Blood Glucose Responses to Intermittent High Intensity Exercise in Individuals with Type 1 Diabetes: A Trial of a Structured Intervention for Insulin and Carbohydrate Adjustment

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Abstract

Exercise is currently recommended for indivduals with type 1 diabetes since it is associated with physiological and psychological benefits (American Diabetes Association Position Statement, 2004; American College of Sports Medicine, 2010). However participation in exercise can increase the risk of experiencing hypoglyceamia, both during exercise and recovery (Rabasa-Lhoret *et al.*, 2001). Through discussions with practitioners that work with individuals that have type 1 diabetes, the development of clear evidence -based guidelines regarding adjustments in insulin doses and carbohydrate intake may help prevent the risk of exercise induced hypoglyceamia. Specifically, there are limited evidence based guidelines for participation in intermittent high intensity exercise (IHE), which represents activity patterns of team and field based sports. Consequently, the aim of this thesis is to investigate the effects of a structured intervention for insulin and carbohydrate adjustment on blood glucose responses during and after IHE that replicates team and field based sports in individuals with type 1 diabetes.

Seven well-controlled participants with type 1 diabetes were tested on three separate occasions and interstitial glucose concentration was measured up to breakfast the following day on each occasion using a Continuous Glucose Monitor (CGM). The first phase of this study compared a 30% post-exercise fast-acting analogue insulin reduction on the blood glucose responses to an afternoon bout of IHE (40 minutes of cycles of walking for 5 minutes at 40% \dot{VO}_2 max, jogging for 3 minutes at 70% \dot{VO}_2 max and sprinting for 5 seconds at 125% \dot{VO}_2 max) vs. continuous moderate intensity exercise (40 minutes at 50% \dot{VO}_2 max). Results showed there was no significant difference between the CGM readings for moderate or IHE (p= 0.59) at any point during the 40 minute exercise protocols and up to breakfast the following day. There was a significant change in interstitial blood glucose concentration over time regardless of exercise condition (p< 0.001). Regardless of exercise condition both moderate and IHE

is characterised by the risk of Late Onset Post-Exercise Hypoglycaemia (LOPEH). In addition there appears to be a problem of hyperglycaemia, particularly two-four hours after the meal and insulin reduction.

The second phase of the study compared the blood glucose responses to a 30% vs. a 50% post-exercise fast-acting analogue insulin reduction after a bout of afternoon IHE in individuals with type 1 diabetes. There was no significant difference in interstitial blood glucose responses as measured by CGM between the two insulin reductions and 50% insulin reduction is no better for the prevention of LOPEH than the 30% reduction after IHE (p=0.06). Blood glucose responses were similar for the same IHE on two separate occasions and there was a significant decrease in in interstitial blood glucose concentration as measured by CGM from 0-40 minutes of exercise (p=0.002). As observed in phase 1, the problem of hyperglycaemia was also evident.

In conclusion, there are two main high-risk periods for the development of hypoglycaemia associated with IHE. The first is immediately after exercise and the second later on during the night. In addition hyperglycaemia seems to be a problem for up to four hours following the evening meal after exercise. It is important to make patients aware of this, in order to prevent the long term complications associated with such. Regardless, individuals vary in their responses to exercise and individual strategies to combat hypoglycaemia may be required. A number of limitations are acknowledged within this study, however is they were eradicated, future research of this kind could have implications for the development of guidelines for the management of blood glucose concentration during and after IHE.

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List of Abbreviations

- ACSM: American College of Sports Medicine
- ADA: American Diabetes Association
- ANOVA: Analysis of Variance

ATP: Adenosine Triphosphate

Bg: Blood Glucose

BMI: Body Mass Index

BNI: British Nursing Index

BP: Blood Pressure

CGM: Continuous Blood Glucose Monitor

CHO: carbohydrate

CINAHL: Cumulative Index of Nursing and Allied Health Literature

CO₂: carbon dioxide

CP: Creatine Phosphate

CPX: Cardiopulmonary Exercise Testing

ECG: Electrocardiography

Ex: Exercise

g : grams

h: hours

HbA_{1c}: Glycosylated Haemoglobin

HR: Heart Rate

HRmax: Maximal Heart Rate

IHE: Intermittent High Intensity Exercise

kg/m²: kilograms per square meter

LOPEH: late onset post exercise hypoglycaemia

LSD: Least Square Difference

m/min⁻¹: meters per minute

MEDLINE: Medical Literature Analysis and Retrieval System Online

mins: minutes

ml.kg⁻¹.min⁻¹ : rate of oxygen per kilogram of body weight per minute

mm/Hg: millimetres of mercury

mmol.l⁻¹ : milli-moles per litre

Mod: Moderate

NHS: National Health Service

NICE: National Institute of Clinical Excellence

O₂: oxygen

PASW: Predictive Analytics Software

Ra: Rate of Appearance

RCTs: Randomised Control Trials

Rd: Rate of Disappearance

RPE: Rate of Perceived Exertion

s: seconds

SBGM: Self Blood Glucose Monitoring

SIGN: Scottish Intercollegiate Guidelines Network

T1D: Type 1 Diabetes

 $\dot{V}O_2$: oxygen consumption

 $\dot{V}O_{2 max}$: maximal oxygen consumption

 $\dot{V}O_{2 peak}$: peak oxygen consumption

VT: Ventilatory Threshold

WR_{peak}: peak work rate

 ${\eta_p}^2$: Partial eta-squared

% : percentage

 \uparrow : Increase

 \downarrow : Decrease

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Chapter 1 Introduction

It is important for those with type 1 diabetes, especially young children and adults, to live a life as close to normal as possible (American Diabetes Association (ADA), 2004). This includes being physically active and having the option to participate in a range of sports and recreational activities. Many individuals have been encouraged by examples of world class sportsmen with type 1 diabetes such as Sir Steve Redgrave and Gary Hall (Gallen, 2005).

Physical activity is an important part of a healthy lifestyle. Most recent government recommendations state that adults should accumulate at least 30 minutes of moderate intensity exercise at least five times a week (Department of Health, 2011). The prescription of exercise for individuals with type 1 diabetes should be considered for its known benefits in controlling serum lipids, reducing blood pressure, improving insulin sensitivity, reducing weight and improving cardiovascular fitness (ADA Position Statement, 2004; American College of Sports Medicine (ASCM), 2010). All of these benefits are likely to be significant for individuals with type 1 diabetes due to the increased risk of macro vascular disease within this population. The ADA (2004) advocates that:

"all levels of physical activity including leisure activities, recreational sports and competitive professional performance can be performed by those with type 1 diabetes who do not have complications and are in a state of good blood glucose control" (S61).

One of the most popular forms of exercise, yet probably the most under-researched with respect to its responses in individuals with type 1 diabetes is known as Intermittent High Intensity Exercise (IHE). This type of exercise is typical of many team and field-based sports such as hockey, basketball, football, rugby (Abdelkrim *et al.*, 2007; Bloomfiled *et*

al., 2007; Lothian and Farrally, 1994; Spencer, 2005; Bailey *et al.*, 1995), training regimes such as Fartlek or interval training, many gym classes and also spontaneous play in children. IHE also accounts for much of the selection of sports played by children and adolescents (Raile *et al.*, 1999). The desire to participate in a team sport and become a team member is very often driven by social reasons and the need for those with type 1 diabetes to not appear different from their peers (Grimm, 2005).

Unfortunately regular exercise for those individuals with type 1 diabetes does not necessarily lead to improved glycaemic control. Through discussions with colleagues and health care professionals in the area of diabetes, the most important issue in those individuals with type 1 diabetes is understanding the impact that exercise has on blood glucose concentrations and developing knowledge and skills to avoid hypoglycaemia and hyperglycaemia. Therefore, those individuals with type 1 diabetes need to learn how to change their insulin administration and carbohydrate intake prior to, during and after exercise. Research, however, would suggest that this is not any easy task since several factors such as duration and intensity of exercise; type and timing of insulin; site of injection and carbohydrate intake, can all influence the blood glucose response to exercise in individuals with type 1 diabetes (Toni *et al.*, 2006). All of the challenges of managing blood glucose concentrations whilst exercising contributes to the fact that less than 40% of people with diabetes are estimated to be physically active (Thomas *et al.*, 2004).

It is apparent that there is a great need for the development of practical guidelines for controlling blood glucose concentrations in those with diabetes when undertaking exercise. In particular there appears to be a need for information on IHE since it has been reported that individuals with type 1 diabetes may avoid team sports to prevent upsetting their peers in case of the possibility of a hypoglycaemic event or the inconvenience of regular blood glucose checks or carbohydrate snacking (Grimm, 2005). This study therefore came about from recognising the evidence gap and the dissatisfaction expressed by health care professionals about the inability to offer reliable advice in this area. As a result, the primary goal of this research is to investigate the effects of an intervention for insulin and carbohydrate adjustment on blood glucose responses during and after IHE. This should provide valuable information for health

care professionals who work with individuals with type 1 diabetes on how IHE may impact their condition and provide them with an understanding of the potential effect this type of training can have on blood glucose concentrations and the best ways to manage this.

This chapter will outline the background in relation to type 1 diabetes and exercise, including demonstrating the need for a greater understanding of the management strategies required for individuals with type 1 diabetes to take part in IHE. The focus of the research is identified and justified and the overall research aims and individual research objectives are identified.

1.1 Type 1 Diabetes

Type 1 diabetes, known as insulin dependent diabetes mellitus accounts for 10-15% of all cases of diabetes and affects around 16 million individuals worldwide (Guelfi *et al.*, 2007b). In 2010 Diabetes UK indicated that there were 27, 367 patients with type 1 diabetes in Scotland. This contributes to Scotland having the third highest incidence rate of type 1 diabetes in the world, behind Finland and Sardinia (The Scottish Government, 2010). Type 1 diabetes can develop at any age however it accounts for over 90% of diabetes in those aged 25 and under in Scotland (SIGN, 2010).

Type 1 diabetes is an autoimmune disease that results from beta-cell destruction of the pancreas, resulting in an inability to produce insulin, a key hormone in the regulation of blood glucose (Grimm, 2005). In non-diabetic individuals the level of circulating insulin is directly controlled by the concentration of glucose in the blood that passes through the beta cells of the pancreas (Henquin, 2000). As the concentration of glucose in the blood rises so do insulin levels, thus lowering the blood glucose concentration. In reverse, a decrease in blood glucose concentration inhibits the secretion of insulin. In

this manner insulin increases or decreases the production and utilisation of glucose as necessary in order to maintain euglycaemia.¹

In contrast, in the absence of circulating insulin, those with type 1 diabetes will experience a build-up of glucose in the bloodstream. This is as a result of lack of both inhibition of hepatic glucose production and stimulation of peripheral glucose uptake (Rizza *et al.*, 1981). Further increases in blood glucose occur in the presence of high levels of counterregulatory hormones including glucagon, growth hormone, cortisol, norepinephrine and epinephrine which all oppose the action of insulin (Pierce, 1999). High levels of counterregulatory hormones combined with insulin deficiency exaggerate the increase in blood glucose concentration (Pierce, 1999; Riddell and Perkins, 2006; Toni *et al.*, 2006).

Individuals with type 1 diabetes face the daily challenge of maintaining their blood glucose within the normal physiological range (4-8 mmol.1⁻¹) through self-administration of exogenous insulin, regular glucose monitoring and careful control of their diet (Guelfi *et al.*, 2007b). Maintaining blood glucose within the normal physiological range is not an easy task for individuals with type 1 diabetes, with consequent problems of excessive or insufficient insulin administration. Too much insulin in relation to carbohydrate intake can cause blood glucose concentration to decline below 4 mmol.1⁻¹ and result in symptoms of hypoglycaemia. These symptoms can be mild, such as loss of coordination, mental confusion, sweating, tremors and hunger, and can be easily recognised by the patient and reversed with a small amount of carbohydrate. It may, however, be severe enough to cause unconsciousness requiring an injection of glucagon. In rare circumstances it may cause brain damage or even death (Cryer, 2003). According to the Diabetes Control and Complications Trial (1993) hypoglycaemia is the most frequent, acute and adverse complication of type 1 diabetes.

While too much insulin in relation to carbohydrate intake can cause hypoglycaemia, a

¹ Key Definition: Euglycaemia is the normal concentration of blood glucose in the blood (4-8mmol.l⁻¹).

relative deficiency in insulin dosage in relation to carbohydrate intake can result in hyperglycaemia (blood glucose > 10 mmol.1⁻¹). Whilst these conditions may reduce the risk of hypoglycaemia, hyperglycaemia can lead to thirst, fatigue, blurred vision, drowsiness, abdominal pain and nausea (Farrell, 2003). Perhaps of more importance, chronic hyperglycaemia over several years can lead to disturbances in metabolism and long term organ damage such as diabetic retinopathy, neuropathy and cardiovascular disease (Pierce, 1999).

1.2 Exercise and the Risk of Hypoglycaemia in Individuals with Type 1 Diabetes

Although all the aforementioned long-term benefits of exercise for individuals with type 1 diabetes are well known, perhaps of more importance to those with type 1 diabetes is the acute metabolic costs of taking part in exercise. The most frequent and dangerous consequence of exercise in individuals with type 1 diabetes is hypoglycaemia during and up to 12-31 hours after exercise (Rabasa-Lhoret*et al.*, 2001). Hypoglycaemic symptoms during exercise are also often difficult to detect as many of the symptoms are common to the exercising individual such as sweating and tachycardia (Grimm, 2005). As a result of the risk of exercise-induced hypoglycaemia, health care professionals have attempted to offer advice to prevent blood glucose concentrations falling too low during and up to 31 hours after exercise. This would seem important since it has been reported that the biggest barrier to participating in regular exercise in adults with type 1 diabetes is the fear of hypoglycaemia (Brazeau *et al.*, 2008).

Although exercise-induced hypoglycaemia is a legitimate fear, the ADA (2003) state that it is possible to safely enjoy the benefits of exercise by balancing exogenous insulin administration and carbohydrate intake. However, effective adjustment of these parameters would require an understanding of the metabolic and hormonal responses to exercise. Several factors such as duration and intensity of exercise, type and timing of insulin, site of injection and carbohydrate intake, can all influence the blood glucose response to exercise in individuals with type 1 diabetes (Toni *et al.*, 2006). Consequently much research has focused on examining the glucoregulatory responses

to different types of exercise in order to develop evidence based guidelines for adjusting carbohydrate intake and insulin doses for safe participation in physical activity.

1.2.1 Moderate Intensity Exercise

Moderate intensity exercise involves continuous aerobic activity between 40-59% $\dot{V}O_2$ max² or 55-69% of maximum heart rate (HR) (ADA Position Statement, 2004). Examples of this type of exercise are continuous aerobic activities such as cycling, swimming and jogging. It is well established that participation in moderate intensity exercise typically lowers the blood glucose concentration and increases the risk of hypoglycaemia during exercise and recovery (Francescato et al., 2004). The natural decline of serum insulin that occurs during moderate intensity exercise in a healthy individual cannot occur in individuals with type 1 diabetes. In contrast, insulin concentrations could rise if the injected insulin has been administered into exercising muscle (Pierce, 1999). As a result hepatic glucose production does not increase adequately to cope with fuel requirements, provoking hypoglycaemia to occur. Furthermore there is a relatively higher insulin concentration in the periphery during exercise which promotes peripheral muscle glucose uptake, and this again predisposes the individual to hypoglycaemia (Lumb and Gallen, 2009a). Evidence suggests that the risk of hypoglycaemia during moderate intensity activities can be minimised by appropriately reducing the pre-exercise bolus insulin dose and/or ingesting additional carbohydrates (West et al., 2010; Lumb and Gallen, 2009a&b; Perry and Gallen, 2009; Robertson et al., 2008; Kordi and Rabbani, 2007; Riddell and Perkins, 2006; Toni et al., 2006; Grimm et al., 2004; Rabasa-Lhoret et al., 2001; Pierce, 1999). The risk of hypoglycaemia can extend for up to 31 hours after exercise (MacDonald, 1987). This is as a result of increased insulin sensitivity and an increase glucose uptake for replenishment of muscle and liver glycogen stores. Hypoglycaemia that occurs more than four hours after exercise has been classed as late-onset post-exercise hypoglycaemia (LOPEH). This can be a considerable issue as LOPEH is often associated with sleep, meaning that the hypoglycaemic episode is less likely to be recognised. Strategies to combat LOPEH include reducing insulin dosage prior to

² Key Definition: VO_2 max is the maximum rate an individual can take up and utilise oxygen during incremental exercise and reflects the physical fitness of an individual.

bedtime following late afternoon exercise and/or increasing carbohydrate intake (MacDonald, 1987).

1.2.2 High Intensity Exercise

High intensity exercise is classified as activity at or above 80% \dot{VO}_2 max or 75% of HR maximum or above (Grimm, 2005). This type of exercise includes sprint activities and can-not be maintained for a long period of time since it relies predominately on anaerobic metabolism. During high intensity exercise in individuals with type 1 diabetes there is a progressive rise in blood glucose concentration due to an exercise-induced increase in hepatic glucose production that exceeds glucose uptake. This has been attributed to the rise in catecholamines in response to exercise (Riddell and Perkins, 2006). During recovery there is an absence in endogenous insulin secretion in response to high concentrations of blood glucose, resulting in prolonged hyperglycaemia. It is therefore recommended that a smaller additional dose of insulin is encouraged if hyperglycaemia is a frequent problem after high intensity exercise (Marliss, 2002).

1.2.3 Intermittent High Intensity Exercise

Although the responses to moderate and high intensity exercise are well established, the response to a combination of these two types of exercise, a form of physical activity known as intermittent high intensity exercise (IHE) has received little attention in the literature. In the current research IHE will be defined as exercise that involves short repeated bouts of intense activity, interspersed with longer periods of moderate intensity activity or rest (Guelfi *et al.*, 2005a). The high intensity periods of exercise associated with IHE in field and team-based sports last between 2-3 seconds in duration and require considerable amounts of energy via anaerobic sources such as Adenosine Triphosphate (ATP), Creatine Phospahte (CP) and muscle glycogen stores (Spencer *et al.*, 2005). The lower intensity periods of exercise in IHE offer a period of recovery for resynthesis of ATP, CP and glycogen stores and removal of lactate. During IHE in

individuals with type 1 diabetes it has been reported that glucose concentrations fall less rapidly during exercise than with moderate intensity exercise and also remain stable during the hour after exercise, even when the total amount of work done in IHE is greater (Guelfi *et al.*, 2005b).

1.3 Research Focus

The lack of research into the blood glucose responses to IHE is reflected in existing guidelines which do not distinguish between continuous and intermittent exercise. At present recommendations are not evidence-based and advice suggests similar management strategies for blood glucose concentrations during and after IHE as for moderate or high intensity exercise alone (Birrer and Sedaghat, 2003; Grimm *et al.*, 2004; Pierce, 1999). Often guidelines suggest the importance of patients monitoring their own blood glucose response to exercise and using this to improve glycaemic control the next time the same exercise is performed (ADA Position Statement, 2004). It has further been suggested that the management of blood glucose concentrations is more difficult during IHE in comparison to continuous moderate or high intensity activities alone (Guelfi *et al.*, 2007). It is therefore important to appreciate that there may be differences in the metabolic responses to IHE compared with other forms of exercise and as a result different management strategies may be required for individuals with type 1 diabetes.

Despite recent studies attempting to address the glucoregulatory responses to IHE in type 1 diabetes (Iscoe and Riddell, 2011; Maran *et al.*, 2010; Guelfi *et al.*, 2005a; Guelfi *et al.*, 2005b), there are still no evidence-based recommendations for insulin and carbohydrate adjustments during this form of exercise for individuals with type 1 diabetes. It may be advantageous for health care professionals and those that work with individuals with type 1 diabetes to have information on how IHE may impact their condition and have an understanding of the potential effect this type of training can have on their blood glucose and the best ways to manage this.

1.4 Aims and Research Objectives

The overall aim of this research is to investigate the effects of a structured intervention for insulin and carbohydrate adjustment on blood glucose responses during and after IHE that replicates team and field based sports in individuals with type 1 diabetes. This should further add to current research on IHE and will contribute to the body of evidence required to develop appropriate insulin dose and carbohydrate supplementation for those with type 1 diabetes, to allow for safe participation in intermittent activities.

Specifically the individual research objectives are to:

- 1. Identify and critically appraise current evidence detailing the impact of IHE on blood glucose concentrations in individuals with type 1 diabetes.
- 2. Compare the effects of a 30% post-exercise fast acting analogue insulin reduction on the blood glucose responses to a bout of IHE vs. continuous moderate intensity exercise in individuals with type 1 diabetes.
- 3. Compare the blood glucose responses to a 30% vs. a 50% post-exercise fast acting analogue insulin reduction after a bout of IHE in individuals with type 1 diabetes.

Objective one will be met by the means of a literature review, objectives two and three through empirical data collection and analysis.

1.5 Structure of Thesis

This thesis is organised as a series of chapters:

Chapter 1: Introduction

This chapter has provided a background on exercise and type 1 diabetes, including illustrating the importance of the understanding of blood glucose control during and after exercise. The focus of the research is identified and the aims and research objectives are highlighted.

Chapter 2: Intermittent High Intensity Exercise and Type 1 Diabetes: A Review of the Literature Carried out in a Systematic Way.

This chapter critically appraises the current evidence base on IHE and exercise in type 1 diabetes. Current guidelines for the management of type 1 diabetes in relation to IHE are also reviewed.

Chapter 3A: Development of the Intervention and the Intermittent High Intensity Exercise Protocol

This chapter discusses and describes the intervention for insulin and carbohydrate adjustment and also the IHE protocol that was designed for use within this study.

Chapter 3B: Methodology

This chapter provides details and justification of the research methods used for empirical data collection in this study. Details of the sample selection, data collection and data analysis methods are also outlined.

Chapter 4: Results

This chapter describes the outcomes of the empirical data collection and provides a description of the results concentrated around research objectives two and three.

Chapter 5: Discussion

This chapter describes, discusses, analyses and synthesises the empirical findings concentrated around research objectives two and three. Results are also compared and contrasted with findings from the literature review in Chapter 2.

Chapter 6: Conclusions

This chapter will revisit the overall aim and specific research objectives of this study. The findings are summarised and conclusions from this research are derived. Limitations of this research are also highlighted, along with directions for future research.

The following chapter - *Intermittent high intensity exercise and type 1 diabetes: A review of the literature carried out in a systematic way* - examines the literature in relation to IHE and type 1 diabetes.

Chapter 2

Intermittent High Intensity Exercise and Type 1 Diabetes: A Review of the Literature

As discussed previously it is important for individuals with type 1 diabetes to be physically active and participate in a range of sports and recreational activities. It is well established within the research that continuous moderate and high-intensity exercise have a contrasting effect on blood glucose concentrations and risk of hypoglycaemia, therefore they require different management strategies to maintain euglycaemia. What remains unclear is the responses to a form of activity known as IHE. Given that there is an increased demand for evidence-based guidance on the management of type 1 diabetes for IHE, this chapter will review the literature on IHE and type 1 diabetes in a systematic way. The focus of this literature review will be based upon the overall study aim detailed in the introductory chapter. This overall aim of this research is to :

"investigate the effectiveness of a structured intervention for insulin and carbohydrate adjustment on blood glucose responses during and after Intermittent High Intensity Exercise (IHE) that replicates team and field based sports in individuals with type 1 diabetes."

Therefore the aim of this literature review is to identify and critically appraise current evidence detailing the impact of IHE on blood glucose in type 1 diabetes, thus addressing objective 1 outlined in sub-section 1.3 in Chapter 1. In addition any current guidelines for managing insulin adjustment and carbohydrate intake for participation in IHE for those with type 1 diabetes will also be reviewed.

2.1 Methods

A systematic approach was undertaken in order to identify relevant literature and to assess the quality of each research article. In contrast to narrative reviews which are often very subjective, have no defined method and are therefore very difficult to replicate (Hek and Langton, 2000), systematic reviews use explicit rigorous methods for searching, critiquing and synthesising the literature (Averyard, 2010). The rationale for the use of a systematic approach to searching for and reviewing the literature was the need to identify empirical findings, appraise all quality research and identify any gaps in the literature regarding blood glucose responses to IHE in type 1 diabetes. A systematic approach also means that the review process is replicable, updateable and should limit bias (Mulrow, 1994). This should allow accurate conclusions to be drawn about the direction of the evidence regarding IHE in type 1 diabetes. This literature review was conducted following general principles from the SIGN (2001) and the Cochrane Collaboration (2006). A systematic approach was taken at each stage in the literature review process: searching the literature based on key words, identifying literature, implementing the inclusion/exclusion criteria on the literature, critiquing and synthesising the literature.

2.1.1 Search Strategy

The following data-bases were used for the search: MEDLINE, BNI, SPORTDiscus, CINAHL and The Cochrane Library (1980-2011). Key words were identified as *Type 1 Diabetes, Blood Glucose, Intermittent Exercise/Intermittent High Intensity Exercise/Team Sports, Insulin Adjustment* and *Carbohydrate Administration*. The search strategy included Medical Subject Headings (MeSH) and terms were truncated with (*) to allow for multiple spellings, endings and common words related to the key terms. In addition the BOOLEAN operators AND and OR were used. The search terms *insulin adjustment, carbohydrate administration* and *self-management* did not find any publications. It was therefore thought that under the term Type 1 Diabetes more related articles would be found. The search strategy employed in the databases relating to this

review is highlighted in Figure 2.1. Individual search information for each database can be found in Appendix 1. The last search was carried out on 28/06/2012.

In addition a hand search of the reference lists of relevant literature was conducted to identify all eligible reports or trials not included in the electronic search. A search of grey literature, Google Scholar, SIGN:http://www.sign.ac.uk, NICE: http://www.nice.org.uk/Guidance/Topic, National Library of Guidelines: http://www.library.nhs.uk/guidelinesFinder/ and Edinburgh Napier University Library Catalogue was also undertaken (1980-2012). A further three articles were found that did not appear in the database search that were deemed relevant.

Initially articles deemed appropriate were identified through examination of abstracts. After the initial literature search it became apparent that due to the lack of randomised control trials (RCTs) assessing the research question any published literature that was relevant would be considered. Foreign articles were not included. It became evident that there was no published literature that specifically addressed or tested any insulin and carbohydrate adjustment for individuals with type 1 diabetes wishing to take part in IHE. Several studies were found within the literature search that made reference to IHE and provided some guidance on this issue. A summary of the advice given within these studies will be included within this review.

2.1.2 Inclusion/Exclusion Criteria for Randomised Control Trials

The following inclusion criteria was applied for any RCT's that were to be included in this review: (1) published in the English language, (2) participants must be adult humans over the age of 18, (3) participants must have Type 1 Diabetes, (4) IHE must be used as the primary intervention, (5) the target clinical outcome must be blood glucose, (6) literature from 1980 onwards. A broad time frame has been selected since it became apparent that there was a relatively small amount of literature available.

2.1.3 Statistics

A meta-analysis has not been conducted mainly due to the heterogeneity of the studies, particularly regarding the methodological differences in exercise protocols and work to recovery ratios used within the RCTs.



Figure 2.1. Search Procedure and Results from the Databases.

2.2 Results

The literature search highlighted a total of 45 articles. These articles were initially screened for suitability of inclusion. Of these 45 articles 32 were excluded since they did not meet the specified inclusion criteria. Some of the studies were conducted in children under the age of 18, one study was a training study and blood glucose was not a clinical outcome, participants from another study were individuals with type 2 diabetes and another study was a Cochrane review in pregnant women with Type 1 Diabetes. Of the 13 studies that were included seven were review articles and six were RCTs. Sample size in the studies range from six-11 participants. Table 2.1 displays a summary of the included RCT studies that address the research aim. Table 2.2 outlines the review articles from the literature search that mentioned IHE and summarises the advice given to individuals with type 1 diabetes.

Author	Participants	Methods	IHE Protocol	Adjustments to Insulin and CHO Advice	Blood Glucose Outcome Measures	Results	Key Messages
Iscoe and Riddell (2011)	11 trained athletes T1D (6 female, 5 male), age 35.1 ± 3.5 years (6 subjects on a pump)	45 mins cycling MOD (55% WRpeak) v IHE	45 mins cycling @ 50% WRpeak with 9 15s sprints 5 mins apart at 100% WRpeak	Standard meal given prior to exercise and 30g CHO given at bedtime following exercise	Capillary glucose taken during exercise. CGM worn 72h before and up to 16h after exercise.	No difference in BG between trials. IHE is associated with less post exercise hypoglyceamia and more post exercise hyperglycemia (p<0.05)	Moderate exercise combined with IHE protects against nocturnal hypoglycaemia compared to moderate exercise alone
Maran <i>et al</i> (2010)	8 Male T1D, Physically Active, Age 34 ± 7 years	30 mins cycling MOD (40% $\dot{V}O_{2}$ max) v IHE	30 mins Cycling @ 40% $\dot{V}O$ _max interspersed with 5s sprints @ 85% $\dot{V}O$ _max every 2 mins	Reduce evening dose of fast acting insulin by 20% at following evening meal	Blood sampled during ex @ 15, 30 mins and up to 150 mins after ex. CGM worn for up to 20h after exercise	BG↓ during both ex protocols. 150 mins after ex plasma BG higher in IHE (not significant). Number of hypos after IHE greater than MOD (p< 0.05).	IHE is associated with nocturnal hypoglycaemia compared to MOD ex. CGMs is a useful approach for those with T1D who exercise.

Table 2.1. Summary of Randomised Control Trials Included in the Review.

Guelfi et al (2007a)	9 (5 male, 4 female) T1D Physically Active, Age 22.6 ± 5.7 years	30 mins cycling MOD (40% \dot{VO}_2 peak) v IHE All done under euglycemic clamp conditions with infusion of glucose	30 mins cycling @ 40% \dot{VO}_{2} peak interspersed with 4s sprints every 2 minutes.	Insulin Infusion	Blood sampled every 5 mins during ex and for up to 2h after recovery	During IHE glucose Ra increased earlier and glucose Rd increased sooner compared to MOD. Lower glucose infusion rate during early recovery in IHE (p< 0.05).	Lesser decline in glycaemia with IHE due to greater increase in glucose Ra during exercise and attenuated Rd during exercise and early recovery.
Guelfi <i>et al</i> (2005a)	8 T1D, Age 18.6 ± 2.1 years	IHE (cycling) v Control (seated with no exercise for 20 mins)	Cycling for 20 mins with eleven 4s sprints repeated every 2 mins	Participants instructed to use usual insulin regime	Capillary and venous blood sampled during exercise and for 1h after	During first 15 mins ex BG \downarrow in IHE compared to Control (p< 0.05). During recovery BG was stable in IHE but \downarrow in Control (p< 0.05).	IHE does not increase the risk of early post exercise hypoglycaemia in those with T1D.
Guelfi <i>et al</i> (2005b)	7 (4 male, 3 female) T1D, Age 21.6 ± 4.0 years	30 mins cycling MOD (40% VO ₂ peak) v IHE	Cycling @ 40% VO ₂ peak with 4s sprints every 2 mins	No adjustments to participants usual insulin and CHO doses were applied	Capillary blood was sampled every 10 mins during exercise and every 15 mins after up to 1h after exercise	Both protocols resulted in a \downarrow of BG, decline was greater in MOD (p< 0.05). During recovery BG remained higher in IHE but continued to \downarrow in MOD (p< 0.05).	The decline in BG is less with IHE than MOD during exercise and recovery in those with T1D.

Ford <i>et</i> <i>al</i> (1999)	6 (2 males, 4 females), Age 19-52 years, Physically Active	30 mins treadmill running at 40% \dot{VO}_2 max v four 2 min walk or runs at velocity at VT, with 2 min walks @ 80m.min ⁻¹	Treadmill: Six 20s sprints at 120% \dot{VO}_{2} max with 2 min walk recovery at 54 m.min ⁻¹	Participants told to manipulate insulin dose prior to own exercise	Capillary BG assessed pre and post ex (immediate and 20 mins following	IHE produces a significantly higher BG than walking (p< 0.01) and VT (p< 0.05). BG values across time did not significantly change during any ex protocol	IHE at 120% \dot{VO}_{2} max tends to moderately \uparrow BG in those with T1D.
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(BG: Blood Glucose, T1D: Type 1 Diabetes, Ex: Exercise, RCT: Randomised Control Trial, MOD: Moderate Exercise, IHE: Intermittent High Intensity Exercise, Mins: Minutes, s: seconds, Rd: Rate of Disappearance, Ra: Rate of Appearance, \downarrow : Decrease, \uparrow : Increase, VT: Ventilatory Threshold, CHO: Carbohydrate).

Table 2.2. Current Guidelines for Managing Intermittent High Intensity Exercise for Individuals with Type 1 Diabetes.

Author	Type of Exercise	Advice for Insulin and Carbohydrate Adjustment	Tested in Practice/Evidence Based Practice
Lumb and Gallen (2009)	IHE eg. Football	Basal dose adjustments may be required.	No
Perry and Gallen (2009)	IHE	Smaller reductions in insulin dose and CHO supplementation than MOD intensity exercise to prevent hypoglycaemia	No
Guelfi <i>et al</i> (2007b)	IHE: team sports	None given as states not enough information on the glucoregulatory responses to this type of exercise	No
Toni <i>et al</i> (2006)	IHE: Team Sports	Reduce pre-meal insulin by 70-90%. May not be necessary to reduce pre-meal insulin if game is < 60 mins. Reduce overnight basal insulin by 10- 30%.	No
Grimm <i>et al</i> (2004)	Cycling, jogging, tennis, football, basketball (20-60 mins)	<60% max HR: 15g CHO; 60-70% max HR: 30g CHO; >75% max HR 75g CHO, insulin dosage ↓ 0- 20%	Yes
Birrer and Sedaghat (2003)	"vigorous competitive activities": swimming, cycling, basketball, soccer	25% reduction in insulin dose and 15- 30g of rapid absorbing CHO prior to and at 30 minute intervals if exercise duration is < 1h.	No
Pierce (1999)	Rugby, football, hockey, marathons, triathlons	70-90% reduction in insulin dose before exercise	No

(CHO: Carbohydrate, MOD: Moderate Intensity Exercise, IHE: Intermittent High Intensity Exercise, max HR: Maximum Heart Rate, \downarrow : Decrease).

2.3 Discussion

Despite the glucoregulatory responses to moderate and high intensity exercise being well established within the literature, the glucoregulatory responses to IHE has received very little research attention in the past and no direct guidelines are available for insulin and carbohydrate adjustment prior to or after this form of exercise. The lack of research in this area is limiting since IHE is typical of activity patterns in many team and field sports such as rugby, hockey and football and is also typical of many forms of interval training. This literature review addressed research objective 1 outlined in section 1.3 in the introduction chapter. The aim was to identify and critically appraise current evidence detailing the impact of IHE on blood glucose concentrations in individuals with type 1 diabetes.

Study findings from the RCTs in this current review are inconclusive regarding the effects of IHE on blood glucose concentration in individuals with type 1 diabetes. Results from one RCT indicate that IHE can moderately increase blood glucose concentration during exercise (Ford *et al.*, 1999). In contrast other studies have found that the short-term decline in blood glucose concentration is lower with IHE compared with moderate exercise of the same duration during both exercise and recovery of up to an hour after exercise (Maran *et al.*, 2010; Guelfi *et al* 2005a; Guelfi *et al* 2005b). It has also been found that compared with moderate intensity exercise, IHE results in a similar decline in blood glucose concentration during exercise but IHE is associated with less post-exercise hypoglycaemia (Iscoe and Riddell, 2011). Interestingly a lesser decline in glycaemia with IHE may be attributed to a greater increment in glucose rate of disappearance during exercise and early recovery (Guelfi *et al.*, 2007a). Additionally it was demonstrated that nocturnal hypoglycaemia is detected in response to IHE performed in the afternoon, a previously unrecognised phenomenon (Maran *et al.*, 2010; Iscoe and Riddell, 2011).

2.3.1 Factors that Influence the Blood Glucose Response to Exercise

In order to critically appraise each RCT and understand the blood glucose responses to IHE it is important to identify and discuss key factors responsible for the blood glucose responses to any form of exercise. These factors have been highlighted by the ADA (2008) who state that the glycaemic response to exercise in individuals with type 1 diabetes can be variable and are dependent on:

- Duration, intensity, type and timing of exercise
- Type and timing of insulin and carbohydrate intake
- Circulating insulin concentration
- Blood glucose concentration before the start of exercise
- Overall metabolic control (expressed as HbA1c)
- Exercise experience of the subjects

The following sections will discuss these key factors that are responsible for the blood glucose response to exercise and how these relate specifically to IHE and the RCT studies highlighted within this literature review. In addition the limitations of these studies will be discussed throughout.

2.3.1.1 Duration, Intensity, Type and Timing of Exercise

The difficulty in conducting research into the blood glucose responses to IHE could be due to the fact that intermittent exercise can encompass a wide range of exercise protocols with varying work to recovery ratios. The heterogeneity of the IHE protocols used within the RCTs in this study could impact upon study findings. Ford *et al* (1999) examined the response of blood glucose concentrations to six repeated bouts of 20 second efforts at 120% \dot{VO}_{2} max, performed every two minutes with an active walking recovery (54 m/min⁻¹) in between. This study was one of the only studies along with Maran *et al* (2010) and Iscoe and Riddell (2011) to quantify the intensity of the sprint component. The walking component used as the recovery period was the same intensity for every participant meaning that training status of the participants was not taken into account (Ford *et al.*, 1999). A further limitation of the protocol used in Ford *et al's* study (1999) was that the work to recovery ratio used does not accurately reflect the intermittent nature of most team sports in which the high intensity intervals are much shorter in duration than the 20 seconds used. Studies that have published time motion analysis during competition, in general have reported that the mean duration for high intensity sprints in sports such as football, hockey and rugby is 2-3 seconds (Duthie *et al.*, 2005; Spencer *et al.*, 2004; Mohr *et al.*, 2003; Bangsbo *et al.*, 1999).

In contrast to Ford *et al* (1999) the remaining RCTs in the review used similar IHE protocols (Iscoe and Riddell, 2001; Maran *et al.*, 2010; Guelfi *et al.*, 2007a; Guelfi *et al.*, 2005a; Guelfi *et al.*, 2005b). The first study examined the effects of repeated bouts of high intensity exercise on blood glucose concentration compared with remaining inactive (Guelfi *et al.*, 2005a). The IHE consisted of a 20 minute cycling protocol with four second sprints performed with two minutes of passive recovery between the sprints. Although the work to recovery ratios used in this study were based on time motion analysis of team and field sports (Spencer *et al.*, 2005), the recovery between the bouts was passive. In the field intense bursts of high intensity activity are often interspersed with periods of lower intensity activity.

This issue was addressed in subsequent studies where the IHE protocol was 30 minutes in duration with four second high intensity sprints interspersed with 2 minutes of moderate intensity exercise at 40% \dot{VO}_2 peak (Guelfi *et al.*, 2005b; Guelfi *et al.*, 2007a). Maran *et al* (2010) also used a similar protocol working at 40% \dot{VO}_2 max for 30 minutes with a five second sprint interspersed every two minutes. Iscoe and Riddell's (2001) IHE protocol consisted of working at 50% Work Rate peak for 45 minutes with nine 15 second bouts at 100% Work Rate peak interspersed every five minutes. In all the RCTs where a similar IHE protocol was implemented the decline in blood glucose concentration was less during IHE in comparison to moderate intensity exercise (Maran *et al.*, 2010; Guelfi *et al.*, 2007a; Guelfi *et al.*, 2005a; Guelfi *et al.*, 2005b). In slight contrast it was also found that interstitial blood glucose declined similarly in moderate intensity exercise and IHE exercise trials (Iscoe and Riddell, 2011). The one study that used a different IHE protocol with different work to rest ratios detected a slight increase in blood glucose concentration (Ford *et al.*, 1999). This indicates that different work to rest ratios used in IHE protocols might alter the blood glucose response. This may have practical implications for athletes in the field where it is impossible to precisely reflect the complex activity and recovery patterns (or different positional demands) common to many team sports. Furthermore the generalisation of these findings within this review to all team sports is limited since most team sports last up to 80-90 minutes, yet the reviewed studies used 20-30 minutes of exercise.

It is also important to note that the variation in the number of sprints performed throughout the protocol, although similar across all the reviewed studies, may also significantly alter the relative energy system contribution and the metabolic demand of exercise thus potentially affecting the blood glucose response. This issue is one that needs to be addressed in further studies.

In addition to the duration, intensity and timing of exercise protocols performed, the exercise mode may also impact upon the blood glucose response to exercise. Within the existing literature all the included studies with the exception of one, who use a treadmill protocol (Ford *et al.*, 1999), perform cycling exercise. This is an oversight since in almost all team based sports the mode of exercise is walking/running/jogging. The lack of research using the exercise mode that is specific to IHE is limiting since it has been found that eccentric muscle actions, such as those that occur during running or walking, can slow down insulin action and glucose uptake for up to 48 hours after exercise in comparison to concentric muscle actions which are typical of cycling exercise (Asp *et al.*, 1996). This implies that the blood glucose responses could be different depending on whether cycling or running exercise is performed. Results from the RCT studies in this review where cycling was used as a mode of exercise (Iscoe and Riddel, 2011; Maran *et al.*, 2010; Guelfi *et al.*, 2007a; Guelfi *et al.*, 2005a &b; Ford *et al.*, 1999)

should be considered with caution when applying the results to team based sports in the field. In order for the findings to be truly applicable to team sports, future studies should investigate the blood glucose responses to IHE using a mode of exercise that is sports specific.

2.3.1.2 Type and Timing of Insulin and Carbohydrate Intake

It is also possible that a different glycaemic response may be observed during exercise performed at varied time intervals following different energy intake and insulin administration. The included studies have employed real life protocols to examine the responses to exercise. Two studies have commenced in the morning with participants injecting their normal insulin dose prior to consuming a standardised breakfast and following three and a half hours after breakfast the exercise sessions took place (Guelfi *et al.*, 2005a; Guelfi *et al.*, 2005b). Other morning exercise designs include an overnight fast with the commencement of exercise before the participant administers their insulin dose and consumes breakfast (Guelfi *et al.*, 2007a). In contrast Maran *et al* (2010) investigated afternoon exercise followed by advice to reduce the evening dose of fast-acting insulin by 20%, and Iscoe and Riddell (2011) in their study, had their participants perform afternoon exercise following a standardised lunch five hours before, followed by 30g of carbohydrate at bed time. Finally Ford *et al* (1999) looked at afternoon exercise one hour after lunch. Participants in this study were allowed to determine the best regime for them in terms of insulin and food intake.

The time of the day in which exercise was performed may influence the blood glucose response to the bout of exercise performed since the bodies need for insulin is lower at certain times within the day. The risk of hypoglycaemia is less for exercise performed in the morning than in the afternoon since circulating insulin levels are lower and muscle glycogen stores are full (Toni *et al.*, 2006). There could thus potentially be a risk for nocturnal hypoglycaemia to occur in individuals who take part in afternoon/evening exercise. This risk could be heightened if participating in IHE since there is a greater utilisation of muscle glycogen in this type of exercise (Guelfi *et al.*, 2007a). Maran *et al* (2010) proved that the risk of nocturnal hypoglycaemia was greater after IHE through the use of a CGM which showed that glucose concentrations between
00:00 and 06:00am were significantly lower (p< 0.05) than after moderate intensity activity (number of hypoglycaemic attacks was 7 and 2 in IHE and moderate trials respectively). Unfortunately participation in any exercise generally increases the risk of hypoglycaemia and blood glucose concentration showed to decrease generally across the board in all studies after the exercise trials. Each study reported hypoglycaemia occurred whether the sessions took place in the morning or afternoon.

In addition it may be important to consider the timing of exercise after insulin injection. Leaving an interval of two-three hours between the last meal/insulin injection avoids exercising during peak insulin action where the risk of hypoglycaemia is high (Grimm, 2005). Two studies left an interval of three and a half hours (Guelfi *et al.*, 2005; Guelfi *et al.*, 2005b) after injection before exercise however one study commenced exercise within an hour (Ford *et al.*, 1999) and one omitted any information about timing of exercise and insulin injection (Maran *et al.*, 2010).

While the real life protocols employed in the formerly discussed studies offer an advantage of providing an element of reality by stimulating normal conditions by which exercise may be commenced in individuals with type 1 diabetes, they sacrifice experimental control in doing so. This is particularly true of Ford *et al*'s (1999) study with blood glucose being difficult to match between experimental trials. One further limitation of the "real life" protocols is that it is difficult to match blood glucose concentrations at a similar time from insulin injection between different trials. In order to overcome this limitation some studies have used a protocol to clamp blood glucose at a constant level by infusing glucose or insulin. In this review one study utilised a euglycaemic clamp protocol where blood glucose was maintained at 5.5 mmol.l⁻¹ for the duration of the exercise trials by infusing 20% of dextrose solution at a variable rate (Guelfi *et al.*, 2007a). Although they may be able to keep blood glucose concentration at a constant this clamp protocol would have been invasive and expensive. Furthermore results may not be applicable compared to those other studies using "real life" protocols since blood glucose does not remain constant in real life.

The difference in experimental design in relation to insulin protocols may in part explain some differences in the results. In contrast to Guelfi *et al* (2005b), Guelfi *et al* (2007a) found that after two hours of recovery the decline in blood glucose concentration for IHE may not be less than moderate intensity exercise. Participants in Guelfi *et al* (2007a) were fasted overnight but in a post-prandial state in the previous study (Guelfi *et al* 2005b). Lower pre-exercise hepatic glycogen concentration resulting from fasting may have impaired the exercise induced rise in glucose production. The levels of circulating insulin was also marginally higher in one study (Guelfi *et al.*, 2007a) which may have slowed the exercise induced increase in glucose production while enhancing glucose uptake. In complete contrast Ford *et al* (1999) found that blood glucose concentration marginally rose after IHE. There was however a lack of control over eating and insulin regimes in this study which may or may not have impacted upon the blood glucose concentration.

2.3.1.3 Circulating Insulin and Blood Glucose Concentration Before Exercise

The amount of circulating insulin and the blood glucose concentration before exercise is also critical to exercise performance and a major determinant to the glycaemic responses to exercise (Wasserman and Zinman, 1994). A major problem for individuals with type 1 diabetes is that plasma insulin concentration does not decrease during exercise as it would normally do. Conversely it may increase due to increased insulin sensitivity, enhanced absorption and if exercise is commenced shortly after insulin injection (especially with rapid analogues) (Robertson *et al.*, 2008). It is therefore of paramount importance that prior to and during exercise a certain concentration of circulating insulin should be maintained to prevent over-insulinization (causing blood glucose concentration to decrease) and under-insulinization (causing blood glucose concentrations to increase). Perry and Gallen (2009) have recommended that ideally exercise should commence with a blood glucose concentration of 7-12 mmol.l⁻¹. Only two studies made reference to blood glucose concentration prior to exercise and both stated that participants blood glucose concentration should be 11 mmol.l⁻¹ (Guelfi *et al.*, 2005b).

Although no study made reference to the site of insulin injection it is worth noting that this can also influence the rate of insulin absorption and thus the response to exercise (Kovisto and Felig, 1978). Individuals should avoid administrating insulin in body parts that will be involved in exercise. This will make it easier to anticipate the blood glucose responses to insulin and aids with the management of exercise (Toni *et al.*, 2006). Care must also be taken to avoid intramuscular injections which can cause hypoglycaemia particularly if followed by exercise (Perry and Gallen, 2009).

2.3.1.4 Metabolic Control and Fitness Level of Participants

The overall metabolic control and fitness level of the participants have been identified as factors that can influence the blood glucose response to any bout of exercise (ADA, 2008). All participants used within the included RCTs were in good metabolic control prior to participation as reported by mean Haemoglobin A_{1c} (Hb A_{1c}) levels (%): 7.0 ± 0.4 (Guelfi *et al.*, 2005a), 7.4 ± 1.5 (Guelfi *et al.*, 2005b), 7.7 ± 0.8 (Guelfi *et al.*, 2007) and 7.14 ± 0.6 (Maran *et al.*, 2010). Ford *et al* (1999) however failed to report Hb A_{1c} levels. This is an important omission as Hb A_{1c} is used as an index of long term blood glucose control, ie blood glucose concentration that existed for the previous 2-3 months. According to the National Institute of Health (2010) an individual with good control over their diabetes will have an Hb A_{1c} level of 7% or less. Results of the Diabetes Control and Complications Trial show that near-normal and normal Hb A_{1c} levels (Cateford) limit the progression of long term complications from diabetes (Diabetes Control and Complications Trial Research Group, 1993). Without information on Hb A_{1c} levels it is difficult to tell if the participants used in the Ford *et al* (1999) study had good glycaemic control.

It is possible that the fitness level or exercise experience of the participants may also play a role in determining the blood glucose response to IHE. Participants used in Maran *et al* (2010), Guelfi *et al* (2007a) and Ford *et al* (1999) were all physically active. The remaining studies made no reference to the exercise experience of their participants (Guelfi *et al.*, 2005a; Guelfi *et al.*, 2005b). All of the studies however performed

exercise at a percentage of the participants \dot{VO}_2 max, in order to account for differing fitness levels of the participants. This is particularly important since research has shown that compared with untrained, physically active individuals utilise less carbohydrates and more free fatty acids, even when working at a relative intensity (Francescato *et al.*, 2005). This would result in a slower decline in muscle and liver glycogen stores for those individuals who are physically active. Exercise performed on a regular basis may also increase insulin sensitivity (Steppel and Horton, 2003), which could theoretically increase the risk of hypoglycaemia.

2.3.2 Current Guidelines for Individuals with Type 1 Diabetes Participating in IHE

The lack of research into the blood glucose responses that reflect the intermittent nature of team sports has not prevented the publication of recommendations for adjusting insulin and carbohydrate doses for this type of exercise. These recommendations can be seen in Table 2.2 and have been summarised to demonstrate the current guidelines for managing the risk of hypoglycaemia associated with IHE for individuals with type 1 diabetes.

An issue with many of these recommendations is that they do not attempt to differentiate between continuous moderate intensity exercise and IHE and many suggest similar management strategies for both types of activity (Grimm *et al.*, 2004; Birrer and Sedaghat, 2003; Pierce, 1999). Guidelines by Grimm *et al* (2004) classify the exercise intensity based on HR and recommend a similar amount of supplemental carbohydrate and reduction in insulin dose for continuous activities such as cycling and jogging to that of intermittent sports such as tennis, football and basketball that result in an equivalent heart rate. The basis of this recommendation was that a greater reduction in insulin and increased carbohydrate supplementation would be required for higher intensity exercise compared to moderate intensity exercise of the same duration.

Pierce (1999) suggests that the management of blood glucose concentrations for vigorous team sports such as rugby and football should be similar to that of prolonged

exercise such as marathons where there should be a 70-90% reduction in insulin dose. Similarly Birrer and Sedaghat (2003) have recommended the same management for intermittent activities such as football and basketball to continuous activities such as cycling and swimming.

While some recommendations do not distinguish between continuous and intermittent activities, other research scarcely mentions advice for IHE and simply makes one or two brief statements while going into great detail regarding advice for moderate intensity activity (Lumb and Gallen, 2009; Perry and Gallen, 2009). The advice given to those with type 1 diabetes wishing to participate in IHE seems to be difficult to interpret and this issue is exaggerated by one study addressed within this review that looks at the responses to intermittent exercise and claim their findings to be applicable to intermittent sports such as hockey, basketball and football (Ford *et al.*, 1999). This is despite the fact that the exercise protocol used does not accurately reflect the work to recovery ratios observed in intermittent sports. Despite a number of recommendations being made regarding the best way for individuals with type 1 diabetes to manage IHE very few of these have been tested in practice therefore advice should be taken with caution.

2.4 Implications, Practical Applications and Directions for Future Research

The literature reviewed here may have implications for the practical application for developing further studies that investigate the effects of IHE on blood glucose concentrations in individuals with type 1 diabetes, in particular the development of this present research.

An important aspect of previous research that should be considered is the limited time frame of examination for the potential development of hypoglycaemia after exercise. Conclusions from the included studies were based on monitoring the subjects using standard self-blood glucose monitoring (SBGM) for as little as 20 minutes after exercise (Ford *et al.*, 1999) and up to 150 minutes after exercise (Maran *et al.*, 2010). These

limited observation periods are too short to draw any firm conclusions on the role of IHE on post exercise hypoglycaemia. Low blood glucose concentrations which can lead to LOPEH may occur up to 31 hours after exercise (MacDonald, 1987). LOPEH is often nocturnal for those who exercise in the afternoon, meaning that the hypoglycaemic episode is less likely to be detected and has been suggested to disturb sleep patterns, alter recovery and therefore affect physical performance the following day (Pierce, 1999).

Isoce and Riddell (2011) and Maran et al (2010), however additionally used a Continuous Glucose Monitoring Device (CGM) and monitored glucose concentrations for 20 hours after the cessation of exercise. One study demonstrated that IHE is associated with a greater risk of nocturnal hypoglycaemia compared to moderate intensity exercise (Maran et al., 2010). This is a clinically important observation particularly as the fear of post-exercise hypoglycaemia discourages those with type 1 diabetes to take part in exercise (Grimm, 2005). This may also be clinically important since some research is recommending that IHE may be preferential over moderate intensity activity or high intensity activity for complication free individuals with type 1 diabetes (Guelfi et al., 2007b). This recommendation is based on study results that show that the decline in blood glucose concentration is less for IHE compared with moderate exercise since the risk of a hypoglycaemia is theoretically less likely (Guelfi et al., 2005b). However this was only based on monitoring blood glucose for 60 minutes after the exercise protocols. These new findings by Maran et al (2010) therefore do not support Guelfis' (2007b) existing recommendations. However Iscoe and Riddell (2011) found that IHE is not associated with the risk of LOPEH. Due to results being conflicting there is the need for further studies that increase the observation window following the cessation of exercise and utilise a CGM to allow for a more precise understanding of the daily glucose fluctuations, particularly during the night after a bout of exercise, are required to characterize the impact of IHE on LOPEH.

Findings from this review also do not support present advice given for insulin and carbohydrate adjustment for individuals with type 1 diabetes participating in IHE. In contrast to studies that suggest similar management strategies for IHE as moderate intensity activities (Birrer and Sedaghat, 2003; Grimm, 2004; Pierce, 1999), the

reductions in insulin dosage required may be less for IHE due to the higher intensity nature of the exercise. This has been suggested by Perry and Gallen (2009) but has never been tested in practice. Additionally the suggestion that short repeated bouts of high intensity activity in IHE will have the same effect on blood glucose concentration as high intensity exercise alone (Mitchell *et al.*, 1998), is also inappropriate given that there is involvement of moderate intensity activity interspersed between the high intensity component of IHE. Guidelines that suggest similar management strategies for continuous exercise that result in similar heart rate responses to IHE are also not supported. In the comparison of moderate and IHE the decline in blood glucose concentration is less for IHE despite this exercise eliciting a higher heart rate response (~85% and ~67% of age predicted HR maximum in IHE and moderate protocols respectively) (Guelfi *et al.*, 2005). HR values in the upper aerobic threshold (70% of maximal HR and above) result in higher rates of glucose oxidation (Perry and Gallen, 2009) and this therefore suggests a greater risk of hypoglycaemia.

Despite the lack of clear guidelines available in the literature for health care professionals IHE could confer added physiological benefits over moderate intensity exercise due to the overall higher intensity nature of the exercise. This greater intensity, if regularly performed would likely result in improvements in aerobic capacity, weight control and also blood lipid (ADA, 2008).

It is important to note that many of the reviewed studies have very small sample sizes. Clearly the nature of the interventions presents challenges to recruitment of patients and that the small sample size is the most prevalent methodological flaw in these studies. In addition in order for the above mentioned findings to be truly applicable to individuals with type 1 diabetes wanting to participate in IHE there is a need to better reflect the complex nature of team and field based sports. This includes using work to recovery ratios and modes of exercise that are sport specific to IHE. In addition there is a need for guidelines for insulin and carbohydrate adjustments during and after IHE that have been tested in practice. If IHE stimulates LOPEH (Maran *et al.*, 2010) then a further decrease in the basal insulin dose after exercise (more than 20%) may be required.

2.5 Conclusions

There remains a gap in evidence to advise health care professionals and individuals with type 1 diabetes wishing to take part in IHE. The studies highlighted in this review have reported potential effects that IHE may have on the blood glucose response in individuals with type 1 diabetes. The protocols within the reviewed studies differ slightly therefore it is difficult to predict with certainty the effects of blood glucose on IHE.

However as mentioned previously it is important to appreciate that the management of exercise and type 1 diabetes requires careful consideration of the complex interaction between multiple factors. These multiple factors are likely to influence the blood glucose response to IHE. Crucially in order to provide clear guidelines for the management of IHE for individuals with type 1 diabetes research needs to distinguish between moderate intensity and IHE and not treat each exercise intensity as alike. In order to develop a greater understanding of the blood glucose responses to IHE and the best ways to manage this, additional studies are required.

This literature review has thus formed the basis for empirical data collection in this study. This study will enhance the research discussed within this review in the following ways:

- This study will attempt to differentiate between moderate and IHE. Much of the advice in the literature for individuals wanting to take part in IHE is often conflicting and suggest similar management strategies for both moderate intensity and IHE (Birrer and Sedaghat, 2003; Pierce, 1999).
- Most other studies investigating IHE in individuals with type 1 diabetes have been conducted in the morning (Guelfi *et al.*, 2007; Guelfi *et al.*, 2005a&b; Ford *et al.*, 1999). The rationale for having participants exercise in the afternoon was that through patient discussions many take part in exercise in the afternoon

following work. In addition, lunch is often consumed around 12-1pm which is around three-four hours prior to exercise. Participants were instructed to inject their lunch insulin dose at least three hours before exercise so that minimal bolus insulin was still active at the time of exercise. The purpose of this was to prevent individuals exercising at a high-risk time for developing hypoglycaemia, considering that peak fast acting insulin action is around 40-90 minutes (Robertson *et al.*, 2008; Noble *et al.*, 1998). Results of this study are likely to be transferable to a real life situation of exercise in the afternoon.

- In addition many of the studies as discussed do not accurately reflect the true nature of IHE and utilise exercise modes and work to recovery ratios that are not representative of IHE (Iscoe and Riddell, 2001; Maran *et al.*, 2010; Guelfi *et al.*, 2007; Guelfi *et al.*, 2005a&b; Ford *et al.*, 1999). This study will thus attempt to utilise a novel IHE protocol that accurately reflects the intermittent nature of team and field based sports (Spencer *et al.*, 2005).
- Due to many results being conflicting there seems to be a need for further studies that will increase the observation window of blood glucose responses following the cessation of exercise. Maran et al (2010) and Iscoe and Riddell (2011) used a CGM in order to do this. In order to further understand the glucose fluctuations, particularly over-night after exercise, this research will also utilise a CGM and monitor interstitial blood glucose up to breakfast the following day.
- Finally, the research in this review has highlighted the need for some clear and practical guidelines for insulin and CHO adjustments both during and after exercise. This research will thus utilise a novel intervention for insulin and carbohydrate adjustment that will be used for exercise performed three hours after a fast-acting analogue dose. While the outcome of this study will not allow for clear guidelines to be developed, this study could be a starting point for providing some important information to health practitioners about the effects that IHE may have on blood glucose level.

In attempt to address some of the limitations outlined in the studies within this review the following chapter will outline the IHE protocol and the intervention for insulin and carbohydrate adjustment that has been designed for the use within this study.

Chapter 3A Development of the Intervention and the Intermittent High Intensity Exercise Protocol

The literature review highlights a gap in the evidence base for blood glucose responses to IHE in individuals with type 1 diabetes. Previous literature demonstrates that IHE can encompass a range of exercise protocols with varying work to recovery ratios however the exercise protocols used are not specific to IHE. In addition, problems managing individuals' blood glucose concentration may arise during and after IHE due to carbohydrate and insulin alterations based on unfounded evidence. As a result the overall aim of this research is to investigate the effectiveness of a structured intervention for insulin and carbohydrate adjustment on blood glucose responses during and after IHE that replicates team and field based sports in individuals with type 1 diabetes.

This chapter will outline the design of the intervention used for insulin and carbohydrate adjustment throughout this study. Furthermore the IHE protocol that was designed with the aim of replicating team and field based sports activity will also be described.

3A.1 Intervention

Within this study, prior to all the IHE and moderate intensity exercise protocols, instructions were given to participants on carbohydrate and insulin adjustment. This was based on a previously devised algorithm for carbohydrate and insulin adjustment for moderate intensity exercise in a laboratory environment at 50% \dot{VO}_2 max (Kilbride *et al.*, 2011). This algorithm was used for exercise performed three hours after a fast-acting analogue dose. In response to gaps in the evidence base for guidelines for insulin

and carbohydrate administration for IHE the intervention in this study was tested for Objectives three and four of this study. Only the acute physiological responses are discussed within this intervention and so the long term effects on glycaemic control are not included in this study. The intervention is shown in Appendix 2 and the following provides a discussion of each component within such.

3A.1.1 Pre-Exercise Fast-Acting Analogue Reduction

Fast-acting insulin analogues such as Insulin Aspart or Insulin Lispro are used as a bolus injection and have been designed to enable patients with type 1 diabetes to mimic the normal meal time insulin response more closely than regular human insulin and therefore improve postprandial glycaemic control. Previous research has demonstrated that patients injecting fast-acting analogue insulin at meal times during a basal-bolus regime had lower postprandial blood glucose concentration and improved glycaemic control when compared to those injecting regular human insulin (Raskin *et al.*, 2000; Rabasa-Lhoret *et al.*, 2001).

Where regular human insulin (e.g. Actrapid,Humilin S) has a slow onset of activity (50-90 minutes) and a prolonged duration of action (up to 12 hours), fast acting insulins taken just prior to a meal or snack have a rapid onset of action (around 0-10 minutes) and have a short duration of action (2-5 hours) (Roberstson *et al.*, 2008). Robertson *et al* (2008) and Noble *et al* (1998) reported that the peak time of action after injection of fast acting insulin analogues is around 40-90 minutes. Additionally West *et al* (2010) states that regardless of insulin dose the peak time of action after insulin injection is 60 minutes. Therefore a high risk time for hypoglycaemia to occur is between 40-90 minutes after injection.

The magnitude of exercise-induced hypoglycaemia with fast-acting insulin analogues will depend in part on the interval between insulin administration and exercise. Practical guidelines suggested within the literature have been considered regarding preexercise insulin dose reductions in order to combat this risk of hypoglycaemia (RabasaLhoret *et al.*, 2001; Grimm *et al.*, 2004; Pierce, 1999; Toni *et al.*, 2006). These reductions in insulin dose vary from 50-75% during 30 or 60 minutes of cycling at 25, 50 and 75% \dot{VO}_2 max (Rabasa-Lhoret *et al.*, 2001), 20-30% for continuous moderate exercise over 60 minutes in duration (Grimm *et al.*, 2004), 30-50% for moderate exercise (Pierce, 1999) and 70-90% for IHE (Pierce, 1999; Toni *et al.*, 2006). However Noble *et al* (1998) states that there is no need to reduce the pre-meal fast acting basal dose if exercise is three hours after the meal.

For this study the participants were required to exercise three hours following a bolus meal related dose. If the pre-meal dose was reduced three hours prior to exercise then the risk of hypoglycaemia is increased. This is considering the carbohydrate ingestion and glucose rise with a reduction in insulin administration. Considering this combined with the peak insulin action suggested by Robertson *et al* (2008), Noble *et al* (1998) and West *et al* (2010) the pre-meal bolus dose was not reduced.

3A.1.2 Post-Exercise Fast-Acting Analogue Reduction

Much of the literature regarding post-exercise fast acting analogue reductions in insulin dosage is equivocal and limited despite the large evidence base describing LOPEH. Literature states that the post exercise basal dose should be reduced in order to prevent delayed onset hypoglycaemia after exercise but does not give any suggestion or guidelines as to how much to reduce the dose by (Kordi and Rabbani, 2007; Rabasa-Lhoret et al., 2001; Perry and Gallen, 2009; Toni et al., 2006). Some research has attempted to make suggestions on how much the fast acting analogue dose should be reduced (Lumb and Gallen, 2009; Pierce, 1999). Lumb and Gallen (2009) suggest that the dose should be reduced by 30% whereas Pierce (1999) suggests a 25-50% reduction based on exercise intensity. These guidelines are however not evidence based and were simply determined through clinical experience. Recently Maran et al (2010) investigated a 20% reduction in the fast acting insulin dose post IHE or moderate intensity late afternoon exercise. This study observed that IHE poses a greater risk for the development of delayed onset hypoglycaemia over moderate intensity exercise, despite a reduction of 20% fast acting insulin dose.

Since a previous study (Maran *et al.*, 2010) reduced the evening meal insulin dose by 20% after a bout of IHE and delayed onset hypoglycaemia was still a problem for participants it was decided to up the fast-acting insulin reduction to 30% in Phase 1 of this study. Due to the need to replace glycogen stores the meal had to be eaten within two hours of finishing exercise. This 30% reduction in fast-acting analogue dose was found to prevent delayed onset hypoglycaemia for 40 minutes of moderate intensity walking/jogging at 50% \dot{VO}_2 max (Kilbride *et al.*, 2011). Phase 2 of this study further reduced the fast-acting insulin dose to 50%. The justification for this will be outlined in Chapter 5: *Discussion*.

3A.1.3 Carbohydrate Amounts

Limited evidence exists regarding carbohydrate quantities to be consumed prior to and during exercise for those with type 1 diabetes, although carbohydrate consumption is recommended to prevent hypoglycaemia (Francescato *et al.*, 2004). Current recommendations from the DAFNE group (2002) state that 10g of CHO would raise the blood glucose concentration by 2.5 mmol.1⁻¹.

This information was used to design the intervention and informed the design of recommended carbohydrate intake depending on pre-exercise blood glucose concentration. If blood glucose concentrations were less than 10 mmol.l⁻¹ prior to exercise carbohydrate was prescribed as per the intervention. If blood glucose concentrations were 4, 6 or 8 mmol.l⁻¹ the amount of carbohydrate taken was 30, 20 and 10g respectively.

3A.1.4 Pre-Exercise Blood Glucose Targets

Participants aimed to commence exercise with a blood glucose concentration of ~ 8 mmol.l⁻¹. Gallen (2005) has suggested that participants should begin exercise with a concentration between 7-10 mmol.l⁻¹, then in a subsequent publication suggests between

7-12 mmol.l⁻¹ (Lumb and Gallen, 2009). When considering the risk of hypoglycaemia and also the risk of delaying exercise due to hyperglycaemia, the target of 8 mmol.l⁻¹ for patients has been selected to represent a typical real life pre-exercise blood glucose level.

3A.1.5 Pre-Bed Blood Glucose and Carbohydrate Amounts

Nocturnal hypoglycaemia has been highlighted as a risk following afternoon and evening exercise (Lumb and Gallen, 2009) For prevention of this, it has been suggested to increase carbohydrate consumption in order to account for increased insulin sensitivity and glucose uptake, to restore muscle and liver glycogen (Lumb and Gallen, 2009) Despite this specific carbohydrate amounts are not suggested anywhere in the literature.

Post-exercise a 30% reduction of the following meal analogue dose was given to prevent delayed hypoglycaemia. The intervention was designed to advise individuals to take an extra 10-20g of carbohydrate before bed if the blood glucose concentration was under 10 mmol.1⁻¹.

3A.1.6 Long-Acting Analogue Adjustment

Long-acting insulin Glargine (Lantus) is a basal insulin replacement that resembles the basal insulin secretion of a non-diabetic pancreatic beta-cell. Basal insulin replacement should provide a reproducible supply of insulin into the blood stream which will remain stable for 24 hours to suppress hepatic glucose production and to facilitate the action of bolus insulin (Peter *et al.*, 2005).

Studies on the effects of exercise on the absorption of long-acting basal insulin lantus are limited. Peter *et al* (2005) reported that 30 minutes of exercise at 65% $\dot{V}O_2$ max

did not increase the absorption rate of basal insulin Lantus. No current evidence exists to suggest the need to adjust long acting doses. Despite some authors simply stating that the dose may need reduced (Lumb and Gallen, 2009) long acting doses were not adjusted due to the potential hyperglycaemic effects that could occur within the following 24 hours.

3A.2 Intermittent High Intensity Exercise Protocol

As previously highlighted in the literature review in Chapter 2 previous research has used IHE protocols that are not entirely specific to the demands of intermittent type activity. The intermittent protocol in this research was designed with the aim of replicating the physiological demands of team and field based sports as closely as possible within the limits of the laboratory. The mode of exercise for the protocols was treadmill running. This was chosen so that the mode is sport specific to many intermittent team sports. The exercise sessions lasted for 40 minutes to mimic one half of a team game. To account for the differing training statuses of the participants the intensity of exercise elicited a treadmill speed that matched a percentage of the individuals predicted \dot{VO}_2 max determined from the initial sub-maximal incremental walking protocol (Described in Chapter 3B).

Spencer *et al* (2005) classified movements in team sports into walking, jogging and striding/sprinting. The IHE protocol therefore consisted of cycles of walking at 40% $\dot{V}O_2$ max for five minutes, jogging at 70% $\dot{V}O_2$ max for three minutes and sprinting at 125% $\dot{V}O_2$ for five seconds. The duration of each bout was determined by matching the percentage total time spent in each separate activity pattern during the protocol to the observed time motion analysis studies in team sports (soccer, hockey and rugby) carried out by Spencer *et al* (2005). A sprint time of five seconds was chosen based on the average duration of high intensity bouts recorded in the field via time motion analysis studies (Abdelkrim *et al.*, 2007; Bloomfield & O'Dooghue, 2007; Duthie *et al.*, 2005; Spencer *et al.*, 2004; Lothian & Farley, 1994; Bangsbo *et al.*, 1991). Walking and jogging for five and three minutes respectively were chosen since walking and jogging together constitute around 73% of game time and thus account for much of the

activity performed during recovery from high intensity bouts during games (Spencer *et al.*, 2005; Spencer *et al.*, 2004; Lothian & Farley, 1994; Bangsbo *et al.*, 1991). The protocol also considered the deduction in total time required for treadmill speed changes. Although this design is a simplification of the very complex and often changing activity and recovery patterns that occur in team games in the field, this is a novel protocol for the investigation of blood glucose responses associated with this type of activity in a laboratory environment.

This chapter has described the design of the intervention for insulin and carbohydrate adjustment and the intermittent exercise protocol. The following chapter: *Methodology* will go on to detail the research methods, including providing details on the search strategy, data collection methods and sample selection.

Chapter 3B Methodology

In order to address objectives two and three outlined in Section 1.3 of the introduction empirical research will be used. Phase 1 of the empirical research will address objective two:

Compare the effects of a 30% post exercise fast acting analogue insulin reduction on the blood glucose responses to a bout of IHE vs. continuous moderate intensity exercise in individuals with type 1 diabetes.

Phase 2 of the empirical research will address objective three:

Compare the blood glucose responses to a 30% vs. a 50% post exercise fast acting analogue insulin reduction after a bout of IHE in individuals with type 1 diabetes.

This chapter discusses and justifies the research design and data collection techniques that were adopted in the empirical collection of data in this study in order to address the research objectives. Details of sample selection and data analysis techniques are also outlined.

3B.1 Research Design

Experimental research in the laboratory was used in order to carry out this study. The justification of conducting experimental research in the laboratory as opposed to the field is that the greater control of the experimental arrangements in the laboratory enhances the internal validity of the study and makes it far more straightforward to replicate the study design. This is an important aspect in order to reduce experimental bias and in order to easily replicate the IHE during the second phase of the study. However there is an argument that the ecological validity of a study conducted in the

laboratory may be poor as it would be difficult to know how well the findings are applicable to exercise that occurs in the real world out in the field. The research is therefore attempting to accurately reflect the nature of IHE common to team sports within a controlled laboratory environment as a starting point for further research.

The research design employed initially in Phase 1 of this study was a randomised repeated measure cross over design (time x exercise protocol) where each participant was randomly allocated to performing the moderate or IHE first. This was done using a list of random numbers. The participants then performed the other exercise protocol two days later. A repeated measures cross over design allows individual differences in the participants to be controlled for as this can often be the largest source of variation in many studies (Thomas et al., 2005). For this reason each participant acted as their own control by performing both the moderate and IHE. In addition through random assignment all known and unknown confounders are equally distributed and at the end of the study the differences in blood glucose can be attributed to the exercise intensity. The comments made justify the reasoning for using a randomised repeated measures design for this research. Phase 2 of the study repeated the IHE exercise protocol with and altered intervention that was based on results from Phase 1. The dependent variable and outcome measure for Phase 1 and 2 of the study was blood glucose concentration. The independent variable for Phase 1 was the exercise protocol, and for Phase 2 the independent variable was the percentage of insulin reduction: 30 v 50%. The outline of the experimental research design can be seen in Figure 3.1.

Phase 1







Figure 3B.1. Outline of the Experimental Research Design.

3B.2 Participants

A total of 261 patients with type 1 diabetes from a hospital in Edinburgh that matched the inclusion criteria (see below) were sent invitation letters (See Appendix 3) in September 2010. A reminder letter was sent one month later to all. By the end of October 2010, 12 participants were interested in participating in the study and 10 participants had been in touch to decline. Common reasons for participants declining were time commitments, they did not feel fit enough or that they did not participate in regular exercise. In addition a few participants had moved recently onto insulin pump therapy. Only four participants had taken part in the study by January 2011. It was then decided to send invitation letters to a further 99 patients from an additional hospital in Edinburgh in February 2011.

Overall a total number of 10 participants were informed of the purpose of the study and the possible risks associated with exercise and the use of a Continuous Glucose Monitor (CGM). They all gave informed consent in accordance with Edinburgh Napier University and the local NHS Ethics Committee, who approved the study. A copy of the consent form can be seen in Appendix 4. Unfortunately one participant dropped out after the pre-assessment day, one only completed the moderate intensity exercise day in Phase 1 of the study and a CGM did not work on one participant for the duration of Phase 1. It was thought that there was insufficient data for these participants so they were excluded from the study. The total number of participants that completed Phase 1 was seven. Only six participants returned and completed Phase 2. The participant characteristics are displayed in Table 3.1.

	Phase 1 (n = 7)	Phase 2 (n = 6)
Age (Years)	36.6 ± 9.21	36.6 ± 9.94
BMI (kg/m^2)	25.6 ± 3.05	25.7 ± 3.29
HbA_{1c} (%)	8.3 ± 0.88	8.4 ± 0.91
$\dot{V}O_2 \max{(ml.kg^{-1}.min^{-1})}$	35.4 ± 4.91	34.6 ± 4.76

Table 3B.1. Participant Characteristics. Numbers are displayed as means and standarddeviations (\pm).

3B.2.1 Sample Size

A power calculation was performed in order to estimate an appropriate sample size for the study. The sample size calculation for a crossover design was described by Hopkins (2009) and estimated a total sample size of 42 participants. This was where the alpha level of statistical significance was set at 0.05 and the smallest change in blood glucose was set at 0.5 mmol.1⁻¹. This was chosen as such a small change in blood glucose during the exercise protocols could be of clinical significance. The type II error rate was set at 20% since Cohen (1988) recommends having an 80% chance of detecting an effect/relationship. Due to there being insufficient published information in the literature about IHE in type 1 diabetes the within subject standard deviation for blood glucose was set at 0.8. This was taken from a study that looked at the responses of blood glucose to IHE compared to moderate intensity exercise in individuals with type 1 diabetes (Guelfi et al., 2005b). It should be noted however that the approaches to sample size estimation provide estimates based on inferences about a population mean effect. Due to the strict inclusion criteria, the significant time commitment required for the trials and the specific clinical population required, the participant numbers were much lower than this sample size calculation and this reduced the statistical power of the study to 13.33% in Phase 1 and 11.4% in Phase 2.

3B.2.2 Inclusion/Exclusion Criteria

The following inclusion/exclusion criteria were applied to the participants in the study:

Inclusion Criteria:

- Male and Female Age 20-40
- $HbA_{1c} < 10\%$
- Type 1 Diabetes for at least two years
- Not on any other medication other than insulin

- Must perform structured exercise for at least 20 minutes or more at least twice a week and undertake a mixture of competitive or recreational sports
- Use a basal bolus insulin regime with analogue insulin and will be experienced with carbohydrate counting and insulin dose adjustments

Exclusion Criteria:

- Hypoglycaemic unawareness
- Proliferative retinopathy
- Peripheral vascular disease
- Hypertension (resting blood pressure > 160/90 mmHg)
- Orthopaedic problems

Both male and female participants were included in the research. Although some quantitative differences do exist in the glucoregulatory responses to exercise in men and women with type 1 diabetes, the pattern of responses is similar (Galassetti et al., 2002). Children and adolescents below the age of 20 were not included to control for any effects of hormonal changes and varying levels of insulin resistance at differing stages of puberty (Moran *et al.*, 1999). Only those with reasonable glycaemic control (HbA1c < 10%) were allowed to participate in the study to prevent any influence of glycaemic control on the results. Participants must have had type 1 diabetes for at least two years since after this duration it will be unlikely that the beta cells will still be producing insulin. Participants could not be on any other medication other than insulin to ensure that any pharmacological substances did not influence glycaemic response. In addition selecting participants that are already physically active will likely make them more tolerable to exercising at various intensities and therefore should be more likely to complete the required exercise bouts. It was also important that patients are experienced with carbohydrate counting and insulin dose adjustments as the research involves adjusting insulin and carbohydrate doses, therefore for safety reasons participants must understand this.

3B.3 Data Collection Tools

The following sections will describe the data collection tools used in this study.

3B.3.1 Pre-Assessment Health Checks

Prior to each exercise session participants gave informed consent and a pre-test health and activity questionnaire was administered (See Appendix 5). Two blood pressure (BP) measurements were taken using an automated BP device (Omron) and the two readings were averaged to give a final result. An automated device was used to eliminate human errors with the standard sphygmomanometer measurement method. Blood glucose concentrations were also checked using a self-blood finger prick.

Standing height was measured using a standard Stadiometer before lowering the headboard to touch the vertex of the head. In this position when the participants head was aligned in the horizontal plane the height was indicated by the stadiometer and recorded. Body mass was measured using a balance beam where the participant was centred on the scales and were asked to remove their socks and shoes.

3B.3.2 Exercise Protocols

All exercise sessions took place in a sport and exercise science laboratory at Edinburgh Napier University, using the same treadmill (Woodway Treadmill ERGO ELG 55) at room temperature.

3B.3.2.1 Prediction of VO, max

Each participant's predicted \dot{VO}_2 max was determined using a sub-maximal incremental walking protocol on a treadmill. The test consisted of seven, three minute workloads with progressive increments in treadmill speed and gradient (Davison, 1994). The test protocol is outlined in Table 3.2 below. The sub-maximal protocol was designed to encompass the anticipated range or aerobic fitness of the participants, ensure all participants completed at least three intensities, ensure a steady state was reached at each intensity, ensure that the total test time is not too long and that the treadmill speeds will not cause the participants to run.

The participants were given the opportunity to familiarise themselves with walking on the treadmill and were fitted with a heart rate monitor (Polar) and a face mask for the breath x breath gas analysis (CPX: ECG-VO₂ Cortex Biophysik GmbH) to measure \dot{VO}_2 . Prior to testing the computerised gas analysis system was calibrated. This was done by firstly calibrating the volume of air measured and then calibrating the concentration of O₂ and CO₂. This procedure was carried out on the computerised gas analysing system.

During the test HR, $\dot{V}O_2$ and Rate of Perceived Exertion (RPE) (Borg, 1982) were recorded at the last 30 seconds of each stage. Blood glucose was also recorded using self-testing blood glucose monitoring (TRUEresult Twist Blood Glucose System) at the beginning, 10 minutes into the test and at the end of the test. The end point of the test was at or just before 85% of the participant's age predicted maximum heart, or for safety reasons when the monitoring system failed or a participant experienced progressive angina, light headiness, confusion, ataxia, nausea, blood glucose drops below 4 mmol.1⁻¹, they experience feelings of discomfort or they ask to stop. Participants maximum predicted heart rate was calculated using the following formulae: 220-age. This age predicted equation is commonly used as a basis for prescribing exercise programmes, as a criteria for achieving maximal exertion and as a clinical guide during exercise testing (Tanaka *et al.*, 2001).

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Workload	Time (mins)	Speed (km/h)	Gradient (%)	Predicted VO ₂ (ml.kg ⁻¹ ¹ ·min ⁻¹)
1	0-3	4	0	10.17
2	3-6	4.8	2.5	15.9
3	6-9	5.3	5	20.25
4	9-12	6	6.5	25.2
5	12-15	6	9.5	30.6
6	15-18	6	12	35.1
7	18-21	6	15	40.5

Table 3B.2. The sub-maximal incremental treadmill walking test (Davison, 1994).

3B.3.2.1.1 Extrapolation of \dot{VO}_2 max and Determination of Treadmill Speed

In order to quantify the exercise intensity that each patient would work at during the exercise protocols data from the sub maximal walking test was used. An example from one patient can be seen in Appendix 6. The steady state \dot{VO}_2 achieved (from the CPX) in the last 30 seconds of each workload was plotted against the heart rate obtained at each workload and a linear extrapolation was fitted using the following equation, where *m* was the slope, *y* was the subjects age predicted heart rate maximum and *c* was the intercept (Figure 3.2):

y = mx + c

Using this equation the subjects predicted $\dot{V}O_2$ max was obtained (x).

The target \dot{VO}_2 was calculated using the following equation (ACSM, 2010):

Target
$$\dot{V}O_2 =$$
 desired % x $\dot{V}O_2$ max

This was completed for 40, 50, 70 and 125% $\dot{V}O_2$ max, since these were the intensities required for the exercise protocols.

In order to determine the treadmill speed that elicited 40, 50, 70 and 125 % of the participants \dot{VO}_2 max the following ACSM equation was used (ACSM., 2010):

 $\dot{VO}_2 = 3.5 + (0.2 \text{ x speed}) + (0.9 \text{ x speed}) \text{ x \% gradient}$

The gradient was kept at a constant 1% to account for the energetic cost of outdoor running (Jones and Doust, 1996).

According to the ACSM (2010) the direct method of exercise prescription using the relationship between heart rate and $\dot{V}O_2$ may be particularly useful when prescribing exercise in persons who have a chronic condition such as type 1 diabetes that may alter the heart rate response to exercise.



Figure 3B.2. Example plot of the relationship between \dot{VO}_2 and HR.

3B.3.2.2 Intermittent and Moderate Intensity Exercise Protocols

Each participant performed the exercise protocols at the same time of the day to account for any variations in circadian rhythm. The time chosen was the late afternoon/evening, at the end of a working day before the evening meal, since it is thought to replicate the most common exercise behaviour amongst patients. This was apparent during patient discussions regarding usual exercise and management. Other protocols have also investigated evening exercise (Iscoe and Riddell, 2011; Maran *et al.*, 2010; Campaigne *et al.*, 1987). This offers the advantage of providing an element of reality by stimulating normal conditions under which exercise may be commenced by individuals with type 1 diabetes.

The IHE protocol was described in detail in Chapter 3B. This protocol consist of cycles of walking at 40% $\dot{V}O_2$ max for five minutes, jogging at 70% $\dot{V}O_2$ max for three minutes and sprinting at 125% $\dot{V}O_2$ max for five seconds.

The moderate protocol was continuous running at 50% $\dot{V}O_2$ max for 40 minutes to stimulate the intensity of a light jog. After the exercise tests a period of active recovery for five minutes was administered on the treadmill at a steady walking pace that was determined by the participant.

The exercise sessions were terminated if the monitoring systems failed, a participant experienced progressive angina, light headedness, confusion, ataxia or nausea. It was also terminated if the participant experienced discomfort and asked to stop or their blood glucose fell beneath 4 mmol.l⁻¹ or they experienced symptoms of hypoglycaemia.

3B.3.3 Instructions for Insulin Dose and Carbohydrate Administration

Chapter 3B provides a detailed explanation of the intervention used in this study. The insulin adjustments in this research are centred around a 30% reduction in the post exercise fast acting analogue insulin at the following meal after the exercise sessions for Phase 1. This meal was dinner for all the participants as the exercise was performed late afternoon. For Phase 2 of the research the reduction in post exercise insulin dose was 50% for exercise performed in the late afternoon prior to dinner.

3B.3.4 Continuous Blood Glucose Monitor Procedures

In order to measure participants blood glucose concentrations throughout the duration of the study a CGM (IPro2: Medtronic) was used and was connected to the participants via a sensor. The sensor will determine how much glucose is in the subcutaneous tissue under the skin and will then send a signal to the monitor with this information, therefore measuring interstitial blood glucose every five minutes for a maximum time of 72 hours. The sensor however did not start recording interstitial blood glucose until one hour after insertion. The Ipro2 CGM system requires repeated calibrations with capillary blood glucose values throughout the day. Participants were thus instructed to take a minimum of four self-blood glucose readings with their meter each day at standardized times. These were recorded in the patient diaries and used to calibrate the CGM.

It should be noted that the CGM does not directly measure glycaemia, rather its main value lies in completing the data obtained during SBGM by permitting visualisation of glucose fluctuations between checks of SBGM. The Ipro2 measures glucose in the interstitial space, while self-blood glucose readings with the participants meter measure glucose from the vessels (mixed capillaries). Given that the two testing areas are completely separate, the glucose takes time to travel from one area to another, making it difficult to extrapolate with certainty glycaemia values measured at a particular instant on the basis of interstitial glucose measurements (Melki et al., 2006., Bevlin, 2010).

When glucose values are stable, such as in a fasting state, the glucose levels between the two areas are almost identical (Bevlin, 2010). However when glucose levels are constantly changing, such as after a meal, the sensor reading may lag behind (Melki *et al.*, 2006; Blevins, 2010; Boyne *et al.*, 2003; Monsod *et al.*, 2002). Boyne *et al* (2003) reported a mean time difference of 4-10 minutes in patients with type 1 diabetes following the ingestion of two liquid meals. In addition Monsod *et al* (2002) noted a delay in blood glucose measured by a CGM on transition from hypoglycaemia to hyperglycaemia. This phenomenon of the physiological effect of insulin on interstitial glucose uptake by peripheral tissues can affect the accuracy of the results obtained from the CGM. The recommendation thus for the use of CGMs issued by the Food and Drug Administration, state that this device does not provide exact data on blood glucose levels but may be used to track changes in glycaemia.

The rationale for the use of the CGM device is that the frequent glucose measurements provide a more comprehensive measure of glycaemic excursions than intermittent selfblood glucose finger pricks which only offer a narrow window. In addition this CGM device did not provide the participant with real-time glucose that could influence their actions to control their blood glucose concentrations. Most importantly from a public health standpoint is the ability of the CGM system to detect asymptomatic hypoglycaemic episodes and to lower HbA_{1c} (absolute decline of 0.3%) as compared with controls (Tavris and Shoaibi, 2004). The investigations of periods when checks of blood glucose are rare for example during the night or after meals have become one of the principle indications of continuous recording in routine practice (Melki et al., 2006). The nocturnal period has been more extensively studied due to decreased patient awareness at this time. In a study on 10 adults with poorly controlled type 1 diabetes (HBA_{1c} = 8.7%) and with normal hypoglycaemia awareness, Cheyne *et al* (2002) observed that in eight patients, one and three episodes of nocturnal hypoglycaemia (< 3 mmol.1⁻¹) were undetected by patients but were detected with the CGM. The CGM is also of value for detecting periods of hyperglycaemia occurring during the daytime which may also be overlooked as a result of insufficient adherence to blood glucose self-monitoring or monitoring that does not cover the whole day. The CGM recordings permit the detection of a large number of post-prandial hyperglycaemic episodes as well as prolonged nocturnal hyperglycaemia (Melki et al., 2006). This is of particular

importance as patients are often trained to monitor blood glucose levels before meals and bedtime, but rarely a few hours after.

Therefore the use of the CGM allows a diurnal glucose profile that would otherwise be difficult to obtain. Periods of glucose instability and variability can be detected in order to identify the past, present and immediate future of glycaemic status. Ultimately this could lead to a more informed clinical decision in terms of altering carbohydrate and insulin doses in relation to exercise.

3B.3.5 Self-Blood Glucose Monitoring

In addition participants were asked to undertake self-testing blood glucose monitoring at 0, 20 and 40 minutes in relation to the exercise trials using a TRUEresult Twist Blood Glucose Meter. Blood glucose concentration was also monitored immediately after exercise and just before the participant leaves the laboratory to ensure that they are within safe limits. A TRUEresult meter was given to each participant at the start of the study and they were instructed to use this meter for the duration of the study. The TRUEresult meter was selected since it provides a small meter and strip package that makes self-blood glucose monitoring easier and more convenient than conventional systems. In particular having a small "all in one" system means that it is convenient for carrying around during exercise. Results are displayed within four seconds using only 0.5 microliters of blood (Bell *et al.*, 2009). First time users have reported that the system was very easy to use and that they were able to achieve clinical performance equal to that of a trained healthcare professional (Bell *et al.*, 2009). 100% of the health care professionals results were within the internationally recognised standards for accuracy for both fingertip and alternate sites (forearm) (Bell *et al.*, 2009).

The purpose of using self-blood glucose testing in addition to the use of the CGM was to reflect glucose control at specific points in time throughout the exercise bouts in order to determine immediate insulin needs in response to hyperglycaemia and hypoglycaemia. In addition the CGM did not start recording blood glucose until one hour after insertion. Self-blood glucose monitoring accuracy has improved over time and has its clinical utility (within \pm 10% reference values), (Mastrototaro *et al.*, 2008). Additionally Davison *et al* (Unpublished) compared continuous blood glucose monitoring to standard measurement (Onetouch Ultrasmart) during a bout of moderate intensity exercise (50% $\dot{V}O_2$ max) in individuals with type 1 diabetics and found that the two methods were comparable over a large range of blood glucose conentration (r = 0.79).

3B.3.6 Monitoring Diaries

Patients were given monitoring diaries to complete for the duration of the study. A copy of the diaries given to the participants can be seen in Appendix 7. These were used to record blood glucose concentrations, insulin doses and carbohydrate intake. Recording this data is part of day to day self-management and participants will be familiar with this. It has now been recognised by health practitioners that patients themselves play a crucial role in collecting useful information by self-monitoring of blood glucose when they exercise (Gallen, 2005) It is acknowledged that this is a subjective measure and the accuracy of them is dependent on the participants being factitious and conscientious. Blood glucose concentrations were recorded before each meal and if participants felt any symptoms of hypoglycaemia or hyperglycaemia. The usual insulin dose plus the adjusted dose was recorded along with any additional insulin administration. This data collection was essential to ensure that participants have followed the intervention. Carbohydrate intake was also recorded. Carbohydrate counting is an integral part of self-management of which some patients may be utilising for insulin dose adjustments. This may have instilled compliancy in some patients. The importance of the accuracy of carbohydrate counting and the recording of specific time points for self-blood glucose readings was emphasized on day one.

3B.3.7 Hypoglycaemia Diaries

Hypoglycaemia diaries were also given to participants. A copy of the hypoglycaemia diaries can be seen in Appendix 8. In this study hypoglycaemia will be defined as: participants experiencing symptoms of hypoglycaemia confirmed with a SBGM (TRUEresult Twist) with a blood glucose of $\leq 4 \text{ mmol.I}^{-1}$ or a SGBM (TRUEresult Twist) reading of $\leq 4 \text{ mmol.I}^{-1}$ without symptoms. These parameters are in line with SIGN guidelines (2010). Participants will decide if the episode was mild or severe with severe requiring help from others. The time in relation to exercise was recorded as this is essential to differentiate between the possible effects of the intervention. Also the treatment method used to treat the episode of hypoglycaemia was recorded as this may cause hyperglycaemia or recurrent hypoglycaemia.

3B.3.8 Heart Rate

During all exercise sessions participants had their HR measured via a HR monitor (Polar) whilst they are on the treadmill. The accuracy of HR monitors has been extensively investigated. HR monitors using electrodes (Polar) produced a mean bias and variability of less than 1.0 beat per minute (bpm) throughout their functional range. In addition Ruha *et al* (1997) reported that the Polar recorders were both reliable and valid when tested against an ECG.

3B.3.9 Rate of Perceived Exertion

RPE was assessed every 10 minutes throughout the exercise trials using a Borg Scale (6-20) of perceived exertion (Borg, 1982). Participants were asked to indicate any number on the scale to rate their overall effort. A rating of six was associated with no exertion at all (sitting/rest) and 20 was associated with the most stressful exercise ever performed and you feel at your maximum physical limits. To improve the accuracy of the scale the following instructions were given to each participant (Ehrman *et al.*, 2003):
"During the exercise test pay close attention to how hard you feel the exercise work rate is. This feeling should reflect the total amount of exertion and fatigue, combining all sensations and feelings of physical stress, effort and fatigue. Do no concern yourself with any one factor such as leg pain, shortness of breath or exercise intensity but try to concentrate on your total inner feeling of exertion. Try not to over or under estimate your feelings but be as accurate as you can" (p88).

The scale has been widely researched for its use in both clinical and exercise settings (Borg, 1998; Noble and Robertson, 1996). Since then the scale has been validated and has become a standard method of measuring the level of intensity experienced during physical activity (Noble and Robertson, 1996).

3B.4 Experimental Procedure

Firstly participants attended the exercise physiology laboratory for a familiarisation session during which anthropometric measurements (height and body mass), BP, prediction of $\dot{V}O_2$ max was performed and a pre-test health and activity questionnaire was administered (See Appendix 5). If resting BP was above 195/60 mm/Hg the participants were deemed not suitable to exercise and were referred to their consultant physician. Prior to the $\dot{V}O_2$ max prediction blood glucose concentrations were checked using a self-blood finger prick and if concentrations were above 17 mmol.l⁻¹ or below 4 mmol.l⁻¹ participants were not allowed to exercise. In addition participants were given information regarding the intervention for insulin and carbohydrate adjustment that they would be following for remainder of the study. Familiarisation with the moderate and IHE protocols was also performed. Since the IHE protocol requires the participants to run at fast speeds on the treadmill, all participants were given a familiarization session on the treadmill to ensure they were fully accustomed with the changing speeds during the IHE protocol.

One week later participants returned to the laboratory in the late afternoon to complete the moderate or IHE trials, which were administered in a randomised order on days 8 and 10.

Prior to the first exercise session on day eight the participants were connected to the Ipro2 CGM. The blood glucose sensor was inserted into the abdomen via an intruder and after 15 minutes the monitor was then connected to the sensor (See Figure 3.3). Once the sensor was successfully sending signals to the monitor it was taped securely into place. Participants were also given monitoring and hypoglycaemia diaries to complete from day eight until day 12 and were carefully instructed on their use.

Prior to the exercise sessions participants were asked to undertake self-blood glucose testing using a TRUEresult Twist blood glucose meter. If participants were within safe limits to exercise a Polar HR monitor was fitted to record HR throughout the exercise trials. The moderate or IHE trial commenced around 30 minutes after the insertion of the CGM. A warm up of five minutes was completed prior to the exercise protocols at a pace set by the participants. At 0, 20 and 40 minutes in relation to the exercise trials RPE (Borg, 1982) and self-blood glucose testing (TRUEresult Twist) was recorded. On completion of the exercise sessions, participants had a cool down for five minutes at a pace again set by themselves. The HR monitor was removed and blood glucose concentrations were checked prior to the participant leaving the laboratory to ensure they were within safe limits.

3B.4.2 Phase 2

Phase 2 of the study took place a month later when participants were invited back to repeat the IHE protocol with different instructions in relation to the intervention. Patients were instructed to reduce the post-exercise fast-acting insulin dose by 50% at

the following meal. The IHE protocol remained unchanged and the procedures in phase 1 on days eight or 10 were repeated, with the same testing conditions and restrictions applying.



Figure 3B.3. Blood glucose sensor and the IPro2 attached to the abdomen.

3B.4.3 Testing Restrictions

All participants were required to adhere to the following restrictions during the period of the study. Participants were instructed to consume a similar diet before each session and avoid caffeine, alcohol and structured exercise 24 hours before and after testing. Caffeine can decrease insulin sensitivity (Keijzers *et al.*, 2002), while alcohol can increase the risk of hypoglycaemia in those with type 1 diabetics (Turner *et al.*, 2001). In addition it has been found that antecedent exercise can blunt the metabolic and glucoregulatory response to subsequent exercise (Galassetti *et al.*, 2001).

Participants were asked to keep a diary of food intake, insulin dose, blood glucose, physical activity levels and hypoglycaemic episodes before each meal, four times a day on exercise days and 24 hours before and after the exercise days for Phase 1 and 2 of the study. If a participant experienced a period of hypoglycaemia 24 hours before testing the session was rescheduled as prior hypoglycaemia can induce counter regulatory failure (Galassetti *et al.*, 2003).

3B.5 Data Analysis

All demographic information was contained on the diabetes management database within NHS Lothian. All data analysis out with the NHS was anonymous and names were replaced with a participant number. Data were stored in a secure place in to which only the researcher and academic supervisors had access too.

3B.5.1 Analysis of Continuous Glucose Monitor Data

After completion of phase 1 and phase 2, CGM data was uploaded using Solutions Software (Medtronic) and stored on an online database that was password protected. For each participant the full results were analysed and blood glucose readings were recorded from the IPro2 at the following meal time after exercise and 2, 4, 6, 8, 10, 12 hours after the meal and at breakfast time the following day. These time points were chosen in order to standardise the times for all participants and to ensure that there was an accurate portrayal of blood glucose excursions during the night after the exercise bouts. In addition it was thought that these times would relate to specific points in the intervention. From the evening meal until six hours after this would relate to the bolus/meal reduction in insulin dose. This was what was reduced for the participants. From six hours until breakfast the following day this would relate to the basal/long-acting insulin dose and the amount of carbohydrate advised to be taken before bed.

The number of hypoglycaemic episodes (blood glucose level of $\leq 4 \text{ mmol.I}^{-1}$) was also calculated at each time point and these were checked against the hypoglycaemic diary entries to assess whether the participants were aware that they had experienced a hypoglycaemic episode. In addition the percentage time spent within the ideal blood glucose range (4-8 mmol.I⁻¹) was also calculated within each time point for each participant.

3B.5.2 Statistical Analysis

Statistical analysis was completed using a Statistical Package for Social Sciences (PASW Statistics v 18). To determine the effectiveness of the intervention for the first phase of the study the responses from the CGMs was compared on the moderate and IHE exercise days and up to breakfast the following day after the exercise bout. For Phase 2 of the study the blood glucose response from the CGMs was compared to the adjusted intervention for IHE.

Results for HR, RPE and blood glucose values were presented as means and standard deviations. All data for Phase 1 and 2 was checked for suitability of parametric analysis and then analysed using a two-way repeated measures ANOVA (time x exercise protocol) with appropriate checks for sphericity. Effect size statistics were also reported to convey whether any observed differences are substantively important. Post Hoc tests

(Bonferroni) were used to determine where, if any differences lie. Statistical significance was accepted at the p < 0.05 level.

This chapter has provided the rationale and details of the research design used within this study. In addition it has outlined the sample selection procedures, data collection tools, procedures and data analysis methods. The next chapter : *Results*, - will display the outcomes of the empirical data collection.

Chapter 4 Results

The previous chapter: *Methodology*, outlined the empirical research design and data collection techniques that were carried out in order to address research objectives two and three outlined in Section 1.3 of the Introduction chapter. Phase 1 of the empirical research addressed objective 2 which aimed to compare the effects of a 30% post exercise fast acting analogue insulin reduction on the blood glucose responses to a bout of IHE vs. continuous moderate intensity exercise in individuals with type 1 diabetes. Phase 2 of the empirical research addressed objective three which aimed to compare the blood glucose responses to a 30% vs. a 50% post exercise fast acting analogue insulin reduction after a bout of IHE in individuals with type 1 diabetes.

This chapter will therefore outline the outcomes of the data collection methods in order to address the aforementioned objectives. In the first instance results of Phase 1 will be discussed, followed by results of Phase 2 from the empirical research.

4.1 Preliminary Analysis

HR and RPE values were averaged across all three exercise conditions: 30% Moderate, 30% IHE and 50% IHE, for each participant. A one-way repeated measures ANOVA was conducted to compare the mean HR scores during each exercise condition (30% Moderate: 100 ± 5.8 ; 30% IHE: 108.5 ± 14.9 ; 50% IHE: 102.1 ± 10 bpm). Results show that there were no effects of exercise condition on HR scores [F(2,10)= 1.05, p=0.38]. Results here are presented as mean and standard deviation (\pm).

A one-way repeated ANOVA was also used to compare the mean RPE scores under each exercise condition (30% Moderate: 8.6 ± 1.8 ; 30% IHE: 9.5 ± 1.7 ; 50% IHE: $10 \pm$

1.8). There were also no effects of exercise condition on RPE scores [F(2,10)=2.86, p=0.10]. Partial eta-squared (η_p^2) values for HR (0.17) and RPE (0.3) indicate that there is a large effect size despite the differences in mean scores being relatively small and failing to reach statistical significance. Again results are presented as mean and standard deviations (±).

4.2 Blood Glucose Responses

Blood glucose responses were measured by SBGM (TRUEresult Twist Meter) before, during and at the cessation of the exercise bouts. From the following meal after the exercise until breakfast the following day blood glucose concentrations were then measured and reported using the CGM (IPro2). The blood glucose results reported using the CGM (Ipro2) are all reported as interstitial blood glucose values.

4.2.1 Pre-Exercise

According to the instructions given to the participants within the intervention for carbohydrate and insulin adjustment, the intervention stated that participants should commence exercise with a starting blood glucose concentration of 8 mmol.1⁻¹. The intervention suggested that additional carbohydrate should be taken if blood glucose concentrations were under 8 mmol.1⁻¹ prior to the commencement of exercise. Prior to the moderate exercise and the 30% IHE protocol starting blood glucose concentrations were within 4-6 mmol.1⁻¹ in two participants therefore 20g of carbohydrate was administered in the form of dextrose tablets as per the intervention. The means and standard deviations for starting blood glucose concentrations prior to each exercise condition are presented in Table 4.1. A one-way repeated measures ANOVA revealed that there was no significant difference between starting blood glucose concentrations across the three exercise protocols [F(2,12)=1.11, p=0.35, $\eta_p^2 = 0.15$].

Exercise Condition	Ν	Mean	Standard Deviation
30% Moderate	7	9.3	1.8
30% IHE	7	9.6	1.3
50% IHE	6	10.8	2.2

Table 4.1. Descriptive Statistics for Starting Blood Glucose Concentrations prior to 30% Moderate, 30% IHE and 50% IHE Exercise Conditions.

4.2.2 Phase 1: 30% Moderate vs 30% IHE

The blood glucose responses for Phase 1 of the research can be seen in Figure 4.1. Figure 4.1 demonstrates that the pattern of response for both IHE and moderate intensity exercise throughout the entire monitoring period is similar. Starting blood glucose levels are similar (MOD: 9.3 mmol. 1^{-1} ; IHE: 9.6 mmol. 1^{-1}) and by the end of the exercise session blood glucose had declined under both conditions (MOD: -2.9 mmol.1⁻ ¹; IHE: -3.6 mmol.l⁻¹). Between the end of exercise and the meal time/insulin reduction blood glucose continues to decrease to 5.5mmol.1⁻¹ in IHE, but increases to 8.2 mmol.1⁻¹ in MOD. From the meal onwards all blood glucose readings are now interstitial measurements recorded by the CGM. Interstitial blood glucose profiles for both IHE and MOD increase from the meal to a peak at four hours post (MOD: 13.1 mmol.l⁻¹; IHE: 11.7 mmol.1⁻¹). One participant under the MOD condition recorded an interstitial blood glucose value of 18 mmol.l⁻¹, indicating that hyperglycaemia in the hours following the meal could also be a problem. Standard deviation values are noticeably high throughout under both conditions but tend to be the highest at two hours and four hours after the meal. From six hours onwards the blood glucose profiles declined under both conditions until 10 hours where they levelled off until breakfast (MOD: 7.4 $mmol.l^{-1}$; IHE:7.6 $mmol.l^{-1}$).

A two-way repeated measures ANOVA (time x exercise) was conducted to examine the impact of exercise intensity (30% Moderate vs. 30% IHE) on blood glucose concentrations. The main effect for exercise condition [F(1,6)=0.32, p= 0.59] and the interaction effect [F(10,60)=0.71, p= 0.70] did not reach statistical significance. The η_p^2 statistic reported for exercise condition and the interaction effect was 0.05 (moderate) and 0.10 (large) respectively.

There was a statistically significant main effect for time [F(10,60)=4.81, p = <0.001]; the effect size was large $(\eta_p^2 = 0.44)$. Post Hoc comparisons using Bonferroni picked up no significant differences between any of the time points. This was likely due to the number of comparisons, the small sample size and the fact that Bonferroni is a very conservative test.



Figure 4.1. Mean blood glucose concentrations during 40 minutes of IHE and Moderate exercise and up to breakfast the next day following a 30% insulin reduction at the following meal post exercise.

Arrow indicates start of CGM (IPro2) readings and a shift from self-blood glucose readings to interstitial blood glucose readings. In addition the arrow indicates time of 30% insulin reduction. Values are presented as means and \pm standard errors for 30% IHE (\blacktriangle) and 30% Moderate (\bullet).

4.2.3 Phase 2: 30% IHE vs 50% IHE

The trend of the blood glucose profile for both the 30% and 50% intervention in IHE is displayed in Figure 4.2 and alike Phase 1, the two profiles are similar throughout the entire monitoring period. Mean reduction in blood glucose from the start to the end of the exercise sessions were similar under both conditions (30% IHE: -3.6 mmol.1⁻¹; 50% IHE -3.4 mmol.1⁻¹). From tea up to four hours blood glucose rises under both conditions, with a greater peak at two and four hours under the 50% IHE condition (2h: 15.3 mmol.1⁻¹; 4h: 14.3 mmol.1⁻¹), indicating hyperglycaemia risks at these times. Again standard deviation values were high at all points across both trials with the highest values being evident at 2h and 4h after the meal. From four hours onwards blood glucose levels decline under both conditions until 10-12 hours post meal.

A two-way repeated measures ANOVA (time x protocol) was conducted to examine the difference between the 30% insulin reduction and the 50% insulin reduction following IHE and their impact on blood glucose concentration over time. There was no significant main effect for exercise condition [F(1,5)= 5.46, p= 0.06]; $\eta_p^2 = 0.52$]. There was also no significant interaction effect [F(10,50)= 0.70, p= 0.71]; $\eta_p^2 = 0.12$.

Similar to Phase 1 there was a statistically significant main effect for time [F(10,50)= 6.88, p= <0.001]; the effect size was again large $(\eta_p^2 = 0.58)$. Post hoc comparisons using Bonferroni showed that there was a significant difference between 0 minutes (M = $9.5 \pm 0.3 \text{ mmol.1}^{-1}$) and 40 minutes (M = $6.0 \pm 0.3 \text{ mmol.1}^{-1}$) in relation to the exercise (p = 0.002). All other comparisons were not significant.



Figure 4.2. Mean blood glucose concentrations during 40 minutes of IHE and up to breakfast the following day with a 30% insulin reduction or a 50% insulin reduction at the following meal post exercise.

Arrow indicates start of CGM (IPro2) readings and a shift from self-blood glucose readings to interstitial blood glucose readings. In addition arrow indicates time of 30% or 50% reduced insulin injection. \blacksquare indicates a significant difference from time point 0 minutes exercise. Values are presented as means \pm standard errors for 30% IHE (\blacktriangle) and 50% IHE (\bullet).

4.3 Time Spent in Ideal Range

The percentage time spent within the ideal range (4-8 mmol.l⁻¹), above and below this range was recorded post laboratory period using the CGM and can be seen in Table 4.1. Ideally a three-way ANOVA (Exercise Protocol x Time x Range) could have been used in order to analyse this data. However due to the sample size being very small (n= 7 for Mod vs 30% IHE; n= 6 for follow up 50% IHE) and the skewness of the data this was not possible. There are also very large standard deviation values (often higher than the mean value), indicating that statistical analysis would not be appropriate. It is for this reason that a descriptive analysis alone will be used when discussing the percentage time spent within the ideal blood glucose range.

		30% MOD	30% IHE	50% IHE
	Ideal (%)	56 ± 37.7	39 ± 30.2	26 ± 28.1
Tea-6h	Above (%)	42 ± 39.5	61 ± 30.6	69 ± 26.6
	Below (%)	2 ± 4	0.57 ± 1.5	5 ± 6.1
6h-	Ideal (%)	62 ± 40.3	56 ± 27.3	49 ± 14.1
Breakfast	Above (%)	24 ± 32.3	39 ± 29.7	44 ± 23.7
	Below (%)	14 ± 36.9	5 ± 8.5	7 ± 9.8

Table 4.2. Percentage time spent above, below and within the ideal blood glucose range (4-8 mmol.l⁻¹) as measured by CGM post-laboratory period for 30% MOD, 30% IHE and 50% IHE exercise conditions. Data are presented as means and \pm standard deviations.

4.3.1 Phase 1: 30% Moderate vs 30% IHE

Tea-6h

The percentage time spent within the ideal range from tea -6h appears to be greater in the 30% Moderate condition compared to the 30% IHE condition (Table 4.1). However the percentage time spent within the ideal blood glucose concentrations ranged from 5-100% in the moderate condition and 0-73% in the 30% IHE condition for all seven participants. One participant in the moderate condition spent 100% of the time in the ideal range, however no-one under the 30% IHE condition spent 100% in ideal. In both exercise conditions only one participant spent any time below the ideal range (< 4 mmol.1⁻¹). Time spent above the range (> 8 mmol.1⁻¹) was greater in the 30% IHE condition (Table 4.1) and one person spent 100% of the time with a blood glucose level above 8 mmol.1⁻¹. The range of time spent above the ideal for all seven participants was 16-94% and 26-100% in the moderate and 30% IHE conditions respectively.

6h-Breakfast

The percentage time within the ideal range appears to still be greater under the moderate exercise condition (Table 4.1), where two participants spent 100% of the time between 4-8 mmol.1⁻¹. The range for all seven participants was 2.2-100%. Within the 30% IHE condition only one person spent 100% time within the ideal blood glucose concentration and this ranged from 20-100%. Within the moderate condition one participant spent 97.7% of the time below 4 mmol.1⁻¹; whereas two participants recorded blood glucose concentrations. Time spent above the ideal range for both conditions is now less compared to tea-6h (Table 4.1). The range for all seven participants for the percentage time spent above 8 mmol.1⁻¹ was 4-80% and 0-80% in moderate and 30% IHE conditions respectively.

Tea-6h

The 50% insulin reduction condition resulted in a greater percentage of time spent above the ideal range in comparison to the 30% insulin reduction condition (Table 4.1). One participant spent 100% of the time under the 50% IHE condition above 8 mmol.l⁻¹. The range of time spent above the ideal range for the six participants in the 50% IHE condition was 27-100%. In comparison to the 30% IHE, under the 50% IHE a greater time was spent below and a lesser amount of time was spent at the ideal range (Table 4.1). Despite the time spent in the ideal range appearing to be relatively small the range for all six participants was 0-72%.

6h-Breakfast

The time spent above and below the ideal range is greater under the 50% IHE condition in comparison to the 30% IHE condition (Table 4.1). Only two participants out of the six spent anytime below 4 mmol.1⁻¹ (17 and 18% of the time) in the 50% IHE condition. This is similar to the 30% condition where again two participants recorded blood glucose concentrations below the ideal range (13 and 20% of the time). The range of time spent above the ideal range in the 50% IHE condition is not as great in comparison to the range spent above in the 30% IHE condition (14-65% vs 0-80% for 50% and 30% IHE respectively). In comparison to 30% IHE the time spent within the ideal range is less for 50% IHE (Table 4.1). This ranged from 34-68% for the six participants in the 50% IHE condition.

4.4 Hypoglycaemia Episodes

Ideally a one-sample chi-squared test could have been used to analysis the hypoglycaemic episodes recorded under each condition, however again due to small numbers this was not possible. It is for this reason that a descriptive analysis alone will be used to discuss the results of this data.

In line with SIGN guidelines (2010) hypoglycaemia in this study was defined as: participants experiencing symptoms of hypoglycaemia confirmed with a SBGM (TRUEresult Twist) with a blood glucose of $\leq 4 \text{ mmol.1}^{-1}$ or a SGBM (TRUEresult Twist) or CGM (Ipro2) reading of $\leq 4 \text{ mmol.1}^{-1}$ without symptoms. Over the course of the study a total of 15 hypoglycaemia episodes (Moderate = 5; 30% IHE = 6; 50% IHE = 4) were recorded either via SBGM during the exercise trials or by the CGM postlaboratory period. The time in which these episodes took place and under which exercise condition these occurred can be seen in Figure 4.3.

Of the seven participants that took part in the first phase of the study two during the moderate exercise protocol and one during the 30% IHE protocol experienced a hypoglycaemic episode between 20-40 minutes in relation to the exercise. These exercise trials were terminated and the participants were treated with carbohydrate as per the intervention. Of the six participants that took part in the follow up 50% IHE trial, one experienced an episode during 20-40 minutes of exercise and the trial was again terminated and the participant was treated with carbohydrate.

Between the following meal after exercise (CGM Tea) and up to breakfast the next day the CGM was used, along with the hypoglycaemia diaries to determine if any hypoglycaemic episodes occurred. A total of 12 episodes were recorded using the CGM however only five of these were recorded in the diaries. A total of seven episodes (Moderate: 1 x tea, 1 x 6h, 1 x 8h; 30% IHE: 1 x 10h, 1 x Breakfast; 50% IHE: 1 x tea, 1 x 10h) went unrecorded indicating that the participants were unaware that they were experiencing hypoglycaemia at these times. Two participants who experienced a hypoglycaemic episode during the exercise then had a further hypoglycaemic episode at the following meal time. This was regardless of exercise condition.

This chapter has outlined the empirical findings that addressed research objectives two and three in sub-section 1.3 of Chapter 1. The next chapter will go on to analyse and synthesize these empirical findings, bringing together the findings from the literature review in Chapter 2.



Figure 4.3. Total number of hypoglycaemia episodes recorded during exercise and up to breakfast the following day in 30% MOD, 30% IHE and 50% IHE conditions.

Chapter 5 Discussion

The previous chapter: *Results*, outlined the empirical findings from the data collection that addressed research objectives two and three of this study. In the first instance the findings of research objective two (Phase 1) of this research will be discussed, followed by a discussion of the results from research objective three (Phase 2). Analysis and synthesis will take place in terms of comparing the 30% insulin reduction on the blood glucose responses to moderate intensity exercise compared to IHE and followed by comparing the 30% vs 50% insulin reductions to the blood glucose responses after IHE. In addition the empirical findings will be compared and contrasted to the findings of the literature review in Chapter 2.

5.1 Phase 1: Comparison of the Effects of a 30% Post-Exercise Insulin Reduction on Moderate and IHE.

The literature review in Chapter 2 demonstrated that advice for those individuals with type 1 diabetes wanting to take part in IHE is often conflicting and difficult to interpret. One of the largest issues is that current recommendations do not attempt to differentiate between continuous moderate intensity exercise and IHE and similar management strategies are suggested for both (Grimm *et al.*, 2004; Birrer and Sedaghat, 2003; Pierce, 1999). It was also apparent that any recommendations that were available had not been tested in practice. Consequently research objective two attempted to address this issue by comparing blood glucose responses to moderate and IHE. This study showed that there was no difference between the decline in blood glucose concentration during moderate or IHE exercise performed in the late afternoon. Despite a 30% post exercise fast acting insulin reduction, both IHE and moderate intensity exercise is characterized by delayed risk in developing LOPEH in some participants. As well as hypoglycaemia,

hyperglycaemia may also be a problem for some participants following the insulin reduction.

5.1.1 Blood Glucose Responses to Exercise

This research has found similar acute blood glucose responses to two differing forms of exercise that were identical in duration but differed in intensity (IHE: -3.6 ± 2.3 ; MOD: -3.2 ± 2.6 mmol.l⁻¹). As expected there was a decline in blood glucose concentration with continuous moderate intensity exercise. This has been previously demonstrated in other studies that investigated the effects of blood glucose responses to moderate intensity exercise in individuals with type 1 diabetes (McMahon et al., 2007; Francescato et al., 2004). The decline in blood glucose concentration that occurs during moderate intensity exercise has previously been attributed to the inability of injected insulin levels to lower at the onset of exercise, therefore causing impaired glucose production and high rates of glucose disposal (McMahon et al., 2007; Wasserman and Zinman, 1994). The similar decline in blood glucose concentration for IHE was however surprising since previous research has suggested that IHE can attenuate the drop in blood glucose concentrations associated with moderate intensity exercise (Bussau et al., 2007; Guelfi et al., 2007a; Guelfi et al., 2005b; Ford et al., 1999). The stabilisation of blood glucose concentration following IHE in previous literature has been associated with elevated catecholamines and growth hormone as a result of the repeated bouts of high intensity exercise (Guelfi et al., 2005b).

The similar reduction in blood glucose concentration for the two different exercise intensities in this study is in agreement with Maran *et al* (2010) and Iscoe and Riddel (2011) and was evident despite methodological differences in the exercise protocols performed in each study. One possible explanation for the similar decline in blood glucose concentrations in this study could be that the total energy expenditure and the total work performed was the same for both exercise trials. It is acknowledged that energy expenditure and total work was not measured in this study; however there was no difference between average heart rate or RPE score for each exercise trial. Other studies confirm that if two types of exercise are different in intensity but similar in

energy expenditure, heart rate and oxygen consumption, then the glycaemic responses are reproducible (Iscoe and Riddell, 2011; Maran *et al.*, 2011; Sills and Cerny, 1983).

In contrast Guelfi *et al* (2005b) found that their IHE (40% \dot{VO}_2 peak with 4 second sprints every 2 minutes) and moderate intensity exercise (40% \dot{VO}_2 peak for 30 minutes) differed in total work performed and heart rate responses, thus potentially explaining in part why discrepancies between this study and the one described by Guelfi *et al* (2005b) have been found. In addition the exercise performed in this study was a greater duration (40 minutes), a different exercise mode (treadmill running) and of a different intensity to that of Guelfi *et al* (2005b). Further explanations for the discrepancies between this study and other previous research (Guelfi *et al.*, 2005b) could in part be due to the time of the day in which the exercise was performed. This study performed the exercise in the late afternoon, however Guelfi *et al* (2005b) performed the thete exercise sessions first thing in the morning. It has previously been demonstrated that blood glucose responses can be quite different for the same exercise performed at different times of the day and at different post-prandial times (Francescato *et al.*, 2005).

5.1.2 Blood Glucose Responses Post-Exercise

All blood glucose values reported after exercise are reported as interstitial blood glucose levels as recorded by the CGM. Between 40 minutes at the end of exercise and the meal time, interstitial blood glucose concentrations continued to decrease after the IHE but appeared to increase after the moderate exercise. The decline in interstitial glucose concentrations in IHE in comparison to the moderate intensity exercise could be explained by the fact that IHE is likely to use predominately more muscle glycogen as a fuel source since the intensity of exercise would be expected to be higher (Guelfi *et al.*, 2007a). Recovery blood glucose concentration may then decline to a greater extent because of the increased need for glycogen replenishment and restoration. Glycogen utilisation has not been measured in this study however it has been demonstrated previously that IHE uses more muscle glycogen than moderate intensity exercise (Iscoe and Riddell, 2011; Guelfi *et al.*, 2007). Despite blood glucose concentrations rising

from the end of the moderate exercise until tea time one participant still experienced hypoglycaemia at tea time. This highlights that individuals differ in their sensitivity to exercise and individualised management strategies should be considered.

Post-hoc tests demonstrated, however, that regardless of exercise condition there was no difference between blood glucose concentrations at 40 minutes exercise and the CGM reading at meal time. Regardless, a total of three hypoglycaemic episodes were recorded at the meal time (IHE: 2; MOD: 1). One participant in the moderate and one in the IHE condition experienced hypoglycaemia at the end of the exercise and again at the following meal time. This could demonstrate stimulation of glucose uptake for the repletion of muscle glycogen stores that were used up during the exercise bout. From a type 1 diabetes perspective it may be important to consider consuming a carbohydrate snack immediately after exercise in order to prevent further decline in blood glucose concentrations prior to the following meal. This may be particularly important if the exercise performed is of a high intensity nature such as IHE.

At present, advice in the research is limited on the best way to deal with post-exercise reductions in insulin dose. Much of the research is focused around pre-exercise dose reductions and advice can vary from 25-90% reductions depending on intensity and duration of exercise (Toni *et al.*, 2006; Grimm *et al.*, 2004; Rabasa-Lhoret *et al.*, 2001; Pierce, 1999). The purpose of the post-exercise 30% insulin dose reduction in this study was to help preserve blood glucose concentration and prevent hypoglycaemia both in the short term and long term following exercise. This was thought to be important due to the increased insulin sensitivity that occurs following exercise (Lumb and Gallen, 2009).

The interstitial blood glucose profiles for both IHE and moderate exercise increased from meal time up to a peak at four hours following the meal. There were also no hypoglycaemic episodes recorded between two and four hours post meal and a high percentage of time was spent above the ideal range under both exercise conditions (Table 4.2). This rise in interstitial blood glucose was expected due to the consumption of a meal and the administration of the insulin dose at meal time which acts to decrease blood glucose concentration. All patients in this study were on fast acting insulin (Lispro or Aspart), which have a quick onset (0-20 minutes) and peak around 40-90 minutes (Noble *et al.*, 1998). The peak in interstitial blood glucose concentrations in this study around two hours demonstrates the time action of the insulin and in part the food absorption. It should be noted that hyperglycaemia (blood glucose > 10 mmol. Γ^1) was an additional problem, in particular at two – four hours after the meal (Figure 4.1). This could have been a result of the continued output of glucose from the liver after exercise and too great an insulin reduction with the following meal (Kordi and Rabbani, 2007). Just as hypoglycaemia is a problem that should be addressed, equally hyperglycaemia is dangerous and if left untreated can lead to ketoacidosis and the production of ketones (Kordi and Rabbani, 2007). In addition frequent bouts of hyperglycaemia can lead to long term organ damage such as diabetic retinopathy, neuropathy, and cardiovascular disease (Pierce, 1999).

The particularly high standard deviation values at two and four hours post-meal could attest to the wide glucose fluctuations in post-prandial glucose excursions between individuals. One factor that could explain this is the meal composition that would affect gastric emptying. The meal content for the participants was not standardized within this study therefore every individual would have ingested a meal with varying carbohydrate, fat and protein content. In individuals with type 1 diabetes the total amount of carbohydrate consumed has the greatest influence on glycaemia (Sheard et al., 2004). Carbohydrate with a low glycaemic index (GI) digests at a slower rate than carbohydrate with a high GI (Thomas et al., 2007). Peak interstitial blood glucose responses would therefore be greater in those participants that consumed carbohydrate of a high GI content compared to those that consumed lower GI carbohydrates, resulting in the large variation in the blood glucose responses seen at two and four hours after the meal. West et al (2011) suggests that a low GI meal may be best for maintaining normal blood glucose ranges post exercise in those with type 1 diabetes. Although individuals were instructed to consume a similar meal content after all the trials it is acknowledged that the lack of standardization of the meal content between participants may limit the ability to demonstrate the true impact of the intervention.

In addition it is acknowledged that additional factors such as pre-meal plasma insulin levels and the reproducibility of insulin absorption between participants may also attest to the large variation in interstitial blood glucose concentration at this particular time after the meal. It is however beyond the scope of this research to discuss every possible variable affecting the blood glucose response.

From six hours onwards the trend in interstitial blood glucose concentrations declined under both exercise conditions then began to level off again around 10-12 hours post meal. The greatest percentage of time spent within the ideal blood glucose range between six hours-breakfast was found in the moderate exercise condition (62 ± 40.3 compared to 56 ± 27.3 % in IHE). Despite this, standard deviations here are again high indicating the large variation between the participants in their blood glucose responses. It is also important to note that from six hours onwards in both exercise conditions hypoglycaemia was evident (Moderate: 2 incidents; IHE: 3 incidents). In a similar way to Isoce and Riddell (2011) this study found that IHE was associated with a more delayed drop in blood glucose concentration since hypoglycaemia did not occur until eight hours post, in comparison to six hours in the moderate condition. This could indicate a more delayed response to the increase in insulin sensitivity following exercise.

Unfortunately there is very little data available on the blood glucose responses in prolonged recovery following exercise, particularly IHE. Only two studies have previously investigated the risk of nocturnal hypoglycaemia after moderate and IHE by using a CGM (Iscoe and Riddell, 2011; Maran *et al.*, 2010). Maran *et al* (2010) found that IHE is associated with an increased risk of LOPEH over moderate intensity exercise, in non-trained individuals with type 1 diabetes. This was despite a 20% insulin reduction at the evening meal. In contrast Iscoe and Riddell (2011) provided their participants with a 30g carbohydrate drink at bedtime and found that in comparison with moderate intensity exercise, IHE has less risk of developing LOPEH.

The differences between these studies (Iscoe and Riddell, 2011; Maran *et al.*, 2010) and results from this one could be attributed to differing interstitial blood glucose

concentrations at bed time and the advice given in terms of insulin and carbohydrate adjustment. All participants in this study were instructed to aim for a blood glucose level of around 10 mmol.1⁻¹ prior to bed, however in the other studies blood glucose concentrations at bed time are unknown (Iscoe and Riddell, 2011; Maran *et al.*, 2010).

The mechanisms thought to contribute to the increased risk of LOPEH after exercise are increased uptake of glucose into the muscles to restore muscle glycogen, increased insulin sensitivity, impaired counter regulatory responses due to previous hypoglycaemia and the timing of the meal and insulin doses (MacMahon *et al.*, 2007). This study was not designed to evaluate these mechanisms and therefore it is not clear what factors determine the timing of this risk.

From a type 1 diabetes perspective the fact that LOPEH is a risk for participants taking part in afternoon exercise may be an important observation, particularly since the hypoglycaemic episodes recorded could be coincident with sleep and that sleep may be a contributing factor to the increased risk for hypoglycaemia. This has previously been demonstrated in another study who investigated adolescents with type 1 diabetes exercising at a moderate intensity in the afternoon (Mcmahon *et al.*, 2007).

Participants in this study were also unaware at certain points that they were experiencing hypoglycaemia. At six and eight hours in the moderate condition and 10 hours and breakfast in the IHE condition, the hypoglycaemic episodes were not recorded by the participants in the diaries. All participants were screened prior to participation in the study and none had a problem of hypoglycaemia unawareness. One potential explanation for the hypoglycaemic unawareness during the night could be due to the fact that previous hypoglycaemia can lower the threshold for the stimulation of counter regulatory hormones and thus the recognition of any symptoms of subsequent hypoglycaemia. This study was not designed to evaluate the counter regulatory responses, though it has been demonstrated previously prior exercise resulting in hypoglycaemia can blunt counter regulatory responses to subsequent hypoglycaemia, decreasing the ability of individuals to recognise symptoms of hypoglycaemia and take action to prevent it (Sandoval *et al.*, 2004; Jones *et al.*, 1998). It could be the case in

this study that prior episodes of hypoglycaemia associated with the exercise results in any LOPEH during the night being difficult to detect.

From a patient perspective it is important to realise that the risk of LOPEH is elevated after both IHE and moderate intensity exercise and for those who tend to experience LOPEH, a low GI snack before bed, such as a wholegrain sandwich, banana or a mixed snack with fat and protein may be consumed to help reduce the risk of nocturnal hypoglycaemia (Shard *et al.*, 2004). It may also be important to warn patients that if they have experienced a previous episode of hypoglycaemia in relation to exercise they could be at risk of LOPEH and that the detection of this may be difficult. It is also important to advise patients that after their meal following exercise where any reduction in insulin dose were made, they should check their blood glucose levels due to the risk of hyperglycaemia up to four hours after their meal. This is particularly important due to the long term implications of repeated episodes of hyperglycaemia.

5.2 Phase 2: Comparison of Blood Glucose Responses to a 30% v a 50% Post -Exercise Fast Acting Insulin Reduction after IHE.

Phase 1 of this research compared the blood glucose responses to moderate or IHE with a 30% post-exercise fast acting insulin reduction. It was then decided to further decrease the insulin dose reduction to 50% following the IHE protocol. The 50% insulin reduction strategy was thus compared to the 30% insulin reduction following a bout of IHE. Results demonstrated that when all variables are reproduced: the intensity, timing and duration of exercise, the blood glucose responses to IHE were similar on two separate occasions. Despite the individual variability in blood glucose responses, a 50% post exercise insulin dose reduction is no better for the prevention of LOPEH than a 30% insulin dose reduction after IHE performed in the afternoon. However a 50% post exercise insulin reduction caused a number of participants to have an episode of hyperglycaemia 2-4 hours post meal.

5.2.1 Blood Glucose Responses to Exercise

This study found a mean reduction in blood glucose of 3.6 ± 2.3 mmol.1⁻¹ for the 30% IHE and 3.4 ± 1.6 mmol.1⁻¹ for the 50% IHE condition. In both exercise conditions one participant experienced a hypoglycaemia episode at the end of exercise. Post-hoc tests indicate that there was a significant difference in blood glucose concentration between the start and end of the exercise trials, regardless of condition. This demonstrates that IHE of this nature can cause a significant reduction in blood glucose concentration. The slightly higher blood glucose concentration during exercise under the 50% condition, albeit not significant could have been obtained at the cost of having a higher starting blood glucose concentration.

Compared to this study, Iscoe and Riddell (2011) showed a larger reduction in blood glucose concentration of 5 ± 0.5 mmol.l⁻¹ for 45 minutes of cycling IHE, whereas Guelfi et al (2005b) reported a reduction of 2.9 ± 0.8 mmol.1⁻¹ with 30 minutes of cycling IHE. It could be that the duration and the composition of the IHE performed could explain in part the differences in the decline in blood glucose concentration between the studies. The largest decline in blood glucose concentrations was found in the study with the longest duration of exercise (45 minutes) and the longest duration of high intensity bouts (9, 15 seconds sprints at 100% WR peak) (Isoce and Riddell, 2011). While Guelfi et al (2005b) demonstrated the smallest decline in blood glucose concnetrations for the shortest duration of exercise (30 minutes) and at a lower intensity (40% \dot{VO}_2 peak with 4 second sprints every 2 minutes) with considerably shorter sprint durations to that of Iscoe and Riddell, (2011). Differences in blood glucose concentrations could also be due to the training status of the participants, with lower \dot{VO}_2 max levels for participants in this study, in comparison to Iscoe and Riddell, (2011) and Guelfi et al (2005b). Despite some of these differences the same pattern of decline in blood glucose response has been demonstrated for IHE.

5.2.2 Blood Glucose Responses Post-Exercise

Similarly, all blood glucose values after the meal, recorded by the CGM (Ipro2) are reported as interstitial blood glucose values. Bonferroni post-hoc results revealed that there was no difference in blood glucose concentrations from 40 minutes until tea time, regardless of exercise condition. Despite tests revealing no significant differences hypoglycaemia was still recorded in one patient under the 50% condition and two under the 30% condition. As previously discussed in the results of Phase 1 of this research, hypoglycaemia at this time could be a result of the need for replenishment of muscle glycogen stores as a result of the exercise performed.

From tea up to four hours interstitial blood glucose concentration rises under both the 30% and the 50% condition, with a greater peak at two and four hours under the 50% insulin reduction condition (average blood glucose increase for 50% IHE = 7.2 v. 4 mmol.1⁻¹ in 30% IHE). It should be noted that despite the seemingly large rise in interstitial blood glucose concentrations there was no significant differences found between the two conditions. Under the 50% IHE: 69 ± 26.6 ; 30% IHE: 61 ± 30.6 %). The greater peak in interstitial blood glucose concentration and the greater time spent above the ideal range in the 50% insulin reduction was expected due to the greater reduction in insulin, stimulating a more pronounced rise in blood glucose concentrations. Previously higher plasma glucose concentrations with lower insulin doses have been attributed to lower concentrations of circulating insulin (Rabasa-Lhoret *et al.*, 2001).

The reduction in 50% insulin dose could perhaps have been too much since interstitial blood glucose concentrations appeared to be quite high, causing episodes of hyperglycaemia and one participant even recorded an interstitial blood glucose concentration of 22 mmol.1⁻¹. It could be the case for some individuals that too little insulin was taken in relation to food intake. However, this is difficult to say as participants were not required to eat a standardised meal with similar carbohydrate content. From a practical point of view avoiding high blood glucose concentrations after exercise is not only beneficial for improved glycaemic control but may also

prevent the occurrence of hypoglycaemia as individuals will be less likely to administer corrective insulin dose, which in a post-exercise insulin sensitive state could cause a rapid decline in blood glucose concentrations (Pierce, 1999). For reasons previously stated in relation to Phase one of this research, it is important for patients to be aware of the risk of hyperglycaemia and the times where this is likely to occur.

It is important to note the individual variation in responses as the increase in interstitial blood glucose concentration across both conditions for all participants ranged from 2.3-14.9 mmol.1⁻¹ from tea – four hours. This variation in response could again attest to the high standard deviation values seen around two and four hours post-meal time. As previously mentioned this in part could be due to different meal compositions (particularly carbohydrate amounts) that affect gastric emptying, pre-meal plasma insulin concentrations and the difference in the insulin absorption rates between participants. It is most likely that the largest flaw in being able to detect the true impact of the intervention within this study was not standardising the post-exercise meal content for every individual.

Interstitial blood glucose concentrations show a decline under both conditions from six hours until 10-12 hours post-meal. Hypoglycaemia was evident in both conditions (30% IHE: 3 episodes; 50% IHE: 2 episodes) however the risk of hypoglycaemia under the 50% condition was only evident at 10 hours. The time spent within the ideal range was greatest in the 30% insulin reduction condition; however again judging by the large standard deviations there was a large variation in the interstitial blood glucose responses between individuals. Despite this, IHE in the afternoon with either a 30% or a 50% insulin reduction is still characterised by the risk of LOPEH. It also appears that hypoglycaemia unawareness is a problem since three episodes went unrecognised overnight. As previously discussed this could be due to the blunting of the counter regulatory response due to prior hypoglycaemia associated with the afternoon exercise as two out of the three individuals experienced hypoglycaemia in relation to the exercise (Sandoval *et al.*, 2004).

Despite a 20% reduction in post-exercise, meal time insulin it has been observed that afternoon IHE puts participants at risk of delayed hypoglycaemia (Maran et al., 2010). As a result Maran et al (2010) suggests that IHE should be considered an undesirable form of exercise for individuals with type 1 diabetes. In contrast it has been reported that IHE results in blood glucose values that are similar to remaining sedentary throughout most of the evening and the early night, and that the risk of LOPEH is not heightened by taking part in IHE (Iscoe and Riddell, 2011). It was thought that the reason for the attenuation in blood glucose concentrations throughout the night was due to a 30g low GI snack given without bolus insulin at bedtime (Iscoe and Riddell, 2011). Considering the results of Iscoe and Riddell (2011) and that of Maran et al (2010) and this study, it may be questionable whether such a reduction in insulin dose is required, given that nocturnal glycaemia is similar to an evening following a sedentary day (Iscoe and Riddell, 2011). In addition without such a reduction in insulin dose, this may help prevent unwanted hyperglycaemia. However it should be noted that 27% of participants still experienced hypoglycaemia during the night after IHE in Iscoe and Riddell's (2011) study, indicating that participants differ in their responses to exercise and advice that is suitable for one individual may not be suitable for another.

This chapter has discussed and analysed the results from the empirical data collection of this study. The following chapter will go on to conclude this work and provide application to patient practice.

Chapter 6 Conclusions

Increasing numbers of individuals with type 1 diabetes want to enjoy and take part in sport and exercise (Gallen, 2005). However since exercise is one of the main causes of hypoglycaemia in individuals with type 1 diabetes, guidelines in order to prevent this are important. Existing guidelines to minimise the risk of hypoglycaemia associated with exercise in those with type 1 diabetes, are often very general and few take into account that different advice is required for exercise of varying intensity and duration. At present, to knowledge there are still no evidence based recommendations for insulin and carbohydrate adjustments during IHE for individuals with type 1 diabetes in this context. It was with this in mind that the overall aim of this research was to investigate the effects of a structured intervention for insulin and carbohydrate adjustment on blood glucose responses during and after IHE that replicates team and field based sports in individuals with type 1 diabetes.

To this end the following research objectives aimed to:

- 1. Identify and critically appraise current evidence detailing the impact of IHE on blood glucose concentrations in individuals with type 1 diabetes.
- Compare the effects of a 30% post exercise fast acting analogue insulin reduction on the blood glucose responses to a bout of IHE vs. continuous moderate intensity exercise in individuals with type 1 diabetes.
- To compare the blood glucose responses to a 30% vs. a 50% post exercise fast acting analogue insulin reduction after a bout of IHE in individuals with type 1 diabetes.

This chapter will revisit the overall aim and specific research objectives outlines above. The findings are summarised and related to the research objectives. Conclusions from this research are derived, limitations of this research are also highlighted, along with directions for future research.

6.1 Summary of Findings and Conclusions

Initially the literature review outlined in Chapter 2 revealed that there were only six studies (Iscoe and Riddell, 2011; Maran *et al.*, 2010; Guelfi *et al.*, 2007; Guelfi *et al.*, 2005a&b; Ford *et al.*, 1999) available in the literature that had examined the blood glucose responses to IHE in individuals with type 1 diabetes. Results of these studies were conflicting and thus advice for insulin and carbohydrate adjustments were not evidence based and had never been tested in practice. For this reason the empirical research within this study has utilised a novel intervention for insulin and carbohydrate adjustment in relation to exercise. In addition previous studies have used exercise modes and work to recovery ratios that were not representative of IHE (Iscoe and Riddell, 2011; Maran *et al.*, 2010; Guelfi *et al* 2007; Guelfi *et al* 2005a&b; Ford *et al.*, 1999). This study therefore used an original IHE protocol that took into consideration time spent in each separate activity pattern in team sports from time motion analysis studies (Spencer *et al.*, 2005).

Research objective two demonstrated that there was no difference between the decline in blood glucose concentrations for IHE or moderate intensity exercise performed in a post absorptive state in the afternoon, in individuals with type 1 diabetes. This observation was unexpected due to the current research that suggests the high intensity sprint component associated with IHE helps to attenuate the decline in blood glucose concentrations that is frequently seen in moderate intensity exercise (Bussau *et al.*, 2007 & 2006; Guelfi *et al.*, 2007a; Guelfi *et al.*, 2005b). It should be noted that the studies used varying exercise modes, intensities and the exercise was performed at different times of the day in comparison to this study. It is therefore possible that the timing and the duration of exercise are important in modulating the blood glucose responses to exercise.

Despite a 30% reduction in post-exercise fast acting insulin at the following meal, there was no difference in the risk of developing LOPEH after IHE or moderate intensity exercise. The 30% insulin dose reduction was insufficient to maintain blood glucose concentrations after IHE, therefore research objective three aimed to compare the 30% reduction to a further 50% insulin dose reduction following IHE. Results demonstrated that blood glucose responses for the same bout of IHE in the afternoon were similar on two separate occasions. Thus advice may be given to individuals based on the fact that the IHE protocol outlined in this study, performed in a post-absorptive state in the afternoon will cause a reduction in blood glucose concentrations of ~ 3.5mmol.l⁻¹. It is important to note, however, that there will be moderate variability in this response. Despite the individual variability in blood glucose responses evident in this study, a 50% post-exercise insulin dose reduction is no better for the prevention of LOPEH than a 30% insulin dose reduction after IHE performed in the afternoon.

General observations from this study suggests that there are two main high-risk periods for the development of hypoglycaemia associated with IHE or moderate intensity exercise performed in the late afternoon in a post-absorptive state. The first of these occurs immediately following the cessation of exercise and the second occurs later on during the night and is potentially coincident with sleep. These two high-risk periods have previously been demonstrated for moderate intensity exercise in the afternoon in adolescents with type 1 diabetes (McMahon *et al.*, 2007). In addition this study revealed that hypoglycaemia unawareness during the night was a potential problem and it was hypothesised that it could be due to inadequate counter regulatory hormone responses. This however remains to be validated as these underlying mechanisms were not investigated in this study.

Although the emphasis throughout this study has been on hypoglycaemia in relation to exercise since this is the most frequent worry in patients, it is worth noting that this study has indicated that there could be a problem of high blood glucose levels leading to hyperglycaemia, particularly up to 4 fours following the evening meal. This could potentially be due to the fact that the insulin reduction for the form of exercise in this study was too great. Again the underlying mechanisms for this were not investigated in

this study. It is however important to make patients aware that not only hypoglycaemia is a problem, but hyperglycaemia may also be a problem, particularly after the evening meal if an insulin reduction strategy is utilised.

One of the biggest observations however was the variation in blood glucose responses between participants. This indicates that individuals vary greatly in their responses to exercise and thus individual strategies to combat the risk of hypoglycaemia and hyperglycaemia may be required.

6.2 Limitations

Although this study has contributed to the understanding of the blood glucose responses to IHE in individuals with type 1 diabetes and the management strategies that may be required, a number of limitations must be acknowledged. Firstly the findings of this research apply to a group of habitual exercisers with type 1 diabetes exercising under particular conditions. These include exercise for 40 minutes at either a moderate intensity (50% \dot{VO}_2) or IHE (cycles of 40% \dot{VO}_2 for 5 minutes, 70% \dot{VO}_2 for 3 minutes, 125% \dot{VO}_2 for 5 seconds). Exercise was performed in a post-absorptive state in the late afternoon with 30% or 50% reductions in fast acting insulin doses postexercise. Therefore caution should be taken when applying these results to other individuals performing exercise of varying intensity and duration, at different times of the day and with different insulin and carbohydrate regimes.

In addition the IHE protocol was performed in the laboratory and only provides the basis for the physiological stress of IHE and will not truly reflect the complex activity patterns performed in the field during team sport activities. Furthermore most team sports last up to 80-90 minutes with a half time break which would allow the intake of carbohydrates and adjustments to insulin regimes. This research only represents a proportion of a game within the field. Caution should therefore be taken when applying these results to team sports.
It is also acknowledged that this study does not identify possible mechanisms for the blood glucose responses found here within this research. Complex metabolic and physiological measures have not been measured during the study. The purpose however for this was to ensure that the focus was on patient information and education. The aim of this study was not to produce physiological or metabolic reasons for blood glucose responses, but to provide some patient information about what is likely to happen as a result of exercise at certain intensity, at a certain time of the day and with certain insulin and carbohydrate adjustments. It was hoped that results would thus allow some application to patient practice.

In addition, as mentioned in the Discussion, Chapter 5, the post-exercise meal was not standardised for every individual and it is acknowledged that this may have in part caused the large variations in the blood glucose responses seen particularly around teafour hours post. As a result it may have impacted upon the true effect of the intervention, and future studies may want to standardise the amount and content of the meal post-exercise in order to take into account the effects of the GI of different carbohydrate types that affect gastric emptying rates.

It is important to note that the lag time associated with the interstitial blood glucose reading with the CGM (noted in methods, Chapter 3B) can limit the accuracy of the CGM for predicting blood glucose levels. This could have been particularly true straight after the post exercise insulin reduction and the meal in this study, as blood glucose concentrations would be changing so rapidly. However the accuracy of these readings were improved through the calibrations that were taken by asking the participants to record their blood glucose at least four times a day using their SBGM. Despite this fore mentioned limitation, the CGM is still a useful tool for the prediction of blood glucose trends, particularly during periods where individuals do not regularly check their blood glucose, ie following meal times and during the night.

It should also be acknowledged that the lack of statistical significance within the study could be due to the very small sample size and the large variation in the blood glucose responses to exercise. Small sample sizes and the skewness of the data relating to the number of hypoglycaemia episodes and time spent in the ideal range, made it impractical to carry out statistical analysis. Caution should be taken thus with the percentage time in the ideal range results as this is a very robust measure due to the large variability between patients, making it very difficult to detect any differences. The small sample size is inevitable however with clinical trials that have a strict inclusion criteria and possess significant time commitments. While the changes may not be statistically significant, results may be physiologically meaningful for the participants and information may be able to be provided on an individual basis regarding safe participation in IHE.

6.3 Implications

Assuming that some of the major limitations in this study: small sample size and lack of control over carbohydrate intake, are addressed in future research, there could be future implications for patient practice.

Recommendations for individuals with type 1 diabetes wishing to take part in IHE are often conflicting and suggest similar management strategies for both continuous moderate intensity exercise and IHE (Birrer and Sedaghat, 2003; Pierce, 1999). This recommendation is not supported by current research which demonstrates that there is a difference in the responses of blood glucose concentrations to moderate and IHE (Iscoe and Riddell, 2011; Maran *et al.*, 2010; Guelfi *et al.*, 2005b). However within this research study it has been found that moderate and IHE result in similar blood glucose responses both during and after exercise, thus indicating a similar risk for the development of LOPEH and also hyperglycaemia. This observation has never been discovered before and therefore the advice that IHE should be performed over moderate intensity exercise to minimise the risk of hypoglycaemia (Guelfi *et al.*, 2005b) is an oversight and is not in agreement with results from this study. Further research into the blood glucose responses to IHE utilising a CGM are required. The use of a CGM aids in raising awareness and provides clinicians and those with type 1 diabetes detailed

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information on glucose responses to exercise. In particular it can highlight blood glucose responses overnight, which has been shown in this study to be a high risk time for the development of hypoglycaemia and also it can highlight the risk of hyperglycaemia immediately after the evening meal, where again participants may not be trained to check blood glucose levels. The use of CGMs' may facilitate insulin and carbohydrate adjustments in relation to exercise.

Instead of reducing pre-exercise insulin doses before exercise, individuals could aim for a pre-exercise blood glucose level of 10 mmol.1⁻¹. This is higher than what was originally suggested in the intervention. This research has shown for the same IHE performed on two different occasions the average blood glucose drop will be ~3.5 mmol.1⁻¹. Therefore for IHE performed in the late afternoon in a post-absorptive state, advice may therefore be offered based on this knowledge . Assuming this, if exercise commenced with blood glucose concentrations at 10mmol-¹, then blood glucose would still remain within a safe range during and after the exercise bout. There may however be variation in the responses between individuals and therefore caution should be taken when applying this advice to all those individuals with type 1 diabetes.

In addition, individuals may require additional carbohydrate supplementation straight after exercise before the following meal. The amount of carbohydrate taken could follow the advice previously given in the intervention prior to exercise and is outlined in Appendix 2. This is based on advice that suggests that 10g of carbohydrate raises blood glucose concentrations by 2.5 mmol.1⁻¹ (DAFNE, 2002). However given the wide range of blood glucose responses and in particular the inter and intra-variation in individuals responses to a particular amount of carbohydrate, it would be difficult to prescribe an exact quantity of carbohydrate to prevent hypoglycaemia in all individuals following IHE.

In order to prevent LOPEH after exercise, Maran *et al* (2010) studied the response to IHE in the late afternoon with a following 20% fact acting insulin reduction. Despite this intervention results reveal that IHE is characterized by the risk of LOPEH (Maran *et al.*, 2010). It would appear that a reduction of the insulin dose after exercise at the

following meal is insufficient to prevent LOPEH in individuals with type 1 diabetes. In fact such an insulin dose reduction could lead to problems of hyperglycaemia, as found in this study. Although not addressed, the mechanisms of hyperglycaemia could be presumed to be related to hepatic glucose output is increasing to a greater extent than muscle glucose uptake (Gallen, 2009). However in order to understand the underlying mechanisms behind this, a more detailed analysis in terms of glucose kinetics and measurements related to counter-regulatory hormones is required, which is beyond the scope of this study.

Various strategies have been employed to prevent LOPEH previously such as reducing the basal insulin dose and consuming extra carbohydrates prior to bed time (Iscoe and Riddell, 2011; Taplin *et al.*, 2010). However the reduction of the basal insulin dose is not ideal since this can affect the blood glucose concentrations for the following 24 hours and there is the risk of developing hyperglycaemia (Taplin *et al.*, 2010). This strategy is thus not practical if exercise is performed on a frequent basis since regular hyperglycaemia can lead to long term complications such as diabetic retinopathy, neuropathy and cardiovascular disease (Pierce, 1999). It also appears, as found in this study, that such a great reduction of insulin dose after exercise with the following meal can also cause high blood glucose levels in the following 2-4 hours after the evening meal, leading to hyperglycaemia, the opposite problem of hypoglycaemia.

Additional carbohydrate intake before bed has been suggested to attenuate LOPEH after afternoon IHE. A 30g carbohydrate drink following IHE appeared to reduce the risk of developing LOPEH in one study (Iscoe and Riddell, 2011). The intervention in this current study suggested taking additional carbohydrate (10-20g) before bed if blood glucose concentrations were under 10 mmol.1⁻¹. Currently there are no standard guidelines in carbohydrate intake after exercise to decrease the risk of hypoglycaemia; however the consumption of complex carbohydrates mixed with fat and protein may help prevent blood glucose decline, by prolonging carbohydrate availability (Wilson *et al.*, 2008). As previously mentioned the amount of carbohydrate intake needed to maintain euglycaemia varies significantly between individuals because of numerous factors, including circulating insulin levels, energy expenditure, levels of glucose counter regulatory hormones, and training status. Frequent blood glucose monitoring

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(at least initially when trying new strategies) is strongly recommended so that various nutritional regimens can be tested.

6.4 Directions for Future Research

Future research efforts should attempt to adhere to rigorous methods whilst striving for larger sample sizes. One strategy may include collaboration with other health care providers to gain access to additional patients. In addition, in order to allow results to be applicable to all complicated free individuals with type 1 diabetes greater efforts should be made to recruit poorly controlled individuals. It is often the individuals who are adherent to exercise and have well controlled type 1 diabetes that will choose to participate in a study. It would be interesting to investigate the impact of this intervention on a group of naïve exercisers with HbA_{1c} levels >10 %.

In relation to intermittent exercise that is specific to team sports, future research may want to consider whether different work to recovery ratios would elicit a different blood glucose response. The effect of a full game duration could be investigated and the blood glucose responses to an actual field game remains to be determined. This would thus bring in additional factors such as half time breaks and the additional stress response to a competitive game situation.

In relation to the intervention described in this research, future work should consider the impact of increasing the starting blood glucose concentrations prior to exercise and the addition of extra carbohydrate administration at the end of exercise prior to the following meal. In addition more research is required in order to confirm if a reduction in insulin dose post-exercise is required in order to preserve blood glucose concentrations after IHE.

Finally gender differences were also not accounted for within this research, partly due to the fact that there were not enough participants to allow a meaningful statistical comparison. This leaves the question of whether a gender difference exists in the responses to IHE and would different management strategies be required? Furthermore, specifically for females would the phase of the menstrual cycle have an impact on the results? Clearly further research of this kind is warranted for the development of more detailed evidence based guidelines for those with type 1 diabetes wishing to take part in IHE.

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Appendices

APPENDIX 1

LITERATURE SEARCH HISTORY

Medline (EBSCO)

Thursday, June 28, 2012 10:45:07AM

#	Query	Limiters/Expanders	Last Run Via	Results
S 8	((MH "Blood Glucose") OR "blood glucose" OR (MH "Blood Glucose Self-Monitoring")) and (S6 and S7)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE	12
S7	(MH "Blood Glucose") OR "blood glucose" OR (MH "Blood Glucose Self-Monitoring")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE	125243
S 6	((intermittent high intensity exercis*) and (S2 or S3 or S4)) and (S1 and S5)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE	6
S5	(intermittent high intensity exercis*) and (S2 or S3 or S4)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE	51
S 4	intermittent high intensity	Search modes -	Interface -	51

	exercis*	Boolean/Phrase	EBSCOhost Search Screen - Advanced Search Database - MEDLINE	
S 3	team* and sport*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE	2890
S2	intermittent exercis*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE	1020
S1	(MH "Diabetes Mellitus, Type 1") OR "type 1 diabetes"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE	56136

British Nursing Index (EBSCO)

Monday, November 28, 2011 11:02:46 AM

#	Query	Limiters/Expanders	Last Run Via	Results
S7	(blood glucose) and (S1 and S5 and S6)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - British Nursing Index	0

\$6	blood glucose	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - British Nursing Index	275
S5	(team* and sport*) and (S1 and S4)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - British Nursing Index	0
S4	team* and sport*	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - British Nursing Index	9
S 3	intermittent high intensity exercise	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - British Nursing Index	0
S2	intermittent exercis*	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - British Nursing Index	0
S 1	type 1 diabetes	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - British Nursing Index	302

SportDISCUS

Thursday, June 28, 2012 11:31:48 AM

#	Query	Limiters/Expanders	Last Run Via	Results
S 8	S7 and S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen -	15

			Basic Search Database - SPORTDiscus	
S7	S4 and S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Basic Search Database - SPORTDiscus	13
S6	DE "DIABETES" OR DE "INSULIN resistance"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Basic Search Database - SPORTDiscus	3902
S5	DE "BLOOD sugar" OR DE "HYPOGLYCEMIA" OR DE "HYPERGLYCEMIA" OR DE "GLUCOSE"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Basic Search Database - SPORTDiscus	3644
S4	S1 OR S2 OR S3	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Basic Search Database - SPORTDiscus	132706
S 3	intermittent high intensity exercise*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Basic Search Database - SPORTDiscus	102
S2	team* and sport*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Basic Search Database - SPORTDiscus	131895
S 1	intermittent exercis*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Basic Search Database - SPORTDiscus	855

CINAHL

Thursday,	June 28,	2012	11:59:33	$\mathbf{A}\mathbf{M}$
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#	Query	Limiters/Expanders	Last Run Via	Results
S8	S6 and S7	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL Plus with Full Text	18
S7	(MH "Blood Glucose") OR "blood glucose" OR (MH "Blood Glucose Self- Monitoring")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL Plus with Full Text	15927
S6	S1 and S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL Plus with Full Text	10
S5	S2 or S3 or S4	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL Plus with Full Text	1829
S4	team* and sport*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL Plus with Full Text	1599
S 3	intermittent high intensity exercis*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database -	19

			CINAHL Plus with Full Text	
S2	intermittent exercis*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL Plus with Full Text	242
S1	(MH "Diabetes Mellitus, Insulin-Dependent")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL Plus with Full Text	8826

Cochrane Library

ID	Search	Hits	Edit	Delete
#1	MeSH descriptor Diabetes Mellitus, Type 1 explode all trees	2810	<u>edit</u>	<u>delete</u>
#2	(intermittent exercis*):ti,ab,kw	804	<u>edit</u>	<u>delete</u>
#3	(team* and sport*):kw	0	edit	<u>delete</u>
#4	(intermittent high intensity exercis*):ti,ab,kw	82	edit	<u>delete</u>
#5	(intermittent exercis*) or (intermittent high intensity exercis*):ti	1072	<u>edit</u>	<u>delete</u>
#6	<u>(#1 AND #5)</u>	3	<u>edit</u>	<u>delete</u>
#7	blood glucose	16009	edit	<u>delete</u>
#8	<u>(#6 AND #7)</u>	6	<u>edit</u>	<u>delete</u>

APPENDIX 2

INTERVENTION FOR INSULIN AND CARBOHYDRATE ADJUSTMENT IN RELATION TO EXERCISE

Before exercise

Bolus/meal insulin

• If exercising within 2 hours of eating a meal, reduce the bolus/meal dose by 50%

Blood glucose

- Aim for blood glucose at 8 mmol immediately before exercise
- If blood glucose over 12mmol,
 - check for ketones
 - take a correction dose
- If blood glucose over 17mmol **do not** exercise
- If blood glucose under 8 mmol have the following carbohydrate (CHO):

Blood glucose prior to exercise	Amount of CHO (gm)
Under A	30
	50
4-6	20
6 - 8	10
8 or over	0

After exercise

Bolus/meal insulin

- If eating within 2 hours of exercise, reduce the bolus/meal dose by 30%
- After 2 hours return to usual dose

Long acting insulin

- Take usual Lantus or Levemir dose **Blood glucose**
 - If blood glucose at 8 mmol or under before bed have 10-30 grammes of CHO

APPENDIX 3

PARTICIPANT INVITES/INFORMATION SHEET



EDINBURGH NAPIER UNIVERSITY Faculty of Health, Life and Social Sciences Research Ethics and Governance Committee

Participant Information Sheet

My name is Lorraine Steel and I am an MSc Research student from the Faculty of Health, Life and Social Sciences at Napier University in Edinburgh. As part of my postgraduate degree course, I am undertaking a research project for my Masters dissertation.

The title of my project is: Blood Glucose Responses to Intermittent High Intensity Exercise in Individuals with Type 1 Diabetes: A Trial of a Structured Intervention for Insulin and Carbohydrate Adjustment

Background:

At present existing guidelines to minimize the risk of hypoglycaemia associated with exercise in type 1 diabetic patients are often general and fail to take into account exercise of different types, durations and intensities. Specifically there are no guidelines for individuals wanting to participate in Intermittent High Intensity Exercise. This type of exercise involves short bouts of intense activity, interspersed with longer periods of lower intensity activity. This type of exercise is typical of many team based sports such as football, rugby and hockey.

The **aim** of the proposed research is to investigate the effects of a structured intervention for insulin and carbohydrate adjustment on blood glucose responses during and after intermittent exercise that replicates team and field based sports in individuals with type 1 diabetes.

It is hoped that the findings will add to the current research on Intermittent Exercise and will lead on to developing appropriate insulin dose reductions and carbohydrate supplementation for type 1 diabetics to allow safe participation in intermittent activities.

What is required of you:

- 1. Prior to inclusion in this study, you will be required to undergo a medical screening by completion of a pre-test questionnaire in order to ensure that you are suitable for this study and that participation will not put you at any risk. Your GP will be informed that you are participating in this research.
- Testing will take place over 4 separate days with 1 week between each testing session. All sessions will take place at the School of Life Sciences (Sport and Exercise Science, Napier University, Colinton Road, Edinburgh). Each session will involve exercise so please come in comfortable clothing and footwear.
- 3. On day 1 you will be asked to attend the lab for a familiarization session during which anthropometric measurements will be taken (height, weight), and blood pressure will be recorded. \dot{VO}_2 max is the maximal capacity of your body to transport and use oxygen during exercise and it reflects your physical fitness. Your \dot{VO}_2 max will be estimated using a sub-maximal incremental walking protocol on the treadmill. This will require you to be being fitted with a heart rate monitor and a face mask for breath by breath gas analysis. This should take no longer than 1 hour.
- 4. On day 2 you will be asked to perform the moderate intensity protocol in the physiology lab. Before exercise you will be fitted with the Guardian RT Medtronic blood glucose monitoring device and given instructions on its use. You will also be taken through the procedures for recording food intake, insulin dosage and physical activity levels that will be required of you throughout the study. The exercise will involve continuous running at 50% VO₂ max for 40 minutes. Your VO₂ max will be determined from your initial VO₂ max test on day 1. During this time heart rate, rates of perceived exertion and blood glucose will be recorded.
- 5. On day 3 you will be asked to perform the intermittent protocol in the physiology lab. Before exercise you will be fitted with the Guardian RT Medtronic blood glucose monitoring device and given instructions on its use. You will again be taken through the procedures for recording food intake, insulin dosage and physical activity levels that will be required of you throughout the study. The exercise will take 40 minutes and will involve

you performing cycles of walking at 40% \dot{VO}_2 max for 5 minutes, jogging at 60% \dot{VO}_2 max for 3 minutes and sprinting at 125% \dot{VO}_2 max for 5 seconds. During this time heart rate, rates of perceived exertion and blood glucose will be recorded. It should be noted that this protocol will require you to run at fast speeds on the treadmill during the sprinting period.

- 6. On day 4 you will be asked to repeat the intermittent protocol outlined above. This will take place approximately 1 month after the last session.
- 7. Prior to all exercise sessions you will be asked to follow your usual insulin regime and ensure that it is the same for both trials. You will be given some advice based on an intervention for insulin and carbohydrate supplementation. In addition your food intake should be similar for both trials and caffeine, alcohol and structured exercise should be avoided 48 hours before testing. This will be explained in more detail to you when you arrive on Day 1 of testing.

Criteria for Inclusion:

In order to participate in this study you must be between the age of 20-50, type 1 diabetic of at least 2 years, have an HbA1c of under 10%, are physically active for 20 minutes or more at least twice a week and undertake a mixture of competitive or recreational sports. All participants should use a basal bolus insulin regime with analogue insulin and will be experienced with carbohydrate counting and insulin dose adjustments.

You will not be eligible for this study if you have any of the following:

diagnosed peripheral vascular disease, orthopaedic problems, diagnosed heart disease, proliferative retinopathy, peripheral neuropathy, hypoglycaemic unawareness.

What are the Risks?

The risks involved are minimal but may involve potential fatigue due to the exercise protocols. Wearing of the Guardian RT monitor may be inconvenient however will provide valuable data on your blood glucose responses during and after exercise.

Should you experience hypoglycaemia or any other complications during any of the exercise sessions a trained diabetic nurse will be present at all times.

You will be free to withdraw from the study at any stage, you would not have to give a reason, and it will not affect your treatment.

All data will be anonymous and your name will be replaced with a participant number or a pseudonym, and it will not be possible for you to be identified in any reporting of the data gathered. Any data collected will be kept in a secure place to which only myself and my academic supervisor has access. This will be kept until the end of the research process.

The results may be published in a journal or presented at a conference. It will also be possible for you to obtain an explanation of the results in written or verbal form to help with your understanding of your diabetes and exercise.

If you have any further questions then please do not hesitate to contact me. If you would like to participate in this study then please see the attached consent form.

Thank you for your time

Lorraine Steel

Email: ****

APPENDIX 4

PARTICIPANT CONSENT FORM



Edinburgh Napier University Faculty of Health, Life and Social Sciences Research Ethics and Governance Committee

Consent Form

Blood Glucose Responses to Intermittent High Intensity Exercise in Individuals with Type 1 Diabetes: A Trial of a Structured Intervention for Insulin and Carbohydrate Adjustment

I have read and understood the information sheet and this consent form. I have had an opportunity to ask questions about my participation.

I understand that I am under no obligation to take part in this study.

I understand that I have the right to withdraw from this study at any stage without giving any reason.

I agree to participate in this study.

Name of participant:

Signature of participant:

Signature of researcher:

Date:

Contact details of the researcher:

Name of researcher: Lorraine Steel, MSc Diabetes and Exercise Student

Address: *****

Email / Telephone: ***** / *****

APPENDIX 5

HEALTH AND ACTIVITY QUESTIONAIRE

School of Life Science Edinburgh Napier University

Questionnaire to be administered at visit 1 to establish routine management of diabetes when exercising.

Your Type of Exercise or Activities

1. How often do you exercise per week? Please circle.

Once a week 2-3 times a week 4-6 times a week Daily

- 2. What type of exercise do you do? (please specify, include more than one if necessary)
- 3. Approximately how long for?

20mins 30mins 45mins 1 hour 2hours Longer

4. What is the usual time of the day?

Before breakfast Morning Afternoon Before Tea Evening

5. Why do you exercise?

To lose weight	To tone up	To get fit	To feel better
To improve your blood	sugars	Other (please specify	y)

- 6. Would you describe your exercise as (please tick):
 - a) Short and Sharp (up to 60 minutes) e.g. exercise or dance class, treadmill, swimming.
 - b) Long and Leisurely e.g. walking, golf.
 - c) Prolonged and Enduring (over 1 hour) e.g. football, tennis, rugby, distance running.

Your Insulin

- 1. What types of insulin do you take?
 - at meal times
 - at bed time
- 2. What are your usual doses?

Breakfast	Lunch	Tea	Bed	Other times
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- 3. Do you adjust your insulin doses when exercising? If yes, what do you do?
- 4. What do you do with your injection sites when exercising?

Your diet

- 1. How do you manage your diet before or after exercising?
- 2. Do you eat or drink anything immediately before? If yes, what?

Problems you may have

- 1. Does exercise cause any problems with your blood sugars? If yes, what?
- 2. How do you try to overcome any problems?
- 3. Do you ever have hypo's either during or after exercise?
- Never Less than half the time Half the time or more Every time
 - 4. Have you ever had a severe hypo where you needed assistance from someone?

Never Once Twice More than twice	Never	Once	Twice	More than twice
----------------------------------	-------	------	-------	-----------------

5. Do you ever have night time hypo's after exercise?

Never Less than half the time Half the time or more Every time

Advice you have been given

5. Is there any information we could have given you that would have helped? (please tick)

- Insulin adjustment Carbohydrate adjustment Hypo management
- Other please specify

School of Life Sciences Napier University, Edinburgh

ASSESSMENT IN THE EXERCISE PHYSIOLOGY LABORATORY

PRE-TEST QUESTIONNAIRE

ALL THE INFORMATION RELATING TO THESE PROCEDURES IS CONFIDENTIAL

NAME

DATE OF BIRTH	 AGE	B.P

.....mm Hg

As you are to be a subject in this laboratory, it is necessary for you to complete the

following questionnaire.

Please circle the appropriate statement.

How would you describe your present level of activity?

Sedentary /moderately active /active /highly active

How would you describe your present fitness level?

very unfit /moderately fit /trained /highly trained

How often do you participate in exercise of a maximal nature?

Never /sometimes /often

How would you consider your present body weight?

Underweight /ideal weight /slightly overweight /very overweight

Are you a regular smoker? Are you an occasional smoker? Are you a previous smoker?	Yes/No – if yes i Yes/No – if yes a Yes/No – if yes i	number per day average per week how long since stoppin 	 ng yrs
Do you drink alcoholic drinks?		Yes/No	
If <i>yes</i> do you: have the occasion have a drink ever	al drink? y day?	Yes/No Yes/No	
Have you had to consult your doctor with details	nin the last 3 montl	hs? Yes/No – if ye	s give
Are you currently taking any form of meadetails	dication?	Yes/No – if ye	s give
Do you suffer, or have ever suffered, from	n		

Asthma? Yes/No

Diabetes?

Yes/No
	Bronchitis?	Yes/No
	Epilepsy?	Yes/No
any form o	f Heart complaint	? Yes/No
Is there a history of heart disease in your family? details	?	Yes/No – if yes give
Do you currently have any form of muscle or joi details	nt injury?	Yes/No – if yes give
Have you had any cause to suspend normal activ	ity in the last two	weeks?
	Yes/N	o – if yes give details
Have you any allergies to plasters, Micropore tap	pe, skin electrodes	, latex gloves
details		res/no – ir yes give
145		

successfully completing the tasks that have been explained to you? Yes/No - if yes give details Have you donated blood in the last week? Yes/No Signature of subject Date Name of Academic Investigator/Project Officer..... Signature of Academic Investigator/Project Officer

To the best of your knowledge is there any other reasons that may prevent you from

.....

Please supply the name, address and telephone number of an emergency contact: (please print)

APPENDIX 6

EXAMPLE $\dot{v}O_2$ MAX CALCULATION

Workload	VO2	HR
1	11.1	86
2	15.1	101
3	19.7	115
4	24.6	133
5	31.3	147
6	35.1	164

Age Predicted HR max = 196bpm

VO2 max 196 = 3.128 x + 52.95 143.05 = 3.128 x x = 45.7



Target VO2 = desired vo2 x vo2					
40%	50%				
		0			
0.40 x 45.7	0.50 x 45.7	4			
18.28	22.85	3			

70%	125%
0.70 x	1.25 x
45.7	45.7
31.99	57.13

Treadmill Speed for 40%

18.28 = 3.5 + (0.2 s) + (0.9 s) x 0.001 14.78 = 0.2009 s s = 73.569 m. min s = 4.4 k/h on treadmill

Treadmill Speed for 50%	
22.85 = 3.5 + (0.2 s) + (0.9 s) x	
0.001	
19.35 = 0.2009 s	
s = 96.32 m.min	
s = 5.8 k/h on treadmill	

Treadmill Speed for 70%

31.99 = 3.5 +(0.2 s) + (0.9 s) x 0.001 xcxxbv28.49 = 0.2009 s s = 141.81 m.min s= 8.5 k/h on treadmill

Treadmill Seed for 125%
57.13 = 3.5 + (0.2 s) + (0.9 s) x
0.001
53.63 = 0.2009 s
s = 266.94 m.min
s = 16 k/h on treadmill

APPENDIX 7

PARTICIPANT MONITORING DIARY

DAILY MONITORING DIARY

Name:	Date:							
	Breakfast	Morning	Lunch	Afternoon	Evening Meal	Evening	Bed	During night
Total CHO eaten								
(g)								
Extra CHO before								
Exercise								
Extra CHO during								
Extra CHO during								
Exercise								
Extra CHO after								
exercise								
Blood glucose	В	В	В	В	В	В	В	В
B=before								
D=during	D	D	D	D	D	D	D	D
A=after								
*if not exercising	Α	Α	Α	Α	Α	Α	Α	Α
record reading in								
before (B) section								
Insulin taken								
Usual insulin dose								

Exercise:				
How long for?				
What did you do?				
Hypo's Tick appropriate box if experience and fill details in hypo diary				

APPENDIX 8

PARTICIPANT HYPOGLYCAEMIA DIARY

Hypoglycaemic Episodes

Please record all hypo's related to exercise.

Please rate as mild or severe i.e. mild = you can treat it yourself and severe = you need help from someone else.

Date/	Mild	During	Within 2	Over 2	During	Blood	Symptoms	Treatment
Time	or	exercise?	hours of	hours	đ	glucose	you had	(please
	severe		exercise?	after	the night?	(using		circle)
				exercise?		meter)		TC 4
								If other
								please
								specify
								Deset as a 1/
								Dextrosol/
	Mild /	Ves / No	Ves / No	Ves / No	Vec /	Ves /		Lucozade/
	wind /	105/10	105/10	105/10	No	No		Chocolate
	Severe				110	INU		Uupostop
								Typostop
								Glucostop
						1/1		Glucagon
						mmol/l		Glucugoli
								Other: