Impact of acute resistance exercise on glycaemia in individuals with type 1 diabetes.

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Impact Of Acute Resistance Exercise On Glycaemia In Individuals With Type 1 Diabetes

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ABSTRACT

The impact of acute resistance exercise (RE) on glycaemia in type 1 diabetes (T1DM) individuals is poorly understood. Yet, such knowledge would have great use in improving our understanding of blood glucose control during and after the performance of RE. Increasing research in this area might help minimise complications associated with blood glucose vulnerability and potentially maximise health benefits related to RE which are known to be obtained by people without diabetes. The overarching aim of this thesis was to examine the impact of acute RE on glycaemia in T1DM individuals, and promote confidence in people with T1DM to partake in this form of exercise and lead a more physically active lifestyle.

Exercise volume, or the total weight lifted during a RE session, is a primary component in the design of a RE session. Therefore, Chapter 3 examined the acute impact of manipulating RE session volume in T1DM individuals. The results demonstrate that exercise volume is an important factor in determining the blood glucose responses to RE; specifically, blood glucose concentrations rose above rest for one hour after one and two sets of similar intensity RE, but this exercise-induced hyperglycaemia was attenuated by increasing the volume of exercise by addition of a similar intensity third set of RE. Additionally, performing morning RE after an overnight fast and in the absence of rapid-acting insulin, did not induce acute hypoglycaemia, ketoacidosis or raise a marker of muscle damage, but caused metabolic acidosis in a dose-dependent fashion.

Exercise intensity is a characteristic that is integral to the design of a RE session, and this characteristic might play a role in explaining the exercise-induced hyperglycaemia caused by the thirty minute (two-set) RE sessions in Chapter 3. The aim of Chapter 4 was to examine the impact of manipulating exercise intensity in T1DM individuals. The findings from this study demonstrate that performing a low intensity RE session evoked a similar magnitude of post-exercise hyperglycaemia and metabolic acidosis than a higher intensity RE session, when sessions were matched for total weight lifted.

In an attempt to alleviate the consistent exercise-induced hyperglycaemia presented by the two-set RE session, the aim of Chapter 5 was to implement a modified algorithm that delivers an individualized dose of rapid-acting insulin after morning RE, to counter acute post-exercise hyperglycaemia in T1DM individuals. The results demonstrate that post-exercise rapid-acting insulin injection delivered by means of an algorithm resulted in reductions to post-RE hyperglycaemia without the occurrence of hypoglycaemia during two hours after exercise. However, during the subsequent twenty hours of freely living conditions, T1DM individuals remained unprotected from post-exercise hypoglycaemia as per a control condition. Overall, the findings of this thesis underpin some important factors that determine the glycaemic and metabolic responses to acute performance of RE, which may facilitate the better management of blood glucose around this form of exercise, in T1DM individuals.

DECLARATION

I hereby declare that this thesis has been composed by myself, that the work is the result of my own investigations except where assistance has been otherwise acknowledged, that the work has not been previously submitted in candidature for any other degree, that all sources of information have been specifically acknowledged by means of reference, and that consent is provided for the thesis to be made available for photocopying and for inter-library loan.

Signature Date

16/01/2015

Daniel Turner

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In my younger years I was once told that I could achieve anything if I set my mind to it. Although such a thought is admittedly naïve, it is a phrase that I still hold close to me. Challenging, is how I describe my past three years of study. But the rollercoaster of emotions and countless matches burned has given me a sense of achievement that inspires me to continue to challenge what I consider my own limits. From every collected blood sample to each written sentence, this thesis is a true reflection of "setting my mind to it"! In all sincerity, the work presented herein would not have been possible without the following people whom I deeply thank:

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LIST OF ABBREVIATIONS

ACSM American College of Sports Medicine

AD Adrenaline

ADA American Diabetes Association

ANOVA Analysis of variance

BG Blood glucose

β-OHB β-hydroxybutyrate

BG_{IAUC} Net incremental blood glucose area under the curve

BMI Body mass index

CHO Carbohydrate

CK Creatine kinase

CRH Counterregulatory hormone

CSSII Continuous subcutaneous insulin infusion

GH Growth hormone

GI Glycaemic index

H^+ Hydrogen ion

Hb Haemoglobin

HbA_{1c} Glycosylated Haemoglobin

Hct Haematocrit

HR Heart rate

IL-6 Interleukin-6

IU Insulin unit

K^+ Potassium

MDI Multiple daily injections

NA Noradrenaline

NEFA Non-esterified fatty acid

NPH Neutral Protamine Hagedorn

RE Resistance exercise

TDD Total daily insulin dosage

T1DM Type 1 Diabetes Mellitus

T2DM Type 2 Diabetes Mellitus

VO_2 peak (or max) Peak or maximum oxygen uptake

%HR_{max} Percentage of age-predicted heart rate maximum

%1RM Percentage of one repetition maximum

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PUBLICATIONS ARISING FROM THIS THESIS

(Also see Appendix P)

ACADEMIC JOURNAL PAPERS

Turner D, West DJ, Campbell MD, Gray BJ, Dunseath G, Luzio S, Bain SC, Bracken RM. Impact of single and multiple sets of resistance exercise in type 1 diabetes. *Scandinavian Journal of Medicine and Science in Sports (in press) DOI: 10.1111/sms.12202.*

Turner D, Kilduff LP, West DJ, Campbell MD, Gray BJ, Dunseath G, Luzio S, Bain SC, Bracken RM. Reductions in resistance exercise-induced hyperglycaemia are associated with circulating interleukin-6 in type 1 diabetes. *Diabetic Medicine 2014,* 31(8):1009-1013. *DOI: 10.1111/dme.12462.*

Turner D, Ayles M, Gray BJ, Bain SC, Luzio S, Rees ED, West DJ, Campbell MD, Bastin L, Bracken RM. Syncope during resistance exercise in an individual with type 1 diabetes. *Practical Diabetes International 2013,* 30(7): 290-293. *DOI: 10.1002/pdi.1795.*

Turner D, Gray BJ, Luzio S, Bain SC, Hanley S, Richards A, Rhydderch DC, Hanley S, Ayles M, Campbell MD, Kilduff LP, West DJ and Bracken RM. Resistance exercise intensity does not influence the magnitude of post-exercise hyperglycaemia in type 1 diabetes individuals. *In submission.*

Turner D, Luzio S, Bain SC, Martin R, Gray BJ, Hanley S, Richards A, Rhydderch DC, Hanley S, Campbell MD, Kilduff LP, West DJ and Bracken RM. An algorithm that delivers an individualised rapid-acting insulin dose after morning resistance exercise counters post-exercise hyperglycaemia in type 1 diabetes patients. *In submission.*

CONFERENCE PROCEEDINGS

Turner D, Gray BJ, Luzio S, Bain SC, Hanley S, Richards A, Rhydderch DC, Campbell MD, Kilduff LP, West DJ and Bracken RM. Efficacy of an individually determined rapid-acting insulin dose algorithm for improving post-resistance exercise glycemia in type 1 diabetes patients. *In proceedings of American Diabetes Association: Diabetes 2014,* 63: A170-A212.

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Turner D, West DJ, Campbell MD, Gray BJ, Dunseath G, Luzio S, Bain SC, Bracken RM. Increasing the duration of an acute resistance exercise session tempers exercise- induced hyperglycaemia in those with type 1 diabetes. *Diabetic Medicine 2013,* 30(S1): 16.

CHAPTER ONE

Introduction

And

Review Of The Literature

1.1 BRIEF INTRODUCTION

Performance of exercise in individuals with type 1 diabetes (T1DM) is complicated by the absence of pancreatic β-cell function, which necessitates the pharmacological and nutritional management of insulin levels to maintain blood glucose homeostasis. Inaccurate management of insulin levels around exercise can expose the individual with T1DM to hypo- or hyper-glycaemia, both of which heighten the risk of acute and chronic health complications. In an effort to improve exercise safety and performance, strategies have been developed which help T1DM individuals to improve euglycaemic stability during and after exercise. However, the generation of effective strategies is complicated by the diverse relationship between different exercise characteristics and glycaemia. Whereas low to moderate intensity aerobic exercise increases the risk of hypoglycaemia in individuals with T1DM, this cohort is more susceptible to hyperglycaemia during and soon after high-intensity exercise. Resistance exercise (RE) is a form of intermittent exercise, recommended to those with T1DM for multiple health benefits. Its versatility means that RE can be composed of multiple different arrangements of exercise characteristics to suit the individual's goals, yet little is understood about the impact of acute RE characteristics on blood glucose in T1DM and, consequently, strategies for the management of blood glucose around acute RE are severely lacking. Therefore, the overarching aim of this thesis was to examine the impact of acute RE on glycaemia in T1DM individuals. Such information could be used to improve the management of blood glucose in T1DM during and after exercise, thereby minimising complications associated with blood glucose vulnerability and potentially maximising health benefits related to this form of exercise.

1.2 TYPE 1 DIABETES

It is estimated that 8% of the world's population suffers from diabetes (International Diabetes Federation, (1)). Recent statistics demonstrate that although the percentage of new cases of type 1 diabetes (T1DM) in the United States is decreasing relative to those with type 2 diabetes (T2DM), the number of people diagnosed with T1DM is on the rise (2). T1DM usually appears before the age of 40, especially in childhood (Diabetes UK, (3)). Within Europe, during the years between 1989 and 2008, the incidence rate of childhood T1DM rose by an average of approximately 3-4% per annum (4). If present trends continue, a doubling of new cases of T1DM in European children younger than 5 years is predicted between 2005 and 2020, and prevalent cases younger than 15 years will rise by 70% (5). In 2011, 2.9 million people in the UK were diagnosed with diabetes (Quality Outcomes Framework, (6)) and it is estimated that 5 million people will have diabetes by 2025 (7), which is equivalent to more than 400 people every day. In 2012, the UK diabetes health organisation estimated that 10% of adults and 15% of children with diabetes have T1DM (8). Life expectancy is shortened in T1DM by more than 20 years (9). The rapidly growing scale of T1DM along with the associated patient care (treatment, intervention and complications) costs is alarming. The UK National Health Service spending on T1DM patient care was approximately £1 billion in 2010/11, and these costs have been projected to almost double by 2035 (10). The majority of this spending went into managing avoidable complications (10).

1.3. BLOOD GLUCOSE REGULATION IN TYPE 1 DIABETES

Type 1 diabetes is characterised by the autoimmune destruction of pancreatic β-cells within the islets of Langerhans, ultimately resulting in the absolute loss of endogenous insulin. The significance of this loss is realised in that insulin plays an integral role in regulation of blood glucose levels, and as such the pharmacological replacement of insulin is crucial to the treatment of T1DM. Blood glucose homeostasis refers to the maintenance of around 4-5 $mmol.L^{-1}$ of glucose within the circulation (11), and this is achieved by the interaction of several hormones which ensure a balance between endogenous glucose production and uptake, with insulin being a hormone critical in lowering blood glucose. Insulin stimulates a net decrease in glycaemia by inhibiting glucose output from the liver and increasing peripheral

glucose uptake (12). While the liver can modulate glucose production in response to changing blood glucose levels independent of hormone and substrate delivery (13), the liver responds directly to the concentration of insulin within the portal vein; insulin exerts its effects by binding to hepatic insulin receptors and stimulating insulin-signaling pathways; hepatic glycogenolysis is inhibited by small increases in portal insulin concentration whereas large increases in insulin concentration occurs before inhibition of hepatic gluconeogenesis (14). Insulin also indirectly suppresses hepatic glucose production, by reducing the availability of FFA, glycerol (through inhibition of adipose tissue lipolysis) and amino acids (through inhibition of proteolysis), and antagonising hypothalamic innervation of liver nerves (15). Insulin augments the peripheral glucose uptake by binding to insulin receptors on extra-hepatic insulin sensitive cells (i.e. predominantly skeletal muscle (16)), which manifests an influx of glucose into the cell via GLUT4 translocation.

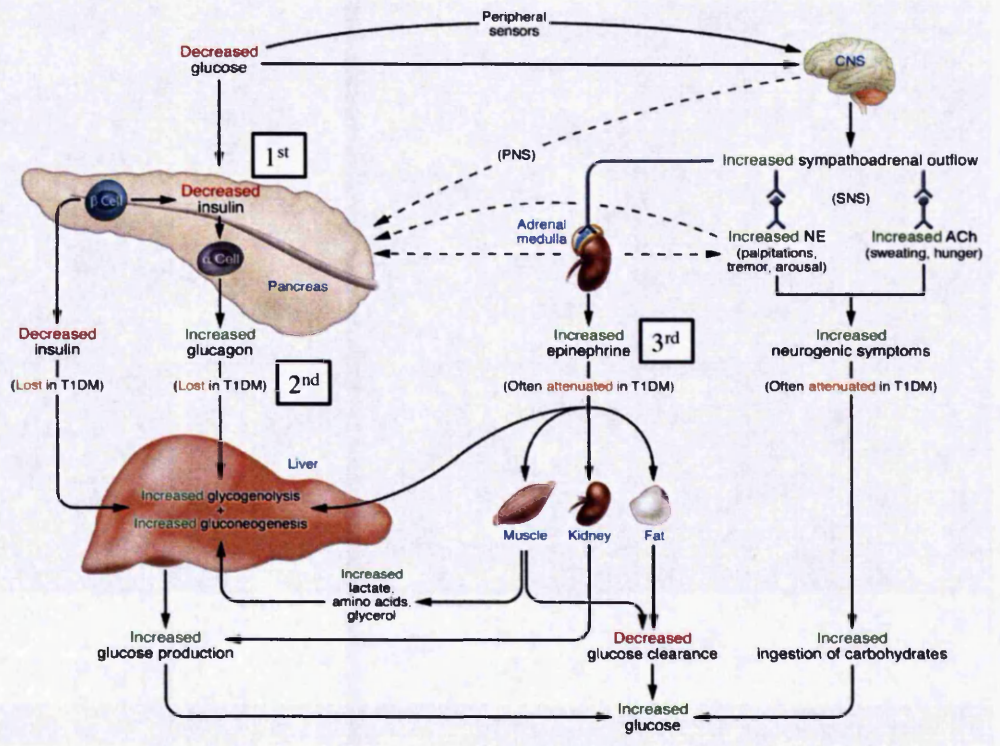


Figure 1.1: Neuroendocrine responses to a decline in glucose concentrations within the bloodstream and potential impairments in the physiological defense to hypoglycaemia in people with T1DM. **1st, 2nd, 3rd** refer to order of responses to falling blood glucose. **ACh**: acetylcholine; **NE**: noradrenaline; **PNS**: parasympathetic nervous system; **SNS**: sympathetic nervous system. Adapted from Cryer et al. (17).

In the healthy individual without diabetes, the rate of endogenous insulin secretion is dictated by the concentration of blood glucose that passes through pancreatic β-cells (18). At rest, a rise in blood glucose concentration triggers an increase in the secretory rate of insulin resulting in a net loss of glucose within the blood stream. Conversely, insulin secretion is repressed at a blood glucose concentration of ~4.4 $mmol.L^{-1}$ (19; 20), which sensitises the liver to glucagon and precedes an increase in pancreatic glucagon production (19-21). The primary objective of this response is to invoke a disproportionate increase in the rate of endogenous glucose production relative to that of glucose uptake. A decrease in the concentration of glucose in the blood of less than ~3.6 to 3.8 $mmol.L^{-1}$ results in the secretion of counterregulatory hormones, catecholamines, growth hormone and cortisol (19; 20), which all oppose the effects on insulin by independently and synergistically stimulating an increase in blood glucose concentration (Figure 1.1).

Catecholamines promote an elevation in blood glucose levels by stimulating a transient increase in hepatic glucose output (22-27) as well as a reduction in the rate of glucose uptake (22), via binding to β-adrenoceptors. This increase in hepatic glucose production is initially accounted for by an increase in glycogenolysis, while gluconeogenesis seems to have a more progressive contribution (23). Catecholamine-induced inhibition of glucose disposal is thought to occur via reductions in insulin-mediated glucose extraction (28; 29) and/or through a build-up of glucose-6-phosphate that inhibits hexokinase activity. High physiological levels of catecholamines have been shown to inhibit the secretion of insulin (30), while at the same time their increased appearance has been shown to augment the release of glucagon (31) and growth hormone (32). Glucagon has been shown to amplify the potency of catecholamines on glycogenolysis, while cortisol tends to convert adrenaline's hepatic action from a transient to a sustained response (22). Notably, there is difficulty in inferring from systemic blood sampling the contribution of glucagon to alterations in circulatory glucose since prior to its appearance within the systemic circulation, glucagon is extracted by the liver following its release into the portal vein (33). Cortisol acts synergistically with both glucagon and adrenaline to increase blood glucose levels (34), but cortisol has also been shown to independently increase blood glucose concentrations within approximately 1 hour (35; 36) to 3 hours (37) of infusion, through augmenting glucose production and decreasing glucose

utilisation. Similarly, elevated growth hormone levels are associated with increased rates of hepatic glucose production (38) and attenuated rates of glucose utilisation (38-40). Studies demonstrate that growth hormone has insulin-antagonistic effects (39; 41; 42), by attenuating the glucoregulatory effects of insulin i.e. to inhibit glucose production and to stimulate glucose utilisation. Studies suggest that the cause of acute growth hormone related insulin resistance is attributed to downstream reductions in glycogen synthase activity (39; 43).

A commonality between these counterregulatory hormones is their lipolytic effects; increased rates of lipid oxidation and elevated circulating levels of FFA have been observed in response to elevated levels of catecholamines (44-46), cortisol (37) and growth hormone (40; 47; 48). The increased availability of these metabolites contributes to hepatic glucose production via their conversion to glucose, thereby preserving liver glycogen stores (38; 49). With a continued loss of circulatory glucose, the intensity of the counterregulatory hormone response (particularly sympathoadrenal activity) increases, resulting in inhibition of peripheral glucose uptake, shunting of blood flow to central organs (i.e. away from splenic bed and muscles), and hepatic glucose production is increased (50).

1.3.1 Hyperglycaemia

The American Diabetes Association (ADA) Standards of Medical Care (51) define a random *plasma* glucose reading of >11.1 $mmol.L^{-1}$ as hyperglycaemia. Hyperglycaemia typically occurs during times of mild insulin deficiency or complete absence of portal and systemic insulin, when there is insufficient restraint of both hepatic glucose production and stimulation of glucose uptake, which favours a net increase in circulating glucose levels. Increased levels of blood glucose coupled with hypoinsulinaemia can result in glucosuria and hypovolaemia which can manifest as symptoms of increased thirst and polydipsia, polyuria and nocturia, blurred vision and drowsiness (52).

The magnitude (or severity) of hypoinsulinaemic-hyperglycaemia is exacerbated by an increase in counterregulatory hormones. Insulin deficiency and raised counterregulatory hormone levels stimulates the production of ketones bodies (β-

hydroxybutyrate, acetoacetate and acetone), as a by-product of elevated rates of hepatic beta-oxidation (53). An accumulation of ketones above normal physiological levels (>1 $mmol.L^{-1}$) increases blood acidity and lowers residual bicarbonate levels with resulting metabolic acidosis and ketonaemia (53), which is clinically deemed as ketoacidosis. Ketoacidosis manifests symptoms of nausea, vomiting, hypotension, tachycardia, and psychological stress (52). Diabetic ketoacidosis (DKA) is clinically identified as ketonaemia of more than or equal to 3 $mmol.L^{-1}$, venous pH < 7.3 and/or bicarbonate < 15 $mEq.L^{-1}$ (54). Hyperglycaemia coupled with DKA reflects a catabolic, severe inflammatory state, in the absence of obvious infection or cardiovascular pathology (55). It has been shown that DKA is the most common cause of death in children and adolescents with T1DM (56). The ADA suggests that caution should be taken if glucose levels exceed 16.6 $mmol.L^{-1}$ without ketonaemia, and it is only essential to avoid exercise if fasting glucose levels are > 13.9 $mmol.L^{-1}$ with ketonaemia (57). The frequent occurrence of hyperglycaemia promotes the generation of microvascular and macrovascular complications (52; 58), which are primarily associated with the formation of advanced glycation end-products that accumulate in proportion to the magnitude of hyperglycaemia and time of exposure. Thus for the purpose of this thesis, hyperglycaemia was defined as a *blood* glucose reading of > 9.9 $mmol.L^{-1}$ (i.e. a *plasma* glucose reading of > 11.1 $mmol.L^{-1}$).

1.3.2 Hypoglycaemia

Hypoglycaemia in diabetes is defined by the ADA as "all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm" (59). However, a single blood glucose concentration cannot define hypoglycaemia in diabetes. This is because glycaemic thresholds for symptoms and neuroendocrine responses to hypoglycaemia are lowered after recent antecedent hypoglycaemia (60-62) and raised in individuals with poorly control diabetes (63). Additionally, those with well controlled diabetes (i.e. frequent hypoglycaemia) often tolerate low blood glucose levels in the absence of symptoms (64). With varying degrees of hypoglycaemia manifests neurogenic (autonomic) symptoms including tremor, palpitations, anxiety/arousal, sweating, hunger and paresthesia, which are also a function of the individuals perception of the sympathetic response associated with hypoglycaemia (65; 66). Brain glucose deprivation *per se* evokes neuroglycopenic

symptoms including cognitive impairments, behavioural changes and psychomotor abnormalities (e.g. confusion, blurry vision, weakness, difficult speaking) and potentially seizure and coma - these symptoms typically occur at glycaemic thresholds of 2.6 to 3.0 $mmol.L^{-1}$. Individuals with T1DM experience an average of two symptomatic hypoglycaemic episodes per week, and one severe, at least temporarily disabling, hypoglycaemia, often with seizure or coma, per year (67). Rabasa-Lhoret et al. (68) investigated the interaction between exogenous insulin dose, carbohydrate supplementation and exercise in T1DM individuals and defined hypoglycaemia as a blood glucose concentration of ≤ 3.5 $mmol.L^{-1}$. However, blood glucose values of ≤ 3.9 $mmol.L^{-1}$ have been shown to trigger a physiological response (50). Furthermore, anecdotally T1DM individuals correct blood glucose concentrations before this "hypoglycaemic" level is attained. Thus, in this thesis a blood glucose concentration of 3.9 $mmol.L^{-1}$ was defined as hypoglycaemia and a value of ≤ 4 $mmol.L^{-1}$ was defined as low blood glucose.

An episode of hypoglycaemia in T1DM is now considered to be the result of interplay between absolute exogenous insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations (17; 19; 60; 67). Circulatory insulin levels can be considered excessive when they inhibit hepatic glucose production to an extent that results in a greater increment in glucose uptake than production leading to net decrease in blood glucose. Exogenous insulin cannot be endogenously regulated. Thus, people with T1DM are marred by the loss of the first and impairment/loss of the second physiological defences to hypoglycaemia, i.e. a reduction in insulin secretion and increase in glucagon secretion (17) (Figure 1.1). The glucagon response to lowered blood glucose is progressively lost over time (69), potentially due to impairments in β-α cell signalling with a resulting loss of α-cell function (70). Failure in these defences necessitates the third response; the sympathoadrenal and sympathetic neural response – resulting in increased catecholamine secretion (19). However, for reason stated above, the secretion of adrenaline in response to low blood glucose if often attenuated in T1DM (17; 60; 64; 71) (Figure 1.1).

That hypoglycaemia blunts the counterregulatory hormone response to a subsequent fall in blood glucose below the physiological level (17; 60; 64), the individual's recognition of physiological changes to hypoglycaemia (i.e. the resultant neurogenic symptom response) is attenuated (65). With this reduced awareness to hypoglycaemia comes a loss of the behavioural defense to hypoglycaemia, i.e. carbohydrate consumption (60; 67). Hypoglycaemia unawareness is also apparent following sleep or exercise (71). Notably, even when the glucagon and adrenaline responses are intact, excessive insulin can blunt hepatic glucose production and increase glucose uptake resulting in hypoglycaemia. In fact, hypoglycaemia unawareness is associated with a 6-fold increased risk of treatment-induced hypoglycaemia (72), and T1DM individuals who experience hypoglycaemia are immediately at risk of recurrent episodes (73). For these reasons, the occurrence of hypoglycaemia is unfortunately a fact of life for the T1DM individual (74). Nevertheless, it is encouraging that the sympathoadrenal response (i.e. the glycaemic threshold at which adrenaline secretion is elevated), lack of cognitive function, and hypoglycaemic unawareness, can be restored following two to three weeks of avoiding hypoglycaemia (75). Consequently, the main defense against hypoglycaemia is early recognition of symptoms in order to increase energy consumption and prevent a further decline in blood glucose levels.

1.4 TREATMENT OF TYPE 1 DIABETES

Type 1 diabetes is currently incurable. However, the normalisation of glycaemia through the administration of exogenous insulin (also known as insulin therapy; section 1.4.1) alongside the frequent monitoring of blood glucose and a healthy diet alleviates some of the burdens of this chronic disease. The Diabetes Control and Complications Trial (DCCT) evidenced from data collected over a mean of 6.5 years that intensive treatment (i.e. with an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring) with the goal of maintaining blood glucose concentrations close to the normal physiological range effectively delayed the onset and slowed the progression of diabetic retinopathy, nephropathy and neuropathy, in people with T1DM, when compared with conventional therapy of one or two daily insulin injections (76-79). The study specifically demonstrated that a 1% fall in HbA_{1c} resulted in a statistically significant decrease in microvascular complications (77). Intensive treatment of T1DM is not

without its challenges; the DCCT trial demonstrated that the occurrence of severe hypoglycaemia increased from two to six-fold with intensive treatment as compared to conventional treatment (80).

Increasing the frequency of monitoring glycaemic levels (involving capillary blood sampling from the fingertip, which is analysed using a portable blood glucose meter) was associated with improvements in metabolic control in T1DM, with a drop of 0.20% in HbA_{1c} for each additional test per day, levelling off after 5 tests per day (81). With the advent of continuous glucose monitoring systems (CGMS), that periodically samples interstitial glucose every 5 minutes, the ability to more frequently monitor glucose levels may better enable T1DM individuals to anticipate a rise or fall in blood glucose outside of the normal physiological range, as opposed to a single sample reading. But the benefit of CGMS over single sampling remains equivocal (82). The ADA Standards of Medical Care currently recommend that diabetes individuals should aim towards HbA_{1c} values of around 7%, and a goal of <6.5% is reasonable if this can be achieved without significant hypoglycaemia or adverse effects of treatment (51). Relevant to glucose monitoring, ADA also state that, "Most patients with type 1 diabetes... should consider self-monitoring of blood glucose prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, and after treating low blood glucose until they are normoglycaemic". In addition to insulin therapy and regular glucose monitoring, improvements in HbA_{1c} of T1DM individuals have been associated with a diet that is; consistent in the amount and source of carbohydrate intake from day-to-day; of low glycaemic index (GI) (83), and rich in vegetable-derived carbohydrates relative to starch-based carbohydrates (84). Primary benefits to T1DM individuals specifically related to the consumption of a low GI diet include lower daily mean blood glucose concentrations (85), reduced incidence of hypoglycaemia and reductions in HbA_{1c} (86). Recent research also demonstrates reduced hypo- and hyperglycaemic excursions during and after exercise with the replacement of high- with low-GI carbohydrates (87; 88). Furthermore, lowering daily carbohydrate intake with a compensatory increase in fat and protein intake resulted in a > 1% reduction in HbA_{1c} over a 12 month period (89).

1.4.1 Exogenous Insulin Administration

The administration of exogenous insulin is an essential component in the treatment of T1DM. The primary aim of insulin therapy is to mimic the natural secretory pattern of endogenous insulin of healthy individuals without diabetes (as depicted in Figure 1.2), with the view of permanently maintaining glycaemia within a normal physiological range.

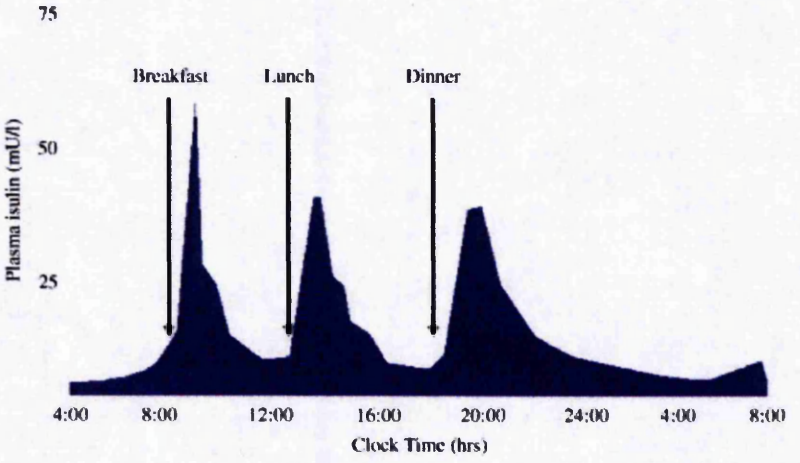


Figure 1.2: Normal insulin secretion throughout a 24-hour period. There exists background insulin secretion upon which is superimposed by secretory bursts in response to meal-time feeding. Basal-bolus insulin injections can closely mimic this pattern. From (90).

As such, there are multiple types of exogenous insulin that differ pharmacokinetically in absorption rate, duration of action and time of peak action (Table 1.1). Regular soluble (short acting) insulin is used as a bolus injection (20-30 minutes before meals) alongside intermediate acting insulin in a twice-daily regimen or a basal analogue given once daily. Alternatives to short acting insulin are rapid acting insulin analogues, which are typically administered before meals (and in some cases, soon after) in combination with longer acting insulin. Basal insulin analogues replace background residual insulin. This form of insulin is taken once daily in the evening or morning, usually in combination with rapid acting insulin. Long acting insulins are similar to basal insulin analogues in that they are designed to exert an effect over 24 hours. However, converse to basal insulin analogues, long acting insulins have a dose accumulative effect that can increase the likelihood of hypoglycaemia. The onset, peak effect and duration of action vary as a function of many peripheral factors, all of which affect the speed and consistency of absorption. For instance, age, fat mass, dose

of injection, site and depth of injection (subcutaneous vs. intramuscular; abdomen vs. thigh), exercise, insulin concentration, and ambient and body temperature, have all been shown to affect the time-action profile of exogenous insulin (91).

Table 1.1: Types of insulin preparations available to T1DM and action-profiles.

Insulin Type	Pharmacokinetics			Reference
	Onset of action (h)	Peak of action (h)	Period of action (h)	
Rapid acting analogue: aspart, glulisine, lispro.	0.15-0.35	0.75-1	3-5	(92-94)
Regular/soluble (short acting)	0.5-1	2-5	6-8	(95)
Intermediate acting				
NPH	2-4	4-12	12-24	(96)
Basal long-acting analogue				
Glargine	1.5	None	20-24	(96)
Detemir	2.5	None	20-24	
Degludec	-	None	>24-42	(97)
Long-acting Ultralente type				
Humulin U	4-6	8-20	20-24	(96)
Novolin Ultralente	4	8-24	28	

h refers to hours. **NPH**: Neutral Protamine Hagedorn insulin.

1.4.2 Calculation Of Daily Insulin Dosage: Basal-Bolus And Bolus Correction

There is currently no strict approach to calculating the optimal basal-bolus dosage, but a common method employed by clinicians is based on the notion that the total daily insulin dosage (TDD) varies as a function of the inverse relationship between body mass and insulin sensitivity (i.e. TDD = body mass/insulin sensitivity; (98)). Thus, with regular glucose monitoring the TDD can be more accurately determined. The basal insulin dose typically accounts for 50% of the TDD (99), but the absolute dosage can vary depending on factors including HbA_{1c}, age and body mass and the clinician's own interpretation of the patient (90; 99).

As an example, the TDD for newly diagnosed individuals with T1DM is in the region of 0.5 $IU.kg^{-1}.day^{-1}$, but for a pre-pubertal child is approximately 0.9 $IU.kg^{-1}$ body

weight/day, rising during the pubertal years by anything up to 50–100 % (90). In relation to calculation of the bolus dosage, carbohydrate counting is a useful strategy prescribed to T1DM individuals that facilitates the adjustment of the rapid-acting insulin dose as a function of carbohydrate (CHO) intake (100). This approach has been shown to positively effect glycaemic control, reflected in lowered HbA_{1c} after one-quarter year (101). The insulin to carbohydrate ratio can be calculated in the following manner (90; 99):

Insulin:CHO ratio ($IU.g^{-1}$ of CHO): 1 IU= 500/TDD. So if the TDD is 50 IU, the insulin:CHO ratio is 1 U of insulin for every 10 g of CHO. If the estimated CHO content of the meal is 30g, then 3 U of insulin will be required.

Nevertheless, this is merely an estimate for the T1DM individual. Refinement of the bolus insulin dosage occurs with regular testing of postprandial glucose at ~2-hours after the meal against pre-prandial glucose concentrations. In this way, the individual/clinician can ascertain how successful the estimation of insulin dose to CHO intake has been. It is important that the T1DM individual is aware of the target blood glucose i.e. euglycaemia; there is no evidence for strict goals, but ADA recommend that pre-meal blood glucose targets generally 7.8 $mmol.L^{-1}$ with random blood glucose 10.0 $mmol.L^{-1}$ are reasonable (51), provided these targets can be safely achieved. The ratio of CHO:insulin units should be considered changeable with physical activity and/or unplanned exercise (100), as well as with diurnal changes in insulin sensitivity (100).

Inevitably, sometimes T1DM individuals administer insufficient insulin relative to their physiological requirement, which is typically due to unfamiliarity of a particular event such as exercise or a dietary change, resulting in hyperglycaemia. In this case a correctional dose of insulin might be necessary. While correctional doses of insulin can be effective at restoring euglycaemia, the timing of injection and dose need to be considered carefully. For example, approximately 50% of the previously injected bolus insulin analogue can have an affect on glucose metabolism for 2 hours after injection, and 20% of the dose remains within the circulation at ~4-hours after injection (90). Thus, if a correction dose is taken within 2 to 3 hours after a previous

dose of rapid acting insulin, the T1DM individual needs to be conscious of an insulin-stacking effect whereby additional insulin could culminate within the bloodstream leading to hyperinsulinaemic-induced hypoglycaemia.

While there are permutations in calculation of the correctional dose (98; 99), these algorithms are fundamentally used to estimate what magnitude of fall in blood glucose concentration will occur per unit of insulin. The accurate insulin management (AIM) system has evolved from earlier systems as it provides a balance of accuracy against opposing benefits of being short, easy to remember, and easy to use, in order to minimise dosing errors (99). Unlike other systems which assume that there exists no inter-individual variability in glucose metabolism each day, this system is more compatible with the physical principle that the magnitude of decline in blood glucose per unit of insulin is inversely related to a person's weight, representing the size of their intravascular and interstitial space, and is inversely related to their insulin sensitivity, representing the ease with which glucose is transported into insulin-sensitive cells (98; 99). For metric users, this system has been referred to as the 100-rule; Figure 1.3 demonstrates how the correction dose is calculated.

RA required to reduce BG by 1 mmol.L^{-1} within 2 hours = TDD/100. For example, if the TDD is 20 U, then 1 IU will reduce BG by 5 mmol.L^{-1}.

Figure 1.3: Calculation of an insulin correction dose using the 100-rule (99). **TDD**: Total Daily Dose of Insulin. **RA**: Rapid-acting insulin. **BG**: Blood glucose.

Ultimately an effective approach to maintaining euglycaemia, is to continually evaluate the interaction between the physiological state of the T1DM individual and the environment (e.g. diet and lifestyle changes) against the acute impact of insulin therapy on glycaemia. For example, a strategy should be aligned to not only the anticipated glycaemic response to a task (e.g. exercise) but specifically take into account the actual real-time glycaemic response on every given occasion. Thus, the derivation of an optimal glucose management strategy is to tailor the adjustment of insulin and diet to each individual as a function of the change in blood glucose evoked by the environment/situation; in turn, the strategy is validated and individualised.

1.5 PHYSICAL EXERCISE IN TYPE 1 DIABETES

When considering the benefits of regular physical activity, it is no surprise that there exists a role for physical exercise in the management of T1DM.

Table 1.2: Diabetes Health Organisation Physical Activity (PA) Guidelines/Recommendations for individuals with type 1 and type 2 diabetes.

Health Organisation	Exercise Recommendation / Guideline
ESSA Position Statement (102)	T2DM/Pre-diabetes: 210 min per week of MOD or 125 min per week of VIG with no more than two consecutive days without training. RE: ≥ 2 sessions per week (2-4 sets of 8-10 repetitions) should be included in the total 210 or 125 min of MOD or VIG, respectively. Exercise training programs should recognise and accommodate comorbidities and complications.
ADA and ACSM Joint Position Statement (103)	T2DM: at least 150 min per week of MOD to VIG aerobic exercise spread out during ≥ 3 days during the week, with no more than two consecutive days between bouts of aerobic activity. Aerobic exercise should be at least at MOD, corresponding approximately to 40–60%VO_2max. Additional benefits may be gained from VIG (>60%VO_2max). RE: ≥ twice weekly on non-consecutive days; training should be of moderate (50%1RM) or vigorous intensity (75-80%1RM) for optimal gains in strength and insulin action; each RE session should include 5-10 exercises involving major muscle groups (in the upper and lower body), progressing over time to heavier weights (or resistance) that can be lifted only 8-10 times; 1-4 sets should be completed; to avoid injury, progression of intensity and volume should occur slowly by firstly increasing repetitions, followed by sets and then by sessions per week.
Diabetes UK (104)	Recommendations are in reference to WHO guidelines (105): Adults aged 18–64 should do at least 150 minutes of MOD or at least 75 min of VIG throughout the week or an equivalent combination of MOD and VIG. MOD (aerobic) should be performed in bouts of > 10 min duration. For additional health benefits, adults should increase their MOD to 300 min per week, or engage in 150 min of VIG per week, or an equivalent combination of MOD and VIG activity. Muscle-strengthening activities should involve major muscle groups on ≥ 2 days a week.
CDCP (106).	T1DM and T2DM: MOD for > 30 min on ≥ 5 days of the week, e.g. walking briskly, mowing the lawn, dancing, swimming, or bicycling. Individuals unaccustomed to PA, may want to start with a little exercise, and work your way up. With increases in strength, add a few extra minutes to your PA. Do some PA every day. It is better to walk 10 or 20 min each day than one hour once a week.
ACSM (107)	T1DM: Exercise 20 to 45 min at an intensity (longer if low intensity) of 40–60%VO_2max (if no neuropathy), for 5–7days/week or daily at low to moderate intensity. Also, moderate intensity circuit, interval or free weights, with progression in number of repetitions in relation to physical ability (i.e. initially starting at 8-10 repetitions building to a maximum of 20 repetitions).

ESSA: Exercise and Sports Science Australia. **ADA**: American Diabetes Association. **ACSM**: American College of Sports Medicine. **CDCP**: Centres For Disease Control And Prevention. **RE**: Resistance exercise, **MOD**: Moderate intensity exercise, **VIG**: Vigorous intensity exercise. **VO_2max**: Maximal Aerobic Capacity. **1RM**: One repetition maximum.

1.5.1 Physical Activity Recommendations

Regular physical activity is advocated for the management of type 1 and 2 diabetes on a worldwide scale by multiple health organisations (57; 102-104; 106; 107). As such, exercise guidelines have been developed with specific reference to exercise modality, intensity, duration, volume and frequency of training (Table 1.2). Along with regular performance of aerobic oriented activities (or submaximal exercise), it is evident from these guidelines (in Table 1.2) that strength training (also known as resistance exercise) is identified as an integral component of a physical exercise programme. It is also clear that the majority of diabetes health organisation advice for exercise relates to type 2 diabetes (T2DM), and by comparison, specific exercise guidelines for T1DM individuals are lacking. Relevant to T1DM, the American Diabetes Association state that, "All levels of physical activity, including leisure activities, recreational sports, and competitive professional performance, can be performed by people with T1DM who do not have complications and are in good blood glucose control" (57). Diabetes UK, a public health organisation based in the United Kingdom, align their exercise guideline for diabetes to that recommended to the general population (Table 1.2).

1.5.2 Health Benefits Of Physical Activity

The importance of physical activity is highlighted by the inverse relationship between risk of all-cause mortality and level of physical fitness in both men and women without diabetes (108). Similarly, in T1DM, a physically active lifestyle is associated with reduced risk of diabetes-related complications (109; 110) and cardiovascular disease (110), increased life expectancy (110; 111), improved mental well-being (112) and overall, better quality of life (113). A staggering finding is that sedentary individuals with T1DM are three times as likely to die than those who are physically active (111). Interventional studies in individuals with T1DM, demonstrate that adherence to a physical exercise programme can improve blood lipid profile (114; 115), blood pressure (116) and endothelial function (115). While the majority of these exercise-related health benefits can be attributed to aerobic-type training and/or a combination of aerobic and resistance exercise (RE) training (i.e. chronic exercise), very few studies have investigated the impact of only chronic RE training on health of people with T1DM (117-119) (Table 1.3).

Table 1.3: Health benefits of chronic exercise in T1DM

Author	Participants	Type of PA	PA Programme	Outcome
Sideraviciute et al. (120)	19 T1DM Females HbA_{1c}: 8.5±0.4	MOD Swim (144–156 beats.min^{-1})	Swimming (pulse rate controlled): 45 min, 2 x per week for 14 weeks	~ 0.7%↓ in HbA_{1c}
Fuchsjäger-Mayrl et al. (115)	18 T1DM (11 males, 7 females)	MOD Cycle (60–70% HR_{max})	Cycling: 3 x 1 hour per week for 8 months	↔ HbA_{1c} , ↑CV fitness, ↑endothelial function, ↓ insulin dose, ↔ HDL, LDL, BP, or body mass
Campaigne et al. (121)	10 T1DM	HIGH Run (>160 beats.min^{-1})	Running/movement activities: 30 min, 3 x per week for 12 weeks	~4.3%↓ in HbA_{1c}, ↔FBG, ↑CV fitness
Durak et al. (119)	8 T1DM	RE	10 upper and lower body exercises: 3 to 7 sets of 12 reps (unknown intensity), with 30-s to 2-min between sets. 3 x per week, 10 weeks	↓ HbA_{1c} from 6.9% to 5.8%. ↑strength. ↓ total cholesterol.
Ramalho et al. (118)	7 T1DM vs. 6 T1DM	MOD to HIGH Run/Walk (60–90% HR_{max}) vs. RE	40 min Run/Walk vs. 3 sets of 8-12 repetitions, upper and lower body, 60-s rest between sets, at 60% to 80% 1RM (40 min); 3 x per week, 12 weeks	MOD ↑ HbA_{1c} but RE ↓ HbA_{1c} (non-statistical) ~8.2% to ~7.6%. Both 20%↓ NPH insulin dosage. Both ↔HDL, LDL, TG, FBG or total cholesterol.
Salem et al. (116)	196 T1DM No Exercise: 48 Exercise once/week: 75 Exercise thrice/week: 73	None vs. MOD to HIGH Cycle/Run (65–95% HR_{max}) + RE + Flexibility	Moderate: 30 min heart rate controlled cycle/run High: Intervals of 1-2 min run RE: 2 exercises (lower body), 3 sets of 10 repetitions at 50 to 75% to 100% 10RM	Both exercise programmes: ↓HbA_{1c}, ↓lipid profile, ↓ insulin dose, ↑ body comp. ↓ DBP in exercise thrice,
D'Hooge et al. (117)	16 T1DM	None vs. RE + MOD Cycle/Run (60–70% $HR_{Reserve}$)	2 x 1 hour sessions per week, for 20 weeks	Exercise: ↔HbA_{1c} or body comp, ↓insulin dose (↑ in no exercise), ↑CV, ↑well-being.

PA: Physical activity. **RE**: Resistance exercise. **MOD**: Moderate-intensity exercise. **HIGH**: High-intensity exercise. **HDL**: High-density lipoprotein. **LDL**: Low-density lipoprotein. **DBP**: Diastolic blood pressure. **FBG**: Fasting blood glucose. **TG**: Triglyceride. **CV**: Cardiovascular fitness. **Body comp**: Body composition. **BP**: Blood pressure.

T1DM individuals demonstrate reductions in blood lipid profiles and increased muscular strength following 10 weeks of RE training (119), and improved cardiovascular fitness and well being after 20 weeks (117). Although the utility of RE in the prevention and management of diabetes has become more apparent during the last decade, the weight of evidence for the benefits of RE resides in studies involving individuals with T2DM and without diabetes. The most obvious roles for RE include the reversal of muscle loss associated with aging (122) and improvement of functional capacity through increases in strength and physical performance (123; 124), but the therapeutic potential of RE has recently become more recognised; regular RE can have positive effects on blood lipidaemia (125), blood pressure (126), bone mineral density (127), and has been shown to reduce major risk factors associated with both cardiovascular disease and T2DM (128).

1.5.3 Benefits Of Physical Activity On Glycaemic Control

The effects of regular physical exercise on chronic glycaemic control have been heavily debated (129-131). Improvements in HbA_{1c} have been observed in T1DM in response to aerobic-based exercise training ((120; 121); Table 1.3). Although one study demonstrated that RE training resulted in a statistical ~1.1% fall in HbA_{1c} in T1DM individuals (119), others have demonstrated no effect of RE on glycaemic control (117; 118); moreover, where no improvement in HbA_{1c} was observed (117; 118), participants reduced their daily insulin dosage independent of any change in dietary intake (Table 1.3). Reduction in daily insulin requirements could be explained by an improvement in insulin sensitivity (132); for instance, improvements in insulin sensitivity have been demonstrated in response to aerobic exercise training (132-134) alongside a reduction in bolus (not basal) insulin dosage (132).

Relevant to RE, improvements in insulin sensitivity (135) and insulin signalling mechanisms (136) have been observed in those with T2DM, in response to several weeks of (chronic) RE training. However, no studies have investigated the effect on chronic RE training on insulin sensitivity in T1DM. From an acute perspective, one study assessed insulin sensitivity in T1DM in response to a single session of RE and witnessed no improvements in insulin sensitivity within 36 hours of a single exercise session (137). In T2DM, improvements in insulin sensitivity or glucose tolerance

have been observed within 24 hours after an acute RE session (138; 139), with higher intensities providing increased benefits. But these results contradict more recent findings, in which no improvements in glucose tolerance were observed at 24, 48 and 72-hours post-exercise (140). Conversely, after acute performance of one to three sets of 8-10 exercises (upper and lower body) at 65-85% (~10 repetitions per set), individuals without diabetes demonstrate increases in insulin sensitivity at 24-hours after exercise (141-143). Improvements in insulin sensitivity have also been observed in those with impaired fasting glucose at 24-hours after a variety of different volume and intensity RE sessions (144), with greater sensitivity observed after higher volume or intensity RE sessions. Aside from possible limitations presented by differences in the methods used to assess insulin sensitivity between these studies (e.g. clamp vs. oral glucose tolerance test), the variability in the effects of RE on insulin sensitivity might be attributed to diversity in RE characteristics, such as alterations in exercise volume and intensity. The findings of these RE studies i.e. in those with and without T2DM offer a framework for investigating the effect of acute and chronic RE in T1DM.

Interestingly, in a recent meta-analysis to determine the overall effects of chronic exercise on glycaemic control in individuals with T1DM – comprising, 13 aerobic training studies; 2 strength training studies; 4 combined (aerobic and strength) training; 6 high-intensity exercise (HIE) training studies – aerobic training was found to be a favourable tool for decreasing chronic glycaemic control, while resistance training, mixed and HIE did not improve chronic glycaemic control, in T1DM individuals (131). This analysis also revealed a trend for improvements in glycaemic control due to chronic RE training, but authors suggested that there were not enough studies in T1DM and/or subjects to confirm this statistically (131). It is difficult to determine why regular exercise has contrasting effects on glycaemic control, but factors such as reductions in insulin dosage or increases in dietary intake could negate an improvement in glycaemic control (albeit a reduction in insulin requirements could be considered as favourable) (133). Moreover, given the variability in blood glucose responses to differing types of exercise modalities (as highlighted later in this review), poor management of blood glucose during and after exercise might negate the effects of exercise training on HbA_{1c} (130).

Despite the lack of literature in RE and T1DM, it is plausible that T1DM individuals could experience all of the same health benefits from this form of exercise that those with and without T2DM experience. Thus, the therapeutic potential of RE holds promise in the management of T1DM.

1.5.4 Physical Inactivity In Type 1 Diabetes

Despite the favourable impact of regular exercise on health of T1DM individuals and rising healthcare costs associated with physical inactivity (145), levels of physical activity in T1DM are often suboptimal (146; 147). In fact, in a study of ~700 individuals with T1DM, approximately two-thirds of this population did not achieve the minimal amount of regular physical activity to maintain good health (146). Research has also demonstrated that physical activity levels in T1DM decrease with age (148).

It is for fear of hypoglycaemia that the majority of T1DM individuals avoid physical exercise (149), but other factors including, loss of glycaemic control, low fitness level, insufficient knowledge about both insulin pharmacokinetics and strategies to minimise the exercise-induced glycaemic imbalances were also perceived as barriers to physical activity (149). In mind of these findings, and that ADA Standards of Medical Care suggest that exercising individuals with T1DM should aim to keep their blood glucose levels before, during and after exercise above 5.5 $mmol.L^{-1}$ and below 13.8–16.7 $mmol.L^{-1}$ (51), it is astounding that only one-half of 103 T1DM individuals were found to be knowledgeable of strategies to minimise exercise-related glycaemic imbalances (149). Furthermore, out of a group of 91 T1DM individuals, only fifty percent of individuals reported monitoring their blood glucose levels during exercise, and the minority (i.e. 32%) adjusted their insulin dose according to blood glucose levels (150). Thus, strategies intended to increase adherence to exercise in T1DM should primarily aim to improve exercise-induced glycaemic imbalances, but also be simple in application to promote practice and allow for inter-individual variations in physical fitness.

1.6 CONSIDERATIONS FOR EXERCISE PRESCRIPTION IN TYPE 1 DIABETES: ALTERATIONS IN METABOLISM RELEVANT TO EXERCISE PERFORMANCE

An awareness of factors that could limit exercise performance is crucial to the design and prescription of exercise guidelines that maximise health benefits but ensure the safety of the participant. Considering the metabolic challenges which individuals with T1DM face, it is understandable that studies have reported impaired exercise performance and reduced tolerance to exercise in T1DM. For example, in male adolescents with and without diabetes, matched by age, weight, height, body mass index, and lean and fat mass, T1DM individuals expressed a 20% lower aerobic capacity (151). Moreover, reductions in endurance exercise capacity were evident in female adolescents with T1DM (152). In T1DM adults, however, reports of exercise performance are more mixed; Nugent et al. (153) reported no difference in maximal oxygen consumption in adults with long-standing diabetes, whereas Veves et al. (154) reported that impaired aerobic capacity was limited to inactive T1DM adults with underlying neuropathic complications. Yet, in T1DM and non-diabetes adults matched for VO_2max, endurance capacity is reduced in T1DM (155). Several studies have reported lower strength in T1DM individuals, when compared to those without diabetes (156-158). It is difficult to explain the exact source of functional impairment in T1DM, but the methods used to assess performance and experimental design both differ greatly across these aforementioned studies. Interestingly, where impairments in maximal VO_2 and exercise capacity in T1DM have been recognised, T1DM individuals expressed marked reductions in stroke volume, cardiac output, muscle blood flow (159) and muscle blood volume (159; 160), when compared to those without diabetes. Furthermore, where reductions in cardiac function during exercise in T1DM individuals have been demonstrated (in female adolescents), this was associated with impaired stroke volume (161).

From a different perspective, acute glycaemic instability could be a factor in attenuated exercise performance. For example, (i) hypoglycaemia severely impaired T1DM individual's ability to successfully carry out basic sports skills, when compared with euglycaemic and hyperglycaemic conditions (162), (ii) Ramires et al. (155) observed a correlation (r=-0.58, p<0.05, n=21) between endurance capacity (in

minutes) and the decline in glucose levels (i.e. concentrations at exhaustion minus resting levels, in mmol.L^{-1}) in T1DM, (iii) isometric muscle strength, but not maximal isokinetic performance, was reduced during hyperglycaemia but not during euglycaemia individuals with T1DM (163).

It is unclear how glycaemia can affect performance in T1DM, but the metabolic consequences of hypo- and hyper-glycaemia provide clues. For instance, an increased reliance on muscle glycogen has been demonstrated while exercising under hyperglycaemia when compared to exercising while euglycaemic (164), and both hyper- and hypo-glycaemia may alter the body's ability to utilise orally ingested carbohydrates (165; 166). Furthermore, in spite of relatively higher blood glucose and insulin concentrations compared to non-diabetes, the respective contributions of plasma glucose and liver glycogen to total energy yield were 50% lower in T1DM, whereas muscle glycogen use was 250% higher than those without T1DM (167). Thus glycaemic imbalances during exercise may restrict energy provision to the muscles. Considering that peripheral glucose uptake was impaired in a group of T1DM individuals during long-duration, low-intensity exercise under hyperinsulinaemia, when compared to individuals without diabetes (168), an impairment in glucose uptake could help explain the increased reliance on muscle glycogen during exercise. The finding that fasting liver glycogen levels were 25-45% lower in T1DM than non-diabetes individuals (where groups were matched for age, height, weight and body composition) (169), indicates that some T1DM individuals have reduced capacity to store energy. Metabolic alterations in a single group of T1DM compared to individuals without diabetes have been observed across different exercise intensities; the contribution of hepatic glycogenolysis to glucose production at rest, and during moderate (35% VO_2max) or high (70% VO_2 max) intensity exercise was 60% lower in those with T1DM compared to those without diabetes (170). Furthermore, during moderate intensity exercise, where glucose was infused to maintain hyperglycaemic levels (8 mmol.L^{-1}) under hyperinsulinaemia (using clamping technique), a disproportionate increase in utilisation of exogenous glucose relative to the increase in carbohydrate oxidation was observed in T1DM (171). Interestingly, it was later found by the same group that these responses were not related to an insulin-mediated inhibition on hepatic glucose production (172).

Encouragingly, with the correct manipulation of insulin therapy and diet it seems that exercise metabolism and/or performance can be restored in those with T1DM. When insulin levels in T1DM are representative of non-diabetics, the overall ratio of carbohydrate to lipid utilisation during exercise performed in the postprandial state can be normalised (173; 174). Conversely, fuel utilisation in T1DM during exercise has been shown to be reflective of individuals without diabetes when insulin levels were three-fold greater in T1DM, but only in the absence of carbohydrate intake (175). Yet, elsewhere it was shown that plasma glucose uptake was restored to normal only when insulin concentrations were around four-fold higher in T1DM compared with individuals without diabetes (176). Interestingly, glucose administration alongside pre-exercise prandial insulin leading to increased resting blood glucose increased endurance exercise capacity in T1DM individuals whose blood glucose decreased during exercise (155), suggesting that increases in pre-exercise blood glucose improves exercise performance in T1DM. Furthermore, when compared to euglycaemia, exercising under hyperglycaemia was without effect on peak power output or other physiological endpoints such as lactate, heart rate, or respiratory exchange ratio (177), and reductions in insulin dose to reduce the likelihood of hypoglycaemia did not influence aerobic capacity during cycling compared to the usual insulin dose (178). Notably, hyperglycaemia *per se* may increase the susceptibility to dehydration and acidosis, which could reduce exercise tolerance. Thus, it is possible that impairments in exercise performance can vary acutely depending on metabolic function, and different states of metabolism can affect T1DM individuals in differing ways.

While these aforementioned metabolic findings relate to T1DM individuals without any apparent diabetes-related health complications, underlying factors might inhibit and/or explain variability in exercise performance within the T1DM population. For example, muscle activation was attenuated during exercise in T1DM relative to non-diabetes individuals, and this was associated with HbA_{1c} (179). In this study, it was unclear why there was an association between HbA_{1c} and exercise performance, but as discussed previously, individuals with poor glycaemic control might be more susceptible to diabetes-related complications. Interestingly, research has demonstrated a decrease in strength with increasing duration of diabetes in T1DM independent of

diabetes-related complications (158). This loss of strength was paralleled by a loss of muscle mass, and although there was a slower rate of decline in muscle mass in T1DM individuals without neuropathy relative to those with neuropathy, muscle mass declined at a far greater rate in neuropathy-free individuals than individuals without diabetes (158). Conversely, where reductions in ankle extension and flexion functionality have been observed in T1DM compared to individuals without diabetes, the T1DM group demonstrate increased knee functionality compared to those without diabetes, and exercise performance was not related to severity of neuropathy or glycaemic control (156).

Together these findings demonstrate the potential for alterations in metabolism and attenuated performance both within the T1DM population and relative to healthy individuals without diabetes. It is clear that further research is needed to determine whether such metabolic alterations associated with T1DM could negatively impact exercise performance. Screening for complications and/or reductions in functional capacity is important to the safe and effective prescription of exercise (where health benefits are maximised), given that attenuated physical capacity could cause additional stress and ultimately reduce exercise tolerance and/or adherence. Certainly, exercise guidelines should acknowledge the variability in exercise tolerance between different T1DM individuals. Exercise sessions should be tailored to individual specific fitness levels.

1.7 MANAGEMENT OF THE GLYCAEMIC RESPONSES TO EXERCISE IN TYPE 1 DIABETES

The general classification of physical activity is an important consideration in the safe prescription of exercise, optimising adherence to an exercise program and maximising the potential benefits to health. However, the management of blood glucose during and after physical activity for the individual with T1DM is complicated by the diverse characteristics of exercise, such as exercise intensity and duration. As such, a fundamental aspect of developing a strategy to improve exercise-induced glycaemic fluctuations is knowledge of glycaemic imbalances caused not only by different exercise modalities but also of the relationship between subtle adjustments in exercise characteristics and blood glucose. Advice on how to appropriately adjust insulin

therapy and diet so that exercise can be performed safely is important to optimal management of blood glucose (i.e. euglycaemic stability) during and after exercise.

1.7.1 Steady State (Continuous) Exercise

During Exercise

Steady state continuous exercise, which is generally performed at a low to moderate intensity within the aerobic threshold (i.e. continuous running, cycling and swimming), is well recognised to expose individuals with T1DM to hypoglycaemia (68; 180). The primary reason why T1DM individuals are predisposed to hypoglycaemia during this type of exercise is because they cannot endogenously suppress exogenously administered insulin, which means that hepatic glucose production cannot fully compensate for the increased utilisation of blood glucose demanded by working muscles during exercise (176). Mechanistically, elevated levels of portal and systemic insulin concentrations desensitises the liver to glucagon thereby impairing hepatic glucose production and promoting insulin-induced peripheral glucose uptake. This relative hyperinsulinaemic induced hypoglycaemia is exacerbated by several factors including, (i) circulating insulin levels can be upheld by a previously administered bolus insulin injection, due to the insulin species' pharmacokinetics (68; 181) (Table 1.1), (ii) exercise *per se* can augment the absorption of insulin from the site of injection through increases in blood flow and temperature (182) (especially when insulin is injected into the exercising limb, (183)), and (iii) glucose disposal and utilisation are enhanced when hyperinsulinaemia is coupled with muscle contraction (172; 184). Even where no bolus insulin has been administered in the hours prior to exercise, those with T1DM still remain unprotected from hypoglycaemia because of elevated circulating basal insulin levels compared to exercise individuals without diabetes (181).

Other factors that may heighten risk of hypoglycaemia in exercising T1DM individuals may be an absence of glucagon secretion (albeit, glucagon responsiveness can vary between individuals) (69) and/or adrenal hormone secretion (185) in response to exercising hypoglycaemia. Moreover, exposure to hypoglycaemia prior to exercise (17), and a diminishment in the stimulatory effect of glucagon on hepatic glucose production (186) associated with T1DM may heighten the risk of exercise-

induced hypoglycaemia. This is an important aspect in understanding the exercise-induced hypoglycaemic response in T1DM, as glucagon is the chief regulator for increments in hepatic glucose output during steady state exercise (187). Lastly, it has been shown that some individuals with T1DM exhibit lower levels of hepatic glycogen independent of diet (170), which might limit capacity to compensate for the decline in glucose during exercise.

The counterregulatory hormone (CRH) responses to continuous and endurance exercise (i.e. low to moderate intensity of long duration) in T1DM are well characterised. Studies demonstrate ~2-3 fold increases in adrenaline (180; 188-190), ~5-fold increases in noradrenaline (180; 188-190), ~20-fold increases in growth hormone (188; 189), increased (189) or unchanged (188) levels of glucagon, and variable cortisol (180; 188-190) concentrations (where subtle increases are only observed late after exercise), in response to endurance exercise. Notably, the measurement of glucagon within the circulation is not necessarily reflective of its contribution to hepatic glucose metabolism due to pancreatic venous drainage, particularly during exercise, where hepatic blood flow is reduced relative to rest (33).

Differences in exercise intensity and duration between studies offers the most obvious reason as to why such variability exists in the CRH response to exercise, but research findings also suggest a number of other factors can affect the CRH responses to exercise. Firstly, in those without diabetes, whereas prior feeding has a suppressive effect on CRH responses to exercise, which consequently reduces endogenous glucose production (191), fasting increases the catecholamine hormone response to exercise (192). Relevant to T1DM, both hyperglycaemia (155; 193) and hyperinsulinaemia (171) during exercise might suppress the CRH responses in those with T1DM. Secondly, in T1DM, previous day exposure to hypoglycaemia has been observed to abolish the glucagon response to subsequent exercise, with participants observed to have experienced 40-80% reductions in both CRH responses and endogenous glucose production (194). Such an impairment in the CRH response to exercise resulting from prior hypoglycaemia was induced in a dose-dependent fashion by differing depths of hypoglycaemia starting at 3.9 $mmol.L^{-1}$ (195). Thirdly, morning exercise might stimulate an attenuated CRH response relative to evening exercise; this

was attributed to diurnal variations in the secretion of hormones (196); in particular, the cortisol response to exercises is diminished in response to morning but not evening exercise (196; 197). Finally, performance of morning exercise has been shown to alter the CRH responses and impair the individual's ability to maintain euglycaemia during subsequent same-day afternoon exercise (198). Aside from this variability in CRH responses, it seems there is some intra-individual reliability in T1DM glycaemic responses to exercise when insulin regimen, diet and the mechanical aspects of exercise remain constant (199).

After Exercise

Type 1 diabetes individuals risk post-exercise hypoglycaemia in a biphasic manner, i.e. early and late after aerobic exercise (200). During recovery from a single bout of endurance exercise, the decline in blood glucose is facilitated by both an inability to decrease circulating insulin levels, and a withdrawal of CRH secretion. Other confounding factors in the risk of acute post-exercise hypoglycaemia include exercise-related reductions is sensitivity to symptoms of hypoglycaemia (17) and the continued non-insulin mediated uptake of blood glucose (201). For example, a study by Campaigne et al. (202) demonstrated that 6 out of 9 T1DM individuals experienced hypoglycaemia within 5 hours after 45 minutes of cycling at 60% VO_2peak independent of prior insulin dosage or post-exercise feeding. Furthermore, T1DM individuals are more susceptible to nocturnal hypoglycaemia following prior low intensity walking exercise (four 15 minute periods of walking at ~140 beats.min^{-1}), when compared to nights when daily exercise was not performed (203). The development of late-onset hypoglycaemia and/or nocturnal hypoglycaemia extends for 31 hours after exercise, as a result of increased insulin sensitivity and continued withdrawal of blood glucose to facilitate the replenishment of muscle and liver glycogen stores (204). Moreover, prior exercise has been observed to blunt both the appearance of adrenaline and elevation in endogenous glucose production in response to subsequent same-day and next-day hypoglycaemia in T1DM (205; 206), meaning exercise *per se* has lasting effects on post-exercise glycaemic regulatory mechanisms that in-turn increases vulnerability to hypoglycaemia.

1.7.1.1 Strategies To Avoid Hypoglycaemia Associated With Steady-State Exercise

Given the wealth of research pertaining to continuous exercise, various strategies have been developed to prevent or minimise the occurrence of hypoglycaemia during and after continuous exercise (Figure 1.4). The most popular approach in research has been to alter the exogenous insulin dose around exercise while several studies have investigated the effect of carbohydrate supplementation (Figure 1.4; Table 1.4).

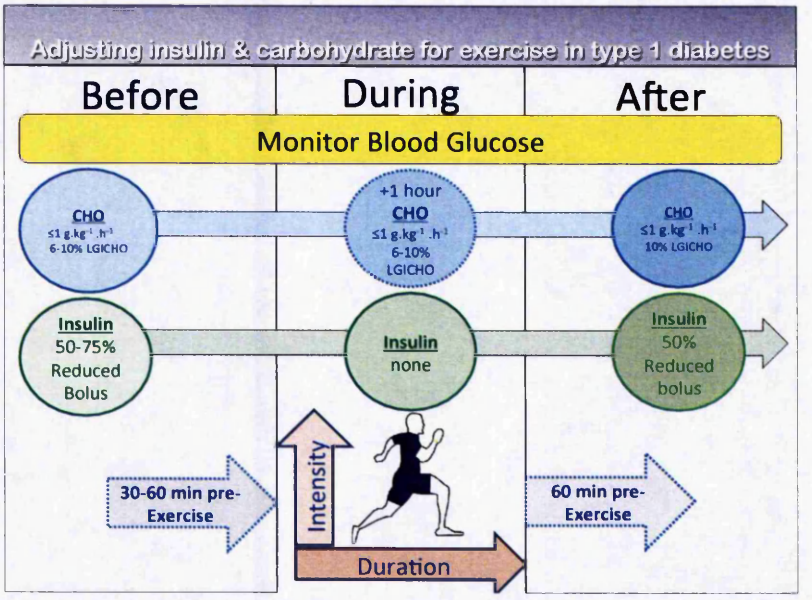


Figure 1.4: A suggested blood glucose management strategy around continuous aerobic exercise for people with T1DM, to minimise their risks of glycaemic imbalances. Most insulin and carbohydrate adjustments can be made prior to exercise and offer protection for up to one hour of activity. Thereafter, further carbohydrate consumption will be required. Blood glucose should be monitored before, during and after activity. Adapted from (207).

Table 1.4: Blood glucose responses to acute insulin and diet adjustments for continuous steady-state exercise in T1DM

Reference	Design	Insulin / CHO	Exercise	Delta BG during ingestion ($mmol.L^{-1}$)	Delta BG during ex ($mmol.L^{-1}$)	Hypoglycaemia frequency
Rabasa-Lhoret et al. (68)	8 T1DM (basal-bolus) completed exercise session 90min after mixed breakfast (75g CHO) with Lispro insulin	Normal basal ultralente. Lispro meal dose as % of full dose: 100%LP 50%LP 25%LP	Cycling: 60min@25%VO_2max 30min@50% VO_2max 60min@50% VO_2max 30min@75% VO_2max	During 90min 100%lispro: +1.1, 50%lispro: +2.1, 25%lispro: +3.6	Ex-time@%VO_2max 100% Lispro 60@25%:-3.0, 30@50%:-3.4, 60@50%:Hypo 30@75%:-3.0 50% Lispro 60@25%:-3.0 30@50%:-2.3 60@50%:-4.2 30@75%: N/A 25% Lispro 60@25%:-3.0 30@50%: N/A 60@50%: -3.1 30@75%: -2.7	4 episodes of hypoglycaemia occurred during exercise - each occurring under 60min@50%VO2 after 100%LP. The remaining episodes occurred during 1h recovery period after exercise.
West et al. (180)	7 T1DM (basal-bolus) completed exercise 2h after 1.12MJ meal (60g CHO) with different bolus insulin.	Normal basal glargine. RA (Lispro or aspart) meal dose as % of full dose: 100%RA 75%RA 50%RA 25%RA	45min treadmill run at 70%VO_2peak	During 120min 100%RA: +3.5 75%RA: +6.2 50%RA: +5.6 25%RA: +7.7	100%: -6.1 75%: -5.3 50%: -5.5 25%: -3.2	3 episodes under 100% (2 at 0min, 1 at 180min). 1 episode each under 75%, 50% and 25% at 180min post-ex.

West et al. (190)	7 T1DM completed exercise after meal consumed at 30, 60, 90 and 120 min before exercise.	Normal basal glargine. RA (Lispro or aspart): 75% reduction in RA insulin. Low GI meal consumed at either 30, 60, 90 or 120min prior to exercise.	45min treadmill run at 70%VO_2peak	Time from feeding + injection to pre-exercise: 30min: +2.8 60min: +3.9 90min: +4.3 120min: +4.1	30min ~-4.4 60min: ~-4.8 90min: ~-5.7 120min:~6.3	30min: None 60min: 1 90min: 2 120min: 5 (all within 3h post-exercise)

BG: Blood glucose. **Delta BG** refers to change in glucose concentration from baseline (pre-exercise) value to either post-ingestion or post-exercise, where stated. **CHO**: Carbohydrate. **Hypo**: Hypoglycaemia stated within results. **RA**: Rapid-acting insulin. **N/A**: No record of data. **GI**: Glycaemic index. **Ex-time**: Exercise time

Basal Insulin Adjustments

Perhaps the least practical approach to improving blood glucose stability in response to exercise is altering the basal insulin dose, as this involves planning an exercise session well in advanced and could complicate subsequent bolus insulin management. Nonetheless, it was recently demonstrated in T1DM individuals (n=51) on a basal-bolus insulin routine that the risk of hypoglycaemia during and for 150 minutes after post-prandial exercise (30 minutes of treadmill running at heart rates of > 120 beats.min^{-1}) was less with the use of evening detemir than NPH, and less with NPH than glargine insulin (208). These different responses between insulins are likely due to the effect of exercise on the time-action profile of the basal insulin. Interestingly, it has been shown that cycling for 30 minutes at 65% VO_2max did not influence the absorption rate of insulin glargine and similar declines in blood glucose and insulin were demonstrated compared to a resting control trial (209).

Bolus Insulin Adjustments

Since the inability of the T1DM individual to endogenously suppress circulating insulin levels during exercise is a primary cause of hypoglycaemia during exercise, a logical approach to countering exercise-induced hypoglycaemia has been to reduce the prandial insulin dose prior to exercise (Figure 1.4). The interaction between exercise mode and its impact on glycaemia in T1DM was acknowledged by Rabasa-Lhoret et al. (68) when they investigated the glycaemic responses to different reductions in rapid acting insulin (relative to the usual carbohydrate to insulin units ratio) across different intensities and durations of cycling (Table 1.4). The results from this study showed that a 75% reduction in rapid acting insulin was most effective at preserving blood glucose during and after exercise, and preventing hypoglycaemia when exercising at 50% VO_2max for an hour and 75% VO_2max for 30 minutes. The effectiveness of this strategy has been investigated during running. West et al. (180) demonstrated that a 75% reduction of prandial insulin taken with a meal at 2-hours before treadmill running at ~70% VO_2peak for 45 minutes better preserved blood glucose during and after exercise, when compared to a full, 75% and 50% dose of prandial insulin (Table 1.4). In this study, however, T1DM participants were exposed to a greater magnitude of hyperglycaemia before, during and after exercise, and hypoglycaemia was encountered during the 24 hours after exercise, under all

insulin reduction strategies. This strategy was strengthened by a subsequent project in which it was found that the consumption of a low GI carbohydrate meal with a 75% reduction in prandial insulin reduced the magnitude of hyperglycaemia experienced before and after exercise, and prevented hypoglycaemia during exercise, when compared to an isocalorific high GI carbohydrate supplement (87). Furthermore, it was shown that this aforementioned strategy was more effective at attenuating the decline in blood glucose during exercise and reducing the occurrence of post-exercise hypoglycaemia when the low GI carbohydrate and rapid acting insulin reduction are prescribed 30 minutes prior to exercise as opposed to 60, 90 and 120 minutes prior to exercise. Together these findings evidence improved euglycaemic stability for exercising T1DM individuals with a reduction in pre-exercise prandial insulin dose taken alongside a bolus of 60 to 75g of carbohydrate, for up to one hour of steady state continuous exercise (Figure 1.4).

The finding that T1DM individuals are susceptible to nocturnal hypoglycaemia following aerobic endurance exercise (68; 180; 202; 210; 211) has necessitated further refinement of exercise-related glucose management strategies. Recent findings demonstrated that large post-exercise bolus insulin dose reductions of ~50% may reduce early (<8 hours post-exercise) – but not late – post-exercise hypoglycaemia following performance of morning steady state continuous exercise (45 minutes running at ~75%VO_2peak (210). However, an implication of reducing post-exercising insulin was that participants experienced a higher frequency of hyperglycaemic occurrences, albeit this strategy did not augment ketonaemia, raise potentially inflammatory cytokines TNF-α and IL-6 above fasting levels, or cause other adverse metabolic or hormonal disturbances (212). Interestingly, the consumption of a low GI meal taken with a 50% prandial insulin reduction at 60-minutes after evening steady state exercise (1700 h) followed by a low GI bedtime snack prevented the occurrence of hypoglycaemia during the initial hours of sleep (~8 hours post-exercise); however, this strategy did not mitigate the occurrence of nocturnal hypoglycaemia (88).

Non-Pharmacological Approach To Prevent Exercise-Induced Hypoglycaemia

The manipulation of exercise intensity has great utility in reducing the threat of hypoglycaemia that is imposed by exercise. For example, the performance of a single

10-s maximal sprint before or after 20 minutes of continuous moderate intensity cycling at 40% VO_2peak has been shown to attenuate the magnitude of decline in blood glucose following exercise in individuals with T1DM (213-215) (Table 1.5). In these studies, the short duration sprint resulted in greater increases in counterregulatory hormone levels and circulating lactate, but it is unclear why there was a lesser decline in glucose during the early post-exercise recovery period after the addition of the sprint, since no differences in glucose infusion rate or glucose uptake were detected relative to a control trial in which only moderate intensity exercise was performed (215). It was also demonstrated that the performance of this 10 second maximal sprint after moderate intensity exercise might not offer protection against the late-onset of post-exercise hypoglycaemia (215). This conclusion was drawn from the finding that the addition of the sprint to 20 minutes of steady state exercise neither increased nor decreased the amount of glucose required to maintain euglycaemia throughout 8 hours of recovery from exercise, and the sprint had no effect on endogenous glucose production or uptake during this time.

1.7.2 High-Intensity Exercise

Oxygen demand is increased with high-intensity (also known as vigorous-intensity or hard effort) exercise beyond that required of moderate intensities, but the demand for energy can exceed the rate at which oxygen delivery and utilisation can support oxidative energy production. Consequently, energy production during high intensity exercise is derived largely from non-oxidative metabolism. This type of exercise is not limited to running, swimming and cycling, but exercise cannot be maintained for a long duration and is therefore generally identified as sprint activities.

Contrary to low to moderate intensity continuous exercise, T1DM individuals have been observed to experience a rise in blood glucose in response to both a 10 second maximal sprint (Table 1.5) and sustained high-intensity exercise (~15 minutes at >80% VO_2max) (216-218), and this response to sustained high-intensity is similar to those without diabetes (216; 217). Interestingly, the cause of this exercise-induced hyperglycaemia appears to differ between different durations of high-intensity exercise. The primary reason for the exercise-induced rise in blood glucose in response to sustained high-intensity exercise, was that exercise elicited a lesser

increment in glucose uptake (~4-fold) than the ~7-fold increase in hepatic glucose production (216; 217). The 10 second sprint increased blood glucose levels by 1.2 ± 0.2 mmol.L^{-1} within a 30 minute recovery period (219), but this exercise-induced hyperglycaemia was attributed to a transient decline in glucose uptake rather than from a disproportionate rise in glucose production relative to glucose clearance.

The growth hormone, catecholamine and glucagon responses to high-intensity exercise are comparable between those with T1DM and without diabetes (220). In response to high-intensity exercise, more concentrated levels of growth hormone and catecholamines appear within the circulation (10 to 14 fold increase in adrenaline and a 10 to 18 fold increase in noradrenaline) when compared to low and moderate intensity exercise, but a slight increase or no change in glucagon concentrations has been demonstrated (216; 217; 221). Thus, it has been proposed that the major contributor to exercise-induced hyperglycaemia in response to high intensity exercise is stimulation of the sympathoadrenal system, as opposed to the release of endocrine pancreas hormones, in both those with and without T1DM diabetes. In fact, research suggests strong increments in glucose production during high intensity exercise occurs irrespective of circulating insulin levels (222; 223), and catecholamines have an inhibitory effect on insulin-mediated glucose uptake (220). In contrast with low and moderate intensity exercise, insulin levels in those without diabetes might slightly decline (224), but generally remain unchanged during high-intensity exercise (191), irrespective of an exercise-induced increase in blood glucose. Furthermore, the rapid combustion of muscle glycogen induced by high-intensity exercise can cause a build-up of glucose-6-phosphate which inhibits hexokinase activity, thereby reducing glucose utilisation (225).

During *recovery* from high-intensity exercise, in those with and without T1DM diabetes, exercise-induced alterations in glucose production and uptake are sustained for the first few minutes of recovery (216), after which the balance between glucose production and uptake equalises with a slower rate of decline in glucose uptake. It is during the initial hour recovery from high intensity exercise that catecholamines (216), blood lactate (216; 217; 221; 226) and FFA (216) return to concentrations corresponding with those prior to exercise. However, in T1DM, post-exercise

hyperglycaemia is sustained as circulating insulin levels fail to rise in response to increases in blood glucose (216). Thus, although high-intensity exercise carries less risk of exercise-induced hypoglycaemia, T1DM individuals are at greater risk of post-exercise hyperglycaemia.

Scant research has aimed to develop strategies to help T1DM individuals effectively manage the exercise-induced hyperglycaemia associated with performance of high-intensity exercise. Interestingly, a doubling of the insulin infusion rate necessary to maintain euglycaemia prior to high-intensity exercise, has been shown to counter post-exercise hyperglycaemia in T1DM individuals (216). This study certainly outlines the necessity for exogenous insulin to help manage the occurrence of exercise-induced hyperglycaemia in T1DM, but limitations exist in that insulin was not administered subcutaneously, and as such the findings lack ecological validity. Interestingly, Harmer et al. (226) showed that seven weeks of interval training attenuated the magnitude of hyperglycaemia experienced by T1DM participants after continuous high-intensity exercise. Unfortunately, however, no practical guidelines or systematic methods for T1DM individuals to correct the acute occurrence of exercise-induced hyperglycaemia currently exist.

Table 1.5: Acute blood glucose responses to intermittent and high-intensity exercise in T1DM

Reference	Design	Insulin / CHO	Exercise	Delta BG during ingestion ($mmol.L^{-1}$)	Delta BG during ex ($mmol.L^{-1}$)	Hypoglycaemia frequency
Guelfi et al. (227)	7 T1DM completed exercise 3.5h after breakfast.	Short and intermediate acting insulin No adjustment in basal or bolus.	Cycling: Moderate: 20min at 40% VO_2peak or Intermittent: 20min at 40%VO_2peak interspersed with 4s sprints every 2min.	Started exercise with BG at 11mM.	Moderate: -4.4 Intermittent: -2.9 During 60min recovery, BG decreased by ~2 under moderate vs. -0.4 under intermittent.	Two episodes under moderate vs. one under intermittent (within 60min post-exercise)
Bussau et al. (213)	7 T1DM completed exercise after breakfast (unknown time).	Short and intermediate acting insulin No adjustment in basal or bolus.	10s sprint prior to 20min cycling at 40%VO_2peak (Sprint) vs. rest prior to 20min cycling at 40%VO_2peak (Control).	Started exercise with BG at 11mM.	Decline 2.9 under both, but during 45min recovery BG decreased by 1.2 under control vs. stable under sprint.	None.
Campbell et al. (228)	9 T1DM completed morning exercise after breakfast	Normal basal glargine or detemir. 50% reduced prandial Lispro/aspart.	45 min treadmill run at ~77% VO_2peak (CON) or games-activity simulation lasting 45min (LIST)	Started exercise with BG at 11mM.	Decline in BG, LIST: -1.1 ± 1.4 vs. CON -5.3 ± 0.4	During 60min post-exercise more patients under CON experienced hypo (BG≤ 3.5; CON n = 3 vs. LIST n=2). Fewer patients under CON experienced hyper-glycaemia (BG≥ 10.9; CON n = 0 vs. LIST n = 6). 6 patients experienced hypo under CON and LIST.

Fahey et al. (219)	8 T1DM vs. 8 NDM completed morning exercise	Euglycaemic clamp used prior to during and after exercise. Infusion rate fixed throughout based on pre-exercise requirements.	10s maximal sprint on cycle ergometer	Start exercise with BG at 4.5 to 5.	T1DM rise in BG of 1.2 vs. NDM 0.4, with 30 min recovery. Resulting from decline in glucose clearance, not greater increase in glucose production over uptake.	None. BG levels returned to pre-exercise with 60 min recovery.
Harmer et al. (218)	8 T1DM completed morning exercise, fasted	Reduced evening basal by 1-2IU and omitted pre-exercise RA.	Cycling: 3min warm-up at 20W, then 110 rpm at power at 130%VO_2peak until exhaustion (~78±21s)	Unknown starting BG.	BG increased 1mmol.L-1 and ~3.5 from baseline during exercise and within 60min after exercise, respectively.	None mentioned.

BG: Blood glucose. **Delta BG** refers to change in glucose concentration from baseline (pre-exercise) value to either post-ingestion or post-exercise, where stated. **CHO**: Carbohydrate. **Hypo**: Hypoglycaemia stated within results. **RA**: Rapid-acting insulin. **LIST:** Loughborough intermittent shuttle test. **NDM**: Non-diabetic individuals.

1.7.3 Intermittent High-Intensity Exercise

Intermittent exercise, also known as interval exercise, refers to the incorporation of different exercise intensities into a single exercise session. This format is typically seen in games activities where athletes are continually moving at a low to moderate intensity but exercise is interspersed with bursts of high-intensity movements.

Research has demonstrated that the incorporation of eleven high intensity four-second sprints (every 2 minutes) into a 20 minute bout of moderate intensity cycling exercise does not increase the risk of hypoglycaemia in T1DM during and for 60 minutes after exercise, when compared to a resting control trial (229) (Table 1.5). Furthermore, post-exercise blood glucose is better preserved, and the occurrence of early, but not late, post-exercise hypoglycaemia is reduced (but not prevented) by substituting intermittent exercise for a session of moderate intensity continuous exercise (227; 230). The lesser decline in glycaemia during this intermittent exercise session was attributed to a greater increment in the appearance of glucose but an attenuation of glucose uptake during exercise and recovery, and authors suggested that this was related to elevated appearance of counterregulatory hormones, when compared to the moderate intensity exercise session (231). Perhaps in mind of exposing T1DM individuals to post-exercise hyperglycaemia and/or a lack of information pertaining to glycaemic control in the presence of intermittent exercise, neither of these aforementioned studies altered macronutrient intake or insulin dose prior to performance of exercise. More recently, after a preparatory 50% reduction in prandial insulin for exercise, compared with 45 minutes of continuous moderate-intensity exercise alone, an exercise session of equal duration involving continuous moderate-intensity exercise plus bouts of intermittent high-intensity exercise was associated with less post-exercise hypoglycaemia (5.2% vs. 1.5% of the time spent with glucose < 4.0 mmol.L^{-1}) and more post-exercise hyperglycaemia (33.8% vs. 20.4% of time $>$ 11.0 mmol.L^{-1}) (232).

Although these aforementioned findings are valuable to the exercising T1DM individual in terms of understanding the mechanical factors which underpin exercise-induced alterations in glycaemia, they lack ecological validity; cycling is a predominantly concentric form of exercise, i.e., the muscle shortens as it contracts.

Contrastingly, in many daily activity patterns including non-body-weight-supported exercises, such as walking, jogging, or running, there is a substantial proportion of eccentric muscle action, where the muscle lengthens in the performance of the movement. Eccentric muscle actions have been demonstrated to hinder insulin action and glucose uptake for many hours following exercise (233; 234). Such data suggest an additional layer of complexity to the understanding of post-exercise glycaemia in response to different patterns of exercise in the T1DM individual.

More recently, a study by Campbell et al. (228) examined the glycaemic responses of T1DM individuals to a 50% reduction in rapid-acting insulin administered in conjunction with a meal prior to an intermittent running exercise which closely simulated real-life team and games-play activity, and on another occasion participants completed an equivalent intensity steady-state run (Table 1.5). The results from this study demonstrated a lesser decline in blood glucose during exercise, and fewer incidences of early post-exercise hypoglycaemia following a games-like exercise session. However, T1DM individuals were more susceptible to hyperglycaemia during games-like exercise than continuous exercise, and participants still experienced late-onset post-exercise hypoglycaemia. These findings help emphasise the complexity of developing glucose management strategies for exercising T1DM individuals, considering that in this instance contrasting glycaemic responses were observed between different modes of exercise despite similar pre-exercise adjustments in insulin therapy and diet. Clearly much more research is needed to explore the glycaemic responses to exercise sessions that are commonly employed by exercising T1DM individuals, as this is crucial to improving exercise safety, glycaemic control, and adherence to a physically active lifestyle. Unfortunately, scant research has focused on developing glucose management guidelines for exercises of an intermittent nature.

Factors That Influence The Glucoregulatory Hormone And Glycaemic Response To High-Intensity Exercise

Various factors could influence the glucoregulatory hormone and glycaemic responses to sprint and intermittent/games-oriented exercise in T1DM. Firstly, training has been found to reduce the magnitude of hyperglycaemia, acid-base

disturbance and noradrenaline responses to high-intensity exercise in T1DM (218), suggesting that training status could influence glucose metabolism during high-intensity exercise. Energy balance or feeding status could be crucial to determining the glycaemic responses to intense exercise; individuals without diabetes elicit an attenuated rise in glycaemia in response to postprandial compared to postabsorptive exercise (191), and restriction of dietary carbohydrate for 3-days prior to sprint exercise enhances catecholamine and glycaemic responses (235), but no such effect is apparent when diet is manipulated 24 hours prior to exercise (236). Thus, it is important that measures are taken to reduce the potential for inter-individual variability when examining the glycaemic and glucoregulatory hormone responses to high intensity exercise.

1.7.4 Resistance Exercise

Resistance exercise (RE) can be viewed as a form of interval/intermittent exercise. Within a typical RE session, exercising individuals engage in a bout of exercise lasting usually ~30 to 60-s and this is immediately followed by a period of passive recovery before completing another effort. There are multiple ways in which each bout of RE can be designed/performed within an acute RE session; these are described in detail below (Section 1.9.4.1).

1.7.4.1 Acute Resistance Exercise Session Design

There exist multiple types of RE (e.g. free-weighs, resistance machines, elastic band, bodyweight, etc.) that each compliment the performance of specific exercises, although RE machines (e.g. Smith machine) appear to pose lower risk of injury (237) and therefore have greater suitability for novice individuals. While the fundamental aspects of designing RE sessions have been thoroughly and extensively reviewed elsewhere (238), it is important for exercising T1DM individuals and health care professionals to recognise the large potential of versatility in a RE session. Fundamentally, it is the specific training outcome (i.e. muscular endurance, hypertrophy, maximal strength, or power) from which the acute programme variables are derived; these include (i) muscle action, (ii) intensity and volume, (iii) exercise selection and order, (iv) rest interval, (v) repetition velocity and (vi) frequency. In

reference to these RE characteristics, the following definitions are relevant to the design of the RE sessions within this thesis.

In relation to muscle action, RE sessions traditionally integrate repetitions of an isotonic nature, i.e. the involvement of eccentric and concentric contractions as opposed to an isometric contraction. A repetition can be performed at multiple velocities to control the length of time that the muscle is under eccentric and concentric tension (e.g. 2 seconds of eccentric and concentric contraction). Thus, a 'repetition' was defined as completion of single exercise movement, which involved an eccentric and concentric muscle contraction under resistance as per the prescribed exercise. For example, one repetition of the squat exercise comprised first starting in a stationary position with feet slightly wider than should width apart, legs straightened (i.e. standing tall with a slight bend in the knee joint), and the weighted bar resting across the upper back, then eccentrically lowering through the knees and hips until the femur was at a 90 degree angle to the tibia, followed by returning to the stationary position. A series of repetitions (e.g. 10 repetitions of squats) was defined as a 'sub-set'. A 'set' of exercises was completed in a circuit-based fashion.

A 'set' was defined as completion of one entire circuit of subsets, e.g. a circuit of 8 successive exercises, each consisting of 10 repetitions (see Figure 2.2). Intensity refers to the absolute mass or resistance assigned to an exercise set relative to a possible maximum (237); thus, exercise intensity was defined as the weight lifted per repetition relative to the maximum weight a participant could lift once (determined using a 3RM protocol), and was therefore expressed as a percentage of 1RM (exercise intensity: %1RM). Exercise volume describes the total weight lifted in kg during a RE session, and was calculated by multiplying the weight lifted during each repetition, by the number of repetitions completed over the duration of the exercise session (see 2.11.2 for example and calculations). RE session volume can be manipulated by altering the intensity and/or the number of repetitions performed within a session. The rest interval is the period of time provided to passively recover between sets and subsets. In this thesis, a passive rest interval separated sets and subsets.

Exercise selection refers to the specific exercises prescribed to / chosen by the participant and is relevant to exercising a particular body segment (i.e. lower-body) or muscle group (i.e. quadriceps); the employment of single-joint exercises (e.g. bicep curl) isolate a particular muscle group requiring less skill and technique, and are therefore less likely to provoke injury when compared to multi-joint exercises (e.g. bench press). Exercise order refers to the sequence of exercises performed within a session, and is a significant factor in the successful completion of all repetitions in a session. Frequency refers to the number of training sessions performed per week, though guidelines for T1DM individuals lack clarity of the possible contribution RE training has to physical activity recommendations.

It is crucial to achieving the specific training outcome and remaining injury-free that the acute programme variables are appropriate to the T1DM participant. For example, prescription guidelines for RE are tailored to individual physical ability and/or fitness goals (239); heavy loads (i.e. high-intensity; 70 to ≥80% 1RM) paired with moderate/high repetitions (8 to 15 repetitions) and multiple sets (2 to 4 sets) are often used for improving *muscular hypertrophy*. Light to moderate loads (i.e. low-intensity; <50% 1RM) coupled with multiple high-repetition (15 to 20 repetitions) sets (≤2 sets) are aimed towards training *muscular endurance,* and this latter design might be best suited to novice and/or previously sedentary individuals (239). It is noteworthy that these RE guidelines were established for individuals without diabetes, but they are somewhat similar to those for T2DM (Table 1.2). Although healthy individuals with T1DM are recommended to partake in all forms of exercise (Section 1.7.1), it seems prudent that exercise is prescribed to an individual with T1DM with knowledge of its impact on glycaemic control. With this in mind, RE guidelines for T1DM, while in no way satisfactory relative to guidelines for T2DM, let alone relative to guidelines for individuals without diabetes, are inadequately validated against the potential for glycaemic imbalances (as described below), and clearly fail to acknowledge the complexities of a RE session. One must question, how could maximum health benefits be gleaned from regular performance of RE when there is a lack of information pertaining to the safe performance of an acute bout of RE? Strikingly very little research has explored the implications of manipulating acute RE programme variables on blood glucose and metabolism of T1DM individuals.

Table 1.6: Acute blood glucose responses to resistance exercise in T1DM

Reference	Design	Insulin / CHO	Exercise	Delta BG during ingestion ($mmol.L^{-1}$)	Delta BG during ex ($mmol.L^{-1}$)	Hypoglycaemia frequency
Yardley et al. (240)	12 T1DM ('physically active'; 7 patients on CSII, 5 patients on MDI) evening exercise	In MDI: No change in basal. 10% decrease in intermediate or long-acting insulin with meals. 25 g CHO snack consumed 1h prior to exercise. In CSII 50% and/or 25% decrease in basal rate leading up to exercise to have BG > 5mmol.L-1	Performed either a session of RE (3 sets of 8 repetitions at an intensity of 8RM, 7 different upper and lower body exercises) before (RA) or after (AE) aerobic exercise (45 min of running at 60% VO_2peak).	AR Baseline 9.1. RA baseline 9.7.	During RE (when performed prior to aerobic), resting BG declined (non-statistically) from 9.7±3.9 to 9.2±4.0. During RA trial BG decreased ~2.8 but increase 0.6 during 0min recovery. During AR trial BG decreased by 1.6, but increased by 1.5 during 60 min recovery.	None during or within 60 after exercise. Nocturnal hypo, AR: 3 participants vs. RA 4 participants.
Yardley et al. (211)	Same as above.	Same as above.	Performed either a session of RE (3 sets of 8 repetitions at an intensity of 8RM, 7 different upper and lower body exercises) before (RA) or aerobic exercise (AE) (45 min of running at 60% VO_2peak).	Baseline ~8 to 9.	During RE (between pre and immediate post-exercise), BG decreased from 8.4±2.7 to 6.8±2.3. During 60min recovery, BG concentrations remained similar to 0min post-exercise. During AE: BG decrease from 9.2 ± 3.4 to 5.8 ± 2.0. During 60min recovery BG increased by 2.2 ± 0.6.	9 T1DM required carbohydrates to prevent hypo under AE. Three required CHO under RE. Nocturnal hypo: RE 6/12 participants, AE 2/10 participants.

Silveira et al. (241)	12 T1DM performed afternoon exercise.	Unknown.	3 different intensity RE sessions (5 upper and lower body exercises, sets and repetitions unknown, 2-min rest intervals at an intensity of 40%, 60%, 80% 1RM).	Baseline ~8 to 9mmol.L^{L-1}.	Change in capillary glucose from pre-exercise to 0-min post-exercise to 30min post-exercise; 40%: 8.1 to 6.7 to 5.8, 60%: 9.4 to 6.4 to 5.3, 80%: 9.1 to 6.3 to 5.2.	None.

BG: Blood glucose. **Delta BG** refers to change in glucose concentration from baseline (pre-exercise) value to either post-ingestion or post-exercise, where stated. **CHO**: Carbohydrate. **Hypo**: Hypoglycaemia stated within results. **MDI**: Multiple daily injections (basal-bolus). **CSII**: Continuous subcutaneous insulin infusion.

1.7.4.2 Resistance Exercise And Glycaemia

The glycaemic and glucoregulatory hormone responses to acute RE in T1DM are far less understood than those of moderate and high-intensity exercises (described previously). This might be partly due to the fact that a single RE session can encompass multiple different arrangements of acute programme variables, but guidelines as to their safe arrangement for T1DM individuals and their impact on glucose metabolism is lacking.

Exercise session design is a key factor in determining the degree of change in the hormonal and metabolic responses to acute RE in those without diabetes (242; 243), such that increases in exercise volume and intensity, and reductions in the rest interval between exercises and sets, have all been shown to augment the sympathoadrenal and pituitary hormone and metabolic responses to RE (242-244). In individuals without diabetes, performance of RE has been shown to evoke ~2-4-fold increases in resting adrenaline and noradrenaline concentrations (244; 245), ~15-20-fold increases in resting growth hormone (243; 244), 40-50% increases (243) or no change (243; 244) in resting cortisol levels, and >10-fold increases in blood lactate (243; 244), but insulin concentrations remain unaltered from rest after RE (246) and glucagon responses to RE have not been reported. Relevant to glycaemia, a single RE session comprising 6 sets of 10 repetitions of back squats at 80%1RM has been found to induce a ~1.8 $mmol.L^{-1}$ increase in blood glucose in non-diabetes individuals (247), and this exercise-induced rise in glycaemia was strongly correlated to increases in both adrenaline ($r=0.57$, $p<0.05$, $n=10$) and noradrenaline ($r=0.85$, $p<0.05$, $n=10$). Other studies in individuals without diabetes have observed marked increases in blood glucose concentrations above baseline in response to 5 sets of lower body RE, with each set performed until voluntary exhaustion (248), and, similarly, also in response to 6 sets of low- (35% 1RM) and high-intensity (70% 1RM) RE (249). Furthermore, subtle adjustments in the ratio of time spent performing the eccentric and concentric component of a repetition (250) and independent adjustments in RE session volume (by number of sets) and intensity (242; 243) have been shown to alter the resultant rise in blood glucose and lactate (250) and appearance of counterregulatory hormones (242; 243; 250) in those without diabetes.

In the context of T1DM, two studies conducted by Yardley et al. (211; 240) (Table 1.6) resulted in conflicting results. In both studies, T1DM participants (on MDI and CSII) performed three-sets of eight-repetitions-maximum with ninety-seconds rest after each exercise (in the evening) and plasma glucose either remained stable throughout the 45 minutes of exercise (240) or fell from 8.4 ± 2.7 to 6.8 ± 2.3 $mmol.L^{-1}$ (211). In the latter study, RE preceded a recovery period in which blood glucose remained similar to concentrations at 0-minutes post-exercise (211). The reasons for the different glycaemic findings between studies is unclear, but inter-study differences pertaining to adjustments in exogenous insulin and dietary intake prior to and during exercise may explain divergent results; specifically, T1DM participants were a combination of insulin pump users and multiple daily insulin injection users (i.e. basal-bolus regimen). Consequently, insulin routines prior to exercise were not homogenous between participants or studies. Furthermore, the lack of control over exercise characteristics such as contraction pacing and intensity relative to 1RM, which have been shown to alter the counterregulatory hormone responses to RE (242; 243), might have contributed to divergent findings between studies. Interestingly, in the study where blood glucose fell during RE (211), none of the participants on a basal-bolus routine required carbohydrate to maintain blood glucose concentrations above ~5 $mmol.L^{-1}$ during and for one hour exercise. Yet, when performing a 45 minute treadmill run at 60% VO_2max instead of RE, carbohydrates were required by 4 out of 5 participants during a one-hour recovery period after exercise, to prevent hypoglycaemia. Indeed, it is somewhat arbitrary to compare two different forms of exercise (i.e. RE to aerobic) but further research is required to elucidate the impact of acute RE on glycaemia in T1DM.

A single study in T1DM has somewhat examined the relationship between the design of a RE session and glycaemia in T1DM. This investigation demonstrated a decrease in resting blood glucose levels during a 30 minute recovery period after three different intensity RE sessions that were performed on separate occasions (Table 1.6) (241). The authors did not, however, report the insulin and dietary intake prior to, during or after RE. It is difficult from this research to determine if intensity of RE *per se* has an impact on the glycaemic responses to RE in T1DM, since altering exercise intensity without fixing the total repetitions within the RE session would inevitably alter the

volume of a RE session. Furthermore, the lack of a non-exercise control trial in this instance means that the changes in blood glucose within each exercise session might not be directly attributed to the exercise session *per se*.

Clearly the acute blood glucose, metabolic and hormonal responses to RE in T1DM is inadequately researched with equivocal findings. Given that the design of a RE session is a key factor in determining the degree of change in hormonal and metabolic responses to RE in those without diabetes (described above), and the varying effects of different exercise intensities/durations/modalities on glycaemia in T1DM, it is likely that different types of RE sessions will have differing effects on blood glucose of T1DM individuals. Indeed, a lack of understanding of the interaction between glucoregulatory hormones, glycaemia and RE programme variables further complicates the ability to safely prescribe RE to T1DM individuals. The attainment of such information therefore has implications in the prescription of RE and might help explain the diversity in acute glycaemic responses to RE between different studies in T1DM. Refinement of participant control before trials, standardisation of participant insulin/carbohydrate routines, and the prescription of well-controlled exercise sessions, could enable a valid examination of the interaction between mechanical characteristics of RE session design and acute glycaemia in T1DM.

1.7.4.3 Strategies To Improve Acute Glycaemic Control During And After Resistance Exercise

No validated strategies have been established to help T1DM individuals manage their blood glucose around the performance of a RE session. This deficiency in information is of clinical concern because it means that many exercising T1DM individuals will have to adopt a trial and error approach to maintain glycaemic control around RE, which unnecessarily heightens the risk of individuals experiencing hypo- or hyperglycaemic episodes during and after exercise. The development of a strategy that reduces exercise-induced glycaemic disturbances is certainly complicated by the lack of understanding between the multiple possible arrangements of exercise characteristics within a RE session and their potential impact on glycaemia in T1DM (as previously described). For instance, increasing the average intensity of cycling exercise lessens the risk of hypoglycaemia, but high-intensity exercise can expose the

T1DM individual to hyperglycaemia; however, it is unknown what effect an adjustment in the intensity of a RE session has on glycaemia in T1DM. Albeit, considering the strong relationship between the appearance of hormones that help regulate glucose metabolism and acute RE session characteristics (242; 243; 247; 250), it is highly possible that adjustments in RE session variables could worsen/improve the acute glycaemic response to exercise. Such knowledge would offer scope to manipulate characteristics within a RE session to improve glycaemic stability around performance of RE. Thus, an understanding of relationships between the design of a RE session and the consequent impact on glycaemia in T1DM is a prudent first phase of developing an effective glucose management strategy for RE.

The correct management of insulin and diet is critical to optimising glycaemic control around performance of RE. Indeed, the development of a guideline to manage diet and insulin around performance of RE, is fundamentally reliant on the effect of exercise *per se* on blood glucose levels. Interestingly, T1DM individuals (anecdotally) struggle to effectively manage hyperglycaemia following performance of RE. On the one hand, unlike the strategies that are recommended for steady state continuous exercise, it would seem inappropriate to consume carbohydrate or reduce rapid-acting insulin prior to RE, since such a strategy might exacerbate the magnitude of hyperglycaemia that is possibly evoked by RE. In this instance it would seem prudent to develop a strategy absent of carbohydrate supplementation, which attenuates post-exercise hyperglycaemia, such as to determine what magnitude of effect exogenous insulin has on blood glucose after RE.

On the other hand, the high rates of glycolytic activity demanded by RE might rapidly deplete muscle glycogen stores (as seen in those without diabetes (248; 249; 251)), resulting in an increased uptake of glucose from the circulation, which could favour a resultant net decrease in blood glucose. In this instance, exercising individuals might benefit from strategies devised for the management of diet and insulin around steady-state continuous exercise (see Figure 1.4). However, it should be considered that the large eccentric component of a RE session favouring muscle damage might impair insulin-mediated up-regulation of skeletal muscle GLUT4 translocation and therefore hinder glucose uptake (233; 234), thereby complicating acute glycaemic control.

Indeed, large increases in creatine kinase reflecting marked muscle damage have been observed following different types of RE sessions (252).

It is an important consideration that, although there exists some intra-individual repeatability with the glycaemic responses to exercise of T1DM individuals under insulin therapy (199), it has been shown that the glycaemic responses to exercise vary across different days independent of differences in insulin therapy and diet (253). Thus, an optimal and more ecologically valid approach to optimise blood glucose during and after exercise would be an individualised strategy; a strategy that can be adapted as a function of the individual glycaemic responses to exercise on any given occasion. Indeed, greater knowledge about insulin pharmacokinetics during exercise and approaches to minimise exercise-induced glycaemic perturbations is likely to increase exercise confidence and participation in T1DM (149).

1.8 THESIS AIMS

The overarching aim of this thesis was to examine the impact of acute resistance exercise on glycaemia in T1DM individuals, to improve euglycaemic stability during and after resistance exercise, and promote confidence in people with T1DM to partake in this form of exercise and lead a more physically active lifestyle.

The aim within each experimental chapter was to:

- Examine the impact of manipulating exercise volume in determining the glycaemic, metabolic and glucoregulatory hormone responses to acute resistance exercise in individuals with type 1 diabetes.

- Examine the impact of manipulating exercise intensity in determining the glycaemic, metabolic and glucoregulatory hormone responses to acute resistance exercise in individuals with type 1 diabetes.

- Implement a modified algorithm that delivers an individualised dose of rapid-acting insulin after morning resistance exercise, to counter acute post-exercise hyperglycaemia in type 1 diabetes individuals.

CHAPTER TWO

Methodology

2.1 ETHICS

The Local Research Ethics Committee of the Dyfed Powys National Health Service Trust approved the research conducted for this thesis (Appendix A).

2.2 TYPE 1 DIABETES PARTICIPANTS

2.2.1 Participant Recruitment

Individuals with type 1 diabetes (T1DM) (both male and female) volunteered to participate in the research described in this thesis. Potential participants were sought through web-based and newspaper advertisements. Volunteers were also recruited through the local diabetes clinics (Singleton and Morriston Hospital, Abertawe Bro Morgannwg NHS trust). Following initial contact with a potential participant, they were provided with a study information pack (Appendix A). Of those who were willing to partake, their medical history and status was obtained by the ABMU-Health Board, and in conjunction with an NHS diabetes consultant, this information was screened against the inclusion/exclusion criteria to determine the volunteer's overall suitability for the study. In addition, information relevant to daily insulin dosage, blood glucose monitoring and diet was obtained from each participant (Appendix D). All procedures relevant to the experimental sessions were clarified with the volunteer and they then provided informed consent (Appendix B). An overview of recruitment processes and participant retention in each study is presented in the CONSORT flow diagram in Appendix B. The selection criteria for inclusion of participants in these studies were as follows:

- Male or female, aged between 18 and 65 years of age,
- Regularly physically active (i.e. partake in physical activities 3+ times per week),
- Free from any diabetes complications other than mild background diabetic retinopathy
- Taking slow acting insulins (e.g. glargine) and rapid–acting insulin analogues for at least 3 months before the study.
- No medication other than insulin
- No musculoskeletal problems

- Every effort was made to include only volunteers with reasonable glycaemic control ($HbA_{1c} < 10\%$).

2.2.2 Justification Of Selection Criteria

To improve the ecological validity of this research both males and females were included in the study. Although gender might influence glucose metabolism in T1DM (189), the pattern of glucoregulatory responses to exercise is similar between males and females. Hence why data was not analysed for gender differences, albeit the minority of participants were females across all chapters and there was an inadequate sample size to make a gender comparison. Furthermore, since the phase of menstrual cycle might affect glucose metabolism during exercise (254), all females that participated were on oral contraception, as the pharmacological effects of this drug apparently reduces the hormone profile of women with regard to circulating oestrogen and progesterone (254).

Age was a factor in the inclusion of participants as children and adolescents can exhibit more varying levels of insulin resistance during different stages of puberty (255). Thus, participants were all above 18 years.

To prevent any possible influence of glycaemic control on blood glucose responses to exercise, a primary aim was to include only participants with good glycaemic control.

Excluding participants on any medication other than insulin negated the potential for pharmacological substances to influence blood glucose or glucoregulatory responses.

Since exercise could possibly increase risk of health complications in individuals with underlying clinical evidence of microvascular, macrovascular and neurological complications related to diabetes (57; 103), only individuals free from diabetes-related complications were included.

Participants were accustomed to physical exercise to ensure they were likely to be able to tolerate the exercise sessions and comfortable with the possibility of muscle soreness and the potential for consequent alterations in glycaemic management.

The requirement of participants to be on a basal-bolus regimen that was unchanged for 3 months prior to testing was necessary to (i) avoid potential metabolic disruptions associated with changes in insulin dosage, (ii) ensure insulin dosage remained similar throughout trials, and (iii) to improve the homogeneity of treatment between participants prior to a trial.

Table 2.1: Chapter 3 participant characteristics and basal-bolus insulin dosage

	Participant ID								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Mean ±SEM**
HbA_{1c} (%)	7.6	8.7	4.6	9.9	9.8	7.7	7.1	14.0	8.7 ± 1.0
Basal (IU)	20	36	14	32	20	30	40	28	27.5 ± 3.1
Bolus ($IU.10g^{-1}$ CHO)	1.0	1.5	0.5	1.0	1.0	1.0	2.0	1.5	1.2 ± 0.4
Age (years)	60	20	25	23	46	22	53	51	38 ± 6
Diabetes Duration (y)	35	12	2	7	23	9	30	2	15 ± 4.5
Height (cm)	170.0	178.5	189.4	187.6	169.1	169	185.8	183.3	179.1 ± 3.1
Body Mass (kg)	74.1	95.0	86.5	69.6	74.5	91.8	108.6	88.9	86.1 ± 4.6
BMI ($kg.m^{-2}$)	25.6	29.8	24.1	19.8	26.1	32.1	31.5	26.5	26.9 ± 1.5
Hip (cm)	89	99	94	96	87	100	99	97	95.1 ± 1.7
Waist (cm)	85	88	83	81	87	80	106	97	88.4 ± 3.1
Body Fat %	24.4	18.0	16.5	13.1	24.5	39.7	32.0	25.7	24.2 ± 3.1

CHO: Carbohydrates. Note: all participants were using bolus insulin aspart and basal insulin glargine.

2.2.3 Participant Insulin regimen

All participants included in this study were using a basal-bolus insulin regimen. Participants in study one were all using basal insulin glargine once daily (Lantus®, Sanofi Aventis, France), and all participants took this in the evening (see Table 2.1). Participants in study two and three were either using basal insulin glargine or insulin detemir (Levemir®, NovoNordisk, Denmark) once daily, and this was administered in

the evening (see Table 2.2). Basal insulin analogues glargine and detemir both exhibit a, similar, peak-less 24-hour insulin profile following subcutaneous injection (256). All participants in all studies were using insulin aspart (Novorapid®, NovoNordisk, Denmark) for the bolus component of their insulin regimen. The prandial rapid-acting insulin is typically absorbed within 5 to 15 minutes and its peak profile in the circulation is typically obtained between 30 and 90 minutes after subcutaneous administration, subsiding after 4 to 6 hours (257). In all studies, although the injection site of insulin was not homogenous between participants, it was standardised between experimental sessions.

Table 2.2: Chapter 4 and 5 participant characteristics and basal-bolus insulin dosage

	Participant ID								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Mean ±SEM**
HbA_{1c} (%)	7.9	15.9	9.1	6.1	8.0	7.1	7.6	8.1	8.73
Basal (IU)	20	42	48	26*	18	40	28	28	31.25
Bolus ($IU.10g^{-1}$ CHO)	1.0	1.0	1.0	0.5	2.0	2.0	1.0	1.0	1.2 ± 0.4
Age (years)	61	18	20	18	55	53	23	23	34 ± 7
Diabetes Duration (y)	36	7	11	1.5	40	31	10	5.5	17.8 ± 5.4
Height (cm)	168.7	185.5	178.0	171.2	174	186.9	169.0	172.0	175.7 ± 2.5
Body Mass (kg)	78.9	64.9	83.3	75.2	85.3	107.8	83.0	78.5	82.1 ± 4.3
BMI ($kg.m^{-2}$)	27.7	18.9	26.3	25.7	28.2	30.9	29.1	26.5	26.7 ± 1.3
Hip (cm)	89.0	95.0	87.0	108.0	91.0	99.0	100.0	101.0	96.3 ± 2.5
Waist (cm)	83.0	80.0	98.0	76.0	93.0	100.0	76.0	84.0	86.3 ± 3.4
Body Fat %	23.9	11.5	17.6	26.1	27.7	28.8	33.1	14.9	23.0 ± 2.7

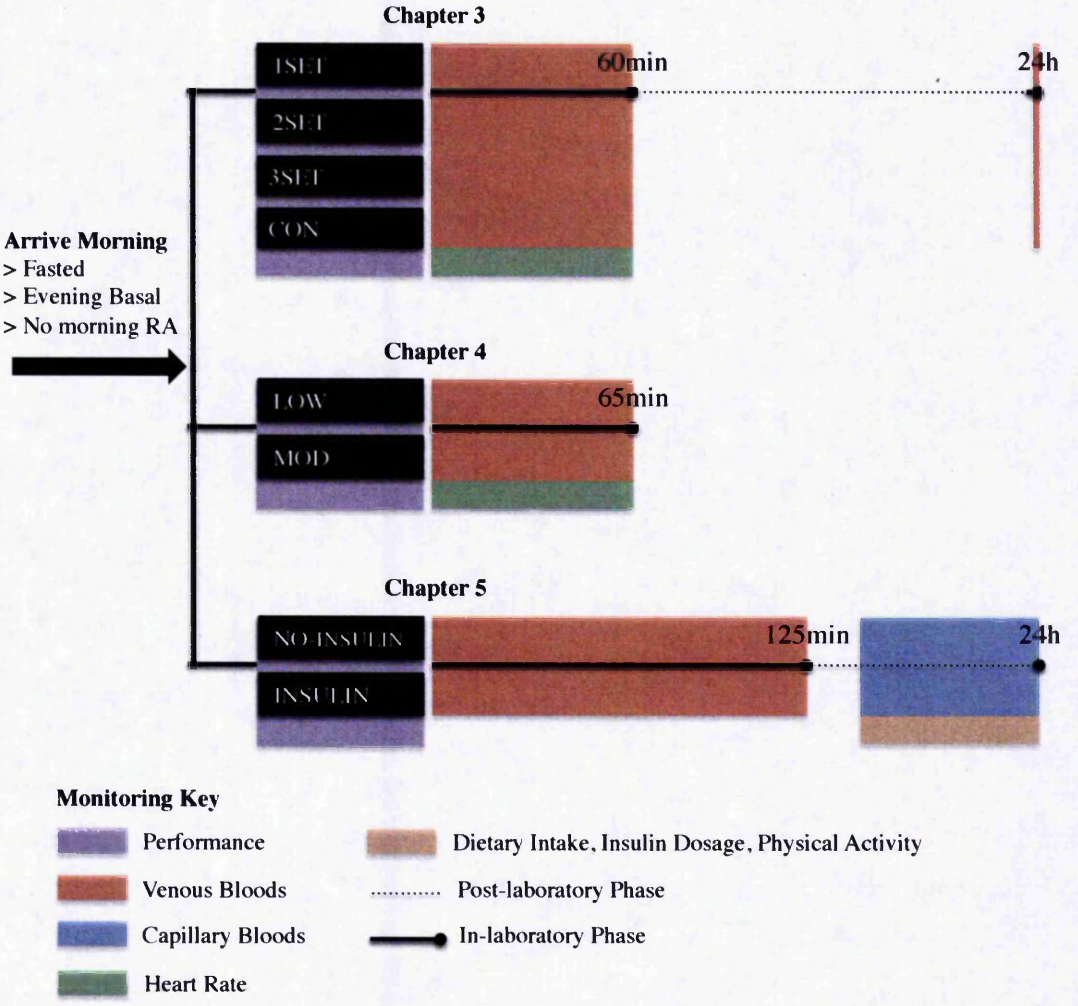
CHO: Carbohydrates. * Note: Except participant number 4 who was taking basal insulin detemir, all participants were using basal insulin glargine.

2.3 EXPERIMENTAL DESIGN CHAPTERS 3-5

Three studies were conducted for this thesis and results from these studies, i.e. studies one, two and three, are presented and discussed in Chapters 3, 4 and 5, respectively. Study one consisted of four main experimental sessions, which were completed in a

repeated measures design by a single group of eight participants. A separate single group of eight participants was recruited to complete both studies two and three in tandem. This meant that participants for Chapters 4 and 5 each completed three experimental sessions (LOW, MOD, INSULIN), and data from the MOD experimental session (within Chapter 4) formed part of the experimental arm for Chapter 5 (i.e. NO-INSULIN). The layout of this design is shown in Figure 2.1.

Figure 2.1: Schematic of general experimental design for Chapters 3, 4 and 5.



Black text boxes indicate resistance exercise sessions within their respective experimental sessions. Notably, the experimental session MOD (Chapter 4) formed part of the experimental session for NO-INSULIN (Chapter 5). **Coloured blocks** indicate monitoring (in reference to the key) over the depicted period. **RA**: Rapid acting insulin. **Basal**: Basal insulin

2.3.1 General Participant Care

Upon each visit to the research facility, participants completed a physical activity and readiness questionnaire (PAR-Q; ACSM, USA, Appendix C), and all procedures for the experimental session were clarified with every participant. A trained medical practitioner was present during all experimental sessions, across studies 1, 2 and 3. Following completion of a study, participants received a comprehensive report of their own responses to the experimental sessions and an interpretation of their results (Appendix A).

2.3.2 General Study Protocol

Across studies one to three, participants initially attended a familiarisation session at least 3 days prior to commencing the main experimental sessions (see section 2.3.3). For the main experimental sessions participants arrived at the Clinical Research Facility, Institute of Life Sciences 2, Swansea University, between 6 and 8 am for study 1 and between 6 and 9 am for studies 2 and 3; arriving after an overnight fast, and having taken their basal insulin the night before but omitted morning rapid-acting insulin. Participant height and mass were then measured (see section 2.3.3.1). Participants were then seated and cannulised (see section 2.4.1) before completing a brief non-weight bearing flexibility warm-up and then proceeded to perform the prescribed exercise session (see section 2.3.4).

Baseline (Rest) venous blood samples were taken prior to exercise (and warm-up) across all chapters. In Chapter 3 venous bloods were obtained following completion of each set of exercise and for 60 minutes after exercise during the recovery phase and at 24 hours after cessation of exercise (see Figure 3.1). Venous bloods were collected periodically for 65 minutes of recovery after exercise in Chapter 4 (see Figure 4.1) and for 125 minutes after exercise in Chapter 5 (see Figure 5.1). During the post-exercise recovery period within experimental sessions, across chapters participants remained in a supine position, drinking water *ad libitum*. Heart rate was measured between pre-exercise and the end of the recovery period (see section 2.5); resting heart rate was obtained during the pre-exercise period, during which participants also completed information sheets reflecting dietary intake, blood glucose levels, insulin

dosage (Appendix E) and physically activity (Appendix F) during the 24 hours prior to an experimental session.

2.3.3 Preliminary Sessions

2.3.3.1 Anthropometric Measurements

Participant anthropometrics are presented in Tables 2.1 and 2.2. Apart from body mass and height, which were measured during the preliminary session and on each experimental session, the following anthropometric measures were obtained during the preliminary session:

Height and Body Mass

Body mass and stature (Seca 763 Digital Column Scale with Stadiometer, Seca, Germany) were measured to the nearest 0.1 kg and 0.1 cm, respectively.

Waist girth

The participant stood in the anatomical position; erect with arms by the sides, palms facing forward, feet together and abdomen relaxed. A tape measure (Seca 201 Body Circumference Measuring Tape, Seca, Germany) was then placed in a horizontal plane at the level of the narrowest part of the torso as seen from the anterior aspect. If a subject's waist was not apparent, a mid-point was located between the costal border and the iliac crest, and a waist measurement was made at this level. The measurement was taken after a normal expiration and on the skin.

Hip (Gluteal) girth

In the anatomical position and without any voluntary contraction of the gluteal muscles the tape measure was placed in the horizontal plane at the level of the greatest posterior protuberance of the buttocks, approximately at the level of the pubic symphysis (anteriorly). The measurement was obtained not against the skin but on a light garment of clothing.

Percentage Body Fat: Bioelectrical impedance analysis (BIA)

Prior to starting the procedure, the BIA (Bodystat Quadscan 4000, Bodystat Ltd, USA) unit was tested for accuracy by running a test against a metal of a fixed

resistance (500 Ohms). After quantification of height and mass participants were required to remain supine for 15 minutes. Participants were positioned so both legs and arms were adducted at 35 – 45 degree angle from the trunk. Alcohol wipes (70 % Alcotip Swabs, Uhs, UK) were used to clean electrode sites on the hands and feet before two injector electrodes (red) were attached to the dorsal surface of the right hand and the right foot and detector electrodes (black) were placed on the ankle of the right foot and just below the radio-ulnar joint on the right hand. After 15 minutes of laying supine had elapsed, and participant details were entered into the BIA device, the procedure was started. The black electrodes were attached to the wrist/ankle and the red electrode was attached to the fingers/toes as per manufacturer's instructions (258). The BIA unit was considered reliable at estimating % body fat (BF), fat free mass (FFM) and total body water, as the coefficient of variation over 5 tests within a one hour period were all < 3%.

2.3.3.2 Assessment Of Maximal Strength

Following medical screening, maximal strength was assessed on a multi-gym Smith machine (Bodymax CF380 Total Smith System; BodyMax Powerhouse Fitness; UK) using a 3-repetition-maximum (3RM) test (i.e. the maximum possible weight lifted per repetition over three lifts), from which 1-repetition-maximum (1RM; i.e. the maximum possible weight lifted in a single repetition) can be accurately determined (259). Generally, individuals who are untrained or inexperienced in RE may not be appropriate participants for a 1RM test because maximal exertion of strength associated with 1RM testing places significant stress on the involved muscles, connective tissues and joints and therefore requires an adequate training status and weight lifting experience. Although participants recruited for this thesis were physically active, they were not experienced weight lifters. A 3RM was determined for the respective exercises within each Chapter. In this session also, participants were familiarised with the format of each resistance exercise (RE) session including discipline in correctly timing repetitions to a metronome (DM70; Seiko UK Ltd, UK), exercise order, rest periods and correct exercise technique.

A detailed example of the 3RM protocol is presented in Appendix G. In short, after a low-intensity warm-up, participants performed up to 3 sets of 3 repetitions of a

selected weight (e.g. bench press). The objective was for the participant to have attained the heaviest weight they can possibly lift for 3 repetitions on the third set. A 3RM was considered valid when three repetitions were performed with correct form in a controlled manner without assistance. During the 3RM test, capillary blood glucose was monitored prior to commencing the test, and after every two exercises, using a portable glucose meter (Freestyle Lite, Freestyle Freedom Lite, Abbott Diabetes Care, UK). In this preliminary test, and this test alone, prior to and/or during exercise, participants expressing a blood glucose reading below 5.5 $mmol.l^{-1}$ were administered a 500ml water solution containing 6% carbohydrates to provide 25g of carbohydrates. In this instance exercise was post-posted and blood glucose was reassessed after 15 minutes; exercise continued if at this time blood glucose was >5.5 $mmol.l^{-1}$. The session was rescheduled for another day if blood glucose rose above 17 $mmol.l^{-1}$ at any point. Participant 3RM and 1RM scores for Chapters 3 to 5 are presented in Tables 2.3 and 2.4.

Table 2.3 Chapter 3 participant 1RM scores.

	Participant ID								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Exercise	**1RM (kg)**								**Mean ± SEM**
Bench Press	37.50	86.00	64.50	23.33	32.22	21.11	45.78	32.22	42.83 ± 7.85
Leg Extension	32.50	75.50	112.50	65.00	50.00	48.00	67.78	60.00	63.91 ± 8.41
Shoulder Press	32.50	75.50	48.00	17.77	23.33	21.11	32.22	26.60	34.63 ± 6.71
Pec Deck	52.50	107.75	96.60	23.33	37.50	32.22	65.00	53.33	58.53 ± 0.65
Squat	50.00	86.00	62.50	32.50	48.00	43.00	75.50	37.78	54.41 ± 6.62
Lateral Pulldown	40.00	75.50	64.50	33.33	46.00	37.78	60.00	37.50	49.33 ± 5.44
Seated Row	60.00	96.60	75.50	53.33	65.00	53.33	70.00	53.33	65.89 ± 5.28
Split-Leg Squat	65.00	53.30	59.00	27.77	75.50	32.22	48.00	30.00	48.85 ± 6.23

Table 2.4 Chapters 4 and 5 participant 1RM scores

	Participant ID								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Exercise	**1RM (kg)**								**Mean ± SEM**
Lateral Pulldown	52.50	32.20	74.29	29.00	44.29	60.00	50.00	90.00	54.04 ± 7.27
Squat	83.00	45.50	96.66	29.00	43.00	86.00	37.80	161.10	72.76 ±15.48
Bench Press	37.77	23.89	45.50	21.11	37.80	43.00	26.70	118.00	44.22 ±11.01
Leg Extension	44.25	32.20	70.00	32.20	32.22	75.55	48.00	53.33	48.47 ± 6.02
Shoulder Press	35.00	18.00	43.00	13.50	26.66	37.77	21.11	81.00	34.51 ± 7.56
Split-leg Squat	64.44	32.20	43.00	35.00	43.00	64.44	64.40	118.00	58.06 ± 9.79

2.3.4 Resistance Exercise Protocols

The resistance exercise (RE) session that was implemented in Chapter 3 set the foundation from which the RE sessions prescribed in Chapters 4 and 5 were derived. Since RE session guidelines for people with T1DM lacked specificity and detail at the time of this thesis, the RE session design was in agreement with exercise guidelines for those with T1DM (57; 107) but adapted from RE session guidelines for those with type 2 diabetes (T2DM) (103) (see section 1.5.1). The guidelines for those with T2DM individuals acknowledge the intricacies of RE session design and were therefore relevant to a participant's experience of RE and also tailored to specific training goals (see section 1.7.4.1). In this thesis, the terms exercise set, repetition, volume and intensity refers to the definitions outlined previously in section 1.10.4.1, and calculation of exercise volume and intensity is described in section 2.11.2.

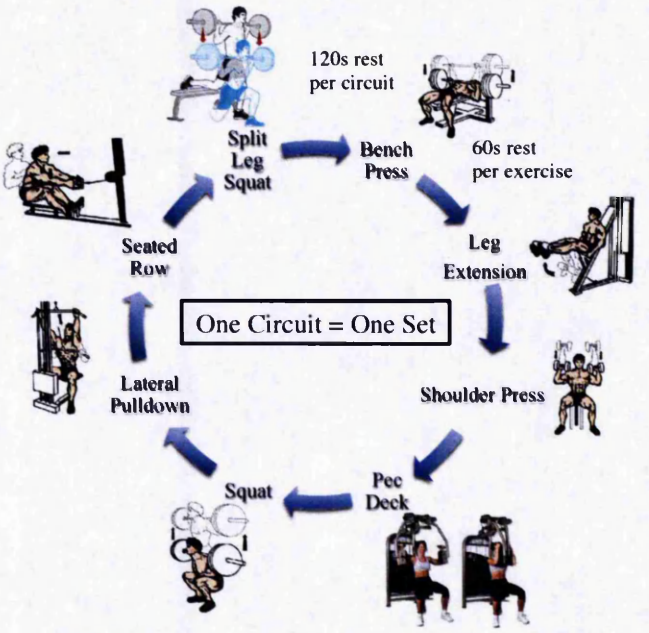


Figure 2.2: Example illustration of resistance exercise protocol adopted in Chapter 3. Ten repetitions of an exercise represented completion of a subset. Subsets were performed in succession and separated by 60 seconds of passive rest. Completion of 8 subsets marked one full circuit, defined as one set. Two sets referred to completion of two full circuits. A passive rest interval of 120 seconds separated each set.

Across Chapters 3 to 5, RE sessions comprised a selection of the following upper and lower body exercises and engaged the corresponding primary groups of muscles (e.g. Figure 2.2): bench press (pectoralis-major), leg-extension (quadriceps), shoulder press (deltoids), pec-deck (pectoralis-major), squat (quadriceps, biceps-femoris, gluteus-maximus), lateral pull-down (latissimus-dorsi), seated row (latissimus-dorsi, rhomboids, trapezius), split-leg squat (quadriceps, biceps-femoris, gluteus-maximus). The exercise order was designed specifically so that the participant would alternate between upper and lower body exercises or opposing (agonist–antagonist relationship) exercises, with the objective to allow some muscles to rest while the opposite muscle groups were trained. This sequencing design (i.e. performance of successive exercises/subsets in a circuit to complete one set as opposed performing one exercise per set) was considered optimal for enabling performance of a whole body circuit-based exercise session of moderate to high training intensities. Furthermore, the following RE session characteristics were kept consistent across chapters: (i) after a standardised 10-minute flexibility warm-up of main muscle groups – ten single arm swings forward and back; ten butterfly swings forward and back; neck and shoulder rolling; fifteen body weight squats – participants undertook

the prescribed RE session, which they were blinded to up until arrival at the research facility, (ii) RE sessions were performed on the multi-gym Smith machine, (iii) exercise repetitions were performed to a metronome at a pace of 2-seconds concentric-phase and 2-seconds eccentric-phase, (iv) where a participant was unable to complete the required repetitions, the weight (kg) for the subset was immediately reduced by 10 – 25% and the remaining repetitions were completed. Any reduction in the number of repetitions and or intensity due to fatigue was replicated across different sessions. The RE sessions for Chapters 3, 4 and 5 are described in detail below.

The Smith machine is a multi-station resistance-training platform that is typically available in all commercial gyms. The Smith machine was chosen specifically for this thesis as it restricts the exercise movement by comprising a closed circuit in which the weight moves freely, but allows for maximal exertion (see Figure 2.3). As such, it was easier for the participants to quickly learn and adopt the correct technique for each exercise, and this in-turn improved performance, but minimised the chance of injury, when compared to free weights resistance training. In this way, this method of resistance training was considered more suitable for the purpose of standardising the technique used between participants and across different exercise sessions.

Figure 2.3: Smith machine used for resistance exercise protocols.

2.3.4.1 Chapter 3 Resistance Exercise Protocol

Chapter 3 comprised three different volume RE sessions involving one (**1SET**) (duration: 14 minutes), two (**2SET**) (28 minutes) and three (**3SET**) (42 minutes) sets of eight exercises at a relativised intensity of 60 to 70% 1RM for ten-repetitions, ascending in volume. Exercises included bench press, leg-extension, shoulder press, pec-deck, squat, lateral pull-down, seated row, split-leg squat, performed in this order. Participants rested for 60 seconds between each exercise (subset) and 120 seconds between each subsequent set. These rest periods provided necessary recovery time for the participant to acquire the correct positioning for each exercise. Participants

undertook a 60-minute period of passive recovery after cessation of exercise. In this Chapter, a resting experimental session (CON) was included, which replicated the 1SET trial in that a period of 14 minutes of rest preceded the 60-minute period of passive recovery.

2.3.4.2 Chapter 4 Resistance Exercise Protocol

Chapter 4 comprised two RE sessions of equal volume but different in intensity; specifically, both RE sessions involved 6 exercises, performed at either a moderate-intensity [two sets of 10 repetitions at 60%1RM] (MOD) or a low-intensity session [two sets of 20 repetitions at 30%1RM] (LOW). Exercises included lateral pull-down, squat, bench press, leg extension, shoulder press and split-leg squat, performed in that order. The passive rest interval between subsets and sets was 120 seconds. The total session duration was 30 and 38 minutes for the MOD and LOW sessions, respectively. Participants undertook a 120-minute period of passive recovery after cessation of exercise.

2.3.4.3 Chapter 5 Resistance Exercise Protocol

The RE sessions comprised within Chapter 5 (NO-INSULIN and INSULIN) were identical to the MOD RE session prescribed in Chapter 4. Exercise session volume and intensity was identical between NO-INSULIN and INSULIN.

2.3.5 Experimental Testing Restrictions

Participants adhered to the following restrictions prior to (and after, where stated) experimental sessions, for the following reasons:

- Participants fasted for 8-10 hours prior to each experimental session; this design was chosen because, (i) the glycaemic impact of resistance exercise in people with T1DM was unclear, (ii) it was hypothesised that resistance exercise would increase blood glucose, (iii) there are inter-individual effects of carbohydrate consumption on blood glucose, thus carbohydrate consumption was considered as a factor that could alter the glycaemic response to exercise and increase variability between participants, thus hindering the ability to detect a relationship between RE session characteristics and blood glucose.

- Participants administered their usual basal insulin dose the night before each experimental session, and abstained from bolus insulin on the morning of each experimental session. Basal insulin is essential to the maintenance of glycaemia control in T1DM. There are currently no guidelines for insulin administration in preparation for RE, and without the consumption of pre-exercise carbohydrates a dose of prandial insulin was considered unnecessary.

- Since antecedent hypoglycemia can impair the counterregulatory hormone responses to subsequent exercise, testing was rescheduled if a participant experienced a hypoglycemic episode during the 24h prior to an experimental session.

- Participants abstained from physical activity (except light walking) for 24 hours prior to testing, because antecedent exercise can alter the counterregulatory hormone responses to subsequent next-day exercise.

- Participants were required to consume a similar diet during the 24 hours prior to testing, as confirmed by dietary records (Appendix E).

- Participants were instructed to maintain a similar insulin dosage and pattern of injection the day before testing (Appendix E).

- Participants abstained from caffeine and alcohol during the 24 hours prior to testing, since both substances can interfere with regular glucose metabolism. Caffeine can decrease insulin sensitivity through activation of lipolytic pathways (260). Ingestion of alcohol can reduce the availability of blood glucose, thereby increasing the risk of hypoglycemia (261).

2.3.6 Characterisation And Treatment Of Hypoglycaemia And Hyperglycaemia

Hypoglycaemia was defined as a blood glucose reading of <3.9 mmol.L^{-1} (see section 1.3.2). Throughout each experimental session participants were closely monitored for signs and symptoms of hypoglycaemia including confusion, pallor, irresponsiveness

to vocal cues, loss of focus, paraesthesia etc. While an experimental session would have been terminated and rescheduled in the event of hypoglycaemia, and carbohydrate feeding would have been used to treat the participant, there were no incidences of hypoglycaemia during any experimental sessions. Hyperglycaemia was defined as a blood glucose reading of > 9.8 $mmol.L^{-1}$. Participants were closely monitored and questioned for hyperglycaemic symptoms including increased thirst and polydipsia, polyuria and nocturia, blurred vision and drowsiness (see section 1.3.1).

2.4 EXPERIMENTAL PROCEDURES

2.4.1 Intravenous Cannulation

In an identical manner across studies, participants were seated while a 20-gauge cannula (Venflon, Becton Dickinson, Helsingborg, Sweden) was inserted into the antecubital vein of the non-dominant arm, and this secured with a Veca-C dressing (Venflon, Becton Dickinson, Helsingborg, Sweden) and micropore tape (3M™ Micropore Surgical Tape, 3M, UK). A 10 cm extension with three-way stop cock was used to allow easy access for venous sampling (Connect, Becton Dickinson, Helsingborg, Sweden) (Figure 2.4). Two to 3 mL of saline (Sodium Chloride BP, 0.9% w/v, Braun, UK) was infused after each sample to keep the cannula patent.

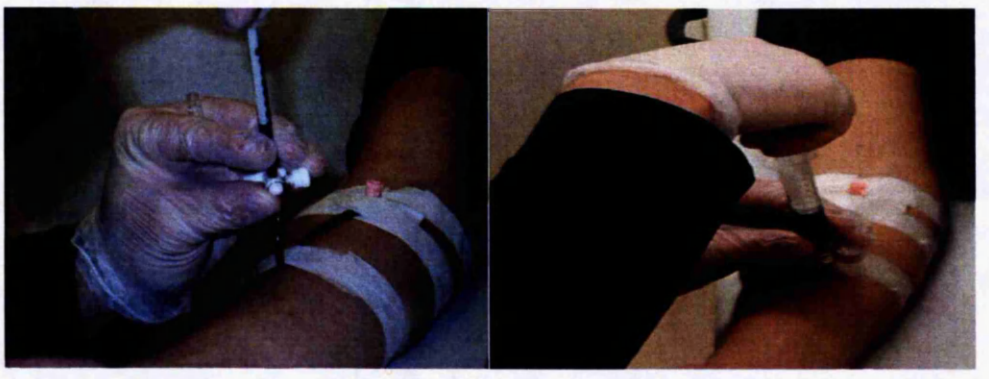


Figure 2.4: Withdrawal of whole blood using a 1 mL lithium heparin syringe (left) and a 10 mL syringe (right).

2.4.2 Blood Sampling

At each sample collection point, 11 mL of whole blood was withdrawn into a 1 mL LH (lithium heparin) syringe (RAPIDlyte, Siemens AG; Germany) and a 10 mL sterile plastic syringe (BD Luer-Lok tip®, BD; UK). Within each study, on the first experimental session, 10 uL of blood obtained from the resting blood sample that was withdrawn into the 1mL syringe, was apportioned into 2 mL of sample diluent and subsequently used to determine was HbA_{1C} (BioRad D-10 Haemoglobin Analyser, Biorad Ltd, UK) by principles of high performance liquid chromatography (Appendix H). Blood that was withdrawn into the 1 mL syringe was immediately analysed for blood glucose, pH, lactate, extra-cellular fluid base-excess (B_{ecf}), K^+ and Hct on a metabolic analyser (GEM Premier 3000; Instrumentation Laboratories, UK). Notably, the results from this analysis were stored on the GEM 3000 internal hardrive and also recorded onto paper data sheets (Appendices I and J). This sample was then placed on ice in case a repeat sample was necessitated by a mechanical error. The 10 mL blood sample was immediately decanted equally into two 6 mL LH plasma vacutainer blood collection tubes (BD Vacutainer®, BD; UK). To one blood-filled vacutainer, 0.1 $mol \cdot L^{-1}$ of both ethylene glycol bis-(β-aminoethyl ether)-N',N',N',N'- tetraacetic acid (EGTA) as anticoagulant and glutathione as antioxidant were added for preservation an subsequent analysis of catecholamines (Appendix K). Both 6 mL vacutainers were then centrifuged at 2.4 RCF for 5 minutes (BOECO Centrifuge S-8, Boeckel + Co; GmbH + Co, Germany). Next, plasma aliquots were pipetted into 1.5 mL microcentrifuge tubes and stored at -80°C for later analyses. In studies 2 and 3, 20 uL from each 1 mL blood sample was used to determine blood haemoglobin (Hemocue AB, Sweden), which, when coupled with haematocrit measurements, allowed for pre and post-exercise quantification of plasma volume shifts via the method of Dill and Costill. (262) (Appendix L).

2.4.3 Quantification Of Blood And Plasma Analytes

Table 2.5 Blood and non-blood based measurements for each experimental theme across chapters three to five.

Theme	Measurement	Chapter 3	Chapter 4	Chapter 5
Glycaemia	Blood Glucose	✓	✓	✓
	HbA_{1c}	✓	✓	✓
Acid-Base	Lactate, pH, B_{ecf}	✓	✓	✓
Glucoregulation	Insulin	✓		✓
	Growth Hormone	✓	✓	
	Adrenaline	✓	✓	
	Noradrenaline			
	IL-6	✓	✓	
	Cortisol	✓	✓	
Ketonaemia	β-hydroxybutyrate	✓		
Kalaemia	Potassium	✓	✓	✓
Lipidaemia	NEFA			✓
Plasma Volume	Hb and Hct		✓	✓
Cardiovascular	Blood Pressure		✓	
	Heart Rate	✓	✓	✓
Perceptual	Muscle Soreness	✓		
	RPE	✓	✓	

2.4.3.1 Blood Glucose, Lactate And Acid-Base Measurements

Blood concentrations of glucose, lactate, potassium and extra-cellular fluid base-excess (B_{ecf}) were determined using the GEM Premier 3000 blood-gas analyser (GEM Premier 300 Blood Gas Instrument, Instrumentation Laboratory, UK). Principles of operation for this device are described in Appendix M (Figures 2.5, 2.6 and 2.7). The reportable range for analytes measured by the GEM 3000, across Chapters 3 to 5, are presented in Table 2.6.

Table 2.6: Reportable range for relevant blood analytes measured by the GEM 3000.

Measured/Derived Analytes	Reportable Ranges
pH	6.80 to 7.80
K^+	1.0 to 20.0 mmol.L^{-1}
Glucose	1.1 to 27.7 mmol.L^{-1}
Lactate	0.3 to 15 mmol.L^{-1}
Hematocrit	15 to 65%
Base-excess (extra-cellular fluid)*	-30.0 to +30.0 mmol.L^{-1}

* Parameter derived from NCCLS guidelines (263) (see Appendix M).

2.4.3.2 Surrogate Blood Lactate Measurement

Blood samples that exceeded the lactate reportable range (>15 mmol.L^{-1}; Table 2.6) on the GEM 3000 were immediately analysed on a hand-held blood lactate analyser (Lactate Pro LT-1710). The system was calibrated each morning prior to testing using the lactate pro calibration strip and the meter's accuracy was tested using a test strip with a known concentration of lactate. For sampling, the lactate pro analyser was used in conjunction with the Lactate Pro blood collection strips, which require a 5 uL sample of blood. The Lactate Pro was considered reliable with a coefficient of variation of < 4%. The measurement range for this device was from 0.8 to 23.3 mmol.L^{-1}. A series of 15 blood samples (low to high concentrations) was measured on both the GEM 3000 and the Lactate Pro; the Lactate Pro readings significantly correlated with the GEM 3000 ($r=0.962, p<0.05$).

2.4.3.3 Plasma Analytes And Assay Principles

Prior to all assays, plasma samples were left to thaw at room temperature and then centrifuged for 5 minutes at 3500 rpm (IKA Vortex, Thermo Fisher Scientific, UK). A description of the assay characteristics and procedures is described below and presented in Table 2.7. Wash phases were performed using a microplate washer (WW004 Wellwash 4 Mk 2, Thermo Fisher Scientific, UK). Where applicable, a microtiter plate shaker was employed (Microplate Orbital Shaker 115 Vac - 60 Hz, Cole-Parmer, UK).

Table 2.7: Overview of hormone and metabolite assays

Analyte	Methods	Manufacturer	Assay (Kit) Reference	Sensitivity	Assay Range	Intra-assay reliability	Plate Reader/Analyser
Cortisol	Competitive ELISA	R&D Systems, UK	Cortisol Parameter Assay Kit KGE008	0.111 $ng.mL^{-1}$	0.156 - 10 $ng.mL^{-1}$	5.4 – 9.2%	VMax® Kinetic, Molecular Devices LLC, USA
Growth Hormone	ELISA	R&D Systems, UK	Human Growth Hormone Quantikine ELISA Kit DGH00	7.18 $pg.mL^{-1}$	25 - 1,600 $pg.mL^{-1}$	2.7 – 4.1%	VMax® Kinetic, Molecular Devices LLC, USA
IL-6	ELISA	R&D Systems, UK	Human IL-6 Quantikine ELISA Kit, HS600B	0.11 $pg.mL^{-1}$	0.156 – 10 $pg.mL^{-1}$	1.6 – 4.2%	VMax® Kinetic, Molecular Devices LLC, USA
Adrenaline	Competitive ELISA	Eagle Biosciences, USA	BCT31-K02	5 $pg.mL^{-1}$	0.5 - 250 $ng.mL^{-1}$	7.7 – 9.0%	VMax® Kinetic, Molecular Devices LLC, USA
Noradrenaline	Competitive ELISA	Eagle Biosciences, USA	BCT31-K02	16 $pg.mL^{-1}$	1.5 - 500 $ng.mL^{-1}$	9.5 – 9.9%	VMax® Kinetic, Molecular Devices LLC, USA
Insulin	ICMA	Invitron, UK	Invitron insulin assay, IV2-001/101	1.2 $pmol.L^{-1}$	0 – 1200 $pmol.L^{-1}$	4.7%	Centro LB 960 Luminometer, Berthold Technologies GmbH and Co, Germany

NEFA	Enzyme colourimetric-immunoassay	Randox Laboratories Ltd, UK	Randox NEFA Kit FA115	0.02 mmol.L^{-1}	0.072 - 2.24 mmol.L^{-1}	4.74 – 4.81%	Randox Daytona Plus, Randox Laboratories Ltd, UK
(β) D-3-hydroxybutyrate	Enzyme colourimetric-immunoassay	Randox Laboratories Ltd, UK	Randox D-3-hydroxybutyrate assay	0.1 mmol.L^{-1}	0.1 – 5.75 mmol.L^{-1}	3.76 – 3.78%	Randox Daytona Plus, Randox Laboratories Ltd, UK
Creatine Kinase	Enzyme colourimetric-immunoassay	Instrumentation Laboratory Ltd, UK	IL Test CK-MB, P/N 0010482200	1 U.L^{-1}	2 – 900 U.L^{-1}	1.8 – 2.6%	ILab 300 Plus, Instrumentation Laboratory Ltd, UK

2.4.3.3.1 Growth Hormone

The assay employs a quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for GH was pre-coated onto a microplate. Standards and samples were pipetted into the wells and the immobilised antibody binds any GH present. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for GH was added to the wells. Following a further wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and until colour developed in proportion to the amount of GH bound in the initial step. The color development was then stopped and the intensity of the color was measured.

2.4.3.3.2 Cortisol

The assay is based on a competitive binding technique in which cortisol present in the sample competes with a fixed amount of horseradish peroxidase (HRP)-labeled cortisol for sites on a mouse monoclonal antibody. During a period of incubation, the monoclonal antibody becomes bound to the goat anti-mouse antibody coated onto the microplate. Excess conjugate and unbound sample was then removed in a wash, and a substrate solution was added to the wells to determine the bound enzyme activity. Colour develops, which is stopped, and the absorbance was read at 450 nm. The intensity of color that developed was inversely proportional to the concentration of cortisol in the sample.

2.4.3.3.3 Interleukin-6

The assay employs a quantitative sandwich enzyme immunoassay technique, with a monoclonal antibody specific for human IL-6 that is pre-coated onto a microplate. Standards and samples were pipetted into the wells and the immobilized antibody bound any IL-6 present. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for human IL-6 was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and colour developed in proportion to the amount of IL-6 bound in the initial step. The colour development was stopped and the intensity of the colour was measured.

2.4.3.3.4 Insulin

The Invitron insulin assay is a two-site immunoassay, employing an insulin-specific solid phase antibody immobilised on microtitre wells, and a soluble antibody labelled with a chemiluminescent acridinium ester. The plasma sample was incubated simultaneously with the labelled antibody solution in the microtitre well, and this was followed by a wash step to remove unbound labelled antibody before measurement. The bound luminescence was quantified by a microtitre plate luminometer capable of in situ reagent addition. The luminescent reaction is a rapid flash type (>95% complete in 1 second), which allowed the entire plate to be read in approximately 5 minutes.

The assay is 100% cross reactive with human insulin, but because T1DM individuals were examined, the influence of residual β-cell function was considered negligible. The assay is also 100% cross reactive with insulins aspart, lispro and glargine. Insulin glargine demonstrates a peak less, steady, insulin concentration for 24 hours (96) and it absorption and clearance is unaffected by exercise (209). Thus, any changes in insulin concentrations detected by this assay were considered to be due to changes in the appearance/disappearance of insulin lispro, aspart or glargine. In addition, the assay is ~300% cross reactive with insulin detemir, therefore, within Chapters 4 and 5, only participants using glargine could be incorporated into analysis.

2.4.3.3.5 Catecholamines (Adrenaline and Noradrenaline)

Noradrenaline and adrenaline were first extracted using a cis-diol-specific affinity gel and acylated to N-acylnoradrenaline and N-acyladrenaline, and were then converted enzymatically into N-acylnormetanephrine and N-acylmetanephrine.

The competitive BI-CAT ® Adrenaline & Noradrenaline ELISA Kit used a microtiter plate format. Adrenaline and noradrenaline, respectively, bind to the solid phase of the microtiter plate. Acylated catecholamine from the sample and solid phase bound catecholamine compete for a fixed number of antiserum binding sites. When the system is in equilibrium, free antigen and free antigen-antiserum complexes are removed by washing. The antibody bound to the solid phase catecholamine is detected by anti-rabbit IgG / peroxidase. The substrate TMB / peroxidase reaction was

monitored at 450 nm. The amount of antibody that bound to the solid phase catecholamine was inversely proportional to the catecholamine concentration of the sample.

2.4.3.3.6 β-hydroxybutyrate

The assay is based on the production of acetoacetate and H^+ after β-hydroxybutyrate has been oxidised by hydroxybutyrate dehydrogenase:

β-hydroxybutyrate + NAD^+ -- 3-hydroxybutyrate dehydrogenase -- Acetoacetate + H^+ NADH.

The change in absorbance at 340 nm was directly correlated with the β-hydroxybutyrate concentration.

2.4.3.3.7 Non-esterified Fatty Acid (NEFA)

The Randox NEFA assay provided a measurement of plasma NEFA, run on the Randox Daytona Plus analyser. Samples were assayed in batches. The method was calibrated using saline and calibration serum (Level 3, Randox Laboratories Ltd, UK). Quality control samples (Multisera Levels 2 and 3) were also assayed prior to analysis. The instrument uses direct photometry to measure a coloured endpoint, from the following reactions:

(i) NEFA + ATP + CoA $\xrightarrow{\text{Acyl CoA Synthetase}}$ Acyl CoA + AMP + PPi

(ii) Acyl CoA + O_2 $\xrightarrow{\text{Acyl CoA Oxidase}}$ 2,3,-trans-Enoyl-CoA + H_2O_2

(iii) $2H_2O_2$ TOOS + 4-AAP $\xrightarrow{\text{Peroxidase}}$ Purple adduct + $4H_2O$

2.4.3.3.8 Creatine Kinase

The enzymatic, colorimetric methodology used, is based on the ability of creatine kinase (CK) to convert ADP to ATP. The ATP is then used to produce glucose-6 phosphate, which in the presence of glucose-6-phosphate dehydrogenase, produces NADH from NAD^+. The enzyme activity was measured by the rate of increase ($\Delta A.min^{-1}$) of NADH, detected colourimetrically at 340 nm. No calibration was required. The enzyme activity was measured by the rate of increase ($\Delta A.min^{-1}$) of NADH. Quality control samples (SeraChem® Levels 1 and 2, Instrumentation Laboratory Ltd, UK) were assayed prior to analysis.

2.5 HEART RATE MONITORING

In Chapters 3 and 4, heart rate was recorded using the Zephyr BioHarness™ system (BioHarness™ BT, Zephyr Technology Corporation, USA) (Figure 2.8). The BioHarness™ module was attached to the participant via a side-strap garment, upon arrival at the laboratory. Electrodes on the garment were lubricated with ECG gel (Spectra®360 Electrode Gel, Parker Laboratories Inc., USA). Once the BioHarness™ was connected to the garment and turned on, the passive sensors within the strap detect heart ECG signals through conductive pads. Data was downloaded from the BioHarness™ following completion of the experimental session, using manufacturer software, and subsequently exported to excel for retrospective analysis. The BioHarness™ module records heart rate within a range of 25 to 240 $beats.min^{-1}$ (± 1 $beats.min^{-1}$).

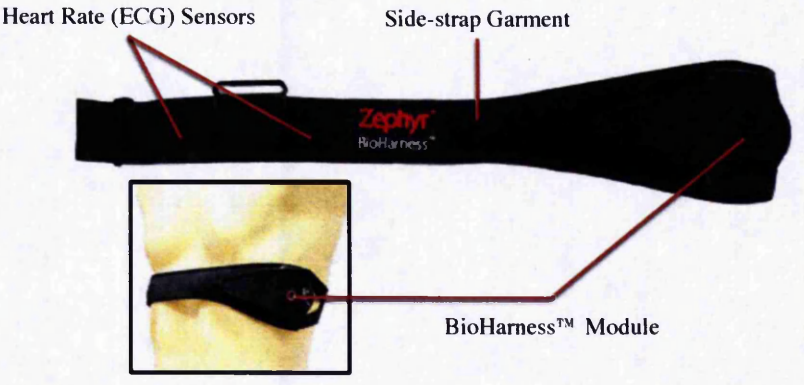


Figure 2.8: Zephyr BioHarness™ system utilised for heart rate monitoring.

2.6 BLOOD PRESSURE MONITORING

In Chapter 4, systolic and diastolic blood pressure were measured over the brachial artery of the non-cannulised arm using a cuff link blood pressure monitor (Welch Allyn 300 Series, Welch Allyn Protocol Inc.; OR, USA), at rest, immediately after exercise and at 1-hour of passive recovery.

2.7 MEASUREMENT OF PERCEIVED EFFORT AND MUSCLE SORENESS.

In Chapter 3, muscle soreness was measured at 24 hours after completion of exercise using a visual analogue scale (VAS) (19) (Appendix N). The VAS has been utilised as an indicator of pain (264) as it has correlated with other indices of muscle damage including maximal voluntary muscle contraction and CK (264), and has obtained reported reliability scores as high as r=0.97 for assessing subjective soreness (265). The OMNI-RES scale (19) (Appendix N) was used to determine ratings of perceived exertion during RE, across Chapters 3 to 5; participants reported perceptual feelings of exertion on a scale of 1-10 (extremely easy – extremely hard) upon completion of each exercise set. The OMNI_RES scale was developed for the purpose of investigating ratings of perceived exertion during resistance exercise, since other models use to rate exertional perceptions such as the Borg 15 category scale have been developed for aerobic exercise modalities, and there functional utility is estimated primarily by the relationship between perceptions of exertion and physiological responses such as heart rate and pulmonary ventilation. Correlations between ratings of perceived effort and weight lifted during a RE session range from 0.79 to 0.91, thereby providing concurrent validation of the OMNI-RES scale for measuring perceptual effort for active muscle and overall body, in upper and lower body RE (19).

2.8 PRE-EXERCISE DIETARY INTAKE, INSULIN DOSAGE AND PHYSICAL ACTIVITY

Under Chapters 3, 4 and 5, and across all experimental sessions, participants were strictly instructed to avoid alcohol and caffeine for 48 hours prior to testing. Similarly, participant dietary intake and pattern for 24 hours prior to testing was replicated across experimental sessions within each Chapter, whereby participants adopted their usual basal-bolus insulin regime, and fasted from 10/11 pm until arrival at the

research facility. Under all chapters, participants administered their usual basal insulin on the evening prior to testing; the time and dose of the insulin injection was standardised across experimental sessions. The structure of this pre-exercise diet and insulin routine was discussed with each participant during the preliminary session (Appendix D). Participants were provided with a one-day diary to record their dietary intake, insulin dosage, and blood glucose using their own glucose monitors, during the 24 hours prior to each experimental session (Appendix E). Under Chapters 3 to 5, for 24 hours prior to each experimental session participants were not permitted to partake in any sport/exercises or strenuous physical activity (i.e. activity demanding exertion beyond a conversational level). For this time period, participants completed a physical activity questionnaire comprising hourly recordings of physical activity levels (Appendix F).

2.9 POST-EXERCISE DIET AND INSULIN

2.9.1 Chapter 3

Following completion of each exercise session, participants remained fasted without bolus insulin for 1 hour, under all experimental sessions. At this point the final laboratory blood sample of the day was taken, and participants were provided with breakfast before leaving the research facility. During the subsequent 24 hours participants were asked to adopt their usual diet and insulin routine, and replicated this across experimental sessions. Fasting was not necessary for the 24-hour post-exercise visit to the research facility.

2.9.2 Chapter 4

Following completion of the exercise session under the LOW experimental arm, participants remained fasted without bolus insulin for 65 minutes. At this point the final laboratory blood sample of the day was taken, and participants were provided with breakfast before leaving the research facility. This marked the end of the experimental session and therefore the end of any commitments pertinent to the study design. Under the MOD session, participants remained fasted without bolus insulin for 65 minutes after cessation of exercise (identical to the LOW protocol), but since a portion of the MOD session data was used as an experimental arm in Chapter 5, the

subsequent diet and insulin protocol is described below as per the NO-INSULIN experimental session.

2.9.3 Chapter 5

Under both the INSULIN and NO-INSULIN experimental sessions, participants remained fasted for 125 minutes after cessation of exercise. During this time, participants abstained from insulin administration under NO-INSULIN, but under INSULIN participants administered a bolus of rapid acting insulin immediately after exercise (see section 2.9.3.1). Under both experimental sessions within Chapter 5, at 125 minutes post-exercise participants adopted a dietary intake routine that was standardised between experimental sessions until the subsequent morning (i.e. ~20 hours after leaving the research facility). This standardised diet was provided to the participant on completion of the 125 minute post-exercise phase and comprised three main meals; breakfast in the research facility, followed by lunch and dinner at home, which aimed to replicate the participants usual eating habits, taking into consideration any allergies and/or dietary restrictions, but was also reflective of current diabetes health organisation guidelines (266). An individualised diet-plan for the 20-hour post-laboratory phase was chosen because subtle differences in dietary composition (e.g. glycaemic index and load, and micronutrient composition) could have altered glycaemia independent of changes in calorific intake, and patient diet recall lacks sensitivity of a controlled diet. Carbohydrate tablets (Glucotabs®; HYPOSITE, BBI Healthcare Ltd., UK) were provided for similar reasons, but also to ensure that patients had available carbohydrates should hypoglycaemia have been an issue during unsupervised conditions. Participants freely administered exogenous insulin in line with their usual routine, and adjusted their insulin dosage with respect to their blood glucose levels. Participants abstained from consumption of caffeinated and alcoholic beverages during the post-laboratory phase.

2.9.3.1 Post-Exercise Insulin Delivery By Means Of An Algorithm

Within the study design of Chapter 5, an injection of rapid acting insulin was administered within 5 minutes after completion of the exercise session. The dose of insulin administered was calculated using an algorithm, which was adapted from the "100-rule" (98; 99) (see section 1.4.2). The algorithm for derivation of post-exercise

rapid acting insulin is illustrated in Figure 2.9. The objective of this algorithm was to determine the number of insulin units necessary to return blood glucose to a target of 7 $mmol.L^{-1}$ within the 2-hour post-exercise recovery period, as a function of the participant's total daily insulin dosage and real time blood glucose concentration. At the time of developing the algorithm, it was unknown to what magnitude of effect a subcutaneously injected dose of rapid-acting insulin could have on glycaemia early after resistance exercise. However, any alteration in insulin sensitivity resulting from exercise would invalidate the method by which the '100-rule' determines an insulin correction dose, because this algorithm is based on an estimation of general insulin sensitivity not specific to exercise. Little is understood about the effects of RE on insulin sensitivity in T1DM; the single study in T1DM demonstrated no effect of RE on insulin sensitivity at 12 and 36 hours after exercise (137), but this does not preclude that insulin sensitivity could be altered at times soon after the cessation of exercise. Factors including increased limb blood flow (267) and improved insulin sensitivity associated with the initial hours after exercise (268) could augment both the absorption of injected insulin into the blood stream (183) and action of circulating insulin on glucose clearance (184). Conversely, it has been demonstrated in those without diabetes that unaccustomed eccentric exercise can impair insulin action in the early hours after exercise cessation (233). Thus, in mind of these aforementioned findings and based on the magnitude of hyperglycaemia experienced after the RE sessions in Chapter 1, it was considered prudent to reduce the insulin dose calculated by the 100-rule ($Full_{Dose}$) by 50%, in an effort to attenuate post-exercise hyperglycaemia but avoid exposing the exercising participant to low blood glucose or hypoglycaemia.

As a working example of the algorithm, participant 'X' with a total daily dose (TDD) of 40IU and a blood glucose concentration of 9.5 $mmol.L^{-1}$ at 0-minutes post-exercise, was determined to require 1U of insulin aspart (i.e. 0.5IU rounded-up) to theoretically reduce blood glucose by 2.5 $mmol.L^{-1}$. The anatomical site of insulin injection chosen by each participant (i.e. abdomen or thigh) was replicated in the remaining experimental session. Insulin aspart was administered using Novopen3® (NovoNordisk, UK).

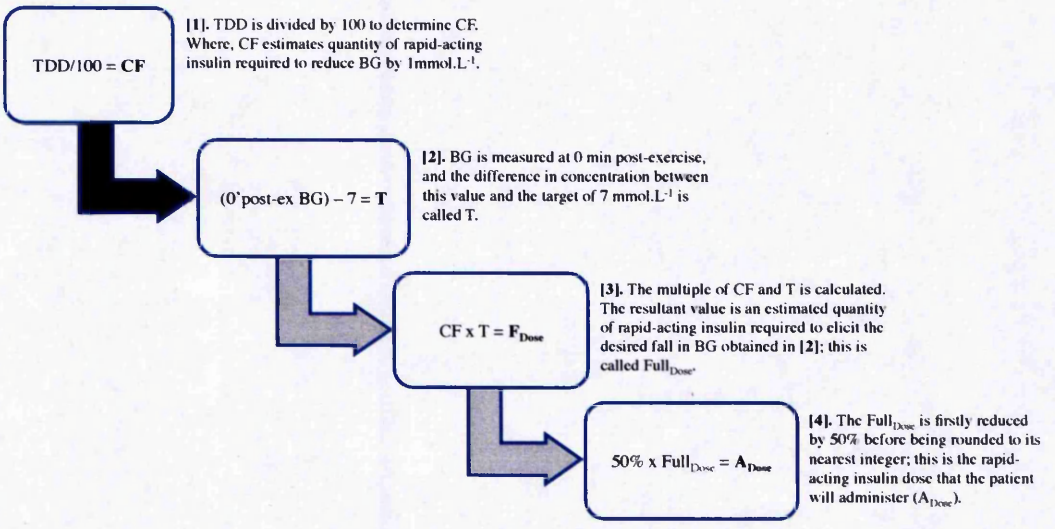


Figure 2.9: Step-by-step guide of algorithm used to determine patient post-resistance exercise rapid-acting insulin dose.

2.10 POST-LABORATORY PROCEDURES

The following procedures were implemented to assess changes in glycaemia, insulin dosage, dietary patterns and physical activity levels during post-laboratory changes in. Notably, during a preliminary session, which was included under all studies, participants were provided with details of how to accurately complete dietary assessment sheets/diaries; specifically, instructions were provided as to how to obtain macronutrient composition from foodstuffs (i.e. on the nutritional content label). They were also instructed on how to accurately record their own physical activity levels and taught the correct procedure to obtain a fingertip blood glucose reading.

2.10.1 Blood Glucose Monitoring

In Chapter 5, participants were provided with a glucose monitor and manufacturer test strips (Freestyle Lite, Abbott, UK). Blood glucose was self-monitored prior to each meal, prior to sleeping, and immediately upon awaking using a log sheet (Appendix O). A further three test strips were provided to the participant should they have wished to obtain any further readings. The frequency of blood glucose monitoring was in agreement with ADA standards of medical care guidelines (51). Hypoglycaemia within the post-exercise laboratory period was defined as a blood glucose reading of <3.9 mmol.L^{-1}, but in an effort to prevent an episode of severe

hypoglycaemia, the consumption of carbohydrate was recommended upon obtaining a low blood glucose reading of ≤4 mmol.L^{-1}.

2.10.2 Physical Activity Patterns

During both the 24-hour post-exercise phase under within Chapter 3 and the 20-hour post-laboratory phase within Chapter 5, participants adopted their usual free-living routine, but they were not permitted to partake in any further sport/exercises or strenuous physical activity (i.e. activity demanding exertion beyond a conversational level). Under Chapters 3 and 5, participants completed a physical activity questionnaire comprising hourly recordings of level of physical activity (Appendix F), which reflected their activity patterns for 24 hours after the experimental exercise sessions. Under Chapter 5 only, physical activity patterns were assessed through estimated energy expenditure as a function of measurements including heart rate and steps taken (Sensewear Pro Armband™; Bodymedia, PA, USA) (269). The Sensewear Pro Armband™ (Figure 2.10) is a lightweight device that is worn over the right triceps, which records vertical and horizontal acceleration from a 2-axis micro-electromechanical accelerometer. The device was allowed to equilibrate to body temperature for 20 minutes prior to monitoring. Data is stored within the device and was retrospectively downloaded to a dedicated software package (InnerView Research Software v.2.2, BodyMedia Inc.), which uses a multiple non-linear regression equation to predict minute-by-minute energy expenditure from the accelerometry data, physiologic sensors and demographic information. The device has been shown to accurately measure energy expenditure during low-intensity physical activity, correlating significantly ($r=0.93$, $p<0.05$) with indirect calorimetry, with high test-retest reproducibility (average 0.85 intra-class correlation compared to 0.90 for indirect calorimetry) (270). The Sensewear Pro Armband™ monitoring of step count in free-living has been shown to be in agreement with other valid activity monitors (271).

Figure 2.10: Outside and inside surface of SenseWear Pro Armband™

2.10.3 Self-Recorded Diet Intake And Insulin Administration

Participants recorded their post-laboratory dietary intake and insulin dosage in a diary provided to them during the preliminary session (Appendix O). A copy of this information was provided to each participant to facilitate replication of dietary intake and timing across experimental sessions. This method also helped the participant to highlight to a member of the research team any adjustments in his/her insulin regimen due to alterations in blood glucose levels.

2.11 DATA ANALYSIS

2.11.1 Blood Glucose Area Under Curve Calculation

The calculation of blood glucose (BG) area under the curve (AUC) was performed using the *net incremental area under curve* method (BG_{iAUC}) (272). This method includes all incremental area below the curve, including the area below the (unless otherwise stated) 0-minute post-exercise concentration. It was calculated by applying the trapezoidal rule to both positive and negative blood glucose increments. To this effect, the area beneath the 0-minute post-exercise level was subtracted from that above. This method was chosen since it can be used to represent the change in post-exercise blood glucose during the acute recovery phase in response to exercise, and as such the post-exercise changes in blood glucose during a time-frame can be represented as a single value (i.e. $mmol.min.L^{-1}$) and therefore these values can be used for comparisons between different experimental sessions. An example of this calculation is described below and shown in Figure 2.11. In Chapter 6, for the purpose

of comparing 'exercise-induced hyperglycaemia' across chapters 3 to 5, BG_{IAUC} values represent changes from pre-exercise, fasting concentrations (see Figure 6.2).

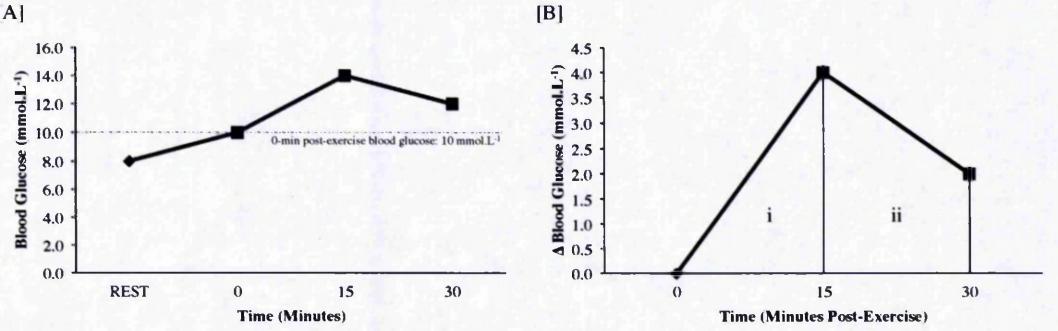


Figure 2.11: Example blood glucose area under curve. Blood glucose responses at Rest (pre-exercise) and at 0, 15 and 30 minutes of recovery after a hypothetical exercise session (i.e. exercise performed between REST and 0 minutes), where [A] represents the absolute change in blood glucose concentration over the sample points and [B] represents the delta blood glucose responses (i.e. 0-minute post-exercise concentration subtracted from absolute concentration) over the accumulative time for the session.

Calculations

In reference to Figure 2.11B;

Area (i) = $[(BG_0 + BG_{15})/2)]*(Time_{Post}-Time_{Pre})$

= $[((0 + 4)/2)]*(15-0)$

= 30 mmol.min.L^{-1}

Area (ii) = $[(BG_{15} + BG_{30})/2)]*(Time_{Post}-Time_{Pre})$

= $[((4 + 2)/2)]*(30-15)$

= 45 mmol.min.L^{-1}

So,

Total (post-exercise) BG_{IAUC} = 15 + (-15)

= 75 mmol.min.L^{-1}

2.11.2. Calculation Of Exercise Volume And Intensity

As described in section 1.10.4.1, exercise 'volume' represented the total weight lifted in a session; calculated by multiplying the weight lifted during each repetition, by the number of repetitions completed over the duration of the exercise session. Exercise 'intensity' was defined as the weight lifted per repetition relative to the maximum weight a participant could lift (determined using the 3RM protocol), and was

therefore expressed as a percentage of 1RM (exercise intensity: %1RM). For example, in Chapter 3 participants exercised at an intensity of ~70%1RM. Thus, a participant with a 1RM of 100kg for squat, would performed each repetition under a load of 70kg. This method of calculating exercise intensity enabled the RE session to be standardised between participants and across sessions. The exercise intensity prescribed was adjusted within the session to accommodate for the actual weight lifted in the session. The actual exercise intensity was then retrospectively calculated in relation to the participant's actual performance.

Session volume calculation, working example:

Participant 'X' was prescribed a resistance exercise session: 2 sets, 6 exercises, 10 repetitions at 60%1RM:

Where,

1RM (kg): Lateral Pulldown (53), Squat (83), Bench Press (38), Leg Extension (44), Shoulder Press (35), Split-leg Squat (64).

Considering the smallest increment in weight on the Smith machine was 1.25 kg, an assuming the participant managed to complete all repetitions at the prescribed intensity, in this instance:

Effective Session Volume = $2*[6 * [10*(60\%1RM_{(n=6)})]]$

Actual Session Volume = 3700 kg at an intensity of 58.1%1RM.

2.11.3 Mean Arterial Pressure

Mean arterial pressure was calculated using the following equation:

$$\sim \text{Mean Arterial Pressure} = 1/3 * SBP + 2/3 * DBP \quad \text{(mmHg)}$$

Where,

SBP and DBP refer to systolic and diastolic blood pressure.

2.11.4 Maximal Heart Rate

Maximal heart rate (HR_{max}) was calculated using the following equation:

$$HR_{max} = 208 - 0.7 * age \qquad (beats.min^{-1})$$

This equation was generation through a regression equation using 18,712 subjects and HR_{max} was cross-validated in laboratory-based studies in which actual HR_{max} was measured in 514 subjects. The regression line was not different between males and females, nor was it influenced by wide variations in physical activity levels (273).

2.11.5 Sample Size Calculation And Retrospective Power

Factors including feasibility, inclusion criteria, geographical location of testing, and the time commitment required of participants for completion of the experimental sessions within this thesis, were unfortunately found to heavily restrict the available pool of T1DM individuals. Following the preliminary session, three participants self-terminated their involvement in the study corresponding with Chapter 3, while two participants self terminated their involvement in Chapters 3 and 4. Additionally, one individual was excluded from studies 2 and 3 after having completed a preliminary session and main experimental session, due to difficulties in venous blood sampling. Despite the small sample size across chapters (n=8), the statistical power for Chapters 3 and 5 (where statistically significant differences were found in glycaemic responses) was 66.9% to 83.6% for primary outcome markers. The similarity in the glycaemic responses within Chapter 4 was reflected in a statistical power of 16.9%. Statistical power analysis was determined via an online power calculator (274).

2.12 STATISTICAL ANALYSIS

Statistical analysis was performed using PASW *Statistics* software (IBM PASW version 19; IBM., NY, USA). A p-value of ≤ 0.05 determined statistical significance for all analysis. In Chapters 3 to 5, data were initially analysed using repeated-measures analysis of variance (ANOVA) on two factors (experimental session and time), with Fishers LSD pairwise comparisons used to examine a time-effect (i.e. within-session changes from baseline). Within Chapter 3, a one-way ANOVA with Fishers LSD was used to determine any effects of experimental session within a

single time point. Within Chapters 4 and 5, where a statistically significant main effect was found, paired samples t-tests were used to perform pairwise post hoc comparison between experimental sessions for each time point. Individualised values were analysed using paired samples t-tests within Chapters 4 and 5, while a one-way ANOVA with Fishers LSD was utilised within Chapter 3. P-values and effect size (partial-eta^2) were reported accordingly. All data (including graphs), unless stated otherwise, are reported as mean ± standard error (SEM). The strength of correlation between an independent and dependent variable was determined by the Pearson product-moment correlation coefficient (Pearson's *r*). Given the variability in resting blood glucose levels, values in Figure 3.2 and 4.2 are presented as absolute and delta (relative to rest) concentrations. Delta values (Δ) were calculated by subtracting pre-exercise (resting) values away from all subsequent sample time-points. Within Figure 5.2, blood glucose values are presented as absolute concentrations and relative to 0-minutes post-exercise (by subtracting subsequent sample points from 0-minutes post-exercise concentrations) to delineate further the effect of insulin administration.

CHAPTER THREE

The Impact Of Manipulating Resistance Exercise Session Volume In Type 1 Diabetes

3.1 INTRODUCTION

The American College of Sports Medicine (ACSM) (107) and American Diabetes Association (ADA) (57), along with multiple public health organisations (104; 106), identify strength training, or resistance exercise, as a component of a physical exercise programme for individuals with type 1 diabetes (T1DM), based upon its potential to benefit the health of the diabetes population (103; 118; 119; 129).

The glycaemic benefits of regular exercise in T1DM are not fully known (131). However, it is recognised that endurance exercise can predispose to hypoglycaemia (210). In contrast, exercise types that demand high rates of glycolytic activity evoke a strong counterregulatory hormone response in T1DM individuals (219; 275), leading to a greater appearance of blood glucose than uptake (275). Interestingly, the addition of a single (213) or multiple acute sprints (227) to endurance exercise can reduce the risk of experiencing hypoglycaemia. Investigation of the glycaemic and metabolic responses to other common forms of exercise containing a large non-oxidative metabolic component is, however, limited.

Resistance exercise (RE), 'weights' or 'strength training', is a form of exercise associated with energy production through mainly non-oxidative pathways (248). A single session is comprised of repeated muscular contractions (i.e. repetitions) of different exercises performed in sets, interspersed with recovery periods. With reference to these RE session characteristics are guidelines specific to exercise intensity and volume (57; 107), for those with well-controlled T1DM (see section 1.5.1). It is however surprising that scant research has validated these RE guidelines with a thorough understanding of the acute glycaemic responses of RE in T1DM individuals, as highlighted in a recent review (276). For example, Jimenez et al. (137) reported that insulin sensitivity was unaltered in well-controlled T1DM participants following a high-intensity, high-volume RE session comprising five-sets of six-repetitions at 80% of 1-repetition maximum (1RM) with 4-minute rest periods between sets. Although blood glucose was stable during euglycaemic-hyperinsulinaemic clamping at 12-hours and 36-hours after cessation of exercise, the immediate glycaemic responses to RE were not measured. The acute blood glucose response to this form of exercise is inadequately researched with equivocal findings.

Two studies conducted by Yardley et al. (211; 240) resulted in conflicting results. In both studies, T1DM participants performed three-sets of eight-repetitions-maximum with ninety-seconds rest after each exercise and plasma glucose either remained stable throughout the 45 minutes of exercise (240) or fell from 8.4±2.7 to 6.8±2.3 $mmol.L^{-1}$ (211). The reasons for the different glycaemic findings across studies are unclear, but inter-individual differences pertaining to adjustments in exogenous insulin and dietary intake prior to and during exercise may explain divergent results. This variability could be minimised by refining participant control before trials and standardising insulin/carbohydrate routines during tightly controlled exercise sessions.

Thus, there is a limited understanding of the acute glycaemic and glucoregulatory impact of RE in T1DM. Guidelines promote circuit-based RE of moderate-intensity (57), and also highlight the importance of progression in number of repetitions in relation to physical ability (107). However, there is no information on the impact that different durations of RE session has on metabolic and glycaemic responses. Clearly, energy expenditure during this form of exercise is greater the longer the session persists, but the net impact on recovery metabolism may be different and potentially expose individuals to different degrees of glycaemic and metabolic disturbances.

Therefore, the aim of this study was to examine the impact of manipulating exercise volume in determining the acute glycaemic, metabolic and glucoregulatory hormone responses to well-controlled resistance exercise sessions performed at a fixed intensity in individuals with type 1 diabetes.

3.2 RESEARCH DESIGN AND METHODS

3.2.1 Participants

Eight physically active male (n=7) and female (n=1) individuals with T1DM (age 38 ± 6 years, HbA_{1C} 8.7 ± 1.0 %, duration of diabetes 15 ± 4.5 years) volunteered and provided written informed consent for the study. Participants anthropometric, glycaemic control and insulin regimen characteristics are presented in Table 2.1 (Page 54). All participants were treated with an insulin regimen composed of bolus insulin glargine and prandial rapid-acting insulin aspart.

3.2.2 Experimental Design

A counterbalanced and randomised, repeated-measures design was selected to compare glycaemic and glucoregulatory responses within-subject and between-experimental sessions (Figure 3.1). Following a single preliminary session, three RE sessions of equal intensity but different volume of work [one, two and three sets] were scheduled in addition to a resting control session. Exercise sessions were separated by 3-9 days; control sessions were separated from exercise sessions by 2-9 days.

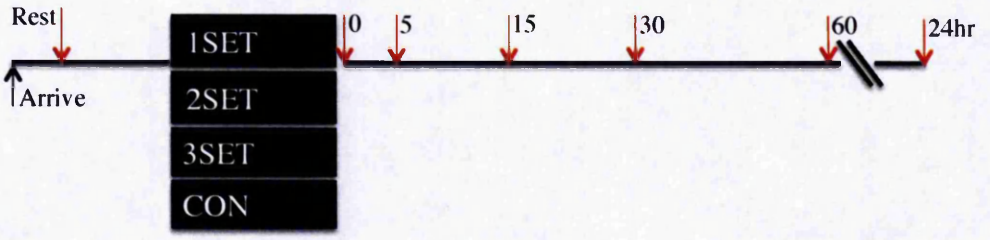


Figure 3.1: Schematic of experimental sessions. Red downwards arrows indicate blood sample points.

3.2.3 Experimental Sessions and Analysis

Participants arrived at the clinical research facility between 0600–0800 h. Participants confirmed they had fasted for 8-10 hours, having taken their usual basal insulin dose (Glargine 27.5±3.1 IU) the night before but omitted rapid-acting insulin on the morning of testing. Upon arrival, a cannula was inserted into the antecubital vein and resting blood samples was withdrawn. Thereafter, a standardised ten-minute warm-up of main muscle groups was performed before undertaking a 1SET (duration: 14 minutes), 2SET (28 minutes) or 3SET (42 minutes) RE session (8-exercises x 10-repetitions) at 70%1-repetition-maximum (1RM) followed by 60 minutes of passive recovery (Section 2.3.4.1; Figure 3.1), or a resting session (CON). Blood samples

were taken for the subsequent hour after exercise (Figure 3.1). All samples were processed and analysed for glucose, pH, lactate, extra-cellular fluid base-excess (B_{ecf}) and K^+, insulin, β-hydroxybutyrate, catecholamines, growth hormone, interleukin-6 and cortisol (Section 2.4.3). Participants then left the research facility and returned for a follow-up session 24 hours after cessation of exercise, in which only plasma creatine kinase levels were determined from a single resting venous blood sample. Heart rate was recorded prior, during and after exercise (Section 2.5). Data (mean ± SEM) were analysed using ANOVA ($p \leq 0.05$) (Section 2.12).

3.3 RESULTS

3.3.1 Exercise Volume and Intensity

The total weight lifted during RE was significantly different across all sessions (1SET 2901 ± 350, 2SET 5713 ± 712, 3SET 8286 ± 1096 kg, *p<0.001*). There was a significant effect of experimental session on overall exercise intensity (*p=0.001*, partial-eta^2 = 0.681; Table 3.1). The 2nd subset was of significantly lower intensity than the 1st subset (*p=0.033*) but of significantly higher intensity than the 3rd subset (*p=0.049*). The 3rd subset was of significantly lower intensity than the 1st subset (*p=0.007*) (see Table 3.1 for values).

Table 3.1: Exercise intensity across different volume experimental sessions, relative to 1RM.

Intensity *% 1RM*	**1st Subset**	**2nd Subset**	**3rd Subset**	**Overall Session**
1SET	69.4 ± 0.6	-	-	69.4 ± 0.6
2SET	69.4 ± 0.6	66.9 ± 1.3	-	68.1 ± 0.9*#
3SET	69.4 ± 0.6	66.9 ± 1.3	63.8 ± 1.6	66.7 ± 1.0*†

Data are presented as means ± SEM. * indicates statistically significant difference to 1SET (*p≤0.05*). † indicates statistically significant difference to 2SET (*p≤0.05*). # indicates statistically significant difference to 3SET (*p≤0.05*).

3.3.2 Heart Rate

Heart rate responses to experimental sessions are present in Table 3.1. Mean estimated HR_{max} was 182 ± 4 beats.min^{-1}. Average heart rates as a percentage of HR_{max} were similar across experimental sessions (1SET 57 ± 2, 2SET 66 ± 4, 3SET 63 ± 3 $\%HR_{max}$, *p=0.165*), respectively. Peak heart rates were similar between different exercise sessions (1SET 149 ± 7, 2SET 162 ± 9, 3SET 153 ± 7 beats.min^{-1}, *p=0.142*).

Table 3.2: Mean heart rates during each set of exercise and recovery under 1SET, 2SET, 3SET and CON.

	Rest	**Exercise**			**Recovery**
Heart Rate *beats.min^{-1}*	**Pre-exercise**	**1stSet (Or sedentary)**	**2nd Set**	**3rd Set**	**0 – 60 min**
1SET	62 ± 3	104 ± 4*	-	-	84 ± 10*†
2SET	70 ± 6	109 ± 8*	131±9*†	-	102 ± 5*†
3SET	58 ± 7	100 ± 5*	117±7*†	126±7*	90 ± 4*†
CON	66 ± 3	68 ± 4	-	-	66 ± 3

Data are presented as means ± SEM. * indicates statistically significant difference (*p≤0.05*) from rest within session and also from CON at equivalent sample point (*p≤0.05*). † indicates statistically significant difference from the 1st set within session (*p≤0.05*). **beats.min^{-1}**: beats per minute.

3.3.3 Blood Glucose

The blood glucose (BG) responses to exercise are presented in Figure 3.2. Baseline BG concentrations were similar between trials (1SET 11.7 ± 1.1, 2SET 11.8 ± 2.0, 3SET 12.2 ± 1.6, CON 11.2 ± 1.5 mmol·L^{-1}, *p=0.977*). There was a significant effect of time (*p=0.011*, partial-eta^2 = 0.469), exercise volume (*p=0.040*, partial-eta^2 = 0.321) and an interaction between exercise volume and time (*p=0.001*, partial-eta^2 = 0.285) for ΔBG responses. RE session volume had a significant effect on post-exercise glycaemia, as reflected in post-exercise BG_{IAUC} (*p=0.022*; Figure 3.2). During recovery, post-exercise BG_{IAUC} was greater under 1SET (42.1 ± 13.9 mmol·60min·L^{-1}, *p=0.024*) and 2SET (41.8 ± 20.4 mmol·60min·L^{-1}, *p=0.033*) versus CON (-23.9 ± 14.9 mmol·60min·L^{-1}) but BG_{IAUC} was similar between 3SET and CON (3SET 8.4 ± 13.0 mmol·60min·L^{-1} vs. CON, *p=0.226*). Individual peak BG concentrations were similar between exercise sessions (1SET 14.0 ± 1.5, 2SET 14.9 ± 2.1, 3SET 13.9 ± 1.9 mmol·L^{-1}, *p*=0.575); moreover, peak BG values were significantly higher than rest under 1SET (*p*=0.020) and 2SET (*p*=0.001) but were comparable to resting values under 3SET (*p*=0.068). Interestingly, after one hour of recovery from exercise, exercise-induced hyperglycaemia (of ≥2 mmol·L^{-1} rise in BG from pre-exercise) was more frequent in participants under 1SET (n=5) and 2SET (n=6) compared to 3SET (n=2). A greater number of participants experienced exercise-induced increases in BG of ≥4 mmol·L^{-1} during 1SET (n=2) and 2SET (n=3) sessions than 3SET (n=1).

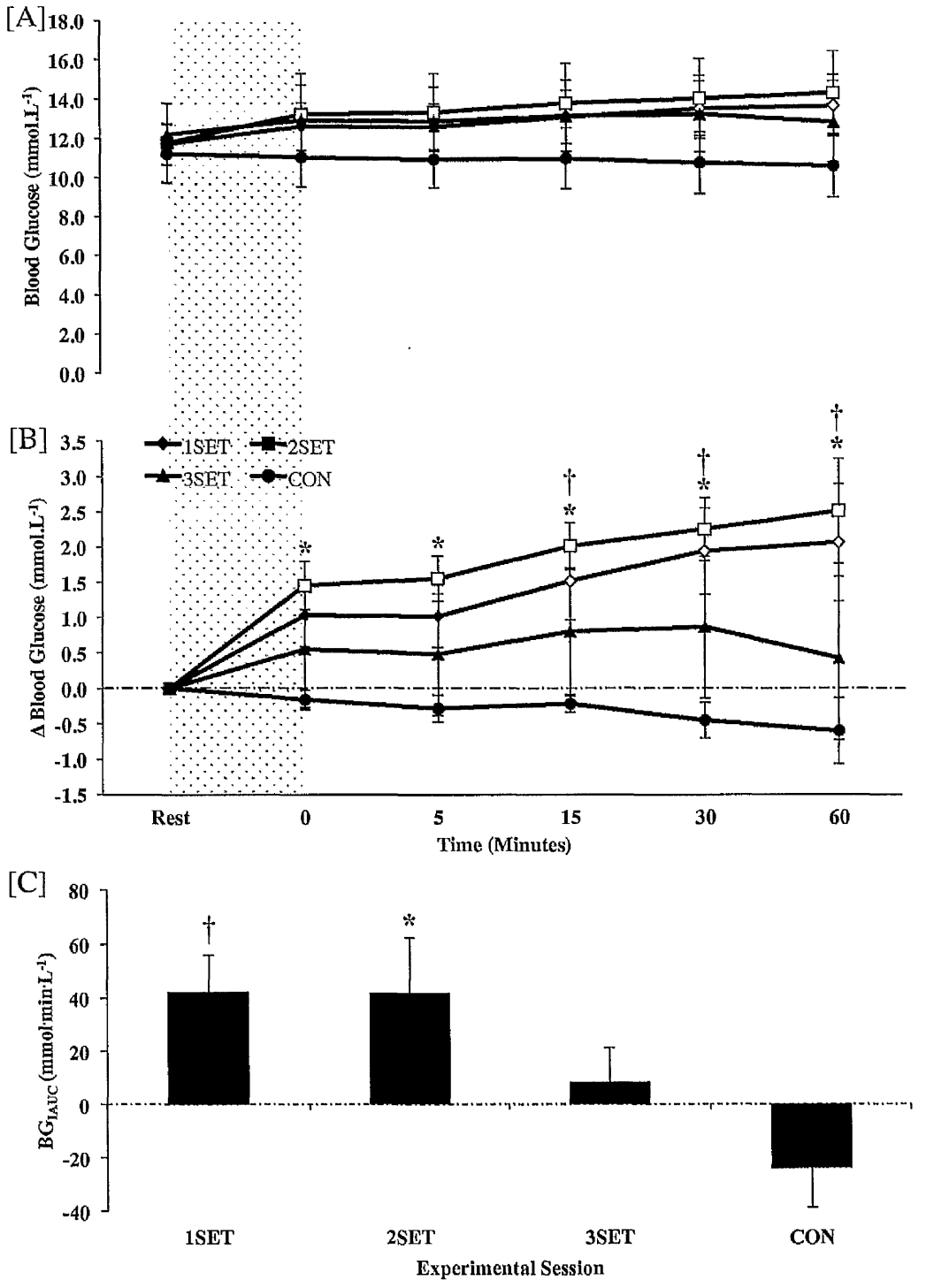


Figure 3.2: [A] Absolute and [B] delta blood glucose responses and [C] net incremental post-exercise BG_{IAUC} (integrated area under curve) during 60 minutes of recovery under exercise and CON experimental sessions. Transparent sample points indicate significant changes from rest within each experimental session ($p<0.05$). † indicates a statistically significant difference ($p<0.05$) between 1SET and CON. * indicates a statistically significant difference ($p<0.05$) between 2SET and CON. Delta blood glucose responses were calculated as a change from rest through the subtraction of baseline concentrations from further glucose values within each condition.

3.3.4 Glucoregulatory Hormones and IL-6

Plasma catecholamines, growth hormone, cortisol and insulin responses across experimental sessions are presented in Table 3.2. Resting concentrations of all glucoregulatory hormones were similar between experimental sessions (*p>0.05*; Table 3.2).

3.3.4.1 Adrenaline and Noradrenaline

For plasma adrenaline (AD) responses (Table 3.2), there was a significant effect of time (*p=0.005*, partial-eta^2 = 0.452), exercise volume (*p=0.020*, partial-eta^2 = 0.367) and a session*time interaction (*p=0.034*, partial-eta^2 = 0.239), with similar peak concentrations irrespective of exercise volume (1SET 0.42 ± 0.12, 2SET 0.47 ± 0.11, 3SET 0.58 ± 0.17 nmol·L^{-1}, *p=0.708*). For plasma noradrenaline (NA) responses (Table 3.2), there was a significant effect of time (*p=0.002*, partial-eta^2 = 0.758), exercise volume (*p<0.001*, partial-eta^2 = 0.631) and an interaction between session and time (*p<0.001*, partial-eta^2 = 0.651), with similar peak concentrations between exercise sessions (1SET 6.42 ± 1.37, 2SET 8.28 ± 1.56, 3SET 9.67 ± 2.03 nmol·L^{-1}, *p=0.405*).

3.3.4.2 Growth Hormone

For plasma growth hormone (GH) responses (Figure 3.3; Table 3.2), there was a significant effect of time (*p<0.001*, partial-eta^2 = 0.662), experimental session (*p=0.001*, partial-eta^2 = 0.556) and a session*time interaction (*p=0.005*, partial-eta^2 = 0.464). Peak GH concentrations occurred between 0-15 minutes post-exercise under all exercise sessions. Exercise volume affected (*p<0.001*) peak GH concentrations; with peaks greatest under 3SET (3SET 5.1 ± 0.7 ng.mL^{-1} vs. 1SET 1.9 ± 0.9 2SET 3.3 ± 0.7 CON 0.6 ± 0.3 ng.mL^{-1}, *p<0.05*).

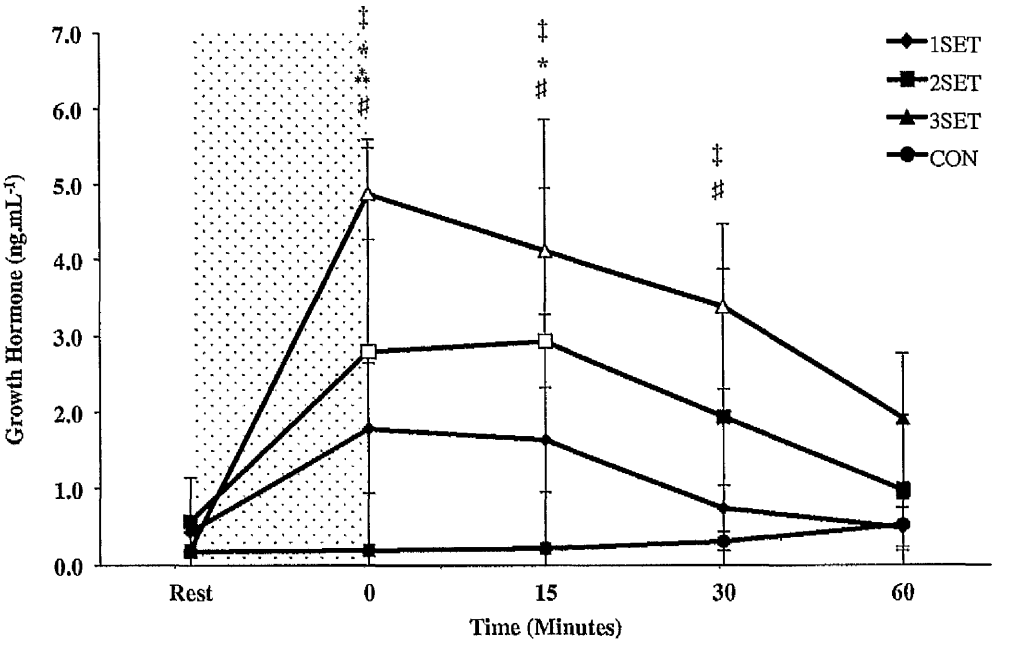


Figure 3.3: Plasma growth hormone responses under exercise and CON experimental sessions. Transparent sample points indicate significant changes from rest within each experimental session ($p<0.05$). † indicates a statistically significant difference ($p<0.05$) between 1SET and CON. * indicates a statistically significant difference ($p<0.05$) between 2SET and CON. ‡ indicates a statistically significant difference ($p<0.05$) between 3SET and CON. ♯ indicates a statistically significant difference ($p<0.05$) between 3SET and 1SET. ⁂ indicates a statistically significant difference ($p<0.05$) between 3SET and 2SET.

3.3.4.3 Cortisol

For plasma cortisol responses (Table 3.2), there was no effect of time (*p=0.129*, partial-eta^2 = 0.268) or experimental session (*p=0.118*, partial-eta^2 = 0.239). Peaks (1SET 84.3 ± 21.3 2SET 105.7 ± 24.0 3SET 121.8 ± 51.3 CON 49.0 ± 10.7 ng.mL^{-1}, *p=0.387*) and minimum (1SET 36.9 ± 9.1 2SET 50.1 ± 11.7 3SET 48.2 ± 18.7 CON 24.0 ± 6.3 ng.mL^{-1}, *p=0.433*) cortisol concentrations were similar across experimental sessions.

Table 3.3: Plasma adrenaline (AD), noradrenaline (NA), cortisol, growth hormone and insulin responses to exercise and CON sessions.

		Rest	0	5	15	30	60
Plasma AD ($nmol.L^{-1}$)	**1SET**	0.13±0.03	0.42±0.12*†	0.20±0.04	-	-	0.06±0.03
	2SET	0.27±0.14	0.47±0.11†	0.18±0.04	-	-	0.09±0.03
	3SET	0.16±0.05	0.48±0.16†	0.39±0.14†	-	-	0.17±0.08
	CON	0.16±0.05	0.03±0.01*	0.12±0.08	-	-	0.04±0.02
Plasma NA ($nmol.L^{-1}$)	**1SET**	1.42±0.12	6.42±1.37*†	3.10±0.43*	-	-	1.02±0.12
	2SET	1.62±0.21	8.24±1.59*†	3.24±0.47*†	-	-	1.12±0.20*
	3SET	1.75±0.28	9.67±2.03*†	4.42±0.96*†	-	-	1.40±0.29*
	CON	1.71±0.29	1.37±0.25*	1.47±0.27	-	-	1.19±0.18*
Plasma Cortisol ($ng.ml^{-1}$)	**1SET**	67.0±17.7	65.5±14.7	-	76.4±21.6	45.2±10.7	50.1±13.3
	2SET	83.7±17.7	80.7±21.6	-	99.6±22.5	74.0±16.6	54.1±12.6
	3SET	76.8±20.1	103.4±49.8	-	87.6±36.3	87.9±35.9	62.6±26.0
	CON	61.5±20.6	46.9±11.6	-	39.9±10.6	28.8±6.9	28.1±6.4
Plasma Growth Hormone ($ng.ml^{-1}$)	**1SET**	0.4±0.2	1.8±0.9	-	1.6±0.7	0.7±0.3	0.5±0.3
	2SET	0.6±0.4	2.8±0.7*†	-	2.9±0.6*†	1.9±0.4	1.0±0.3
	3SET	0.2±0.1	4.9±0.6*†‡§	-	4.1±0.8*†‡	3.4±1.1*†‡	1.9±0.8
	CON	0.2±0.1	0.2±0.1	-	0.2±0.1	0.3±0.1	0.5±0.3
Plasma Insulin ($pmol.L^{-1}$)	**1SET**	82.9±10.5	-	75.1±12.3	77.9±15.1	72.7±12.8*	72.0±11.2
	2SET	87.2±11.2	-	66.4±10.1	70.9±13.2	68.0±7.7*	73.3±10.4
	3SET	135.7±44.7	-	85.0±19.6	89.1±18.3	84.1±15.2	84.3±13.6
	CON	119.1±19.6	-	93.4±11.3	114.4±19.4	106.1±15.9	97.9±12.1

Data presented are means ± SEM. Time points represent minutes post-exercise. * indicates a statistical significant difference ($p<0.05$) to rest. † indicates a statistical significant difference ($p<0.05$) to CON. ‡ indicates a statistical significant difference ($p<0.05$) to 1SET. § indicates a statistical significant difference ($p<0.05$) to 2SET.

3.3.4.4 Insulin

For plasma insulin (Figure 3.4; Table 3.2), there was no session effect ($p=0.126$, partial-eta^2 = 0.256) or session*time interaction ($p=0.501$, partial-eta^2 = 0.120), but there was a significant time effect ($p=0.034$, partial-eta^2 = 0.394) relating to a minor reduction in resting plasma insulin levels under 1SET and 2SET at 30-minutes post-exercise ($p<0.05$). Average post-exercise insulin concentrations were comparable

between trials (1SET 74.5 ± 12.5, 2SET 69.6 ± 9.1, 3SET 85.6 ± 16.2, CON 103.0 ± 12.6 pmol·L^{-1}, *p=0.284*).

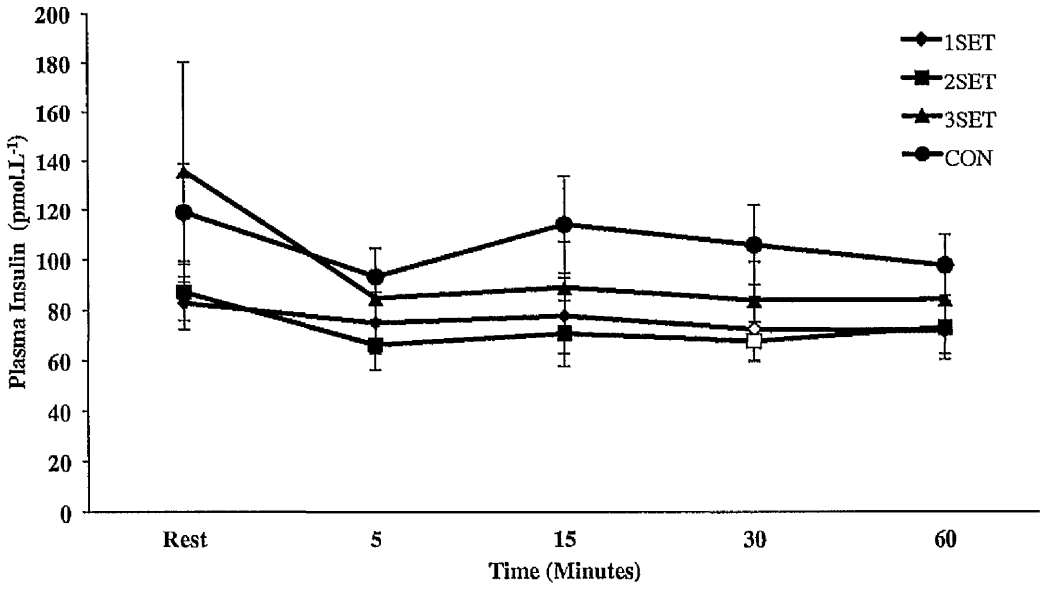


Figure 3.4: Plasma insulin responses at rest and during 60 minutes of recovery under exercise and CON sessions. Sample points reflect pre-exercise (Rest) and at 5, 15, 30 and 60 minutes post-exercise. Transparent sample points indicate significant changes from rest within each experimental session (*p<0.05*).

3.3.4.5 Interleukin-6

Plasma IL-6 responses are presented in Figure 3.5. For plasma IL-6, there was an effect of time (*p=0.010*, partial-eta^2= 0.482) and a tendency for an effect of exercise volume (*p=0.094*, partial-eta^2= 0.288), but no interaction effect between session and time (*p=0.463*, partial-eta^2= 0.117). Resting IL-6 (mean across experimental sessions) correlated with duration of T1DM (r=0.759, *p=0.015*) and participant age (r=0.773, *p=0.012*). Whereas under the 1SET resistance exercise session where IL-6 remained similar to baseline (pre-exercise) concentrations (baseline: 2.32 ± 1.14 pg.mL^{-1}) at 30-minutes (2.48 ± 1.14 pg.mL^{-1}, *p=0.287*) and 60-minutes (3.03 ± 1.29 pg.mL^{-1}, *p=0.318*) post-exercise, IL-6 was statistically greater than baseline at 60-minutes post-exercise under the 2SET session (2.94 ± 0.94 pg.mL^{-1}, *p=0.002*) and doubled at both 30 (4.01 ± 1.00 pg.mL^{-1}, *p=0.048*) and 60 (4.28 ± 1.25 pg.mL^{-1}, *p=0.084*) minutes post-exercise under the 3SET session. The absolute rise from baseline IL-6 to peak concentrations was greatest under 3SET (3SET +1.99 ± 0.82 vs. CON +0.38 ±

0.38 pg.mL^{-1}, *p=0.050;* 2SET +1.05 ± 0.27 [*p=0.350*] and 1SET +0.82 ± 0.65 pg.mL^{-1} vs. CON [*p=0.298*]), and correlated with the magnitude of acid-base disturbance (peak IL-6 & *nadir* pH r=-0.92, *p=0.008;* B_{ecf} r=-0.87, *p=0.007*). Under 3SET, post-exercise BG_{IAUC} significantly correlated with IL-6 concentrations at 30 (r=0.920, *p=0.001*), 60 (r=0.816, *p=0.013*) minutes post-exercise and also with peak post-exercise IL-6 concentrations (r=0.855, *p=0.007*). The difference in post-exercise BG_{IAUC} between 3SET and 2SET sessions significantly correlated with IL-6 concentrations at 30 (r=0.794, *p=0.019*) and 60 minutes (r=0.825, *p=0.012*) post-exercise.

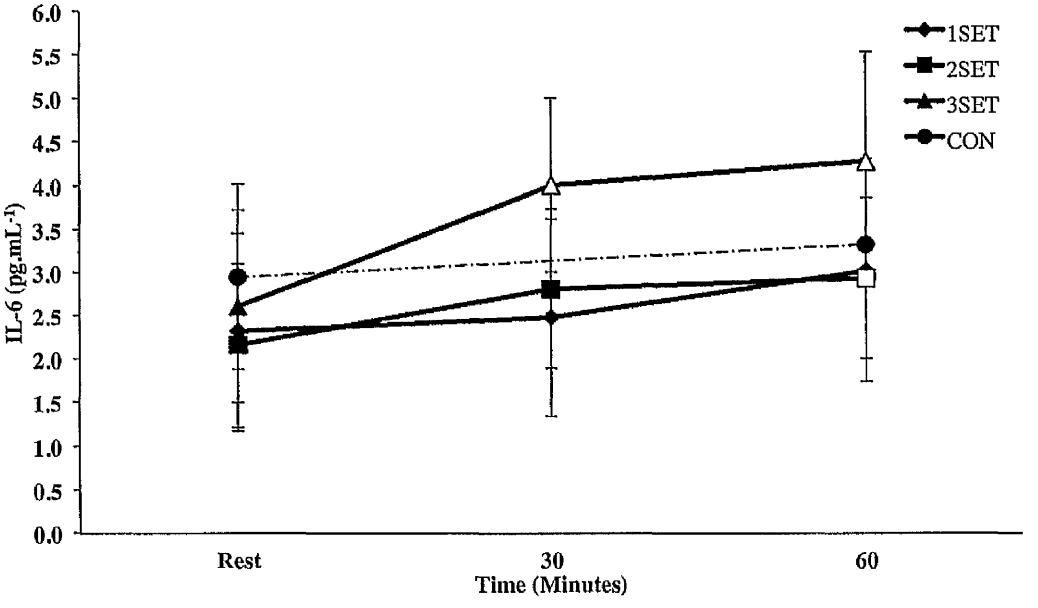


Figure 3.5: Plasma IL-6 at rest and during 60 minutes of recovery under exercise and CON sessions. IL-6 sample points reflect pre-exercise (Rest) and 30 and 60 minutes post-exercise. Transparent sample points indicate significant changes from rest within each experimental session (*p<0.05*); note, under 2SET: 60min, *p=0.084*. † indicates a statistically significant difference ($p<0.05$) between 1SET and CON. * indicates a statistically significant difference ($p<0.05$) between 2SET and CON.

3.3.5 Blood Acid-Base Balance

For blood lactate responses (Figure 3.6), there was a significant effect of time (*p<0.001*, partial-eta^2 = 0.840), session (*p<0.001*, partial-eta^2 = 0.888) and a session*time interaction (*p<0.001*, partial-eta^2 = 0.813), with peak concentrations greater under 3SET (14.0 ± 1.3 mmol·L^{-1}) than 1SET (10.6 ± 1.2 mmol·L^{-1}; *p=0.049*)

but comparable with 2SET (13.1 ± 1.5 mmol·L^{-1}, *p=0.568*). Peak blood lactate significantly correlated positively with total exercise volume (r=0.51, *p=0.005*). For blood pH responses to exercise (Figure 3.6), there was a significant effect of time (*p<0.001*, partial-eta^2 = 0.823), session (*p=0.013*, partial-eta^2 = 0.509) and a session*time interaction (*p<0.001*, partial-eta^2 = 0.659). There was an effect of experimental session on nadir pH (*p<0*.001), since values were significantly lower under exercise compared with CON (CON 7.38 ± 0.01 vs. 1SET 7.20 ± 0.03, 2SET 7.16 ± 0.03, 3SET 7.15 ± 0.03, *p>0.05*), but concentrations were similar across exercise sessions (*p>0.05*). Extra-cellular fluid base-excess (B_{ecf}) responses (Figure 3.6) were affected by time (*p<0.001*, partial-eta^2 = 0.863) and session (*p<0.001*, partial-eta^2 = 0.768) with a session*time interaction (*p<0.001*, partial-eta^2 = 0.789). Nadir B_{ecf} was lower under 3SET (-12.5 ± 2.5 mEq·L^{-1}) than 2SET (-9.9 ± 2.4 mEq·L^{-1}, *p=0.023*) and 1SET (-6.9 ± 1.8 mEq·L^{-1}, *p=0.005*) and CON (5.6 ± 1.6 mEq·L^{-1}, *p<0.001*).

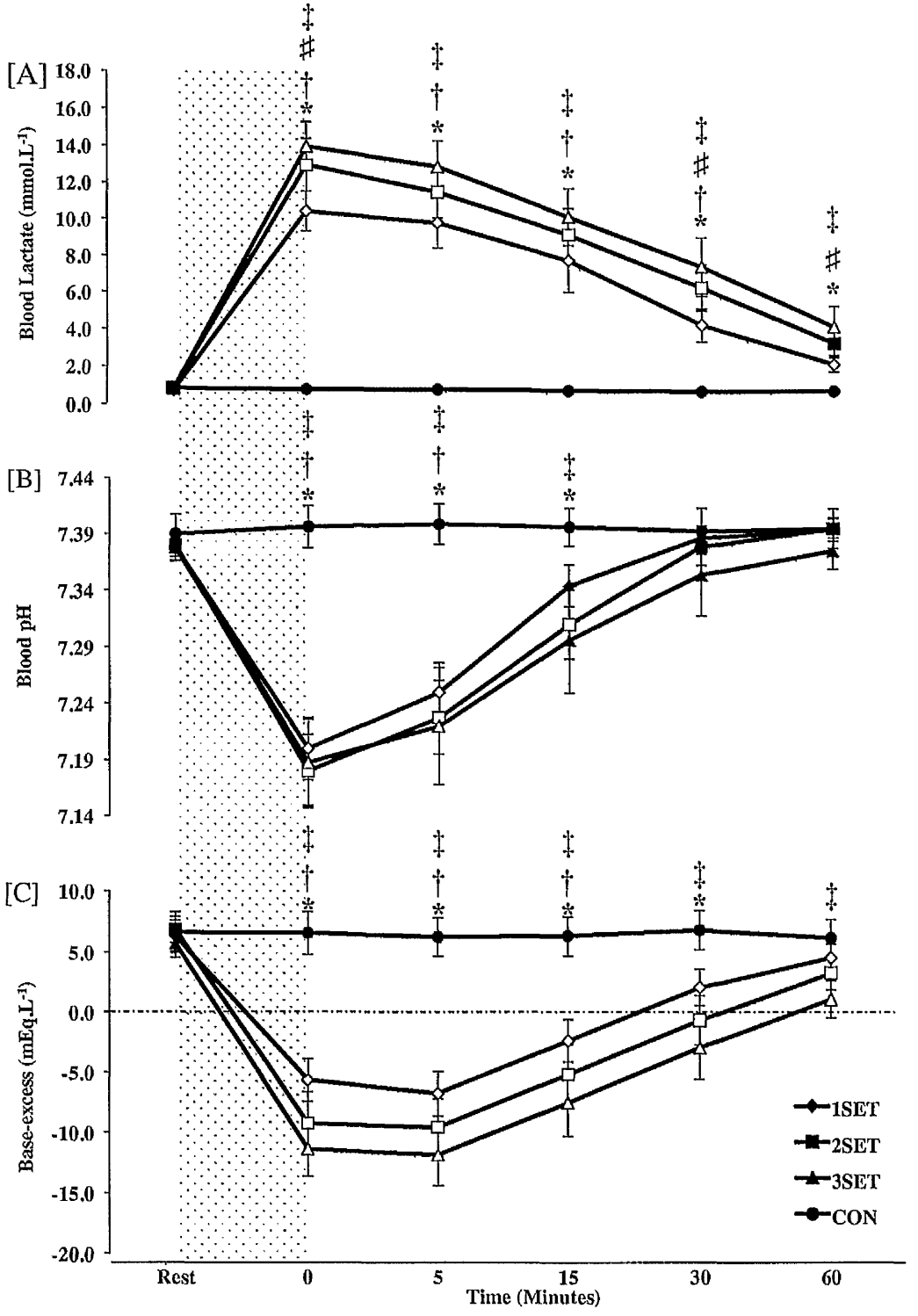


Figure 3.6: [A] Blood lactate [B] blood pH and [C] base-excess (extra-cellular fluid) responses under exercise and CON sessions. Transparent sample points indicate significant changes from rest within each experimental session ($p<0.05$). † indicates a statistically significant difference ($p<0.05$) between 1SET and CON. * indicates a statistically significant difference ($p<0.05$) between 2SET and CON. ‡ indicates a statistically significant difference ($p<0.05$) between 3SET and CON. ♯ indicates a statistically significant difference ($p<0.05$) between 3SET and 1SET.

3.3.6 Blood Potassium and Plasma β-Hydroxybutyrate

For blood potassium (K^+) responses to exercise (Figure 3.7), there was a significant time effect (*p<0.001,* partial-eta^2 = 0.494) and session*time interaction (*p=0.005,* partial-eta^2 = 0.255), but no effect of experimental session (*p=0.101,* partial-eta^2 = 0.305). Peak K^+ concentrations, occurring at ~60-minutes post-exercise, were similar between exercise sessions (1SET 4.3 ± 0.1 vs. 2SET 4.4 ± 0.1 vs. 3SET 4.7 ± 0.1 mmol·L^{-1}, *p>0.05*), but 3SET was greater than CON (4.0 ± 0.2 mmol·L^{-1}, *p=0.019*). Plasma β-hydroxybutyrate (β-OHB) responses (Figure 3.7) were not affected by time (*p=0.141,* partial-eta^2 = 0.252) or experimental session (*p=0.818,* partial-eta^2 = 0.042). There was no effect of experimental session on peak concentrations (1SET 0.1 ± 0.0 vs. 2SET 0.1 ± 0.0 vs. 3SET 0.1 ± 0.1 vs. CON 0.1 ± 0.0 mmol·L^{-1}, *p=0.850*).

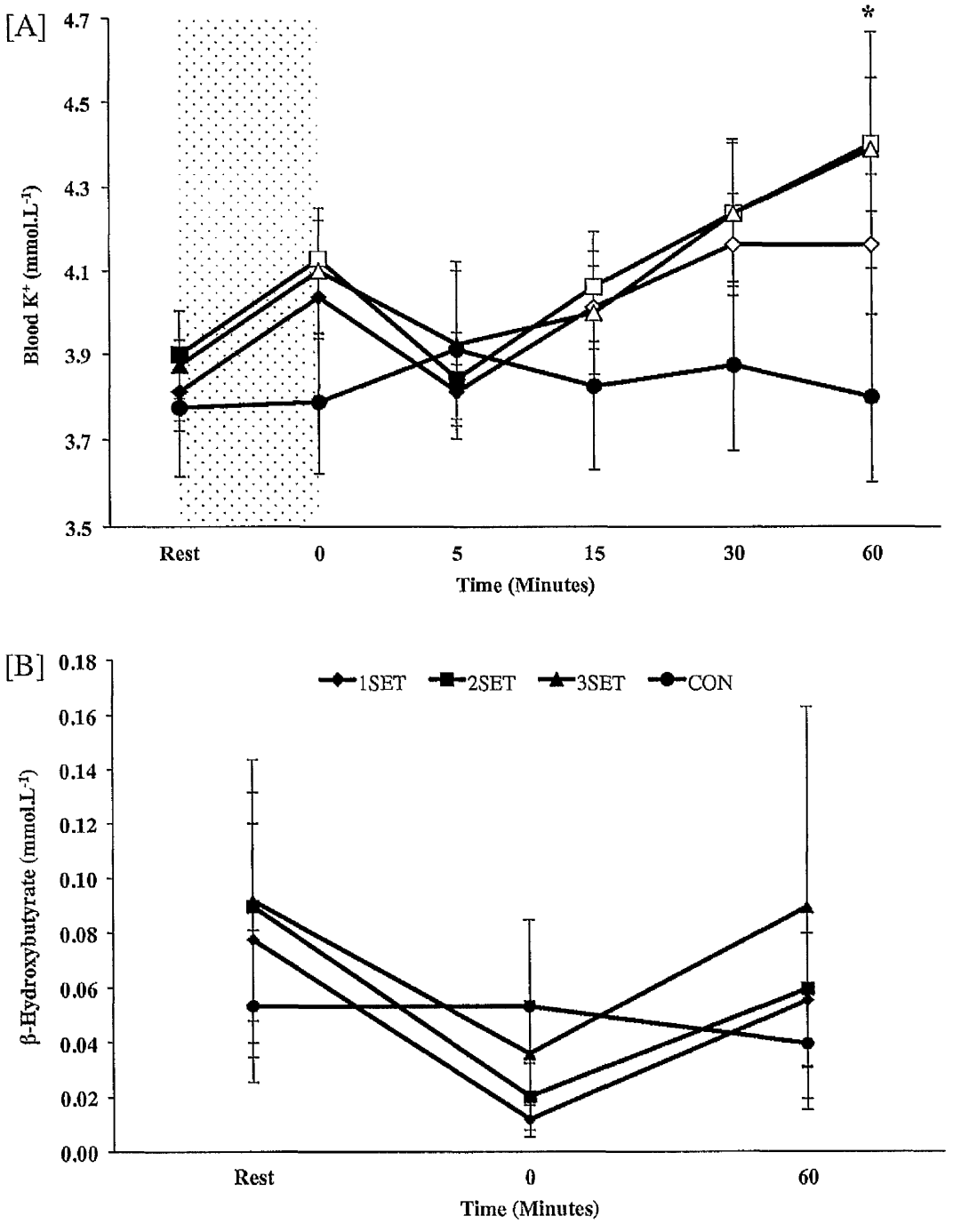


Figure 3.7: [A] Blood potassium (K^+) and [B] plasma β-hydroxybutyrate responses under exercise and CON sessions. Transparent sample points indicate significant changes from rest within each experimental session ($p<0.05$). * indicates a statistically significant difference ($p<0.05$) between 2SET and CON.

3.3.7 Muscle Damage and Ratings Of Perceived Exertion And Soreness

Resting plasma creatine kinase (CK) levels were similar between sessions (1SET 113 ± 18, 2SET 220 ± 85, 3SET 219 ± 101, CON 104 ± 20 UL^{-1}, *p=0.453*). Post-exercise CK levels were recorded at a similar time after cessation of exercise (1SET 24.6 ± 0.3, 2SET 24.7 ± 0.2, 3SET 24.3 ± 0.2, CON 24.5 ± 0.3 hours, *p=0.686*). CK levels at ~24-hours after cessation of exercise (1SET 107 ± 9, 2SET 292 ± 117, 3SET 222 ± 47, CON 83 ± 12 UL^{-1}) were similar to rest (*p>0.05*) under all experimental sessions. During exercise, under all trials ratings of perceived exertion corresponding to subjective intensity of "*somewhat easy*" and "*hard*" (1SET 5 ± 1, 2SET 7 ± 1, 3SET 7 ± 1). At 60-minutes and 24-hours post-exercise, perception of muscle soreness corresponded with feelings of "*no pain* (0) *to mild pain* (2)".

3.4 DISCUSSION

This study characterised the acute glycaemic, metabolic and glucoregulatory hormone responses to well-controlled RE of different volumes in T1DM individuals. The novel finding from this study was that blood glucose climbed above rest for one-hour after one and two sets of RE, but the inclusion of a third-set attenuated this exercise-induced hyperglycaemia and returned blood glucose values to those of a control session. This is the first study to recognise the importance of exercise volume in determining the blood glucose responses to RE in T1DM.

During recovery from one to three sets of RE, blood glucose was largely stable between 12.3 and 14mmol.L^{-1}, with no evidence of exercise-induced hypoglycaemia or requirement for exogenous carbohydrates. These findings are very different to those of aerobic exercise (210) during which blood glucose is typically reduced. A direct comparison between glycaemic responses to evening aerobic and RE in T1DM has been reported by Yardley et al. (211), but in this study plasma glucose declined during a three-set RE session (albeit not as much as in the aerobic exercise trial). The clinical measures taken in this study for morning RE sessions i.e. overnight fasting, omission of morning rapid-acting insulin but continuation of usual basal dose (taken the night before) differed to the strategies adopted by Yardley et al. (211) and this provides potential clues for contrasting glycaemic responses.

After performance of one and two sets of RE, peak blood glucose concentrations were 21% and 29% greater than those during the resting control session, respectively. The hormonal and metabolic responses to the RE sessions within this study were a likely driver for the exercise-induced hyperglycaemia. For example, the 4-5–fold increases in plasma adrenaline and noradrenaline concentrations, respectively, were likely to have stimulated a net gain in circulatory glucose by β-adrenoceptor mediated hepatic glycogenolysis (223) and inhibition of peripheral glucose uptake (277). It is interesting to note that 3SET offered the most potent stimulus for the release of catecholamine hormones; combined peak NA and AD values were 28% greater under 2SET than 1SET, and 17% greater under 3SET than 2SET trials, yet blood glucose concentrations during recovery were similar to a resting experimental session.

GH responses to RE evidenced a 1.5-fold greater increase under 3SET than 2SET, and a ~2-fold further rise after 2SET than 1SET. GH antagonises the metabolic action of insulin (278); particularly, intravenous GH infusion can directly inhibit glucose uptake in a dose/time dependent manner (42); thereby manifesting a physiological milieu sufficient to augment blood glucose concentrations. Furthermore, GH stimulates fatty-acid mobilisation via β-adrenergic receptors (278; 279), as do catecholamines (223; 279). Essentially, increased availability of non-carbohydrate derived fuels might have offset the utilisation of circulatory glucose. It should however be considered that the effects of GH on glucoregulation might have affected glycaemia at a time after the recovery period within the present study (42). However, it is unknown whether blood glucose concentrations would have continued to rise after one-hour of recovery from performing one to two sets of RE.

It is unlikely that cortisol was related to the glycaemic changes induced by the RE sessions, given that resting circulatory levels of this hormone remained comparable with the control session, irrespective of exercise volume.

The metabolic consequences of non-oxidative glycolytic activity were likely to have contributed to exercise-induced hyperglycaemia. The rapid combustion of muscle glycogen induced by high-intensity exercise causes a build-up of glucose-6-phosphate which inhibits hexokinase activity, thereby reducing glucose utilisation (225). During this time, a surplus of pyruvate accumulates outside of the mitochondria; this is then converted to lactate acid before disassociating to lactate and H^+ in blood. The results in this Chapter demonstrate 10 to 14-fold increases in blood lactate that are indicative of high rates of non-oxidative glycolysis. Recent research has demonstrated a progressive increase in blood lactate with performance of each set of RE in those without diabetes (280), which is in line with the responses to RE in this thesis. Interestingly, results from this study (280) also demonstrate further increases in blood lactate during the rest interval between sets of RE, and a net loss in blood lactate during performance of each set of repetitions in the second and third sets of RE. The authors suggested that the lactate generated by the exercising muscles during each set of RE was removed into the blood stream during each rest interval and consequently utilised by tissue during exercise. Blood lactate is likely to have been converted into

glucose by the liver and/or within the skeletal muscle (281; 282), indicating an increase in aerobic metabolism with increasing volume RE. From a clinical viewpoint, if the large amounts of lactate produced during RE replenished liver and muscle glycogen stores, via gluconeogenic pathways, then this recycling could have offered protection against the onset of post-exercise hypoglycaemia.

These described mechanisms lend support to a volume-dependent effect of RE on glucose production in T1DM. It therefore seems paradoxical to observe that the addition of a third-set diminished the magnitude of exercise-induced hyperglycaemia so that blood glucose concentrations after exercise remained similar to those of the control session. Circulating insulin concentrations were similar between experimental sessions before starting RE and throughout recovery across different exercise sessions (Figure 3.4; Table 3.2). The statistical power of the differences in post-RE glycaemia was moderate (75%) and it is accepted that a portion of the findings may be accounted for by the small sample size (i.e. a type II error) in this preliminary study. Health care professionals should be conscious of potential variability in glycaemic responses to different volumes of RE across different T1DM individuals. Nevertheless, participant basal insulin dose (glargine, n=8) and macronutrient intake taken the night prior to each experimental session was consistent across sessions; moreover, under CON where insulin concentrations were observed to be higher (albeit not significantly) than exercise sessions, blood glucose concentrations declined by a mere 0.6±0.5mM over 75 minutes. The time-course changes in plasma insulin support recent research by Peter et al (209), in which it was evidenced that the absorption rate of subcutaneously injected basal insulin glargine was unaffected by 30 minutes of aerobic exercise.

Interestingly, in impaired fasting glucose individuals, insulin sensitivity is better improved following four-sets in comparison to a single-set of RE (144). Authors reflected that the greater energy expenditure incurred by increasing exercise volume demanded more blood glucose. BG_{IAUC} data revealed that a net loss of 80% in circulatory glucose during 60 minutes of recovery was incurred as a result of the additional 2573±394kg of weight lifted during the third-set of RE, that was performed during an extra 14 minutes. This circulatory glucose was most likely extracted by tissue employed for exercise to replenish glycogen stores via GLUT4 translocation

(283), during exercise and recovery. Whether the exercise-induced hyperglycaemia after one and two-sets of RE was attenuated by an enhanced rate of glucose uptake in response to performing more work during a third-set, remains to be elucidated. Conceivably, performance of a third-set was likely to have relied more heavily on energy derived from oxidative than non-oxidative glycolytic sources, compared with prior sets. The potential for subtle differences in fuel-metabolism between different volume sessions could be involved in explaining volume-mediated differences in post-exercise glycaemia.

An improvement in indices of insulin sensitivity after RE has been related to the increased appearance of post-exercise IL-6, in those without diabetes; specifically, greater increments in IL-6 were observed after higher volume RE sessions, which coincided with larger improvements in insulin sensitivity (141). In the present study, a single-set of resistance exercise evoked a two-fold greater rise in IL-6 concentrations than those observed when participants remained sedentary (one-set: +0.8 ± 0.7 vs. control: +0.4 ± 0.4 $pg.mL^{-1}$ from baseline). Two sets of RE evoked a further rise in IL-6 concentrations (+1.1 ± 0.3 $pg.mL^{-1}$ from baseline), and inclusion of a third-set induced a five-fold rise in IL-6 concentrations (+2.0 ± 0.8 $pg.mL^{-1}$ from baseline) above control. These findings demonstrate a dose-dependent response in the post-exercise appearance of circulatory IL-6, given the 2-ton increment in total weight lifted with completion of each set. No previous research has explored IL-6 responses to resistance exercise in T1DM, but the present IL-6 responses are in line with those without diabetes: post-exercise IL-6 values of 5.2 to 7.4 $pg.mL^{-1}$ after performance of greater volume resistance exercise sessions (13,160-17,729kg) at intensities of 65 to 85% 1RM (141). However, it is unknown from these findings whether IL-6 was a factor in the volume-dependent differences in glycaemic responses to RE, i.e. as a function of possible direct/indirect alterations in glucose metabolism.

In agreement with the present findings that a relationship exists between RE session volume and increased appearance of IL-6, it has been established that IL-6 production within skeletal muscle of those without diabetes is sensitive to the duration and intensity of exercise (284), and rises in intramuscular IL-6 can be reflected in circulating concentrations (285). Interestingly, metabolic and hormonal stress and

stimulation of calcium-pump activity are factors that augment the transcription rate of skeletal muscle-derived IL-6 (for mechanistic review; (284; 286)). Acid-base disturbance, indicative of metabolic stress (287), was correlated with increased IL-6 appearance under the three-set RE session, but not under the two-set and one-set sessions. Thus, sustained metabolic stress resulting from greater amount of muscular activity with the three-set RE session was a possible trigger for increasing the appearance of IL-6 following exercise. Alternatively, with prolonged exercise reductions in muscle glycogen becomes a factor involved in the generation of skeletal muscle IL-6, potentially via activation of p38 MAPK and AMPK (284; 288). Further research is required to determine the precise stimulus for exercise volume-mediated increases in IL-6 after RE in T1DM, and whether transient increases in plasma IL-6 existed during or immediately after resistance exercise, given its short half-life (approx. 5 minutes; (285)).

The present data found statistically significant correlations between IL-6 and post-exercise hyperglycaemia, suggesting a potential role for IL-6 in glucose regulation in T1DM, which was potentially elicited by including a third-set of RE. It has been shown that IL-6 infusion stimulates insulin-dependent glucose uptake via enhancing GLUT4 expression and activation of AMPK in skeletal muscle (289). Thus, whether the upstream pathways that potentially led to muscle contraction-induced production of IL-6 and/or the downstream effects of IL-6 appearance indirectly or directly played a role in glucose metabolism after RE, respectively, the exercise-induced increases in IL-6 might have facilitated the clearance of circulatory glucose following performance of a third-set of RE. Indeed, these conclusions cannot be drawn from this clinical study. But these findings highlight that further work in this area is necessary to determine whether improvements in post-exercise glycaemia are causal to the degree of rise in circulating IL-6 with RE session volume.

To consider that RE session volume can alter the balance between glucose uptake and production may help to reconcile disparate glycaemic responses to other RE sessions (211; 240). However, acute counterregulatory hormone responses to RE are sensitive to even small modifications in a RE protocol (242) and consequently blood glucose might also be receptive to different RE sessions differing in subtle ways. The

opportunity for variability in the RE protocols was minimised by a number of controlling factors. Firstly, exercise intensity was relativised to a percentage of individual maximal-strength scores and total weight-lifted within a session was 'relatively' equal between participants. Secondly, exercises to a metronome added to control by enabling consistency in duration of each muscle contraction. Collectively, these manipulations enabled the reliable performance of a fixed ratio of work to rest comprising eight intermittent bouts of 40 seconds of continuous isotonic muscle contractions equating to 5 minutes and 20 seconds of mechanical work per set. This clarity has not been established by previous work in T1DM (211; 240); rather, in these studies, more emphasis was placed on exploring 24-hour changes in post-resistance exercise glycaemia using continuous glucose monitoring devices. Overcoming factors that limit reliability is crucial to the development of efficacious RE-oriented glycaemic management strategies for T1DM individuals. Nevertheless, the present study findings are limited to the acute changes in post-RE glycaemia, yet it is unknown to what effect altering RE volume could have on later post-exercise glycaemia in T1DM.

Various measurements are useful to convey the potential application of the RE sessions within this Chapter as part of a physical exercise programme. The finding that HR during exercise was on average 57±2% to 66±4% of age-predicted-HR_{max}, over 15-45 minutes, which corresponded with an average exercise-intensity of 68±0%1RM, indicates that RE is a useful stimulus for the cardiovascular system. Additionally, the performance of eccentric exercise, a component of the RE protocols, can subsequently impair post-exercise insulin action and thus disturb glucoregulation in those without diabetes (233), which is paralleled by demonstrable increases in muscle damage markers including creatine kinase. Nevertheless, perceptual muscle soreness and physiological inflammation assessed in creatine kinase levels at 24-h after exercise were negligible, and considerably less than other RE protocols (233; 252).

Prolonged fasting, elevated levels of counterregulatory hormones, metabolic acidosis and hypoinsulinaemia are factors which can augment ketoacidosis (53). In this light, a window of opportunity for greater ketone body production during these experimental

sessions may have been possible. Ketonaemia was negligible on arrival to the research facility (average 0.08±0.01mmol.L^{-1}) and was not exacerbated by exercise (Figure 3.7).

From a clinical viewpoint, the findings showed evidence that K^+ concentrations were elevated after 60 minutes of recovery, but not under CON, reaching peak levels of 4.4±0.7 mmol.L^{-1}. This finding is in agreement with previous research, in which it was shown that overnight fasted, and relatively hypoinsulinaemic T1DM individuals displayed a rise in plasma K^+ concentrations that were reflective of hyperkalaemia (>5.0 mmol.L^{-1}), during recovery from high-intensity exercise (218). Hypoinsulinaemic-hyperglycaemia in T1DM has been shown to raise plasma potassium concentrations at rest (290; 291). This is probably because insulin augments the affinity of the Na^+-K^+ pump for intracellular Na^+, and enhances intracellular Na^+ uptake, with a resulting increase in the intracellular K^+/Na^+ ratio (292); as such, relative insulin deficiency promotes both a net movement of K^+ out of the cells and/or a failure of K^+ uptake, with resulting systemic hyperkalaemia (293). Thus, the post-exercise rises in K^+ in the present study, are reflective of an extracellular shift in K^+, and appear not to be related to hyperglycaemia *per se*, rather to a culminating effect of exercise-induced hyperglycaemia paralleled by participants being in a transient recovery state of relative hypoinsulinaemia (given the lack of morning insulin). The administration of a post-exercise dose of exogenous insulin might have offset this response, since insulin increases intramuscular K^+ uptake (294).

Conclusion

Performing a morning RE session after an overnight fast and omission of pre-exercise rapid-acting insulin does not induce acute post-exercise hypoglycaemia or raise a marker of muscle damage. One or two sets of RE induces hyperglycaemia for at least an hour after exercise, but this response could be negated by performing a third-set of RE. The attenuation of exercise-induced hyperglycaemia by inclusion of a third-set may result in greater utilisation of circulatory glucose generated from counterregulatory responses to prior sets and an increased appearance of IL-6. Increasing exercise volume could be a useful non-pharmacological strategy for T1DM individuals to ameliorate the magnitude of acute exercise-induced hyperglycaemia

associated with one and two sets of RE. Further research is required to determine the extent to which manipulating RE characteristics such as volume could impact later post-exercise glycaemia of T1DM individuals.

CHAPTER FOUR

The Impact Of Manipulating Resistance Exercise Session Intensity In Type 1 Diabetes

4.1 INTRODUCTION

Regular performance of resistance exercise (RE), or weights training, is advocated to individuals with diabetes (103; 295; 296) and research suggests that this could have a beneficial effect on health in people with both type 2 (103; 297) and type 1 diabetes (T1DM) (118; 119). Prescription guidelines for RE are tailored to individual physical ability and/or fitness goals (239). For example, heavy loads (i.e. high-intensity; 70 to ≥80%1RM) paired with a moderate/high number of repetitions (8 to 15 lifts) and multiple sets (2 to 4 sets) are undertaken when the aim is to elicit muscular hypertrophy. In contrast, light to moderate loads (i.e. low-intensity; <50%1RM) coupled with multiple high-repetition (15 to 20 lifts) sets (≤2 sets) is aimed towards training muscular endurance. Such an exercise session is best suited to novice and/or previously sedentary individuals or those with certain diabetic related complications or weight-bearing abilities (239; 295).

The effects of RE on blood glucose in T1DM are scant and responses vary between studies; earlier research demonstrates a net increase (298) or decrease (211), or no change in blood glucose (240; 298) in response to a single session of RE. It is unclear how specific RE session characteristics such as the load, volume, work to rest interval, contraction velocity (or pacing) etc., might affect glycaemia in T1DM. Yet, such knowledge is likely to facilitate the development of better glucose management routines for exercising T1DM individuals and ultimately favour the preclusion of exercise-induced glycaemic disturbances – a primary cause of low exercise participation and adherence rates in T1DM (149).

In a recent study, Turner et al. (298) demonstrated that the total weight lifted during a RE session (i.e. exercise volume) had a strong bearing on post-exercise blood glucose, with one and two sets of RE increasing blood glucose but with the addition of a third set post-exercise blood glucose was returned to values similar to that of a resting control trial. So, thirty-minutes of RE performed at ~70% one-repetition maximum consistently elicits a hyperglycaemic excursion for up to one-hour after exercise (298). However, despite clinical recommendations for people with T1DM to conduct RE, the occurrence of post-exercise hyperglycaemia could detract from the host of possible health benefits gained through regular RE training, since hyperglycaemic per

se could contribute to a worsening of glycaemic control. Somewhat anecdotally, the administration of a small bolus of insulin can resolve the occurrence of exercise-induced hyperglycaemia, although in clinical practice this strategy often increases the likelihood of hypoglycaemia. Another approach is to examine the influence of manipulating exercise characteristics. While it has been consistently shown that performance of moderate intensity aerobic exercise lowers blood glucose (68), high-intensity or sprint exercise results in a strong counterregulatory hormone response that attenuates the decline in glycaemia during aerobic exercise (214; 227), and can in fact increase blood glucose concentrations (218-220). Thus, the intensity of RE (i.e. the amount of weight lifted per repetition relative to maximal exertion) might play a role in explaining the magnitude of post-RE hyperglycaemia in T1DM. Such knowledge is important to both developing strategies to improve glycaemic stability during and after RE and accurately prescribing RE in this clinical cohort.

Therefore, the aim of this study was to examine the impact of manipulating resistance exercise session intensity by comparing the acute glycaemic, metabolic and glucoregulatory hormone responses to tightly controlled moderate and low intensity RE sessions matched for total weight lifted in T1DM individuals.

4.2 RESEARCH DESIGN AND METHODS

4.2.1 Participants

Eight physically active male (n=6) and female (n=2) individuals with type 1 diabetes (age 34 ± 7 years, HbA_{1C} 8.7 ± 1.1 %, duration of diabetes 18 ± 5 years) volunteered and provided written informed consent for the study. Participants anthropometric, glycaemic control and insulin regimen characteristics are presented in Table 2.2 (Page 55). All participants were treated with an insulin regimen composed of bolus insulin glargine or detemir and prandial rapid-acting insulin aspart.

4.2.2 Experimental Design

A randomised and counterbalanced, repeated-measures design was conducted to compare glycaemic and glucoregulatory responses within-subjects and between-treatments (Figure 4.1). Following a single preliminary session to determine the maximal weight a participant could lift once over a range of exercises (Section 2.3.3.2), a further two RE sessions of different intensity but similar in the total weight lifted, were scheduled. For the low intensity RE session (LOW), the weight lifted per repetition was 30% of the maximum amount a participant could lift for one repetition (LOW), whereas moderate intensity RE (MOD) was set at 60% of maximal repetition (Section 2.3.4.2). Experimental sessions were separated by at least 3 days.

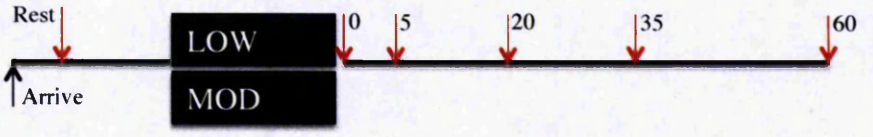


Figure 4.1: Schematic representation of study design, with two repeated measures experimental arms (LOW and MOD). Red arrows indicate venous sample points during the laboratory phase.

4.2.3 Experimental Sessions and Analysis

Participants arrived at the clinical research facility between 0630 – 0900 h. Participants were fasted for 8-10 hours, having taken their usual basal insulin dose (31.3 ± 3.8 IU) the night before but omitted rapid-acting insulin on the morning of testing (Section 2.8). Retrospective analysis revealed that dietary intake (MOD 2358±150 vs. LOW 2368±139 calories, *p=0.488*) and insulin dosage (basal-insulin:

MOD 31±4 vs. LOW 31±4 IU; bolus-insulin: MOD 29±3 vs. LOW 29±3 IU, $p>0.05$) during the 24 hours prior to exercise were replicated between the two experimental sessions. After a standardised 10 minute warm-up of the main muscle groups, participants undertook one of two RE sessions followed by a 65 minute period of passive recovery; 6 exercises performed at either a moderate-intensity [two sets of 10 repetitions at 60%1RM] (MOD) or a low-intensity session [two sets of 20 repetitions at 30%1RM] (LOW). Venous blood glucose (BG) concentrations were measured for 65 minutes after resistance exercise (Figure 4.1). Heart rate and blood pressure was recorded at prior to RE and during recovery. Mean arterial pressure was determined as per section 2.11.3. All blood samples were processed and analysed for glucose, pH, lactate, extra-cellular fluid base-excess (B_{ecf}) and K^+, catecholamines, growth hormone, IL-6 and cortisol (Section 2.4.3). Percentage of heart rate maximum ($\%HR_{max}$) was determined using a maximal heart rate equation based on age (Section 2.11.4). Data (mean ± SEM) were analysed using ANOVA ($p\leq0.05$) (Section 2.12).

4.3 RESULTS

4.3.1 Exercise Volume And Intensity

Total weight lifted during RE was similar between sessions (Volume: MOD 3675 ± 651 vs. LOW 3725 ± 674 kg, *p=0.124*). Intensity was 2-fold greater under MOD than LOW (59 ± 1 vs. 29 ± 0 %1RM, *p<0.001*), meaning that weight lifted per minute was significantly greater under MOD than LOW (MOD 459 ± 81 vs. LOW 232 ± 42 $kg.min^{-1}$, *p=0.027*).

4.3.2 Blood Glucose

The blood glucose (BG) responses to exercise are presented in Figure 4.2. Pre-exercise fasting BG concentrations were similar between sessions (MOD 11.2 ± 1.3 vs. LOW 11.2 ± 1.2 $mmol{\cdot}L^{-1}$, *p=0.995*). There was a significant effect of time (p=0.041, partial-eta^2 = 0.448), but no effect of session (p=0.768, partial-eta^2 = 0.013) and no interaction between exercise intensity and time (p=0.393, partial-eta^2 = 0.133), for absolute BG responses. BG rose by similar concentrations immediately after exercise (MOD +1.5 ± 0.8 vs. LOW +2.2 ± 0.9 $mmol{\cdot}L^{-1}$, *p=0.382*). Individualised peak BG concentrations occurred at 35-minutes post-exercise under both sessions, and these values were similar (MOD 13.2 ± 1.6 vs. LOW 14.3 ± 2.1 $mmol{\cdot}L^{-1}$, *p=0.701*). During recovery, BG_{IAUC} was similar between experimental sessions (MOD 9.8 ± 10.9 vs. LOW 28.0 ± 14.5 $mmol.min.L^{-1}$, *p=0.222*). From an observational perspective, after 65 minutes of recovery from exercise, a similar number of participants were observed to experience a ≥2 $mmol{\cdot}L^{-1}$ rise from pre-exercise BG concentrations under LOW (n=5) and MOD (n=6), and two (LOW) or one (MOD) participants experienced exercise-induced BG excursions of ≥4 $mmol{\cdot}L^{-1}$ from pre-exercise. There were no occasions of hypoglycaemia (BG ≤3.9 $mmol{\cdot}L^{-1}$) experienced by any participant under either experimental session.

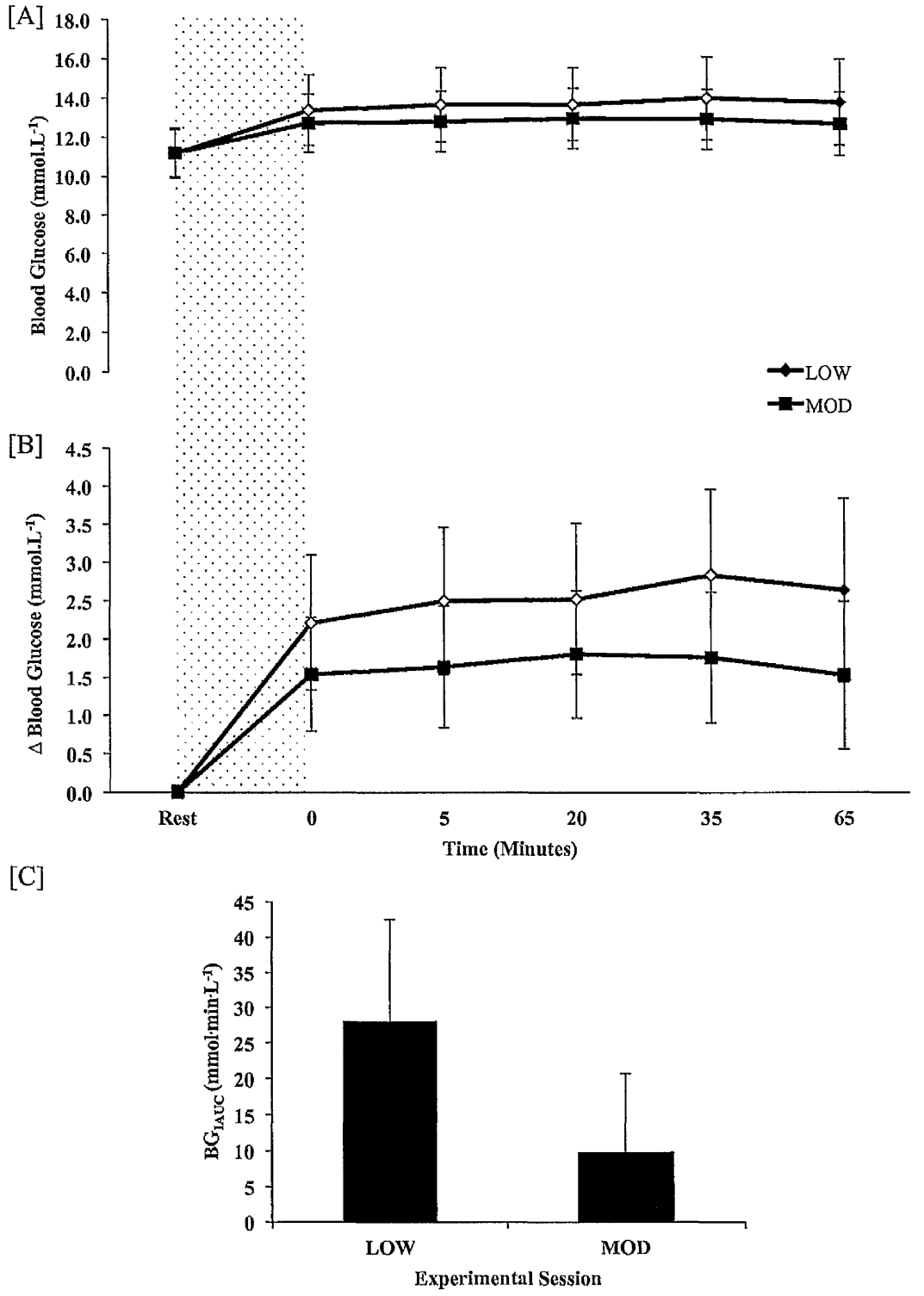


Figure 4.2: [A] Absolute and [B] delta blood glucose responses and [C] post-exercise BG_{IAUC}, to MOD and LOW sessions. Transparent sample points indicate significant changes from baseline within each session ($p<0.05$).

4.3.3 Blood Acid-base Balance

The blood lactate, pH and B_{ecf} responses to exercise are presented in Figure 4.3. The blood lactate responses to exercise are presented in Figure 4.3A. There was a significant effect of time (p=0.000, partial-eta^2 = 0.729), but no effect of session (p=0.303, partial-eta^2= 0.150) and no session*time interaction (p=0.669, partial-eta^2= 0.084), for blood lactate responses. Baseline blood lactate concentrations were similar between sessions (MOD 1.1 ± 0.2 vs. LOW 1.1 ± 0.2 mmol·L^{-1}, *p=1.000*). Individualised peak concentrations (MOD 9.8 ± 2.4 vs. LOW 10.6 ± 1.9 mmol·L^{-1}, *p=0.381*) were similar between sessions.

Baseline blood pH was slightly higher under LOW resulting in a statistically significant difference between sessions (MOD 7.35 ± 0.01 vs. LOW 7.38 ± 0.01, *p=0.016*). As such, blood pH values were expressed relative to baseline levels and analysed in this way. There was a significant effect of time (p=0.002, partial-eta^2= 0.714), but no effect of session (p=0.566, partial-eta^2= 0.049) and no session*time interaction (p=0.344, partial-eta^2 = 0.139), for blood pH responses. In response to exercise, individualised nadir blood pH occurred immediately after exercise under both sessions, with no difference in values between sessions (MOD -0.08 ± 0.02 vs. LOW -0.10 ± 0.03, *p=0.946*). The time-course changes in blood pH were similar between sessions throughout recovery (*p>0.05;* Figure 4.3B); meaning blood pH had returned to resting levels by 20 minutes post-exercise under both MOD and LOW.

There was a significant effect of time (p=0.000, partial-eta^2= 0.603), but no effect of session (p=0.185, partial-eta^2= 0.236) and no interaction between exercise intensity and time (p=0.996, partial-eta^2= 0.010), for B_{ecf} responses. Resting B_{ecf} concentrations were similar between sessions (MOD 4.9 ± 1.1 vs. LOW 9.2 ± 2.6 mEq·L^{-1}, *p=0.206*). In response to exercise, B_{ecf} declined to similar values between sessions (MOD -5.7 ± 1.9 vs. LOW -2.4 ± 2.3 mEq·L^{-1}, *p=0.295*) and nadir B_{ecf} was similar between sessions (MOD -6.3 ± 1.9 vs. LOW -7.14 ± 2.13 mEq·L^{-1}, *p=0.614*). Under both sessions, B_{ecf} had returned to resting values (*p>0.05*) following 65 minutes of recovery (Figure 4.3C).

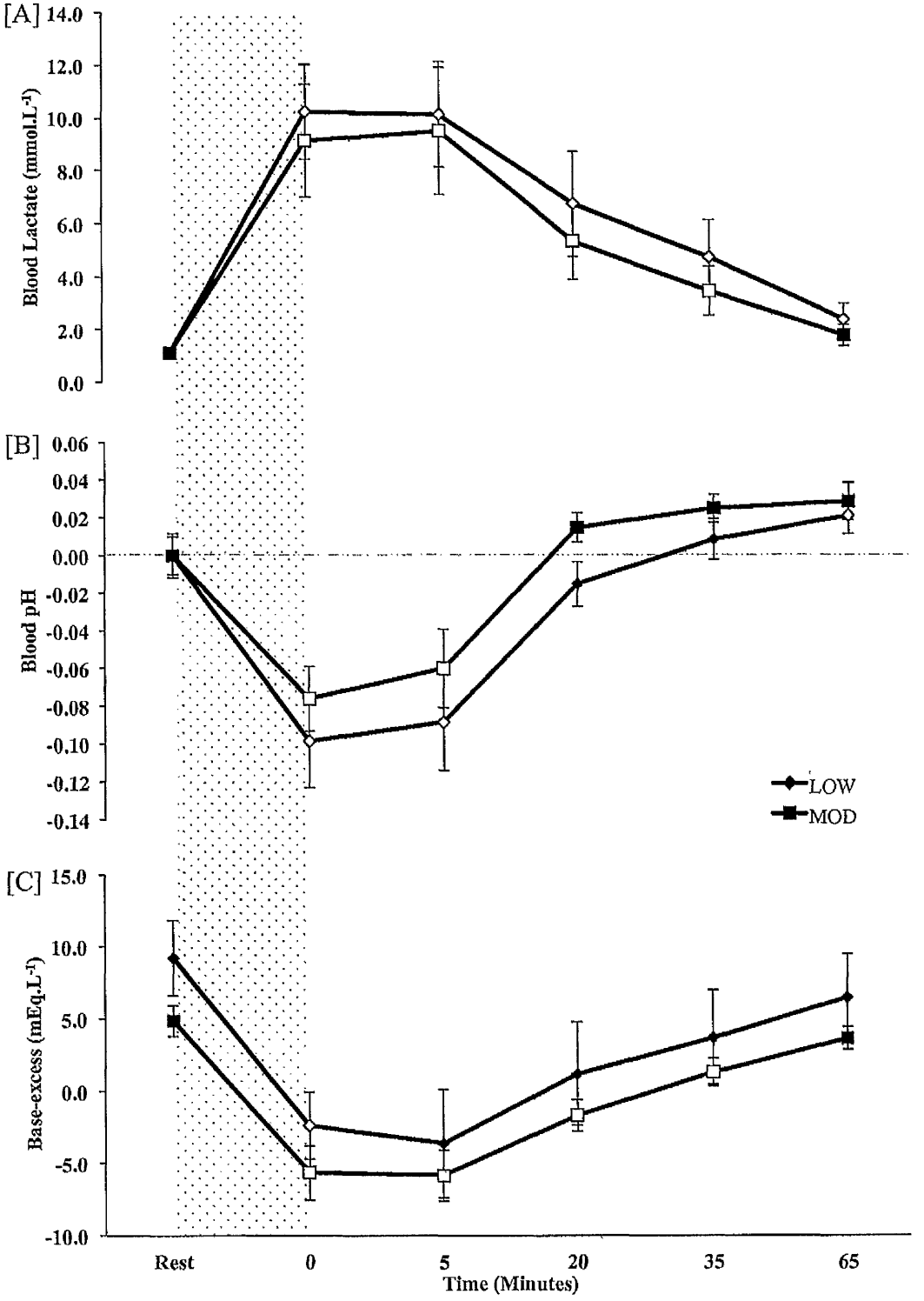


Figure 4.3: [A] Blood lactate [B] blood pH (expressed relative to Rest) and [C] extra-cellular fluid base-excess responses to MOD and LOW sessions. Transparent sample points indicate significant changes from rest within each session ($p<0.05$). * indicates a statistically significant difference ($p<0.05$) between MOD and LOW.

4.3.4 Blood Potassium

Blood potassium (K^+) responses to exercise are presented in Figure 4.4. There was a significant effect of time (p=0.015, partial-eta^2 = 0.480) and session (p=0.004, partial-eta^2 = 0.712), but no session*time interaction (p=0.589, partial-eta^2 = 0.078) for K^+ responses. Resting K^+ concentrations were similar between sessions (MOD 4.0 ± 0.1 vs. LOW 3.9 ± 0.1 mmol·L^{-1}, *p=0.065*). During exercise K^+ rose to similar values across sessions (MOD 4.5 ± 0.1 vs. LOW 4.3 ± 0.1 mmol·L^{-1}, *p=0.447*), but values at 5-minutes post-exercise were higher K^+ under MOD than LOW (4.2 ± 0.1 vs. LOW 3.9 ± 0.1 mmol·L^{-1}, *p=0.012*). Under both sessions, K^+ concentrations were markedly greater than rest at 0 and 20-65 minutes post-exercise (*p<0.05*). K^+ values under MOD were greater than LOW from 5-65 minutes of recovery (*p<0.05*). Individualised peak K^+ concentrations were greater under MOD than LOW (4.8 ± 0.2 vs. 4.35 ± 0.1 mmol·L^{-1}, *p=0.036*).

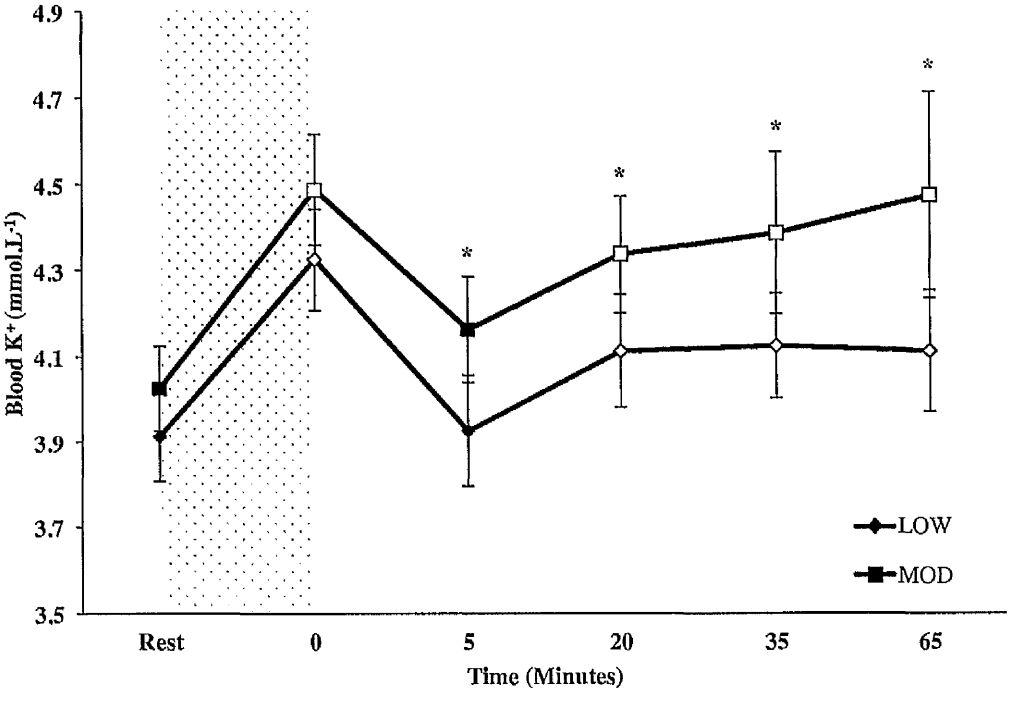


Figure 4.4: Blood potassium (K^+) responses to MOD and LOW sessions. Transparent sample points indicate significant changes from baseline within each session (p<0.05). * indicates a statistically significant difference (p<0.05) between MOD and LOW.

4.3.5 Glucoregulatory Hormones and IL-6

The plasma adrenaline (AD) and noradrenaline (NA), growth hormone (GH), interleukin-6 (IL-6) and cortisol responses to the experimental sessions are presented in Table 4.1. Baseline concentrations for all glucoregulatory hormones and IL-6 were similar between experimental sessions (*p>0.05;* Table 4.1).

4.3.5.1 Catecholamines

There was a tendency for a significant effect of time (p=0.079, partial-eta^2= 0.360) but no effect of experimental session (p=0.140, partial-eta^2 = 0.283) on plasma adrenaline (AD) responses. For plasma noradrenaline (NA) responses, there was an effect of time (p=0.000, partial-eta^2= 0.615) but no effect of session (*p=0.145*, partial-eta^2= 0.278) or interaction between experimental session and time (*p=0.118*, partial-eta^2= 0.295). Individualised peak concentrations of AD (MOD 0.55 ± 0.13 vs. LOW 1.04 ± 0.37 nmol.L^{-1}, *p=0.155*), NA (MOD 4.59 ± 0.86 vs. LOW 7.11 ± 1.82 nmol.L^{-1}, *p=0.082*) tended to be greatest under LOW. There were significant correlations between catecholamines and blood glucose, lactate and K^+ responses to LOW and MOD sessions (Table 4.4 & 4.5).

4.3.5.2 Growth Hormone

There was a significant effect of time (p=0.001, partial-eta^2= 0.420), but no effect of session (p=0.110, partial-eta^2 = 0.323) and no session*time interaction (p=0.656, partial-eta^2= 0.086), for plasma growth hormone (GH) responses. Individualised peak GH concentrations were similar between sessions (MOD 3.52 ± 0.80 vs. LOW 3.66 ± 0.93 ng.mL^{-1}, *p=0.644*). Whereas GH concentrations remained above baseline (*p<0.05*) from 0-20 minutes post-exercise under LOW, concentrations were comparable with baseline (*p>0.05*) from 5-65 minutes post-exercise under MOD, this meant that the GH_{IAUC} (absolute values, including exercise and recovery) was greatest under LOW (MOD 209.16 ± 57.86 vs. LOW 238.45 ± 68.89 ng.mL^{-1}, *p=0.043*).

Table 4.1: Plasma adrenaline, noradrenaline, cortisol, growth hormone and interleukin-6 responses to **MOD** and **LOW** sessions.

		Rest	0	5	20	35	65
Plasma AD (nmol.L^{-1})	**LOW**	0.35±0.07	0.99±0.38	0.59±0.20	-	-	0.47±0.12
	MOD	0.24±0.05	0.52±0.14*	0.36±0.07*	-	-	0.27±0.06
Plasma NA (nmol.L^{-1})	**LOW**	1.91±0.32	6.89±1.88*	5.03±1.44*	-	-	1.64±0.18
	MOD	1.58±0.31	4.59±0.86*	2.93±0.66*	-	-	1.71±0.32
Plasma Cortisol (ng.mL^{-1})	**LOW**	70.77±15.40	90.92±18.49	90.62±17.77	80.81±19.88	78.50±18.28	61.39±13.51
	MOD	84.68±18.97	58.80±10.71	62.38±11.39	67.89±13.61	54.11±10.77	34.88±8.46*
Plasma Growth Hormone (ng.mL^{-1})	**LOW**	1.27±0.47	2.77±0.73*	2.77±0.73	3.32±1.00	2.23±0.71	1.81±0.66
	MOD	1.52±0.65	3.15±0.82*	2.43±0.91*	2.64±0.82*	1.99±0.67	1.50±0.46
Plasma IL-6 (pg.mL^{-1})	**LOW**	2.64±1.21	2.54±1.04	-	2.60±1.02	2.73±0.95	2.70±1.08
	MOD	1.76±0.50	2.02±0.67	-	1.83±0.61	1.99±0.55	1.96±0.50

Data presented as mean ± SEM. * indicates a statistical significant difference ($p<0.05$) to rest. Time-points indicate minutes post-exercise.

4.3.5.3 Cortisol

There was a significant effect of time (p=0.031, partial-eta^2 = 0.286) and session*time interaction ($p=0.016$, partial-eta^2 = 0.318), but no effect of session (p=0.191, partial-eta^2 = 0.230), for plasma cortisol responses, with lower cortisol concentration observed under MOD at the end of recovery ($p<0.05$). Individualised nadir (MOD 34.88 ± 8.46 vs. LOW 57.73 ± 13.89 ng.mL^{-1}, $p=0.141$) and peak (MOD 74.89 ± 13.46 vs. LOW 101.54 ± 19.42 ng.mL^{-1}, $p=0.175$) cortisol concentrations were similar between sessions.

4.3.5.3 IL-6

For plasma interleukin-6 (IL-6), there were no significant effects of time (p=0.750, partial-eta^2 = 0.064) or session (p=0.217, partial-eta^2 = 0.208), with similar individualised peak concentrations between sessions (MOD 2.3 ± 0.6 vs. LOW 3.0 ± 1.0 pg.mL^{-1}, $p=0.195$).

4.3.6 Cardiovascular Responses

4.3.6.1 Heart Rate

The heart rate (HR) responses to exercise are presented in Table 4.2. Resting HR was similar between sessions (*p=0.568*). Average HR during exercise relative to estimated $\%HR_{max}$, was significantly greater under LOW than MOD (*p=0.039;* Table XX). Average recovery HR was similar between sessions (*p=0.112*), and greater than rest under both sessions (*p<0.05*). The average heart rate during exercise as a $\%HR_{max}$ (Mean HR_{max} 184 ± 5 $beats.min^{-1}$) was significantly less under MOD (67±6%) than LOW (80±7%) (*p=0.039*). There was a greater frequency of heartbeats during exercise under LOW than MOD (LOW 5881±525 vs. MOD 3830±344 beats, *p=0.005*). A greater percentage of time during the exercise session under LOW was spent at heart rates of ≥ 50%HRmax (92 ± 2 $beats.min^{-1}$) (LOW 93± 3 vs. MOD 78 ± 7 %, *p=0.038*) and 60%HRmax (111 ± 3 $beats.min^{-1}$) (LOW 72 ± 9 vs. MOD 50 ± 11 %, *p=0.039*), but not at heart rates of ≥ 70%HRmax (129 ± 3 $beats.min^{-1}$) (LOW 51 ± 13 vs. MOD 30 ± 12 %, *p=0.113*). Heart rates during recovery correlated positively with adrenaline and noradrenaline responses to RE under both LOW and MOD (see Tables 4.4 & 4.5).

Table 4.2: Heart rate (HR) responses to LOW and MOD experimental sessions.

	Rest	Exercise	Recovery	Ex-Peak	Ex-Min
LOW					
beats.min^{-1}	61±2	147±13†*	88±3*	195±13*	70±11
%HR$_{max}$	-	80±7†	48±2	106±6	38±6
MOD					
beats.min^{-1}	61±2	124±11*	83±3*	167±16*	76±5*
%HR$_{max}$	-	67±6	45±2	91±9	41±3

* indicates a statistical significant difference (*p<0.05*) from rest. † indicates a statistical significant difference to LOW (*p<0.05*). ***beats.min^{-1}***; beats per minute. **Ex-Peak**; Peak HR during exercise. $\%HR_{Max}$; values relative to estimated HR maximum. **Ex-Min**; minimum HR during exercise. Exercise: average HR during exercise. **Recovery**; average HR during 60 minutes post-exercise.

4.3.6.2 Blood Pressure

There was no significant effect of time (*p>0.05*) or session (*p>0.05*) on any cardiovascular marker (Table 4.3). There was tendency for a reduction from rest to 60-minutes post-exercise in MAP under LOW (*p=0.065*) but not MOD (*p=1.00*).

Nadir MAP was similar between sessions (MOD 87 ± 3 vs. LOW 82 ± 3 mmHg, *p=0.315*).

Table 4.3: Markers of blood pressure under MOD and LOW sessions.

	Rest (mmHg)	0 min (mmHg)	60 min (mmHg)
MOD			
SBP	128 ± 4	125 ± 3	124 ± 4
DBP	76 ± 4	73 ± 4	70 ± 4
MAP	93 ± 4	90 ± 3	88 ± 3
LOW			
SBP	129 ± 5	126 ± 4	116 ± 8
DBP	76 ± 3	69 ± 3	72 ± 3
MAP	94 ± 3	88 ± 2	86 ± 3

Data (mean ± SEM). **SBP**: Systolic blood pressure, **DBP**: Diastolic blood pressure, **MAP**: Mean arterial pressure. No statistical differences between or within sessions (*p>0.05*). **0** and **60** min represent post-exercise samples.

Table 4.4: Correlations (Pearson's *r*) between catecholamines and blood glucose, lactate and K^+, and heart rate (HR), under LOW.

	Glucose			**Lactate**			**HR**	**K^+**
AD	**0**	**60**	**Peak**	**0**	**65**	**Peak**	**Rec**	**5**
0	0.580*	0.600*	0.594*	**0.901**	**0.972**	**0.882**	**0.694**	**-0.692**
5	0.616*	**0.634**	**0.639**	**0.739**	**0.855**	**0.708**	**0.741**	-0.509
65	**0.696**	**0.714**	**0.720**	**0.636**	**0.781**	**0.618**	**0.743**	-0.398
Peak	0.598*	0.620*	0.614*	**0.891**	**0.958**	**0.869**	**0.698**	**-0.655**
	Glucose			**Lactate**			**HR**	**K^+**
NA	**0**	**60**	**Peak**	**0**	**65**	**Peak**	**Rec**	**5**
0	0.560*	0.583*	0.572*	**0.942**	**0.951**	**0.905**	0.578*	**-0.697**
5	0.590*	0.604*	**0.606**	**0.852**	**0.945**	**0.809**	**0.734**	**-0.759**
65	0.158	0.189	0.175	**0.820**	**0.710**	**0.778**	0.453*	-0.441
Peak	0.555*	0.575*	0.567*	**0.940**	**0.967**	**0.900**	0.609*	**0.765**

0, 5 and **60** represent sample time in minutes after exercise. **Rec** refers to mean HR (beats.min^{-1}) during the 65-minute post-exercise recovery period. **Peak** refers to individualised peak concentration. **Bold**: p<0.05. * indicates trend (*p<0.07*). **Plain text**: no statistical correlation (*p>0.05*).

Table 4.5: Correlations (Pearson's *r*) between catecholamines and blood glucose, lactate and K^+, and heart rate (HR), under MOD.

	Glucose			Lactate			HR	K^+
AD	**0**	**60**	**Peak**	**0**	**65**	**Peak**	**Rec**	**5**
0	0.294	0.356	0.306	**0.982**	**0.918**	**0.962**	**0.954**	**-0.401**
5	0.316	0.344	0.298	**0.792**	**0.709**	**0.749**	**0.788**	-0.278
65	0.551*	0.595	0.433	0.681*	**0.749**	0.608	**0.638**	-0.081
Peak	0.306	0.366	0.316	**0.970**	**0.901**	**0.947**	**0.956**	-0.375
	Glucose			**Lactate**			**HR**	K^+
NA	**0**	**60**	**Peak**	**0**	**65**	**Peak**	**Rec**	**5**
0	0.121	0.257	0.097	**0.907**	**0.837**	**0.867**	**0.887**	-0.585*
5	0.384	0.144	0.349	**0.869**	**0.899**	**0.789**	**0.812**	-0.488
65	0.079	0.392	0.047	0.318	0.276	0.259	0.330	-0.080
Peak	0.121	0.115	0.097	**0.907**	**0.837**	**0.867**	**0.887**	-0.585*

0, 5 and **60** represent sample time in minutes after exercise. **Rec** refers to mean HR (beats.min^{-1}) during the 65-minute post-exercise recovery period. **Peak** refers to individualised peak concentration. **Bold**: $p<0.05$. * indicates trend ($p<0.07$). **Plain text**: no statistical correlation ($p>0.05$).

4.3.7 Ratings Of Perceived Exertion

Ratings of perceived exertion (OMNI-RE Scale) were similar between sessions after the first set of exercise (MOD 6 ± 1 vs. LOW 6 ± 0, $p=0.492$), corresponding with feelings of "somewhat hard". Following completion of the second set, perceptual ratings significantly increased from the initial set ($p<0.05$) to similar values under both sessions (MOD 7 ± 1 vs. LOW 8 ± 1, $p=0.269$), corresponding with feelings of "somewhat hard" to "hard".

4.4 DISCUSSION

The aim of this study was to examine the impact of manipulating resistance exercise session intensity by comparing the acute glycaemic, metabolic and glucoregulatory hormone responses to tightly controlled moderate and low intensity RE sessions of equal volume in T1DM individuals. The results from this study are the first to demonstrate that despite a tendency for different counterregulatory hormone responses, performing a low-intensity RE session results in a similar magnitude of post-exercise hyperglycaemia compared to that of moderate-intensity RE session matched for total weight lifted.

Participants commenced both exercise sessions in a mildly hyperglycaemic state (~11 $mmol{\cdot}L^{-1}$). They avoided hypoglycaemia during and throughout recovery, with blood glucose rising to similar concentrations of 13.4 ± 1.8 and 12.7 ± 1.5 $mmol.L^{-1}$ during low and moderate intensity RE, respectively. During one-hour of recovery from the low and moderate intensity RE sessions blood glucose concentrations rose by 3.1 ± 1.1 and 2.0 ± 0.9 $mmol.L^{-1}$ greater than baseline (pre-exercise), respectively, noting that participants replicated the same pre-exercise diet and insulin adjustments across the experimental sessions. The binding of catecholamines to β-adrenoceptors augments hepatic glycogenolysis and inhibits glucose uptake (223; 277). The resultant greater increment in glucose production over uptake is a major factor in the development of post-exercise hyperglycaemia in T1DM individuals (275). The low intensity RE session elicited a ~3-fold and ~4-fold increase in adrenaline and noradrenaline concentrations, respectively, whereas the moderate intensity RE session produced a ~2-fold increase in adrenaline and ~3-fold increase in noradrenaline. These increases in catecholamines reflect increased sympathoadrenal medullary activity, which was likely a component in the occurrence of exercise-induced hyperglycaemia (218; 275). In further support of this mechanism, positive correlations were observed between post-exercise catecholamine and blood glucose concentrations (Tables 4.4 & 4.5). The tendency for greater sympathetic activity in response to low over moderate intensity RE without differences in the magnitude of post-exercise hyperglycaemia highlights the complex relationship between RE characteristics and exercise-induced changes glycaemic regulation.

The magnitude of the growth hormone response was similar between different intensity RE sessions, with 2 to 3-fold rise in baseline concentrations appearing after exercise. Considering that GH might stimulate hepatic glucose production and impair glucose uptake through multiple mechanisms (278), the marked exercise-induced appearance of GH could have contributed to a rise in blood glucose in response to exercise. Considering that the exercise-induced peak rise in GH was similar between RE sessions but there was a tendency for greater catecholamine responses to low than moderate intensity RE, it is unexpected that the magnitude of post-exercise glycaemia was unaffected by adjusting the intensity of exercise. Interestingly, intravenous adrenaline infusion in adrenalectomised humans during exercise has been shown to both suppress the appearance of GH and increase hepatic glucose production (223), but it cannot be determined from this study what interactions might have occurred between these counterregulatory hormones in response to exercise.

Although speculative, perhaps a possible interaction between adrenaline and GH explains why the time-course changes in GH during recovery were different between LOW and MOD sessions (i.e. prolonged increase in GH values under MOD, yet later peak concentrations during recovery under LOW; Table 4.1). Alternatively, temporal changes in GH after exercise has been shown to indicate differences in oxygen utilisation during exercise (299). Interestingly, (in those without diabetes) twelve-times as much energy (kcal) is required to perform one repetition at 80%1RM when compared to one repetition at 20%1RM, despite a four-fold increase in mechanical work (300). Furthermore, rates of muscle glycogenolysis are raised by increasing the intensity of RE relative to repetition-maximum, but an equal decline in muscle glycogen content during exercise has been observed when different intensity RE sessions are matched for total weight lifted (249). Muscular force generated during LOW was probably served predominantly by type I (fatigue-resistant) fibres, which would have contrasted the majority of type II and IIx fibres utilised for contraction under heavier external loads-lifted during MOD. It is also logical to assume that contraction under higher loads demanded activation of additional stabilising muscles, thereby adding to total energy costs of exercise. Together these findings suggest that altering the intensity of RE could affect fuel utilisation and/or energy expenditure during and after RE.

IL-6 has a significant role in the balance between glucose uptake and production (284); in those without diabetes IL-6 infusion stimulates insulin-independent glucose uptake via enhancing GLUT4 expression and activation of AMP-activated kinase in skeletal muscle (289) and has also been evidenced to increase endogenous glucose production (301). Nevertheless the findings from this Chapter demonstrate that neither of the RE sessions increased the appearance of this myokine (Table 4.1), which is perplexing since previous findings from the previous Chapter demonstrate increased appearance of IL-6 in T1DM following RE (302). Hyperglycaemia has been shown to attenuate the IL-6 response in T1DM to cycling exercise (303). Yet, results from the previous Chapter demonstrated statistically significant increases in plasma IL-6 in fasted, moderately hyperglycaemic (~11mmol.L^{-1}), and well-controlled, T1DM participants at 60-minutes after greater volume (>5713 to >8286kg) and higher intensity sessions of RE (70%1RM) than the present study (302). Weight lifted and intensity of exercise could provide a clue as to why no change was observed in IL-6 appearance in the present study, since a dose-dependent relationship between total weight lifted during a RE session and IL-6 appearance has been demonstrated elsewhere (141; 284), with post-exercise IL-6 values of 5.2 to 7.4 pg.mL^{-1} observed after participants lifted more than 4-fold greater weight (i.e. 13,160-17,729kg) than the present study at intensities of 65% to 85%1RM (141). Interestingly, with increase IL-6 concentrations, improvements in insulin sensitivity were also observed under higher volume RE sessions (141). Thus, it is possible that pre-exercise hyperglycaemia suppressed the IL-6 response to RE, but more likely that the exercise volume in this study was insufficient to stimulate IL-6 production. The findings from this study suggest that IL-6 did not contribute to any exercise-induced change in blood glucose or alteration in glucocorticoid activity (304).

The decline in resting cortisol concentrations following RE, irrespective of exercise intensity, reduces the possibility that exercise-induced changes in BG were related to this glucoregulatory hormone. These findings are in line with the previous Chapter in which cortisol concentrations remained similar to baseline values during one-hour after performance of one, two and three sets of RE at ~70%1RM (298). Resting hyperglycaemia (305) and/or usual diurnal patterns in circadian rhythm (197) offer

plausible reasons as to why cortisol might not have increased in response to morning RE in this cohort. It is a limitation that cortisol concentrations were not measured outside of exercising days. It is speculated that the differences in the magnitude of decline in plasma cortisol during recovery between the present RE sessions was likely attributed to daily changes in circadian decline (197) as, although sessions were all performed in the morning, session days were not standardised.

It is difficult to explain why catecholamine hormone response to RE were greater (although not statistical in this sample size, n=8) under LOW than MOD. A possible reason for this response was a subtle difference in exercise session design. For instance, it is important to recognise that the following RE characteristics were fixed across all sessions: (i) rest intervals between exercises (subsets) and sets (120 seconds) (ii) the duration of each repetition (4 seconds) and (iii) the total weight lifted (~3600 to 3700kg). This meant that a further 8 minutes of accumulative exercise time was performed during LOW than MOD. Therefore participants had half the amount of rest to time spent exercising during the LOW RE session (i.e. MOD: 3 seconds rest for every 1 second of exercise vs. LOW: 1.5 seconds rest for every 1 second of exercise) despite that participants lifted double the amount of weight per minute during MOD when compared with LOW.

It was somewhat counterintuitive to observe a tendency for a greater catecholamine hormone response to low over moderate intensity RE since these adrenal hormones share a strong relationship with glucose regulation and post-exercise blood glucose concentrations remained similar between different RE sessions. One theory for the slightly greater increased catecholamine concentrations under LOW is that the appearance of circulatory catecholamines trends linearly with fixed intensity and increasing duration exercise (306), and free plasma catecholamines diminish within 2-3 minutes of secretion (307). Considering these findings, there was most likely a slower rate but protraction of catecholamine production during LOW over MOD, which could be attributed to the longer accumulative exercise time, coupled with short (2-minute) but similar rest intervals to MOD. Further research is required to determine the impact of altering the exercise to rest interval during RE on glycaemia

in T1DM, since it could be possible that increasing the rest interval might help prevent exercise-induced hyperglycaemia.

Interestingly, under both exercise sessions, there were succinct reductions in blood pH (nadir pH 7.28) and extracellular fluid base-excess (nadir B_{ecf} <-6.0 $mEq{\cdot}L^{-1}$), which reflect the 10-fold increase in post-exercise blood lactate concentrations, and is indicative of the significant non-oxidative metabolic component (287) to RE. From these results it is shown that a reduction in the absolute weight lifted per repetition by ~50% did not alleviate exercise-induced metabolic stress when matching total weight lifted. This finding helps reconcile similarities in ratings of perceptual difficulty (i.e. "somewhat hard to hard") between moderate- and "low-intensity" RE. However, the similarity in blood lactate accumulation between different RE session is paradoxical when considering that catecholamines tended to be further raised under LOW than MOD; adrenaline has powerful effects on muscle glycogenolysis by binding to β-adrenergic receptors on the skeletal muscle membrane initiating a cascade of events that augment glycogen breakdown (via activation of phosphorylase *a*) and resulting in increased lactate appearance (308). Indeed, under both LOW and MOD, there were strong relationships between exercise-induced increases in catecholamines (both adrenaline and noradrenaline) and the increased appearance of blood lactate (Table 4.4 & 4.5), which is possible reflective of the impact that catecholamines have on glycolytic turnover within skeletal muscle. However, it cannot be determined from this study design whether the contribution of lactate to endogenous glucose production by hepatic gluconeogenesis differed between low and moderate intensity RE – albeit the sparing effect that lactate could have on muscle glycogen utilisation could be of benefit to the T1DM individual in preventing the onset of post-exercise hypoglycaemia. Furthermore, the presence of adrenaline is not essential to glycolytic activity since muscle glycolytic turnover has been shown to occur independent of the conversion of phosphorylase *b* to *a* (309). Thus, there are complex relationships between counterregulatory hormones and manipulations of RE session characteristics warranting further work to improve understanding of the glycaemic impact and metabolic stress caused by RE in T1DM individuals.

It is acknowledged that differences in circulating insulin could have affected the time-course changes in glycaemia under the experimental sessions. It is therefore a limitation that plasma insulin was not measured. However, in the previous Chapter, in which T1DM participants implemented the same pre-exercise glucose management routine as in the present study, demonstrated that plasma insulin levels remained stable and comparable during and for one-hour after 15 to 45 minutes of RE at an intensity of ~70%1RM (298). Moreover, basal and bolus insulin dosage were similar between experimental sessions. Another limitation in this study was the brief (albeit intensive) window of monitoring participant glycaemia. Previous research by Yardley et al (211) has shown that a three-set session of RE could put T1DM individuals at greater risk of later post-exercise and nocturnal hypoglycaemia, and T1DM individuals have been observed to experience late-onset hypoglycemia following performance of high-intensity intermittent exercise (228).

Between 5 and 65 minutes of recovery, K^+ concentrations were consistently, significantly ($p<0.05$) greater under MOD than LOW (Figure 4.4), with K^+ values under MOD observed to drift towards what is clinically deemed as hyperkalaemia (>5 $mmol/L^{-1}$) by 65-minutes post-exercise (LOW 4.1 ± 0.1 vs. MOD 4.5 ± 0.2 $mmol.L^{-1}$), which of course is of clinical concern, considering the potential health complications associated with hyperkalaemia (310). It is difficult to explain the difference in K^+ responses between the different intensity RE sessions, but a recent study observed a similar response in T1DM individuals during the hour after performance of brief high-intensity cycling exercise and attributed this to hypoinsulinaemic-hyperglycemia (218). Indeed, in line with this previous finding, the progressive rise in blood K^+ concentrations under both LOW and MOD could be explained by the omission of morning raid-acting insulin combined with post-exercise hyperglycaemia, but given the similarities in both insulin dosage and post-exercise glycaemic status between LOW and MOD, this finding does not explain different K^+ responses between the different intensity sessions.

Interestingly, through activation of protein kinase A, rises in catecholamines induce conformational changes in Na^+/K^+-ATPase activity, pumping K^+ back into intracellular compartments (predominantly adrenaline; (292) to maintain intracellular

K^+ concentrations; in isolated rat soleus muscle Na^+/K^+ pump activity can be elevated about two-fold with physiological increases extracellular adrenaline and noradrenaline (311). In support of this mechanism, negative relationships were observed between post-exercise concentration of catecholamines and blood K^+ concentrations (Tables 4.4 & 4.5). Thus, comparatively greater elevations in catecholamine concentrations evoked by the LOW session might have accelerated the movement of K^+ from extra- to intra-cellular space, explaining lower circulating levels of K^+. Although, plasma K^+ levels were not determined, it is of clinical relevance that the exercise-induced rise in catecholamines could have offered protection against the possibility of hyperkalaemic-associated disturbances in myocardial excitability during and in the early minutes after exercise by increasing the calcium conductance of the sarcolemma, resulting in increases in calcium influx that would have helped stabilised the electrophysiological activity of cardiac cells in the presence of perturbing concentrations of K^+ and/or helped restore intracellular K^+ concentrations (312). However, the rapid tapering of post-exercise catecholamines levels during initial recovery coupled with hyperglycaemia and climbing K^+ concentrations warrants the administration of exogenous insulin. Alternatively, it would be interesting to explore whether acute exercise-induced hyperglycaemia and hyperkalaemia that follows RE could be alleviated by training, as it has been demonstrated that post-exercise hyperglycaemia and K^+ levels in T1DM are reduced following seven weeks of intermittent cycling training (218).

From a cardiovascular perspective, these are the first observations of heart rate and blood pressure in response to RE in T1DM. These findings are important to the clinical prescription of RE, since (anecdotally) many clinicians avoid prescription of RE to T1DM, which is partly due to a lack of awareness of different forms of RE; for instance, although the acute rises in heart rate and blood pressure associated with high-intensity *isometric* RE has been thought to provoke ischemia, stroke or retinal haemorrhage in susceptible cohorts, a census by the American Heart Association showed that there is little cardiovascular risk associated with *isotonic* RE, which may actually have an acute hypotensive effect in both healthy individuals and patients with coronary problems (313); in fact, the myocardial demands of high-intensity RE are no greater than those occasionally required for activities of daily living (314) or

moderate-intensity aerobic exercise (315). It is important to emphasise that there were no valsalva manoeuvres during the isotonic RE sessions involved in this study.

In this study, cardiovascular parameters (SBP, DBP, MAP; Figure 4.3) remained similar to baseline when measured immediately and at 60-minutes post-exercise, irrespective of exercise intensity. After one hour of recovery MAP had decreased by 5% and 10% (from a resting level of ~94mmHg) under MOD and LOW sessions, respectively. Indeed, each bout of exercise could have temporarily raised SBP and DBP depending on the type of muscle contraction (314); early work by Benn et al. (314) demonstrated that peak SBP, DBP and MAP during exercise varied depending on whether upper or lower body and/or single or double limb RE was performed. Peak SBP and DBP were in response to a single set of single-arm military press and leg press of 10-12 repetitions at 70-80%1RM and values were approximately 2-fold greater than those observed in the present study. However, the cardiovascular responses to each subset of exercise were not investigated in this study, rather the net impact of an entire RE session. In those without diabetes, it has been shown that the degree of post-exercise hypotension is amplified by increasing RE session intensity from 30% to 60% to 90% 6RM (316). The low sample frequency may have precluded detection of exercise intensity-related differences in cardiovascular markers. Nonetheless, it could be proposed that the rest interval of 2 minutes between exercises and sets in the LOW and MOD RE sessions was sufficient to preclude any potential additive effect of consecutive exercises on blood pressure, since no change in blood pressure markers was measured immediately after completion of the final 10/20 repetitions.

It was unexpected that the heart rate demands associated with low intensity RE were greater than those of moderate intensity exercise, considering that previous research has demonstrated a positive linear relationship between mechanical intensity of exercise, oxygen uptake and heart rate (317). It seems that this response was not attributed to the longer exercise duration of LOW over MOD because a greater percentage of the total exercise session time (~22%) was spent with heart rates above 60%HRmax (Table 4.2; Section 4.3.5.1). Notably, this finding explains the greater total frequency of heart-beats during the LOW RE session (see section 5.3.5.1). A

factor that could help explain elevated heart rates during LOW over MOD is the tendency for a greater increase in catecholamines; adrenaline and noradrenaline increase myocardial contractility and force and hastening of relaxation that augments heart rate through β-adrenoceptors, i.e. catecholamines instigate the G-protein-adenylyl cyclase-cAMP-protein kinase pathway resulting in phosphorylation of target enzymes by protein kinase A-catalysed phosphorylation (318). The positive correlations between heart rate and catecholamines adrenaline and noradrenaline (Tables 4.4 & 4.5) are in support of this mechanism.

The findings from this study are important to T1DM individuals and practitioners because current exercise guidelines for this cohort lack information pertaining to the acute metabolic stress and glycaemic impact resulting from performance of different RE sessions, and this lack of awareness could compromise exercise safety. From the scant amount of research in this area it is difficult to identify the optimal balance between acute exercise safety and chronic impact, but these findings taken together with results from Chapter 3 (298) suggest that individuals should be judicious of possible hyperglycaemia soon after low to high volume and intensity RE sessions, and that low to moderate intensity RE sessions can result in substantial metabolic stress.

Conclusion

In conclusion, the magnitude of post-exercise hyperglycaemia, acid-base disturbance and perceptual difficulty were similar in response to moderate and low intensity RE sessions where total weight lifted was matched between sessions. Despite different exercise intensities, the longer exercise duration of the low-intensity RE session may be responsible for comparable if not greater glucoregulatory hormone responses, leading to similar post-exercise changes in blood glucose. The lighter weights lifted with low-intensity RE (i.e. low-resistance coupled with high-repetitions) is likely to be more suited to less physically active T1DM individuals, and it might be prudent to prescribe longer rest intervals between sets of exercises when performing this form of RE.

CHAPTER FIVE

Glycaemic And Metabolic Impact Of An Algorithm That Delivers An Individualised Rapid-Acting Insulin Dose After Morning Resistance Exercise To Counter Post-Exercise Hyperglycaemia In Type 1 Diabetes

5.1 INTRODUCTION

Physical activity that involves high rates of non-oxidative glycolytic activity (e.g. high-intensity continuous and intermittent exercise) can pose less threat of hypoglycaemia than moderate-intensity aerobic exercise (e.g. endurance running and cycling) in individuals with type 1 diabetes (T1DM) (211; 214; 220; 227; 228; 232). Resistance exercise (RE) involves predominantly energy utilisation through non-oxidative metabolic pathways (248) that, as demonstrated in Chapters 3 and 4, evokes a strong counterregulatory hormone response. This form of exercise is recommended to T1DM individuals (295) and offers a multitude of benefits to health and well-being (319).

In Chapters 3 and 4 a glycaemic management routine for morning RE in individuals with T1DM was tested (298). After an overnight fast, individuals omitted morning rapid-acting insulin prior to performing three different volume RE sessions in line with ACSM guidelines (295), and neither session resulted in hypoglycaemia or requirement for carbohydrate supplementation. Considering that the fear of exercise-induced hypoglycaemia is a major cause of low exercise participation and adherence in T1DM (149), the avoidance of hypoglycaemia during and for one hour after RE with this routine is encouraging. Nevertheless, this study also demonstrated that individuals experienced hyperglycaemia following both a 15 and 30 minute RE, with blood glucose values increasing by up to ~3 $mmol.L^{-1}$ above a resting control trial during a one-hour recovery period (298). Indeed, sustained hyperglycaemia could ultimately lead to severe health complications (320). Importantly, since a lower volume, shorter duration, RE session did not diminish post-exercise hyperglycaemia (Chapter 3; (298)), the effects of reducing the intensity of the 30 minute RE session was investigated in Chapter 4 (321). Unfortunately, adjusting the intensity of the RE session had little influence on the magnitude of post-exercise hyperglycaemia (321).

In an effort to counter the anticipated rise in blood glucose caused by this format of morning RE (298; 321) it seems intuitive for a T1DM individual to administer a dose of rapid-acting insulin immediately after exercise, since this strategy would not unnecessarily increase susceptibility to hypoglycaemia during RE. However, there is currently no systematic and/or validated method of correcting hyperglycaemia

following RE. From a clinical standpoint, insufficient guidance to help T1DM individuals appropriately manage post-RE glycaemic fluctuations certainly increases vulnerability to continued hyperglycaemia or exposure to hypoglycaemia, with a resulting loss of glycaemic control. Understandably, such an approach is further complicated by the fact that it is currently unknown to what magnitude of effect a subcutaneously injected dose of rapid-acting insulin could have on glycaemia early after RE. For instance, while Jimenez et al. (137) reported unaltered insulin sensitivity in T1DM individuals at 12 and 36 hours after a session of RE, when compared with non-exercise control session, factors including increased limb blood flow (267) and insulin sensitivity associated with the initial hours after exercise (268) could augment both the absorption of injected insulin into the blood stream (183) and action of circulating insulin on glucose metabolism (184). Conversely, it has been demonstrated in those without diabetes that unaccustomed eccentric exercise can impair insulin action in the early hours after exercise cessation (233). Additionally, the recommendation to consume macronutrients soon after exercise in an effort to replenish muscle glycogen and reduce the likelihood of exposing the T1DM individual to late-onset hypoglycaemia (322), adds complexity to managing glycaemia after RE, since consumption of carbohydrate would favour an increase in blood glucose levels, thereby exacerbating the magnitude of post-exercise hyperglycaemia.

The development of a post-RE insulin adjustment guideline to help the individual effectively manage exercise-induced hyperglycaemia would facilitate the safe prescription of RE. But considering the lack of research in this area and the multiple factors that could influence post-exercise insulin action, a prudent approach to creating an effective glucose management strategy is to first understand the effect that an injection of exogenous insulin immediately after RE has on post-exercise glycaemia. The 100-rule is an algorithm that has been derived for correcting individual-specific hyperglycaemic excursions with bolus insulin in a non-exercise environment (99), and this tool offers a logical starting-point from which to develop a protocol for understanding how to restore euglycaemia following morning RE. This individualised approach would allow for potential inter-individual variability in glycaemic responses to exercise (199) but this algorithm could also be adapted to

provide an insulin dose based on the individuals' real-time glycaemic response to the exercise session.

Therefore, the aim of this study was to implement a modified algorithm that delivers an individualised dose of rapid-acting insulin after morning RE, to counter acute post-exercise hyperglycaemia in T1DM individuals.

5.2 RESEARCH DESIGN AND METHODS

5.2.1 Participants

Eight physically active male (n=6) and female (n=2) individuals with T1DM (age 34 ± 7 years, HbA_{1C} 8.7 ± 1.1 %, duration of diabetes 18 ± 5 years) volunteered and provided written informed consent for the study. Participants anthropometric, glycemic control and insulin regimen characteristics are presented in Table 2.2 (Page 55). All participants were treated with an insulin regimen composed of bolus insulin glargine or detemir and prandial rapid-acting insulin aspart.

5.2.2 Experimental Design

Following a single preliminary session (Section 2.3.3), participants completed two experimental sessions, which were prescribed in a randomised and counterbalanced order using a repeated-measures design. Both experimental sessions involved performance of a single RE session followed by a 125-minute recovery period, which was spent in the research facility, and a subsequent 20-hour period of monitoring that was spent outside of the research facility. Experimental sessions were separated by at least 3 days.

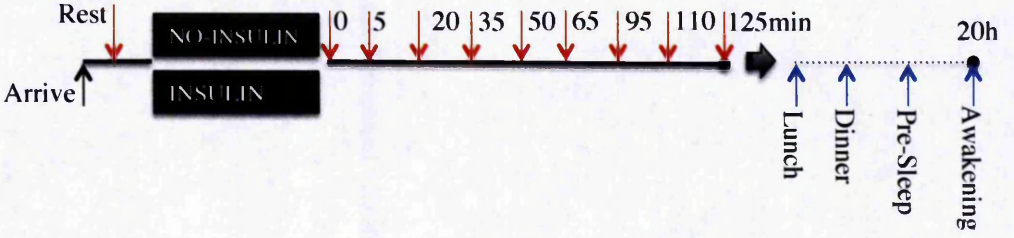


Figure 5.1: Schematic representation of study design, with two repeated measures experimental arms (INSULIN and NO-INSULIN). Red arrows indicate venous sample points during the laboratory phase. Blue arrows indicate capillary blood samples during the post-laboratory phase.

5.2.3 Experimental Sessions and Analysis

Participants arrived at the clinical research facility between 0630 – 0900 h. Participants were fasted for 8-10 hours, having taken their usual basal insulin dose (31.3 ± 3.8 IU) the night before but omitted rapid-acting insulin on the morning of testing (Section 2.8). After a standardised 10-minute flexibility warm-up of main muscle groups, participants undertook a RE session (two sets of six exercises

performed at a moderate-intensity (60%1RM; Section 2.3.4.3), and then remained sedentary in the laboratory for a further two hours during which participants either administered an interventional rapid-acting insulin dose (INSULIN) immediately after exercise or abstained from exogenous insulin (NO-INSULIN) (Section 2.9.3). Participants remained fasted during this time. The post-exercise subcutaneously injected insulin bolus was administered in the form of rapid acting insulin aspart; the dose was determined by means of an algorithm (Section 2.9.3.1, Page 81) and was administered within 5 minutes of completing the RE session. The objective of the algorithm-derived dose was to return blood glucose to a target of 7 $mmol.L^{-1}$ during the 2-hour recovery after RE. Dietary intake and physical activity patterns for 20 hours following the laboratory session was standardised between experimental sessions (Section 2.10). Participants continued with their usual daily-living routine during this time, and were free to administer exogenous insulin in line with their usual routine, but they abstained from vigorous physical exercise of an intensity that was beyond a conversational level; note, vigorous activity related to manual work was replicated across sessions. Capillary blood glucose measurements were taken prior to lunch, dinner, and sleep and upon waking on the following morning (Section 2.9.3). Venous blood glucose (BG) concentrations were measured for 125 minutes after RE and participant-reported capillary BG was recorded for 20 hours after leaving the laboratory (Figure 5.1). All venous blood samples were processed and analysed for glucose, pH, lactate and potassium (K^+), NEFA and insulin (Section 2.4.3). Data (mean ± SEM) were analysed using ANOVA ($p \leq 0.05$) (Section 2.12).

5.3 RESULTS

5.3.1 Laboratory Phase

5.3.1.1 Exercise Volume and Intensity

There were no session differences in total weight lifted (Volume: INSULIN 3675 ± 651 vs. NO-INSULIN 3675 ± 651 kg) or intensity (Load: INSULIN 59 ± 1 vs. NO-INSULIN 59 ± 1 %1RM) during RE (*p>0.05*).

5.3.1.2 Acid-base Balance

Blood lactate and pH responses are presented in Table 5.1. There was a significant time effect (*p<0.001*, partial-eta^2=0.709) but no effect of session (*p=0.843*, partial-eta^2 =0.006) or session*time interaction (*p=0.444*, partial-eta^2 =0.100) for blood lactate responses, with similar individualised peak blood lactate concentrations (INSULIN 10.2 ± 1.2 vs. NO-INSULIN 9.8 ± 2.4 mmol.L^{-1}, *p=0.910*). For blood pH responses, there was a significant time effect (*p<0.001*, partial-eta^2=0.686) but no effect of session (*p=0.081*, partial-eta^2=0.373) or session*time interaction (*p=0.785*, partial-eta^2=0.046), with similar nadir pH values (INSULIN 7.28 ± 0.02 vs. NO-INSULIN 7.28 ± 0.02, *p=0.960*) between trials. Blood lactate concentrations and pH had returned to values similar to rest (*p>0.05*) by 65 minutes post-exercise.

Table 5.1: Blood pH, lactate and potassium and plasma NEFA and insulin responses to INSULIN and NO-INSULIN sessions.

		Rest	0	5	35	65	95	125
Blood pH	**INSULIN**	7.37 *0.01*	7.28† *0.02*	7.30† *0.02*	7.39† *0.01*	7.40† *0.01*	7.39† *0.01*	7.40† *0.01*
	NO-INSULIN	7.35 *0.01*	7.28† *0.02*	7.29† *0.02*	7.38 *0.01*	7.38† *0.01*	7.38† *0.01*	7.39† *0.01*
Blood Lactate (mmol.L^{-1})	**INSULIN**	0.8 *0.1*	10.1† *1.8*	9.3† *2.0*	3.6† *0.8*	1.9 *0.3*	1.3 *0.2*	1.0 *0.1*
	NO-INSULIN	1.1 *0.2*	9.1† *2.1*	9.5† *2.4*	3.5† *0.9*	1.8 *0.4*	1.3 *0.2*	1.0 *0.1*
Plasma NEFA (mmol.L^{-1})	**INSULIN**	0.6 *0.1*	-	-	0.5† *0.1*	0.3†* *0.1*	0.4†* *0.1*	0.4†* *0.1*
	NO-INSULIN	0.7 *0.1*	-	-	0.6† *0.1*	0.7 *0.2*	0.6 *0.1*	0.7 *0.2*
Blood Potassium (mmol.L^{-1})	**INSULIN**	4.1 *0.1*	4.7 *0.3*	4.8 *0.7*	4.2 *0.2*	4.1* *0.2*	4.1 *0.1*	4.0 *0.1*
	NO-INSULIN	4.0 *0.1*	4.5† *0.1*	4.2† *0.1*	4.4† *0.2*	4.5† *0.2*	4.2 *0.2*	4.1 *0.2*
Plasma Insulin (pmol.L^{-1})	**INSULIN**	72.7 *14.0*	-	-	113.8†* *13.4*	124.9* *20.1*	111.1* *16.3*	107.6 *14.6*
	NO-INSULIN	83.5 *19.7*	-	-	75.1 *14.2*	81.6 *15.9*	90.8 *18.4*	98.1 *17.6*

Data presented as mean ± SEM. * indicates a statistical significant difference ($p<0.05$) to NO-INSULIN. † indicates a statistical significant difference ($p<0.05$) to rest. Time-points in column headers indicate minutes post-exercise.

5.3.1.3 Blood Glucose and Plasma Insulin

Blood glucose responses to INSULIN and NON-INSULIN are presented in Figure 5.2. Resting blood glucose (BG) concentrations were similar between sessions (INSULIN 11.3 ± 1.5 vs. NO-INSULIN 11.2 ± 1.3 mmol.L^{-1}, $p=0.900$). For acute (baseline to 125-minute post-exercise) blood glucose responses, there was a significant time effect ($p=0.026$, *partial-eta*$^2=0.438$) and an interaction between

experimental session and time (*p=0.011, partial-eta^2=0.495*), but no session effect (*p=0.655*).

BG rose to similar concentrations during RE (i.e. prior to insulin administration) (INSULIN 13.0 ± 1.6 vs. NO-INSULIN 12.7 ± 1.5 mmol.L^{-1}, *p=0.834*). For INSULIN, participants then administered 2±1 U of rapid-acting insulin within 5 minutes of finishing exercise (see Table 5.2 for participant specific values). The adjustment in stage [4] (depicted in Figure 2.9) to convert F_{Dose} to A_{Dose} corresponded with a 53±10% reduction in experimental sessions (see Table 5.2 for algorithm-predicted doses of insulin administered). For plasma insulin (n=7; Table 5.1; Figure 5.2), there was an interaction between time and experimental session (*p=0.015, partial-eta^2=0.475*), with a tendency for higher individualised peak concentrations under INSULIN (INSULIN 135.1 ± 18.8 vs. NO-INSULIN 99.5 ± 18.0 pmol.L^{-1}, *p=0.059*).

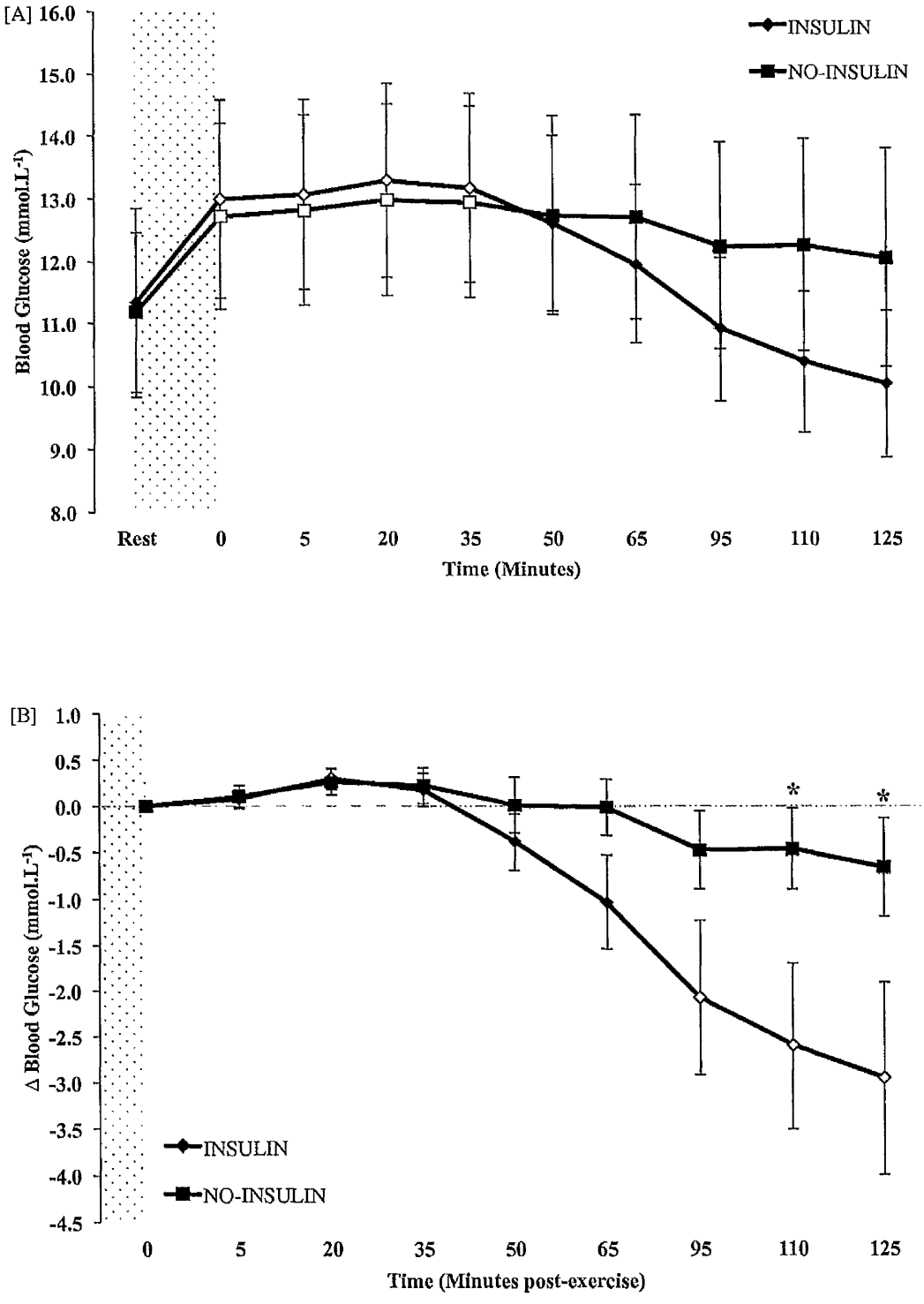


Figure 5.2: [A] Absolute blood glucose and [B] delta blood glucose (as a change from 0-minutes post-exercise) responses to INSULIN and NO-INSULIN experimental sessions. Transparent sample points indicate significant changes from rest (Figure 5.2A) or 0-post-exercise (Figure 5.2B) within each respective experimental session ($p<0.05$). * indicates a statistically significant difference ($p<0.05$) between INSULIN and NO-INSULIN.

Peak BG occurred at 20 minutes post-exercise under both experimental sessions, and concentrations were comparable between sessions (INSULIN 13.4 ± 1.5 vs. NO-INSULIN 13.4 ± 1.6 mmol.L^{-1}, *p=0.992*). Between the time of peak plasma insulin concentrations (i.e. 65-minutes post-exercise) and 125-minutes post-exercise, there was a greater decline in BG under INSULIN (INSULIN 1.9±0.6 vs. NO-INSULIN 0.7±0.3 mmol.L^{-1}, *p=0.006*). Moreover, the magnitude of decline from peak BG concentrations to 125-minutes post-exercise was statistically greater under INSULIN (INSULIN 3.3 ± 1.0 vs. NO-INSULIN 1.3 ± 0.4 mmol.L^{-1}, *p=0.015*). Individualised nadir BG concentrations were statistically less under INSULIN (INSULIN 9.9 ± 1.1 vs. NO-INSULIN 12.4 ± 1.5 mmol.L^{-1}, *p=0.035*). There was a tendency for lower BG_{IAUC} values under INSULIN (INSULIN -176.8 ± 76.6 vs. NO-INSULIN -25.3 ± 37.7 mmol.125min.L^{-1}, *p=0.069*). There were no hypoglycaemic occurrences during the laboratory phase under either experimental session.

Table 5.2: Factors used in derivation of the post-exercise rapid-acting insulin dose, and number of rapid acting insulin units administered, under INSULIN.

Participant ID	1	2	3	4	5	6	7	8	**Mean± SEM**
TDD *IU*	40	60	63	35	55	70	60	53	55±4
Basal *IU*	20	42	48	26	18	40	28	28	31±4
CF	0.40	0.60	0.63	0.35	0.55	0.70	0.60	0.53	0.55±0.04
BG *mmol.L^{-1}*	9.5	16.1	9.8	7.5	12.6	10.5	19	19	13.0±1.5
Post-exercise Dose *IU*	1	3	1	0	2	1	4	3	2±1

TDD: total daily insulin dose, **Basal**: basal insulin dose, **CF**: Correction factor, **BG**: refers to 0-minutes post-exercise BG concentration, **Post-exercise Bolus**: interventional dose of rapid-acting insulin.

5.3.1.4 Plasma NEFA and Blood Potassium

Blood plasma non-esterified fatty acid (NEFA) and blood K^+ responses are presented in Table 5.1 and Figures 5.3 and 5.4, respectively. A significant interaction between time and experimental session was observed for plasma NEFA (*$p=0.003$, partial-$eta^2=0.419$*) indicating that NEFA concentrations were suppressed under INSULIN, but no effect of time (*$p=0.280$*). Although peak NEFA concentrations were similar between conditions (INSULIN 0.6 ± 0.1 vs. NO-INSULIN 0.8 ± 0.2 $mmol.L^{-1}$, *$p=0.198$*), nadir concentrations were significantly less under INSULIN (INSULIN 0.3 ± 0.1 vs. NO-INSULIN 0.5 ± 0.1 $mmol.L^{-1}$, *$p=0.018$*).

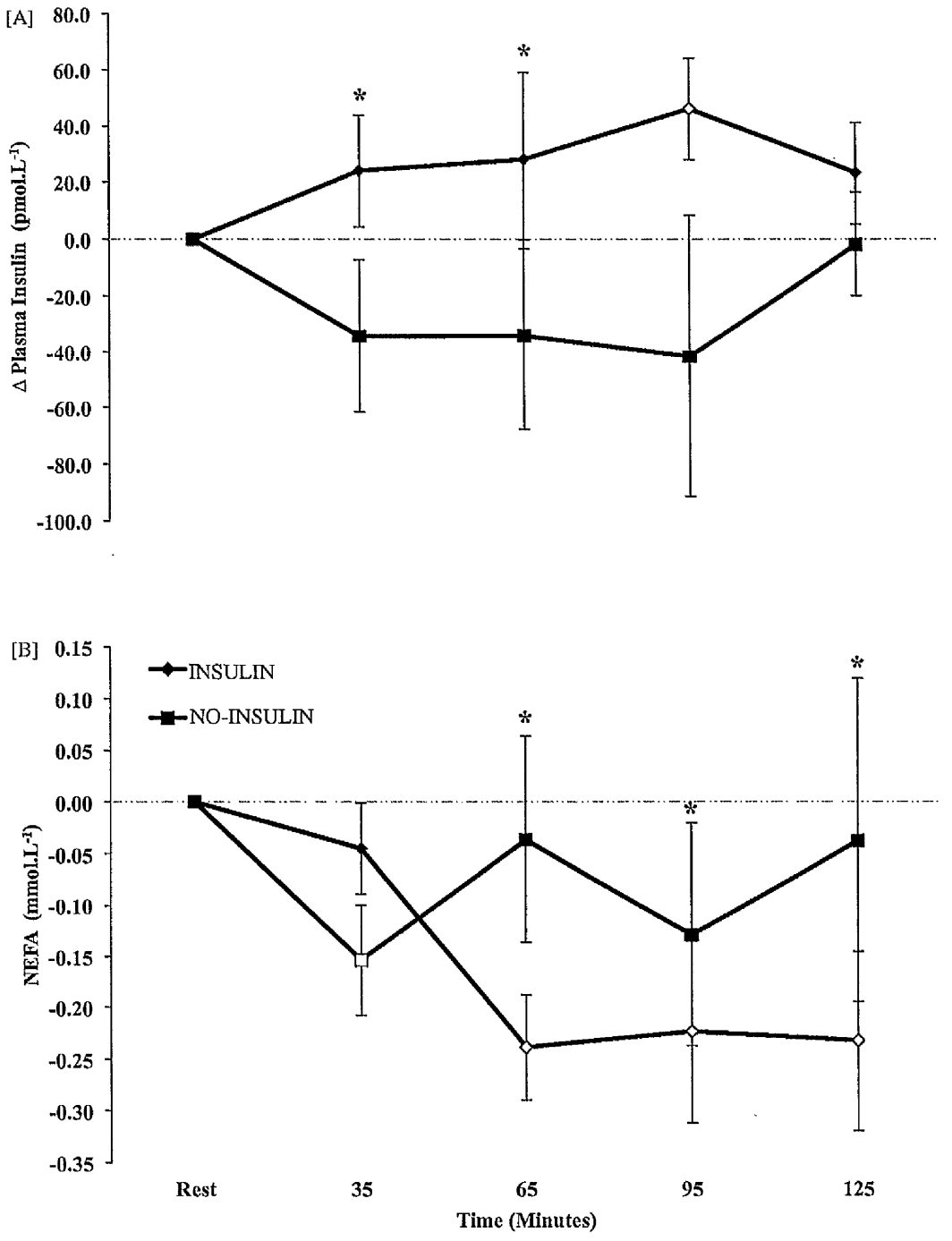


Figure 5.3: Delta plasma [A] insulin and [B] NEFA (as a change from baseline) responses to INSULIN and NO-INSULIN experimental sessions. Transparent sample points indicate significant changes from rest within each respective experimental session ($p<0.05$). * indicates a statistically significant difference ($p<0.05$) between INSULIN and NO-INSULIN.

For blood K^+ responses, there was a significant effect of time ($p=0.036$, *partial-eta*$^2=0.237$) but no effect of session ($p=0.605$) or session*time interaction ($p=0.266$), with similar individualised peak concentrations (INSULIN 4.8 ± 0.3 vs. NO-INSULIN 4.8 ± 0.2, $p=0.501$).

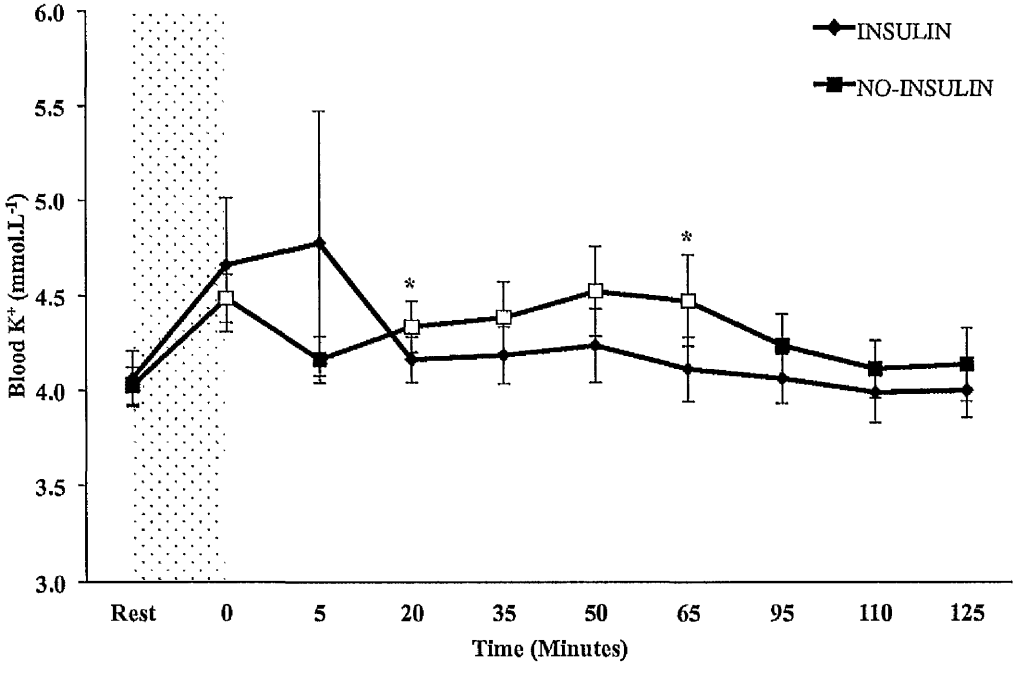


Figure 5.4: Blood potassium (K^+) responses to INSULIN and NO-INSULIN experimental sessions. Transparent sample points indicate significant changes from rest or 0-post-exercise within each respective experimental session ($p<0.05$). * indicates a statistically significant difference ($p<0.05$) between INSULIN and NO-INSULIN.

5.3.2 Post-laboratory Phase

5.3.2.1 Self-Reported Blood Glucose and Insulin Administration

At 125-minutes of recovery from RE, BG concentrations were similar between sessions (Figure 5.2), albeit concentrations were less under INSULIN (INSULIN 10.1 ± 1.2 vs. NO-INSULIN 12.1 ± 1.7, $p=0.091$). Breakfast was then consumed where participants chose to administer a similar quantity of insulin units irrespective of session (INSULIN 8.3 ± 1.9 vs. NO-INSULIN 9.5 ± 2.0 IU, $p=0.659$). For post-laboratory BG responses (expressed in Figure 5.5), there was a statistically significant effect of time ($p=0.011$, *partial-eta*$^2=0.365$), but no effect of experimental session ($p=0.941$) and no difference in individual peak BG concentrations between sessions

(INSULIN 11.1 ± 0.9 vs. NO-INSULIN 10.8 ± 0.9 mmol.L^{-1}, *p=0.750*). Mean BG during 20 hours following exercise was similar between sessions (INSULIN 7.5±0.8 vs. NO-INSULIN 8.1±0.8 mmol.L^{-1}, *p=0.552*). During the 20-hour post-laboratory phase, there were five recorded hypoglycaemic occurrences in four participants (all prior to sleep) (BG ≤ 3.5 mmol.L^{-1}) under INSULIN compared to seven (six occurrences prior to sleep and one upon wakening) in four participants under NO-INSULIN. In addition, there were ten recorded episodes of hyperglycaemia in five participants under NO-INSULIN), compared with seven occurrences in four participants recorded under INSULIN. There was a trend for a larger total dosage of exogenous insulin to be taken under NO-INSULIN (INSULIN 58 ± 5 vs. NO-INSULIN 60 ± 5 IU, *p=0.063*), which was accounted for by the rapid-acting insulin dosage (INSULIN 27 ± 3 vs. NO-INSULIN 29 ± 3 IU, *p=0.063*), since basal-insulin dose was identical across experimental sessions (31 ± 4 IU).

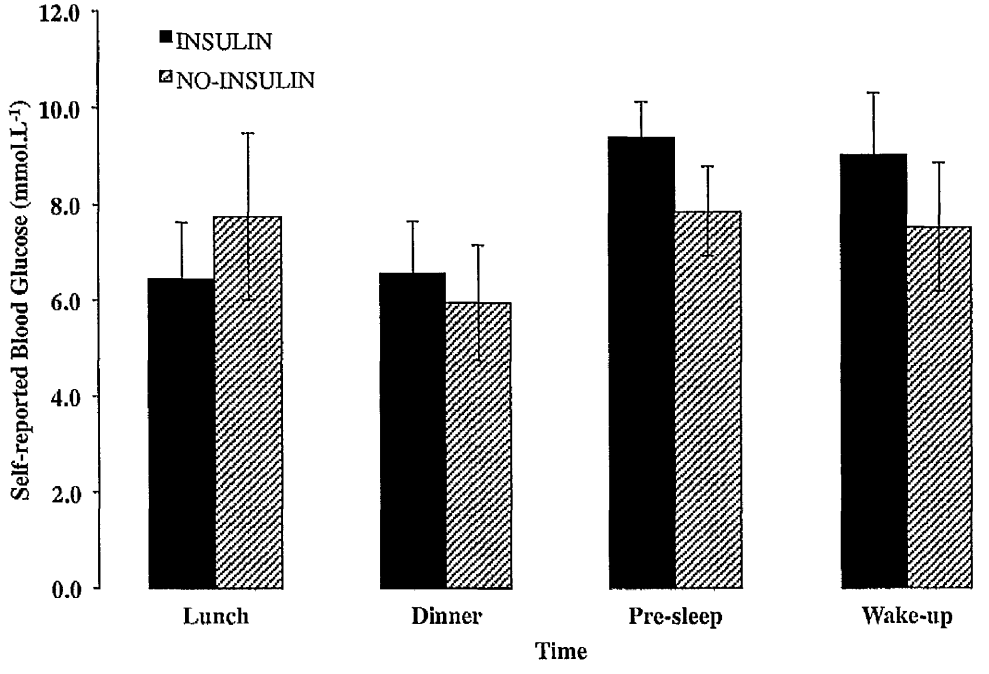


Figure 5.5: Participant self-reported capillary blood glucose responses during the 20-hour post-laboratory period. No statistical differences between INSULIN and NO-INSULIN.

5.3.2.2. Twenty-Hour Accelerometry and Dietary Intake

During the post-laboratory phase, estimated energy expenditure and accelerometry profiles were comparable between sessions (*p>0.05*); specifically, participants performed a similar number of steps between conditions (INSULIN 7038 ± 926 vs. NO-INSULIN 6569 ± 889 steps, *p=0.264*). Participants spent 47.8±3.5% and 45.3±2.4% of this time being sedentary (<3 MET) under INSULIN and NO-INSULIN (*p=0.540*), respectively. Participants were physically active for a similar number of hours between conditions (INSULIN 2.2 ± 0.4 vs. NO-INSULIN 2.2 ± 0.5 hours, *p=0.961*). Of which, a similar proportion of time was spent performing activity that equated to moderate metabolic rates of 3-6 MET (INSULIN 95 ± 1.0 vs. NO-INSULIN 97.0 ± 1.5 %, *p=0.138*); vigorous activity (non-exercise) (6-9MET) (INSULIN 3.8 ± 0.8 vs. NO-INSULIN 2.6 ± 1.1 %, *p=0.103*) and very vigorous (non-exercise) (MET >9) (INSULIN 0.4 ± 0.3 vs. NO-INSULIN 0.4 ± 0.4 %, *p=0.857*), and estimated energy expenditure was comparable (INSULIN 10.0 ± 0.5 vs. NO-INSULIN 9.8 ± 0.6 MJ, *p=0.462*), between experimental sessions.

Dietary intake and insulin dosage data are presented in Table 5.3. As meals were provided and meal composition and eating patterns were standardised between experimental sessions, total calorific intake comprised of 51±2 % CHO, 17±1 % protein and 33±2 % fat. The additional carbohydrate consumed in the form of carbohydrate tablets (if blood glucose was recorded as low) was similar between sessions (INSULIN 292.9 ± 101.2 vs. NO-INSULIN 284.5 ± 95.3 KJ, *p=0.685*), and therefore there was no effect of experimental session on total energy intake (INSULIN 10.0 ± 0.7 vs. NO-INSULIN 10.0 ± 0.7 MJ, *p=0.688*). Notably, energy intake (INSULIN 9.8 ± 0.6 vs. NO-INSULIN 9.9 ± 0.6 MJ, *p=0.488*) and total insulin dosage (*p=0.723*) during the 24 hours prior to exercise were similar between experimental sessions.

Table 5.3: Post-laboratory fixed dietary composition for each participant and self-prescribed exogenous insulin and carbohydrate tablets under INSULIN and NO-INSULIN experimental sessions.

ID	Study-prescribed Dietary Composition *g*			Self-prescribed			
	CHO	FAT	PRO	INSULIN *U*		CHO TABS *No.*	
	INSULIN & NO-INS			INSULIN	NO-INS	INSULIN	NO-INS
1	259	89	74	41	48	8	9
2	343	84	96	60	60	0	0
3	392	96	111	85	86	11	9
4	211	76	78	42	41	0	0
5	279	81	82	53	53	8	8
6	250	49	83	71	74	4	4
7	382	110	128	57	60	4	4
8	246	96	114	56	59	0	0
Mean± SEM	295±24	85±6	96±7	58±5	60±5	4±2	4±1

CHO TABS: number of self-prescribed carbohydrate tablets. **INSULIN**: dosage of self-prescribed exogenous basal and bolus insulin.

5.4 DISCUSSION

The aim of this study was to implement a modified algorithm that delivers an individualised dose of rapid-acting insulin after morning resistance exercise (RE) to counter post-exercise hyperglycaemia in T1DM participants. These findings report for the first time that a small dose of insulin administered after exercise by means of an algorithm reduces the magnitude of post-RE hyperglycaemia without the occurrence of hypoglycaemia during the early hours (<2 hours) after exercise. Consequent dietary energy intake, carbohydrate consumption and insulin dosage for 24 hours after exercise in a free-living environment were similar between experimental sessions.

Following an overnight fast and the omission of morning food and rapid-acting insulin, participants started RE with a blood glucose of ~11 $mmol.L^{-1}$ on both experimental days. Although these baseline glycaemic levels fell within the acceptable parameters for exercise (323; 324), the results from this study demonstrate that RE increased resting blood glucose by ~2$mmol.L^{-1}$, and without post-exercise exogenous insulin blood glucose levels remained elevated above 12$mmol.L^{-1}$ throughout the 2 hour recovery period. Abstention from feeding following exercise is somewhat controversial because it had been 12 to 14 hours since participants had consumed any macronutrients, and carbohydrate supplementation following exercise is considered necessary to replenish muscle glycogen stores in an effort to reduce the likelihood of late-onset hypoglycaemia in T1DM participants (322). Nevertheless, the results from this study confirm previous findings that this routine protects T1DM participants from exercise-induced hypoglycaemia during and soon after exercise (Chapters 3 and 4; (298; 321)), in which it was demonstrated that a two set session of RE raised post-exercise blood glucose levels above that of a resting control trial (298). It is likely that carbohydrate consumption during and/or immediately after RE would have exacerbated the exercise-induced occurrence of post-exercise hyperglycaemia. Thus, the findings from this present study highlights that it might be unnecessary for participants to supplement carbohydrates through drinks or snacks prior to or during morning RE when participants administer their usual basal insulin the night prior to exercise.

Our findings show that the present algorithm (Section 2.9.3.1, Page 81), which was developed to conservatively estimate the dose of post-exercise rapid-acting insulin, was successful at countering the sustained exercise-induced rise in blood glucose shortly after RE, but it was not successful in returning post-exercise glycaemia to our target of 7 mmol.L^{-1}. For instance, the administration of 2±1 U of rapid-acting insulin immediately after RE was favourable; blood glucose had dropped to concentrations below rest under INSULIN (10.1±1.2 mmol.L^{-1}) but not under NO-INSULIN (12.1±1.7 mmol.L^{-1}), meaning that administration of the small post-exercise rapid acting insulin dose evoked a 2.3±0.8 mmol.L^{-1} greater fall in blood glucose than without insulin.

Indeed, a limiting factor in the design of this study was that little is known as to what effect the current RE session has on insulin action during the early hours after exercise. Early findings report that a doubling of the insulin infusion rate necessary to maintain pre-exercise euglycaemia is required to restore glucose homeostasis after performance of high intensity exercise (216). Unfortunately, however, these methods have little ecological application, as insulin infusion does not accurately reflect the pharmacokinetic profile of subcutaneously injected insulin. As such, it was difficult to predict what magnitude of effect a bolus of insulin could have on blood glucose after RE, and it was therefore considered that a bolus of insulin taken by means of this algorithm might serve as a useful tool to restore euglycaemia after RE.

Interestingly, in the present study, this simple dose calculation seems sensitive to individual glycaemic responses to RE, and as such no participants were exposed to early (<~2 hours) post-exercise hypoglycaemia. For example, participant number 4 (Table 5.2) finished RE with the lowest post-exercise blood glucose concentration (7.5 mmol.L^{-1}), and where the algorithm was applied with their data (i.e. based on the immediate post-exercise blood glucose reading) the result was administration of no rapid-acting insulin. Thus, pragmatically, health care professionals should be aware that in the absence of carbohydrate consumption some T1DM individuals might not require exogenous insulin to maintain euglycaemia soon after morning RE. Conversely, it would seem that this algorithm could be less conservative by lessening the reduction of F_{Dose} (i.e. which in this study was 53±10%). Overall, these findings

help bridge a gap between knowledge of post-exercise insulin action on glycaemia and the development of a useful tool for individuals with T1DM to safely and effectively manage the glycaemic disturbances associated with acute RE. Although the findings from this preliminary data reflect a reasonable statistical power (blood glucose at 125 minutes post-exercise, 83.6%; decline in blood glucose from 0 to 125 minutes post-exercise, 66.9%), the ecological validity of these findings could be improved with a larger sample size.

Under INSULIN the results demonstrate that insulin concentrations peaked in plasma at 65-minutes post-injection, and concentrations at this time-point were ~1.5-fold greater than those under NO-INSULIN (Table 5.1). At one-hour after insulin injection and throughout the subsequent hour of recovery under INSULIN, NEFA concentrations were 50% less than those under NO-INSULIN. Insulin has anti-lipolytic effects; suppressing hormone-sensitive lipase activity and lipolytic rate and also stimulating re-esterification of circulating NEFA (325). Furthermore, it is following the initial 60 minutes of recovery from RE where catecholamines and growth hormone, which stimulate the release of NEFA from adipose tissue (279), returned to resting levels (as previously shown in Chapter 3 (298) and 4). The lack of increase in plasma NEFA in response to RE is somewhat counterintuitive when considering this association between elevated counterregulatory hormone concentrations and the increased appearance of plasma NEFAs and increased rates of fat oxidation (279). Research in individuals without diabetes demonstrated a progressive increases in rates of lipolysis and reduction in intramuscular triglyceride concentrations during RE (251; 326-328), suggesting that a portion of energy expenditure during RE in individuals without diabetes is related to an increase in fat oxidation. Although fuel oxidation was not measure in this study, the finding that NEFA levels were suppressed by the administration of bolus insulin could have implications for weight management in T1DM individuals, i.e. bolus insulin could negate the contribution of adipose tissue to exercising energy expenditure. Similarly, as could the effect of hyperglycaemia, since high levels of glucose can inhibit fatty-acid oxidation (329). However, this response does not completely mitigate the possibility of an increase in the utilisation of fat during RE in T1DM, since glycerol could contribute to the aerobic energy yield during RE (327) and/or the utilisation of

intramuscular triglycerides would not be reflected in circulating NEFA concentrations. The lack of increase in circulating fatty acids response to RE under NO-INSULIN could be attributed to an adrenaline related reduction in adipose tissue blood flow during exercise (330) and/or the anti-lipolytic effects of insulin, since basal levels of circulating insulin were three-fold greater than typical concentrations in those without diabetes.

During the final 75 minutes of recovery, it is also possible (albeit speculative) that the greater fall in glycaemia observed under INSULIN (INSULIN -1.9±0.6 vs. NO-INSULIN -0.7±0.3 mmol.L^{-1}) could be primarily attributed to rapid-acting insulin-induced inhibition of hepatic glucose production (331). Although it is recognised that the observation window in this study may be insufficient to completely profile the time-course changes in circulating insulin aspart (332), the findings in this Chapter provide clues towards optimising the timing of feeding and prandial insulin following RE with the omission of pre-exercise bolus insulin and carbohydrates. For instance, while a 50% reduction in prandial insulin dose administered at 60-minutes post-exercise can improve glycaemic stability in T1DM participants following aerobic exercise (210), the present results show that it is following 50 minutes of recovery from RE where blood glucose concentrations began to fall slightly irrespective of whether rapid-acting insulin was administered immediately after RE. Thus, participants should be wary of the ratio of prandial insulin to carbohydrate intake during early hours following RE. Further research is required to determine an optimal glycaemic management strategy after morning RE; for instance, should participants increase the ratio of prandial insulin to carbohydrate intake soon after morning RE?

Blood pH levels fell below 7.3 and lactate concentrations increased above 9 mmol.L^{-1} reflecting the contribution of non-oxidative metabolism to energy turnover during this two-set RE session, and yet all participants comfortably completed the prescribed exercise volume, reflecting the utility of this exercise session in exercising T1DM that are unaccustomed to RE.

From a clinical standpoint, it is important that blood K^+ concentrations fell short of hyperkalaemia (>5.0mmol.L^{-1}) during both experimental sessions, but the

administration of post-exercise rapid-acting insulin negated the substantial elevation in blood K^+ (observed under NO-INSULIN, thereafter 20 minutes of recovery; Figure 5.4). Interestingly, it is possible that exogenous insulin might offset the rise in potassium concentration elicited by carbohydrate induced hyperglycaemia, in those with T1DM (290; 291; 294). Considering that hyperkalemia can heighten vulnerability to cardiac arrhythmias (310), the findings from the present study demonstrate the protection that post-exercise exogenous insulin offers over the possibility of hyperkalaemic-related complications. On the other hand, the restoration of potassium concentrations to normal levels that occurred during the initial 20 minutes post-exercise period (under both INSULIN and NO-INSULIN) is of clinical importance. Soon after intense exercise individuals may be at a greater risk of cardiac arrhythmias and grand-mal seizures, in which hypokalaemia (2.5–3.0 $mmol.l^{-1}$) can delay ventricular repolarisation thereby provoking cardiac arrhythmias (333; 334). Although K^+ concentrations remained greater than that deemed hypokalaemic (<3.6$mmol.L^{-1}$; (335), one must be circumspect when extrapolating these to a larger number of participants; notably, HbA_{1c}, hypertension, distal symmetrical polyneuropathy, retinopathy and exposure to hyperglycaemia have all been shown to be risk factors for developing abnormalities in cardiac function (336). Thus, clinicians should be aware that some T1DM individuals might experience a greater exchange of potassium, independent of dietary intake and insulin levels, of whom might be more susceptible to cardiac dysrhythmia soon after exercise.

There were no reported hypoglycaemic occurrences during the initial 5 hours following RE under INS, but two of the eight participants experienced hypoglycaemia during this same time frame under NO-INS. Furthermore, there were no clear differences in glycaemic stability during the 20 hours post-exercise; four participants experienced hypoglycaemia under both sessions; five and four participants had a hyperglycaemic episode under NO-INS and INS, respectively. Admittedly, the measurement of diurnal changes in blood glucose without continuous glucose monitoring could mean that only symptomatic (not asymptomatic) hypoglycaemia/hyperglycaemia was reported unless detected at the designated sample times. Although each participants' daily sample frequency for glucose monitoring during the experimental days was in line with American Diabetes Association

recommendations (51), this is not the gold standard of tracking glycaemia in T1DM. In a study by Yardley et al. (211), continuous glucose monitor data showed multiple episodes of hypoglycaemic in T1DM participants during the initial 6 hours following evening RE, and this study also demonstrated that evening RE increased the occurrence of nocturnal hypoglycaemia compared to a day without exercise, despite that participants completed exercise postprandially, and in comparison to the present study, participants were not restricted to fasting (i.e. participants consumed foods and administered insulin freely) during the early hours after exercise. Together these findings demonstrate that the current practice by some T1DM individuals is inadequate to prevent glycaemic disturbances late after (>2 hours) RE. Guidelines recommend that T1DM individuals consume between 60 to 120 grams of carbohydrates early after aerobic exercise, with the view to replenished muscle glycogen stores and decrease the susceptibility to late-onset hypoglycaemia (322). Recent research from our group suggests that a reduction in prandial insulin alongside the consumption of low glycaemic-index carbohydrates soon after exercise is a useful approach to preserving euglycaemia after moderate-intensity running exercise (88). However, guidelines are lacking with regard to dietary and insulin requirements/adjustments to help T1DM individuals improve glycaemic control after RE.

We chose to prescribe to participants an individualised meal-plan for the 20 hours post-laboratory phase because subtle differences in dietary composition (e.g. glycaemic index and load, and micronutrient composition) could have altered glycaemia independent of changes in calorific intake, and participant diet recall lacks sensitivity of a controlled diet. Carbohydrate tablets were provided for similar reasons, but also to ensure that participants had available carbohydrates should hypoglycaemia have been an issue during unsupervised conditions. Participant total energy intake (i.e. carbohydrate, fat and protein) was similar between experimental sessions, but participants chose to administer an additional 2±1 U of rapid-acting insulin under NO-INS during this phase of the experimental session. Thus, since our participants experienced hypoglycaemia following exercise, it is clear that energy intake was inadequate to account for the energy expended for exercise and/or insulin dosage was overestimated during the 20 hours following RE in the minority of our

participants. Alternatively, it should a consider that factors including elevated levels of circulating insulin prior to exercise coupled with less time awake to manage blood glucose after exercise, and the calmative effect of sleep on counterregulatory hormone production (337), could possibly complicate post-exercise glycaemic management for exercising T1DM individuals. Therefore, as shown previously using aerobic exercise modalities (338), it may be favorable for T1DM individuals to perform RE before breakfast to decrease the likelihood of post-exercise hypoglycaemic episodes. Further research is required to determine the optimal balance of carbohydrate to insulin around RE, as such an approach is complicated by the hyperglycaemia caused by RE vs. the risk of late-onset post-exercise hypoglycaemia.

Conclusion

In conclusion, the results from this study demonstrate for the first time that the administration of an individualised algorithm to T1DM participants performing morning RE reduced acute post-exercise hyperglycaemia without causing early hypoglycaemia. These findings serve as a foundation to improve glycaemic stability of T1DM participants performing RE.

CHAPTER SIX

General Discussion

6.1 SUMMARY OF AIMS AND MAJOR FINDINGS

The overarching aim of this thesis was to examine the impact of acute resistance exercise (RE) on glycaemia in type 1 diabetes (T1DM) individuals, to improve euglycaemic stability during and after RE, and promote confidence in people with T1DM to partake in this form of exercise and lead a more physically active lifestyle. Thus, Chapter 3 examined the impact of manipulating exercise volume in determining the acute glycaemic, metabolic and glucoregulatory hormone responses to acute RE in individuals with T1DM. The results demonstrate that exercise volume is an important factor in determining the blood glucose responses to RE; specifically, blood glucose climbs considerably above rest for one hour after one and two sets of similar intensity RE, but this exercise-induced hyperglycaemia can be attenuated by increasing the volume of exercise by addition of a similar intensity third set. Additionally, performing one to three sets of morning RE after an overnight fast and in the absence of rapid-acting insulin, does not induce acute hypoglycaemia, ketoacidosis, or raise a marker of muscle damage, but causes metabolic acidosis in a dose-dependent fashion. The aim of Chapter 4 was to examine the impact of manipulating exercise intensity in determining the acute glycaemic, metabolic and glucoregulatory hormone responses to acute RE in individuals with T1DM. The findings from this study demonstrate that performing a low intensity RE session evokes a similar magnitude of post-exercise hyperglycaemia and metabolic acidosis than a higher intensity RE session when sessions are matched for total weight lifted. It was encouraging that these exercise sessions were performed with no risk of hypoglycaemia, but the occurrence of exercise-induced hyperglycaemia is of clinical concern. The aim of Chapter 5 was to implement a modified algorithm that delivers an individualised dose of rapid-acting insulin after morning RE, to counter acute post-exercise hyperglycaemia. The findings from this study demonstrate that post-exercise rapid-acting insulin injection delivered by means of an algorithm results in reductions to post-RE hyperglycaemia without the occurrence of hypoglycaemia during the initial two hours after exercise.

6.2 IMPACT OF RESISTANCE EXERCISE ON BLOOD GLUCOSE

Across all chapters, a pre-exercise routine involving overnight fasting and omission of pre-exercise rapid acting insulin was adopted prior to every experimental session. This routine was primarily implemented to improve validity in examining the glycaemic, metabolic and glucoregulatory hormone responses to adjustments in the volume and intensity of a RE session. Interestingly, in all chapters, there were no incidences of hypoglycaemia during or within at least one hour after performance of RE, and this was in spite of varying RE characteristics (Table 6.1). Conversely, the findings from this thesis demonstrated that pre-breakfast RE evoked a net increase in blood glucose levels (Figure 6.1), independent of session design, which was defined as exercise-induced hyperglycaemia, given the stability in blood glucose during the resting control session in Chapter 3.

Table 6.1: Resistance exercise session characteristics in Chapters 3 to 5.

	1SET	2SET	3SET	LOW	MOD
No. of Exercises	8	8	8	6	6
Sets, Repetitions	1 Set, 10 Reps	2 Sets, 10 Reps	3 Sets, 10 Reps	2 Sets, 20 Reps	2 Sets, 10 Reps
Volume (kg)	2901±989	5712±2013	8286±1096	3725±674	3675±651
Intensity (%1RM)	69±1	68±1	67±1	30±0	59±1
Rest Intervals	Subsets 60s Sets 120s	Subsets 60s Sets 120s	Subsets 60s Sets 120s	Subsets and Sets 120s	Subsets and Sets 120s
Session Duration (min)	14	28	42	38	30
Exercise Duration	5min 20s	10min 40s	16min	16min	8min

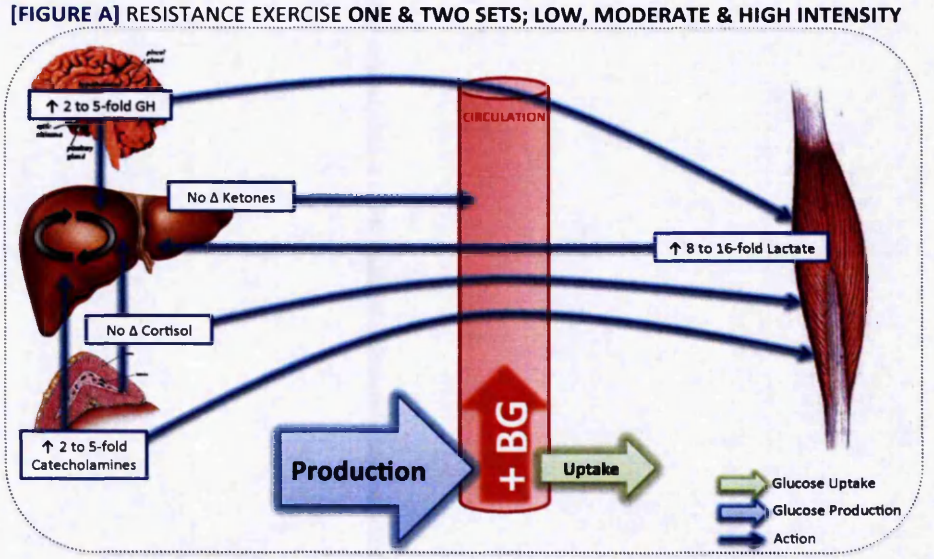
All sessions paced at 2:2 seconds eccentric:concentric contraction. Note, INSULIN and NO-INSULIN sessions in Chapter 5 replicated MOD Session. **Exercise Duration**: Total time spent exercising, excluding rest intervals.

6.2.1 Factors Involved In Resistance Exercise Induced Hyperglycaemia

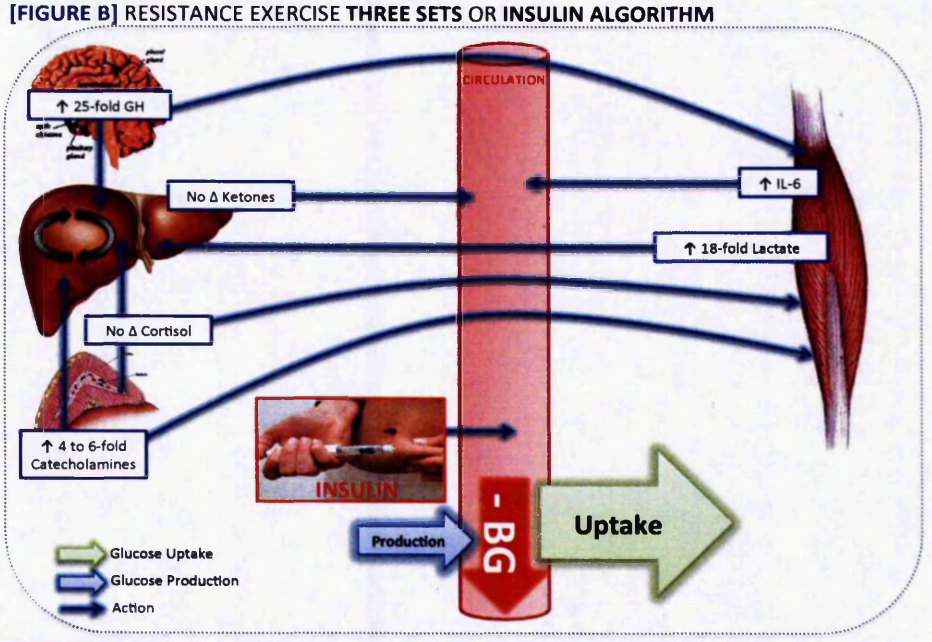
Catecholamines

Exercise-induced hyperglycaemia results from a mismatch between endogenous glucose production and glucose uptake. For instance, the rise in blood glucose levels of T1DM individuals in response to a 10-second bout of high-intensity exercise has been attributed to a transient decline in glucose clearance rather than from a disproportionate rise in glucose production relative to glucose uptake (219). This response may have resulted from catecholamine mediated inhibition of glucose uptake (223) and/or a rapid glycolytic flux associated with high-intensity exercise,

[FIGURE A] RESISTANCE EXERCISE **ONE & TWO SETS; LOW, MODERATE & HIGH INTENSITY**



[FIGURE B] RESISTANCE EXERCISE **THREE SETS** OR **INSULIN ALGORITHM**



[FIGURE C] NET GLYCAEMIC IMPACT OF ACUTE RESISTANCE EXERCISE

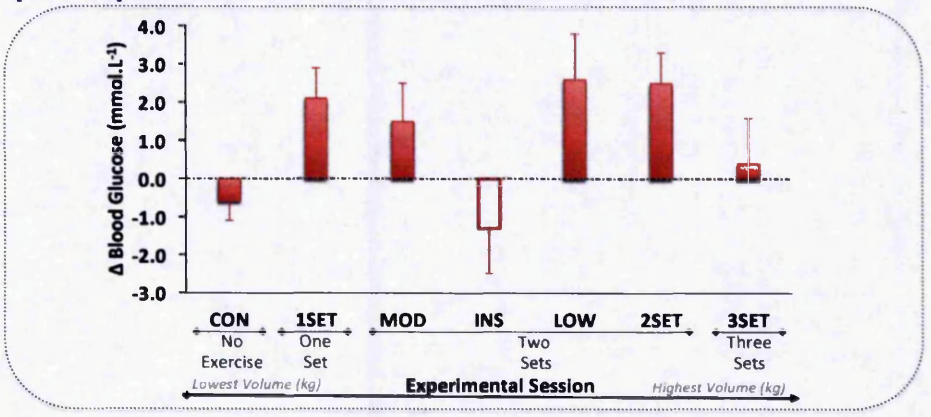


Figure 6.1: Glycaemic impact of acute RE in T1DM individuals. In **Figure A** hepatic glucose production exceeds glucose uptake due to high levels of counterregulatory hormones, thereby resulting in exercise-induced hyperglycaemia. In **Figure B** hepatic glucose production is almost balanced with skeletal muscle glucose uptake, despite elevated appearance of counterregulatory hormones, with a resulting lesser net increase in blood glucose than one and two sets of RE and restoration of baseline blood glucose levels. With the administration of insulin by means of the algorithm, glucose uptake exceeds production thereby attenuating the exercise-induced hyperglycaemia shown in Figure A. **Figure C** presents the net change in blood glucose (between baseline and ~1 hour post-exercise for each RE session within Chapters 3 and 4, and baseline and ~2 hours post-exercise under Chapter 5).

which supresses glucose utilisation due to G-6-P inhibition of hexokinase activity (339; 340). In contrast to an extremely short bout of exercise, in the post-absorptive state, 12 minutes of continuous high-intensity exercise is accompanied by a 7-fold increase in glucose production and 4-fold increase in glucose uptake resulting in hyperglycaemia in T1DM individuals (217). Furthermore, in response to ~14 minutes of continuous high-intensity exercise a 16-fold exercise-induced increase in adrenaline and noradrenaline corresponded with a 7-8-fold increase in endogenous glucose production (275), and both adrenaline and noradrenaline strongly correlated (r=0.84 and r=0.79, respectively, $p<0.05$) with rates of endogenous glucose production during exercise, where an increment in the rate of endogenous glucose production exceeded glucose uptake resulting in exercise-induced hyperglycaemia (275). Considering that catecholamines have been shown to increase both hepatic glucose production (341) and glucose uptake (24; 25), via activation of β_2-adrenoceptors by adrenaline (223) and/or sympathetic activation of liver nerves by noradrenaline (27; 223), it seems reasonable to agree with these aforementioned studies (217; 275) that the marked appearance of catecholamines (Table 6.2) was a primary factor in the development of RE-induced hyperglycaemia in T1DM (Figure 6.1). These responses might reflect a continuous rise in sympathoadrenal medullary secretion, to ultimately increase fuel production to meet the demands of the prescribed exercise session.

Table 6.2: Counterregulatory hormone, IL-6 and lactate responses in Chapters 3 and 4.

	AD	NA	GH	C	IL-6	LAC
1SET	↑3x	↑5x	↑5x	↔	↔	↑14x
2SET	↑2x	↑5x	↑5x	↔	↔	↑16x
3SET	↑4x	↑6x	↑25x	↔	↑2x	↑18x
LOW	↑3x	↑4x	↑2x	↔	↔	↑9x
MOD	↑2x	↑3x	↑2x	↓	↔	↑8x

Values represent change in analyte concentration from baseline, e.g. ↑**3x** refers to 3-fold mean increase from baseline to individual peak concentrations. **AD**: Adrenaline. **NA**: Noradrenaline. **GH**: Growth hormone. **C**: Cortisol. **LAC**: Lactate.

Although hyperglycaemic-hyperinsulinaemia has been shown to suppress endogenous glucose production during aerobic exercise in those without diabetes (342), levels of circulating insulin observed in Chapters 3 and 5 (with reference to NO-INSULIN) at baseline and after RE were approximately one-third less than concentrations required

to completely suppress hepatic glucose production at rest in individuals without diabetes (12). Moreover, the large catecholamine response to exercise has been shown to override the potential suppressive effect insulin on glucose production (222). Thus, it is possible that the occurrences of exercise-induced hyperglycaemia in response to the different format RE sessions within the thesis (Table 6.1) might be partly attributed to the large appearance of catecholamines, via a gross increment in glucose production that exceeded glucose uptake (Figure 6.1).

Growth Hormone and Cortisol

Statistically significant increases in growth hormone were observed during all RE sessions within Chapters 3 and 4 (Table 6.2), with post-exercise values increasing by 2- to 25-fold above baseline and the largest gains in concentration were observed in response to the highest volume, 3SET RE session. It is likely that growth hormone facilitated the rise in blood glucose in response to the RE sessions within this thesis, since it has been demonstrated that growth hormone can indirectly stimulate hepatic glycogenolysis and gluconeogenesis (38; 42) and can also transiently impair glucose uptake in a dose-dependent manner, that is, within a time frame relevant to all experimental sessions (40). The dose-response relationship between exercise volume and growth hormone that was observed in Chapter 3 was corroborated in Chapter 4, because the magnitude of increase in post-exercise growth hormone concentrations was similar between the two different intensity RE sessions that were matched for exercise volume.

Unlike growth hormone, the lack of increase in cortisol concentrations within Chapters 3 and 4 (Table 6.2) suggest that this hormone had little bearing on the acute hyperglycaemic effect of RE. In Chapter 3 cortisol concentrations in response to one, two and three sets of RE remained comparable with both baseline and control session levels. In Chapter 4 cortisol concentrations slightly declined from baseline in response to MOD but did not change under LOW. These cortisol responses the within Chapters 3 and 4 are in agreement with the usual diurnal shift in cortisol concentrations during a non-exercising day in individuals without T1DM (197). They are also in line with those of similar aged T1DM individuals in response to morning continuous moderate-intensity exercise (180), in which cortisol concentrations were statistically

significantly lower than pre-exercise levels at three-hours after exercise. However, these findings conflict with those of pubertal T1DM individuals responses to morning endurance and interval exercise, in which cortisol concentrations were observed to rise above pre-exercise levels at 30-minutes post-exercise, and also conflict with those individuals without diabetes in response to RE (243), in which cortisol concentrations were increased by exercise. These inter-study variations in cortisol responses to exercise could be attributed to factors including time of day when exercise took place (197) and/or the age of the cohort under investigation (i.e. cortisol responses to RE have been shown to vary with age and gender in those without diabetes (244)). Furthermore, variations in exercise-induced changes in cortisol could be attributed to RE session volume (243), where increases in plasma cortisol levels has only been observed after high volume RE sessions in those without diabetes (albeit the results from Chapters 3 and 4 suggest that exercise volume has little impact on cortisol regulation in T1DM), and/or it should be considered that the hyperglycaemic state of the T1DM individuals within this thesis could have suppressed cortisol secretion (305). Indeed, it is difficult to explain the lack of cortisol response to the RE sessions within this thesis, but it is likely that the combination of morning exercise coupled with hyperglycaemia had suppressive effects on cortisol secretion.

6.2.2 Effects Of Resistance Exercise Volume And Intensity On Blood Glucose

There existed a close relationship between RE session design and the magnitude of exercise-induced hyperglycaemia (depicted in Figures 6.1 & 6.2). With reference to Table 6.1 (see for specific RE session characteristics), results from Chapter 3 show that doubling the volume of the single set RE session (1SET) by including a subsequent, similar intensity second set (2SET) further increased the net gain in blood glucose during exercise from 1.0 ± 0.5 to 1.5 ± 0.3 $mmol.L^{-1}$. Thereafter, during the subsequent one-hour recovery period, blood glucose increased further to concentrations that were 2.1 ± 0.8 and 2.5 ± 0.8 $mmol.L^{-1}$ greater than baseline, in response to 1SET and 2SET, respectively. Conversely, the net increase in blood glucose at one-hour after the 3SET RE session was 0.4 ± 1.2 $mmol.L^{-1}$, despite that the total weight lifted during this session was approximately triple that of the 1SET RE session. In Chapter 4, performance of low intensity RE resulted in a similar pattern and magnitude of rise in blood glucose during 65 minutes of recovery (i.e. ~2

mmol.L^{-1} rise in blood glucose above baseline) when compared to the equal volume, higher intensity RE session. The findings from Chapter 4 strengthen the findings from Chapter 3, that exercise volume was a major factor in determining the glycaemic responses to RE in T1DM, secondary to other possible RE characteristics such as exercise intensity and the rest interval. Little is known about the interaction between the design of a RE session and acute glycaemia in T1DM.

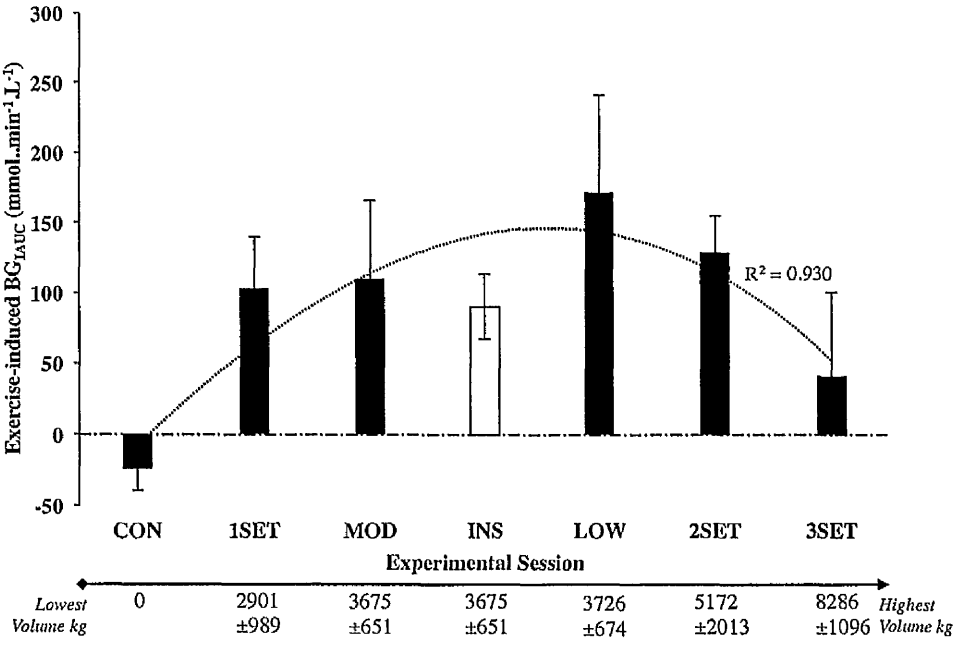


Figure 6.2: Net incremental exercise-induced BG_{IAUC} (area under curve) across Chapters 3 to 5. Exercise-induced BG_{IAUC} represents the area between the pre-exercise fasting value and subsequent delta blood glucose values (relative to pre-exercise concentrations) for the blood glucose curve up to 60 to 65 minutes post-exercise (but not including during exercise, that is, in an effort to compare changes in resting, pre-exercise, glycaemia resulting from exercise and to account for differences in exercise duration between sessions). Note the inverted 'U' relationship between exercise volume and the magnitude of exercise-induced hyperglycaemia [dotted line]. R^2 value is exclusive of the INSULIN session. See Table 6.1 for specific resistance exercise session characteristics.

The effects of different intensity RE sessions were recently investigated in T1DM, with exercise sessions resulting in a marked fall in blood glucose levels (241) (Table 1.6). But in this study there was no report of RE characteristics including sets, repetitions (nor volume) or pacing of exercises. Furthermore, there were no reports of dietary and insulin routines around exercise. In mind of the findings from this thesis, the validity of the findings from this study (241) is questionable, that is, given the lack of control over RE session characteristics and participant diet and insulin routines. Yardley et al. demonstrated on two separate occasions that a group of T1DM

individuals on MDI or CSSII, presented stable (240) or a fall in plasma glucose concentrations (from 8.4 ± 2.7 to 6.8 ± 2.3 mmol.L^{-1}) (211), during a three set RE session (Table 1.6). In the latter study, glucose concentrations remained stable throughout a one-hour post-exercise recovery period (211). The lack of control over pre and post-exercise insulin therapy and dietary intake between participants and/or insufficient standardisation of exercise protocols with respect to exercise intensity, volume and pacing might help explain the disparity in glycaemic responses to the same RE sessions within these two studies by Yardley et al (211; 240). Unfortunately, differences in study design and a lack of characterisation of the counterregulatory hormone and metabolic responses within these previously described studies (211; 240; 241), makes it difficult to compare these results to the findings within this thesis, to better understand the relationship between RE session design and glycaemia in T1DM. To add support to this statement, subtle adjustments in the ratio of time spent performing the eccentric and concentric component of a RE repetition (250) and independent adjustments in RE session volume (by number of sets) and intensity (242; 243) have been shown to alter the resultant rise in blood glucose and lactate (250) and appearance of counterregulatory hormones (242; 243; 250) in those without diabetes. Interestingly, increases in blood glucose have been observed in response to low- (249) and high-intensity RE in those without diabetes (248; 249).

It is difficult to explain why the net increase in blood glucose levels within one hour after performance of the highest volume, three-set RE session was substantially less than all other two set and the one set RE sessions within this thesis (Figure 6.1); this is highlighted in that the magnitude of hyperglycaemia during the one-hour recovery period was substantially less after three-sets of RE (3SET) when compared to the lower volume one and two set RE sessions within Chapters 3, 4 and 5 (as reflected in BG_{IAUC}; Figure 6.2). This was a perplexing finding when considering the 3SET RE session evoked the greatest overall increase in the appearance of counterregulatory hormones (Table 6.2), noting the previously described relationships between counterregulatory hormones and increased appearance of circulating glucose. A multiple linear regression was run to determine the proportion of variance in the magnitude of hyperglycaemia related to exercise, as reflected in the *exercise-induced* BG_{IAUC} (see Figure 6.2). Under 1SET and 2SET, 78.3% and 97.2% of the variance can

be explained by the change during RE in adrenaline, noradrenaline, growth hormone, insulin and cortisol concentrations and exercise volume. Contrastingly, under 3SET only 28.7% of the variance in *exercise-induced* BG_{IAUC} could be explained by these same independent variables. These findings indicate, firstly, that the rise in blood glucose in response to one and two sets of RE was likely to be have been due to the counterregulatory hormone stimulus on glucose production and uptake. These hormones however, less explain the change in glycaemia in response to the three-set RE session. As such, others factors might outweigh or augment the possible effect that the exercise-induced counterregulatory hormone response had on the balance between glucose production and utilisation.

In mind of the synergistic interaction between exercise and insulin to increase muscle glucose uptake (184), an important finding of this thesis was that plasma insulin levels remained similar between different volume sessions (Section 3.3.4.4), and the pre-exercise insulin regimen was fixed across Chapters 3-5. This is indicative that circulating insulin *per se* was probably not a factor in explaining the differences in post-exercise glycaemia between the different volume RE sessions. Though the presence of circulating insulin throughout exercise and recovery might have facilitated the transport of glucose into the skeletal muscle.

According to previous research, exercise-induced increases in the appearance of circulating lactate and catecholamines are indicative of heightened rates of metabolism of muscle glycogen and increased rates of carbohydrate oxidation (308; 343; 344). For instance, individuals without diabetes demonstrate a progressive loss of muscle glycogen content during high-intensity intermittent exercise, which was paralleled by a two-fold increase in noradrenaline after completion of the first sprint, and upon completing the tenth sprint noradrenaline and adrenaline concentrations were 15-fold and 6-fold greater than resting concentrations, respectively (344). The findings also demonstrated that while non-oxidative metabolism of muscle glycogen and phosphocreatine were the major contributors to energy production during the initial exercise interval, ATP synthesis during the tenth exercise interval was mainly derived from increased rates of oxidative metabolism (344). In this way, the relative diminishment in rates of blood lactate accumulation during the two and three set RE

sessions given the initial 14-fold increase in blood lactate concentrations after one set of RE (Table 6.2) might reflect an increased contribution of muscle derived lactate to hepatic glucose output and/or reductions in release of lactate from the working muscles during exercise as described previously (280; 282); such a response might be indicative of a greater reliance on oxidative metabolism and/or circulating substrates by the muscle during two and three sets of RE than during the single set of RE (282). Furthermore, the sustained elevated appearance of plasma catecholamines (Table 6.2) under the three-set RE session might reflect a continued utilisation of muscle glycogen, meaning a lower muscle glycogen content after the three set RE session relative to the lower volume RE sessions. Skeletal muscle sarcolemma GLUT4 content is inversely associated with muscle glycogen content (345), and rates of muscle glucose uptake and glycogen resynthesis are stimulated relative to GLUT4 appearance (346) and the loss of muscle glycogen (346-348). It is unknown whether alterations in energy metabolism and/or post-exercise muscle glycogen content might account for the variability in the magnitude of exercise-induced hyperglycaemia between the different volume RE sessions (Figure 6.2). Interestingly, muscle glycogen contributes to energy production during RE in those without diabetes, with progressive reductions in muscle glycogen content observed alongside increasing exercise volume (249). In this way, the lesser magnitude of hyperglycaemia observed after the three set RE session relative to the lower volume RE sessions, might be explained by an larger gross and/or accelerated rates of blood-borne glucose utilisation to satisfy the greater energy demands and/or replenish muscle glycogen after exercise.

In Chapter 3 a statistically significant elevation in plasma IL-6 concentrations was observed in response to the three-set RE session but not after the two and one set RE sessions (Table 6.2). In fact, under 3SET, the exercise-induced rise in IL-6 to peak concentrations significantly inversely correlated (r=-0.65, *p=0.041*) with exercise-induced BG_{IAUC} (presented in Figure 6.2), and the difference in the magnitude of exercise-induced BG_{IAUC} between 3SET and 2SET sessions significantly correlated with the difference in the absolute rise in IL-6 from baseline to 60-minutes post-exercise (r=-0.640, *p=0.044*). These findings imply that the greater the exercise-induced increase in IL-6 the larger the reduction in exercise-induced hyperglycaemia

under 3SET. In Chapter 4, however, it was found that a reduction in the intensity of the two-set RE session did not alter the IL-6 response to exercise (albeit IL-6 remained unchanged from baseline concentrations; Table 6.2). The finding from this thesis that the appearance of IL-6 in the bloodstream is primarily mediated by RE session volume is in agreement with previous research in which greater increases in IL-6 are observed after higher volume RE sessions (141). The finding that exercise-induced IL-6 production is increased by a decline in muscle glycogen content (288) is in support of a greater decline in muscle glycogen after the three set RE session, when compared to lower volume sessions. The exercise-induced increase in circulating IL-6 might have increased GLUT4 mediated glucose transport via activation of AMP-activated protein kinase (AMPK) (289); the energy sensor AMPK acts upstream from GLUT4 in a feed-forward mechanism facilitating glucose uptake (349; 350); similar to IL-6 (286), AMPK activity is stimulated by altered energy status such as a reduction in muscle glycogen content (351) and increased intramuscular metabolic rate (352). Interestingly, greater improvements in glucose tolerance have coincided with larger increases in IL-6 concentrations after high volume RE sessions in those without diabetes (141). These findings coupled with those from this thesis highlight that RE session volume has implications for improving post-RE euglycaemic stability in T1DM.

The concomitant decline of catecholamine concentrations across all RE sessions (across Chapters 3 to 5; irrespective of volume and intensity) probably reflects a waning of catecholamine driven hepatic glucose production via inhibition of phosphorylase activity. For example, in T1DM exercising rates of glucose production are returned to resting values within 30 minutes of recovery from performance of ~14 minutes of high-intensity exercise, which evoked a ~16-fold increase in circulating catecholamines (275). Alternatively, as a consequence to sustained exposure of adrenoceptors to elevated catecholamine concentrations, β-adrenoceptors at the surface of the cell can transiently reduce in number (i.e. reduced receptor density) and/or ability to interact with catecholamines (353; 354): a process known as adrenoceptor desensitisation. The affinity of β-adrenoceptors for agonists is lower at pH 6.69 than at pH 7.65 (355), and reductions in lymphocyte β-adrenoceptor responsiveness (as reflected in reduced cyclic AMP production) has been observed

soon after only 15 minutes of exercise at 90% maximal heart rate (356). Thus, the progressive increases in acidosis with performance of each set (with the greatest decline in pH and base-excess under 3SET, Section 3.3.5) and/or the sustained elevation in counterregulatory hormones during one to three sets of RE might have contributed to an attenuation of adrenoceptor sensitivity. In this way repressed rates of glucose production might have contributed to the lesser net increase in blood glucose during the higher volume, three-set RE session.

6.3 EFFICACY OF THE TREATMENT OF RESISTANCE EXERCISE INDUCED HYPERGLYCAEMIA WITH THE INSULIN ALGORITHM

Continued exposure to hyperglycaemia can detract from the potential health benefits reaped by regular physical exercise by restricting improvements in glycaemic control, and might also increase susceptibility to severe health complications (320) (as described in Section 1.3.1). Up until Chapter 5 was conducted it was unclear whether the magnitude of sustained hyperglycaemia that participants experienced during the 60 minutes after performance of the different volume and intensity RE sessions examined in Chapters 3 and 4 would diminish or increase with time. Previous research in T1DM demonstrated that an episode of exercise-induced hyperglycaemia is sustained for at least 2 hours after continuous high-intensity exercise, which was only diminished by increasing circulating insulin levels via intravenous insulin infusion (216). However, at the time of this thesis it was unknown what effect (if any) an exogenous insulin injection might have on glycaemia following RE, given the lack of research in this area and the multiple factors associated with exercise that might influence insulin action (described in Section 5.1). With these findings in mind, it was decided that the most prudent and ecologically valid approach to assess the efficacy of post-RE insulin administration (i.e. to determine what magnitude of effect exogenous insulin might have on blood glucose) in T1DM individuals was through the delivery of exogenous insulin injection by means of an individualised insulin algorithm (Figure 2.9, Page 81). As such, an objective of the insulin algorithm (used to determine the insulin dose) was to account for the potential inter-individual variability in the severity of exercise-induced hyperglycaemia experienced by each exercising participant. This user-friendly algorithm is the first clinical strategy developed to

assist exercising T1DM individuals with the pharmacological management of exercise-induced hyperglycaemia resulting from RE.

Interestingly, the magnitude of post-exercise hyperglycaemia during the initial 60 minutes of recovery was comparable between INSULIN (90 ± 24 mmol.min.L^{-1}) and MOD (110 ± 56 mmol.min.L^{-1}), but was > 2-times greater under INSULIN than 3SET (41 ± 59 mmol.min.L^{-1}). This finding is indicative that the rapid acting insulin had little effect on post-RE blood glucose levels during the initial 60 minutes of recovery, and within this time frame this blood glucose management strategy was less effective at reducing the magnitude of exercise-induced hyperglycaemia than increasing exercise volume (by addition of a third set of RE) (see Figure 6.2). In an earlier study, the effect of post-exercise hyperinsulinaemia by intravenous insulin infusion on blood glucose regulation was assessed in T1DM individuals (216). In this study it was demonstrated that a doubling of the insulin infusion rate necessary to maintain euglycaemia was required to return post-exercise blood glucose concentrations to euglycaemia during 2 hours after performance of ~14 minutes of high-intensity continuous exercise that resulted in a ~3 mmol.L^{-1} rise in blood glucose during exercise. The restoration of post-exercise euglycaemia was attributed to an insulin-mediated enhanced rate of blood glucose clearance, which occurred within 5 minutes of a rise in plasma insulin concentrations i.e. within 5 minutes of exercise cessation (216). Furthermore, insulin concentrations peaked within the bloodstream at a concentration of 110 pmol.L^{-1} at ~30 minutes post-exercise, and findings demonstrate a progressive decline in plasma glucose concentrations onwards of 5-minutes post-exercise, which reached a plateau at ~4.5 mmol.L^{-1} at 120-mintues post-exercise (216). Under the INSULIN experimental session in Chapter 5, the group peak insulin concentration occurred at 95-minutes post-exercise (notably, at ~90 minutes following insulin injection), at concentrations of 111 ± 16 pmol.L^{-1}; moreover, the increased rate of fall in blood glucose (compared to the NON-INSULIN session) occurred onwards of 50 to 65 minutes post-injection and resulted in a 3.0 ± 1.0 mmol.L^{-1} fall in blood glucose within 2 hours of exercise cessation (Figure 5.2).

The comparison of findings between Chapter 5 and those of Sigal et al. (216) are interesting, when considering that similar levels of post-exercise insulinaemia resulted

in a comparable 3 mmol.L^{-1} decline in blood glucose within a similar time-frame (i.e. 2 hours post-exercise), despite differing rates of exogenous insulin appearance within the circulation and contrasting forms of exercise. The fact that the method by which insulin was administered differed between these studies (i.e. subcutaneously injected insulin vs. intravenous insulin infusion) makes it difficult to speculate about the effect of different exercise modalities on the time-action profile on exogenous insulin in the post-exercise period. But, it is likely that the insulin-mediated post-exercise decline in blood glucose was elicited by a combination of an increase in glucose uptake (as described by Sigal et al. (216)) and suppression of endogenous glucose production (331).

In mind of these findings, together with the finding that the algorithm developed in Chapter 5 was not successful in returning post-exercise glycaemia to the target of 7 mmol.L^{-1}, it could be concluded that the 53±10% reduction in the algorithm-determined insulin dose ($Full_{Dose}$; Figure 2.9) was too conservative to restore post-exercise euglycaemia. It is therefore questionable whether this ~53% reduction in bolus insulin was necessary. Nevertheless, the algorithm-derived insulin dose of 2±1 IU along with its timing was effective at restoring baseline blood glucose concentrations within 2 hours following RE, but without the ingestion of carbohydrates. In other words, the algorithm was effective at countering the occurrence of *exercise-induced* hyperglycaemia. The algorithm was sensitive to the participant's glycaemic status after RE; this was reflected in a positive correlation between the magnitude of post-exercise hyperglycaemia at 0-minutes and the number of insulin units administered after exercise ($r = 0.941$, $p<0.001$); moreover, the algorithm-calculated insulin dose was zero units for the participant with a moderate total daily dose and a 0-minute post-exercise blood glucose concentration of within 0.5 mmol.L^{-1} of the target value (Table 5.2). Furthermore, considering the relatively small sample size (n=8) (albeit, despite reasonable statistical power; see Section 2.11.5), one should be mindful that this strategy might have a more severe impact on post-exercise glycaemia when measured in a larger population. As such, a less conservative approach might translate to a greater and/or more rapid fall in post-exercise glycaemia in some T1DM individuals, thereby increasing vulnerability to subsequent glycaemic instability. Thus, it could be suggested that the algorithm

developed in this study promotes euglycaemic stability and also offers an individualised solution to counter the rise in blood glucose caused by a single session of RE, when the exercising T1DM individual's pre-exercise blood glucose levels are euglycaemic. Notably, as discussed in Chapter 5, the abstention of carbohydrates following the RE session could explain why participants were exposed to hypoglycaemia during the 20 hours following exercise, and/or it should be considered that the requirement for exogenous insulin is lessened during the remaining part of the day following a morning RE session.

6.4 IMPACT OF RESISTANCE EXERCISE ON KETONAEMIA

During times of fasting, a resultant elevation in the production of ketones can suppress glucose utilisation (357), but this adaptation is negated by the restraining effect of insulin on ketone enzyme activity (53). However, low insulin levels coupled with concomitant rises in counterregulatory hormone concentrations can lead to the release of free fatty acids into the circulation from adipose tissue and to unrestrained hepatic oxidation of this metabolite in the liver resulting in ketone body formation, with resulting metabolic acidosis (358). With these findings in mind, there was a potential opportunity for ketogenesis, or even ketoacidosis, during the experimental sessions within Chapters 3 to 5; i.e., due to the omission of morning rapid-acting insulin combined with overnight fasting, raised counterregulatory hormones, and/or alterations in blood acid-base balance, associated with performance of RE. Yet, results from Chapter 3 demonstrate that this pre-exercise routine did not elevate baseline β-hydroxybutyrate concentrations, with concentrations remaining well below what is clinically deemed as hyperketonaemia (>1 $mmol.L^{-1}$) (53) for the duration of the non-exercise control session. Furthermore, baseline β-hydroxybutyrate concentrations were unaffected by different volume RE sessions remaining similar to control levels throughout recovery.

A possible explanation for this response is that participants maintained their usual basal insulin dosage. One of the primary traits of the basal insulin dose is to restrict excessive hepatic glucose production and in this way prevent the formation of excess ketones (359). Glargine could be particularly useful in this respect, given that its absorption is unaffected by exercise (209), and this finding is corroborated by the

maintenance of baseline plasma insulin levels throughout the experimental sessions in Chapters 3 (Section 3.3.4.4) and 5 (Section 5.3.1.3). It was encouraging that the acidosis generated by RE only temporarily compromised blood acid-base balance, since under all experimental sessions, blood pH and extra cellular fluid base-excess had returned to baseline concentrations within one hour after cessation of exercise, with these values falling within clinically acceptable ranges (51).

6.5 INTERACTION BETWEEN RESISTANCE EXERCISE INDUCED CHANGES IN GLYCAEMIA AND POTASSIUM (K^+) REGULATION

The fluctuations in blood K^+ concentrations observed within this thesis are clinically important to T1DM individuals. Both hyper- (310) and hypokalaemia (334; 360) have been associated with prolonged cardiac repolarisation, potentially resulting in serious arrhythmias. The exercise-induced marked and progressive rise in potassium concentrations observed during the recovery period from RE (Sections 3.3.6 and 4.3.4) was somewhat paradoxical, given that there is typically a sustained restoration of (or decline below) pre-exercise (resting) K^+ concentrations within 5 minutes of exercise cessation in individuals without diabetes, as a result of inhibition of muscular K^+ release and a high rate of K^+ uptake (310). Typically during hyperglycaemia there exists an increase in osmolarity associated with the elevation in plasma glucose levels, which drives water from within the cells into the interstitium and the blood. In this way, hyperglycaemia would have effectively diluted K^+ concentrations in the blood. Thus, the elevation in post-exercise K^+ concentrations cannot be explained by changes in fluid balance.

Across Chapters 3, 4 and 5, resting potassium concentrations were somewhat recovered during the initial 5 minutes of recovery, thus, the rise in blood K^+ concentrations during remaining recovery period might be explained by a disproportionate increase in intracellular potassium release over uptake. Catecholamines and insulin have a stimulatory effect on the Na^+-K^+ pump and therefore play an important part in K^+ regulation (290; 291; 294; 361); thus, this increase in circulating K^+ was potentially related to a withdrawal of morning insulin therapy resulting in under activation of the Na^+-K^+ pump and excessive K^+ leakage. Furthermore, the net release of K^+ from the liver that has been observed in response to

exercise (362) could be a factor that contributed to the post-exercise elevations in blood K^+ concentrations.

In Chapter 5, the injection of insulin had somewhat of a transient suppressive effect on blood K^+ concentrations. DeFronzo et al (363) demonstrated that the fall in plasma K^+ concentrations at rest under constant insulin infusion to maintain hyperinsulinaemia was the result of a rapid uptake of K^+ into the splanchnic bed during the first hour of hyperinsulinaemia and the consequent decline in plasma K^+ concentrations is maintained during a subsequent hour of insulin infusion by an increase in peripheral K^+ uptake. The effect of insulin administration on K^+ regulation during the post-exercise recovery period is poorly researched. But these aforementioned findings together with those from Chapter 5 indicate that a small dose of insulin counters the post-exercise rise in blood K^+ concentrations (observed without insulin) within ~20 minutes of insulin administration (i.e. 20 minutes after exercise cessation and 75 minutes prior to peak plasma insulin concentrations). This response might be attributed to a combination of central and peripheral K^+ uptake.

It is difficult to explain the restoration of K^+ concentrations during the latter 60 minutes of recovery under the NO-INSULIN experimental session; for instance, whereas the clearance of blood K^+ is likely to be augmented by an increase in endogenous insulin secretion in healthy individuals without diabetes (292), such a mechanism is probably diminished, if not abolished in T1DM. However, given the maintenance of baseline insulin levels throughout the recovery period (which were at least two to three-fold greater than levels expected in those without diabetes (267)) and in mind of the findings by DeFronzo et al (363), this late post-exercise clearance of blood K^+ could be explained by a net increase in peripheral K^+ uptake. Indeed, further research is needed to examine the interaction between post-exercise K^+ regulation and glycaemia in T1DM. Importantly, it has been demonstrated that prolongation of ventricular repolarisation that occurs during hyperinsulinaemic-euglycaemia is primarily related to the effects of insulin on plasma K^+ concentrations as opposed to its effects on glucose (360). In mind of the aforementioned alterations in K^+ regulation associated with RE, particularly during the early minutes and hours after exercise, clinicians should be cautious of the potentially insidious effects that a

post-exercise insulin injection could have on cardiac function via alterations in blood K^+ balance *per se*; some T1DM individuals might experience a greater exchange of K^+ and/or have less capacity to regulate intra- and extra-cellular K^+ balance due to diabetes-related impairments in Na^+-K^+ pump activity (292), and might be more susceptible to cardiac dysrhythmia soon after exercise.

6.6 EFFICACY OF RESISTANCE EXERCISE RELEVANT TO TYPE 1 DIABETES PATIENT CARE AND EXERCISE PRESCRIPTION

6.6.1 Impact Of Resistance Exercise On Heart Rate And Blood Pressure

In Chapter 3, average heart rates during exercise ranged from the lowest values under 1SET (104 ± 4 beats.min^{-1}) to the highest values under 2SET (120 ± 8 beats.min^{-1}) and 3SET (114 ± 6 beats.min^{-1}), with peaks ranging from 142 ± 7 to 162 ± 9 beats.min^{-1}. These values corresponded with an average heart rate of 62 ± 3 %HR_{max}, i.e. during one to thee sets of RE at an average exercise intensity of 68 ± 0 %1RM. In Chapter 4, during two sets of RE at 59 ± 1 %1RM (MOD) average heart rates were 124 ± 11 beats.min^{-1}, which corresponded with values of 67 ± 6 %HR_{max}, and elicited during exercise were peaks of 167 ± 16 beats.min^{-1}. Conversely, heart rates during two sets of RE at 30 ± 0 %1RM (LOW) were on average 147 ± 13 beats.min^{-1}, which corresponded with 80 ± 7 %HR_{max}, and peak heart rates during exercise were 195±13 beats.min^{-1}. Interestingly, the majority of time during the two set RE sessions in Chapter 4, was spent at heart rates reflecting >60 %HR_{max} (section 4.3.5.1). Together these findings demonstrate that although only approximately one-third of these RE sessions comprised actual exercise (Table 6.1), with the remaining time spent in passive recovery between sets and subsets, the RE sessions within this thesis offer a stimulus, and possibly a training regime, for the cardiovascular system, in physically active T1DM individuals of whom are not trained specifically in RE. It is also important to recognise that reducing exercise intensity independent of volume does not necessarily lessen heart rate demands of RE, and in this case (as reflected in Chapter 4) average and peak heart rates were statistically significantly greater during low intensity RE, when compared with a shorter duration but higher intensity RE session with matched rest intervals. Thus, there is a complex relationship between RE session characteristics and the cardiovascular system, and these findings suggest that

exercise duration is a primary factor in determining the heart rate demands associated with acute RE.

In Chapter 4 it was demonstrated that neither low nor moderate intensity RE altered systolic or diastolic blood pressures from baseline levels, when these measurements were taken at 0- and 60-minutes post-exercise. Consequently, there were no statistically significant exercise-induced changes in estimated mean arterial pressure (MAP). The timing of these cardiovascular measurements reflects more of an accumulative effect of the entire RE sessions as opposed to the possible transient changes in blood pressure evoked by each set or subset of RE. For instance, bi-lateral leg press (i.e. an exercise similar in technique to squatting) and military press (a kin to shoulder press) are associated with marked increases in circulatory stress as reflected in systolic and diastolic blood pressures of 224 to 261 mmHg and 128 to 151 mmHg, with increases in MAPs to ~ 145 to 158 mmHg, respectively (314). Additionally, increases in MAP have been observed within performance of a single set of squats, across different intensities in healthy individuals without diabetes (316); this study observed increases in MAP as load and repetitions increased, e.g. 122 ± 9 (2 repetitions) vs. 135 ± 11 mmHg (6 repetitions) and 128 ± 13 vs. 143 ± 14 mmHg, at 30 and 60 %1RM, respectively. Furthermore, increases in MAP were greater during RE at an intensity of 90%1RM, when compared to the lower intensity RE sessions. Interestingly, this study also demonstrated that higher relative intensities produced greater post-exercise hypotension, when cardiovascular measurements were taken during 2 minutes after cessation of exercise at a sample frequency of 1kHz (316).

More recently, it has been shown that the changes in blood pressure during RE at 40% and 60% 1RM appear to be no greater than those during low to moderate intensity (40% and 60% VO_2peak) aerobic exercise (364). Thus, it is likely that participants experienced marked increases in circulatory stress during performance of the RE sessions within this thesis, but the RE sessions as a whole in Chapter 4 could have been of insufficient intensity to elicit a post-exercise hypotensive effect, or the technique by which blood pressure was assessed might have been insensitive and/or of insufficient frequency to detect subtle cardiovascular alterations. Indeed, the possibility of underlying micro-and macrovascular complications associated with

diabetes warrants further research into the acute stress versus tolerability and safety of acute RE in individuals with T1DM, but it is encouraging that regular performance of moderate intensity RE for 8 weeks results in marked improvements autonomic and submaximal exercise cardiovascular regulation in patients with non-alcoholic fatty liver disease (365). In this way, RE could quite possibly have a role in the clinical management of T1DM.

6.6.2 Interaction Between Interleukin-6 And Exercising Glycaemic Control

Research by Rosa et al (366) has demonstrated in T1DM individuals that resting IL-6 levels and the IL-6 response to moderate intensity continuous exercise is increased in magnitude depending on the frequency of exposure to hyperglycaemia during the 3 days prior to assessment, with higher post-exercise increases in IL-6 observed in those with poorer glycaemic control. Additionally, it was demonstrated in T1DM that in response to 45 minute treadmill run at ~73% VO_2peak, post-exercise IL-6 concentrations were inversely related to circulating insulin concentrations (r=-0.484, *p=0.017*, n=8) (212), where reductions in post-exercise insulin dosage was associated with greater IL-6 values relative to a higher insulin dosage, and post-exercise increases in IL-6 and TNF-α accompany hyperglycaemia but not euglycaemia (88). Hyperglycaemic crisis is associated with a state of severe physiological inflammation characterised by a rise in proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), IL-6 and IL-8, possibly alongside increases in c-reactive protein, lipid peroxidation, reactive oxygen species, as well as cardiovascular risk factors (e.g. fatty acids and plasminogen activator inhibitor-1) in the absence of infection or pathology (55); specifically, where chronically elevated systemic IL-6 is associated with both excessive levels of glucose in the endothelium and downstream effects of biochemical pathways yielding advanced glycation end-products (367) i.e. which triggers leukocyte infiltration into the vascular basement membrane and release of IL-6, IL-8, IL-10 and TNF-α. Albeit, increases in IL-6 might evoke a mass anti-inflammatory effect by stimulating IL-1-receptor antagonist and IL-10, which suppress and/or have protective effects over the appearance of TNF-α (368). In mind of these findings, the IL-6 concentrations measured within this thesis are relevant to not only acute glucose metabolism (as discussed previously; Section 6.2) but also to chronic glycaemic control and immune function in T1DM.

In an effort to mitigate any effect of pre-exercise glycaemic control on the blood glucose responses during the experimental sessions in this thesis, all participants in this thesis adhered to a standardised diet and insulin routine for 24 hours prior to each experimental session, and sessions were rescheduled if a participant experienced a hypoglycaemic episode or prolonged hyperglycaemia during this time. But results by Rosa et al (366) highlight a limitation of this thesis in that participants were not screened more rigorously for exposure to hyperglycaemic during the 72 hours leading up to each experimental session. With these findings in mind, nevertheless, it was an important observation that resting IL-6 concentrations across studies in this thesis were quantitatively no greater than healthy individuals without diabetes (141) and considerably lower than those observed in the aforementioned studies by Campbell et al (88; 212); moreover, IL-6 concentrations remained comparable to baseline levels throughout the non-exercise control session in Chapter 3 (Section 3.3.4.5), despite that participants remained mildly hyperglycaemic throughout this session.

In Chapters 3 and 4, basal IL-6 was correlated with duration of diabetes (r=0.759, r=0.781, $p<0.05$, respectively), yet it was not related to glycaemic control or adiposity. Indeed, IL-6 may be a useful biomarker in the prognosis of diabetes-related health complications attributed to obesity and glycaemic control, of which have been incriminated in the preservation and exacerbation of the inflammatory response (369). Perhaps the small cohort tested in this thesis explains the lack of relationship between glycaemic control and IL-6 levels as described previously (366). Furthermore, that post-exercise IL-6 responses were not related to glycaemic control, adiposity or duration or diabetes (across Chapters 3 and 4), and any increase in circulating IL-6 was only observed in the exercise sessions, it seems that an increase in IL-6 was related to the physiological changes evoked by exercise and not individual-oriented traits.

6.6.3 Muscle Damage And Perceived Exertion

During exercise, under all experimental sessions ratings of perceived exertion corresponded with subjective intensities of "*somewhat easy*" to "*hard*". At 60-minutes and 24-hours post-exercise, perception of muscle soreness corresponded with feelings

of "*no pain* (0) *to mild pain* (2)" (Chapter 3). These measurements highlight the varying levels of effort required of this physically active (but not RE trained) cohort to perform RE sessions of differing volumes and intensities. However, despite the substantial metabolic, perceived and cardiovascular (as aforementioned) stress that was imposed by RE, the findings from Chapter 3 show that plasma creatine kinase concentrations remained unaltered from pre-exercise levels at 24 hours after cessation of exercise. Muscle membrane permeability is sensitive to exercise intensity. When strenuous exercise is performed where the exertion/loading that the muscle can withstand is exceeded, the muscle membrane permeability changes and/or muscle membrane breakage occurs and creatine kinase leaks into the interstitial fluid, is extracted by the lymphatic system, and appears in the bloodstream (370). Thus, increases in circulating creatine kinase levels are indicative of damage to the skeletal muscle structure at the level of Z-disks and sarcolemma (371; 372), typically with ensuing muscle soreness and pain. In this way, the lack of post-exercise increase in creatine kinase levels is in line with the lack of perceived post-exercise muscle soreness, and is suggestive that these RE sessions did not expose T1DM participants to muscle damage (albeit creatine kinase concentrations may peak within plasma at 48-hours after weight-bearing exercise (370)).

It is encouraging that these RE sessions did not raise creatine kinase concentrations as have other forms of RE (233; 252), since increases in post-exercise creatine kinase concentrations has been associated with impairments in GLUT4 mediated insulin signalling (233), which could ultimately lend support to a loss of glycaemic control associated with T1DM. From a practical viewpoint, it is plausible that the extra stability offered by the Smith machine might have lessened the muscular stress on the exercising individual, when compared with other forms of RE such as 'free-weights' that offers less external support.

When extrapolating these findings to other T1DM individuals it should be realised that the effects of exercise on perception of effort, metabolic and cardiovascular stress, and muscle damage, will inevitably vary with individual fitness levels. This thesis offers insight into a variety of different RE sessions that challenge the

cardiovascular and metabolic system of the physically active but untrained T1DM individual, in the absence of muscle damage or soreness at 24 hours after exercise.

6.7 PRACTICAL RECOMMENDATIONS FOR THE EXERCISING TYPE 1 DIABETES INDIVIDUAL: A PATIENT CARE PERSPECTIVE

Firstly, the continuation of evening basal insulin but omission of morning bolus insulin in the absence of pre-exercise macronutrient consumption is likely to protect T1DM participants from the occurrence of hypoglycaemia during and soon after a single session of morning RE. The findings from this thesis also indicate that the exercising T1DM is more likely to experience a rise in blood glucose after performance of a one or two set morning RE session than after a higher volume three set RE session.

A useful tool for the T1DM individual would be an ability to predict whether blood glucose would continue to rise during the post-RE recovery period, as demonstrated under the one and two set RE experimental sessions, or remain stable as observed after the three-set RE session. Interestingly, a positive correlation was observed between the magnitude of rise in blood glucose during both one-set (1SET: r=0.704, *p=0.026*) and three-sets (r=0.741, *p=0.018*) of RE and the magnitude of rise in blood glucose during the 60-minute post-exercise recovery period. Furthermore, the mean magnitude of rise in blood glucose between the end of 2SET and end of 3SET RE sessions positively correlated with the magnitude of rise in blood glucose during the 60-minute post-exercise recovery period (r=0.891, *p=0.002*). These observations suggest that exercising T1DM individuals whom demonstrate a considerable rise in blood glucose during RE are more likely to experience a greater rise in blood glucose during the hour after a session of RE. Thus, if the net increase in blood glucose can be diminished *during* the RE session then it seems that participants are at less risk of experiencing an episode of hyperglycaemia soon *after* RE. An approach to better manage blood glucose responses to RE could be to sample blood glucose prior to exercise, and also following completion of each set or circuit of RE; for example, if an elevation in blood glucose is identified after performance of two sets of RE, then the T1DM individual could benefit from performing an additional set or circuit of RE to reduce the likelihood of post-exercise hyperglycaemia, or the individual might

choose to administer a correctional dose of exogenous insulin using the algorithm developed in Chapter 5.

6.8 LIMITATIONS

Although the studies within this thesis were designed to generate results that have useful applications, the following limitations do apply:

- The findings and recommendations reported within this thesis may be limited to the participants tested within each respective study.

- Considering the multiple different arrangements in resistance exercise session characteristics, strict control of these exercise variables alongside insulin and diet was necessary to determine the impact exercise volume and intensity on blood glucose. As such, the physiological responses reported within this thesis are most likely only applicable to the exact nature of each experimental session. Thus, alterations to the resistance exercise characteristics and/or insulin or dietary routines adopted within this thesis could result in differing physiological responses.

- The findings from this thesis demonstrate that there exists a close relationship between the acute design of a resistance exercise session with respect to exercise volume and intensity and the post-exercise glycaemic status of T1DM individuals (depicted in Figures 6.1 and 6.2). However, it is a limitation that there existed subtle differences in resistance exercise session design between the two-set resistance exercise sessions within Chapters 3 and 4, i.e. Chapter 4 comprised two less exercises and an additional 60 seconds of rest between subsets (Table 6.1). This was to better accommodate for inter-individual fitness levels (albeit the exercise intensity was standardised between participants; Table 6.1). In this way, it remains to be determined whether a reduction in exercise session volume by a reduction in intensity and not the number of repetitions (as conducted in this thesis) might alter the glycaemic response to resistance exercise in T1DM individuals. Furthermore, it remains

unknown what impact an alteration in the rest interval has on the glycaemic response to resistance exercise in T1DM individuals.

- Although there exists some intra-individual repeatability with the glycaemic responses to exercise of T1DM individuals under insulin therapy (199), it has been shown that the glycaemic responses to exercise may vary across different days independent of differences in insulin therapy and diet (253). As such, it is a limitation that each participant only completed each experimental arm once. Thus, the validity and reliability of the findings within this thesis could be improved by within-subject repeated trials.

6.9 GENERAL CONCLUSIONS

The results within this thesis show that:

- Exercise volume is a primary factor in determining the acute impact of resistance exercise on blood glucose in T1DM individuals, where performance of one and two sets of resistance exercise evokes a sustained elevation in blood glucose for at least one hour after exercise but the addition of a third set attenuates the magnitude of hyperglycaemia caused by two sets and returns post-exercise blood glucose to concentrations comparable with a non-exercise control session.

- A low intensity resistance exercise session results in a similar magnitude of exercise-induced hyperglycaemia following exercise, when compared to a higher intensity but overall equal volume resistance exercise session.

- The administration of an individualised dose of post-exercise insulin by means of an algorithm to T1DM individuals performing morning resistance exercise reduces the magnitude of acute post-exercise hyperglycaemia without causing early (within 2 hours) post-exercise hypoglycaemia, but the exposure to hypoglycaemia ensures during later hours after exercise.

- The omission of pre-exercise exogenous insulin but continuation of the usual basal dosage protects individuals with T1DM from the occurrence of hypoglycaemia during and soon after pre-breakfast, morning resistance exercise, but this routine does not contribute to the appearance of blood ketones.

- The relationship between the post-exercise appearance of counterregulatory hormones and IL-6 and resistance exercise session design is complex, but the magnitude of exercise-induced appearance in catecholamines, growth hormone and IL-6 appears to be related to the volume and/or duration of exercise.

- One to three sets of resistance exercise results in strong acid-base disturbances and increases in heart rate, which return to levels reflective of a rested state within one hour of recovery, but resistance exercise is unlikely to acutely alter post-exercise blood pressure nor induce 24-hour muscle damage.

6.10 SUGGESTIONS FOR FUTURE RESEARCH

The following are considerations for future investigation;

- In mind of the improvements in the magnitude of exercise-induced hyperglycaemia and hyperkalaemia observed in T1DM individuals after several weeks of high-intensity intermittent exercise training by Harmer et al (218), it is highly possible that the hyperglycaemic and hyperkalaemic responses to resistance exercise could diminish with regular training. Such research warrants investigation.

- Further exploration of different formats of resistance exercise session design alongside the examination of metabolic factors such as fuel oxidation and muscle metabolism during exercise and recovery would help elucidate the relationship between exercise volume and glycaemia.

- While interleukin-6 might have a role in glucose regulation during certain types of resistance exercise, appearance of this cytokine is also associated with alterations in immune function. Thus, further research is required to determine the impact of resistance exercise on immune function in T1DM individuals, whom may be particularly susceptible to states of poor immunity.

- The consumption of a carbohydrate could help replenish muscle glycogen stores during the early hours after resistance exercise, in an effort to prevent the occurrence of late onset post-exercise hypoglycaemia. But in mind of the hyperglycaemic response to this form of exercise; it should first be explored whether T1DM individuals could benefit from increasing their prandial insulin dose when macronutrients are consumed during the early hours of recovery from resistance exercise, since carbohydrates and proteins are likely to promote a further rise is post-exercise glycaemia.

- As popularity increases in the use of insulin pump therapy to treat individuals with T1DM, an understanding of the impact of resistance exercise in this cohort warrants research.

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APPENDICES

APPENDIX A

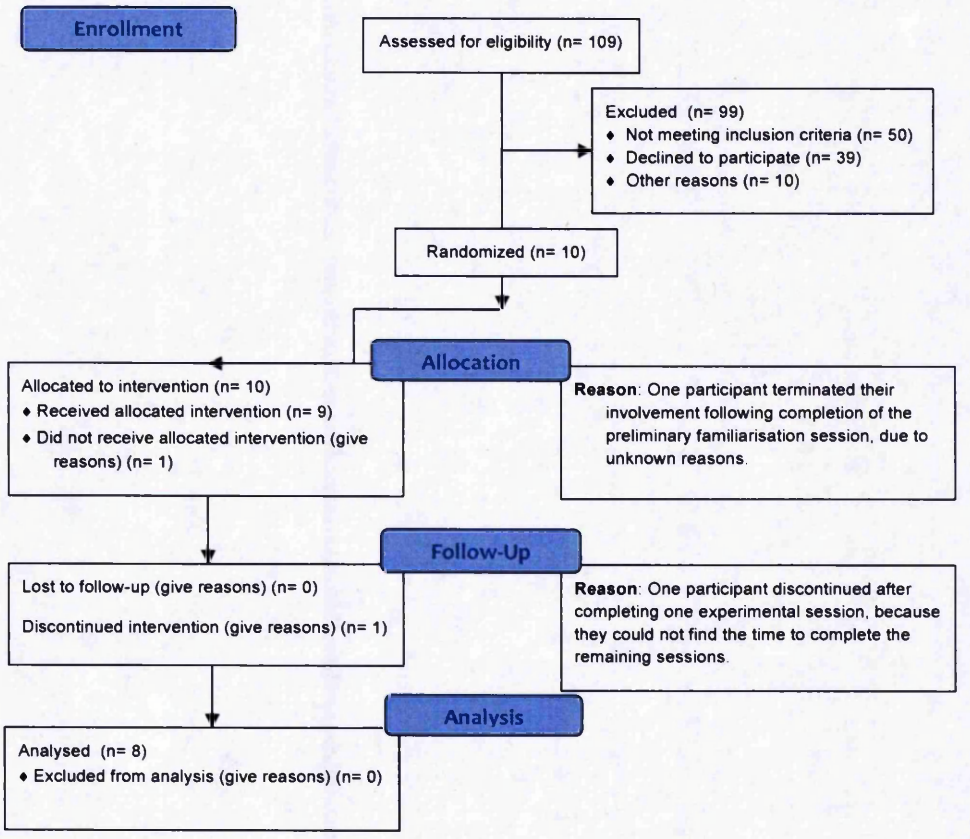
(Compact Disc)

- A1 – LREC ETHICS APPROVAL
- A2 – CHAPTER 3 PARTICIPANT PRE-STUDY INFORMATION PACK
- A3 – CHAPTER 4 & 5 PARTICIPANT PRE-STUDY INFORMATION PACK
- A4 – EXAMPLE POST-STUDY PARTICIPANT REPORT

APPENDIX B1
CHAPTER 3 CONSORT FLOW DIAGRAM

CONSORT
TRANSPARENT REPORTING of TRIALS

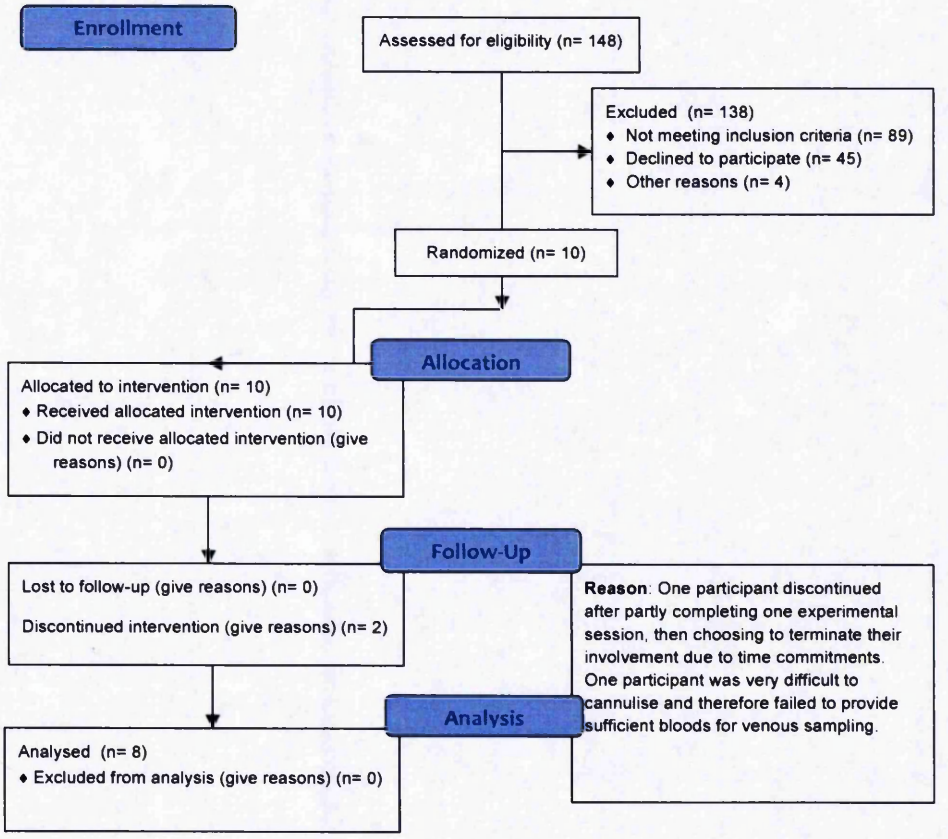
CONSORT 2010 Flow Diagram



CHAPTER 4 & 5 CONSORT FLOW DIAGRAM

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



APPENDIX B2
INFORMED CONSENT FORM, CHAPTERS 3 TO 5

Swansea University
Prifysgol Abertawe

Study Number: 1/2/3 Patient Identification Number:

CONSENT FORM

Title of Project:

Name of Researcher: Dan Turner **Please initial box:**

1. I confirm that I have read and understood the information sheet date …….. for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without medical care or legal rights being affected. ☐
3. I understand that relevant sections of any of my medical notes and data collected during this study may be looked at by responsible individuals from Swansea University, from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in the study. **Yes / No**
   If **No,** I am held liable for any consequences incurred during the study. ☐
5. I agree to take part in the above study.

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

APPENDIX C
ACSM HEALTH SCREENING QUESTIONNAIRE

AHA/ACSM Health/Fitness Facility Preparticipation Screening Questionnaire.

Assess your health needs by marking all true statements.

History
You have had:
- ❑a heart attack
- ❑heart surgery
- ❑cardiac catheterization
- ❑coronary angioplasty (PTCA)
- ❑pacemaker/implantable cardiac defibrillator/rhythm disturbance
- ❑heart valve disease
- ❑heart failure
- ❑heart transplantation
- ❑congenital heart disease

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

Symptoms and other health issues:

- ❑You experience chest discomfort with exertion.
- ❑You experience unreasonable breathlessness.
- ❑You experience dizziness, fainting, blackouts.
- ❑You take heart medications.
- ❑You take prescription medication(s).
- ❑You have musculoskeletal problems.
- ❑You have concerns about the safety of exercise.
- ❑You are pregnant.

Cardiovascular risk factors
- ❑You are a man older than 45 years.
- ❑You are a woman older than 55 years or you have had a hysterectomy or you are postmenopausal.
- ❑You smoke.
- ❑Your blood pressure is greater than 140/90.
- ❑You don't know your blood pressure.
- ❑You take blood pressure medication.
- ❑Your blood cholesterol level is >240 mg/dL.
- ❑You don't know your cholesterol level.
- ❑You have a close blood relative who had a heart attack before age 55 (father or brother) or age 65 (mother or sister).
- ❑You are diabetic or take medicine to control your blood sugar.
- ❑You are physically inactive (i.e., you get less than 30 minutes of physical activity on at least 3 days per week).
- ❑You are more than 20 pounds overweight.

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

❑None of the above is true.
You should be able to exercise safely without consulting your healthcare provider in almost any facility that meets your exercise program needs.

Signature: _____ Date: _____

AHA/ACSM indicates American Heart Association/American College of Sports Medicine.

APPENDIX D
PARTICIPANT PRELIMINARY QUESTIONS

Preliminary Questions

Name: ***Date:***

What insulin(s) are you currently taking?
Brand names

What typical insulin doses do you usually administer?
Basal and short/rapid

What time of day do you usually administer them?
Morning, midday, afternoon, prior to bed

Basal:

Bolus:

How do you take them?
Insulin Pen, Type brand names etc.

How long have you been on this regimen?

What regimen were you previously on?
Reasons for change

What is your typical pre-breakfast blood glucose level?

How often do you exercise a week (include type and intensity?

What do you do with regards to insulin & carbohydrate before you exercise?
Food and drink consumed? How much? What type of Exercise?

Have you ever experienced a hypo/hyper during or after exercise (please specify exercise)?

How long after exercise did it occur?

What did you eat or drink to clear it?

Are you aware of when you are hypo/hyperglycaemic?
(refer to Clark hypoglycaemia awareness scale)

Do you consume caffeine? E.g. coffee, Red Bull

How much?

How does it affect your glucose and insulin regimen?

What is your usual morning blood glucose before breakfast?

Are you on any other prescribed medication?
If so, how long have you been taking this particular medication?

Have you experienced any medical complications relating to your diabetes?

Are you involved in any other research outside of this project?

Dietary Requirements

Do you have any food allergies or diet restrictions?

What do you usually eat for;

Breakfast:
Time? Amount?

Lunch:
Time? Amount?

Dinner:
Time? Amount?

Supper:
Time? Amount?

Snacks:
Fruit / Vegetables?

Would you be willing to replicate a diet plan for one day before and after each experimental session, and what would this diet ideally be?

Would you be willing to abstain from caffeine and alcohol for the duration of the study, including three days leading up to the study?

Would you be happy to regularly monitor and report you blood glucose for one day before and after each experimental session?

APPENDIX E

PRE EXPERIMENTAL SESSION DIETARY INTAKE, INSULIN DOSAGE AND BLOOD GLUCOSE DIARY

Participant: Day: Date:

Pre Trial [ ] Glucose Readings		
Time	**Blood Glucose**	**Comments**
Awakening		
11am		
Lunch		
3pm		
Dinner		
Pre-sleep		

Pre Trial [ ] Dietary Intake and Insulin Dosage Log Sheet			
Time	**Food/ Drink**	**Insulin Dose (Type; Units)**	**Comments**

APPENDIX F
PHYSICAL ACTIVITY RECORD

ACTIVITY RECORD

Please read these important instructions carefully

- Please record the time you got out of bed in the morning.
- Please record the time you went to bed in the evening.
- Please record any travelling time and the type of transportation used.
- Please record all the activities (in 15 minute blocks) you undertake in the day.
- Remember to include all activities (including, housework, child care, programmed exercise, etc.).

DESCRIBING THE INTENSITY OF ACTIVITY

Classify the intensity of activity, using the 0-10 scale listed below, whilst you are undertaking the activity or exercise. If the intensity changes during the activity choose the 1-10 classification that best describes the overall intensity of the activity (use the table provided to help you with the classifications).

1. ***Lying down (sleeping and resting)***
2. ***Seated***
3. ***Standing; light activity***
4. ***Between 3&4***
5. ***Light manual work***
6. ***Light leisure activities***
7. ***Moderate manual work***
8. ***Moderate leisure activities***
9. ***Intense manual work and sporting activities***
10. ***Strongest intensity***

In each box, write the number which corresponds to the activity which you have carried out during this 15 minute period. Please consult the activity list provided to establish the proper intensity. If an activity is carried out over a long period (e.g. sleeping) you can draw a continuous line in the rectangular boxes which follow until such a time when there is a change in activity. To understand this further we suggest that you take a look at the example that follows.

Participant: **Day:** **Date:**

TRIAL: **PRE / POST:** **24 HOUR**

Minutes	0-15	16-30	31-45	46-60
Hour				
12am				
1am				
2am				
3am				
4am				
5am				
6am				
7am				
8am				
9am				
10am				
11am				
12pm				
13pm				
14pm				
15pm				
16pm				
17pm				
18pm				
19pm				
20pm				
21pm				
22pm				
23pm				
24pm				

NOTES:

APPENDIX G
3RM PROTOCOL

3-repetition maximum testing protocol

1. Estimate a *light warm-up* weight that you can lift easily for 6-8 reps.
2. Lift the weight for 6-8 reps.
3. Rest for 1 minute.

4. Estimate a *warm-up* weight with which you can complete 5-7 reps, by adding 10-20 pounds (4-9 kg) or 5-10% to your light warm-up weight.
5. Lift the weight for 5-7 reps.
6. Rest for 2 minutes.

7. Estimate a conservative, *near-max weight* with which you can complete 4-6 reps, by adding 10 to 20 pounds (4-9 kg) or 5-10% to your warm-up weight.
8. Lift the weight for 4-6 reps.
9. Rest 2 to 4 minutes.

10. Increase the weight by adding 10 to 20 pounds (4-9 kg) or 5-10%.
11. Lift the weight for 3 reps. Rest for 2 to 4 minutes.

If you were **able** to perform 3 reps then **increase** the weight by 10-20 pounds (5-10%).

If you were **unable** to perform 3 reps then **decrease** the weight by 5 to 10 pounds (2-4 kg) or 2.5-5%.

12. Lift the weight for 3 reps. Rest for 2 to 4 minutes.

If you were **able** to perform 3 reps then **increase** the weight by 10-20 pounds (5-10%).

If you were **unable** to perform 3 reps then **decrease** the weight by 5 to 10 pounds (2-4 kg) or 2.5-5%.

13. Lift the weight for 3 reps. Rest for 2 to 4 minutes. If you were able to complete 3 reps using proper technique, but no more, then record this weight as your 3 rep max. If not continue:

If you were **able** to perform 3 reps then **increase** the weight by 10-20 pounds (5-10%).

If you were **unable** to perform 3 reps then **decrease** the weight by 5 to 10 pounds (2-4 kg) or 2.5-5%.

3RM testing protocol example:

1. *Light warm-up*: 100 lb
2. 8 reps – very easy.
3. Rested for 1 minute.

4. *Warm-up weight*: 110 lb (added 10lb or 10% of light warm-up)
5. 7 reps – easy.
6. Rested for 2 minutes.

7. *Near-max weight*: 125 lb (added 15lb of warm-up)
8. 5 reps – fairly easy.
9. Rest 3 minutes.

10. **1st testing weight**: 135 lb. (added 10 lb OR 9.6% of near-max)
11. 3 reps – felt good.
12. Rested 3 minutes.

13. **2nd testing weight**: 145 lb. (added 10 lb OR 7.4% of 1st testing weight)
14. 2 reps – couldn't do 3 reps.
15. Rested 3 minutes.

16. **3rd testing weight**: 140 lb. (decreased by 5 lb or 3.4% of 2nd testing weight)
17. 3 reps – barely.
18. Record 3 rep max (3RM) as 140 lb.

Protocol Adapted from *Essentials of Strength Training and Conditioning* 3rd Edition

APPENDIX H

DETERMINATION OF GLYCOSYLATED HAEMOGLOBIN (HBA_{1C})

Whole blood was analysed for HbA_{1c} on the Bio-Rad D-10 Haemoglobin Analyser (Bio-Rad Laboratories Ltd, UK).

Overview and Principles of Operation

The D-10 Haemoglobin Analyser is an automated system that provided integrated an method for sample preparation, separation and the determination of the relative percentage of specific haemoglobin in whole blood.

The D-10 Haemoglobin Analyser uses principles of high performance liquid chromatography (HPLC). The HPLC pump and proportioning valve deliver a buffer solution to the analytical cartridge and detector. Whole blood samples underwent a two-step dilution process prior to delivery to the analytical flow path. The vial adaptor in the sample rack identifies pre-diluted samples and the dilutions steps are omitted. The samples were aspirated directly and introduced into the analytical flow path. The process required a sample solution of 10 uL of whole blood in 2 mL of diluent. The detectable range for this device was an HbA_{1c} 3.8 – 18.5%, with an intra-assay precision of 0.48% to 0.81%.

APPENDIX I

CHAPTER 3 DATA SHEET

							Trial		Exercise	
Participant		Height		Temperature		Date	Arrive Time		Start Time	
Trial		Body Mass		Pressure			Leave Time		End Time	
	Baseline Rest	After 1 Set	After 2 Sets	0 Post-Ex	5 Post-Ex	15 Post-Ex	30 Post-Ex	60 Post-Ex	Exercise Duration	
Blood pH									Follow-Up	
pCO2 (mmHg)									Absolute Time	
pO2 (mmHg)									Time after END-ex	
Na+ (mM)									Height	
K+ (mM)									Body Mass	
Ca++ (mM)									C-Glucose (mM)	
Glucose (mM)										
Lactate (mM)										
Hct (%)										
RPE										
HR (BPM)										
Becf										
HCO3-										

APPENDIX J

CHAPTER 4 & 5 DATA COLLECTION SHEETS

LOW 30% 1RM							Trial	Exercise
Participant		Height		Temperature			Arrive Time	Start Time
Date		Body Mass		Pressure/Humidity			End Time	End Time
	Baseline Rest	0 Post-Ex	5 Post-Ex	20 Post-Ex	35 Post-Ex	65 Post-Ex		Exercise Duration
Blood pH								
pCO2 (mmHg)								
pO2 (mmHg)								
Na+ (mM)								
K+ (mM)								
Ca++ (mM)								
Glucose (mM)								
Lactate (mM)								
Hct (%)								
RPE	1st Set: 2nd Set:							
HR (BPM)								
HCO3-								
Becf								
Hb (%)								

HIGH 60%: [INSULIN / NO-INSULIN]						Trial		Exercise				
Participant		Height		Temperature		Arrive Time		Start Time		BG Rise from Target =		
Date		Body Mass		Pressure/Humidity		End Time		End Time		CF: TDD/100 =	Insulin Units (CF x Target BG) =	
	Baseline Rest	**0 Post-Ex**	**0 Post-Treatment**	**15 Post-Treatment**	**30 Post-Treatment**	**45 Post-Treatment**	**60 Post-Treatment**	**90 Post-Treatment**	**105 Post-Treatment**	**120 Post-Treatment**		
Blood pH												
pCO2 (mmHg)												
pO2 (mmHg)												
Na+ (mM)												
K+ (mM)												
Ca++ (mM)												
Glucose (mM)												
Lactate (mM)												
Hct (%)												
RPE	**1st Set:** **2nd Set:**											
HR (BPM)												
Becf												
HCO3-												
Hb (%)												

APPENDIX K

ANTIOXIDANT SOLUTION

For Chapters 3 and 4, 100 uL of antioxidant solution was added to selected vacutainers, for the preservation of plasma adrenaline and noradrenaline.

Antioxidant Procedures

Into a beaker containing 15mL of deionised water, 1.22 g of L-glutathione reduced and 1.52 g of EGTA were added and left to mix on an unheated stirrer (FB70806 Fisherbrand unheated stirrer, Fisher Scientific, UK). Once partly dissolved, a pH meter (InoLab pH 720, WTW, GmbH, Germany) was placed within the beaker and either 0.2 to 1 mL of HCl or NaCl was added at a time until a pH of 7.0 was achieved. Once the solution was stable at 7.0, further deionised water was added to achieve a final solution volume of 20 mL. The solution was stored at 4 to 6 degrees Celsius for 6 weeks maximum.

APPENDIX L

CALCULATION OF CHANGES IN PLASMA VOLUME

Plasma volume shifts between pre- and post-exercise were calculated via the method of Dill and Costill (262):

Where, BV = blood volume, CV = cell volume, PV = plasma volume. $BV_{pre} = 100$

i. $BV_{pre} = BV_{post} \times (Hb_{post} / Hb_{post})$

ii. $CV_{pre} = BV_{pre} X (Hct_{pre})$

iii. $PV_{pre} = BV_{pre} - Cv_{pre}$

Calculations of % changes in BV, CV and PV.

i. $\Delta BV\% = 100 * (BV_{post} - BV_{pre}) / BV_{pre}$

ii. $\Delta CV\% = 100 * (CV_{post} - CV_{pre}) / CV_{pre}$

iii. $\Delta PV\% = 100 * (PV_{post} - PV_{pre}) / PV_{pre}$

Table: Percentage changes in plasma volume from pre- to post-exercise, across Chapters 4 and 5.

ΔPV%	**LOW**	**MOD / NO-INSULIN**	**INSULIN**
Mean	-8.9	-10.0	-9.4
SEM	3.3	2.9	1.5

No statistical difference between experimental sessions ($p>0.05$).

APPENDIX M

GEM 3000 ANALYSER: DETERMINATION OF BLOOD GLUCOSE, LACTATE AND ACID-BASE PARAMETERS

Principles Of Operation

Overview

A reagent cartridge forms the central component of the GEM 3000, which contains the analytical sensors, flow system, calibrators, process control modules, wash solution and waste receptacle. When the cartridge is installed in the instrument, the chamber resides in a thermal block that maintains a temperature of 37 ± 0.3 degrees Celsius and provides the electrical interface to chemically sensitive membrane sensors (Figure 2.5).

Calibration and Quality Control

Within the cartridge are two solutions, A and B, which enable calibration and internal process control checks. The A and B solutions provide low and high concentrations for all parameters determined by the GEM, except haematocrit, which calibrates only at a single level using the B solution. Prior to calibration, the "A" and "B" solutions are read as unknown solutions, and these values are recorded in the instrument's database. During calibration, these values are adjusted for any slope or drift that may occur over time.

The C solution is used for calibrating the pO2 electrode at a low oxygen level, conditioning the glucose and lactate sensors, removing micro clots, and cleaning the sample path.

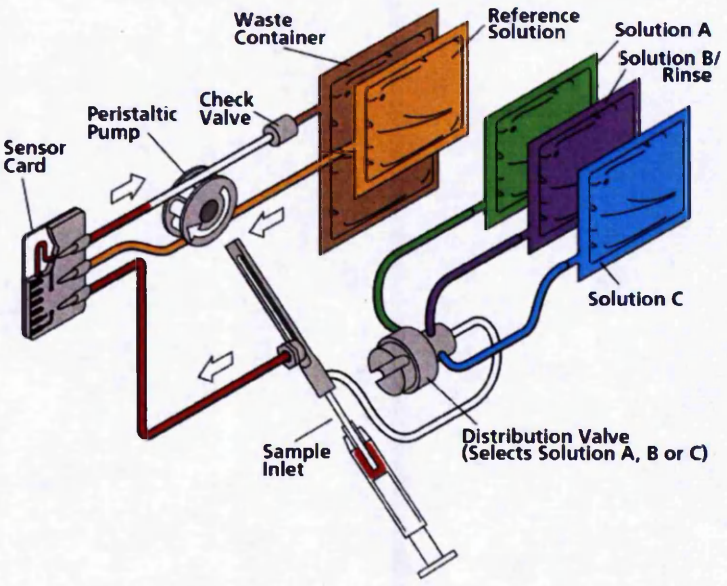


Figure 2.5: Illustration of GEM 3000 cartridge. The cartridge also includes a reference solution, distribution valve, pump tubing, sampler, and waste bag. Blood samples that have been analysed are prevented from flowing back out of the waste bag due to the presence of a one-way check valve in the waste line.

Operating procedure

Prior to blood sampling, the GEM disposable cartridge is first installed into the analyser (GEM iQM, Intelligent Quality Management). Then the device runs through an automated calibration, which precedes the insertion of GEM 3000 validation standards (GEM Calibration Validation Products, CVPs); three levels of blood-gas controls and 2 levels of hematocrit controls are required. The iQM programme automatically analyses a minimum of 2 levels of internal liquid quality controls (QC) every 4 hours and a third level every 24 hours; it evaluates QC data and notifies the operator when results exceed tolerance limits, it initiates corrective actions when tolerance limits are exceeded and disables the affected analyte(s) when self-correction is not achieved. It also continuously performs a series of function checks that monitor for system failure and adverse environmental conditions, including clots in the blood sample. The GEM requires 150uL of heparinised whole blood for analysis.

Determination Of Blood Analyte Levels

The reportable ranges for analytes measured across Chapters 3 to 5 are presented in Table 2.6.

Electrochemical Sensors

The electrochemical sensors used in the GEM Premier 3000 PAK disposable cartridge are all formed on a common plastic substrate. The reference electrode on the sensor card provides a highly stable reference potential for the system. The individual sensors, with the exception of hematocrit and reference, are formed from layers of polymer films that are bonded to the substrate. A metallic contact under each sensor is brought to the surface of the substrate to form the electrical interface with the instrument.

Blood pH and Potassium (K^+)

The pH and electrolyte sensors are all based on the principle of ion-selective electrodes; that is, an electrical potential can be established across a membrane which is selectively binds to a specific ion. This simplified form of the Nernst equation can describe the potential:

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

Where E is the measured electrode potential, E' is the standard potential for that membrane, S is the sensitivity (slope), and C is the ion activity or concentration of the desired analyte. E' and S can be determined by the sensor response to the calibration solutions, and the concentration of the analyte (C) can be calculated for the measured electrode potential (E). For pH, "log C" is replaced by "pH" and the equation solved accordingly. The pH and electrolyte sensors are polyvinyl chloride (PVC) based ion selective electrodes, consisting of an internal Ag/AgCL reference electrode and an internal salt layer. Their potentials are measured against the card reference electrode. Figure 2.6 demonstrates the flow of a solution through an ion-selective sensor. If pH cannot be measured, then PCO_2, HCO_3^-, base excess, are not reported.

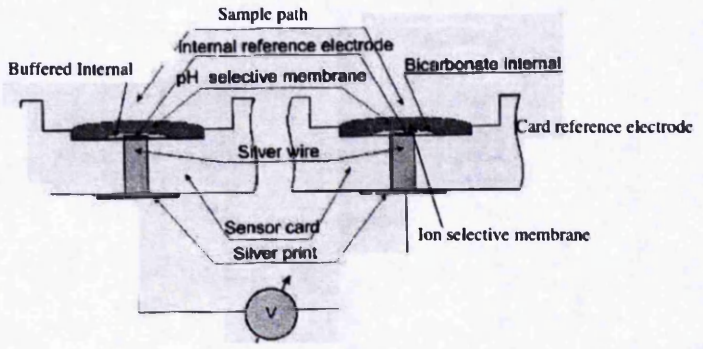


Figure 2.6: Cutaway view of ion, pH and pCO2 sensors, in the GEM 3000.

Carbon Dioxide (PCO_2 mmHg)

Measurement of PCO_2 is essential to the determination of base-excess (ecf). The PCO_2 sensor is a pH sensor electrode covered by a CO_2 gas permeable outer membrane (Figure 2.6). The sensor has an internal *Ag/AgCl* reference electrode and an internal bicarbonate buffer. The PCO_2 of the internal solution comes to equilibrium with the PCO_2 of the blood sample, when the blood is in contact with the outer surface membrane. The pH of the internal solution relates to the PCO_2 as a function of the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log\left(\frac{[HCO_3^-]}{0.03 \times pCO_2}\right)$$

where pKa is an equilibrium constant, HCO_3^- is the bicarbonate ion concentration, and "a" is the solubility coefficient of CO_2 in water. The generated potential versus the pH sensor is related to the logarithm of PCO_2 content in the sample.

Using these measurements, bicarbonate and base excess (ecf) were estimated in accordance with the manufacturer's instructions, which are based on NCCLS guidelines (263):

Actual bicarbonate (HCO_3^-) = pH + log pCO2 – 7.608

Base Excess (ecf) = $cHCO_3^-$ - 24.8 + 16.2(pH-7.40)

Glucose and Lactate

The glucose and lactate sensors are platinum amperometric electrodes poised at a positive potential with respect to the card reference electrode. Glucose or lactate are determined by enzymatic reaction with oxygen in the presence of glucose oxidase or lactate oxidase to produce hydrogen peroxide, which reacts at the platinum electrode. The current flow between the platinum electrode and the ground electrode is proportional to the rate at which hydrogen peroxide molecules diffuse to the platinum and are oxidised, which in turn is directly proportional to the metabolite (glucose or lactate) concentration:

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

where I is the electrode current, S is the sensitivity, and IZ is the zero current. The value of S and IZ can be calculated from the calibration data for the sensor. The equation can then be solved for the metabolite concentration, where I becomes the electrode current produced by the blood sample. Figure 2.7 shows the configuration of this sensor.

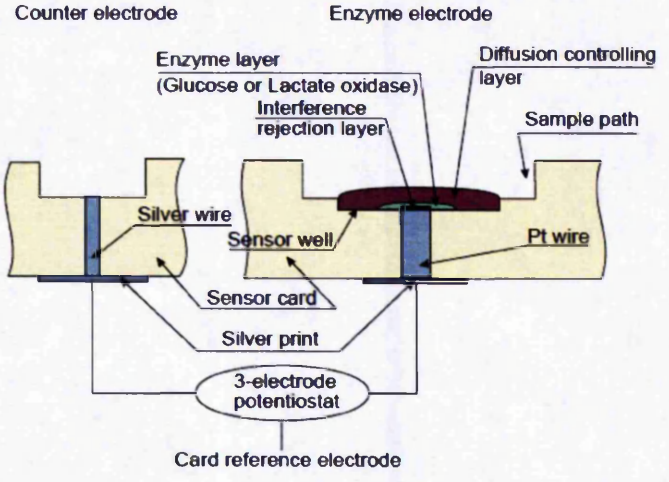
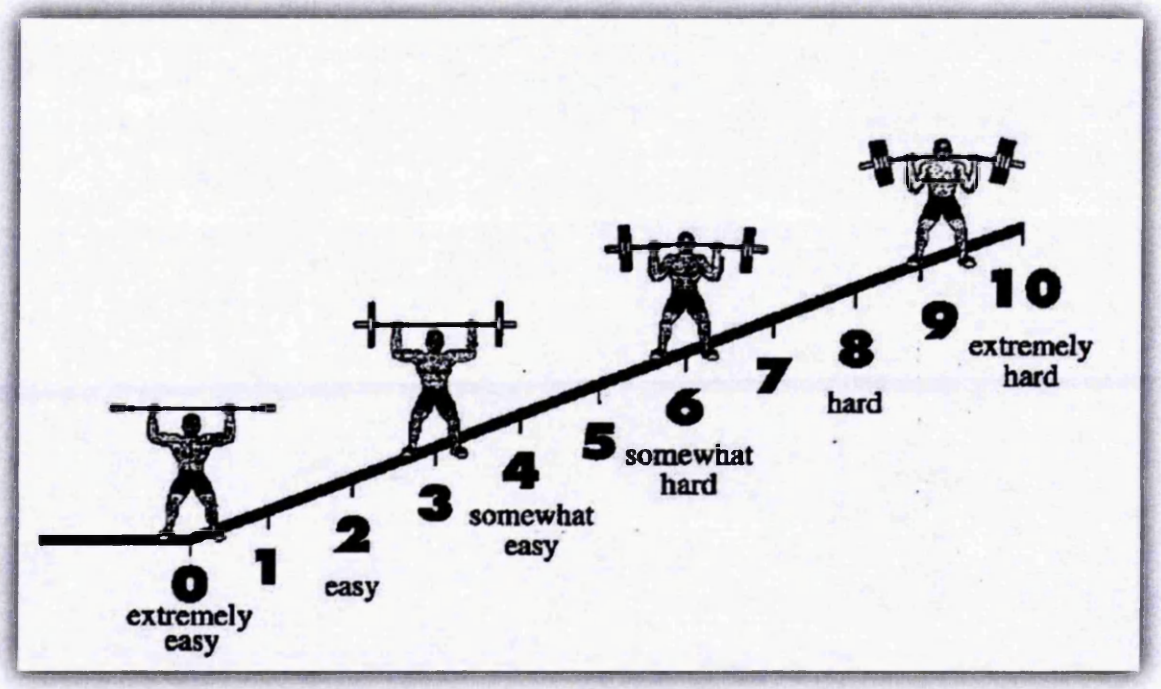


Figure 2.7: Blood glucose and lactate sensor within the GEM 3000. The sensor is constructed of a three- layer composite membrane consisting of an inner layer for screening out the interferences, the enzyme for oxidation reaction, and the outer layer for controlling the metabolite diffusion in the enzyme layer.

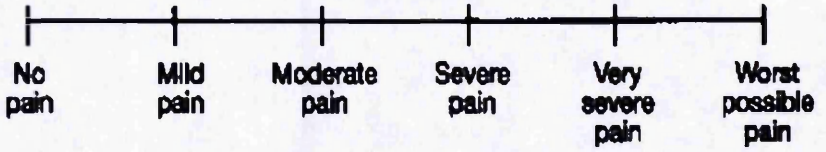
APPENDIX N
SUBJECTIVE DATA SHEETS

OMNI-RES SCALE

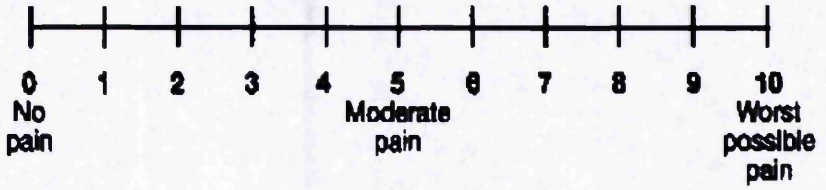


The definition of perceived exertion and scaling instructions are as follows: **Definition**: The perception of physical exertion is defined as the subjective intensity of effort, strain, discomfort, and/or fatigue that you feel during exercise. **Instructions**: We would like you to use these pictures to describe how your body feels during weightlifting exercise (show subject the OMNI-RES). You are going to perform resistance exercises using your upper and lower body. Please look at the person at the bottom of the scale who is performing a repetition using a light weight. If you feel like this person when you are lifting weights the exertion will be EXTREMELY EASY. In this case, you would respond with the number zero. Now look at the person at the top of the scale who is barely able to perform a repetition using a very heavy weight. If you feel like this person when you are lifting weights the exertion will be EXTREMELY HARD. In this case, you would respond with the number 10. If you feel somewhere in between Extremely Easy (0) and Extremely Hard (10), then give a number between 0 and 10. We will ask you to give a number that describes how your active muscles feel and then a number that describes how your whole body feels. Remember, there are no right or wrong numbers. Your number can change as you lift weights. Use both the pictures and the words to help select the numbers. Use any of the numbers to describe how you feel when lifting weights.

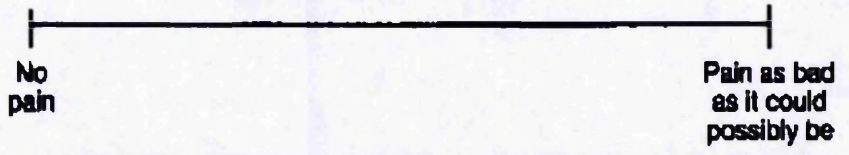
Simple Descriptive Pain Intensity Scale[1]



0–10 Numeric Pain Intensity Scale[1]



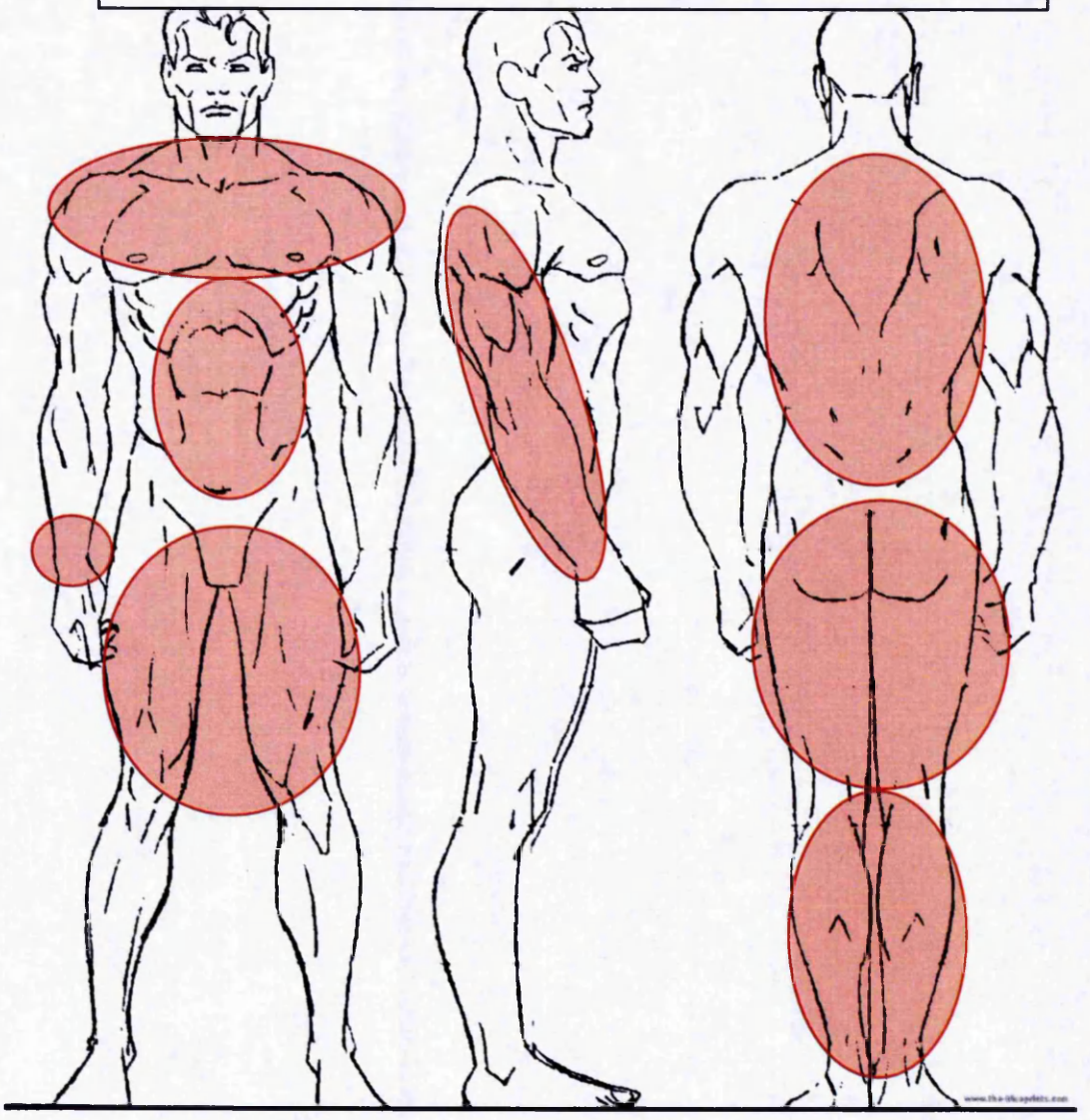
Visual Analog Scale (VAS)[2]



[1] If used as a graphic rating scale, a 10 cm baseline is recommended.
[2] A 10-cm baseline is recommended for VAS scales.

MUSCLE SORENESS INDICATOR

Name:	Trial:	Date:	Time:



+ 24 hour post-exercise test exercises to be scored;

1. Lateral abduction of both arms from hips to above head and return.
2. Squat movement
3. Bicep Curl

APPENDIX O

POST-LABORATORY BLOOD GLUCOSE, INSULIN DOSAGE AND DIETARY INTAKE LOG SHEETS (DIARY)

Participant: Basal/Bolus: Blood Glucose Site: [e.g. Fingertip]
Day: Date: Trial:

Time	Blood Glucose	Number of CHO Tabs	Additional Notes
+1h [TIME.....]		[TIME.....]	
1pm		[TIME.....]	
		[TIME.....]	
4pm		[TIME.....]	
		[TIME.....]	
7pm		[TIME.....]	
Pre-Sleep [TIME.....]		[TIME.....]	
	[TIME.....]	[TIME.....]	
Wake-up **(Fasted)**		[TIME.....]	

Meal Plan

	Time	Insulin Dose (Type; Units)
Breakfast	End of Trial: [Time.....]	[Time.....]
[Additional Food]		[Time.....]
Lunch	1pm +/- 1h [Time.....]	[Time.....]
[Additional Food]		[Time.....]
Dinner	~7pm [Time.....]	[Time.....]
[Additional Food]		[Time.....]
Supper?	[Time.....]	[Time.....]
[Additional Food]		[Time.....]

Notes...

Participant: Insulin Administration Site: Blood Glucose Site:
Day: Date: Trial:

Time	Blood Glucose (Before Meal)	Insulin (Type, Units)	CHO Tabs (Quantity, Time)	Food Consumed (including set meal plan and additional foods) / Additional Notes
Breakfast Time:				
Additional Food/Snack Time:	[redacted]			
Lunch Time:				
Additional Food/Snack Time:	[redacted]			
Dinner Time:				
Supper (Optional Food) Time: (Pre-sleep B'Glucose)				
Wake-up (Fasted B'Glucose) Time:				

> Dan's Mobile: [redacted], E-mail: [redacted]

> **Accelerometer** to be worn **at all times** until the following morning. **Not to be worn when showering.**

> No need to record dietary constituents of meal plan, but **please record constituents of any additional foods consumed**.

APPENDIX P

PUBLICATIONS ARISING FROM THIS THESIS

(Compact Disc)