brown & Wilson 2000; Birrer & Sedaghat 2003). The collated data recommended from a safety point of view that depending on blood glucose concentrations, 10 – 15 g carbohydrate should be consumed for low intensity, short duration exercise, 10 – 50 g carbohydrate for moderate intensity, moderate duration exercise, and 30 – 50 g carbohydrate would account for high intensity, moderate duration exercise with no carbohydrate supplementation required for high intensity, short duration exercise.

Hernandez and colleagues (2000) also commented that 1 $g \cdot kg^{-1} \cdot BM \cdot h^{-1}$ was also enough carbohydrate to benefit performance, even values of 1 – 2 $g \cdot kg^{-1} \cdot BM$ consumed 1 hour prior to exercise have been recommended to enhance performance as this maximises pre-exercise glycogen values and therefore providing energy for oxidation (Riddell & Perkins, 2006). However, in a review article, Jeukendrup (2004) concluded that ingestion of carbohydrate greater at a value greater than 75 $g \cdot h^{-1}$ did not appear to improve performance when compared to amounts ranging from 45 – 75 $g \cdot h^{-1}$. In the same article, the author recommended that carbohydrate ingestion of 1.0 – 1.1 g per minute during exercise would maximise performance.

Delivery of carbohydrate is usually provided in a liquid form prior to or during exercise in research trials (Perrone, Laitano & Meyer, 2005; West et al., 2011a; West et al., 2011b). Again within this literature there are disparities within concentrations of these drinks, it has been suggested that a 6% carbohydrate-electrolyte beverage may have better absorption rates than higher concentrated beverages which may delay gastric absorption and cause stomach upset (Riddell & Perkins, 2006). Although, in other research four individuals had to withdraw from exercise after consumption of an 8% solution as a result of declining blood glucose

levels (Perrone et al., 2005). Fluid concentrations of 10% carbohydrate solution have been demonstrated to prevent hypoglycaemia during and after exercise (Perrone et al., 2005; West et al., 2011a; West et al., 2011b). Furthermore, no gastrointestinal symptoms were reported and participants kept euhydrated throughout (Perrone et al., 2005), the better hydration of these individuals is due to more fluid being retained in drinks with higher carbohydrate concentrations (Evans, Shirreffs & Maughan, 2009).

The type of carbohydrate recommended to reduce the potential of developing hypoglycaemia is usually referred to as simple which is a categorisation normally associated with the glycaemic index.

2.5.2.2 Glycaemic index (GI) of carbohydrates

The glycaemic index (GI) was a concept first introduced in 1981 by Jenkins and colleagues categorised on postprandial blood glucose responses after ingestion of foodstuff in direct comparison to the responses after ingestion of an identical amount of a reference food usually either white bread or glucose. Research has continued in this discipline to the present day and lists are being compiled and constantly updated to account for most commercially available food products (Foster-Powell, Holt & Brand-Miller, 2002; Henry, Lightowler, Strik, Renton & Hails, 2005; Atkinson, Foster-Powell & Brand-Miller, 2008). A table compiled of everyday foodstuffs and their glycaemic index values is detailed below (Table 2.2).

Table 2.2 Everyday foodstuff and respective glycaemic index values (Atkinson et al., 2008)

Foodstuff	Glycaemic Index (GI)
Dextrose (Glucose Powder)	*100*
Cornflakes	81
White Bread	75
Potato Crisps	56
Sweet Corn	52
Lentils	32
Isomaltulose	*32*
Kidney Beans	24

Carbohydrates are normally termed simple or complex according to their chemical structure (O'Reilly, Wong & Chen, 2010). Simple carbohydrates are usually high GI, contain mono-, di- or oligo-saccharides and thought unhealthy whilst complex carbohydrates are generally considered healthier containing starches or polysaccharides and calculated as low GI (Venter, Slabber & Vorster, 2003). This is maybe an unfair generalisation as glycaemic responses can also be influenced by other factors such as food processing (Brand, Nicholson, Thorburn & Truswell, 1985), particle size or the cooking of starch foodstuff which splits the granules, increasing the availability to amylase (Collings, Williams & MacDonald, 1981). Exceptions to this loose terminology include French fries that are deemed 'complex' but are high in fat while healthy options that provide vitamins and protein such as yoghurt and fruit are classified as 'simple' (O'Reilly et al., 2010). The glycaemic index of carbohydrates can also have an effect on digestion rates. Monosaccharides are of a molecular size that easily permits the crossing of the mucosal cell membrane by simple diffusion and passive diffusion down a concentration gradient is one explanation of absorption, whilst on the other hand disaccharides are too large and require hydrolysis to cross the mucosal cell membrane (Southgate, 1995).

Incorporating low GI foods (e.g. brown basmati rice, peaches, kidney beans) into daily diets of T1DM individuals as opposed to higher GI foodstuff (e.g. white bread, mashed potatoes, cornflakes) has shown to reduce peak blood glucose and daytime mean blood glucose values with no difference in nadir or nocturnal blood glucose levels. These reductions in blood glucose excursions benefited glycaemic control with concentrations within a target range of 3.9 – 9.9 $mmol \cdot L^{-1}$ for longer periods of time and less bolus insulin required per 10 g of carbohydrate (Nansel, Gellar & McGill, 2008). Another 12 month intervention study (Gilbertson et al., 2001) observed improved HbA_{1c} scores with no increased risk of hypoglycaemia and enhanced quality of life after adherence to a diet emphasised on low GI foods. Moreover, selecting low GI foodstuff as an alternative to conventional meals has a small but clinical benefit similar to that of pharmacological therapies that combat postprandial hyperglycaemia (Brand-Miller, Hayne, Petocz & Colagiuri, 2003).

A low GI or low GI with added sucrose breakfast as opposed to a high GI breakfast results in a significantly lower energy intake at lunchtime (Warren, Henry & Simonite, 2003). This effect only appeared to be a short-term benefit for that day as over a long-term study of ten weeks no significant difference was found after low GI breakfasts, although daily energy

intake tended to be less (Henry, Lightowler & Strik, 2007). Cognitive performance has also been evidently sustained after a low GI breakfast with individuals achieving greater memory and accuracy scores in tasks towards the latter stages of the morning period (Benton et al., 2003; Ingwersen, Defeyter, Kennedy, Wesnes & Scholey, 2007). Additionally, consumption of low GI meals for both breakfast and lunch can also decrease hunger ratings for a 3 hour postprandial period following lunch (Stevenson, Williams & Nute, 2005), with increased ratings of satiety reported after low GI meals it has been further speculated that long term adoption of this strategy may reduce caloric intake and therefore benefit weight loss and/or control (Ball et al., 2003).

One such example of a low GI foodstuff that has been used in diet intervention studies (Holub et al., 2010) and also supplied as a pre-exercise drink to avoid hypoglycaemia (West et al., 2011a, West et al., 2011b) is isomaltulose (Palatinose®, Beneo Group, Germany).

2.5.2.3 Isomaltulose

This naturally occurring disaccharide (chemical name: 6 – O – α – D – glucopyranosyl – D – fructofuranose) found in honey, is composed of glucose and fructose linked by a α – 1,6 glycosidic bond (Lina, Jonker & Kozianowski, 2002). Commercially available isomaltulose (Palatinose®) derived from food grade sucrose and manufactured by enzymatic rearrangement of (1,2)-fructoside to (1,6)-fructoside has been used as sugar replacement in Japan and other Asian countries for over twenty years (Holub et al., 2010; Lina et al., 2002). In the latest published tables (Atkinson et al., 2008; Table 2.1) isomaltulose has been calculated to have a glycaemic index value of 32 and therefore classified as very low GI. The associated decreased insulin and blood glucose responses with isomaltulose are characteristics particularly desirable to individuals with diabetes (Kawai, Yoshikawa, Murayama, Okuda & Yamashita, 1989). Isomaltulose is hydrolysed in the same manner as sucrose by the active site of isomaltase in the sucrose-isomaltase complex and absorbed in the small intestine (Goda & Hosoya, 1983). Once hydrolysed the resultant glucose and fructose are digested through classical processes (Lina et al., 2002). During this digestion period fructose bypasses the phosphofructokinase regulatory point in glycolysis which leads to an increased flux through the glycolytic pathway that in turn leads to an accumulation and subsequent release of lactate (Kaye, Williams & Barbero 1958; Sahebjami & Scalettar 1971). Although the chemical composition of isomaltulose and sucrose are somewhat similar, a 1,6

glycosidic bond between glucose and fructose in isomaltulose as opposed to 1,2 in sucrose there are many differences between the two sugars. Research has shown that hydrolysis of disaccharides with α-1,6 glycosidic bonds is much slower than disaccharides with either α-1,2 or α-1,4 glycosidic bonds (Günther & Heymann, 1998). However, even though these hydrolysis rates are slower in isomaltulose, it has been commented that 50 g can be ingested without any gastrointestinal discomfort (Lina et al., 2002).

During exercise the oxidation rates are lower in isomaltulose compared to sucrose with peak and mean oxidation 42% and 50% lower respectively, resulting in a 59% lower oxidation rate overall (Achten, Jentjens, Brouns & Jeukendrup, 2007). These lesser oxidation rates were mainly credited to the slower hydrolysis, therefore reducing the absorption rate of metabolised fructose and glucose and subsequently decreasing the rates of oxidation (Achten et al., 2007). Additional research (van Can, Ijzerman, van Loon, Brouns & Blaak, 2009) comparing these two sugars in healthy, overweight individuals observed a 14% increase in postprandial fat oxidation after isomaltulose ingestion whilst further witnessing lower insulin responses and lesser excursions in blood glucose. An increased reliance on lipid oxidation during subsequent exercise following isomaltulose consumption can also improve post-exercise glycaemia in T1DM individuals as discussed later (West et al., 2011b; Chapter 2.6.2).

2.6 Substrate utilisation during exercise

The four main components to fuel exercise in healthy individuals are muscle glycogen, muscle triglycerides, plasma free fatty acids and plasma glucose, the utilisation of these four components vary depending on the intensity of exercise performed (Romijn et al., 1993). However, in T1DM individuals there is more reliance in oxidation of glycogen stores in either the liver or muscle, with a compensatory increase reported in muscle glycogen utilisation rather than plasma glucose oxidation to fuel exercise (Robitaille et al., 2007).

2.6.1 Exercise intensity

An increase in exercise intensity typically results in more reliance on oxidation of carbohydrates to fuel the exercise as individuals cannot oxidise lipids fast enough to provide sufficient energy at these increasing intensities (Coyle, 1995). Carbohydrates are stored in the

body as glycogen in either the muscles or liver and during high intensity exercise energy is primarily supplied by carbohydrate oxidation predominantly via breakdown of these glycogen stores (Coyle, 1995).

The regulation and reliance on carbohydrates is relatively well understood, however the regulation and utilisation of lipid as a fuel is less clear. There are suggestions that lipid oxidation is regulated directly by carbohydrate availability (Coyle, Jeukendrup, Wagenmakers & Saris, 1997) or that there is a 'crossover' concept where at a certain exercise intensity the energy derived is equal between both carbohydrates and lipids but beyond this point carbohydrate is the dominant substrate (Brooks & Mercier, 1994). Lipid oxidation can also be influenced by repeated bouts of exercise, following an initial exercise bout, exercise-induced increases in extracellular glycerol concentrations in adipose tissue and plasma glycerol concentrations were both higher in a second exercise bout (Stich et al., 2000). Repetitive bouts also enhance fat metabolism compared with a single bout of exercise at the equivalent total duration of exercise (Goto, Ishii, Mizuno & Takamatsu, 2007).

Recently there has been an emerging focus that has investigated the exercise intensity that promotes the peak rates of lipid oxidation, commonly referred to as 'fatmax' (Jeukendrup & Achten, 2001). The intensity value that has been documented to induce maximal levels of fat oxidation are 64 ± 4% $\dot{V}O_{2\,MAX}$ which is equivalent to 74 ± 3% maximum heart rate in non-diabetic individuals (Achten, Gleeson & Jeukendrup, 2002). This intensity was determined by an incremental protocol which lasted 3 minutes although no differences were found in increments lasting for 5 minutes (Achten et al., 2002). Previous research (Bergman & Brooks, 1999; Romijn, Coyle, Sidossis, Rosenblatt & Wolfe, 2000; van Loon, Greenhaff, Constantin-Teodosiu, Saris & Wagenmakers, 2001) that investigated substrate utilisation at differing exercise intensities over prolonged durations which lasted between 30 – 120 min also witnessed peak rates of lipid oxidation at comparable exercise intensities. Further research (Bircher, Knechtle & Knecht, 2005) measured blood lactate concentrations at fatmax using both a standard protocol as defined by Achten et al. (2001) and an individualised exercise program tailored to the participant. Blood lactate concentrations at fatmax were found to be between 1.06 – 1.18 and 1.98 – 2.19 $mmol \cdot L^{-1}$ in the standard and individual protocols respectively. However, the reliability of fatmax has also been questioned and documented large individual variability imply that a definitive exercise intensity cannot be

designated for exercise prescription in regards to health benefits (Meyer, Folz, Rosenberger & Kindermann, 2009).

Direct comparison between non-T1DM and T1DM individuals has proven that after pre-exercise glucose feeding and engagement in moderate intensity exercise, substrate and exogenous glucose oxidation was similar, however, plasma glucose oxidation was lower in T1DM which is associated with a compensatory increase in muscle glycogen utilisation (Robitaille et al., 2007). A further consideration with exercising T1DM and substrate utilisation is levels of glycaemia. Performing a prolonged period of exercise in levels of hyperglycaemia (clamped at 11 $mmol \cdot L^{-1}$) has been demonstrated to suppress lipid oxidation with a tendency to favour carbohydrate oxidation compared to euglycaemia (Jenni et al., 2008). Carbohydrate oxidation in hyperglycaemia is also elevated above those oxidation levels observed in a controlled level with blood glucose concentrations at 10.8 ± 0.4 and 4.2 ± 0.2 $mmol \cdot L^{-1}$ respectively, whilst hyperglycaemia can also promote increased glucose disposal rates (Coyle, Hamilton, Gonzalez Alonso, Montain & Ivy, 1991).

2.6.2 Ingestion of pre-exercise carbohydrates with differing GI values

The manipulation of pre-exercise carbohydrate ingestion with different glycaemic indexes was carried out first by Thomas, Brotherhood & Brand (1991) who observed after consumption of lentils in comparison to other foodstuff, participants increased their cycling endurance by up to 20 minutes. Further literature in non-T1DM participants (Febbraio, Keenan, Angus, Campbell & Garnham, 2000; Wee, Williams, Tsintzas & Boobis, 2005; Wu, Nicholas, Williams, Took & Hardy, 2003) demonstrates that high glycaemic index carbohydrates augments muscle glycogen utilisation during subsequent exercise and therefore, when a low glycaemic index carbohydrate is consumed prior to exercise exogenous and endogenous carbohydrate is spared due to increased fat oxidation during exercise.

The ingestion of different GI carbohydrates prior to exercise in T1DM individuals has recently been investigated (West et al., 2011b), where isomaltulose (low GI) was consumed 2-hours prior to 45 minutes of running exercise as an alternative to dextrose (high GI). Levels of glycaemia were significantly improved for a 3-hour recovery period in the isomaltulose trial alongside a significant increase in lipid oxidation and significant decrease in carbohydrate oxidation during the final ten minutes of exercise when compared to dextrose.

This increased reliance on lipids to fuel exercise and reduced carbohydrate oxidation could explain the reduced excursions in blood glucose responses and regularly employing this strategy has the potential to benefit long-term glycaemic control. Current recommendations (Lumb & Gallen, 2009) promote consumption of high GI carbohydrates before exercise to reduce the incidence of hypoglycaemia whilst low GI consumption has been shown in the research of West et al. (2011b) to be as equally effective.

The duration of exercise could be an important consideration in the research of non-T1DM and T1DM individuals as mentioned the dominant fuel use only shifted in the final ten minutes of a 45 minute protocol in T1DM (West et al., 2011b) and in non-T1DM the duration of exercise was at least 30 minutes long. One of the unanswered questions within the research of West et al. (2011b) is whether the lower blood excursions reported would impact upon subsequent exercise performance. At present there is little research investigating performance in T1DM individuals, with a body of evidence suggesting performance being improved in non-T1DM due to carbohydrate sparing, it warrants examining the performance effects after ingestion of differing GI pre-exercise carbohydrates. Greater reliance on lipid oxidation during submaximal exercise may benefit later performance or it could be that performance is compromised for the better glycaemia in T1DM individuals following low GI supplementation.

2.7 Exercise performance

2.7.1 Methods to measure performance

Testing performance is one of the most important factors in sports science and physiology (Currell & Jeukendrup, 2008) with two commonly used examples to measure exercise performance being time to exhaustion (TTE) and time trial (TT) protocols (Laursen, Francis, Abbiss, Newton & Nosaka, 2007). Both of these methods were adopted in some of the previously discussed glycaemic index performance interventions (Sparks et al., 1998; Thomas et al., 1991; Wong et al., 2008; Wu & Williams, 2006).

TTE trials involve an individual to exercise until volitional exhaustion at a given intensity and are sometimes referred to as a measure of endurance capacity (Currell & Jeukendrup,

2008). On the other hand, TT experiments require an individual to complete a set distance or workload as quickly as possible or the measurement of distance covered within a defined time limit. Using TT assessment allows the participants to adjust their workload periodically and pace themselves accordingly to the previously notified endpoint (Tucker & Noakes, 2009).

One limitation with the TTE model is the perceived low reliability of the test procedure which is reflected in high co-efficient of variation (CoV) values. Typically, TTE experiments can result in CoV of between 13.2 – 15.1% even as high as 26.6% (Jeukendrup, Saris, Brouns & Kester, 1996), CoV scores between 2.0 – 3.6% were reported in TT protocols (Jeukendrup et al., 1996; Laursen et al., 2007). These lower CoV values in TT compared to TTE has resulted in this protocol to be claimed a more validated method to measure performance (Jeukendrup et al., 1996).

However more recently, TTE methods have been defended by some researchers (Hopkins, Schabort & Hawley, 2001) who claim that the high CoV in such trials can be influenced by a small change in an individual's ability to output power and the large changes seen in duration of time are in addition to a lot more noise. Hopkins et al. (2001) continue and indicate that if changes or noise in duration were converted back to changes in mean power over the TTE period the CoV would be reduced and the TTE protocol would be more reliable than other testing methods.

2.7.2 Factors that impact upon performance

Fatigue is one of the major contributors that can impair exercise performance, fatigue is caused by a number of factors one of which being glycogen depletion. Carbohydrate utilisation has been shown to be correlated with reductions in glycogen stores and concluded that the ability to perform high intensity exercise prior to the onset of fatigue is directly determined by availability of glycogen (Ahlborg, Bergström, Ekelund & Hultman, 1967; Bergström, Hermansen, Hultman & Saltin, 1967). Muscle glycogen stores and subsequent availability can decrease performance in both short-term and prolonged intermittent assessments (Balsom, Gaitanos, Söderlund & Ekblom, 1999). Depletion of glycogen stores is of interest in regards to exercising T1DM individuals as there has been shown to be a compensatory increase in muscle glycogen utilisation when exercising when directly

compared to healthy counterparts (Robitaille et al., 2007). This finding may influence the choice of carbohydrate ingested prior to or during exercise as it appears that assimilation and ability to store as glycogen for oxidation are the most important factors in T1DM.

Carbohydrate ingestion before and during exercise is recommended to improve performance as a means to delay glycogen depletion and subsequent fatigue (Coyle, 1995; El-Sayed, MacLaren & Rattu, 1997; Jeukendrup, 2004). Carbohydrate feeding may also improve endurance performance via a number of other mechanisms of which these include sparing endogenous glycogen, synthesising glycogen at low intensity exercise and maintaining both high rates of carbohydrate oxidation and levels of blood glucose (Jeukendrup, 2004). Low glycaemic index carbohydrates as previously discussed (Chapter 2.6.2) can spare endogenous and exogenous carbohydrate through increased rates of lipid oxidation (Febbraio et al., 2000; Thomas et al., 1991; Wee et al., 2005; Wu et al., 2003). Exercise performance may be enhanced as a result of this carbohydrate sparing effect as improvements has been observed in both time trial (Wong et al., 2008) and time to exhaustion (DeMarco, Sucher, Cisar & Butterfield, 1999; Thomas et al., 1991; Wu & Williams, 2006) scenarios following a low GI meal. However, there is also evidence that contradicts the performance benefits of low GI supplementation where no change in power output was witnessed even though there was observed differences in pre-exercise metabolism (Sparks, Selig & Febbraio, 1998). Several amounts of carbohydrate have been mentioned to benefit performance with suggestions of up to 1 – 2 $g.kg.BM.h^{-1}$ (Hernandez et al., 2000; Riddell & Perkins, 2006) have been suggested, however carbohydrate ingestion over 75 $g.h^{-1}$ does not further enhance performance in comparison to provisions of 45 – 75 $g.h^{-1}$ (Jeukendrup, 2004).

Table 2.3 Existing pre-exercise CHO manipulation and performance responses in non T1DM

Study (Author, Year)	**Substrate Use and/or Metabolic Responses**	**Subsequent Performance**
DeMarco et al., 1991	Reduced plasma insulin levels in LGI trial RER higher during exercise in HGI trial Increased plasma glucose following 2 hours of exercise in LGI trial	TTE was 59% longer at 100% $\dot{V}O_{2\,MAX}$ in LGI trial
Sparks et al., 1998	Increased plasma glucose concentrations at rest and decreased during and after exercise in HGI trial Plasma FFA concentrations higher at start and end of exercise in LGI trial CHO oxidation higher during exercise in HGI trial	No difference in work output during 15 min self-paced performance cycle
Thomas et al., 1991	FFA concentrations higher in LGI trial Plasma glucose and insulin levels lower in LGI trial	Cycling endurance increased by up to 20 min after lentil consumption
Wong et al., 2008	Increased rates of lipid oxidation during exercise after LGI meal	Faster time in 16 km performance run in LGI trial
Wu & Williams, 2006	Lipid oxidation during exercise was higher in LGI trial	Greater endurance capacity in TTE assessment in LGI trial

KEY: CHO, Carbohydrate; FFA, Free Fatty Acids; HGI, High Glycaemic Index; LGI, Low Glycaemic Index; RER, Respiratory Exchange Ratio; TTE, Time To Exhaustion

During high intensity, blood flow and oxygen demand can fall behind the requirements needed by the working muscles. To meet the demand the body metabolises anaerobically, producing a number of metabolites of which include lactate and hydrogen ions, these ions in particular inhibit muscle contraction thus causing fatigue (Noakes, 2000). During incremental or graded exercise, muscle contraction alone stimulates glycogenolysis and subsequent lactate production (Billat, 1996). The lactate threshold is the exercise intensity performed where an individual is exercising below a 1 $mmol \cdot L^{-1}$ increase from resting blood lactate concentrations (Farrell, Wilmore, Coyle, Billing & Costill, 1979). Exercising at intensities

higher than this threshold promotes the accumulation of lactate which can result in fatigue. Another consideration when measuring blood lactate considerations and exercise in carbohydrate supplementation research is that carbohydrate feeding alone promotes glycolysis and produces lactate even at rest (Houston, 1995). Decreases in muscle pH are also linearly associated with an increase in lactate and pyruvate concentrations (Sahlin, Harris & Hultman, 1975).

Aside from lactate concentration, the combination of heat generated through exercise and sweat loss can further lead to dehydration (Coyle, 1999) which can also impact upon exercise performance. Fluid loss is usually accompanied with a reduction in plasma volume and can influence the capacity of the working muscles as blood flow to the muscles needs to be maintained at high levels to provide required oxygen and substrates (Maughan, 2003). Research shows that in dehydration the blood flow to the working muscles is decreased as a result of a lowering in systemic blood flow and perfusion pressure (González-Alonso, Calbet & Nielsen, 1998). Therefore with a restriction of blood flow to working muscles, the substrate and oxygen supply is diminished and exercise performance is compromised. Blood haematocrit ratio increases continually during heat exposure to levels of dehydration (Senay, 1970) and is a commonly used marker of hydration status in practical assessments (Harvey, Meir, Brooks & Holloway, 2008; Shirreffs, 2003).

An important consideration in exercising T1DM individuals is that some symptoms of dehydration (dry mouth and thirst) are also markers of hyperglycaemia (Warren et al., 2003) whilst sweating, a physiological response to exercise, is also a hypoglycaemic symptom (Deary et al., 1993). The danger is that these warning signs associated with either high or low levels of blood glucose could be confused as physiological responses to exercise rather than hypo- or hyperglycaemia. Furthermore, exercising in hyperglycaemia has been suggested to increase extracellular glucose availability and theoretically increase rates of oxidation. Although in reality this availability does not result in the increase of intracellular glucose oxidation with lactate, peak power output and respiratory exchange ratio (RER) all equivalent in comparison to euglycaemic conditions (Stettler et al., 2006) and therefore no advantage in performance in T1DM.

Performance can also be enhanced by the supplementation of caffeine prior to exercise. Caffeine ingestion has been shown to improve endurance performance (Costill, Dalsky &

Fink, 1978; Kovacs, Stegen & Brouns, 1998), caffeine increases lipid oxidation and has a positive influence on nerve impulse transmission which could explain the performance benefits (Costill et al., 1978). Therefore caffeine intake would need to be restricted prior to any nutritional interventions examining exercise performance such as carbohydrate feeding as these results could be influenced by previous caffeine ingestion and not only the carbohydrate manipulation.

2.8 Electrolyte responses to exercise

Irrespective of carbohydrate ingestion, electrolytes responses are influenced by exercise and associated increased demands of the working muscles. During exercise, an increase in muscle contractions is required to perform the workload being demanded. The essential component for muscle activation is the uptake of calcium ions and the subsequent regulation of the contractile processes of muscle through the troponin-tropomyosin (Ebashi, 1972). High intensity demanding exercise such as performance bouts have witnessed impaired calcium ion uptake and transport which suggests that this may contribute to fatigue (Leppik et al., 2004).

Blood potassium concentrations are dependent on exercise intensity and increase with higher levels of exercise. The rise in potassium is attributed to the rapid loss of potassium from the exercising muscles and release into the blood circulation (Vøllestad, Hallén & Sejersted, 1994). On cessation of exercise the uptake of potassium from the blood is immediate (Vøllestad et al., 1994) this uptake is principally regulated by the sodium-potassium (Na^+ - K^+) pump in the exercised muscles (Medbø & Sejersted, 1990). Potassium clearance during exercise is regulated during exercise via Na^+-K^+-ATPase in the skeletal muscle where potassium is exchanged for sodium, this process is crucial in protecting both muscle membrane contractility and excitability (Sejersted & Sjøgaard, 2000). Sodium concentrations are usually between the normal range of 135 – 146 $mmol \cdot L^{-1}$ (Vrijens & Rehrer, 1999). During prolonged periods of exercise and via subsequent sweat loss sodium concentrations can fall which if not sufficiently replaced with fluid can result in dehydration (Vrijens & Rehrer, 1999). Dehydration as previously discussed can impact upon exercise performance, therefore both sodium and haematocrit measurements could indicate levels of hydration.

In specific regards to individuals with T1DM, following intense exercise decreased levels of sodium accompanied by elevated potassium concentrations have been observed, the potassium levels remaining elevated until insulin is exogenously administered (Harmer et al., 2006).

2.9 Cognitive function and levels of glycaemia

Levels of glycaemia is previously discussed can be influenced by engagement in exercise (Chapter 2.4.3). Dependent on the exercise performed blood glucose can become elevated towards hyperglycaemic levels or start to decline towards hypoglycaemic levels. The next chapters discuss how cognitive function can be affected by levels of glycaemia, other influences that impact upon cognitive function, a recognised method to test cognitive function and primarily by addressing hypoglycaemia unawareness.

2.9.1 Hypoglycaemia unawareness

Hypoglycaemia unawareness is simply the failure to identify hypoglycaemia and commonly reflects deficient sympathoadrenal activation (Heller, 2011). Individuals that suffer from hypoglycaemia unawareness have no endocrine protection against insulin-induced hypoglycaemia, having previous lost their glucagon responses (Heller, 2011). Early warning indications of hypoglycaemia such as anxiety and nervousness are caused by the release of adrenaline, however these adrenergic responses are not present in hypoglycaemia unawareness as adrenaline is impaired (Fowler, 2008). An association between severe hypoglycaemia and hypoglycaemia unawareness has been previously documented (Gold, MacLeod & Frier, 1994; Mokan et al., 1994), with hypoglycaemia unawareness also implying repeated episodes of hypoglycaemia (Cryer et al., 2003). It has been suggested that avoidance of hypoglycaemic for a period of 2 – 3 weeks may help to improve hypoglycaemia unawareness (Cryer et al., 2003).

2.9.2 Cognitive function in hypoglycaemia

A number of studies (Draelos et el., 1995; Evans, Pernet, Lomas, Jones & Amiel, 2000; Sommerfield, Deary, McAuley & Frier, 2003) have investigated cognitive function in hypoglycaemia by regulating blood glucose levels using either a hyperinsulinemic (Evans et al., 2000; Sommerfield et al., 2003) or hypoglycaemic clamp (Draelos et al., 1995).

Comparisons were made between cognitive function in a series of tests at hypoglycaemia and euglycaemia. Hypoglycaemic levels in the studies were 2.2 $mmol \cdot L^{-1}$ (Draelos et al., 1995), 2.5 $mmol \cdot L^{-1}$ (Sommerfield et al., 2003) and 2.65 $mmol \cdot L^{-1}$ (Evans et al., 2000), whilst euglycaemic values were 4.5 $mmol \cdot L^{-1}$ (Sommerfield et al., 2003), 5.01 $mmol \cdot L^{-1}$ (Evans et al., 2003) and 8.9 $mmol \cdot L^{-1}$ (Draelos et al., 1995) respectively. In each of the studies cognitive performance weakened in the hypoglycaemic state in comparison to euglycaemic conditions. Cognitive function was noticed to decline immediately on onset of hypoglycaemia (Evans et al., 2000) with more profound deterioration witnessed in memory and immediate processing tasks (Sommerfield et al., 2003).

Gender differences were also noticed with hypoglycaemia negatively effecting males more than females (Draelos et al., 1995). One further important observation made by Evans et al. (2000) was that cognitive function can become impaired prior to any symptomatic awareness.

Another factor to consider when discussing cognitive function in hypoglycaemia is the rate as to which blood glucose falls. It is established from the examples described previously that cognitive function is compromised in a hypoglycaemic state, furthermore cognitive function is greater impaired after a rapid decline of blood glucose. Fanelli et al. (2003) showed that a fast fall (0.1 ± 0.003 $mmol \cdot min^{-1} \cdot L^{-1}$) compared to slow fall (0.03 ± 0.001 $mmol \cdot min^{-1} \cdot L^{-1}$) in blood glucose to a hypoglycaemic level of 2.4 $mmol \cdot L^{-1}$ in the postprandial state resulted in further deterioration in memory tasks.

In a recent review article (Warren & Frier, 2004), the authors acknowledged that simple tasks can still be performed despite moderate hypoglycaemia, however the tasks would take longer to complete, thus suggesting a cognitive 'spare capacity'.

Table 2.4 Cognitive function studies in hypoglycaemia

Study	**Cognitive Functioning Tests**	**Results (In Hypoglycaemia Compared to Baseline or Euglycaemia)**
Draelos et al., 1995	*Neuropsychological Testing*: Simple Reaction Time, Choice Reaction Time, Digit Vigilance (Number of Items and % Errors), Trail-Making Part B, Word Recall, Serial Digit Learning and Verbal Fluency	Slower Choice and Simple Reaction Times, Lower Digit Vigilance (Both Number of Items and % Errors), Lower Trail-Making Part B Score, Less Word Recall, Lower Serial Digit Learning Score, Lower Verbal Fluency.
Evans et al., 2000	Four Choice Reaction Time, Stroop Word and Colour Word Subtests, Trail-Making Part B	Slower Four Choice Reaction Time, Slower Stroop Word and Colour Word Times
Sommerfield et al., 2003	*Verbal Memory Tests*: Auditory Verbal Learning Test (AVLT), Logical Memory Test *Visual Memory Tests*: Visual Reproduction Test, Benton Visual Retention Test *Working Memory Tests*: Working Digit Span Test, Letter/Number Sequence Test, Validation Span Test *Other Mental Tests:* Trail-Making Part B, Digit Symbol Test	Lower Scores in immediate AVLT and Logical Memory Tests, Lower Score in Benton Visual Retention Test, Lower Scores in all delayed verbal and visual memory tests, Slower times in all working memory tests apart from digit span forward test

2.9.3 Cognitive function in hyperglycaemia

Other literature (Draelos et al., 1995; Gschwend, Ryan, Atchinson, Arslanian & Becker, 1995; Cox et al., 2005; Gonder-Frederick et al., 2009) has examined the effects of hyperglycaemia on cognitive performance compared to euglycaemia. These studies either regulated blood glucose by clamp techniques (Draelos et al., 1995; Gschwend; 1995) or relied on self-entered blood glucose levels (Cox et al., 2005; Gonder-Frederick et al., 2009). Hyperglycaemic blood glucose values were manipulated in the clamp studies to levels of 20 $mmol \cdot L^{-1}$ (Gschwend et al., 1995) and 21.1 $mmol \cdot L^{-1}$ (Draelos et al., 1995), whilst in studies that relied on self-reported data, blood glucose values above 15 $mmol \cdot L^{-1}$ (Cox et al., 2005) and 22.1 $mmol \cdot L^{-1}$ (Gonder-Frederick et al., 2009) were classified as hyperglycaemic.

The findings in the studies were inconsistent as some studies reported no deterioration in cognitive performance in hyperglycaemia (Draelos et al., 1995; Gschwend et al., 1995) with slowing in cognitive function also being reported (Cox et al., 2005) and observed to be as impaired as in a hypoglycaemic condition (Gonder-Frederick et al., 2009). The studies that witnessed impaired cognitive function (Cox et al., 2005; Gonder-Frederick et al., 2009) took place over a 4 – 6 week long period and relied on self-entering of blood glucose levels.

Engaging in strenuous exercise has also lead to improvements in cognitive abilities after cessation of the activity (Ferris, Williams & Shen, 2007; Hogervorst, Riedel, Jeukendrup & Jolles, 1996). These observed improvements in cognitive function have been attributed to the individual still being in a highly aroused state that in turn leads to increased activation of the central nervous system (Hogervorst et al., 1996). However, exercising at high intensities as previously reported leads to a rise in blood glucose as hepatic production exceeds the rate of utilisation (Mitchell et al., 1988). Therefore it may be the combination of both the state of arousal and the potentially hyperglycaemic conditions that caused the improvements witnessed in these studies.

Table 2.5 Cognitive function studies in hyperglycaemia

Study	**Cognitive Functioning Tests**	**Results (In Hyperglycaemia Compared to Baseline or Euglycaemia)**
Cox et al., 2005	Hand Held Computers which presented a number of tasks; 1. Psychomotor Test 2. 10 Mental Subtractions 3. 15 Four-Choice Reaction Time Tests (After tasks user entered blood glucose)	Levels of hyperglycaemia (BG: >15 $mmol{\cdot}L^{-1}$) lead to deterioration in all tasks
Draelos et al., 1995	*Neuropsychological Testing*: Simple Reaction Time, Choice Reaction Time, Digit Vigilance (Number of Items and % Errors), Trail-Making Part B, Word Recall, Serial Digit Learning and Verbal Fluency	Lower Digit Vigilance (Number of Items only), Lower Trail-Making Part B, Higher Verbal Fluency
Gonder-Frederick et al., 2009	Personal Digital Assistant (PDA) Tests that presented a mental math test followed by a choice reaction time (After tasks user entered blood glucose)	Math Time was significantly longer (BG: > 22 $mmol{\cdot}L^{-1}$), Trend for significance (P = 0.08) in reaction time (BG: > 22 $mmol{\cdot}L^{-1}$)

2.9.4 Other influences on cognitive function and recognised methods

Low GI foodstuff as previously discussed (Chapter 2.5.2.2) eaten at breakfast has been proven to sustain cognitive performance for a longer period in comparison to high GI foodstuff, more specifically in memory and accuracy tasks (Benton et al., 2003; Ingwersen et al., 2007). An explanation for this observation could be related to emerging evidence that insulin has a key role between mental performance and glucose flux mainly via impaired glucose tolerance (Benton et al., 2003). Low GI diets have been shown to produce a lesser

release of postprandial insulin (Jenkins et al., 1987), this potentially reduced insulinaemia results in a favourable pathway between glucose flow and the brain when the demand occurs as opposed to glucose being directed to more insulin sensitive tissues such as the muscles (Benton et al., 2003).

An established method of measuring cognitive function is the Stroop colour-word test (SCWT), named after the individual who first made the observation in 1935, using congruent (shapes of colour) and incongruent cards (words spelt in a colour that was incorrect i.e. 'blue' spelt in green letters). Stroop (1935) observed that individuals encountered a disruption and delay in naming the colour patches that were shaped to spell an incongruent word. The most important finding in these series of tests is the difference in timing to name incongruent and congruent examples (Dyer, 1973) this time difference is commonly referred to as the 'Stroop interference' or 'Stroop effect' (MacKinnon, Geiselman & Woodward, 1985). The Stroop colour word was used as part of an array of tests to assess cognitive function in some of the previous discussed research (Evans et al., 2000; Ferris et al., 2007; Hogervorst et al., 1996) and is a recognised tool at measuring selective attention, critical in the ability to process task-related stimuli (Leung, Skudlarski & Gatenby, 2000). A recent functional magnetic resonance imaging (fMRI) study has determined a number of regions are activated in the brain when performing the SCWT, these being the anterior cingulate, insula, premotor and inferior frontal regions (Leung et al., 2000). Incorporating a selective attention task into a research protocol could evaluate whether the choice of carbohydrate has any influence on cognitive function prior to and following exercise. Task-relating stimuli may replicate the decisions made in real life situations i.e. if following exercise cognitive function is impaired after consumption of some carbohydrates, provisions would then need to be made in this clinical population to counteract this impairment.

2.10 Aims and Null Hypotheses

2.10.1 Aims

Within the current literature there is little research that directly investigates exercise performance in T1DM and the consequences on glycaemia during and after. Performance testing is generally high intensity running which can lead to hyperglycaemia in the T1DM population following exercise. The current guidelines in regards to carbohydrate consumption and reduction of insulin dosage are more geared towards preventing hypoglycaemia. The equally detrimental condition of hyperglycaemia is rarely discussed with very few strategies to limit the occurrence.

This study will therefore examine the blood glucose responses after ingestion of high and low GI CHO supplementation and whether the lower excursions previously reported (West et al., 2011b) limit the incidences of negative hyperglycaemia in T1DM and how this may impact upon exercise performance. The main question is whether exercise performance is compromised for improved levels of glycaemia. The study will also take into consideration cognitive functioning and perceived hunger and fullness ratings after manipulation of pre-exercise CHO.

Additionally prior to any main experimental research a series of pilot studies will take place. These studies will:

a) Validate the currently reported GI value for isomaltulose

b) Observe the lactate responses after isomaltulose consumption of differing concentrations

c) Trial the time to exhaustion (TTE) protocol following a bout of submaximal exercise in non-T1DM individuals

d) Investigate whether a learning effect is present following use of the Stroop Colour Word Test (SCWT) software

2.10.2 Null Hypotheses

i. Ingestion of pre-exercise carbohydrate with different GI values will not influence glycaemic or metabolic responses at rest or during subsequent exercise
ii. Ingestion of pre-exercise carbohydrate with different GI values will not influence substrate utilisation at rest or during submaximal incremental exercise
iii. Ingestion of pre-exercise carbohydrate with different GI values will not influence high intensity exercise performance
iv. Ingestion of pre-exercise carbohydrate with different GI values will not influence cognitive function accuracy or reaction times
v. Ingestion of pre-exercise carbohydrate with different GI values will not influence perceived feelings of gut fullness or hunger

3.0 METHODOLOGY

3.1 Participants and Control

To be considered for recruitment, potential participants had to meet a set of criteria. Individuals could be either male or female, aged between 18 – 60 years old, in moderate glycaemic control (assessed by a HbA_{1c} score < 11.0% or < 97 $mmol \cdot mol^{-1}$), engaging in physical activity at least twice a week, currently on a basal-bolus insulin regimen for at least three months comprising either a combination of insulin glargine (Lantus®) or detemir (Levemir®) and insulin aspart (NovoRapid®) or lispro (Humalog®) and no cardiovascular or diabetic complications apart from background retinopathy.

Participants were recruited from individuals that had expressed an interest in previous trials conducted by the research team, local diabetes clinics and university e-mail advertisements. Nine individuals volunteered to take part and completed the preliminary session, of these nine, two withdrew through commitment issues, one was excluded due to a level of physical inactivity and one individual unfortunately experienced a hypoglycaemic episode outside of the laboratory and had to change their insulin regimen and subsequently withdraw from the study. Continued advertisement enabled a further two individuals to be recruited for participation in this research. Characteristics of these seven participants, two male and five female are detailed in the table below.

Table 3.1 Characteristics of participants who completed the research study

Participant Characteristics	
Age	34 ± 5 years
Height	168.2 ± 2.9 cm
Body Mass	69.8 ± 2.0 kg
BMI	24.9 ± 1.4 $kg \cdot m^{-2}$
Body Fat	23.8 ± 1.9 %
HbA_{1c}	76.6 ± 6.5 $mmol \cdot mol^{-1}$
$\dot{V}O_{2\ PEAK}$	38.7 ± 1.7 $ml \cdot kg^{-1} \cdot min^{-1}$
Duration of diabetes	16 ± 5 years

For the day prior to laboratory attendance, participants were asked to record their dietary intake (Appendix 8.3), abstain from unaccustomed physical activity and refrain from drinking alcohol. Participants then underwent an overnight fast and were allowed to drink only water, avoiding caffeine. Participants administered their long acting insulin, glargine (Lantus®, n = 6) or detemir (Levemir®, n =1), as normal either the night before or morning of the experimental trial.

3.2 Experimental Apparatus, Calibration and Principles of Operation

3.2.1 GEM Calibration and Intelligent Quality Management (iQM^{TM})

Prior to experimental sampling, calibration took place using a number of GEM Calibration Validation Product (CVP) solutions. Four CVP ampoules (CVP 1, CVP 2, CVP 3 and CVP 4) were used for this calibration procedure, each ampoule consisted of 2.5ml of a buffered bicarbonate solution containing inorganic salts and organic metabolites which were equilibrated with concentrations of carbon dioxide and oxygen. Each CVP was composed of a different configuration, CVP 1 comprised a solution containing low pH, pO_2, Na^+, K^+, glucose and lactate values and high pCO_2 and Ca^{++} values. CVP 2 solution comprised of high pH, pO_2, Na^+, K^+, glucose and lactate values and low pCO_2 and Ca^{++} values. The CVP 3 and CVP 4 solutions comprised of low and normal haematocrit values respectively.

Each CVP solution is designated a barcode that corresponded to a specified lot number with a pre-determined material value that are recognised by the GEM Premier 3000 (Table 3.2). The four barcodes are scanned and then a sample was individually aspirated from each of the ampoules, these samples were analysed and cross-referenced against the recognised values and either 'PASSED' or 'FAILED'. Once all four samples passed, the Intelligent Quality Management (iQM^{TM}) feature had been configured and the GEM Premier 3000 was ready for use.

The iQM™ feature is an active control system that ensures that reliable results are produced sample upon sample. The iQM™ continually monitors operation of the testing process, including sensors, fluidics and electronics and if an error is detected then it will perform and document the corrective actions. These checks included:

- Performing special rinse cycles if micro-clots were detected and subsequently verifying cartridge function.
- Disabling a failed sensor permanently if the function could not be recovered
- Rejecting a cartridge for process stability failure
- Alerting user upon detection of an interfering substance in a sample

Table 3.2 GEM CVP values for each variable for the three cartridges used in the experimental trials. Values in brackets indicate the acceptance ranges.

	Cartridge 1	Cartridge 2	Cartridge 3	Mean	CoV
CVP 1					
pH (7.16 – 7.23)	7.16	7.22	7.18	7.19 ± 0.02	< 0.01%
pCO_2 (65 – 79 mmHg)	79	66	75	73 ± 4	0.09%
pO_2 (46 – 64 mmHg)	64	58	56	59 ± 2	0.07%
Na^+ (122 – 133 mmol·L^{-1})	129	129	126	128 ± 1	0.01%
K^+ (2.5 – 3.3 mmol·L^{-1})	2.8	2.8	2.9	2.8 ± 0.0	0.02%
Ca^{++} (1.42 – 1.65 mmol·L^{-1})	1.51	1.47	1.46	1.48 ± 0.02	0.02%
Glucose (2.1 – 3.0 mmol·L^{-1})	2.5	2.4	2.7	2.5 ± 0.1	0.06%
Lactate (0.7 – 1.1 mmol·L^{-1})	0.9	0.8	0.9	0.9 ± 0.0	0.07%
CVP 2					
pH (7.61 – 7.67)	7.64	7.65	7.64	7.64 ± 0.00	< 0.01%
pCO_2 (28 – 34 mmHg)	31	30	31	31 ± 0	0.02%
pO_2 (133 – 157 mmHg)	138	150	154	147 ± 5	0.06%
Na^+ (154 – 165 mmol·L^{-1})	164	162	164	163 ± 1	0.01%
K^+ (6.2 – 7.0 mmol·L^{-1})	6.6	6.5	6.5	6.5 ± 0.0	0.01%
Ca^{++} (0.37 – 0.51 mmol·L^{-1})	0.46	0.42	0.42	0.43 ± 0.01	0.05%
Glucose (14.8 – 17.5 mmol·L^{-1})	16.5	16.0	16.6	16.4 ± 0.2	0.02%
Lactate (4.8 – 6.1 mmol·L^{-1})	5.4	5.4	5.7	5.5 ± 0.1	0.03%
CVP 3					
Haematocrit (21 – 25 %)	23	23	23	23 ± 0	< 0.01%
CVP 4					
Haematocrit (41 – 48 %)	44	44	44	44 ± 0	< 0.01%

3.2.1.1 Blood Gas, Electrolyte and Metabolite Calculations

For all main experimental testing the GEM Premier 3000 was used to analyse capillary blood for the following variables; pH, pCO_2, pO_2, Na^+, K^+, Ca^{++}, glucose, lactate and haematocrit. These variables were determined by a series of electrochemical sensors located in the self-contained disposable GEM Premier 3000 PAK cartridge. These sensors combined with the reference electrode and bonded chemically sensitive membranes were fundamental components of the chamber body. The sensors with the exception of haematocrit were fashioned from layers of polymer films bonded to the substrate. Under each of the sensors was a metallic contact that was brought to the surface to form an electrical interface with the instrument when sampling occurred.

3.2.1.2 pH and Electrolytes (Na^+, K^+ and Ca^{++})

These samples were based on the principle of ion-selective electrodes and the electrical potential established from specific ions and calculated by a simplified version of the Nernst equation:

$$E = E' + (S \times \text{Log } C)$$

E is the electrode potential, E', the standard potential of the specific membrane, S, the slope sensitivity and C, the ion activity. E' and S are determined from the responses from the calibration solutions and the equation solved for the ion activity. In the instance of pH 'log C' is replaced by pH and the equation solved accordingly.

3.2.1.3 Ca^{++} correction to pH = 7.4

To determine Ca^{++} the following equation was used with the pH constant value of 7.4:

$$Ca^{++}\text{ (corrected)} = (Ca^{++}\text{(measured)} \times 10^{(-0.178 \times (7.4 - pH))})$$

3.2.1.4 Carbon Dioxide (pCO_2 mmHg)

The pCO_2 sensor relied on a pH selective polymer as a gas permeable outer membrane. The pCO_2 in the internal solution reached equilibrium with the pCO_2 of the blood when it came in contact with the outer surface of the membrane. The internal solution pH value varies with pCO_2 in agreement with the Henderson-Hasselbalch equation:

$$pH = pKa + \log (HCO_3^- / pCO_2 \times a)$$

pKa is a constant (equilibrium), HCO_3^-, the bicarbonate ion concentration and 'a', the solubility coefficient of carbon dioxide in water. The pH sensor versus the generated potential is related to the logarithm of the pCO_2 sample content.

3.2.1.5 Oxygen (pO_2 mmHg)

The oxygen sensor consisted of a small platinum electrode primed at a negative potential in regards to the reference electrode of the instrument card. The flow of electrical current between the ground electrode and platinum surface was proportional to the rate at which oxygen molecules diffused to the platinum and was subsequently reduced. This rate of diffusion and reduction was directly proportional to the pO_2 value and the relationship described by the equation:

$$I = (S \times pO_2) + IZ$$

I is the electrode current, S, the sensitivity and IZ, the zero current, both the values for S and IZ can be calculated from the calibration readings for the sensor. The equation for pO_2 can be solved when I is substituted for the electrode current from the blood sample.

3.2.1.6 Metabolites (Glucose and Lactate)

The glucose and lactate sensors comprised of a platinum electrode primed at a positive potential in regards to the reference electrode of the instrument card. Determination of the metabolites resulted from enzymatic reactions of either glucose or lactate with oxygen in the presence of glucose or lactate oxidase and the resulting hydrogen peroxide detected on the platinum electrode. The current flow between the ground and platinum electrodes was proportional to the rate of diffusion and oxidisation of the hydrogen peroxide molecules. Glucose and lactate concentrations were directly proportional to this rate of diffusion and oxidisation and the relationship describes as:

$$I = (S \times \text{metabolite}) + IZ$$

I is the electrode current, S, the sensitivity and IZ, the zero current, both the values for S and IZ can be obtained from the calibration readings for the sensor. The metabolite concentrations can be calculated when I is substituted for the electrode current from the blood sample.

3.2.1.7 Haematocrit (Hct)

An electrical conductivity technique was employed to determine blood haematocrit. The technique was based on the rule that blood plasma is more conductive than blood cells as a result of the high resistance of cell membranes. The resistivity of blood determined by an alternating current within the sensor, will therefore increase as the concentration of cells increases and this relationship shown by the Maxwell–Fricke equation:

$$r = Rp \times (1 + Hct/100) / (1 - Hct/100)$$

r is the blood resistivity, Rp, a constant based on plasma resistivity and Hct, haematocrit.

3.2.2 YSI 2300 Stat Plus (YSI Incorporated, Yellow Springs, Ohio)

3.2.2.1 Linearity Procedure

The YSI 2300 Stat Plus (YSI Incorporated, Yellow Springs, Ohio) was used in two of the four pilot trials; (Chapter 3.3.2.1 and Chapter 3.3.2.3) to analyse blood glucose and lactate concentrations. Each morning prior to experimental sampling, the instrument was tested for linearity and membrane structural integrity using a number of pre-determined standard solutions.

The linearity procedure involved five glucose and five lactate samples of different concentrations to determine the instrument was working correctly. D-Glucose 25.0 $mmol \cdot L^{-1}$ standard (YSI 2369) was used as the first sample, the four remaining glucose samples were mixed with distilled water to create 12.5, 6.25, 3.125 and 1.56 $mmol \cdot L^{-1}$. For the five lactate samples, L-Lactate 15.0 $mmol \cdot L^{-1}$ standard (YSI 2328) was used first, with the four other concentrations being 7.5, 3.75, 1.875 and 0.938 $mmol \cdot L^{-1}$.

Structural integrity was measured by a 25µl sample of Potassium Ferrocyanide (FCN, YSI 2363), FCN readings above 0.3 $mmol \cdot L^{-1}$ (glucose) or above 0.6 $mmol \cdot L^{-1}$ (lactate) would highlight potential membrane structural problems.

Once the linearity procedure was completed and results were within accepted levels, the YSI 2300 Stat Plus was ready for experimental use, every 30 minutes the instrument would automatically calibrate to ensure there were no differences in the baseline currents.

3.2.2.2 Blood Glucose and Lactate Calculations

Blood substrate concentrations were determined by sensor and probe technology that incorporated patented immobilised membranes. Each probe located in a buffer filled sample chamber was fitted with a three layer membrane that contained an immobilised membrane as the middle section. When a sample was injected into the chamber, some of the substrate diffused through the membrane. On contact with this immobilised oxidase enzyme, it was rapidly oxidised to produce hydrogen peroxide (H_2O_2). The glucose reaction is displayed

below. The produced H_2O_2 was then oxidised at the platinum anode within the chamber and subsequently, electrons were produced (Reaction 2). Equilibrium between H_2O_2 production and the rate the H_2O_2 leaves the enzyme layer ensues. The rate of electron flow was linearly proportional to this equilibrium and in turn, proportional to the concentration of substrate.

REACTION 1 (glucose): β-D-glucose + O_2 $\xrightarrow[GOx]{}$ Glucono-δ-lactone + H_2O_2

REACTION 2: $H_2O_2 \xrightarrow[\text{Pt anode}]{} 2H^+ + O_2 + 2e^-$

3.2.3 Portable Gas Analyser (Metamax 3b, Cortex Biophysik, Germany)

3.2.3.1 Calibration of gas analyser

On each morning of the experimental trials and before use in the preliminary trials, the portable gas analyser (Metamax 3b, Cortex Biophysik, Germany) was calibrated. The unit was calibrated in each instance for air pressure, gas concentrations and volume.

Air Pressure

To calibrate for air pressure, the day to day pressure was input (mbar).

Gas Concentrations

To calibrate gas concentrations for oxygen (O_2) and carbon dioxide (CO_2), a two-point calibration took place. The first gas sample used was ambient air (20.93% O_2, 0.03% CO_2), which validated the upper limits for O_2 and lower limits for CO_2. The second gas sample validated lower limits of O_2 and upper limits for CO_2, and was unique to the concentration in the gas bottles in the laboratory (15.2% O_2, 4.88% CO_2) for this reason the values had to be manually entered into the computer software (Metasoft, Cortex Biophysik, Germany)

Volume

To calibrate volume, a known volume had to be selected and validated, for this procedure a 3 litre calibration syringe (Hans Rudolph Incorporated, USA) was used. Five valid inspiration and expiration strokes were needed for calibration, once accepted calibration of volume had been completed.

3.3 Procedures

3.3.1 Measurement Procedures

3.3.1.1 Capillary Blood Sampling

Blood samples (170 µl) were obtained via capillary puncture from the fingertip for subsequent analysis using either the YSI 2300 Stat Plus (YSI Incorporated, Yellow Springs, Ohio)(Chapter 3.3.2.1 and Chapter 3.3.2.3) or GEM Premier 3000 (Instrumentation Laboratories, UK)(Chapter 3.3.2.2 and Chapter 3.3.3). Once the area for puncture had been allocated, the site was cleaned using a 70% isopropyl alcohol swab (Universal Hospital Supplies Limited, UK) and wiped with a tissue. The side of the fingertip was then punctured with a lancing device (Accu-Chek Safe T-Pro Plus, Roche, UK) and the first drop of blood cleaned away with a tissue. The finger was then massaged and blood collected, ~75 µl was collected in sodium heparinised capillary tubes (Hawksley and Sons, Sussex, UK) for YSI samples and ~ 170 µl collected in plastic lithium heparinised capillary tubes (Instrumentation Laboratories, UK) for GEM samples. 25 µl samples were presented to the YSI for glucose and lactate analysis and a minimum 145 µl sample was aspirated by the GEM for blood gas, electrolyte and metabolite analysis.

3.3.1.2 Determination of body composition

Percentage body fat of participants in the main experimental trials was calculated with the bio-impedance analyser (BIA, Bodystat Quadscan 4000, Bodystat Limited, UK). Individuals were required to remove all metallic objects and rest in a supine position away from any metallic contact.

The BIA contains four electrodes, two positive and two negative, two electrodes were placed on the wrist the positive electrode placed proximal to the third metacarpophalangeal joint and the negative electrode positioned on the wrist next to the ulnar head. The remaining two electrodes were placed on the ankle the positive electrode positioned proximal to the third metatarsophalangeal joint and the negative electrode between the medial and lateral malleoli. A number of small currents (5, 50, 100 and 200 kHz) are passed through the electrodes, the BIA works on the basic principle that lean muscle retains water and adipose tissue does not. Water is a very good conductor of electricity and therefore the resistance of the current is measured which would be the adipose content.

Participant characteristics such as age, height, body mass, waist and hip circumferences are all input into the device. Using these variables the BIA calculates and displays a percentage body fat value on the screen.

3.3.1.3 HbA_{1c} Analysis

On one of the two experimental mornings, a 4 ml venous blood sample was obtained from each of the participants and collected in a Na^+ EDTA tube. This sample was then sent to a local hospital and analysed for HbA1c using the method of high performance liquid chromatography (HPLC) with cation exchange. Once analysis was complete the results were posted back to the research team.

3.3.2 Pilot Studies

As stated in the aims (Chapter 2.10.1) a series of pilot studies were to take place prior to any research in the T1DM participants taking place. The next few pages documents these pilot studies and their findings and how these findings contributed to the final methodology adopted for the research protocol.

3.3.2.1 Pilot Study 1: Determination of glycaemic index (GI) of isomaltulose and metabolic responses following ingestion

As previously stated (Chapter 2.5.2.3), isomaltulose (ISO, Palatinose®, Beneo Group, Germany) has been reported to have a very low GI of 32 (Atkinson et al., 2008). To verify this low GI value, the methodology documented by Brouns et al. (2005) was adhered to. Brouns et al. (2005) recommend that blood samples should be taken at seven determined time points, at least ten individuals participate in the study, the test food is trialled on two occasions, 50 g of carbohydrate is provided within the test and reference food and that the reference food is glucose or white bread. In addition, low GI diets as discussed beforehand (Chapter 2.5.2.2) have been shown to be beneficial to people with type 1 diabetes in controlling levels of blood glucose (Nansel et al., 2008) and therefore further research in novel CHOs such as ISO warranted investigation. Therefore, the aim of this study was to determine and verify the reported GI value of ISO using a recommended reference food (DEX, Glucose Powder).

Ten participants (23 ± 1 year; BMI, 25.0 ± 1.1 $kg \cdot m^{-2}$) were recruited, advised of project details (Appendix 8.1) , provided informed consent (Appendix 8.1) and completed this study. Participants attended the laboratory on four mornings at the same time after an overnight fast and abstaining from unaccustomed physical activity for 24 hours. On arrival, stature (Stadiometer, Holtain Limited, UK) and body mass (Seca 770 Digital Scales, Seca Limited, UK) were recorded before participants were asked to remain seated prior to a resting blood sample being taken. Blood samples were obtained via capillary puncture (Chapter 3.3.1.1) and taken at specified time points throughout a 2 hour rest period. The first of these samples was taken at rest and analysed immediately (YSI 2300 Stat Plus, YSI Incorporated, Yellow Springs, Ohio) for levels of blood glucose and lactate.

Once the resting sample had been obtained and analysed, participants were provided with 50 g of either the test food, ISO or reference food, dextrose (glucose powder) (DEX, Thornton & Ross, UK) dissolved in 250 ml distilled water, 20% solution, on two occasions each in a randomised, counterbalanced fashion. Participants were instructed to consume the solution within 5-minutes and to remain at rest throughout the 2-hour period. Further capillary blood samples were taken 15, 30, 45, 60, 90 and 120-minutes following ingestion of the carbohydrate and again analysed immediately for blood glucose (BG) and lactate (YSI 2300 Stat Plus).

Peak BG values in DEX (7.63 ± 0.20 $mmol \cdot L^{-1}$) were significantly higher than the peak response in ISO (5.89 ± 0.11 $mmol \cdot L^{-1}$, $P < 0.001$), however there were no differences between lowest BG values between conditions (DEX; 4.17 ± 0.21 vs. ISO; 4.46 ± 0.11 $mmol \cdot L^{-1}$, $P > 0.05$). The BG incremental area under the curve (IAUC, Equation D) for DEX (166.78 ± 18.36 $mmol \cdot min \cdot L^{-1}$) was significantly higher ($P < 0.001$) than ISO (89.19 ± 8.42 $mmol \cdot min \cdot L^{-1}$), from these values the GI of ISO was calculated to be 53.

Lactate values over the 2 hour resting period were found to be significantly higher after ingestion of ISO when compared to DEX, ($P < 0.05$), this fact was translated in the peak lactate levels where ISO had a significantly higher value than DEX, (1.43 ± 0.07 vs. 0.92 ± 0.06 $mmol \cdot L^{-1}$, $P < 0.001$).

The different GI of 53 calculated in this study could be attributed to a number of factors. In the reported data (Atkinson et al., 2008) only 50 g of the product was supplied as the test food, which differed in this study as 50 g of available CHO was given both as the test and reference foods. 50 g of available CHO is recommended by Brouns et al. (2005) and this may lead to more than 50 g of the test food being supplied if the food does not have a carbohydrate content of 100 g/100 g product. (i.e. if the test food contains 94.6 g CHO per 100 g of the product then participants would be provided with a 52.9 g serving so that 50 g of CHO is available). It has been further documented that up to ten reference foods have been provided in the compilation of earlier GI lists (Foster-Powell et al., 2002), however glucose and white bread are deemed the recommended reference foodstuffs (Brouns et al., 2005). With no definitive test portions or reference foods, it is likely to observe discrepancies in GI values between studies.

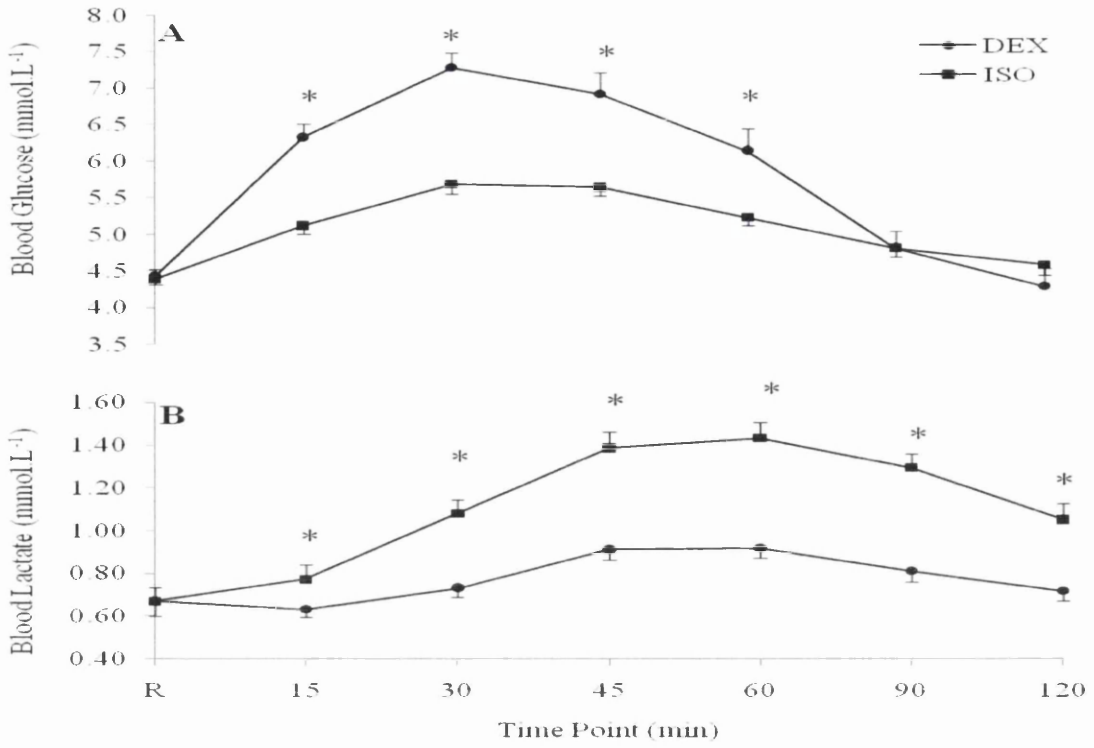

Figure 3.1 Blood glucose (A) and blood lactate (B) responses following ingestion of CHO. (*) denotes significant difference between conditions ($P < 0.05$).

Blood lactate levels were elevated in ISO throughout the sample points due to the nature of metabolism where ISO is broken down into glucose and fructose. This fructose bypasses the phosphofructokinase regulatory point in glycolysis and results in an increased flux through the glycolytic pathway that in turn leads to a build-up and release of lactate (Kaye et al., 1958; Sahebjami & Scalettar 1971).

ISO was found to have a higher GI than previously reported, 53 as opposed to 32, however this score is still classified as low (Atkinson et al., 2008). This low GI value resulted in fewer undulations over the 2 hours when compared to DEX and also in the lower peak BG value. The lactate values at rest are of interest as these higher values in ISO may have a potentially detrimental effect on performance.

3.3.2.2 Pilot Study 2: Blood lactate and glucose responses after ingestion of isomaltulose at different concentrations

Taking into account the lactate findings after completion of Pilot Study 1 (Chapter 3.3.2.1), it was decided to investigate whether there was a conditional effect in regards to blood lactate production with differing concentrations of isomaltulose. Lactate accumulation can prove detrimental to exercise performance and elevated levels prior to performance testing could hinder the effect of the carbohydrate supplementation. Alongside investigating the potential for a conditional effect of lactate, this study would also allow for drink concentration to be examined as mentioned previously (Chapter 2.5.2.1) the literature is inconsistent as to which is the optimum concentration to provide with values suggested ranging from 6% (Riddell & Perkins, 2006) up to 10% (Perrone et al., 2005; West et al., 2011a; West et al., 2011b). Drink concentration is also of importance in regards to glucose provision with individuals more susceptible to hypoglycaemia after consumption of lower concentration fluids (Perrone et al., 2005). The aim of this study is therefore to investigate the lactate and glucose responses following drink concentrations of 5 and 10% isomaltulose and to examine whether a dose response is present.

Five males (25 ± 2 years, BMI, 26.1 ± 1.3 $kg \cdot m^{-2}$) participated and completed this pilot trial, attending the laboratory twice in the morning after an overnight fast. On arrival stature and body mass were recorded and participants were asked to remain at rest prior to a capillary blood sampled being obtained (Chapter 3.3.1.1). Participants were then provided in a randomised fashion either 5% (12.5 g ISO) or 10% (25 g ISO) in a 250 ml distilled water solution which was consumed within five minutes. Further capillary blood samples were obtained at 30, 60, 90 and 120 minutes following consumption of the test drink. All blood samples were analysed immediately for blood glucose and lactate (GEM Premier 3000, Instrumentation Laboratories, UK).

Peak lactate values were significantly higher in the 10% condition compared to the 5% condition (10% solution; 2.3 ± 0.1 vs. 5% solution; 1.9 ± 0.2 $mmol \cdot L^{-1}$, $P < 0.05$). This observation is reflected in the relative peak values, where a two-fold increase is shown (10% solution; 1.2 ± 0.3 vs. 5% solution; 0.5 ± 0.2 $mmol \cdot L^{-1}$, $P = 0.05$). Over the time points the only significance difference between conditions was apparent at 30 minutes following

ingestion when relative lactate responses are measured, (10% solution; 0.7 ± 0.2 vs. 5% solution; 0.4 ± 0.2 mmol·L^{-1}, $P < 0.05$).

Absolute glucose values were significantly higher in the 10% condition when compared to the 5% condition (10% solution; 6.7 ± 0.4 vs. 5% solution; 5.8 ± 0.2 mmol·L^{-1}, $P < 0.05$). Relative peak values were also significantly higher between conditions (10% solution; 1.4 ± 0.4 vs. 5% solution; 0.5 ± 0.2 mmol·L^{-1}, $P < 0.05$) which were the values that corresponded to the 30-minute time point.

Resting lactate and glucose levels were similar between conditions (Lactate: 10% solution; 1.1 ± 0.3 vs. 5% solution; 1.3 ± 0.3, Glucose: 10% solution; 5.4 ± 0.2 vs. 5% solution; 5.2 ± 0.1 mmol·L^{-1}, $P > 0.05$).

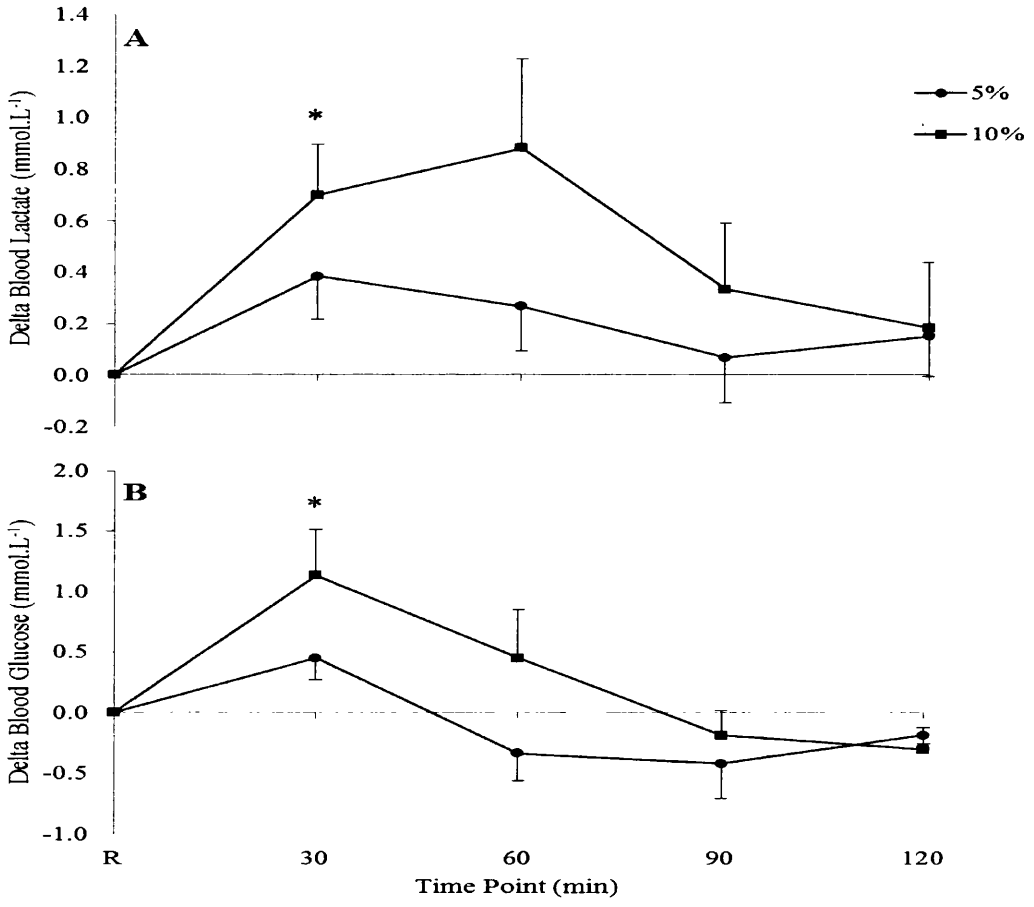

Figure 3.2. Relative blood lactate (A) and blood glucose (B) responses following ingestion of 5% and 10% ISO solutions. (*) denotes values significantly higher ($P < 0.05$).

These findings show that a dose response relationship is present in isomaltulose. However, with a 2-hour resting period to allow for digestion of carbohydrate, the lactate responses in the 10% solution are comparable with the 5% solution whilst preserving higher levels of blood glucose.

3.3.2.3 Pilot Study 3: Trial of potential methods in non T1DM individuals

Exercise performance is one of the most important components of research in sport (Currell & Jeukendrup, 2008). The reliability of time to exhaustion (TTE) protocols has recently been questioned (Laursen et al., 2007) and defended (Hopkins et al., 2001) due to the high variation in the results obtained. However, with the potential for carbohydrate sparing in some research trials (Febbraio et al., 2000; Thomas et al., 1991: Wee et al., 2005; Wu et al., 2003) use of a TTE assessment to explore this possibility may be a preferential method in the future research. Therefore, the aim of this study was to investigate the reliability and suitability of a TTE protocol instead of a time trial (TT) assessment for adoption in the future research. The participants would also trial the Stroop Colour Word Test (SCWT) software and also the gut fullness and hunger scales , providing feedback on their usability.

Eight individuals (23 ± 1 year, BMI, 23.8 ± 1.0 $kg \cdot m^{-2}$, Peak $\dot{V}O_2$, 51.3 ± 0.4 $ml \cdot kg^{-1} \cdot min^{-1}$) were recruited, notified of project details (Appendix 8.1) and provided both informed consent (Appendix 8.1) and medical history (Appendix 8.1) before completing this trial. Each participant attended the laboratory on three occasions, primarily for a preliminary session to quantify $\dot{V}O_{2\ PEAK}$. This value was determined by a 3-minute stage continuous running treadmill (ERGO ELG55, Woodway GmbH, Germany) protocol, beginning at 8 $km \cdot h^{-1}$ and increasing by 1 $km \cdot h^{-1}$ until volitional exhaustion. Expired air samples were collected in Douglas bags in the last minute of each stage and analysed for gas concentrations (Hi-Tech GIR250 Dual Gas Analyser, Luton, UK) and volume (Harvard Dry Gas Meter, Kent, UK).

Participants attended for two further visits after an overnight fast, on arrival to the laboratory stature (Stadiometer, Holtain Limited, UK) and body mass (Seca 770 Digital Scales, Seca Limited, UK) were measured and individuals were then seated. Participants then completed the online Stroop colour word test (SCWT) and indicated their perceived feelings of hunger and gut fullness (Appendix 8.4) prior to a resting blood sample being taken via capillary

puncture (Chapter 3.3.1.1). Individuals were then provided in a randomised counter balanced fashion either 0.6 $g \cdot kg^{-1}$ body mass of dextrose (DEX, Thornton & Ross, UK) or waxy barley starch (WBS, Vitargo®, Swecarb AB, Sweden), 9% solution, which they were required to drink within five minutes. Further capillary blood samples were taken at 30, 60 and 120 minutes after carbohydrate consumption, with the SCWT and perceived feelings of hunger and gut fullness completed again at 110 minutes.

At 120 minutes, participants started a discontinuous incremental exercise protocol beginning at 6 $km \cdot h^{-1}$ and increasing by 1 $km \cdot h^{-1}$ every 5 minute stage. Participants were required to run for four minutes of each five minute stage, in the non-exercising minute, participants would place one foot either side of the treadmill belt and a capillary blood sample obtained, this procedure was continued until 85% of peak $\dot{V}O_2$ was reached. After a 90 s rest period, individuals then performed a TTE trial at this 85% intensity, participants were blinded from the duration of the TTE trial.

On cessation of exercise a capillary blood sample was taken, with a further blood sample obtained 15 minutes into the recovery period. The SCWT test and gut fullness and hunger ratings were recorded for a final time after the recovery blood sample had been obtained. All capillary samples were analysed immediately for blood glucose (BG) and lactate values (YSI 2300, Yellow Springs, Ohio). Expired air samples were collected in the last exercising minute of each stage, and analysed for gas concentrations (Hi-Tech GIR250, Luton, UK) and volume (Harvard, Kent, UK), no expired air samples were collected during the TTE trial. Substrate utilisation was calculated using principles of indirect calorimetry derived by Jeukendrup and Wallis (2005).

As stated in the aims, the purpose of this study was not to examine metabolic or substrate responses to carbohydrate ingestion and exercise per se, the primary focus being to evaluate whether the TTE trial proposed would allow a potential subtle performance effect to be discovered. TTE between conditions were similar, (DEX: 934 ± 140 vs. WBS: 1058 ± 191 s, $P = 0.61$) however the large values for standard error and co-efficient of variation (CoV) were both causes for concern.

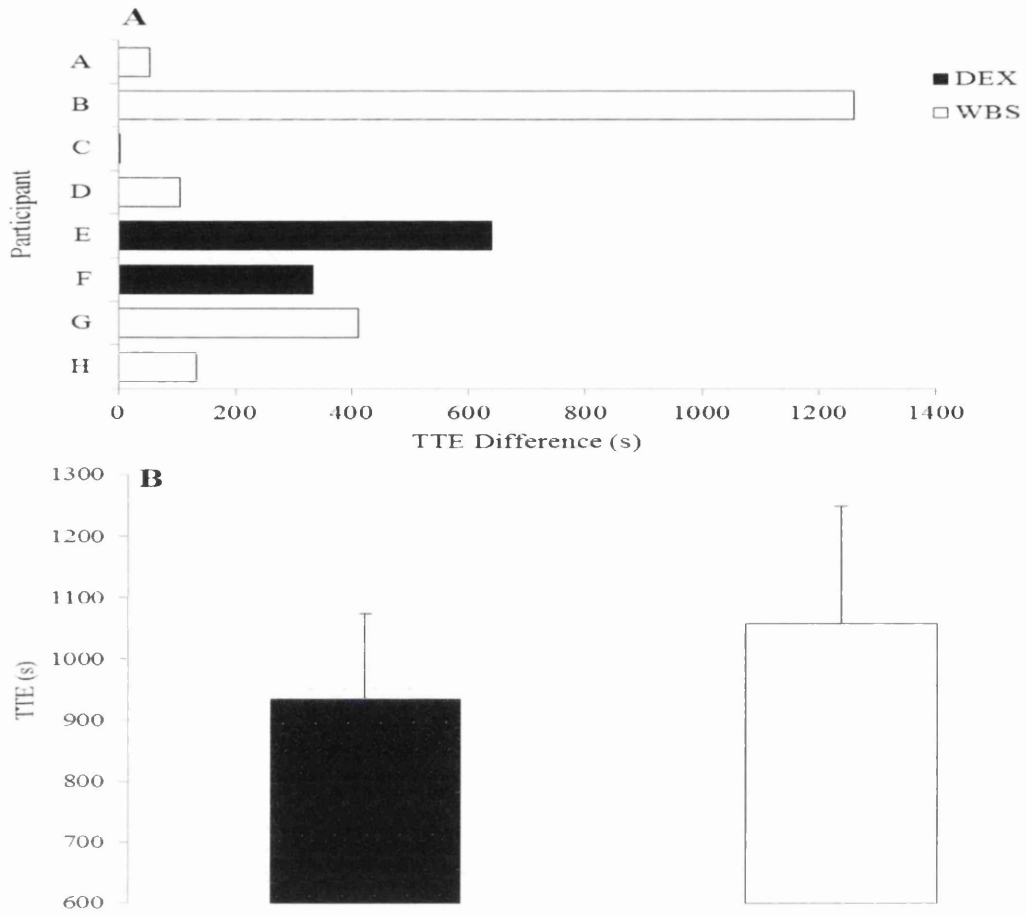

Figure 3.3. TTE results following ingestion of CHO. (A) illustrates individual participant results and improvement after consumption of CHO. (B) illustrates average participant TTE between conditions.

With these findings from this pilot study, it was decided that for the main experimental trials, that a time trial (TT) would be used as opposed to a TTE performance test. The higher CoV values have been previously documented (Jeukendrup et al., 1996) to suggest that adoption of the TTE protocol has low reliability, this was one of the main reasons for the decision taken. It was also proposed that to ensure all participants were exercising similar in the submaximal bout that exercise intensities would be incorporated in the methods opposed to set velocities. With all participants exercising at relative intensities the workload completed in the submaximal protocol would be comparable between individuals. A set workload followed by a time trial protocol is recognised as a validated and reliable technique to measure performance (Jeukendrup et al., 1996). Participants reported that they had no issues with either the SCWT software or the gut fullness and hunger scales.

3.3.2.4 Pilot Study 4: Potential learning effect of Stroop colour word test

Ingestion of breakfast alone (Wesnes, Pincock, Richardson, Helm & Hails, 2003), carbohydrate supplementation of varying glycaemic indexes (Benton et al., 2003; Ingwersen et al., 2007) and exercise (Ferris et al., 2007; Hogervorst et al., 1996) are all independent factors that influence cognitive function. To eliminate the chance that any potential differences found in the research were attributable to familiarisation (learning effect) a small pilot trial took place. The aim of this study was to examine whether participants improved their scores and reaction times following continued use of the Stroop colour word test (SCWT) software.

The online package (http://cat.xula.edu/thinker/flash/stroop.swf) shows a series of twenty words, either blue, black, yellow, green or red, and ten of these words are written in the corresponding colour that they spell (congruent) or ten written in one of the remaining four colours (incongruent). Users have to click the colour that is shown, not necessarily the word displayed, the package displays the scores and average reaction time (seconds) for both congruent and incongruent sections.

Five individuals (23 ± 1 year) volunteered for this study and were required to attend the laboratory on one morning after completion of an overnight fast. Participants completed the SCWT on three occasions, at 0, 110 and 180 minutes, these time points being representative of the time points in the main study. Participants were allowed to drink water ad libitum, however they were instructed to remain at rest and refrain from eating.

Congruent scores over time were similar (0 min; 10 ± 0.0, 110 min; 10 ± 0.0, 180 min; 9.8 ± 0.2, $P > 0.05$), however reaction times decreased through use (0 min; 1.38 ± 0.10 s, 110 min; 1.12 ± 0.03 s, 180 min; 1.09 ± 0.06 s), but this increased response was not significantly different ($P > 0.05$). With regards to incongruent reaction times, when compared against baseline the subsequent time points were significantly different (0 min; 1.62 ± 0.06 s vs. 110 min; 1.17 ± 0.05 s, $P < 0.05$) and (0 min; 1.62 ± 0.06 s vs. 180 min; 1.15 ± 0.06 s, $P < 0.05$), again the correct scores were similar across conditions (0 min; 9.6 ± 0.2, 110 min; 10 ± 0.0, 180 min; 10 ± 0.0, $P > 0.05$).

These findings present that regardless of supplementation, reaction times increase through usage of the online SCWT software. Using this information it was decided that within the familiarisation session, participants would be exposed to the SCWT software prior to the main experimental trials. Thus, removing the potential learning effect and allowing subtle between condition differences (if any) to be located.

3.3.3 Experimental Trials

3.3.3.1 Familiarisation Session and Protocol for determination of $\dot{V}O_{2\ PEAK}$ and HR_{PEAK}

Prior to the main experimental trials, each participant attended the laboratory either once or twice for a familiarisation session which incorporated preliminary testing. The main purpose of this testing was primarily to determine individual peak values of oxygen uptake ($\dot{V}O_{2\ PEAK}$) and heart rate (HR_{PEAK}) and to provide the opportunity for each participant to adapt to both the laboratory surroundings and the experimental equipment. In addition to the preliminary protocol, participants completed three five minute bouts on the non-motorised treadmill (Curve, Woodway GmbH, Germany) and completed the online SCWT three to five times. All participants were notified of research details (Appendix 8.2), completed both informed consent (Appendix 8.2) and provided full medical history (Appendix 8.2) before engaging in any exercise pertaining to this research study.

To determine peak rates of oxygen uptake and heart rate each of the participants completed a running protocol on a motorised treadmill (ERGO ELG55, Woodway GmbH, Germany). On arrival to the laboratory stature (Stadiometer, Holtain Limited, UK) and body mass (Seca 770 Digital Scales, Seca Limited, UK) were recorded. Individuals were all required to wear a heart rate monitor (RS400, Polar Electro, Oy, Finland) positioned under their clothing just below the xiphoid process and also the portable breath-by-breath gas analyser (Metamax 3b, Cortex Biophysik, Germany).

For this preliminary session, participants were asked to prepare in the fashion that they would for an exercise session, prior to exercise all participants were required to check their blood glucose with their own meters. If values were deemed too low, < 8 $mmol \cdot L^{-1}$ participants were supplemented with 20 g of dextrose mixed with 200 ml distilled water.

After monitoring blood glucose, participants were asked to perform a warm up on the treadmill, beginning at a low intensity (~5 $km \cdot h^{-1}$) to become familiar with the treadmill and wearing the portable gas analyser, the speed of the treadmill was manipulated periodically and heart rate was continually assessed. From this brief warm-up and assessment of heart rate

responses, the initial velocity for the protocol was determined, six participants started at 8 $km \cdot h^{-1}$ and the remaining individual began the protocol at 6 $km \cdot h^{-1}$.

The running protocol that was used to determine $\dot{V}O_{2\ PEAK}$ and $HR_{\ PEAK}$ was continuous in nature and consisted of 3-minute stages that increased by 1 $km \cdot h^{-1}$, participants received verbal encouragement towards the latter end of the protocol and were required to continue until volitional exhaustion. On completion of the protocol, the portable gas analyser was removed and participants engaged in an active cool down walking at a comfortable intensity. $\dot{V}O_{2\ PEAK}$ and $HR_{\ PEAK}$ values were taken from the last completed full minute of exercise. HR and breath-by-breath data was continuously collected and recorded via radio-telemetry software (Metasoft, Cortex Biophysik, Germany).

After sufficient recovery participants were then given the opportunity to familiarise themselves with the online SCWT software. The software included a screen that provided detailed instructions to how the program works, all participants read these instructions and were given the opportunity to ask any questions or queries that they may have had. Once any queries were answered and resolved, participants completed the task between three to five times to a level that they were comfortable with the software.

Participants were then given the option to either partake in a series of exercise bouts on the non-motorised treadmill after completion of the SCWT or to make arrangements and return to the laboratory at another convenient time. The purpose of these exercise bouts on the non-motorised treadmill were so that both the individual and ourselves were confident that they could control the belt of the treadmill, allowing for either acceleration or deceleration to occur. Participants were firstly given around 7 – 10 minutes of free running on the treadmill, before completing three 5 minute bouts at a speed that could be easily controlled. At the end of the 5 minutes, the distance completed was recorded. The second and third distances were compared together for treadmill competency, over these final two exercise bouts participants completed 0.53 ± 0.04 km, CoV = 2.23 ± 0.55%, with individual competency shown in Table 3.3.

Table 3.3 The familiarisation of each individual and their competency in using the non-motorised treadmill over 3 x 5 min runs

	Run 2 (km)	Run 3 (km)	Average (km)	CoV
Participant A	0.45	0.47	0.46	3%
Participant B	0.52	0.54	0.53	3%
Participant C	0.47	0.49	0.48	3%
Participant D	0.73	0.74	0.74	1%
Participant E	0.64	0.68	0.66	4%
Participant F	0.46	0.46	0.46	0%
Participant G	0.41	0.42	0.42	2%

3.3.3.2 Main Experimental Trial

Participants attended the laboratory on two occasions, separated by at least 48-hours after completion of an overnight fast (10 – 14 hours) and abstaining from unaccustomed physical activity for the previous 24 hours.

3.3.3.3 Rest Period

On arrival to the laboratory, participants were asked to change into the clothing that they would be exercising in and remove their footwear before body mass (BM) was recorded (Seca 770 Digital Scales, Seca, UK) subsequently followed by stature being noted (Stadiometer, Holtain Limited, UK). Participants were then asked to comment about their perceived feelings of gut fullness and hunger (Appendix 8.4) prior to completing the SCWT. Once these resting scores for the gut fullness and hunger and the SCWT had been recorded, a resting blood sample was obtained via capillary puncture (Chapter 3.3.1.1) and immediately analysed (GEM Premier 3000, Instrumentation Laboratories, UK). Participants were then made aware of the carbohydrate amount that would be provided and reduced their normal rapid-acting insulin (Aspart 'NovoRapid®', n =5) or (Lispro 'Humalog®', n = 2) dose by 50% (2.7 ± 0.3 Units), which was administered in the leg, arm or abdomen by individual preference.

Participants were then supplied with 0.6 $g \cdot kg^{-1}$ BM of either isomaltulose (ISO, Palatinose®, Beneo Group, Germany, 41.82 ± 1.26 g) or dextrose (DEX, MyProtein.com, UK, 41.89 ± 1.15 g) mixed to a 10% solution in a 1 litre opaque sports bottle. Participants were given 5 minutes to consume the solution once they had started to drink and were advised of this beforehand.

Individuals were instructed to remain at rest for a 2-hour period where they either sat or lay on a bed. Further capillary blood samples were obtained 30, 60, 90 and 120 minutes after carbohydrate consumption and these were again analysed immediately (GEM Premier 3000). Between 100 – 115 minutes participants wore the portable gas analyser (Metamax 3b, Cortex Biophysik, Germany) alongside a heart rate monitor (Polar RS400, Electro Oy, Kempele, Finland) and resting expired air concentrations and heart rate were recorded via radio-telemetry software (Metasoft, Cortex Biophysik, Germany). After the rest samples, participants again completed the SCWT and were asked about their perceived feelings of gut fullness and hunger.

On one of the two mornings a venous blood sample was collected for analysis of HbA_{1c} (Chapter 3.3.1.3) and body composition was calculated (Bio-impedance analyser (BIA), Bodystat Quadscan 4000, Bodystat Ltd, UK, Chapter 3.3.1.2).

3.3.3.4 Submaximal Exercise

Two hours following carbohydrate ingestion, participants (still wearing the portable gas analyser (Metamax 3b) and heart rate monitor (Polar RS400)) mounted a large motorised treadmill (ERGO ELG55, Woodway GmbH, Germany) to perform a discontinuous incremental 5.5-minute stage exercise bout comprised of 5 bouts of 4-min walking or running interspersed with 90 s rest. The incremental running velocities were a percentage of the final speed reached in the preliminary maximal exercise protocol. The increments performed were 31 ± 1% (4.3 ± 0.2 $km \cdot h^{-1}$), 41 ± 2% (5.4 ± 0.3 $km \cdot h^{-1}$), 53 ± 2% (6.4 ± 0.3 $km \cdot h^{-1}$), 69 ± 3% (7.5 ± 0.4 $km \cdot h^{-1}$) and 80 ± 2% (8.6 ± 0.5 $km \cdot h^{-1}$) of maximal oxygen uptake.

Participants ran for the first 4-minutes of each stage and then placed one foot each side of the treadmill belt so that a capillary blood sample could be obtained and analysed immediately (GEM Premier 3000). Once the 90 s stationary period had elapsed, participants eased

themselves back on to the treadmill belt and carried on running at the next increment speed. Once the running component of the final stage was completed, the treadmill belt was stopped and a 5-minute rest period began. During this rest period participants drank water ad libitum.

3.3.3.5 Performance Running and Recovery

After 5 minutes, participants completed a 3 minute warm-up period on the non-motorised treadmill (Curve, Woodway GmbH, Germany), which when completed participants placed one foot either side of the treadmill belt and a pre-performance capillary blood sample was obtained and analysed (GEM Premier 3000). The non-motorised treadmill was then programmed for 10 minute duration and participants were blinded from the speed that they were performing exercise at. Video recording (Nikon D5000, Nikon, UK) of the exercise bout was synchronised with the start of the performance test. Distance was noted every 2.5 minutes and participants received strong vocal encouragement throughout. In the final twenty seconds of exercise, participants were asked their perceived ratings of physical exertion (Borg, 1973). On cessation of exercise, the breath-by-breath and heart rate recording was stopped, the portable gas analyser (Metamax 3b) removed and a post-performance capillary blood sample taken.

Participants then remained at rest for the following 15 minutes, and were allowed to drink water ad libitum. A final capillary blood sample was obtained and analysed (GEM Premier 3000), alongside a 0.3 µl blood sample which was analysed with a glucose meter (Freestyle Lite, Abbott Diabetes Care, UK). The SCWT was completed for the final time together with the perceived feelings of gut fullness and hunger.

Participants were then free to leave the laboratory, provided with a glucose meter (Freestyle Lite, Abbott Diabetes Care, UK) and asked to self-record their blood glucose values 3 and 6 hours after leaving (Appendix 8.3) alongside their dietary intake and insulin doses administered (Appendix 8.3).

3.4 Calculations and Data Analysis

3.4.1 Substrate Utilisation and Energy Expenditure

Substrate utilisation was measured at rest, from the last minute of each submaximal stage and quarterly throughout the performance bout and calculated using the principles of indirect calorimetry via the methods proposed by Jeukendrup and Wallis, (2005).

Carbohydrate oxidation ($g \cdot min^{-1}$) (Equation A)

$= 4.344 \times \dot{V}CO_2 - 3.061 \times \dot{V}O_2$ (Low intensity exercise, 40 – 50% $\dot{V}O_{2\,MAX}$)

$= 4.210 \times \dot{V}CO_2 - 2.962 \times \dot{V}O_2$ (Moderate to high intensity exercise, 50 – 75% $\dot{V}O_{2\,MAX}$)

Fat oxidation ($g \cdot min^{-1}$) (Equation B)

$= 1.695 \times \dot{V}O_2 - 1.701 \times \dot{V}CO_2$ (All exercise intensities)

Energy expenditure was calculated from the carbohydrate and fat oxidation rates via the methods of Frayn (1983).

Energy Expenditure ($kJ \cdot min^{-1}$) (Equation C)

= 15.6 x Carbohydrate oxidation ($g \cdot min^{-1}$) + 39 x Fat Oxidation ($g \cdot min^{-1}$)

3.4.2 Blood Glucose

Incremental area under the curve (IAUC) was calculated following the equations outlined by Brouns et al. (2005) (Equation D)

For the first time point, if $BG_1 > BG_0$, then $S_1 = (BG_1 - BG_0) \times (T_1 - T_0) / 2$, otherwise $S_1 = 0$.

For the remaining time points using BG_1 and BG_2 as an example the following equations were performed.

If both BG_1 and $BG_2 > BG_0$, then $S_2 = (BG_1/2 + BG_2/2) \times T$

If $BG_1 > BG_0$ and $BG_2 < BG_0$, then $S_2 = (BG_1^2/(BG_1 - BG_2)) \times T/2$

If $BG_1 < BG_0$ and $BG_2 > BG_0$, then $S_2 = (BG_2^2/(BG_2 - BG_1)) \times T/2$

If both BG_1 and $BG_2 < BG_0$, then $S_2 = 0$.

BG_0 is the blood glucose resting or first concentration, BG_1... are relative blood glucose values, T is equal to time and S represents segment number.

All segments would be totalled together to calculate IAUC.

3.4.3 Data Analysis

Statistical analysis was carried out using SPSS Version 16 software (SPSS Incorporated, Chicago, USA). Data were tested for normal distribution (Shapiro-Wilk test) and subsequently analysed using repeated-measures ANOVA on two factors (treatment x time). Mauchly's test was consulted and Greenhouse – Geisser correction factor applied if sphericity was violated. Bonferroni adjustment was also performed and dependent t-tests carried out where necessary. Data are represented as mean ± SEM. Significance was set at $P < 0.05$.

4.0 RESULTS

4.1 Laboratory Conditions

The ambient air temperature in the laboratory was recorded and found to be comparable between trials, (DEX; 20.9 ± 0.2 vs. ISO; 21.1 ± 0.4 °C, P = 0.66) as was barometric pressure which was also recorded and found to be similar (DEX; 1019 ± 7 vs. 1027 ± 5 mbar, P = 0.44).

4.2 Pre-Laboratory Dietary Intake

Dietary records for the previous 24 hours were analysed and participants (n = 6) consumed similar amounts of energy intake (DEX; 5684 ± 951 vs. ISO; 5252 ± 682 kJ, P = 0.61) with comparable amounts of CHO ingested (DEX; 191 ± 30.7 vs. ISO; 165.8 ± 27.5 g, P = 0.34).

4.3 Glycaemic and Metabolic Responses

4.3.1 Blood Glucose

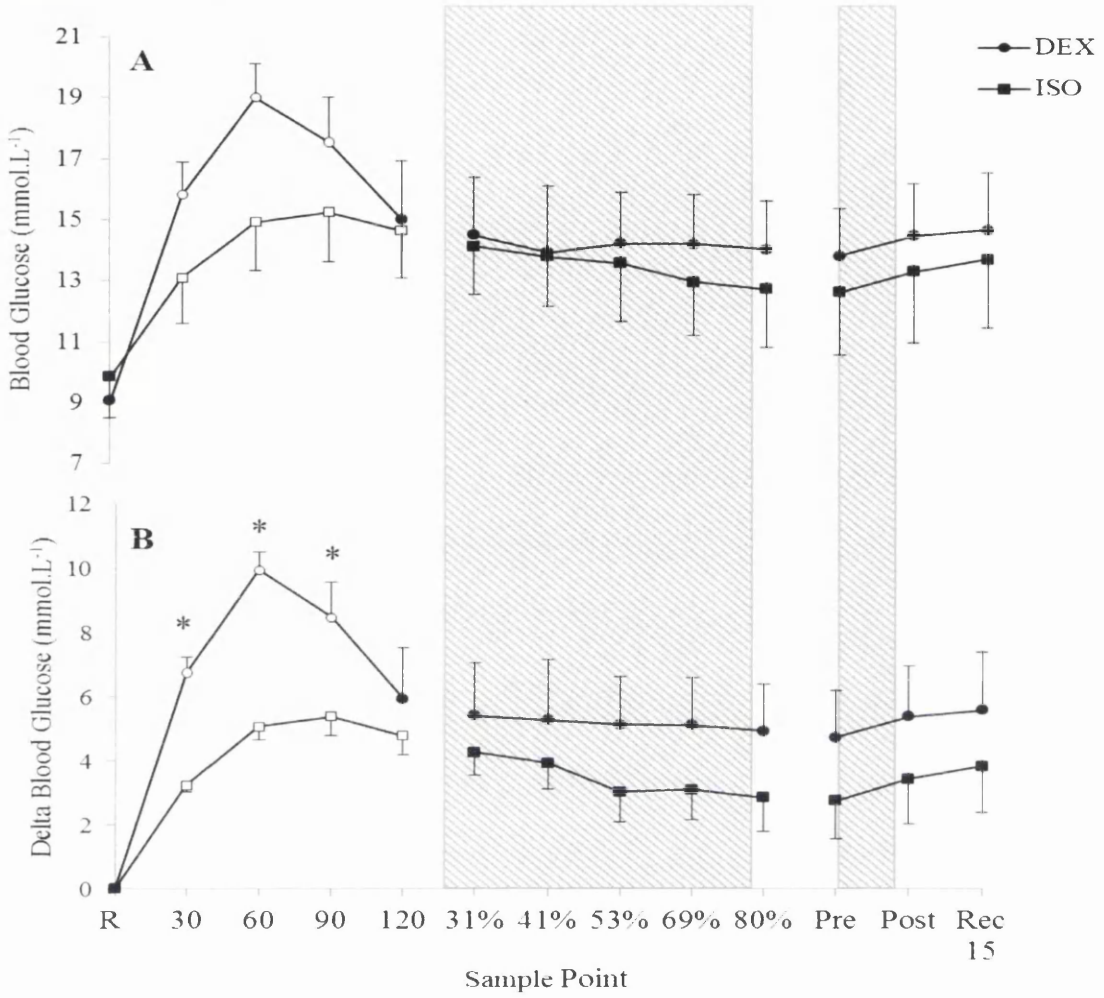

Figure 4.1. Blood glucose responses following ingestion of CHO, during submaximal exercise, during the performance protocol and subsequent recovery period (A) illustrates absolute blood glucose responses and (B) illustrates relative blood glucose responses compared to resting sample. (○) hollow markers demonstrate significant changes from resting sample (P < 0.05). (*) denotes significant changes between conditions (P < 0.05). The first shaded area is representative of the submaximal exercise and the second shaded area representative of the high intensity performance running.

Resting blood glucose values were similar between conditions (DEX; 9.1 ± 0.9 vs. ISO; 9.8 ± 1.3 mmol L^{-1}, P = 0.64). There were no conditional differences in the absolute data, however pre-exercise relative blood glucose responses in the 2 hour resting period were lower in ISO (P = 0.001). Relative resting peak BG was 46% lower after ingestion of ISO compared to DEX (ISO; +5.6 ± 0.4 vs. DEX; +10.3 ± 0.7 mmol L^{-1}, P < 0.001), and the time to reach this peak value took longer in ISO (86 ± 8 min) compared to DEX (64 ± 4 min) (P < 0.001).

BG fell throughout the submaximal exercise and these reductions were similar between trials (DEX; -1.0 ± 0.5 vs. ISO; -1.9 ± 0.5 mmol·L^{-1}, P = 0.21), whereas after the performance bout BG levels had increased, again these changes were similar between conditions (DEX; 0.7 ± 0.3 vs. ISO; 0.7 ± 0.4 mmol·L^{-1}, P = 0.98).

The lower glycaemic response after ingestion of ISO in the resting period for the first 90 minutes is reflected in the IAUC (Equation D) data (Table 4.1). This response also results in the Total IAUC being significantly lower in ISO and also lower values for both of the exercise protocols.

Table 4.1 Incremental area under curve (IAUC) values throughout laboratory experimental period. (*) denotes significant higher values between conditions (P < 0.05).

	DEX	**ISO**	**P - value**
Rest IAUC (mmol·min·L^{-1})	847.6 ± 72.4*	483.9 ± 40.5	0.001
Submaximal IAUC (mmol·min·L^{-1})	99.3 ± 23.2	64.3 ± 12.3	0.251
Performance IAUC (mmol·min·L^{-1})	64.7 ± 17.4	44.3 ± 11.2	0.342
Total IAUC (mmol·min·L^{-1})	1057.9 ± 119.8*	624.2 ± 67.1	0.009

One individual experienced an episode of hypoglycaemia (BG < 3.5 mmol·L^{-1}) in each of the two trials and was supplemented with CHO. In DEX, an extra 30 g of DEX was administered prior to the submaximal exercise and in ISO, 30 g of DEX was provided after completion of the performance exercise bout. Both CHO were equally effective in preventing hypoglycaemia during submaximal and maximal exercise.

4.3.2 Blood Lactate and pH

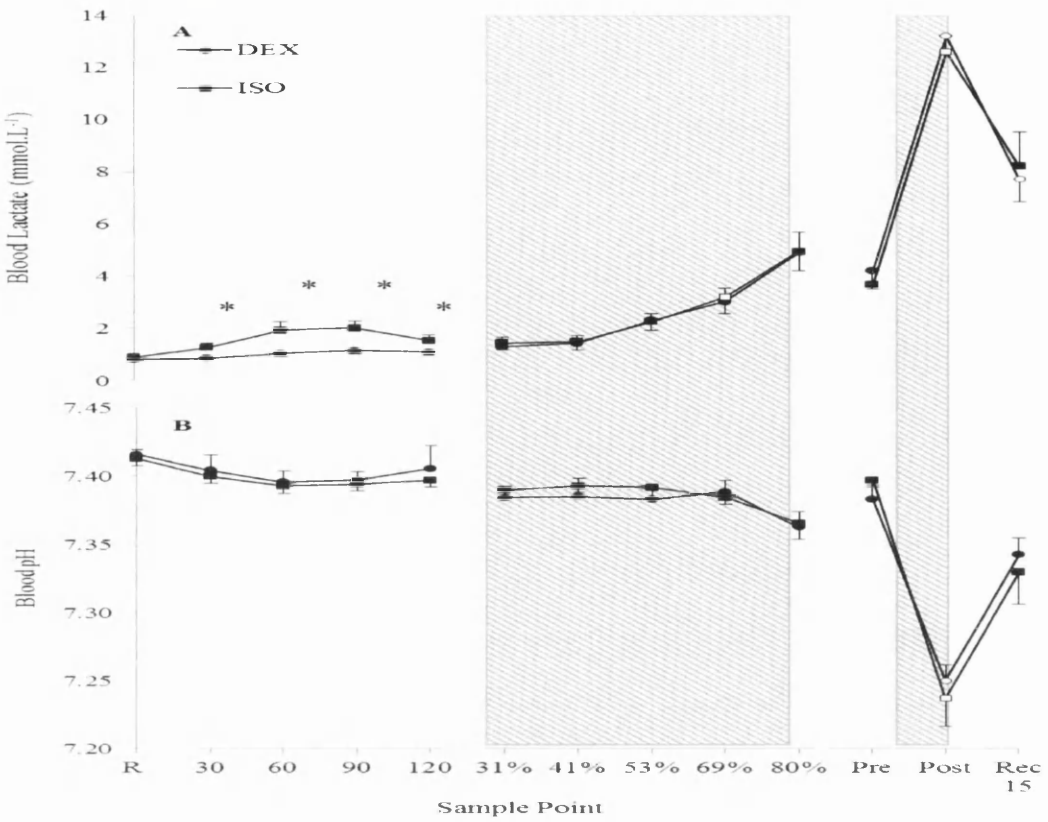

Figure 4.2. Blood lactate (A) and blood pH (B) responses following ingestion of CHO, during submaximal exercise, during the performance protocol and subsequent recovery period. (○) hollow markers demonstrate significant changes from resting sample (P < 0.05). (*) denotes significant changes between conditions (P < 0.05). The first shaded area is representative of the submaximal exercise and the second shaded area representative of the high intensity performance running.

Blood lactate values were significantly elevated throughout the pre-exercise resting period in ISO when compared to DEX (P = 0.009). This finding is reflected in the peak resting values where peak values are higher in ISO when compared to DEX (ISO; 2.2 ± 0.3 vs. DEX; 1.3 ± 0.1 mmol L^{-1}, P = 0.10). Once exercise had begun there were no conditional differences between lactate concentrations (P = 0.85) and the onset of blood lactate accumulation (OBLA; 4 mmol L^{-1}) was reached by participants either in the final two increments or not at all during the submaximal exercise in both treatments. Blood lactate concentrations increased with exercise intensity with peak lactate values occurring after completion of the performance bout, these values were similar between conditions (DEX; 13.2 ± 0.7 vs. ISO; 12.6 ± 0.6 mmol L^{-1}, P = 0.53).

There was no conditional effect present in blood pH between trials (P = 0.99). Lowest blood pH values occurred after the performance bout and were similar between trials (DEX; 7.25 ± 0.01 vs. ISO; 7.24 ± 0.01, P = 0.60).

4.3.3 Blood Electrolytes

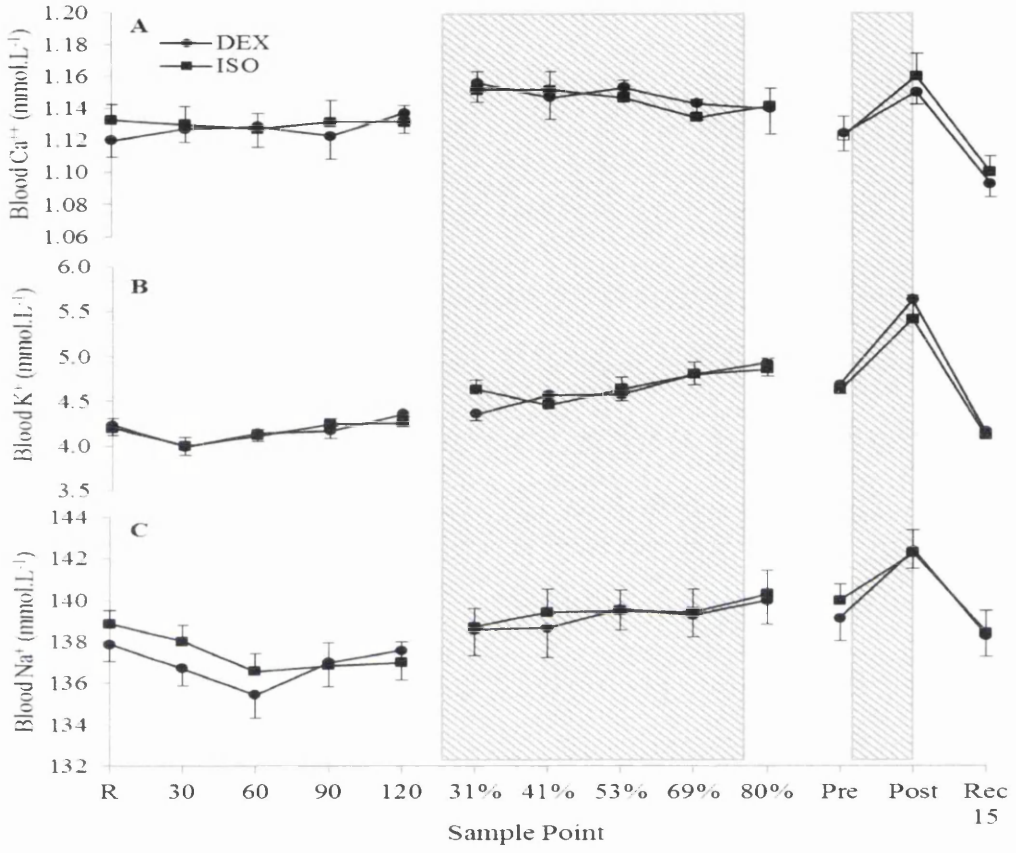

Figure 4.3. Blood electrolyte responses following ingestion of CHO, during submaximal exercise, during the performance protocol and subsequent recovery period. (A) illustrates changes in blood Ca^{++} (B) illustrates changes in blood K^{+} and (C) illustrates changes in blood Na^{+} levels. The first shaded area is representative of the submaximal exercise and the second shaded area representative of the high intensity performance running.

No conditional differences were present between any of the electrolyte concentrations (Ca^{++}; P = 0.94, K^{+}; P = 0.84, Na^{+}; P = 0.89).

Concentrations of K^{+} and Na^{+} slowly increased with an increase in exercise intensity during the submaximal exercise, this relationship was not present in levels of Ca^{++}. All electrolyte

concentrations increased after completion of the performance test. Peak levels of electrolytes were also similar between conditions, (Ca^{++}, DEX; 1.17 ± 0.01 vs. ISO; 1.17 ± 0.01, P = 0.94, K^{+}, DEX 5.6 ± 0.2 vs. ISO 5.4 ± 0.03, P = 0.54 , Na^{+}, DEX; 142 ± 1 vs. ISO 142 ± 1 mmol L^{-1}, P = 1.00).

4.3.4 Blood Gases

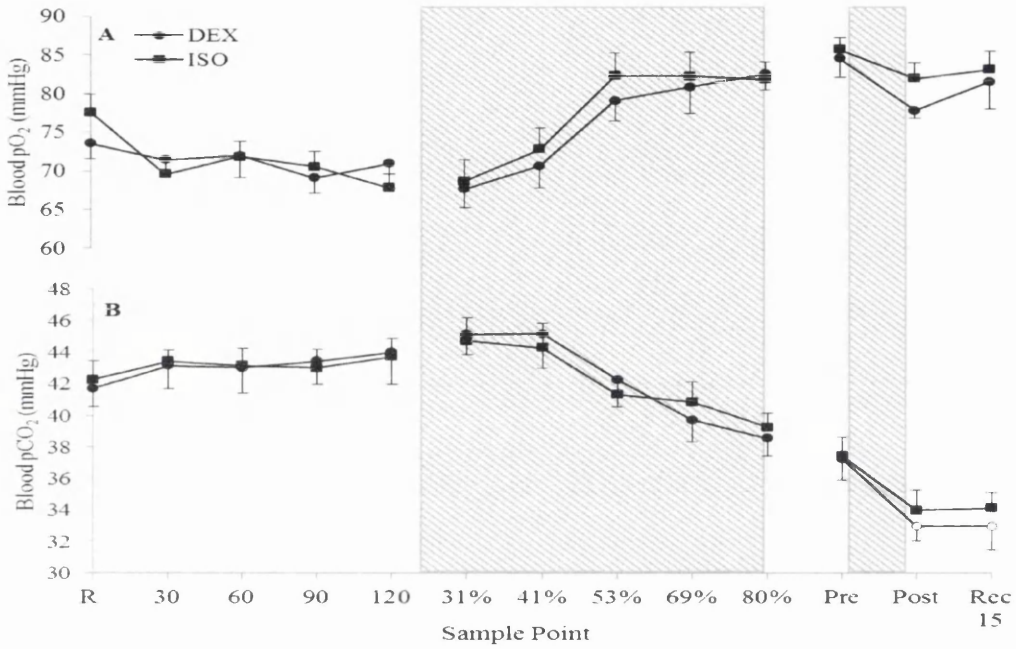

Figure 4.4. Blood gas responses following ingestion of CHO, during submaximal exercise, during the performance protocol and subsequent recovery period.(A) illustrates changes in blood pO_2 and (B) illustrates changes in blood pCO_2. (○) hollow markers demonstrate significant changes from resting sample ($P < 0.05$).The first shaded area is representative of the submaximal exercise and the second shaded area representative of the high intensity performance running.

There were no conditional differences in either of the blood gas concentrations in each of the trials (pO_2; P = 0.44, pCO_2; P = 0.87).

Levels of blood pO_2 were consistent during the rest period and for the first exercise intensity, following the first exercise intensity levels of blood pO_2 increased during the submaximal exercise and continued to rise before commencement of the performance test. Levels of blood pO_2 then fell in both trials at a similar rate (DEX; -7 ± 2 vs. ISO; -4 ± 2 mmHg, P = 0.32) after completion of the performance test. There were no conditional differences in peak levels of blood pO_2 (DEX; 89 ± 2 vs. ISO; 89 ± 1 mmHg, P = 0.95).

Blood pCO_2 levels were constant during the rest period and after a slight increase following the first exercise intensity, the levels fell throughout the submaximal exercise and continued to fall until cessation of the performance test. There were no conditional differences in minimum levels of blood pCO_2 (DEX; 32 ± 1 vs. ISO; 33 ± 1 mmHg, P = 0.46).

4.3.5 Blood Haematocrit

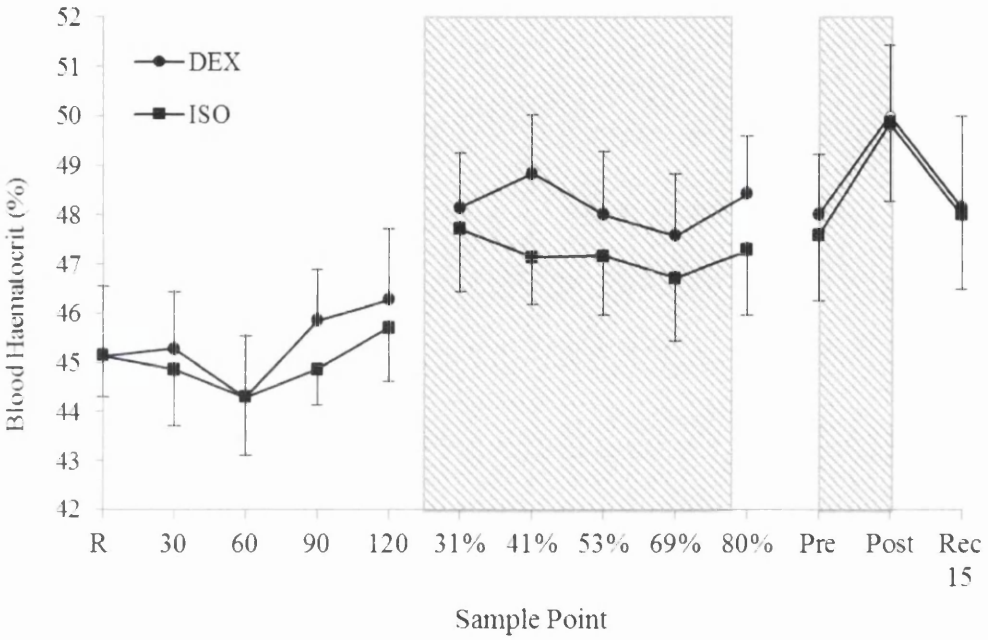

Figure 4.5. Changes in blood haematocrit levels following ingestion of CHO, during submaximal exercise, during the performance protocol and subsequent recovery period. (○) hollow markers demonstrate significant changes from resting sample (P < 0.05). The first shaded area is representative of the submaximal exercise and the second shaded area representative of the high intensity performance running.

No conditional differences between CHO were present in levels of blood haematocrit (P = 0.59). Minimum levels of blood haematocrit occurred 60 minutes after ingestion of CHO, minimum levels were similar between trials (DEX; 44 ± 1 vs. ISO; 44 ± 1%, P = 0.93).

Throughout the submaximal exercise DEX haematocrit levels fluctuated whilst ISO levels remained fairly constant. Haematocrit levels rose after completion of the performance test to peak values, the rise observed (DEX; 2 ± 1 vs. ISO; 2 ± 1%, P = 0.60) and peak levels (DEX; 50 ± 1 vs. ISO; 50 ± 1%, P = 1.00) were similar between conditions.

4.4 Submaximal Exercise

4.4.1 Cardiorespiratory Responses

Table 4.2. Cardiorespiratory responses to exercise in each of the trials. (#) denotes variable significantly higher than rest ($P < 0.05$).

		Rest	31%	41%	53%	69%	80%
$\dot{V}_E$ ($L \cdot min^{-1}$)	DEX	7.75 ± 0.54	19.22 ± 1.20#	26.58 ± 2.21#	37.09 ± 2.97#	50.87 ± 4.07#	62.54 ± 3.64#
	ISO	9.83 ± 0.79	19.25 ± 0.89#	25.00 ± 1.13#	36.32 ± 2.37#	51.11 ± 3.17#	62.00 ± 3.52#
$\dot{V}O_2$ ($L \cdot min^{-1}$)	DEX	0.28 ± 0.01	0.84 ± 0.05#	1.11 ± 0.05#	1.43 ± 0.10#	1.90 ± 0.14#	2.24 ± 0.10#
	ISO	0.31 ± 0.02	0.84 ± 0.04#	1.08 ± 0.06#	1.43 ± 0.09#	1.89 ± 0.15#	2.11 ± 0.11#
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	DEX	0.24 ± 0.02	0.72 ± 0.06#	1.04 ± 0.08#	1.48 ± 0.14#	2.00 ± 0.18#	2.47 ± 0.11#
	ISO	0.29 ± 0.02	0.72 ± 0.05#	0.99 ± 0.06#	1.47 ± 0.12#	2.02 ± 0.16#	2.36 ± 0.11#
RER	DEX	0.87 ± 0.02	0.86 ± 0.03	0.93 ± 0.04	1.02 ± 0.04#	1.05 ± 0.04#	1.11 ± 0.04#
	ISO	0.92 ± 0.03	0.86 ± 0.03	0.92 ± 0.03	1.02 ± 0.03#	1.07 ± 0.03#	1.12 ± 0.02#
Heart Rate ($beats \cdot min^{-1}$)	DEX	73 ± 5	102 ± 6#	114 ± 5#	134 ± 5#	150 ± 5#	168 ± 7#
	ISO	79 ± 5	101 ± 5#	116 ± 5#	132 ± 6#	150 ± 5#	164 ± 7#

Manipulation of pre-exercise carbohydrate did not influence cardiorespiratory responses between trials as there was no conditional effect present in any of the variables ($P > 0.05$). Apart from RER responses all other variables increased on the commencement of the first exercise intensity and continued to increase after each increment. RER responses increased from the resting value in the 41% intensity in DEX and 53% intensity in ISO.

At rest there is strong suggestion of a ventilatory cost and carbon dioxide output after ingestion of ISO and this factor is represented in the $\dot{V}_E$ (P = 0.051) and $\dot{V}CO_2$ (P = 0.155) values.

4.4.2 Substrate Utilisation and Energy Expenditure

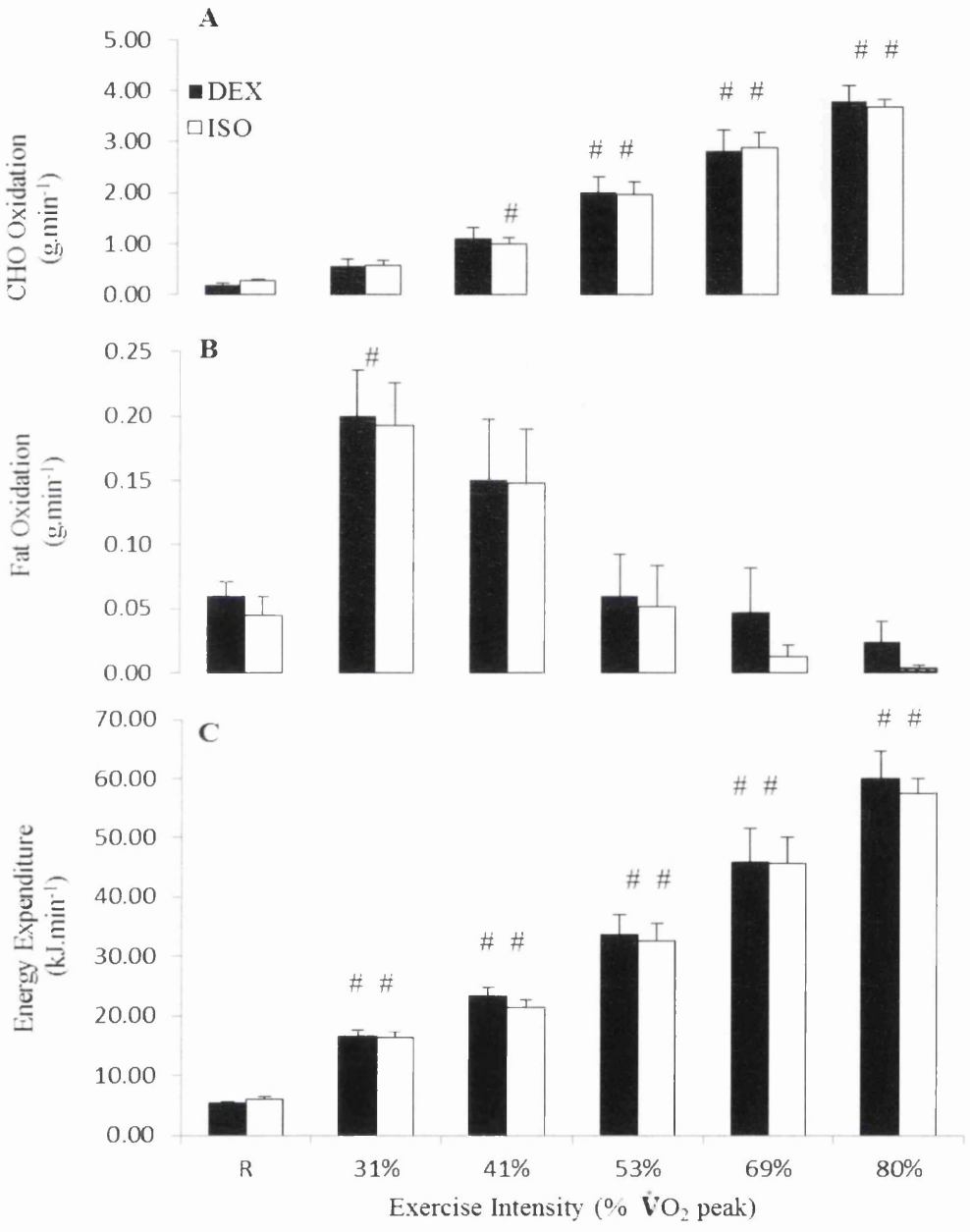

Figure 4.6. Rates of substrate utilisation and energy expenditure at rest and throughout submaximal exercise (A) illustrates changes in carbohydrate (CHO) oxidation and (B) illustrates changes in fat oxidation (C) illustrates changes in energy expenditure (#) denotes oxidation rate significantly greater than rest ($P < 0.05$).

Resting rates of substrate utilisation (Equations A and B) were similar between conditions (DEX CHO; 0.19 ± 0.04, ISO CHO; 0.27 ± 0.04 $g \cdot min^{-1}$, P = 0.16., DEX Fat; 0.06 ± 0.01 vs. ISO Fat; 0.04 ± 0.01 $g \cdot min^{-1}$, P = 0.34). During exercise, CHO combustion rates (Equation A) increase as exercise intensity increases in both conditions, whilst rates of fat combustion (Equation B) follow an inverse relationship and decrease as exercise intensity increases. CHO combustion was significantly higher in both conditions from the 53% exercise intensity onwards and additionally from 41% onwards in ISO. Fat oxidation was significantly higher than rest at the 31% stage in ISO but not in DEX.

There were no significant differences in combustion rates between conditions throughout the incremental intensities (CHO; P = 0.77, FAT; P = 0.46). No differences in exercising peak rates of CHO (DEX; 3.79 ± 0.32 vs. ISO; 3.67 ± 0.17 $g \cdot min^{-1}$, P = 0.75) or fat (DEX; 0.22 ± 0.04 vs. ISO; 0.20 ± 0.04 $g \cdot min^{-1}$, P = 0.73) oxidation between conditions were present either.

An increase in exercise intensity was accompanied with a rise in energy expenditure (EE), EE was comparable between treatments ($P < 0.05$) with peak levels in the final increment (DEX; 60.01 ± 4.56 vs. ISO; 57.38 ± 2.58 $kJ \cdot min^{-1}$).

4.4.3 Substrate Contributions to Energy Expenditure

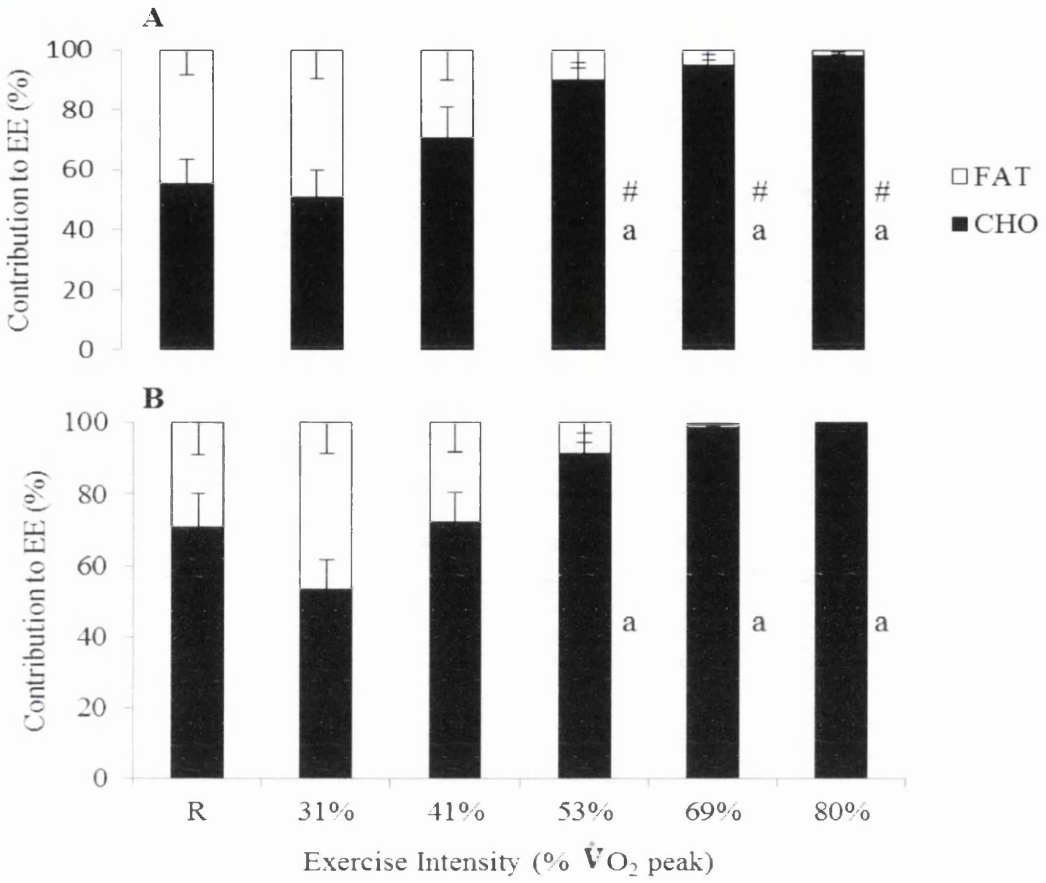

Figure 4.7. Fuel use contributions to energy expenditure at rest and throughout submaximal exercise (A) illustrates DEX contributions to EE (B) illustrates ISO contributions to EE (#) denotes oxidation contributions significantly different than rest ($P < 0.05$), (a) denotes oxidation contributions significantly different to first exercise intensity ($P < 0.05$).

Resting carbohydrate contributions were similar between conditions (DEX; 55.3 ± 8.3, vs. ISO 70.9 ± 9.1%, P = 0.23) and there were no conditional differences in the submaximal exercise (P = 0.46).

As exercise intensity increased the reliance of CHO as the primary contributor to energy expenditure also increased. In the latter three incremental stages the EE contribution of CHO was higher than the first exercise stage in both conditions and also higher than rest contributions in DEX. CHO contributions to EE were not different at any exercise intensity in the ISO trial. These changes in contributions were also mirrored in the rates of substrate utilisation (Figure 4.6).

4.5 Performance Responses

4.5.1 Performance Variables

Table 4.3. Characteristics of performance trial for each condition, categorised into 2.5 minute quartiles. (c) denotes significantly longer than third exercising quartile.

Variable	Quartile	DEX	ISO
Stride Length (m)	2.5 min	0.70 ± 0.06	0.69 ± 0.05
	5.0 min	0.72 ± 0.06	0.71 ± 0.04
	7.5 min	0.69 ± 0.06	0.71 ± 0.04
	10 min	0.75 ± 0.04	0.78 ± 0.04[c]
	Mean	0.72 ± 0.05	0.72 ± 0.04
Average Speed ($km \cdot h^{-1}$)	2.5 min	6.93 ± 0.63	6.48 ± 0.58
	5.0 min	6.72 ± 0.59	6.65 ± 0.57
	7.5 min	6.69 ± 0.58	6.82 ± 0.50
	10 min	7.23 ± 0.49	7.47 ± 0.50
	Mean	6.89 ± 0.55	6.86 ± 0.51
Number of Steps	2.5 min	409 ± 9	388 ± 17
	5.0 min	389 ± 12	387 ± 15
	7.5 min	401 ± 10	400 ± 10
	10 min	401 ± 10	400 ± 10
	Total	1600 ± 36	1576 ± 39
Distance (km)	2.5 min	0.29 ± 0.03	0.27 ± 0.02
	5.0 min	0.28 ± 0.02	0.28 ± 0.02
	7.5 min	0.28 ± 0.02	0.28 ± 0.02
	10 min	0.30 ± 0.02	0.31 ± 0.02
	Total	1.15 ± 0.09	1.14 ± 0.09
RPE		18.1 ± 0.5	18.0 ± 0.7

There were no conditional differences in any of the variables at any of the quartiles during the performance trial ($P > 0.05$). In the final exercising quartile, participants covered the most difference and maintained the fastest speed in each trial and although number of steps did not increase, stride length did to compensate for the extra distance covered. The extra distance covered in the final quartile of the tests is also reflective on the cardiorespiratory variables (Table 4.4).

4.5.2 Cardiorespiratory Responses

Table 4.4 Cardiorespiratory responses to the performance trial in each of the conditions categorised in 2.5 minute quartiles (a) denotes variable higher than first exercise quartile ($P < 0.05$), (b) denotes variable higher than second exercise quartile ($P < 0.05$), (c) denotes variable higher than third exercise quartile ($P < 0.05$).

Variable		2.5 Min	5 Min	7.5 Min	10 Min	Mean
$\dot{V}_E$ ($L \cdot min^{-1}$)	DEX	61.47 ± 5.16	84.04 ± 8.15[a]	86.80 ± 7.99[a]	94.43 ± 7.43[a,b,c]	81.69 ± 6.99
	ISO	56.07 ± 6.14	76.43 ± 7.25[a]	84.39 ± 7.19[a,b]	92.92 ± 7.62[a,b,c]	77.45 ± 6.84
$\dot{V}O_2$ ($L \cdot min^{-1}$)	DEX	1.99 ± 0.18	2.40 ± 0.22[a]	2.41 ± 0.22[a]	2.45 ± 0.19[a]	2.31 ± 0.20
	ISO	1.88 ± 0.20	2.32 ± 0.23[a]	2.43 ± 0.22[a]	2.44 ± 0.20[a]	2.27 ± 0.21
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	DEX	2.27 ± 0.24	3.10 ± 0.32[a]	3.05 ± 0.31[a]	3.18 ± 0.27[a]	2.90 ± 0.28
	ISO	2.07 ± 0.27	2.88 ± 0.33[a]	3.05 ± 0.32[a]	3.17 ± 0.28[a]	2.79 ± 0.29
Exercise Intensity ($\%\dot{V}O_{2\,PEAK}$)	DEX	73 ± 5	88 ± 6[a]	88 ± 6[a]	90 ± 5[a]	85 ± 5
	ISO	69 ± 6	85 ± 6[a]	89 ± 6[a]	90 ± 5[a]	83 ± 6
Heart Rate ($beats \cdot min^{-1}$)	DEX	163 ± 6	178 ± 6[a]	182 ± 5[a,b]	186 ± 4[a]	177 ± 5
	ISO	160 ± 5	177 ± 5[a]	182 ± 5[a,b]	187 ± 4[a,b,c]	176 ± 5

No conditional differences through CHO manipulation were present between cardiorespiratory responses in the performance test ($P > 0.05$). Participants were exercising at a higher intensity for the last three exercising quarters in both conditions when compared to the first exercise quartile ($P < 0.05$). The increased exercise intensity is reflected in the other variables, a relationship similar to that observed in the submaximal exercise protocol data (Table 4.2).

Minute ventilation was higher in the final exercising quartile of both DEX and ISO when compared to the three previous exercising quartiles, furthermore in ISO the heart rate was also higher than all three previous exercise quartiles ($P < 0.05$).

4.5.3 Substrate Utilisation and Energy Expenditure

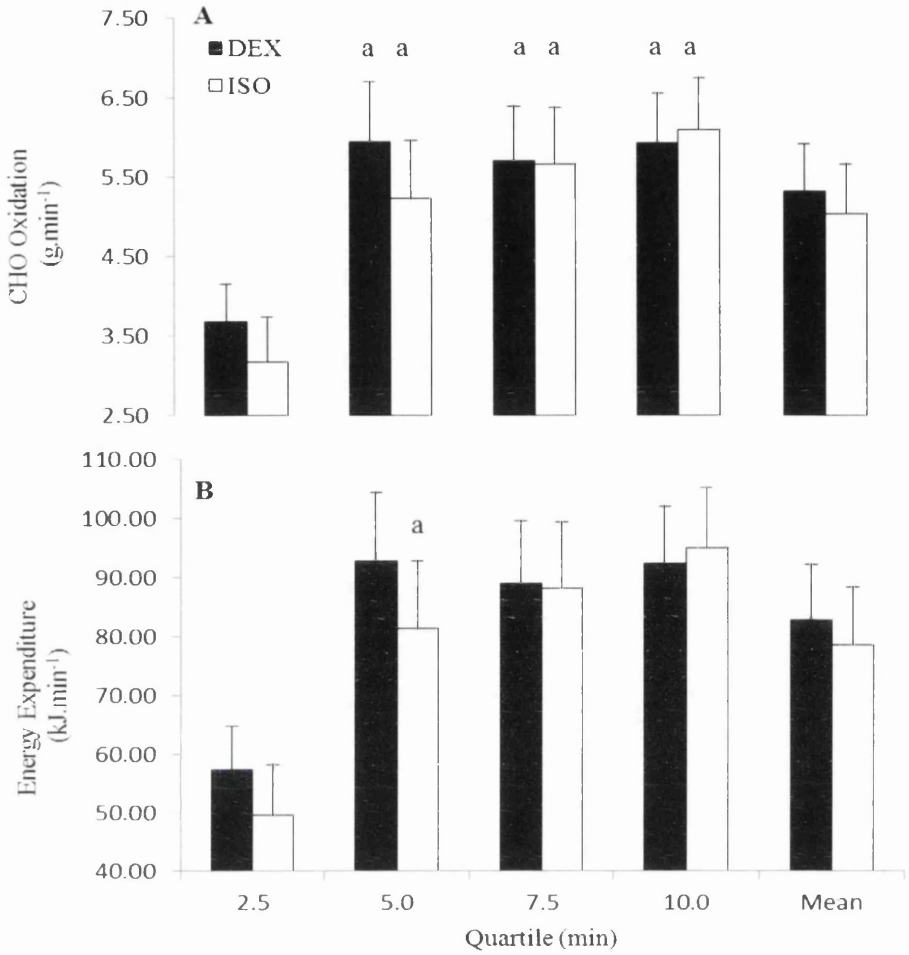

Figure 4.8 Fuel use and energy expenditure in the performance test. (A) illustrates rates of carbohydrate oxidation and (B) illustrates energy expenditure for each of the high intensity quartiles

Substrate utilisation during the performance running was dependent fully on CHO oxidation, rates which was comparable between treatments ($P > 0.05$). Peak CHO rates were observed in the first exercising quartile in DEX and in the final exercising quartile in ISO and were comparable (DEX; 5.95 ± 0.75 vs. ISO; 6.10 ± 0.64 g·min^{-1}).

As fuel oxidation was fully dependent on CHO oxidation, the EE values followed the same relationship as the carbohydrate oxidation with peak values comparable between treatment at the first and last quartiles in DEX and ISO respectively (DEX; 92.82 ± 11.63 vs. ISO; 95.12 ± 10.04 kJ·min^{-1}).

4.6 Stroop Colour Word Test (SCWT)

Table 4.5. SCWT responses and scores in both trials. (#) denotes significantly quicker time than rest (P < 0.05).

	DEX			ISO		
	Rest	Pre – Ex	Post – Ex	Rest	Pre – Ex	Post – Ex
Congruent Score	9.9 ± 0.1	10 ± 0	10 ± 0	10 ± 0	10 ± 0	10 ± 0
Congruent Time (s)	1.233 ± .063	1.215 ± .084	1.115 ± .076	1.157 ± .099	1.155 ± .065	1.067 ± .064
Incongruent Score	10 ± 0	10 ± 0	10 ± 0	9.7 ± 0.3	10 ± 0	10 ± 0
Incongruent Time (s)	1.387 ± .070	1.374 ± .089	1.222 ± .075	1.392 ± .076	1.257 ± .099#	1.209 ± .090#
Stroop Effect (s)	0.154 ± .038	0.159 ± .065	0.107 ± .040	0.235 ± .077	0.102 ± .077	0.142 ± .041

There were no conditional differences in scores or times for either the congruent (word and colour identical; score; P = 0.36, time; P = 0.19) or incongruent (word and colour different; score; P = 0.36, time; P = 0.39) elements of the SCWT. No conditional differences were present either in regards to the Stroop effect (P = 0.59).

In both trials, congruent times were quicker than incongruent times, and subsequent incongruent times after consumption of ISO were quicker than the resting value (Rest vs. Pre-Ex; P = 0.01, Rest vs. Post-Ex; P < 0.01).

Scores for both congruent and incongruent elements were similar at all sample points and also between conditions.

4.7 Gut Fullness and Hunger Ratings

Table 4.6. Perceived ratings of gut fullness and hunger in both trials. (#) denotes perceived rating significantly different to rest (P < 0.05).

	DEX			ISO		
	Rest	Pre – Ex	Post – Ex	Rest	Pre – Ex	Post – Ex
Perceived Gut Fullness Rating	3.6 ± 0.3	4.0 ± 0.5	4.7 ± 0.4#	2.4 ± 0.5	3.9 ± 0.3	4.1 ± 0.6
Perceived Hunger Rating	6.7 ± 0.3	6.3 ± 0.5	5.1 ± 0.7	6.9 ± 0.5	5.7 ± 0.2	6.1 ± 0.5

Perceived feelings of gut fullness increased in both trials after consumption of CHO, fullness was reported to be greatest after completion of exercise, although there were no conditional differences between trials (P = 0.11).

Perceived hunger ratings were also highest at rest before CHO ingestion and ratings were lower in both conditions at the pre and post exercises stages. In DEX there is a suggestion of appetite suppression after completion of exercise where a drop in hunger feeling is observed as opposed to an increase in ISO. There were no conditional differences between carbohydrates (P = 0.54).

4.8 Post Laboratory Results

4.8.1 Blood Glucose

Table 4.7 Self-reported BG values 3 and 6 hours after leaving the laboratory (#) denotes value significantly different to 0h.

	DEX			ISO		
	0 h (n = 6)	3 h (n = 6)	6 h (n = 5)	0 (n = 6)	3 (n = 6)	6 (n = 5)
BG ($mmol.L^{-1}$)	13.8 ± 2.0	12.8 ± 2.7	9.0 ± 0.9#	12.0 ± 1.8	10.4 ± 1.3	9.2 ± 1.6
Relative BG ($mmol.L^{-1}$)	4.7 ± 1.9	3.7 ± 3.3	- 0.6 ± 1.8#	2.9 ± 1.3	1.4 ± 2.0	- 0.4 ± 2.0

BG levels fell over the 6 hour self-reported period in both trials, with no conditional effect between treatments in either absolute or relative BG values (P > 0.05). 6 hour reported BG

values were significantly lower in DEX when compared to BG levels when leaving the laboratory. In both conditions 6 hour values were lower than baseline values taken at rest.

4.8.2 Insulin Doses and Dietary Intake

Participants (n = 5) self-reported their dietary intakes after leaving the laboratory for the remainder of the day. Participants tended to consume less energy intake after completion of the ISO trials (DEX; 5258 ± 616 vs. ISO; 4008 ± 503 kJ, P = 0.17) with less CHO intake also reported (DEX; 152.0 ± 18.8 vs. ISO; 113 ± 20.0 g, P = 0.10).

There were no differences in meal time insulin doses between trials (DEX; 18.0 ± 3.3 vs. ISO; 17.4 ± 2.3 U, P = 0.89). Two participants also reported that after the DEX trial they administered corrective doses of 4 and 2U respectively of their rapid acting insulin in an attempt to lower their elevated levels of BG. There were no reports of corrective doses administered post ISO trials.

5.0 DISCUSSION

5.1 Aim and Main Findings

This study investigated the metabolic, substrate and exercise performance responses in T1DM individuals after ingesting 0.6 $g \cdot kg^{-1}$ BM (10% solution) of either DEX (high GI) or ISO (low GI) in combination with a 50% reduced dose of rapid-acting insulin 2 hours prior to exercise. Levels of glycaemia were found to be improved after ingestion of ISO without any performance differences on subsequent high intensity running.

5.2 Rest

Pre-exercise relative blood glucose concentrations were higher in DEX (GI = 100, Chapter 3.3.2.1) compared to ISO (GI = 53, Chapter 3.3.2.1), these observations would have a result of the different GI values between CHO and the 2 hour IAUC responses associated with calculating GI (Brouns et al., 2005; Jenkins et al., 1981). The lower glycaemic responses and associated relative peaks (ISO; +5.6 ± 0.4 vs. DEX; +10.3 ± 0.7 $mmol \cdot L^{-1}$, $P < 0.001$) witnessed are consistent with previous investigations (West et al., 2011b; Chapter 3.3.2.1). The longer time to reach peak resting blood glucose concentration in ISO is also reflective of the different GI values. The process of hydrolysis and subsequent absorption of derived fructose and glucose in ISO results in a somewhat slower, lesser peak than that observed in DEX (Lina et al., 2002). In order to cross the brush border membrane fructose needs to be aided by the transport protein, GLUT 5, moving down a concentration gradient before uptake into mucosal cells can take place via the process of facilitated diffusion (Frayn, 1996). The derived glucose in ISO and DEX can readily cross the brush border membrane and pass into the enterocytes by active transport mediated via the sodium glucose co-transporter 1 (SGLT1) and increase BG levels quickly (Frayn, 1996; West et al., 2011b). These findings resulted that null hypothesis i could be rejected for glycaemic responses at rest.

Throughout the 2 hour resting period blood lactate was higher after ingestion of ISO at all sample time points with this observation translated in the higher resting peak values (DEX; 1.3 ± 0.1 vs. ISO; 2.2 ± 0.3 $mmol \cdot L^{-1}$, $P = 0.016$) of which similarities have been witnessed in previous investigations (West et al., 2011b: Chapter 3.3.2.1). Conditional differences in regards to lactate meant that null hypothesis i was rejected for the rest period. The time to

reach these peak lactate values were similar between conditions (DEX; 94 ± 8 vs. ISO; 86 ± 8 min, P = 0.454). Carbohydrate feeding alone promotes glycolysis and lactate production even at rest, glucose entering the resting muscle is phosphorylated to glucose-6-phosphate and this subsequently leads to glycolysis (Houston, 1995). The further elevated levels of blood lactate in ISO can be explained by the metabolism of this disaccharide into fructose and glucose. The resultant fructose bypasses the phosphofructokinase regulatory point in glycolysis and leads to an increased flux through the glycolytic pathway which in turn leads to a build-up and subsequent release of lactate (Kaye et al., 1958; Sahebjami & Scalettar 1971).

In addition to the increased lactate levels in ISO, are higher rates of minute ventilation ($\dot{V}_E$) and carbon dioxide output ($\dot{V}CO_2$). The pyruvate resulting from glycolysis has two fates, one of which is the reduction to lactate and appearance in the bloodstream via the enzyme lactate dehydrogenase (LDH) and the second is the entrance into the mitochondria. Once in the mitochondria, pyruvate is converted into acetyl CoA using pyruvate dehydrogenase for subsequent oxidation to water and carbon dioxide (Houston, 1995). This second fate of pyruvate may explain the recorded higher $\dot{V}_E$ and $\dot{V}CO_2$ (Table 4.2, Figure 5.1) witnessed in this study.

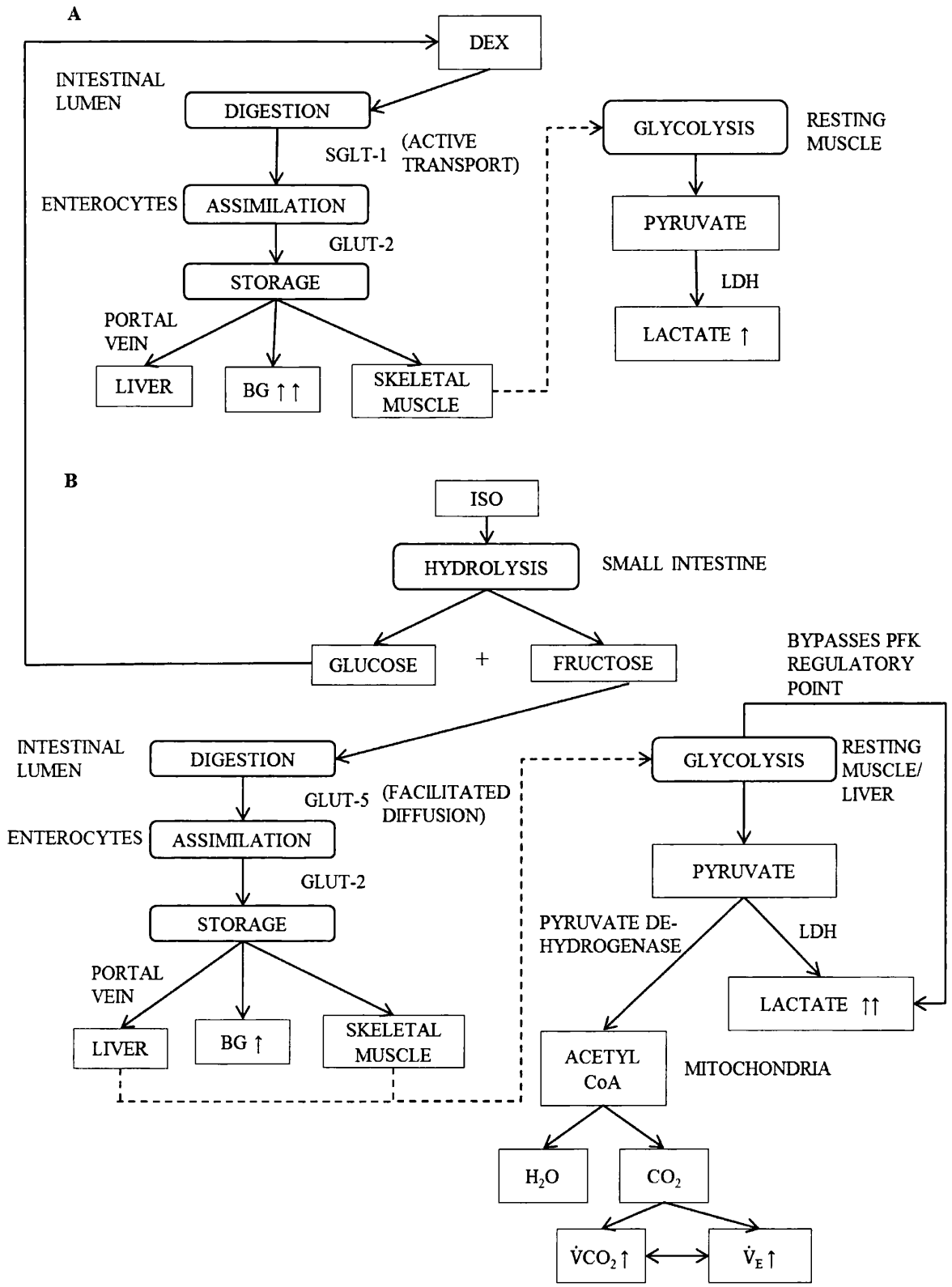

Figure 5.1 Schematic representations of blood glucose and lactate responses following ingestion of either DEX (5.1.A) or ISO (5.1.B), compiled using data from Frayn (1996); Houston (1995); Kaye et al., (1958); Lina et al., (2002); Sahebjami & Scalettar (1971)

5.3 Submaximal Exercise Protocol

During discontinuous incremental submaximal exercise, blood glucose concentrations declined at a comparable rate from the start of the exercise until the last increment (DEX; - 1.0 ± 0.5 vs. ISO; - 1.9 ± 0.5 mmol·L^{-1}, P = 0.21). Although there were no differences between the total level of decline throughout the submaximal exercise the rate of fall was different between treatments. In DEX blood glucose dropped at a steady rate of 0.1 mmol·L^{-1} regardless of exercise intensity following each increment after an initial 0.6 mmol·L^{-1} decline at the onset of exercise, however, in ISO blood glucose fell 0.5 mmol·L^{-1} at the beginning of exercise and then dropped a further 0.2 – 0.5 mmol·L^{-1} per exercise increment with the rate of fall slowing slightly as exercise intensity increased. As blood glucose concentrations were comparable during the submaximal protocol the criteria for null hypothesis i was fulfilled.

The blood glucose decline observed in this time period could be attributable to the levels of circulating insulin in the bloodstream. As insulin is exogenously administered levels do not decrease at the start of exercise as they do in healthy individuals which in combination with an insufficient glucagon response results in no change in the ratio of insulin to glucagon. An unchanged ratio means that there is an increased risk that the fuel requirement required for exercise will not be matched by hepatic glucose production (Lumb & Gallen, 2009). In addition, the usual portal to systemic insulin ratio is reversed which results in a higher insulin concentration in the periphery (Lumb & Gallen, 2009), the increased insulin concentration promotes peripheral muscle glucose uptake further reducing levels of blood glucose (Goodyear & Kahn, 1998). Furthermore, the observed reductions in blood glucose could be related to the time length of the submaximal exercise (26 minutes) as for the initial 20 – 60 minutes of exercise, individuals with T1DM are more susceptible to exercise induced hypoglycaemia (Riddell et al., 1999).

By the end of the first 4 minutes of exercise no differences were longer evident between conditions in blood lactate concentrations (DEX; 1.3 ± 0.1 vs. ISO; 1.4 ± 0.2 mmol·L^{-1}, P = 0.28). As the first increment of exercise was of low intensity similar to the intensity used (29% vs. 31% $\dot{V}O_{2\ PEAK}$) during active recovery it is possible that the removal of lactate in ISO occurred within the skeletal muscles (McGrail, Bonen & Belcastro, 1978). Additional increases of exercise intensity as the incremental protocol progressed also resulted in an

increase of blood lactate concentrations with these levels again comparable between treatments ($P > 0.05$), therefore similar anaerobic threshold running intensities were observed between conditions in spite of the higher lactate levels at rest in ISO. An increase in exercise intensity beyond 50 – 60% $\dot{V}O_{2\ MAX}$ promotes an increase in rate of glycolysis and the subsequent increase in pyruvate production. The derived pyruvate is produced at a quicker rate than the rate of glycolysis such that a significant amount is reduced to lactate (Houston, 1995). The levels of blood pH are reportedly linearly related to blood lactate and pyruvate concentrations (Saltin, 1975), therefore as blood lactate rises as the exercise intensity increases, an associated decrease in blood pH is observed (Figure 4.2). Therefore, null hypothesis i was fulfilled in regards to blood lactate and pH concentrations.

Hyperglycaemic levels at the onset (DEX; 15.0 ± 1.9 vs. ISO; 14.6 ± 1.5 $mmol \cdot L^{-1}$) and throughout the submaximal exercise protocol (DEX; 14.5 – 14.0 vs. ISO; 14.1 – 12.7 $mmol \cdot L^{-1}$) may have suppressed lipid oxidation (Jenni et al., 2008; West et al., 2010; West et al., 2011b) and therefore the potential for any carbohydrate sparing witnessed in previous studies (Febbraio et al., 2000; Wee et al., 2005) to be blunted. The short duration of intervals and/or only a relatively small decline in blood glucose ~ 1.0 $mmol \cdot L^{-1}$ may also have attributed to no differences observed in regards to lesser suppression of lipid oxidation as observed in previous research comparing these two carbohydrates (West et al., 2011b).

However, the suppression of lipids could simply be a result of pre-exercise carbohydrate provisions and oxidation shifting to predominately carbohydrate after the 'crossover' point at a certain exercise intensity (Brooks & Mercier, 1994). Exercise is typically fuelled by four main components: muscle glycogen, muscle triglycerides, plasma free fatty acids and plasma glucose, the utilisation and selection of these choices vary and are determined in relation to exercise intensity performed (Romijn et al., 1993). Exercising at different intensities is reflective in the energy expenditure, i.e. the higher the intensity of exercise performed the greater the energy expenditure and vice versa. As exercise intensity increases lipids cannot be oxidised quickly enough to supply the required fuel and therefore carbohydrates become the dominant substrate with glycogen stores in the liver and muscles providing this required energy (Coyle, 1995, Figure 4.7). This also offers an explanation as to the higher rates of carbohydrate oxidation as the increments progressed and the energy intensity and

expenditures both increased. Comparisons in substrate utilisation in both treatments resulted in the criteria for null hypothesis ii to be fulfilled.

Pre-exercise provision of carbohydrate could also offer explanation as to the peak oxidation rates in this study were lower than the documented 'fatmax' values in which the participants exercised in the fasted state (Achten et al., 2002). Individual peak oxidation rates occurred in the initial increments at the low exercise intensities 31 or 41% $\dot{V}O_{2\ PEAK}$ independent of treatment and fat utilisation was comparable with resting oxidation values in the latter stages of the incremental protocol. Lipid oxidation has been shown to be directly regulated by the availability of carbohydrate (Coyle et al., 1997; Turcotte, Swenberger & Yee, 2002), high carbohydrate availability promotes long chain fatty acid uptake and decreases oxidation in the muscle most likely due to malonyl-CoA inhibition in the mitochondria (Sidossis, Gastaldelli, Klein & Wolfe, 1997; Turcotte et al., 2002). Carbohydrate (glucose) can also be observed as the dominant fuel at lower intensities where an insulin response to a recent meal or continued carbohydrate feeding inhibits lipolysis (Marliss & Vranic, 2002).

Electrolyte responses were comparable between treatments during the submaximal exercise protocol ($P > 0.05$) and therefore fulfilled the criteria for null hypothesis i to be accepted. The initial rise and then consistent decline in calcium ions is explained due to the transport and increased uptake for subsequent regulation of contraction of the working muscles through the troponin-tropomyosin (Ebashi, 1972) and as the intensity of exercise increases so does the demand on the working muscles and associated calcium ion uptake for contraction (Ebashi, 1972). Potassium levels are intensity related and concentrations rise after every incremental stage of the submaximal protocol as exercise intensity increases and more potassium is released into the circulation from the working muscles (Vøllestad et al., 1994). Sodium and potassium concentrations follow a similar relationship due to the regulation of these ions at the Na^{++}/K^{+} pump and interchange of ions against their respective concentration gradients (Medbø & Sejersted, 1990). This relationship is the major influence in regulating both sodium and potassium levels as via skeletal Na^{+}-K^{+}-ATPase cellular sodium is released in exchange for potassium uptake. The exchange is crucially important in protecting both excitability and contractility of the muscle membrane (Sejersted & Sjøgaard, 2000).

5.4 Performance Test

In contrast to the decline in blood glucose witnessed in both conditions during the submaximal exercise protocol, blood glucose increased after the completion of the performance test. The increases observed were comparable between treatments (DEX; + 0.7 ± 0.3 vs. ISO; + 0.7 ± 0.4 mmol·L^{-1}, P = 0.98) with the rise in blood glucose a resultant of the increased exercise intensity. Similar responses have been seen in previous research after a period of high intensity exercise with the reasoning attributed to a rise in hepatic glucose production that exceeds the rate of utilisation (Mitchell et al., 1998). Hepatic production of blood glucose is generally accepted to be regulated by the release of catecholamines (Howlett, Febbraio & Hargreaves, 1999; Kjaer, Kiens, Hargreaves & Richter, 1991; Mitchell et al., 1998), production is said to increase seven to eightfold in comparison to utilisation which only increases three to fourfold at exercise intensities above 80% $\dot{V}O_{2\,MAX}$ (Marliss & Vranic, 2002; Purdon et al., 1993). Glucose utilisation decreases quicker than glucose production at exhaustion and in non-diabetic individuals is accompanied by a substantial rise in insulin for 40 – 60 minutes to restore euglycaemia. T1DM individuals do not have this insulin response and this absence results in a sustained period of hyperglycaemia (Lumb & Gallen, 2009; Marliss & Vranic, 2002).

The increased intensity of exercise sustained during the performance test also led to an increase in the levels of blood lactate, so much so that at the end of the exercise blood lactate concentrations were at their peak in both conditions (DEX; 13.2 ± 0.7 vs. ISO; 12.6 ± 0.6 mmol·L^{-1}, P = 0.53). Given the further increase in exercise intensity than performed during the submaximal running there was an even greater dependence on anaerobic metabolism to continue to fuel the working muscles during this performance test. As discussed previously in both the rest period (Chapter 5.2) and the submaximal exercise protocol (Chapter 5.3), pyruvate is produced as a result of glycolysis and the fate of some of this pyruvate is the conversion into lactate (Houston, 1995, Figure 5.1). The greater appearance of lactate the bloodstream in both treatments also suggests that the exercising muscles are unable to oxidise the pyruvate generated by glycolysis via the tricarboxylic acid cycle as efficiently at higher intensities (Marliss & Vranic, 2002). Levels of pH are reportedly linearly related to the blood lactate and pyruvate concentration values (Saltin et al., 1975), the decrease in pH after the

performance test reflects the increase in acidity of the blood somewhat suggestive of a higher concentration in circulating H^+ ions in the bloodstream.

The rates of carbohydrate combustion and energy expenditure were both higher in the final three quartiles of the performance test than during any of the increments in the submaximal protocol. The increases in rates of energy expenditure are reflective of the higher effort exerted by the participants in the performance test. As witnessed with the incremental stages in the submaximal protocol, in order to carry out the extra effort required the body needs to meet the energy demands of the working muscles. The increased energy expenditure also resulted in an increased rate of carbohydrate oxidation, at exercise intensities above 80% $\dot{V}O_{2\ MAX}$ fuelling of working muscles is almost entirely dependent on glucose and glycogen with little or no dependence on lipid oxidation (Marliss & Vranic, 2002). One reason for this dependence is that the body cannot oxidise lipids at a quick enough rate to efficiently fuel the muscles (Coyle, 1995) and secondly with a higher level of pyruvate generation from glycolysis, most of the end product is lactate where only a small fraction of ATP is available (Marliss & Vranic, 2002). Fuelling of intense high intensity exercise is derived from intramuscular and liver glycogen stores as well as from circulating glucose (Coyle, 1995; Marliss & Vranic, 2002). With no differences between rates of carbohydrate oxidation or distance covered in total or in each 2.5-minute quartile observed it can be assumed that both treatments are equally effective at fuelling subsequent high intensity exercise. The greater rate of exertion in the performance test is also mirrored in the respiratory variables ($\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2$, RER and HR. Table 4.4).

Electrolyte changes during the high intensity performance running were comparable between treatments ($P > 0.05$). The running assessment resulted in a rapid loss of potassium from the exercising muscles which would have been released into the circulation (Vøllestad et al., 1994) with these circulating levels dropping during the rest period reflective of the immediate uptake by the muscles regulated somewhat by the Na^+ - K^+ pump (Medbø et al., 1990). This regulation in combination with loss through sweat could offer an explanation as to the similar observation in the concentration pattern of sodium ions (Vrijens & Rehrer, 1999). However in contrast to recent literature (Harmer et al., 2006) levels of potassium declined without the administration of insulin at the 15 minute recovery sample point as opposed to remaining elevated. The pre-exercise hyperglycaemic blood glucose levels may have accounted for this

observation in this study as the relationship was reportedly only present in late recovery when the individual was not mildly hyperglycaemic (Harmer et al., 2006). After completion of the performance running, the 15 minute sodium levels were reduced which is consistent with the work of Harmer and colleagues (2006). In regards to calcium, the drop in blood pH observed may inhibit the binding of ions to troponin lessening the contraction force and potentially contribute towards muscular fatigue (Frayn, 1996; Leppik et al., 2004). Inhibition of the binding of these calcium ions offers some explanation to the increased concentrations observed following the performance running.

No research has previously directly investigated the performance responses of T1DM individuals after manipulation of their pre-exercise carbohydrate. In this study there were no observed differences between distances covered in the ten minute time limit (Table 4.3), thus meaning the criteria for null hypothesis iii to be accepted was fulfilled. The short duration of the performance test may have accounted for the comparable distances covered in the treatments, no differences were found previously in a performance test of similar length in which power output was measured (Sparks et al., 1998) with improvements in performance in both time to exhaustion and time trial tests lasting between 98.7 – 108.8 minutes in non-diabetic individuals. Differences in performance bouts of short duration has also been observed (DeMarco et al., 1999) however in this instance the participants were exercising maximally (100% $\dot{V}O_{2\ MAX}$) to exhaustion as opposed to 83 – 85% $\dot{V}O_{2\ PEAK}$ in a time trial protocol in this study. It appears that low GI CHO supplementation is potentially more beneficial to performance in prolonged duration/distance events or for very short maximal intensity activities. However, the important finding in this research is that performance is not compromised by low GI CHO supplementation and lower blood excursions in exercising T1DM individuals. Therefore, T1DM individuals can improve their glycaemic control with the knowledge that their exercise performance would be maintained and the same as if they had consumed a high GI CHO prior to exercising.

5.5 Further observations, recovery, post laboratory period and clinical significance

In general, glycaemia as reflected in IAUC values (Table 4.1) was improved throughout the laboratory period after ingestion of ISO in comparison to DEX with the lesser excursions in

the rest period accounting mainly for this finding. Post-performance recovery blood glucose levels in participants, however, were still high in both conditions (DEX; 14.7 ± 1.9 vs. ISO; 13.7 ± 2.2 $mmol \cdot L^{-1}$) to levels of hyperglycaemia which is a possibility when T1DM individuals engage in exercise at high intensities such as those encountered during the performance test (Mitchell et al., 1988). BG concentrations remained elevated for the 6 hour post-laboratory period (Table 4.7) which could be detrimental to the individual's health if continually or frequently experienced as hyperglycaemia has many associated risk factors (Peirce, 1999). A potential clinical treatment for improving these levels of glycaemia may be the administration of corrective doses of rapid-acting insulin and/or the adoption of lesser reductions in pre-exercise rapid-acting dosage if engaging in high intensity exercise. In regards to corrective insulin administration two individuals reported administrating corrective doses following DEX, thus further suggesting ISO better limited hyperglycaemia. Another important consideration is that both treatments were equally effective at preventing hypoglycaemia with only one individual experiencing symptoms of hypoglycaemia in each of the trials, similar observation were witnessed when comparing these two carbohydrates during and after continuous moderate intensity exercise (West et al., 2011b).

The post laboratory blood glucose responses in this research could also conceivably be compared to those responses witnessed by Bussau and colleagues (2007) as the participants in the final moments of the ten minutes all (without direction) performed a 'sprint finish' in an attempt to maximise their distance covered.

A final small observation is in regards to hydration and the similar range of values observed between treatment in both the sodium which throughout the laboratory period were between the normal range of 135 – 146 $mmol \cdot L^{-1}$ (Figure 4.3) and haematocrit (Figure 4.5) values demonstrate individuals were kept euhydrated and consistent with previous literature (Perrone et al., 2005).

The clinical significance of this study is based around the glycaemia findings as expressed in the blood glucose IAUC values. All of the participants had a lower IAUC value after consumption of ISO, with the main finding indicative of the lower blood glucose excursions witnessed in the rest period. Glycaemic control is of great importance in T1DM and any nutritional interventions that can improve glycaemic responses are of clinical significance. ISO consumption has previously been shown to be as effective at preventing the incidence of

hypoglycaemia as DEX (West et al., 2011b) and this research has now established that exercise performance is also not compromised after ISO consumption. Therefore, ISO could be recommended to those T1DM individuals who wish to improve their glycaemic responses during and after exercise without impacting upon their ability to perform exercise at a high intensity.

5.6 Cognitive function and gut fullness

Resting blood glucose values were 9.1 ± 0.9 and 9.8 ± 1.3 $mmol \cdot L^{-1}$ in DEX and ISO respectively with pre-exercise (DEX; 15.0 ± 1.9, ISO; 14.6 ± 1.5 $mmol \cdot L^{-1}$) and post-exercise (DEX; 14.7 ± 1.9, ISO; 13.7 ± 2.2 $mmol \cdot L^{-1}$) concentrations deemed hyperglycaemic. Cognitive function improved slightly in hyperglycaemia when compared to 'euglycaemia' more evidently in the incongruent ISO scores, more importantly cognitive abilities did not appear to be weakened by hyperglycaemia and function sustained as reported in previous literature (Draelos et al., 1995; Gschwend et al., 1995).

The sustained and slightly improved cognitive functioning may also be due to carbohydrate supplementation especially after ISO supplementation where low GI interventions have witnessed prolonged memory and accuracy answering (Benton et al., 2003; Ingwersen et al., 2007) generally credited with the potentially lower insulin response with low GI foodstuff (Jenkins et al., 1987) and the link between insulin and cognitive function (Benton et al., 2003). The observed decreased times on the Stroop test following exercise is likely due to increased activation of the central nervous system after strenuous exercise (Hogervorst et al., 1996) and may suggest why no conditional differences were found.

Gut fullness and hunger were not different between treatments in the laboratory period at any of the time points, these findings are consistent with Stevenson et al., (2005) where no differences were observed after the breakfast meal. Another potential reason for no treatment differences, even though there are published findings in regards to satiety and weight management after low GI intervention could be the moderately small amounts of carbohydrate provided in each instance (DEX; 41.89 ± 1.15 vs. ISO; 41.82 ± 1.26 g). The reported gut fullness scores (Table 4.6) with no indication of any gastrointestinal discomfort with a similar drink concentration is in agreement with previous literature (Perrone et al., 2005).

Although there were no recorded perceived feelings of satiety, interestingly in the six hour self-reported dietary intake, there was a tendency for less energy intake ($P = 0.17$) and fewer carbohydrates ($P = 0.10$) to be consumed after ISO ingestion. These findings are of important consideration as they are similar to those of long term follow up interventions (Henry et al., 2007) thus suggesting that weight management could be enhanced with low GI supplementation. Improvements in weight management can further benefit insulin sensitivity and glycaemic control as reflected in decreased HbA_{1c} scores (Kaukua, Pekkarinen & Rissanen, 2004).

Although these findings in regards to cognitive function and gut fullness and hunger ratings fulfilled both the null hypotheses iv or v, differences were present in other literature (Benton et al., 2003; Ingwersen et al., 2007; Warren, Henry et al., 2003) in either the assessment of cognitive functioning or perceived feelings of gut fullness and hunger, the methods adopted could be questioned. The gut fullness and hunger scales were only values between 0 – 10, and with a small sample of participants and only a few scores on the scale could have contributed to no differences being located. Increasing the values on the scales from 0 – 20 would double the choices available to the participants and may locate the differences that have been previously documented (Warren, Henry et al., 2003). In regards to the cognitive functioning assessment, the SCWT assessment has been recognised to be an established method. However, in a sporting and exercise context, a more ecological method could have been incorporated into the testing protocol. For example, reaction times are a very simple measurement to record and by testing for reaction times instead of assessing a more thinking cognitive test, the findings could be more applicable in exercise and competition.

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

Limited research is available in regards to exercise performance and choices of carbohydrate supplementation in T1DM.

After ingestion of ISO compared to DEX there is demonstration of improved glycaemia with less blood glucose excursions evident during the 2 hour rest period and throughout the experimental period as demonstrated in IAUC values. Lactate levels were also elevated in ISO during the rest period and there was a concern that these levels could influence subsequent performance. However, once the individuals began to exercise, the levels of lactate were comparable between conditions and exercise performance was not compromised.

Supplementation of either ISO or DEX prior to exercise does not appear to influence substrate utilisation in subsequent submaximal exercise of progressive incremental intensities. This suppression may be influenced by a number of reasons, these include beginning exercising in hyperglycaemia, the availability of carbohydrate and the potential that the cross-over point of substrate utilisation was shifted before the reported 'fatmax' exercise intensity (Achten et al., 2003). Exercising at intensities that predominantly utilise lipid oxidation could be potentially beneficial to T1DM individuals as lesser reliance on carbohydrate oxidation can influence later levels of glycaemia.

Therefore in conclusion, 2-hour pre-exercise supplementation of 0.6 $g \cdot kg^{-1}$ BM of ISO in combination with a 50% reduced dose of rapid-acting insulin improves glycaemia pre-, during and post-exercise with no decline in running performance. ISO supplementation has now been documented to equally protect against incidences of hypoglycaemia (West et al., 2011b) and also limit the level of hyperglycaemia following high intensity running when compared to a high GI CHO. The improved glycaemia, sustained exercise performance and other documented benefits of incorporating low GI CHO in the daily diets of T1DM individuals (Brand-Miller et al., 2003; Gilbertson et al., 2001; Nansel et al., 2008) are all important observations in this study.

6.2 Limitations and recommendations for future research

6.2.1 Limitations

This present study only intended to give a simplistic insight in the metabolic responses during exercise with more emphasis on the performance responses, repeating this study with the additional analysis of hormones (insulin, catecholamines etc.) could provide a more definitive answer to the glycaemic responses witnessed in the exercise protocols, especially in the post-performance setting. The main limitations of this study are listed below:

a) This study only had a small population cohort (n = 7), the recruitment of further individuals may have highlighted some subtle differences that require more statistical power to be generated. On the recommendations of Rabasa – Lhoret et al., (2001) and West et al., (2010) a cohort of around 33 would generate 80% statistical power.

b) The reliance on participants to self-report post laboratory blood glucose concentrations and dietary intake was a limitation in this research as some participants either did not return or fully complete the recording sheets. For this reason the potential for findings (if any) in the post laboratory/exercise period could have been lessened.

c) As no differences were found between the gut fullness scores or the cognitive functioning assessments even though previous research had shown there to be differences when low GI foodstuff had been provided. This may be a limitation of the methods adopted in assessing both perceived hunger and fullness rating and cognitive functioning.

6.2.2 Recommendations

a) Adopting a longer observational period following the performance testing would allow for a range of post-exercise insulin strategies to be adopted. Administration of insulin units following high intensity exercise would mimic the response in non T1DM individuals however it would be of importance to investigate the optimum dose to administer.

b) In a recent review article, O'Reilly et al., (2010) suggested that glycaemic load (GL; GL = GI x amount of carbohydrate available (g)) would be a much better predictor of glycaemic responses than CHO amount/percentage or GI alone. The article also commented that the effect of the GI and GL on exercise performance is an issue that should be investigated further in an attempt to develop more comprehensive guidelines on the topic that could be developed in the future. Both GI and GL have their practical origins in a more clinical setting. Few studies have investigated the importance of the glycaemic load in regulating blood glucose responses during subsequent exercise. An experiment conducted by Chen et al., (2008) investigated the impact of three meals with varying GLs and GIs on metabolic responses during and after exercise. No differences were found between the low GL meals (Low GI – Low GL and High GI – Low GL), although both had findings that were significantly different to that of the High GL meal. Thus suggesting that the GL has an important role is determining subsequent metabolic responses. With the suggestion that GL has importance in a clinical setting, supplementation of a high GI carbohydrate matched for GL with a low GI carbohydrate ingested pre-exercise in T1DM warrants investigation. Potentially findings especially in reference to the glycaemic responses before, during and after exercise would certainly be of some interest.

c) In T1DM glycogen utilisation during exercise is more important than plasma glucose oxidation. In regards to this it may be beneficial to investigate the optimum osmolality that promotes better gastric emptying and quicker liver and muscle glycogen storage.

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