Feasibility of integrating faster-acting insulin aspart with dose adjustments as part of multiple daily insulin regimen around physical exercise in adults with type 1 diabetes

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Declaration

I declare that the thesis is the result of my own investigations, except where otherwise stated and that other sources are acknowledged by footnotes giving explicit references and that a bibliography is appended. I have taken reasonable care to ensure that the work is original and does not, to the best of my knowledge, break any UK law or infringe any third party's copyright or other Intellectual Property Right.

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Abstract

The increased metabolic demands of physical exercise place significant stress on blood glucose homeostasis in the effort to supply working muscles with energy substrate. In people with type 1 diabetes (T1D), this adds to the already challenging task of daily glucose control and requires additional management strategies to avoid dysglycaemia. Adjusting doses of insulin taken with the meal before exercise is recognised as a key strategy for preserving blood glucose concentrations and avoiding hypoglycaemia. However, the landscape for insulin therapy is in constant motion. Faster-acting insulin aspart (Fiasp) represents the latest generation of mealtime insulins, which have been developed with earlier onsets of appearance, exposure, and peaks than previous insulins. It is therefore of interest to i) evaluate from the available literature how reducing the dose of (previous generation) mealtime insulins prior to exercise affects glycaemia during exercise and ii) to investigate the application of these dose reductions when using Fiasp.

There is limited information on the use of Fiasp around exercise. Current studies have not yet investigated the feasibility of administering Fiasp with different dose adjustments as part of multiple daily insulin (MDI) regimen to preserve glucose around exercise. Hence, the overarching aim of this thesis was to identify the glycaemic effects of pre-exercise bolus insulin dose reductions, with application in using Fiasp as part of an MDI regimen in real-world and clinical trial settings in recreationally active individuals and trained athletes with T1D.

Three studies were performed (across Chapters 3, 4, and 5 in this thesis) to address this aim. Chapter 3 was a systematic review and meta-analysis of studies in which the protocol made at least one comparison in the rate of change of blood glucose decline during exercise between a full dose and reduced dose of pre-exercise mealtime insulin. The meta-analysis revealed the rate of change of blood glucose during exercise was greater when using a full insulin dose compared to a reduced dose (standardised mean difference = 0.59, CI 95%: 0.17, 1.01; p=0.006). Chapter 4 was an observational exploratory analysis of interstitial glycaemia in professional road cyclists with T1D who performed prolonged endurance training rides using Fiasp and insulin aspart, in addition to a race event using Fiasp only. Time in euglycaemia was similar in the use of Fiasp or insulin aspart (75.8 ± 32.7% *vs.* 76.6 ± 29.6%; p=0.915), alongside all other glucose metrics (all p>0.05). When reducing daily bolus insulin dosing, riders were able to maintain near-target time in range during an international competitive event (68.1 ± 9.6%). Chapter 5 was a prospective, two-site, double-blind, randomised, four-arm crossover,

clinical trial to compare the effects of Fiasp and insulin aspart across different dose reductions around exercise. There were no differences between the decline of blood glucose during exercise when taking a 50% reduction in Fiasp (-4.0 ± 2.8 mmol.L^{-1}) prior to exercise compared to a 75% reduction in Fiasp (-2.8 ± 3.3 mmol.L^{-1}), a 75% reduction in insulin aspart (-3.4 ± 3.3 mmol.L^{-1}), or a 50% reduction in insulin aspart (-5.1 ± 3.0 mmol.L^{-1}). There was, however, a greater decline in blood glucose when taking the 50% reduction in insulin aspart compared to 75% in either insulin.

Collectively, this thesis advances the current understanding of i) how pre-exercise dose reductions can influence exercise glycaemia and ii) how Fiasp can be used in people with T1D on MDI regimens when employing dose reduction strategies around exercise. In both acute and prolonged exercise, Fiasp exerts similar glucose-lowering effects to insulin aspart; hence, these data indicate that clinicians or the individual with T1D looking to switch between these insulins can do so without significant impact on exercise-related glycaemia.

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II. List of abbreviations

A50	Chapter 5 trial arm in which insulin aspart doses were reduced by 50%
A75	Chapter 5 trial arm in which insulin aspart doses were reduced by 75%
AID	Automated insulin delivery system
ANOVA	Analysis of variance
AUC	Area under the curve
ATP	Adenosine triphosphate
BG	Blood glucose
BMI	Body mass index
CGM	Continuous glucose monitor
COVID-19	Coronavirus disease (2019)
CPET	Cardiopulmonary exercise test
CSII	Continuous subcutaneous insulin infusion
CVD	Cardiovascular disease
ECG	Electrocardiogram
F50	Chapter 5 trial arm in which Fiasp doses were reduced by 50%
F75	Chapter 5 trial arm in which Fiasp doses were reduced by 75%
Fiasp	Faster-acting insulin aspart
GLUT-4	Glucose transporter 4
HbA_{1c}	Glycated haemoglobin
HLA	Human leukocyte antigen
INS	Insulin (Chapter 5)
IAsp	Insulin aspart (group, Chapter 4)
IPAQ	International Physical Activity Questionnaire
L1Hyper	Level 1 Hyperglycaemia
L2Hyper	Level 2 Hyperglycaemia
L1Hypo	Level 1 Hypoglycaemia
L2Hypo	Level 2 Hypoglycaemia
MDI	Multiple daily insulin (regimen)
O_2	Oxygen

OGTT	Oral glucose tolerance test
PD/PK	Pharmacodynamic/pharmacokinetic
PICO	Population, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
R0	Relative to timepoint 0 min (Chapter 5)
R240	Relative to timepoint 240 min (Chapter 5)
REML	Restricted maximum likelihood
RPE	Rating of perceived exertion
UI	Unit of insulin
T1D	Type 1 diabetes
VO_{2peak}	Peak volume of oxygen uptake

III. List of figures

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IV. Acknowledgements

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Chapter 1

Introduction and Literature Review

Introduction

1.1 Brief Introduction

Type 1 diabetes mellitus (T1D) is an autoimmune disease characterised by the destruction of pancreatic β-cells and subsequent loss of endogenous insulin production. The capacity to secrete insulin decreases as the disease progresses concurrently with the body's gluco-regulatory capacity. Irreversible damage to the pancreas leads to the requirement of exogenous insulin administration for life. Management of the condition extends to adjusting carbohydrate consumption, individualised exogenous insulin therapy, and vigilant monitoring of blood glucose concentrations to maintain time in range (3.9-10.0 $mmol.L^{-1}$)[1] or time in tight range (3.9-7.8 $mmol.L^{-1}$) [2]. Careful management can help avoid long-term macro- and micro-complications of hyperglycaemia (e.g., diabetic retinopathy, nephropathy, and neuropathy [3]) as well as the acute symptoms of hypoglycaemia (e.g., sweating, palpitations, and seizures[4]).

Regular exercise has been advocated for people with T1D by multiple national health organisations and charities to improve insulin sensitivity and help minimise long-term complications (Section 1.9). However, the stress of exercise brings about a challenge in blood glucose regulation for people with T1D. Depending on the characteristics of exercise, blood glucose can rise or fall to a far greater extent than in individuals without T1D.

Considerable research has aimed to develop strategies that can mitigate the risk of exercise-induced dysglycaemia so that people with T1D can reap the health benefits of a physically active lifestyle. Given the synergistic and independent effect of physical exercise in increasing tissue glucose uptake, the most advocated strategies involve adjustments to insulin dosing and carbohydrate consumption that take place around exercise. However, with the advances of recombinant DNA technology to facilitate the development of exogenous insulins with differing properties, the goal for optimal glucose management around exercise becomes a moving target. Research investigating the safety and efficacy of insulin-based strategies to manage glucose around exercise must consider the pharmacodynamic properties of specific insulins to provide up-to-date information to the >400,000 people living in the UK with T1D.

We have now passed the 100th anniversary of the discovery of insulin, with mealtime insulin analogues developed to be even faster, basal insulins even more prolonged, and integrated technological devices contributing to tighter glucose management. Building upon the previous

generation of mealtime insulins, Faster-acting insulin aspart (Fiasp) is an ultra-rapid-acting insulin most recently made available for prescription in the UK. With a faster onset of action than its predecessor insulin aspart, Fiasp can quickly enter the bloodstream and provide added flexibility to previously regimented dosing schedules at mealtimes.

Notwithstanding, information is currently limited on how Fiasp, as part of the latest generation of ultra-rapid-acting insulins, can be safely integrated into a glycaemic management strategy around acute physical exercise; hence, studies that define potential insulin adjustments around exercise that include Fiasp are required. Current guideline recommendations relating to insulin reductions are based on a small number of studies which have demonstrated success in reducing insulin prior to aerobic exercise in preserving blood glucose concentrations [5,6]. Given the relative novelty of ultra-rapid-acting insulins, these guidelines do not yet include information pertaining to different generations of mealtime insulin.

Studies that have previously investigated the role of insulin reductions in glycaemia around exercise represent isolated cases with relatively small sample sizes. Further still, emphasis is placed on the pre-exercise elevations in blood glucose concentrations as providing a buffer to hypoglycaemia - a cited barrier to regular participation in physical activity by those with T1D [7]. With an effective left-shift in the action profile of Fiasp compared to previous generations, it is plausible that the blood glucose concentrations will be affected not only prior to exercise but also during exercise when being performed in the post-prandial period. It is therefore warranted that further information to assist people with T1D in administering injection around exercise be provided on two fronts: i) characterise the effects of insulin dose reductions on blood glucose concentrations during exercise and ii) to investigate the application of these dose reductions when using Fiasp.

Therefore, the aim of this thesis is to identify the glycaemic effects of pre-exercise bolus insulin dose reductions, with application in using Fiasp as part of a multiple daily injection regimen in real-world and clinical trial settings in recreationally active individuals and trained athletes with T1D.

Literature Review

1.2. Epidemiology of T1D

Recent estimates of the global prevalence of T1D range from 8.4-13.0 million, with incidence rates estimated between 0.2-0.5 million per year since 2017 [8–10]. Prevalence is highly heterogeneous between countries (e.g., 4.6 cases per 1000 prevalence in Finland <20 year olds contrasting with 0.17 per 1000 in China) and regions (higher in North America and Europe than in Africa and Asia) [11]. Reasons for such significant heterogeneity are unknown, but proposed reasons include inherent environmental factors with geographical differences (e.g., vitamin D deficiency distant from equatorial regions [12]) and underreporting or poor access to healthcare in less economically developed countries [9,10]. There were an estimated ~404,000 people living with T1D in the UK in 2021 [9].

T1D, previously referred to as juvenile-onset diabetes, is diagnosed more frequently in the late childhood and early adolescent years than any other years (**Figure 1**). Diagnosis can, however, occur throughout the lifespan into older adulthood, yet only one third of diagnoses occur in those aged >30 years old [13].

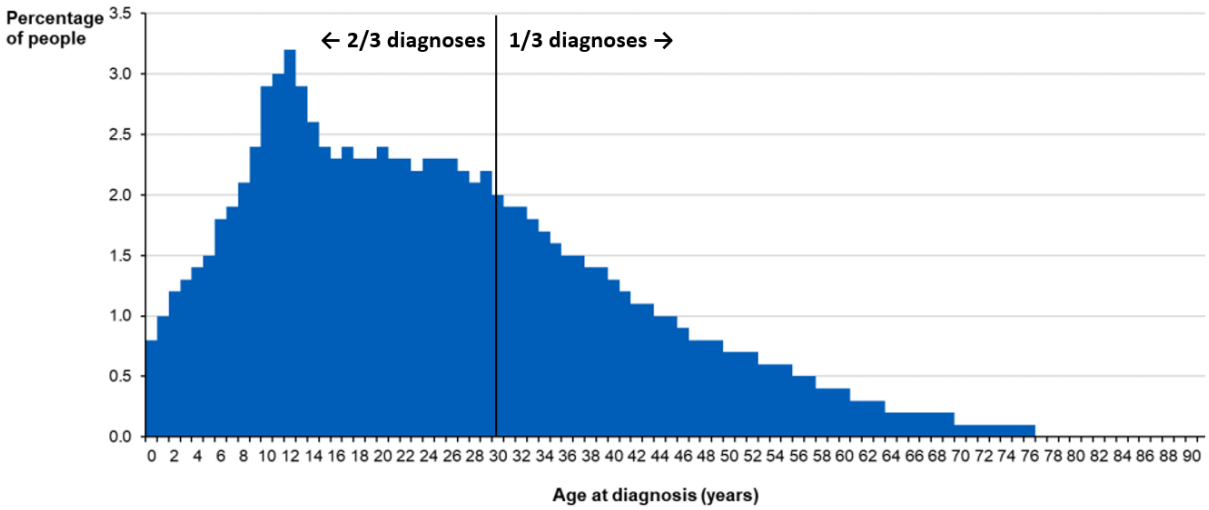


***Figure 1**: Proportion of people diagnosed with T1D by age at diagnosis in England and Wales (adapted from NHS Audit, 2021 [13]).*

1.3 Aetiology

1.3.1 Genetic factors

The precise cause or set of predisposing factors towards the development of T1D is not yet known. By virtue of the inaccessible anatomical location of the pancreas, direct investigative research and routine medical examination of the organ is challenging, limiting functional studies to blood-derived or cadaveric samples. However, susceptibility to T1D has been evidenced to have a strong genetic component by disease concordance in families and monozygotic pairs. Concordance rates for T1D in monozygotic twins have been reported at 50-70%, far greater than that of dizygous twins and non-twin siblings [14,15].

Over 60 genetic loci have been identified as being associated with an increased T1D susceptibility [16]. Of these, variations in the human leukocyte antigen (HLA) region confer the greatest risk of developing T1D [17]. The HLA region on chromosome 6(p21) codes for cell-surface proteins used in the body's differentiation between self and non-self, playing a vital role in the immune system's recognition of foreign threats. Loci that contribute significantly to disease risk, secondary to the risk carried by certain HLA haplotypes, are thought to influence insulin recognition in the thymus [18] and immune cell signalling [17]. Taken together, T1D is a polygenic condition with genotypes relating to abnormal immune system signalling, which predisposes the individual to the disease.

1.3.2 Environmental factors

Variations in disease development in the presence of genetic susceptibility - alongside the rapidly increasing incidence of T1D and a tapering of concordance rates of monozygotic twins with older age-of-onsets - implicate a significant role of non-genetic factors in the development of T1D [19]. Comprehensive assessment of environmental input in the disease progression is limited by the longitudinal requirement that comes with tracking individuals at risk of T1D in terms of participant identification and retention. Nevertheless, multiple environmental factors have been linked with T1D development, with varying significance in their impact, via epidemiological association studies [20], large-cohort prospective longitudinal studies [21–23], and observational studies using pancreas biopsies [24].

Environmental factors can exist as harmful factors that initiate or accelerate T1D pathogenesis, or protective factors that may reduce risk or slow disease progression [25]. Among those factors with the highest likelihood of harmful casual association are having an increased body mass at

birth (and early childhood) and viral infection [25,26]. While precise mechanisms are not yet known, increased weight may induce β-cell stress and chronic inflammation which augments the rate of β-cell function loss, as described in the 'accelerator hypothesis' [27]. Viral infection has, in part, been evidenced by detection of enterovirus infection in stool [28] and pancreas samples [24,29] of those at risk of, and those already diagnosed with, T1D. Putative mechanisms for the pathogenic relation to viral infection include: i) direct β-cell infection (and subsequent cytolysis); ii) molecular mimicry (whereby viral peptides are similar to islet peptides, leading to an overlapping immune response) and/or; iii) bystander recruitment (of further immune response to local inflammation) [30].

Taken together both environmental factors and genetic susceptibility contribute to T1D. Nevertheless, the contribution from any one of the identified haplotypes or environmental triggers remains modest, leaving gaps in our understanding on the extent to which nature *vs.* nurture must interplay to generate the conditions required to initiate pathogenesis [31].

1.4 Pathology of T1D

1.4.1 The healthy pancreas

The pancreas is an elongated 'comma-shaped' glandular organ lying transversely in the upper abdomen. Its 'head' sits within the C-shape of the duodenum and its 'body' lies posterior to the stomach [32]. The pancreas has both exocrine and endocrine functions. The exocrine tissue makes up >98% of the pancreas volume and is tasked with secreting digestive enzymes into the duodenum of digestive tract [33]. The endocrine component consists of islets of Langerhans dotted throughout the exocrine mass, which may only total 2 cm^3 in pancreatic volume [34,35]. Each islet is made up of >1000 cells, and is comprised of the following hormone secretory cells: ~60% insulin-secreting β-cells, ~30% glucagon-secreting α-cells, <10% somatostatin-secreting δ-cells, <5% pancreatic polypeptide-secreting γ-cells, and <1% ghrelin-secreting ε-cells [35]. By means of its capacity for insulin and glucagon secretion, the pancreas plays a leading role in blood glucose homeostasis. The islet cellular layout is highly heterogeneous between individuals and even within the same pancreas, but typically follows a pattern where α cells are predominant in an outside layer closest to the islet membrane and vasculature, while β-cells and other secretory cells predominate the central areas [36]. The islet structure allows for multiple routes of intercellular communication, namely neural, paracrine chemical, and cell-to-cell contact – mechanisms which become disrupted in T1D and other disease states [37].

1.4.2 Pancreatic pathogenesis in T1D

Evidence of an immune system insult on pancreatic β-cells at the time of diagnosis represents a hallmark feature of T1D and contributes to its classification as an autoimmune condition. Initial evidence of T1D pathogenesis, however, can long precede overt clinical presentation of the disease. Autoantibodies of insulin (IAA), glutamic acid decarboxylase enzymes (GADA), tyrosine phosphatase 2 protein (IA-2), zinc transporter 8 (ZnT8), and other molecules (as antigens of pancreatic β-cells) appear in circulation with high incidence during early infancy; thus, they can be present many years prior to symptomatic onset [38,39]. While positivity of a single autoantibody is largely unassociated with T1D development, the presence of two or more of these autoantibodies carries an 84% risk of T1D onset before adulthood [40]. Despite the mechanistic connection between autoantibodies and T1D pathogenesis remaining unclear, and the significant heterogeneity in the development of T1D between individuals, the presence of (two or more) of these antibodies can serve as a meaningful predictor of T1D incidence for at-risk individuals and is used as a screening tool for presymptomatic T1D [41].

Islet autoantibody formation is a defining feature of the first of the three stages (**Figure 2**) of 'presymptomatic' T1D, set out in a recent consensus statement [42]. Individuals in this stage present two or more T1D-associated autoantibodies but otherwise have normal blood glucose concentrations. The second stage is described as individuals who have developed dysglycaemia due to a loss of pancreatic β-cell mass and insulin-producing function. Dysfunction of the immune system[43] and vulnerability of the T1D β-cells[44] is apparent at multiple levels, cumulating in the immune system destruction of the body's own pancreatic β-cells.

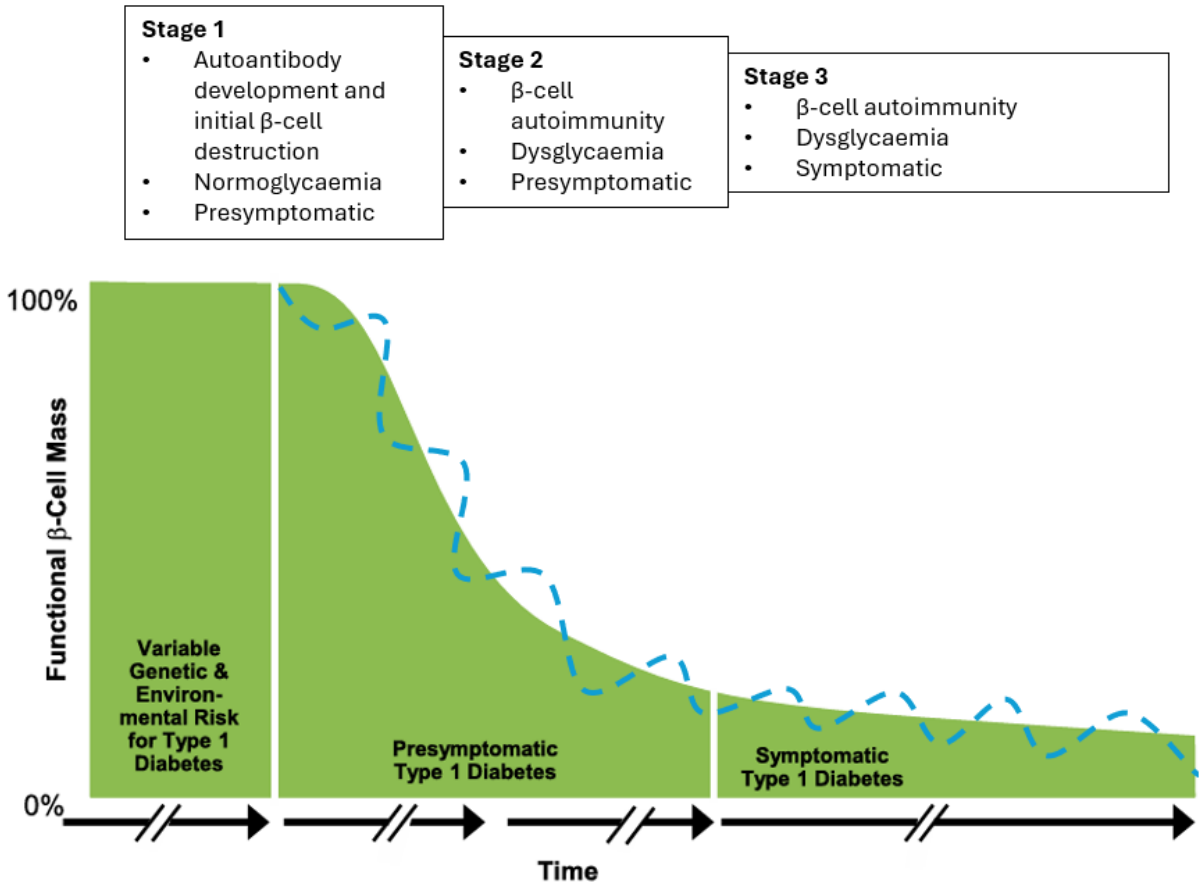


***Figure 2**: Three stages of early T1D. Dotted blue line represents heterogeneity in β-cell mass decline and scope for non-linearity. Adapted from Insel et al*[42] *and Pugliese* [45].

Early in the autoimmune process, suboptimal presentation of the pancreatic antigens to the immune system's T cells occurs in the thymus, leading to pancreatic islet-reactive T cells escaping negative selection [43]. In the periphery, antigen-presenting cells present islet autoantigens to T cells, erroneously activating T cells in a process which should otherwise be downregulated [46]. A complex array of coordinated immune cells, including islet-reactive T cells, migrate towards and surround the β-cell-containing pancreatic islets and begin the process of islet inflammation (insulitis). Immune cells, most prolifically CD8+ T cells, progressively infiltrate the islet and destroy the β-cells, causing a loss of functional β-cell mass during mild insulitis through to severe insulitis [47]. The loss of β-cell mass and resultant dysglycaemia prior to symptoms of T1D represent Stage 2. The autoimmune attack process is potentially exacerbated by β-cell hyperexpression of HLA molecules, facilitating presentation of autoantigens to the activated T cells [48]. Akin to the autoantibody development and

aetiological factors of T1D, precise mechanisms of the disease pathophysiology are not fully understood but are comprehensively reviewed elsewhere [43,49,50].

Despite the loss of functional β-cell mass and initial dysglycaemia, symptomatic onset of T1D does not occur until relatively late in the autoimmune process at a point where a critical β-cell mass has been destroyed [51]. The third stage describes individuals who present dysglycaemia *and* symptoms of T1D. While some individuals may reach the point of complete loss of β-cell mass, others with long-standing T1D may retain a small amount of functional β-cell mass, represented by consistent (and adaptable) blood C-peptide concentrations. Those with higher residual β-cell mass may also benefit from improved auto-regulatory management of the condition in terms of glucose control [52,53].

1.5 Diagnosis of T1D

At the time of diagnosis, people with T1D most often present with signs and symptoms of polyuria (increased urination), polydipsia (increased thirst), polyphagia (increased appetite), and weight loss. As these symptoms are all conditions of high blood glucose (and low cellular glucose), it is unsurprising that the diagnosis criteria for T1D revolves around quantifying blood glucose concentrations. Current ADA guideline[54] criteria for the diagnosis of diabetes are any of the following:

- Fasting (no calorie intake for 8 hours) plasma glucose of ≥7.0 $mmol.L^{-1}$ (126 $mg.dL^{-1}$).
- 2-h plasma glucose of ≥11.1 $mmol.L^{-1}$ (200 $mg.dL^{-1}$) during oral glucose tolerance test (OGTT). OGTT represents the consumption of 75 g glucose dissolved in water.
- Glycated haemoglobin (HbA_{1c}) of ≥6.5% (48 $mmol.mol^{-1}$).
- Random plasma glucose of ≥11.1 $mmol.L^{-1}$ (200 $mg.dL^{-1}$).

These criteria, however, overlap with diagnosis criteria of other diabetes types; hence, diagnosis of any type of diabetes is done in the context of disease characteristics and presentation. T1D is predominantly associated with an age of diagnosis younger than 35 years, a rapid onset of disease presentation, and ketosis at diagnosis [55–57]. Nevertheless, even with differential clinical features, misclassification of type 2 diabetes instead of T1D may still occur in over 40% of adults over the age of 30 years [57].

1.6 Insulin regulates blood glucose homeostasis

1.6.1 Whole-body blood glucose homeostasis

Concentrations of glucose in the blood are tightly regulated in the person without diabetes. Insulin is the paramount endocrine hormone responsible for lowering blood glucose concentrations. Primary tissues for insulin-related glucose disposal are skeletal muscle, adipose tissue, and the liver (glucose uptake in the brain occurs independently of insulin concentrations) [58]. Conversely, multiple (counterregulatory) endocrine hormones play a role in increasing blood glucose concentrations, namely glucagon, adrenaline, and cortisol [59]. At any given time, the glucose concentrations are a product of a balance of the rate of glucose input into the blood and the rate of glucose removal from the blood, which, in turn, is heavily dependent on the balance of insulin against the counterregulatory hormones. In the fasted state, pancreatic secretion of insulin is low. This allows greater glucagon secretion, greater glucose output from the liver via glycogenolysis and gluconeogenesis, and greater free fatty acid release from adipose tissue. Concurrently, there is lower glucose removal from the blood into tissues via insulin-dependent mechanisms. In the fed state, insulin is secreted from the pancreas in proportion to the increase in blood glucose concentrations from gastrointestinal absorption, so blood insulin concentrations rise. Liver glucose production is subsequently inhibited, and glucose is instead stored as glycogen. Lipolysis in adipose tissue is also inhibited and more glucose is removed from the blood via insulin-related mechanisms, lowering blood glucose concentrations (**Figure 3**).

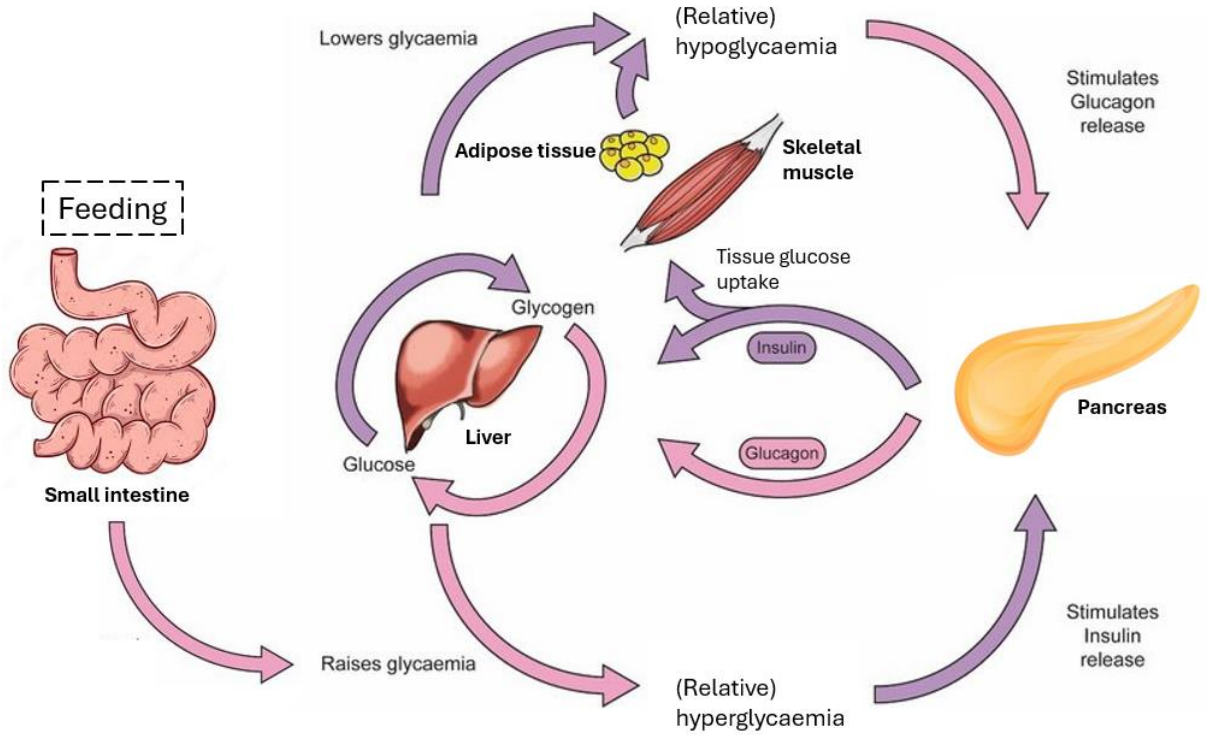


Figure 3*: The roles of insulin and glucagon in blood glucose homeostasis. Arrows in pink emphasise the contribution of glucagon in gluconeogenesis and glycogenolysis. Arrows in purple emphasise the contribution of insulin in glycogenesis and insulin-mediated glucose uptake. Organs are highlighted in bold. Adapted from Pasquier (2019)*[60].

1.6.2 The action of insulin

A number of mechanisms can stimulate insulin secretion from pancreatic β-cells (for full review, see Campbell et al. [61]). At mealtimes, insulin secretion is initiated early in the ingestion process, where the taste of food prompts a neuronally-mediated initial release of insulin, 'preparing' the body for digestion [62]. Processing and breakdown of food through the digestive system releases the hormone glucagon-like peptide 1, which can act via neural and endocrine-hormonal pathways to stimulate insulin secretion (and inhibit glucagon) [63]. Carbohydrates broken down during digestion circulate as glucose which can enter β-cells and, subsequent to metabolism in the mitochondria, activates the exocytosis of insulin granules [64]. Lipids and amino acids can also act as insulin secretagogues; however, glucose-related secretion is the dominant stimulus [65].

Upon secretion, insulin is released into local vasculature which feeds into the portal vein, through which insulin is transported firstly to the liver. Insulin is filtered through the liver, where it can bind to insulin receptors on hepatocytes. When binding, insulin is effectively

removed from circulation as it is either internalised into the cell and broken down, or degraded while bound to the receptor on the cell's surface [66]. Up to 80% of insulin has been calculated to be extracted by the liver in humans during the first pass of the liver, rendering the liver as the 'gatekeeper' for insulin secretion to the periphery [67]. Conversely, the liver is the first major site at which endogenous insulin exhibits its metabolic functions, suppressing gluconeogenesis and glycogenolysis.

Insulin not cleared by the liver is circulated and delivered to key sites of glucose uptake in the periphery, namely the adipose and skeletal muscle tissue. In a process that increases local tissue glucose uptake, insulin acts as a moderate vasodilator when binding with vascular endothelial cells, increasing blood flow to these target tissues [68]. The endothelium itself, however, presents a barrier to insulin movement into the target tissue interstitial space; it is still debated as to whether insulin is able to diffuse freely through this barrier or enters via transcytosis-related mechanisms [69]. Upon entering the interstitium, insulin can bind with insulin receptors present on both adipose and skeletal muscle cell membranes and exert its functions. Binding of insulin to the insulin receptor, in terms of glucose transport, initiates a cascade of intracellular pathways. This pathway culminates in reaching vesicles storing glucose transporter-4 (GLUT-4). Insulin stimulates GLUT-4 vesicles to translocate to and bind with the plasma membrane, enabling glucose uptake across the otherwise impermissible membrane via GLUT-4 [70].

Insulin plays a critical role in glucose homeostasis, among multiple other functions. Indeed, prior to insulin's discovery and first administration in 1921 by Banting, Best and team, prognosis for people with T1D was poor. While the healthy pancreas can quickly respond to glycaemic challenges, such as a carbohydrate-rich meal, those with T1D must rely upon appropriate glucose management strategies to avoid large swings in glycaemia and the acute and chronic complications that accompany them.

1.7 Hyperglycaemia

High blood glucose concentrations are a primary indicator of diabetes. Although polydipsia and polyuria remain classic symptoms of acute hyperglycaemia, there are many symptoms associated with high blood glucose including agitation, dizziness, light-headedness, and headaches [71]. Severe hyperglycaemia and ketoacidosis can, however, be fatal, while milder versions represent common presenting symptoms in T1D [72,73]. Beyond these adverse acute

effects, chronic hyperglycaemia leads to long-term health complications. Seminal clinical trials including the Diabetes Control and Complications Trial (patients with T1D) and UK Prospective Diabetes Study (UKPDS; patients with type 2 diabetes) convincingly demonstrated that glycaemic control, via intensive insulin treatment, delays the onset and slows the progression of these complications [3,74]. More recently, the impact of poor glycaemic control and several other health markers, have been integrated in a risk engine to accurately predict risk of cardiovascular disease (CVD) in people with T1D [75].

Long-term complications in diabetes are generally split into macrovascular and microvascular complications. Macrovascular complications result from arterial dysfunction and accelerated atherosclerotic process, increasing the risk of cardiovascular diseases such as ischemic heart disease and cerebrovascular disease [76]. Microvascular complications include retinopathy, neuropathy, and nephropathy, which stem from damage in smaller vessels [76]. The pathways that lead to these complications are complex and occur through multiple pathways, many of which overlap and interact. Two processes that have been consistently linked with complication development are the increased production of reactive oxygen species (ROS) and increased formation of advanced glycation-end products (AGEs) [77–79]. Although both ROS and AGE formation occur naturally throughout the lifespan, augmentation of both during chronic hyperglycaemia directly and indirectly lead to cellular dysfunction and the degeneration of cellular structures which are critical in initiating vascular-related complications [77–80].

Long-term hyperglycaemia is associated with substantial increases in morbidity and mortality [81]. Although intensive insulin therapy can delay diabetes complications, reductions in average daily glucose increase the risk of hypoglycaemia which has severe, and potentially fatal, short-term consequences.

1.8 Hypoglycaemia

Iatrogenic hypoglycaemia occurs at the point where relative hyperinsulinaemia (from excess exogenous insulin supply) causes blood glucose concentrations to fall below the euglycaemic range. Current guidelines advocate <3.9 mmol.L^{-1} be used as threshold for (Level 1) hypoglycaemia [1]. Symptoms of hypoglycaemia, however, do not typically tend to start until lower glucose concentrations have been reached (e.g., 3.5-3.0 mmol.L^{-1}), although people with T1D may be able to detect a rapid decline in blood glucose prior to reaching thresholds of hypoglycaemia [82]. At concentrations of ~3.1 mmol.L^{-1}, common symptoms of hypoglycaemia

manifest as sweating, hunger, with more severe symptoms occurring with declining glucose concentrations, such as cognitive dysfunction, seizures, and loss of consciousness [4]. Notably, some of the common symptoms of hypoglycaemia overlap with common symptoms of exercise, making identification of a 'hypo' during exercise even more challenging. Nevertheless, hypoglycaemia is recognised as being unavoidable over the lifespan of T1D, with consensus guidelines advocating <4% be spent with blood glucose as <3.9 mmol.L^{-1}, which still equates to approximately <1 hour of time in this range per day [1].

There is a hierarchical physiological defence to hypoglycaemia [83–85]: 1) At 4.5 mmol.L^{-1}, endogenous insulin secretion is attenuated; 2) Glucagon secretion is stimulated at 3.6-3.9 mmol.L^{-1}; 3) failing a response from glucagon, sympathoadrenal release of adrenaline and noradrenaline is initiated; 4) at ~3.1 mmol.L^{-1}, autonomic symptoms of hypoglycaemia prompt behavioural actions (food consumption). In people with T1D, the hierarchical response to hypoglycaemia is compromised. Exogenous circulating insulin concentrations cannot be altered, bypassing the first line of defence. Further, β-cell failure is associated with α-cell dysfunction in the T1D pancreas, such that glucagon response occurs at a lower glycaemic threshold in T1D than in those without [86]. The sympathoadrenal response to low blood glucose is also attenuated and occurs at lower glycaemic thresholds; hence, each stage of defence to hypoglycaemia is marred [83]. Compounding the compromised physiological response to hypoglycaemia is the attenuated symptomatic response that occurs with repeated hypoglycaemia, labelled hypoglycaemia unawareness, which can itself increase the risk of iatrogenic hypoglycaemia and thus creates a vicious cycle [87].

There are severe consequences of dysglycaemia in people with T1D. Chronic hyperglycaemia is associated with long-term morbidity and mortality, while acute hypoglycaemia is associated with rapid onset of symptoms and risk of requiring third-party assistance. There is, therefore, the need to maintain blood glucose within the tight euglycaemic ranges.

1.8 Managing T1D: Exogenous Insulin

1.8.1 Route of insulin delivery

In T1D, endogenous insulin secretion is minimal as a consequence of the autoimmune response, thus imposing the requirement that insulin be provided exogenously for life to sustain gluco-regulation. There are several challenges to deliver exogenous insulin via routes used when administering other drugs. Orally consumed insulin is subject to the harsh acidic

environment of the stomach and proteolytic enzymes present in the small intestine, capable of degrading insulin into smaller amino acid structures no longer able to exert the functions of insulin [88]. Inhaled delivery of insulin is feasible and is currently on the market in the USA (Afrezza, MannKind, USA) but not the UK or European markets. Afrezza appears to have overcome the initial barriers to inhaled insulin, where inter-individual variation in alveoli surface and structure would lead to varied insulin absorption; however, its long-term safety and efficacy are still unclear and there is an associated with high financial cost [89].

Injecting insulin into the adipose tissue that lies beneath the skin, the subcutaneous tissue, provides a stable route of entry, with most insulin entering into the interstitial space before diffusing reproducibly into systemic circulation and presents the most widely used route of entry by far in T1D insulin therapy (**Figure 4**) [90]. Even so, there are several outstanding drawbacks with subcutaneous delivery such as injection pain, some variation in absorption from the subcutis[91,92], and relative hyperinsulinaemia in the periphery (compared to physiological hyperinsulinaemia occurring first in the portal vein).

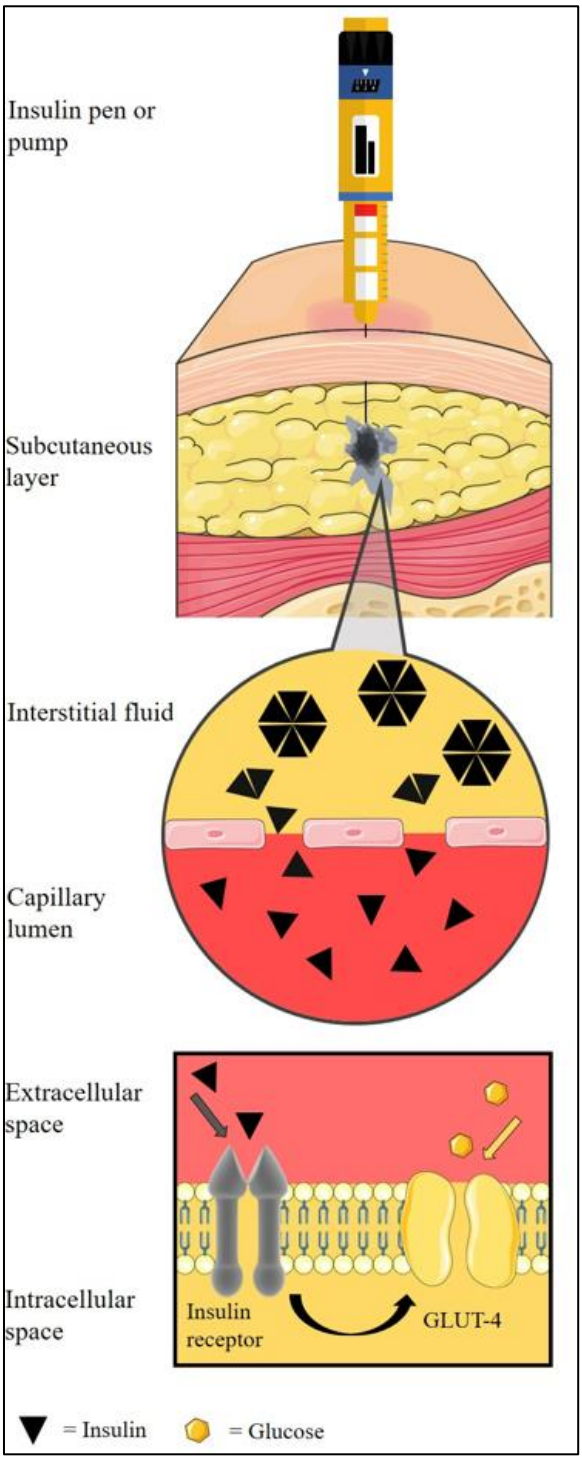
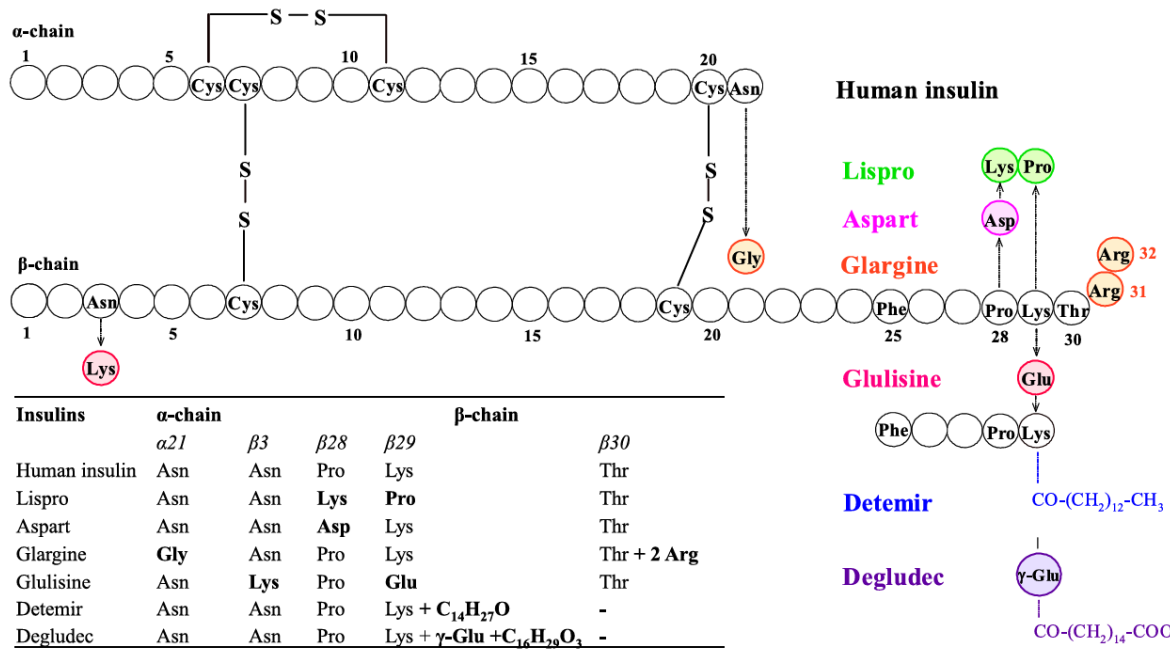


***Figure 4**: Subcutaneous route of entry of injected exogenous insulin, from pen (or pump) to target cells. Adapted from Pitt et al.* [92]

1.8.2 The development of insulin analogues

Insulin is a peptide hormone, structurally comprised of an A chain and B chain joined by two disulphide bridges, with another disulphide bridge within the A chain, in its single monomer state [93]. At high concentrations, such as when stored in the pancreas [94], insulin associates into hexameric complexes. At low concentrations, found in systemic circulation, insulin can rapidly dissociate into dimer and monomer units [95]. The demand for pharmaceutical insulin was initially supplied with animal insulins, namely bovine and porcine, and regular human insulins [96]. However, to supply the quantity of insulin needed after a meal, these insulins needed to be injected at concentrations where the molecules would aggregate into the hexameric state. Hexamers can only slowly dissociate into biologically active insulin monomers that are small enough to pass from the subcutis injection site into circulation [97]. This results in serum insulin concentrations inadequate to match the post-prandial peak in blood glucose, while remaining too high after meal absorption and risking low blood glucose [98]. The need for advancements in insulin therapy was met with the discovery that modifications to the distal end of the B chain created insulin analogues that could more rapidly dissociate from hexamers to monomers in subcutaneous tissue [99]. Modification of the distal end of the B chain, specifically swapping the amino acids Pro B28 and Lys B29, produced the first rapid-acting analogue, Lispro (Humalog®, **Figure 5**) [100]. The rapid onset and peak of the insulin enabled users to inject their bolus dose closer to mealtimes. The insulin's profile in pharmacodynamic and pharmacokinetic studies depicts the insulin peaking concurrent with blood glucose levels from mealtime absorption, and a transient drop off period after peak concentrations (**Table 1**) [101]. This allows for enhanced glycaemic control as blood glucose levels better approach euglycaemia during prandial and post-prandial states [102]. Subsequently, efforts to rearrange and/or add to the insulin amino acid sequence led to the development of insulin aspart (Novorapid®, Novo Nordisk), and insulin glulisine (Aprida®, Sanofi) all with similar peak times of 45-60 min to far better match prandial glucose [100,103,104]. As a result, the first generation of rapid-acting insulin analogues were developed to facilitate a superior pharmacodynamic/pharmacokinetic (PD/PK) profile over human insulin, reducing prandial hyperglycaemia and post-prandial hypoglycaemia [105].



Insulins	α-chain		β-chain		
	α21	*β3*	*β28*	*β29*	*β30*
Human insulin	Asn	Asn	Pro	Lys	Thr
Lispro	Asn	Asn	**Lys**	**Pro**	Thr
Aspart	Asn	Asn	**Asp**	Lys	Thr
Glargine	**Gly**	Asn	Pro	Lys	Thr + **2 Arg**
Glulisine	Asn	**Lys**	Pro	**Glu**	Thr
Detemir	Asn	Asn	Pro	Lys + $C_{14}H_{27}O$	-
Degludec	Asn	Asn	Pro	Lys + γ-Glu +$C_{16}H_{29}O_3$	-

***Figure 5**: Visualised molecular structure of insulin analogue types relative to the human insulin molecule. Adapted from Hamidli et al.* [106]

1.8.3 Current Therapy options

Current primary insulin therapy administration options for individuals with T1D consist of continuous subcutaneous insulin infusion (CSII) pump therapy or multiple daily injections (MDI) regimens [107]. Despite advancements in technology incorporating continuous glucose monitors (CGMs) into CSII pump therapy, thus approaching an automated closed-loop system, an NHS audit revealed MDI regimens remain substantially more used than pump therapy in the UK, with only 17.7% and 5.8% of the population using pumps in England and Wales respectively [108]. MDI combines a long-acting insulin with a mealtime rapid-acting insulin to mimic natural gluco-regulatory patterns [109,110]. Long-acting insulins, also termed basal insulin, are typically administered once or twice daily and provide a constant background of insulin for the individual. The insulin profile therefore must be relatively smooth, last a large portion of the day, and be without a significant peak [111]. Short- and rapid-acting insulins, or bolus insulin, are designed to be taken at mealtimes (e.g. 3-4 times per day) to counter the release of glucose into the blood from feeding. Hence, they exhibit a steep peak and transient drop-off in their insulin profile characteristics [99].

***Table 1**: Pharmacokinetic characteristics of basal insulin analogues currently available to T1D individuals in the UK*

Action Type	Insulin Name	Onset	Peak	Duration	Reference
Mealtime/bolus insulins					
Ultra-rapid-acting	Fiasp	2.4 min	63 min	3 – 5 h	[112]
	URLi	2 min	45-60 min	5 h	[113]
Rapid-acting	Aspart	5 – 15 min	31 – 70 min	3 – 5 h	[114]
	Lispro	10 – 30 min	45 – 60 min	3 – 5 h	[103]
	Glulisine	10 – 30 min	44 – 93 min	3 – 5 h	[104,115]
Basal insulins					
Ultra-long-acting	Degludec	1 – 9 h	No peak	> 42 h	[116]
	Glargine (U300)	6 h	No peak	> 36 h	[117]
Long-acting	Glargine (U100)	1 – 4 h	8 – 12 h	22 – 24 h	[117]
	Detemir	1 h	8 h	20 h	[118,119]

Fiasp, Faster-acting insulin aspart; URLi, Ultra-rapid-acting lispro.

1.8.4 Monitoring glycaemia

Self-monitoring blood glucose is a key component of care in T1D. The principal form of self-monitoring blood glucose (SMBG) is a fingertip capillary sample for the point measurement of blood glucose. This provides an accurate point-of-care reading for blood glucose, but lacks indication of the direction of glucose.

Glycated haemoglobin (HbA_{1C}) provides a measurement of long-term exposure to raised blood glucose levels. HbA_{1C} represents the haemoglobin A (HbA) molecules, found as part of erythrocytes in the blood, that have irreversibly bound to glucose also being transported by the blood, forming HbA_{1C} [120]. The frequent occurrence of hyperglycaemia promotes the formation of HbA_{1C}; hence, measures of glycated haemoglobin are proportionate to the magnitude and time of exposure to high blood glucose levels [120]. Given the irreversible formation of HbA_{1C}

and the lifespan of erythrocytes, HbA_{1C} levels reflect the status of glycaemia over the previous 2-3 months, providing an objective measurement for both diagnosis and management of diabetes [121]. HbA_{1C} can be likened to the average of blood glucose readings over this period and is therefore not an indicator of glycaemic variability or acute individual response patterns (e.g., OGTT response). Further, HbA_{1C} values are typically only available to the individual with T1D upon visits to their diabetes healthcare team.

CGMs are currently available on prescription in the UK (e.g., Libre 2, Abbott). A sensor is inserted, typically on the back of the arm or the abdomen, into the interstitial space in the subcutaneous adipose tissue. Enzymes immobilized on the sensor surface facilitate glucose oxidation reactions, the products of which can be measured by the sensor and subsequently converted to, and displayed as, glucose concentrations via a couple reader or mobile phone. Sensor readings are averaged over set epochs (e.g., 1-15 minutes), providing 'continuous' interstitial glucose concentration measurements over the course of the sensor lifetime, typically 10-15 days. CGMs can therefore provide direction of blood glucose, average blood glucose concentrations over a period of time, time in range metrics, glycaemic variability (among other metrics), and a platform for sharing data [122]. Nevertheless, there is a lag time of 5-15 minutes between interstitial and blood glucose concentrations, and inaccuracies to the degree of ≥8% mean average relative difference (MARD) that are likely inherent to the technology; hence, simultaneous SMBG readings are recommended to intermittently confirm CGM readings (e.g., when approaching hypoglycaemia)[123–125].

1.9 Physical Activity recommendations for T1D

Regular exercise has been advocated to improve management of T1D by multiple health organisations and consensus statements (ACSM, 2008; ADA, 2016; Diabetes UK, n.d.; Lancet, 2017; Diabetes Canada, 2018). Current recommendations for people exercising with T1D strongly overlap with recommendations to people without the conditions (**Table 3**).

***Table 2**: Health organisation recommendations on physical activity for adults with T1D.*

Health Organisation	PA Type	Duration	Intensity	Frequency	Notes and Examples
ACSM (2008)[127]	Aerobic	20-45 min per session	40-60% VO_{2max}	5-7 days per week	Avoid exercise time with peak insulin activity
	Resistance	8-10 REPs – building to max of 20 REPs	Low weight	2-3 days per week	
ADA (2016)[6]	Aerobic	150 min (minimum per week)	Moderate to vigorous	3-7 days per week	E.g., walking, cycling, swimming
	Resistance	8-10 exercises, completing 1-3 sets, completing 10-15 REPs	MOD: 15 REPs, where 15 is fatigue VIG: 6-8 REPs, where 6-8 is fatigue	Minimum of 2 non-consecutive days per week, preferably 3	E.g., resistance machines, free weights
Diabetes Canada (2018)[130]	Aerobic	150 min (minimum per week)	MVPA (MOD: 64-76% HR_{max}, VIG: > 76% HR_{max})	No more than 2 consecutive days without exercise	E.g., brisk walking (MOD), jogging (VIG)
	Resistance	1 set. Progressing in steps to reach 3 sets with heavier weights	Fatigue at 15-20 REPs maintaining proper form. Progressive steps to reach 3 sets,	2-3 times per week	E.g., Exercise with weight machines

			fatigue at 8 REPs maintaining proper form		Progress to free weights
Diabetes UK, based on WHO general guidelines (2014)[131]	Aerobic + Resistance	150 min (minimum per week) 30 min per day (X5)	MOD - VIG	5 days per week Muscle-strengthening activity twice per week	

ACSM, American College of Sports Medicine; ADA, American Diabetes Association; HR_{max}, heart rate maximum; WHO, World Health Organisation; REP, (Exercise) Repetition; MOD, Moderate-intensity; PA, Physical activity; VIG, Vigorous-intensity; VO_{2max}, maximum rate of oxygen uptake.

1.9.1 Exercise adherence

Despite consensual recommendations of exercise, and its associated benefits to people with T1D, common barriers appear to prevent regular physical activity. In the Finnish Diabetic Neuropathy study [132], 43% of 1,945 participants were reported to take part in less than 1 session of Leisure-Time Physical Activity per week. This is in striking contrast to the worldwide physical activity guidelines that typically consist of 150 min moderate-intensity physical activity per week (**Table 2**). Brazeau et al. identified that the fear of hypoglycaemia and the loss of control over diabetes were main barriers to exercise in 100 patients with diabetes [133]. Correlations between answers to the validated questionnaire being used in the study by Brazeau and colleagues[133] study revealed that fewer barriers towards exercise were associated with knowledge of insulin pharmacokinetics, and that a higher HbA_{1c} was associated with more barriers. Although associations do not necessarily determine a cause, these findings suggest that education of exercise and glycaemia would help people with T1D to avoid both hyper- and hypoglycaemia. These barriers are understandably very relevant to T1D; however, patients still report barriers to exercise that are common in non-diabetic individuals. Interviews with 26 people with T1D revealed the majority of barriers to physical activity were consistent with barriers to people without the condition [134]. Although there was no indication of each barrier's weighting, these findings show motivational strategies previously established in healthy individuals have potential application to individuals with T1D.

1.10 Benefits of physical activity for people with T1D

Numerous benefits of regular physical activity have been identified that are common in both people with T1D and their non-diabetic peers. These include reducing the risk of heart disease, cancer, osteoporosis, and improving well-being [135,136]. The positive effects of physical activity on the management of diabetes and progression of diabetes have also been demonstrated, although compelling results have been found more in type 2 diabetes than T1D. Meta-analyses exploring the topic of T1D and exercise are limited by heterogeneity between study methodologies, statistical power, and a lack of consideration for diet [137]. Nevertheless, it has been suggested that exercise can play a key role in T1D individual's health by reducing the risk of some macro- and micro-vascular complications [132] and improving insulin sensitivity [138,139]. The evidence base for exercise-induced improvements in glycaemic control remains inconclusive. Highlighting the importance of physical activity, Tikkanen-Dolenc et al. (2017)

found that incidence rates of all-cause mortality were 0.67 and 0.24 in individual's completing moderate and high levels of physical activity, respectively, relative to low levels (1.0).

1.11 Continuous moderate-intensity exercise

Hydrolysis of adenosine triphosphate (ATP) provides the energy for crossbridge cycling in myofibers. Following expenditure of the limited stores of ATP, the energetic need for ATP resynthesis must be met by the following pathways: i) phosphocreatine breakdown, ii) glycolysis, or iii) oxidative phosphorylation [141]. Both phosphocreatine and glycolysis can produce ATP rapidly without the involvement of oxygen (O_2); hence, their contribution to moderate-long duration physical exercise is minimal.

Continuous exercise, such as walking and jogging, involves continuous activation of large muscle groups that predominantly employ oxidative energy systems. At low-moderate intensity exercise, both carbohydrates and fats contribute significantly as energy substrates to oxidative phosphorylation [141]. As the duration of the activity increases, there is a progressive shift away from carbohydrate-derived energy expenditure towards the use of fats, with increases in lipolysis and gluconeogenesis [142]. Conversely, exercise intensity has an exponential relationship with carbohydrates, which become the dominant fuel supply after ~45-65% VO_{2max}, depending on training status and diet, and become nearly the sole fuel source at higher intensities [143].

To facilitate the increased work demands, the supply of fuel increases to the working muscles via increased breakdown and mobilization of stored triglycerides and glycogen (i.e., lipolysis and glycogenolysis), increased cardiac output, increased blood flow to contracting muscles, and upregulated transporter mechanisms for carbohydrate and fat uptake [144–146]. Indeed, glucose may increase up to 100-fold during intense leg exercise [147]. Glucose uptake during exercise is promoted via insulin-independent mechanisms in skeletal muscle. Like insulin, these mechanisms depend on GLUT-4 translocation from intracellular storage depots to the sarcolemma; however, GLUT-4 is instead postulated to be stimulated by Ca^{2+}, ROS, nitric oxide synthase, and/or ROS via pathways that are not yet fully elucidated [70,148]. The physiological response to this increased glucose uptake from the blood is a lowering of insulin secretion to preserve blood glucose concentrations [149]. The pancreas of an individual with T1D, however, cannot adjust insulin secretion, and circulating insulin is therefore the product of prior exogenous insulin injection. Maintained serum insulin concentrations from previous basal and

bolus insulin injections therefore maintain whole-body glucose disposal rates and inhibit the pathways of glycogenolysis and gluconeogenesis in the liver, thus blunting the counterregulatory mechanisms that act to preserve blood glucose [150]. Hence, the serum insulin concentrations that are higher relative to the normal secretory response of a healthy individual contribute to a higher rate of glucose disappearance than rate of appearance into the blood, and a decline in blood glucose follows [151].

During prolonged mild- to moderate-intensity aerobic exercise, the decline in blood glucose concentrations increase the risk of hypoglycaemia [152]. Although the glycaemic response to exercise is highly individualised, a meta-analysis revealed the average reported decline in blood glucose levels during continuous exercise of moderate-intensity (~65% VO_{2max}) is -4.43 $mmol.L^{-1}.h^{-1}$ [153]. Additional considerations for the exercising individual with T1D are the effects of exercise on glycaemia that persist for many hours even after the exercise session is complete. Exercise sensitises skeletal muscle to subsequent insulin stimulation, postulated to occur via enhanced vasodilatory effects and molecular signalling [70,154]. Hence, the same insulin therapy (either basal or bolus) biologically active in the hours following exercise will exhibit a greater glucose-lowering effect, potentially increasing the risk of hypoglycaemia [155].

Given the cited barriers to exercise in T1D include the risk of hypoglycaemia and the loss of glycaemic control, the need to develop and employ glucose management strategies to preserve glucose is emphasised in aerobic exercise, where a net decline of blood glucose is prominent.

1.11.1 Exogenous insulin absorption during exercise

Muscular exercise induces rapid changes in the physiological systems of the person with T1D to supply working muscles with oxygen and nutrients. These changes extend to the area within and around the subcutaneous tissue into which insulin is injected from a pen or pump system. Haemodynamics, thermoregulation, muscular contraction, metabolic shifts and other factors all have the potential to impact the depot of injected insulin and, quite plausibly, a subsequent impact on the pharmacokinetics of that insulin.

A recent review investigated the effect of acute exercise on the rate of insulin absorption with comparisons against a control arm (at rest) [92]. While there is considerable variation in the findings, results from the pooled studies suggests that bolus insulins are more likely to experience a rise in insulin absorption from the subcutaneous tissue into the blood stream than basal insulins (only insulin glargine U100 was measured). The cause of the increase in

absorption during exercise is likely due to a myriad of factors including capillary recruitment, massage-effect, blood flow, temperature, and flushing effect; however, further studies are required to clarify their relative importance. This phenomenon further emphasises the disturbed gluco-regulatory milieu in T1D during exercise which favours factors which facilitate glucose uptake from circulation.

1.12 Resistance exercise, high-intensity exercise, high-intensity interval exercise

O_2 demand during high-intensity activity (e.g., >85% VO_{2max}) exceeds the rate in which it can be delivered and utilized. Under these conditions, non-oxidative metabolism is the main driver of energy production which requires predominantly carbohydrate-derived fuel sources and can typically be sustained for only a brief period of time [143]. Despite this, glucagon secretion only modestly increases during bouts of 100% VO_{2max} [156]. Instead, increased adrenaline and noradrenaline cause an overriding increase in rate of glucose appearance from the liver while rates of glucose disappearance and utilization are reduced [157]. Consequently, in both people with and without T1D, blood glucose concentrations increase with high-intensity exercise [158].

High-intensity interval exercise (HIIE) and resistance exercise are modalities of exercise that may include bouts of high intensity interspersed with periods of recovery or low-moderate intensity. In resistance exercise, this would apply to exercise regimens focusing on hypertrophy and strength gains rather than muscular endurance. Combination of high- *vs.* low-intensity bouts will result in different physiological response depending on the intensity of exercise and the periods of recovery; however, in general, HIIE and resistance exercise with recovery periods will cause blood glucose concentrations to either decline at a lower rate compared to aerobic exercise or maintain an approximately steady state [128,159]. Exercise sessions incorporating high-intensity exercise, where an increase in glucose is expected, may be managed with a conservative correction dose prior to exercise when the person with T1D is experiencing hyperglycaemia [5]. Nevertheless, dose adjustments made after exercise should be done with the consideration that insulin sensitivity may persist in the hours following exercise.

1.13 Faster-acting insulin aspart

1.13.1 Background

Despite therapeutic advancements, glycaemic control remains a challenge with T1D. At rest, deviations from normoglycaemia often occur at mealtimes, whereby the composition of the meal can lead to varying rates of carbohydrate absorption into the blood and, thus, varied glucose responses to food. As insulin analogues have been developed, the ability of bolus insulin injections at mealtimes to counter the post-prandial rise in glucose has been enhanced, resulting in less time spent in hyperglycaemia immediately after mealtimes. However, the absorption rates of rapid-acting insulins remain such that the optimal time of administration is 15 minutes prior to the meal to avoid post-prandial glycaemic excursions [160]. Despite recommendations for an interval prior to the meal when injecting meal-time insulins, patients often either use a shorter injection-meal interval or abstain completely for convenience [161]. Considering this, Faster-acting insulin aspart ([Fiasp®] Novo Nordisk, Denmark) is a new formulation of insulin where two excipients (L-arginine and niacinamide) have been added to insulin aspart. The addition of niacinamide purportedly increases the rate of absorption from the subcutis into circulation, potentially bypassing the preference for an injection-meal interval and improving the response time to bolus corrections [162,163]. The Manufacturing company of Fiasp, Novo Nordisk, state that Fiasp can be injected at the start of a meal for ease of use for people with T1D [164].

To analyse the pharmacology of Fiasp, Heise et al [165] pooled data from six clinical trials in which the pharmacodynamic and pharmacokinetic profiles of Fiasp and insulin aspart were compared in people with T1D. All trials were deemed methodologically similar enough to provide comparative data in the analysis, totalling 218 adult participants who used multiple daily injections. All trials consisted of laboratory visits, separated by wash-out periods, where participants administered 0.2 U/kg of Fiasp or insulin aspart in a randomised, crossover design, before 12 h of frequent blood sampling. To measure the pharmacodynamic profiles, three of the trials performed an automated euglycaemic clamp for 12 h after insulin injection, during which blood samples were frequently taken. The collective results from these studies found that the onset of appearance of Fiasp was 4.9 min (5.3 – 4.4 min) earlier than aspart (p<0.001) and that peak serum Fiasp concentrations occurred 7.3 min (11.1 min – 3.6 min) earlier than peak aspart concentrations (p<0.001). This shows a left shift in the mean serum insulin concentration-time curve for Fiasp compared to insulin aspart (**Figure 6**).

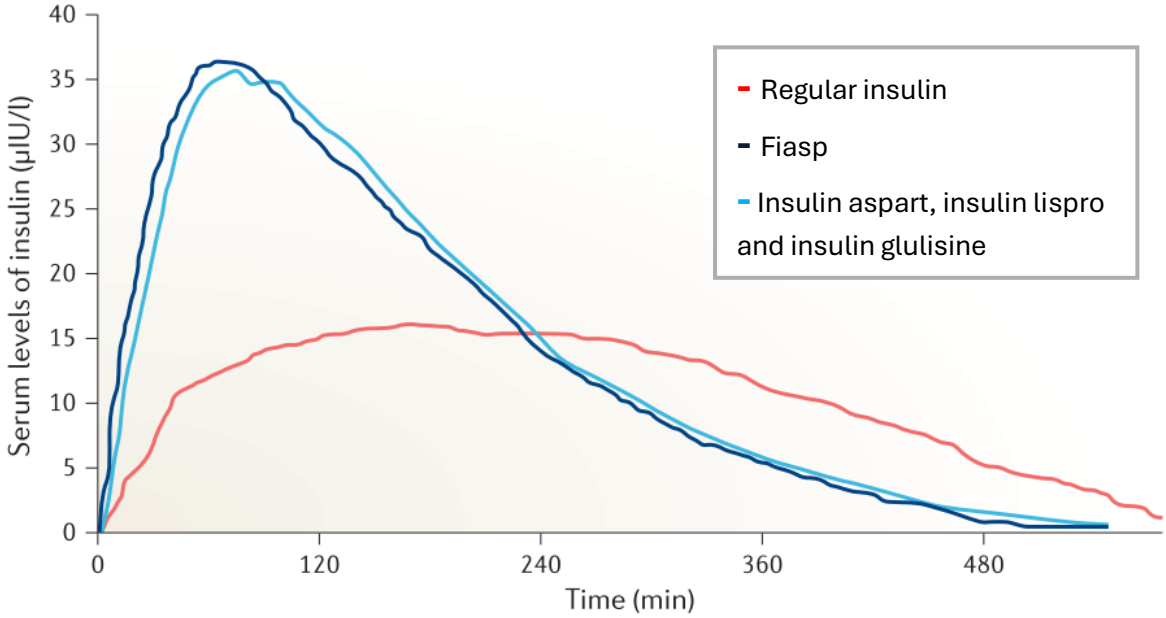


Figure 6: *Pharmacokinetic action profiles of rapid-acting insulins. Compared with other insulin analogues, Fiasp has a faster onset of appearance and peak, shifting the curve to the left, though maintaining a similar area under the curve. Adapted from Mathieu et al.* [166].

Participants in the studies used by the pooled analysis were all measured in a resting state, reflecting day-to-day use of the insulin. However, glycaemic control around exercise differs considerably to that during rest and even between different exercise characteristics. Given the array of health benefits accessible to those who exercise, it is of interest that the pharmacological behaviour of Fiasp in and around exercise be characterised to promote safe and efficacious practice for people with T1D exercising.

As Fiasp's 'predecessor', insulin aspart has been available for over 20 years and is currently a widely used rapid-acting insulin. Within this period, multiple studies have been performed investigating its use around exercise (**Table 3**). These studies provide a basis of reference for the expected interaction between Fiasp use and exercise, given their similarity in pharmacokinetic profile, albeit with a left-shifted time curve for Fiasp.

***Table 3**: Glycaemic response to acute reduced pre-exercise bolus insulin aspart in people with T1D on MDI regimen.*

Reference	Design	Basal / bolus regime	Pre-exercise meal bolus reduction (meal dose as % of full dose)	Dietary adjustments around exercise	Exercise	Glycaemia-related outcomes
Campbell et al. (2013)[167]	11 male participants completed 45 min CON exercise in between meals with 75% reduced pre-exercise prandial bolus dosages and 100%, 75%, or 50% post-exercise prandial bolus dosages	Glargine U100 (n = 8) or detemir (n = 3) / aspart (n = 10) or lispro (n = 1)	25% (post exercise meal = 100%, 75%, or 50%)	Pre-exercise meal = 1.0 CHO $g.kg^{-1}$ BM (60 min before exercise) Post-exercise meal = 1.0 LGI/HGI CHO $g.kg^{-1}$ BM (60 min after exercise)	45 min morning treadmill run at 73% VO_{2peak}	Exercise start to end ΔBG (Mean±SEM): -6.80±0.03 (100%) vs -6.90±0.03 (75%) vs -6.2±0.03 $mmol.L^{-1}$ (50%) (NS) AUC 4 – 8 h post exercise (evening): 1,706±247 (100%) vs 1,860±244 (75%) vs 2,709±245 $mmol.L^{-1}min^{-1}$ (50%)
Campbell et al. (2014)[168]	10 male participants completed 45 min CON exercise in between meals with reduced prandial bolus dosages and LGI or HGI CHO post-exercise feeding.	Glargine U100 / aspart	25% (post-exercise meal = 50% reduction)	Pre-exercise meal = 1.0 CHO $g.kg^{-1}$ BM (60 min before exercise) Post-exercise meal = 1.0 LGI/HGI CHO $g.kg^{-1}$ BM (60 min after exercise)	45 min evening treadmill run at 70% VO_{2peak}	Exercise start to end ΔBG: -6.8±1.3 $mmol.L^{-1}$ (LGI) vs -5.4±1.6 mmol/L (HGI) (NS) BG concentration 2 h post-exercise: 7.7±2.5 $mmol.L^{-1}$ (LGI) vs 13.5±3.3 $mmol.L^{-1}$ (HGI)

Campbell et al. (2015)[169]	10 male T1D participants completed 45 min CON exercise in between meals with reduced prandial bolus dosages and LGI CHO feeding, against 100% or 80% basal insulin dose.	Glargine U100 (n = 8) or detemir (n = 2) / aspart	25% (post-exercise meal = 50% reduction)	Pre-exercise meal = 1.0 CHO $g.kg^{-1}$ BM (60 min before exercise) post-exercise meal = 1.0 CHO $g.kg^{-1}$ BM (60 min after exercise)	45 min evening treadmill run at 70% VO_{2peak}	Exercise start to end ΔBG: -6.4±0.4 $mmol.L^{-1}$ (100%) vs -5.9±0.6 $mmol.L^{-1}$ (80%) Time spent in nocturnal euglycaemia (up to ~13 h post-exercise): 397±56 min (80%) vs 122±28 min (100%)
Heise et al. (2016)[170]	40 T1D participants completed 30 min CON exercise after reduced CHO content and reduced bolus insulin dosage for pre-exercise meal against a background of basal insulin degludec or insulin Glargine	Degludec or glargine U100 (cross-over trial) / aspart	40% (post-exercise meal information not supplied)	Pre-exercise individualised meal reduction by 60% of CHO (median 40 g CHO)	30 min on cycle ergometer at 65% VO_{2peak}	Difference between treatments' exercise start to end ΔBG: 0.14 mmol/L; 95% CI -0.15, 0.42 Estimated mean BG during exercise: 7.28 (degludec) vs 7.43 mmol/L (Glargine) Number of hypoglycaemic episodes during 24 h after exercise start: 18 (degludec) vs 23 (Glargine)
McCarthy et al. (2020)[171]	16 participants (13 M:3F) completed 45 min CON exercise with pre- and/or post-exercise 50% reduced bolus insulin dosing.	Degludec / aspart	Pre-exercise: 100% or 50%. (Post-exercise: 100% or 50%)	Pre-exercise meal = 1.0 LGI CHO $g.kg^{-1}$ BM (60 min before exercise) Post-exercise meal = 1.0 LGI CHO	45 min on cycle ergometer at 60% VO_{2peak}	Exercise start to end ΔBG: (100% pre-, 100% post-exercise) = -3.45±2.94 $mmol.L^{-1}$ (100% pre-, 50% post-exercise) = -4.41±2.29

				$g.kg^{-1}$ BM (60 min after exercise)		$mmol.L^{-1}$ (50% pre-, 100% post-exercise) = -3.37±1.40 $mmol.L^{-1}$ (50% pre-, 50% post-exercise) = -3.59±2.13 $mmol.L^{-1}$)
Moser et al. (2015)[172]	7 trained male participants completed both HIIE and CON with reduced pre-exercise meal bolus insulin doses	Degludec / aspart (n = 4) or lispro (n = 3)	5% below LTP1 = 75% 5% above LTP1 = 50% 5% below LTP2 = 25% (same doses for post-exercise meal)	Pre-exercise meal = Standardised clinical nutrition fluid (39% CHO, 36% fat, 25% protein; 4 h before exercise) Post-exercise meal = same (immediately after exercise)	30 min exercise on cycle ergometer at 5% below LTP1, 5% above LTP1, and 5% below LTP2 during different trials. HIIE same intensities and duration as CON, but with 1:6, 1:3, and 1:1 work to rest ratios respective to the above intensities	Exercise start to end ΔBG: 3.00 ± 1.54 $mmol.L^{-1}$ (5% above LTP1) Mean BG 24 h post-exercise: 9.38 ± 3.27 $mmol.L^{-1}$ (5% above LTP1)
West et al. (2010)[173]	7 participants (6M:1F) completed 45 min CON exercise after standardised meal	Glargine U100 / aspart (n = 5) or lispro (n = 2)	100%, 75%, 50%, or 25%	Pre-exercise meal = 1.12 MJ, 60g CHO (120 min before exercise) Post-exercise meal = N/A.	45 min treadmill run at 70% VO_{2peak}	Exercise start to end ΔBG (Mean±SE): 100%, -6.1±0.4 $mmol.L^{-1}$ 75%, -4.3±0.5 $mmol.L^{-1}$ 50%, -5.5±0.5 $mmol.L^{-1}$ 25%, -3.2±0.4 $mmol.L^{-1}$

						Baseline to 180 min post-exercise ΔBG: 100%, -2.4±0.8 mmol.L^{-1} 75%, 1.1±0.8 mmol.L^{-1} 50%, -2.1±0.9 mmol.L^{-1} 25%, 4.1±0.6 mmol.L^{-1}

AUC, Area under the curve; BG, Blood glucose; BM, Body mass; CHO, Carbohydrate; CI, Confidence Interval; CON, Continuous exercise; HGI, High glycaemic index; HIIE, High Intensity Interval Exercise; LGI, Low glycaemic index; LTP1, First lactate turn point; LTP2, Second lactate turn point; MJ, Megajoules; NS, Not Significant (difference); Data are presented as Mean±SD unless otherwise specified. Note: study by Molveau et al. [174] *included in* ***Table 4***.

The studies in **Table 3** represent a diverse range of protocols which provide glycaemic-related information during exercise in people with T1D using insulin aspart. Over a series of studies [167,169,175] it was demonstrated that different glycaemic management strategies could be combined to best preserve blood glucose around exercise. In the most recent study Campbell et al.[169] demonstrated that a pre-exercise insulin aspart dose reduction of 75% in combination with a 20% reduced dose in basal insulin (glargine U100 or detemir), a low glycaemic index post-exercise meal with 50% reduced insulin aspart dose, and a low glycaemic index bedtime snack could be used to avoid hypoglycaemia before, during, and for 24 h after exercise. Moser et al. [172] showed that hypoglycaemia could be avoided during exercise when employing different insulin aspart or lispro dose reductions with the meal prior to exercise depending on the exercise intensity. Heise et al. [170] also found that hypoglycaemia could be avoided when reducing insulin aspart dose by 40% using either insulin degludec or glargine U100 as a basal insulin. Participants in other studies however, did experience hypoglycaemia during exercise, despite pre-exercise insulin reductions [171,173].

From the glycaemic outcomes presented in **Table 3**, it can be observed that there are different glycaemic outcomes possible when including insulin aspart dose reductions in the approach to exercise. Nevertheless, people with T1D can be encouraged that there are examples in protocols where blood glucose concentrations have been preserved to avoid hypoglycaemia without severe hyperglycaemia. However, it is important to consider that unless a strict routine is adhered to, effective glycaemic management protocols in controlled clinical trials are not always replicable in daily life, where exercise sessions (or any bouts of physical activity) may occur spontaneously. Therefore, an insight into what can influence blood glucose before, during, and after exercise is crucial for implementing these strategies effectively. One such example is that better knowledge of pharmacokinetics has been correlated with people with T1D perceiving fewer barriers towards exercise [133].

Current guidelines refer to a small number of studies when recommending pre-exercise insulin reductions. The American Diabetes Association (ADA)[6] and The Lancet[128] both cite a combination of Campbell et al. [167], Campbell et al. [176], Moser et al. [172], Shetty et al. [177], and Rabasa-Lhoret [178]. Subsequent guidelines [5] refer back to ADA and The Lancet guidelines, effectively citing the same studies, which each have differing methodologies. In determining recommendations for different insulin dose reductions, these guidelines may therefore benefit from a comprehensive assessment of comparable pre-exercise dose reductions, particularly in currently used insulins. Given the limitations of comparing studies employing different

research methods, research is warranted that identifies and assesses the effect of pre-exercise insulin dose reductions in an intra-study manner.

1.14 Fiasp and exercise

There are few studies that have incorporated the use of Fiasp in the regimens used by the participants during exercise. These can be broadly split into randomised controlled lab-based trials (RCT), with a controlled exercise component, and observational studies with uncontrolled exercise sessions (**Table 4**). Three of the five RCT studies that investigate Fiasp within the primary glycaemia-related endpoint use closed-loop systems as the administration method for insulin. While the technology for closed-loop systems has advanced significantly since their conception, users are often still required to count carbohydrates and announce exercise. With recent developments attempting to fully close the loop with automated glucose sensing and insulin delivery, these systems may benefit from the use of a more rapid-acting insulin, such as Fiasp, to improve the 'response time' of the system to bolus dosing [179].

The methodologies applied to the exercise sessions in the studies using Fiasp in closed-loop systems share comparable characteristics. Duration (all ~40 min), exercise mode (all cycling), and time of day (afternoon) are comparable, while intensities are a mix of continuous steady-state exercise and interval exercise. The participants in all three studies [180–182] that administered Fiasp in a closed-loop system averaged >70% glucose sensor time in range (TIR), meeting recommendations for non-athletes with T1D from exercise-related guidelines [183] as well as recommendations for daily living, not specific to exercise [1]. Non-inferiority was shown in studies that compared the use of Fiasp vs insulin aspart on the basis of no significant differences in TIR or other glycaemic metrics around exercise [180,182]. Dovc and colleagues [180] demonstrated that people using a closed loop system with a machine learning algorithm (GlucoSitter™) to deliver Fiasp can still achieve target glucose concentrations and TIR metrics during unannounced exercise. Further evidence of Fiasp safety and efficacy in both continuous moderate-intensity and high-intensity interval exercise was shown using a 2nd generation MiniMed™ Advanced hybrid closed-loop system, with a temporarily elevated glucose target of 8.3 mmol.L^{-1} [182]. It is interesting to note that in both these studies total insulin delivery per day with exercise was numerically, albeit not statistically, higher in Fiasp trial arms, yet glycaemic metrics were still comparable to insulin aspart trial arms. In-line with previous

findings, Tsoukas et al. [181] demonstrated high TIR that exceed current recommendations around a bout of moderate-intensity continuous exercise, both with and without the addition of pramlintide (an amylin analogue). Overall, these data demonstrate the potential for good glycaemic control using Fiasp during exercise; however, this has been shown using modern generations of hybrid closed-loop systems that are not (yet) commonly used for many with T1D. These findings do not necessarily extend to the efficacious use of Fiasp around exercise administered from insulin pens, which demands additional planning.

Two RCTs include participants using insulin pens or CSII to deliver either Fiasp or insulin aspart [174,184]. In a study by Momeni et al.[184], glucose concentrations fell during exercise similarly to the decline in glucose seen in other moderate-intensity continuous studies using insulin aspart (**Table 3**). While 24-h post-exercise TIR reached >70% in the study trial arm where BG at exercise start was in-line with recommendations (73.3%), while starting BG above BG recommendations resulted in 24-h post-exercise TIR <70% (63.8%), this comparison did not reach statistical significance. Given the primary endpoint for this study was removed from insulin comparisons, data were neither split between insulin types used by participants (Fiasp and insulin aspart) nor the insulin delivery methods; hence, assessment of the efficacy of Fiasp specifically with these data is limited.

Molveau and colleagues[174] compared a pre-exercise dose of Fiasp or insulin aspart when taken either 60 or 120 min prior to 60 minutes of cycling at 60% VO_{2peak} in a crossover design. All participants in this study used insulin pens as part of their MDI regimen. The decline in blood glucose between exercise onset and within-exercise nadir was found to be less when using Fiasp than when using insulin aspart (-4.1 ± 2.3 *vs.* -4.4 ± 2.8 mmol.L^{-1}; p=0.037). Nevertheless, time within all glycaemic ranges were similar during exercise (p>0.05). During exercise, a similar number of hypoglycaemic events occurred between the two insulins, yet post-exercise hypoglycaemia occurred less frequently in Fiasp (n=0 *vs.* n=15). Regarding the comparison between exercise timings, participants spent less time in hyperglycaemia prior to exercise when taking insulin 60 minutes before exercise compared to 120 minutes (56.6 *vs.* 78.0%; p<0.001), equal amounts of time in hypoglycaemia prior to exercise (0.0 *vs.* 0.0%), and experienced a smaller decline in blood glucose during exercise compared to 120 minutes (-3.8±2.7 *vs.* 4.7±2.5 mmol.L^{-1}; p<0.001). There were no time X insulin type interactions. Collectively, these findings indicate that Fiasp and insulin are comparable when taken at either 60 or 120 minutes prior to exercise; however, a smaller decline in blood glucose during exercise may occur when taking Fiasp. Consuming a mixed meal 60 minutes prior to exercise with a

50% reduced bolus reduction in either Fiasp or insulin aspart elicits favourable glycaemic outcomes compared to 120 minutes.

The second subsection in **Table 4** refers to studies that include the use of Fiasp in a field-based observational setting with participants using MDI regimens. Uniquely, all three studies comprise of participants who are elite professional cyclists [185,186]. Consequently, the daily challenges to glucose homeostasis are more pronounced given the professional riders train in tremendous volumes of over 25,000 km per year and individual races lasting over 4 hours performed on consecutive days. In these athletes, management of blood glucose concentrations must be weighed against the performance benefits of high carbohydrate consumption (up to 90 $g.h^{-1}$) while exercising [187,188].

Despite performing multiple bouts of prolonged endurance exercise, even during competition, the riders being observed in all studies averaged the majority of time within target interstitial glycaemia range (≥63% TIR). Furthermore, the time spent in hyperglycaemia, resultant from high carbohydrate intake, was also within range for training (≤25% hyperlgycaemia/time above range [TAR] 1) and racing (≤25% TAR1) conditions, according to guidelines specific for athletes with T1D [188]. These data demonstrate promising glycaemic control can be achieved during prolonged and competitive endurance exercise. However, direct comparison of the use of Fiasp in these riders is limited by the grouped data between riders using different mealtime insulins and data being taken reported from differing sources (e.g., in-ride or 24-h).

***Table 4**: Studies investigating glycaemic outcomes in people with T1D using Fiasp in an exercise setting.*

Reference	Rapid-acting insulins used	Insulin regimen	Study primary end point (Number of participants)	Exercise Methodology	Exercise-related glycaemic outcomes
Randomised controlled trials					
Dovc et al. (2020)[180]	Fiasp, aspart	Hybrid CL system	Difference in TIR using Fiasp vs aspart in CL system. (n=20)	Time post-prandial: 1.5-3.8 h Time of day: 15:00 Duration: 40 min Type: Cycling Intensity: 55% VO_{2max} with five 20-s sprints at 80% VO_{2max}.	Similar TIR using Fiasp (79.2 [62.5-100.0] %) vs insulin aspart (83.3 [52.1-100.0] %) from exercise start to 2 h post-exercise (p=0.49).
Tsoukas et al. (2021)[181]	Fiasp	Hybrid CL system	Difference in TIR using Fiasp alone or using Fiasp plus pramlintide in CL systems. (n=11)	Time post-prandial: 3 h Time of day: 16:30-19:30 Duration: 40 min (2 X 20 min separated by 5 min rest) Type: Cycling Intensity: 40-60% heart rate reserve.	Similar TIR using Fiasp plus pramlintide (77±38%) vs insulin aspart (75±29%) from start of exercise to 1 h post-exercise (p=0.79).
Morrison et al. (2022)[182]	Fiasp, insulin aspart	Hybrid CL system	Difference in TIR for 24 h after MOD or VIG exercise using Fiasp vs insulin aspart. (n=16)	Time post-prandial: ND Time of day: 14:30-17:00 Duration: 40 min Type: Cycling	Similar TIR using Fiasp (100.0 [79.2-100.0] %) vs insulin aspart (100.0 [95.8-100.0] %) from exercise start to 2 h post-MOD (p=0.42) and post-VIG exercise (89.6 [77.7-100.0] vs 100.0 [77.1-100.0] %, respectively; p=0.94).

				Intensity: 50% VO_{2max} (MOD) or 40% VO_{2max} for 5 min between 6 X 2 min intervals at 80% VO_{2max} (VIG).	
Molveau et al. (2024)[174]	Fiasp, insulin aspart	MDI	Difference in hypoglycaemic risk between two postprandial timings of exercise onset (60 vs 120 min) and two insulin types (Fiasp and insulin aspart) with 50% pre-exercise reduction. (n=40)	Time post-prandial: 1-2 h Time of day: 9:00 or 10:00 Duration: 60 min Type: Cycling Intensity: 60% VO_{2peak}	Lesser decline in blood glucose during exercise in Fiasp *vs.* insulin aspart (-4.41±2.3 *vs.* -4.4±2.8 mmol.L^{-1}; p=0.037). No difference between TBR, TIR, or TAR during exercise.
Momeni et al. (2023)[184]	Fiasp, insulin aspart	MDI or CSII	Hydration status and serum electrolyte concentrations during exercise with BG at recommended concentrations at exercise start (MOD), or at above recommended concentrations at start (HI). (n=12)	Time post-prandial: ND Time of day: 17:00 Duration: 45 min Type: Cycling Intensity: 80% VO_{2peak}	No change in ΔBG in MOD from start ([Mean±SEM] 10.4±0.4 mmol.L^{-1}) to end (7.5±0.7 mmol.L^{-1}; p>0.05) of exercise. Change in ΔBG found in HI from start (13.7±0.7 mmol.L^{-1}) to end (10.1±0.6 mmol.L^{-1}; p<0.05) of exercise. All CGM metrics were comparable throughout all post-exercise periods (all p>0.05).
Observational studies					
McCarthy et al. (2020)[185]	Fiasp, insulin aspart, glulisine	MDI	To assess glycaemic, dietary, and physiological demands during a training camp in professional cyclists with T1D during training. (n=16)	*Duration: 4.3 h Type: Road cycling Intensity: 60-75% HR_{max}.	TIR during rides for all participants averaged 77%.
Moser et al. (2020)[186]	Fiasp, insulin aspart	MDI	To assess insulin therapy, macronutrient intake and glycaemia in professional	**Duration: ND Type: Road cycling Intensity: 63% anaerobic threshold	TIR on racing days (24 h) for all participants averaged 75%.

			cyclists with T1D during a competitive race setting. (n=7)		
Scott et al. (2020)[189]	Fiasp	MDI	To investigate factors related to glycaemic management among a professional cycling team over a 7-day international race event. (n=6)	***Duration: 4.8 h Type: Road cycling Intensity: 137±6 beats.min^{-1}	TIR on racing days during rides for all participants averaged 63%.

Note: Data presented as mean±SD or median (IQR), unless otherwise indicated. CL, Closed-loop; CSII, Continuous subcutaneous insulin infusion; HIE, High-intensity exercise; MIE, Moderate-intensity exercise; MDI, Multiple daily insulin regimen; MOD, Moderate-intensity; ND, No data; TAR, Time above range; TBR, Time below range; TIR, Time in range; VIG, Vigorous-intensity.

* Observational data averaged from 9 days at training camp.

** Observational data averaged from 5-day racing competition.

***Observational data averaged from 7-day racing competition.

Collectively, the studies listed in **Table 4** have marked a first step in providing information about the use of Fiasp around exercise in people with T1D. The use of Fiasp has been shown to be safely used as part of different hybrid closed-loop systems under well-controlled laboratory settings when performing exercise. There currently exist two studies which have investigated the use of Fiasp around exercise as part of an MDI regimen; however, only one of these focused on insulin type in the analysis of glycaemic outcomes. Through Molveau et al.[174], we currently have an understanding of how Fiasp performs when reduced by 50% with a meal either 60 or 120 minutes prior to aerobic exercise; however, information around different dose reductions is not yet available. Given alterations to rapid-acting (insulin aspart) dosing quantity can vary substantially (see **Table 3**), investigation into different insulin reductions prior to exercise in Fiasp is warranted.

1.15 Thesis Aims

The overall aim of this thesis is to identify the glycaemic effects of pre-exercise bolus insulin dose reductions, with application in using faster-acting insulin aspart (Fiasp) as part of a multiple daily injection regimen in real-world and clinical trial settings in recreationally active individuals and trained athletes with type 1 diabetes (T1D).

The primary aim within each experimental chapter is:

- To compare the intra-study rate of change of blood glucose concentrations during aerobic exercise when using different pre-exercise bolus insulin doses in people with T1D.

- To explore the glycaemic impact of incorporating Fiasp in a multiple daily injection insulin regimen, in comparison to insulin aspart, in professional endurance cyclists with T1D.

- To compare the effect of different dose reductions in Fiasp and insulin aspart on the rate of change of blood glucose concentrations around aerobic exercise in recreationally active people with T1D.

Chapter 2

Materials and Methods

2.1 Summary of study designs

This thesis is comprised of three studies. The first study (Chapter 3) is a systematic review of existing published literature. The second study (Chapter 4) is a retrospective, observational study performed under 'real-world' conditions. The third study (Chapter 5) is a laboratory-based prospective, double-blinded, two-site, four-arm, randomised cross-over clinical trial.

Study 1 methods

2.2 Protocol standardisation

Study 1 systematic review was conducted in accordance with The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2020) [190]. The research question and primary objective was formed using the Patient, Intervention, Comparison and Outcome (PICO) format (**Table 15**).

***Table 5**: PICO framework for this systematic review*

Patient	People with type 1 diabetes using insulin therapy.
Intervention	Acute exercise performed with an insulin reduction and measured effects on blood glucose.
Comparison	Comparisons primarily between different (reduced) doses of insulin; secondarily between other quantifiable variables that influence exercise or blood glucose.
Outcome	Blood or interstitial glucose concentrations or other derived metrics from these measurements.

2.3 Eligibility criteria

2.3.1 Inclusion criteria

For a study to be eligible to be included in the systematic review, it was required to meet all of the following criteria:

- Search items must be studies published in peer-reviewed journals.
- Participants must be people with type 1 diabetes. Diabetes type must be specifically reported. Variations of this term include: T1D, type 1 diabetes mellitus, T1DM, insulin-dependent diabetes (mellitus), IDDM, autoimmune diabetes (mellitus), OR juvenile onset diabetes (mellitus).
- Participants must be using MDI regimen (insulin pens). Injections should be made in-line with standard care (e.g., into the subcutaneous tissue).

- Participants must be studied performing an acute session(s) of defined exercise with defined intensity and duration (either 'aerobic' continuous exercise, 'anaerobic' high-intensity exercise, resistance exercise, high-intensity interval exercise, OR 'in vivo/simulated games situations (e.g., playing football). For the purposes of this meta-analysis, it was expected that dose reductions would be made prior to aerobic exercise.
- The pre-exercise meal must be consumed within 4 hours prior to exercise, with the carbohydrate content of the meal being defined and the time until exercise being reported.
- The precise reductions (reported, or able to be calculated, as percentage of normal dosage) and identification of insulin (basal/long-acting or bolus/rapid-acting) before exercise must be reported.
- For primary outcome analysis, the relative or absolute change in blood glucose from the start to end of exercise must be included and reported in SI units.

2.3.2 Exclusion criteria

A study was deemed ineligible to be included in the systematic review if any of the following criteria were met:

- Blood glucose must not be subject to another conflicting intervention (e.g., intravenous supply of carbohydrates in clamp studies).
- Studies with a focus on those with recently diagnosed (<12 months) T1D.
- Studies where the exercise component is an exercise stress test/VO_{2max} test/cardiopulmonary exercise test.
- Pilot studies or case studies with low sample size (<4 participants).
- The full text must be available and accessible in the English language.

2.4 Search strategy

2.4.1 Database selection

The systematic review was performed on electronic bibliographic databases. These databases are listed in **Table 6**, alongside the platform through which they were accessed. Alternative search tools (internet hand and Google scholar) were used in periphery searches for studies that may not have been included in the final list of database-derived studies.

***Table 6**: List of databases and the interface platform used*

Database	**Platform**
CENTRAL	Cochrane Library
CINAHL	EBSCOhost
Embase	Embase
MEDLINE	EBSCOhost
SPORTDiscus	EBSCOhost
Web of Science	Web of Science

The current databases were selected to include those that have been demonstrated to have effective coverage in systematic reviews (Embase, MEDLINE, Web of Science) [191], those that are specific to the subject areas of healthcare sciences and sport and exercise sciences (SPORTDiscus and CINAHL), and CENTRAL as the overarching database to include a broader range of sources [192].

2.4.2 Search terms

The search terms employed in this systematic review were split into four key themes, in-line with the PICO research question: 1) The inclusion of people with type 1 diabetes, 2) the inclusion of an exercise component, 3) the inclusion of a blood glucose related outcome, and 4) the exclusion of references to type 2 diabetes. Limitations that were applied to the search included: articles only, English language only, no minimum date, up to 12th July 2023, and searched in the title and abstracts only. All search terms were applied - and individualised/formatted according to the platform - to all databases and are listed in **Table 7**.

***Table 7**: Search terms applied to the database search. MeSH=Medical Subject Headings.*

Search Term Number	**Term**
#1	"type 1 diabetes [MeSH]"
#2	T1D
#3	T1DM
#4	"type 1 diabetes"
#5	"insulin dependent diabetes"
#6	"insulin-dependent diabetes"
#7	IDDM
#8	"autoimmune diabetes"
#9	"auto-immune diabetes"
#10	"juvenile onset diabetes"
#11	"juvenile-onset diabetes"
#12	"type I diabetes"
#13	#1-#12 OR
#14	"exercise" [MeSH]
#15	exercis*
#16	"physical activit*"
#17	preexercise
#18	"pre-exercise"
#19	postexercise
#20	"post-exercise"
#21	#14-#20 OR
#22	blood glucose [MeSH]
#23	glucose
#24	glycaem*
#25	glycem*
#26	"time in range"
#27	"time below range"
#28	"time above range"
#29	hypoglyc*
#30	hyperglyc*
#31	euglyc*
#32	#22-#31 OR
#33	type 2 diabetes mellitus [MeSH]
#34	"type 2 diabetes"
#35	T2D
#36	T2DM
#37	"type II diabetes"
#38	"non insulin dependent diabetes"
#39	"non insulin-dependent diabetes"
#40	"non-insulin dependent diabetes"
#41	"non-insulin-dependent diabetes"
#42	"noninsulin dependent diabetes"
#43	"noninsulin-dependent diabetes"
#44	NIDDM
#45	#33-#44 OR
#46	#13 AND #21 AND #32
#47	#46 NOT #45

The search strategy was developed to balance including as many relevant studies as possible *versus* excluding as many irrelevant studies as possible. A list of studies that were known to be relevant to the research question was generated and initial search strategies were developed against their inclusion of these studies (**Appendix A**). The search strategy was further peer-reviewed by an independent specialist via the Peer Review of Electronic Search Strategies (PRESS) checklist [190].

2.4.3 Selection process

Search results were exported via a referencing software (Endnote, Clarivate, USA) to a systematic review manager software (Covidence, Australia). Duplicate records were logged and removed automatically at this stage (**Figure 10**). Two reviewers independently screened the title and abstract of each record (J.P. and C.N.). Instances of a conflict of decisions were discussed and resolved between the reviewers, involving the consultation of a third reviewer (R.B., who otherwise did not perform screening) where necessary. Records that were deemed eligible underwent full review independently by the same two reviewers. Relevant data from these studies were then extracted, listed, and, for the primary outcome, grouped.

Studies 2 and 3 only materials and methods

2.5 Studies 2 and 3 governance and ethical approval

All studies involving participants were performed in accordance with Good Clinical Practice and the Declaration of Helsinki for the care and interests of the participants and their data. Ethical approval and study registration details are provided in **Table 8** and Appendix B.

Table 8*: Ethical approval and study registration details.*

Study Number	Ethical approval	Registration
Study 1	N/A	N/A
Study 2	Swansea University Research Ethics Committee (2018-140)	1. DRKS00019923 2. DRKS00019928
Study 3	National Research Ethics Committee (Wales REC 3; 18/WA/0421)	DRKS00015855

2.6 Participant recruitment and consent

Participants for Study 2 were recruited from Team Novo Nordisk (TNN), a professional cycling team composed entirely of male athletes with T1D. TNN riders compete in the UCI ProSeries, an elite international road cycling tour; hence, TNN represent the highest tier of professional cyclists with T1D. Conducting research on these riders offers a unique opportunity to collect data from a complete cohort of elite athletes who follow similar treatment protocols, training camps, and team activities, despite the inherent challenges of accessing personal diabetes-related measures in this population. Publications independent to Chapter 4 have used data collected from TNN (see also Section 2.5) [185,186,189,193]. All members of the team were informed by their team management of the chance to have their diabetes and cycling data monitored over the course of a training camp as part of an observational research study. Those who expressed interest were provided with an information pack which included an explanation of the purpose of the study, the methods of data collection, and the role and handling of the participant. Informed written and verbal consent was taken from participants prior to the start of any testing by the cycling team medic. Thirteen cyclists volunteered to participate in this study.

Study 3 was split over two sites: 1) Swansea University and 2) Medical University of Graz. To achieve a total sample size of 44 participants, each site recruited 22 participants and performed trials at the respective sites. The methodology (including eligibility criteria, laboratory equipment, and trial day procedures) between the sites was identical. All PD/PK samples (**Table 24**) were analysed at the Medical University of Graz. Swansea University has custody of study data, and all data analyses were conducted by Swansea University (J.P.). To recruit participants for Study 3 at Swansea University, advertisements were placed as a poster on university campus, in local hospitals, in local clinics, and in local health care practices. A newspaper article in the local newspaper and an online newspaper article were also used as advertisement. University-wide emails were delivered to staff and students with study information and contact details. Individuals who had expressed an interest in taking part in clinical trials and were deemed potential candidates against inclusion criteria were contacted via telephone call by nurses at the research facility (Joint Clinical Research Facility, Swansea University, Swansea). Participants who had taken part in previous studies conducted by the research team who were deemed as potentially appropriate for this study and had contact data on record were also contacted by the nursing team. People who expressed interest were sent an information pack which included an explanation of the purpose of the study, the methods of

data collection, and the role and handling of the participant and their data. After confirming further interest, volunteers were preliminarily screened against eligibility criteria over the telephone with a member of the research team or nurse team (Section 2.4) and, if successful, were invited to attend the research facility for a comprehensive screening visit.

All research activities for Study 3 were halted during national lockdowns in both the UK and Austria from governmental response to COVID-19 pandemic. Subsequent re-start of experimental trials was carried out following the development of COVID-19-related standard operating procedures (Appendix C), which were tailored to the respective sites. An additional grant was secured (J.P. and R.B.) to provide personal protective equipment in-line with the COVID-19-related standard operating procedures for the study. The study pause during national lockdowns and the time required to research, write, and implement standard operating procedures and risk assessments delayed study completion time. Furthermore, COVID-19 was associated with additional risk in people with T1D, which may have discouraged participation in clinical studies even after national lockdowns; hence, the full effects of COVID-19 on the timeline of this study are significant but difficult to accurately quantify.

2.7 Eligibility criteria

2.7.1 Inclusion criteria

Eligibility criteria for studies 2 and 3 overlapped. Eligibility criteria in Study 3 were more extensive than those of Study 2; hence, criteria that overlap with, or apply solely to, Study 2 are denoted in brackets (all other criteria apply to Study 3 only). To be eligible to participate in this study, participants were required to meet the following criteria:

- Informed consent prior to trial-related activities. *(Studies 2, and 3)*
- Male or female aged 18-65 years. *(Studies 2 and 3)*
- Clinically diagnosed with type 1 diabetes mellitus for ≥12 months. *(Studies 2 and 3)*
- Insulin therapy using multiple daily injections regimen ≥12 months. *(Studies 2 and 3)*
- Member of professional cycling team. *(Study 2 only)*
- Body mass index (BMI) 18.0-29.9 $kg.m^{-2}$. In instances of BMI values outside this range, body composition will be considered (as measured via bioelectrical impedance

analysis [BIA]) to avoid misinterpretation of BMI values. If body fat mass is within 5% of normal reference values for the individual based on gender and age, then inclusion may be permitted.

- Mass-specific VO_{2peak} >20 $ml.kg^{-1}.min^{-1}$.
- Performing regular physical activity in-line with Department of Health Guidelines during the last 3 months prior to screening, as assessed via short International Physical Activity Questionnaire (IPAQ; Section 2.8.6).
- Glycated haemoglobin (HbA_{1c}) ≤ 9.5% (≤80 $mmol.mol^{-1}$).

2.7.2 Exclusion criteria

A participant was deemed ineligible to take part in this study if any of the following criteria were met:

- Known or suspected hypersensitivity to the trial insulins used (insulins aspart, fiasp or degludec) or other related products.
- Receipt of any investigational medicinal product within 1 month prior to screening in this trial
- Known haemoglobin < 8.1$mmol.L^{-1}$ (< 13 $g.dL^{-1}$, male) and < 7.4$mmol.L^{-1}$ (< 11.5 $g.dL^{-1}$, female), total leukocyte count < 3.0 x $10^9.L^{-1}$, thrombocytes < 100 x $10^9.L^{-1}$, serum creatinine levels ≥ 126 $\mu mol.L^{-1}$ (male) or ≥ 111 $\mu mol.L^{-1}$ (female), alanine aminotransferase > 2 x the upper limit of normal (ULN), bilirubin > 3 x ULN, alkaline phosphatase > 2 x ULN.
- Suffer from or have a history of a life-threatening disease (e.g. cancer judged not to be in full remission except basal cell skin cancer or squamous cell skin cancer), or clinically severe diseases that directly influence the study results, as judged by the investigators. Participants were not prohibited in taking medications that influence metabolism (e.g. statin) or the cardio-respiratory system (e.g. asthma spray, ACE-inhibitors) as long as the therapy is stable and was not adapted throughout the run of the trial. Furthermore, participants were not excluded who have celiac disease (or similar diseases or allergies), provided the disease and any specific diet was stable (e.g. gluten-free diet). *(Studies 2 and 3)*
- Heart rate < 40 beats per minute at screening (after resting for 5 minutes in supine position).

- Cardiac problems defined as decompensated heart failure (New York Heart Association class III and IV) at any time and/or angina pectoris within the last 12 months and/or acute myocardial infarction at any time.
- Supine blood pressure at screening (after resting for 5 minutes in supine position) < 90 or > 140 mmHg for systolic, and/or < 50 or > 90 mmHg for diastolic (excluding white-coat hypertension; therefore, if a repeated measurement on a second screening visit showed values within the range, the participant was included in the trial). This exclusion criterion also pertained to participants on antihypertensives (provided that the blood pressure was within range).
- Clinically significant findings from an electrocardiogram (ECG) at screening, as judged by a medical professional from the study medical team (from the respective study sites).
- Proliferative maculopathy or retinopathy and/or severe neuropathy, in particular autonomic neuropathy, as judged by a medical professional.
- Any chronic disorder or severe disease which, in the opinion of the investigators might jeopardize participant's safety or compliance with the protocol.
- Known positive for Hepatitis B surface antigen or Hepatitis C antibodies (or diagnosed with active hepatitis), for HIV-1 antibodies, HIV-2 antibodies or HIV-1 antigen.
- History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction (except celiac disease – participants were requested to exclude foods that contain gluten from the diet).
- Surgery or trauma with significant blood loss (more than 500 mL) within the last 3 months prior to screening.
- Current treatment with systemic (oral or intravenous) corticosteroids, monoamine oxidase inhibitors, non-selective or selective beta-blockers, growth hormone, herbal products or non-routine vitamins. Furthermore, participants taking thyroid hormones were excluded unless the use of these has been stable during the past 3 months.
- Significant history of alcoholism or drug/chemical abuse as per investigators' judgement.
- Smoker/vaping (defined as a participant who is smoking more than 5 cigarettes or the vaping equivalent per day). Participants were excluded if they were not able or unwilling to refrain from smoking or use of nicotine substitute products during the inpatient period.
- Recurrent severe hypoglycaemia (more than one severe hypoglycaemic event [that

which requires third-party assistance] during the past 12 months).

- Hypoglycaemic unawareness as judged by the investigators.
- Hospitalisation for diabetic ketoacidosis during the previous 6 months.
- Participant with mental incapacity or language barriers precluding adequate understanding or cooperation or who, in the opinion of their general practitioner or the investigators, should not participate in the trial.
- Potentially non-compliant or uncooperative during the trial, as judged by the investigators.
- Any condition that would interfere with trial participation or evaluation of results, as judged by the investigators. *(Studies 2 and 3)*
- Female of childbearing potential who is pregnant, breast-feeding or intends to become pregnant or is not using adequate contraceptive methods (adequate contraceptive measures include sterilisation, hormonal intrauterine devices, oral contraceptives, sexual abstinence or vasectomised partner).

2.8 Pre-observation assessments (Study 2) and Screen Visit Procedures (Study 3)

Recruited participants from Study 2 underwent anthropometric assessments and data were transferred from their medical notes for age and duration of diabetes. Potential candidates from Study 3 who were willing to take part in the study attended a screen visit at the research facility to gauge eligibility criteria via anthropometric, cardiovascular, diabetes-related, and blood-related measurements. Blood or interstitial glucose was monitored using the participant's personal devices during the visit for safety.

2.8.1 Anthropometric measurements

Participant height (Holtain Stadiometer, Holtain Ltd, UK) was measured with participants standing straight, without shoes, with their back against the measuring column, with natural eye-line parallel to the floor, on intake of breath. Participant mass (Seca Digital Scales, Seca Ltd, UK) was taken wearing under-layered clothing (e.g. sports shorts and t-shirt). From these measurements, body mass index (BMI) was calculated (Equation 1). Hip circumference was measured with the tape positioned at the level of the greater trochanter in Study 3. For waist

circumference, the tape was positioned as the level of noticeable waist narrowing, also only in Study 3.

$$\frac{Body\ mass\ (kg)}{Height^2\ (m)} = BMI\ (kg.m^{-2})$$

Equation 1

Study 3 only measurements

2.8.2 Bioelectrical impedance analysis

For the quantification of body composition, BIA (Bodystat 1500, Bodystat Ltd, USA) was used in Study 3. Primary factors that may influence BIA results beyond pre-visit requests were identified as being fluid intake and acute physical activity status [194]. The BIA test was therefore performed prior to the cardiopulmonary exercise test (CPET) and participants were asked not to drink excessive amounts of fluid prior to the test. Age, sex, physical activity level and required anthropometric information was inputted into the BIA device while participants were asked to lie in the supine position with a gap between their legs and between their arms and torso. Alcohol wipes (70% Medisave professional, Medisave, UK) were used to clean electrode sites. One injector electrode was placed just superior and parallel to the metacarpophalangeal joints on the participant's right hand, and another placed just superior and parallel to the metatarsophalangeal joints on the right foot. An equivalent detector electrode was placed parallel to the detector electrodes in line with the pisiform bone and at the ankle in line with the lateral malleolus, also on the right-hand side. The device was used according to manufacture guidelines and estimated body composition data were recorded in the screen visit case report form (CRF) and reviewed against inclusion criteria where applicable (body fat mass percentage) or noted separately in the CRF (lean mass, dry lean mass, water content, basal metabolic rate, estimated daily calorie requirement, waist/hip ratio).

2.8.3 Non-exercise cardiovascular measurements

Participants remained lying down rested in the supine position while blood pressure (FlexiPort, Welch Allyn, USA) and electrocardiogram (ECG) (MAC 2000 ECG Analysis System, General Electric Company, USA) measurements were taken. Blood pressure was reviewed against eligibility (exclusion) criteria and the ECG trace was printed and provided for the medical

professional for inspection to reference against eligibility (exclusion) criteria. The medical professional also reviewed the patient's medical history and referenced relevant information against the inclusion/exclusion criteria.

2.8.4 Blood-based measurements

2.8.4.1 HbA_{1c} measurement

Fingertip blood capillary sampling was used to extract the blood sample for HbA_{1c} measurement for a marker of long term (~3 months) glucose control. Standard blood capillary sampling technique was as follows: the site of sampling was cleaned using an alcoholic wipe, left to dry by air, and punctured using a single-use spring-loaded lancet (Accu-chek safe T-pro plus lancets, Roche, Switzerland). After wiping away the initial appearance of blood, gentle pressure was used to form a droplet of blood. For HbA_{1c} measurements, a 4 µL blood sample was dispensed into test-kit cartridges (Quo-Test HbA_{1c} test kit, EKF, UK). The cartridge was inserted into the associated analyser (Quo-Test HbA_{1c} Analyzer, EKF, UK) and results were recorded and reviewed against the exclusion criterion. In Study 2, HbA_{1c} values were determined from the most recent clinical visit (Mean±SD: 6.8±0.6% [50.8±7.0 $mmol.mol^{-1}$]).

2.8.4.2 Haemoglobin measurement

10 µL of blood was directly drawn from a fingertip sample into a microcuvette (HemoCue 201+ Microcuvette, HCE, UK) and inserted into an analyser (HemoCue 201+ Analyser, HCE, UK) to determine haemoglobin concentrations. The subsequent results were referenced against study eligibility criteria.

2.8.4.3 Other blood samples

For the analysis of other blood-borne analytes, 5 mL (SST Vacutainer, Becton, Dickinson and Company, USA) and 4 mL (EDTA Vacutainer, Becton, Dickinson and Company, USA) of venous blood was drawn. The sample was analysed in the Biochemistry lab of Singleton Hospital and the results were recorded in the screen visit CRF. As these remaining analytes were viewed as long-term safety markers, it was not necessary for the results of the venous blood analysis to be returned on the day of the screen visit.

2.8.5 Urine measurement

Participants who were female of child-birthing potential were asked to complete a urine sample pregnancy test (CLINITEK Status®+, Siemens, Germany).

2.8.6 IPAQ

All participants were asked to complete a questionnaire to gauge the quantity and intensity of physical activity they performed on a weekly basis and ensure changes in exercise habits were not apparent between trials. The international physical activity questionnaire (IPAQ) was provided for participants to fill out themselves, with further clarification provided by the researcher where necessary [195]. The short version IPAQ was chosen due to its simplicity, quick implementation time, and validity against the long version and accelerometry data [196]. Responses were analysed in accordance with author recommendations [197].

2.8.7 Cardiopulmonary exercise test protocol

Upon confirmation of the participant meeting all the anthropometric, cardiovascular, urine, and blood markers eligibility criteria, participants were asked to carry out a CPET. Participants performed the CPET on an electromagnetically workload-controlled cycle ergometer (Lode Corival CPET, Cranlea, UK) pedaling with slight bend in the knee when pedaling at the lowest point during the rotatory cycle. The test began with a 3-minute passive seated phase with no pedaling, followed by a further 3 minutes of cycling at 20 W as a warm-up. The next phase consisted of incremental pedal workloads of either 20, 15, or 10 W (depending on IPAQ score and training status) that progressed each minute. During this phase, participants were asked to cycle between 70-80 rpm and to maintain this cadence for as long as possible, stopping at volitional exhaustion. The test progressed to the next phase once the participant either stopped cycling or once 50 rpm was not reached for more than 5 seconds. At the point of exercise cessation, the workload immediately decreased, and participants engaged in an active cooldown, cycling for 3 minutes at 20 W. Lastly, a 3-minute passive cooldown phase was performed seated, without pedaling, on the ergometer.

2.8.8 Cardiopulmonary exercise test measurements

The purpose of conducting a CPET with participants was two-fold: 1) to test relative VO_{2peak} met the >20 $ml.kg^{-1}.min^{-1}$ inclusion criterion and 2) to gauge the workload intensity employed in the subsequent experimental trial days relative to the participant's lactate turn points (Section 2.8.9).

2.8.8.1 Spirometric measurements

A breath-by-breath system (METAMAX 3B, Cortex, Germany) was used to provide visual tracking of performance during the CPET via associated computer software (MetaSoft Software, Cortex, Germany) and measured inspired oxygen volume ([VO_2] $L.min^{-1}$]), expired carbon dioxide volume ([VCO_2] $L.min^{-1}$), and total ventilation ($L.min^{-1}$ or $L.min^{-1}.kg^{-1}$) in breath-by-breath analysis. Participants wore a mouthpiece which was manually connected to the METAMAX system just before the exercise was due to begin. A proper seal around the mouthpiece was checked prior to every trial.

2.8.8.2 ECG and heart rate measurements

A 3-lead ECG (eMotion Faros 180°, Bittium Biosignals Ltd., Finland) was placed for continuous measurement, and live visualisation, of an ECG trace and heart rate variability metrics. Electrodes were placed: 1) under the middle of the clavicle within the ribcage frame on the right side, 2) under the middle of the clavicle within the ribcage frame on the left side, 3) lower left abdomen within the ribcage frame (as per manufacture instructions). A heart rate monitor (Polar T31, Polar, Finland), placed around the chest just beneath the sternum, was linked with the computer software (MetaSoft Software, Cortex, Germany) to provided live, continuous heart rate ($beats.min^{-1}$).

2.8.8.3 Rating of perceived exertion

To gauge subjective effort during the exercise session, participants were asked to indicate how hard they found the exercise in that moment against the Borg scale [198]. This rating of perceived exertion (RPE) was explained to the participants prior to the exercise bout and was reported once every 4 minutes.

2.8.8.4 Capillary sampling

To determine a participant's lactate turn points, blood samples were collected at the same time resistance was increased during the CPET (i.e. once per minute), in addition to at rest, and at the ends of the active and passive cooldown periods. Samples were collected from the outer line of the right earlobe, near the lower lobule. Standard sampling technique to that of fingertip capillary blood sampling was used. The blood sample was drawn into a 20 µL capillary tube (EKF Diagnostics, Germany) and placed in an Eppendorf pre-filled with haem solution (EKF Diagnostics, Germany). This was inverted to ensure full diffusion of blood sample. Analysis of these samples for blood lactate and glucose concentrations were conducted after the CPET was

concluded using enzymatic-amperometric methods (Biosen C-Line, EKF Diagnostics, Germany). Because the results of the earlobe capillary sampling were determined post-exercise, within-exercise fingertip sampling was performed every 4 minutes using the FreeStyle Libre (FreeStyle Libre, Abbott, USA) in-built blood glucose meter to measure blood glucose as a safety precaution. Capillary sampling followed the same procedure as earlobe sampling until the point of blood draw, which instead used manufacture-recommended blood glucose strips (FreeStyle Optimum glucose strips, Abbott, USA).

2.8.9 Cardiopulmonary exercise test analysis

Classic methods of determining relative (%) exercise intensity that are based on heart rate or VO_2 and VCO_2 suffer from inaccurate estimation of lactate concentrations during exercise and, hence, fail to reflect true exercise-induced metabolic changes [199]. Regular blood sampling during an incremental test is a recommended technique to reveal lactate turn points and to express exercise intensity more consistently than other heart rate or ventilatory variables [199]. Lactate turn points were calculated from the 1-minutely blood lactate samples via CPET analysis software (Vienna CPX, University of Vienna, Austria), as performed previously in a relevant study [171]. Lactate turn point 1 was defined as the first increase in blood lactate concentrations above baseline [200]. Lactate turn point 2 was defined as the point at which lactate concentrations exceeded the maximal steady state of increase [200], after which concentrations increased rapidly leading to termination of exercise. The exercise intensity prescribed for this study reflects an exercise challenge that participants can maintain for 45 minutes without surpassing lactate turn point 2. Specifically, the exercise intensity set for the subsequent exercise trials was defined as the mid-point between lactate turn points 1 and 2.

Figure 7 provides an example of the spirometric data measured during a CPET from one participant. Investigators can judge the CPET test visually and in addition to receiving objective determination of lactate turn points 1 and 2. CPET metrics are detailed in **Table 25**.

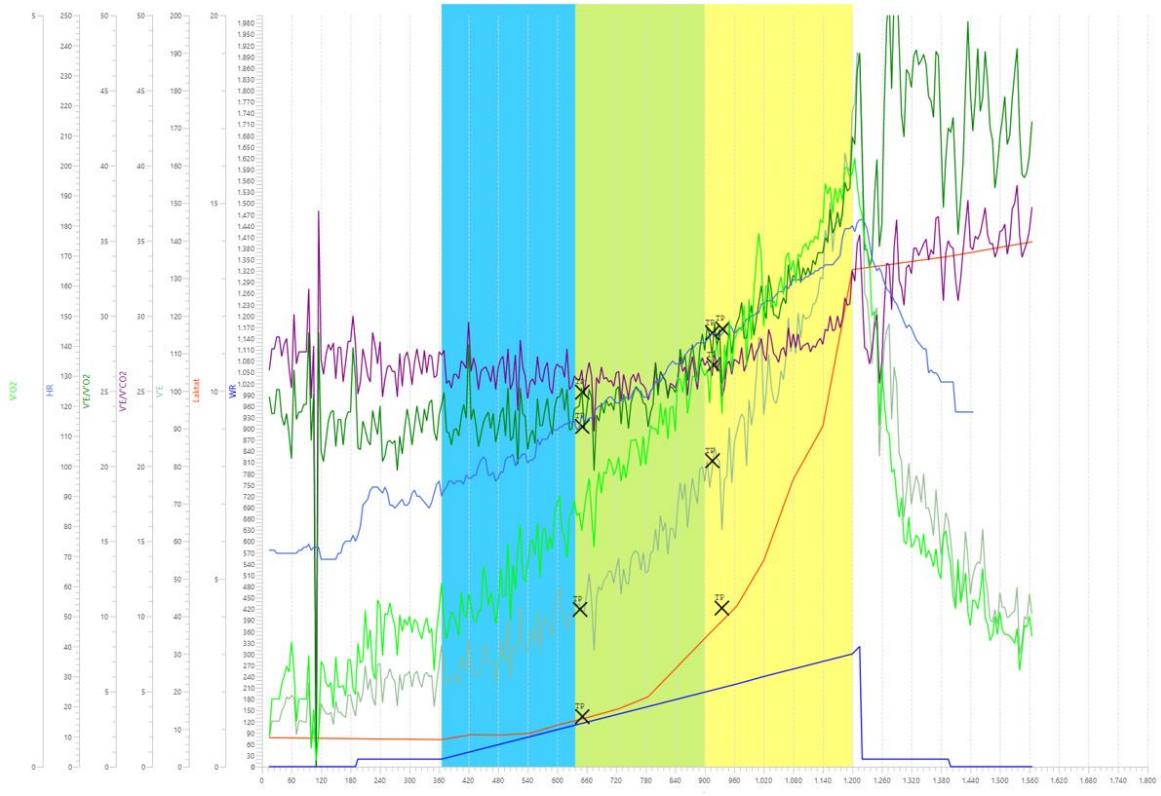


Figure 7: Example from one participant of spirometric and blood lactate changes during a CPET (Vienna CPX software). Calculated lactate turn points are highlighted with crosses.

2.9 Participant allocation

After all pre-observation/screen measurements were complete, eligibility of the participant was determined. If the participant was eligible, they were assigned a unique identification (ID) number, thus anonymising their data. If the participant was ineligible, they were thanked for attending the screen visit and they were not invited back for the experimental visits.

2.10 Participant characteristics

The combined pre-observation assessments are listed in **Table 9**.

Table 9*: Participant characteristics from Study 2 (Chapter 4) and Study 3 (Chapter 5). Data are presented as Mean±SD.*

Anthropometric parameter	Study 2	Study 3
Sex (M/F)	13 M / 0 F	30 M / 14 F
Age (years)	26.7±4.5	38.8±13.3
BMI ($kg.m^{-2}$)	21.6±1.5	24.4±3.5
Duration of diabetes (years)	11.0±5.2	15.2±12.0
HbA_{1c} (%)	6.8±0.6	6.9±1.0
VO_{2peak} ($mL.kg^{-1}.min^{-1}$)	71.7±4.4	36.7±9.0

BMI, Body mass index; HbA_{1c}, glycated haemoglobin; VO_{2peak}, peak volume of oxygen uptake.

2.11 Participants' insulin regimes and groups

2.11.1 Study 2

MDI regimen was used by all athletes in Study 2. To compare the efficacy of using Fiasp, riders were retrospectively split into those using Fiasp (Fiasp group; n=6) or Novorapid® (IAsp group; n=7) as their rapid-acting insulin for data analysis. Long-acting insulins used in the Fiasp group were: Toujeo (n=1), Lantus (n=3), Levemir (n=2), whereas those in IAsp group consisted of: Toujeo (n=1), Lantus (n=4), Levemir (n=2). Levemir was taken twice-daily by a rider from each group and once-daily by a rider in each group. All other long-acting insulins were taken once-daily.

2.11.2 Study 3

Participants in Study 3 were switched from their usual basal-bolus therapy to ultra-long-acting insulin degludec (Tresiba® [100 $U.mL^{-1}$], NovoNordisk, Denmark) in 3 mL pre-filled investigational pens and rapid-acting insulin aspart (NovoRapid® [100 $U.mL^{-1}$], NovoNordisk, Denmark) in 3 mL FlexPens. Participants who were already using Fiasp were exempt from switching to Novorapid. Titration over to this regimen was overseen by the study physician. It was requested that insulin degludec was administered in the morning, in-line with trial day protocol. One participant whose glucose control deteriorated with switch from evening to morning dosing of insulin degludec was switched back to evening dosing. The participant took a reduced insulin degludec dose on the morning of trial visits and omitted dosing on the evening of the trial day. All participants, regardless of previous basal-bolus therapy, were required to demonstrate glycaemic stability using insulin degludec as judged by the investigator and study diabetes consultant. General glucose control was also checked via the CGM system data prior to each experimental visit. Participant insulin regimens are reported in **Table 10**.

Table 10*: Participant insulin regimens.*

Insulin parameter	Study 2	Study 3
Rapid-acting insulin total daily dose (UI)	12±4	21±14
Long-acting insulin total daily dose (UI)	15±11	24±18
Total daily dose (UI)	26±15	45±30
Relativised total daily dose ($UI.kg^{-1}$)	0.4±0.2	0.57±0.27

Data are expressed as Mean±SD.

2.12 Continuous glucose monitoring

Riders in Study 2 were each provided with a CGM system (Dexcom G6, Dexcom, USA) and wore the interstitial glucose sensor for the entire training week. Recorded data from the sensor was linked to an online platform (Clarity, Dexcom, USA) which was later exported and analysed.

After confirmation of successful enrollment in the study, participants in Study 3 were provided with a CGM (FreeStyle Libre 2, Abbott, USA), its associated sensor (FreeStyle Libre Sensor 2, Abbott, USA), and glucose- and ketone-measuring test strips (FreeStyle Libre Optimum B-Ketone, Abbott, USA and FreeStyle Libre Optimum, Abbott, USA, respectively) for self-tests throughout the duration of the study. If participants were already using either the Libre 1 or Libre 2 via UK prescription, their own device and consumables were kept. A full verbal explanation of how to apply and use the sensor was given to participants in addition to written and pictured instructions at the screen visit. All participants wore the sensor on the back of either the right or the left arm (approximately over the middle of the triceps), as per manufacture instructions. The device is factory calibrated, so it was only asked that the sensor was not due to expire within 24 hours either side of the trial day and for the device to be fully charged when attending the experimental visits. FreeStyle Libre sensors can be scanned intermittently ‘ad libitum’, but by default measurements of interstitial glucose concentrations are 15-minutely, which users can view on the system display. For data analysis of interstitial glucose values, the sensor was scanned as per study protocol and was retrospectively exported using associated software (LibreView, Abbott, USA) and converted into spreadsheets (Excel, Microsoft, USA).

Participants wore their FreeStyle Libre sensor for the duration of each experimental visit. Sensor scans were conducted frequently throughout the trial day and results were recorded in the case report form along with the trend arrow on the sensor display for the direction of glucose (**Figure 8**).

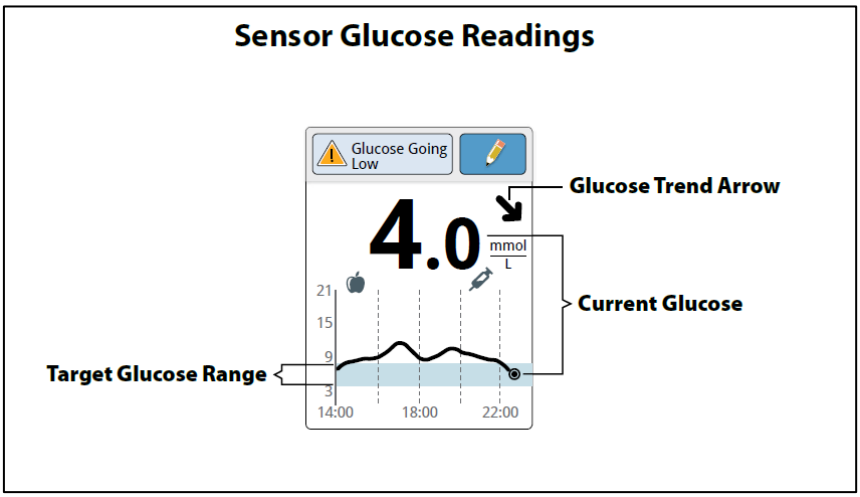


***Figure 8**: Display on FreeStyle Libre reader depicting current interstitial glucose concentration, glucose trend arrow, target glucose range, glucose alerts, and tracked glucose readings over the previous day/customised period.*

When interstitial glucose was indicated to be approaching the study threshold of either hypo- or hyperglycaemia, confirmatory fingertip capillary blood glucose was measured using the in-built blood glucose meter in the FreeStyle Libre reader. The blood glucose meter was used to define hypo- or hyperglycaemia due to potential discrepancies between sensor values and blood glucose meter values, particularly around exercise [183].

All participants were provided with a data entry log to record information about their feeding, physical activity, and glucose activities (including the extent and frequency of hypo- or hyperglycaemia) in the 24 hours prior to each trial day. The entry logs were looked over by the investigators at the beginning of each trial day and data was transferred into the CRF for data analysis. In addition to the pre-trial requirements, participants were also asked to maintain the same routine and activities where possible in the run-up to trial days.

2.13 Experimental visits Study 3

2.13.1 Overview of experimental visits

Participants who passed the screen visit were invited to attend the clinical research facility on four separate occasions to complete experimental trial days. A final follow-up visit was used one week later to take final measurements (to compare against pre-trial measurements and ensure participant's health) and to conclude the individual's part in the study. The four main experimental trial day visits consisted of a 9-hour in-patient visit to the facility, scheduled

feeding and rest periods, and a 45-minute bout of moderate-intensity cycling exercise. On each experimental visit, participants were randomised to one of four trial arms relating to a reduction in the bolus dose of insulin being taken with the breakfast meal (pre-exercise dose) and with the midday meal (post-exercise dose). The dose reductions were always identical for the two meals on each trial day. The investigative bolus insulin doses were either that of insulin aspart (NovoRapid [100 $U.mL^{-1}$], NovoNordisk, Denmark) or insulin fiasp (Fiasp [100 $U.mL^{-1}$], NovoNordisk, Denmark). The randomised trial arms comprised of: 1) A 50% reduced dose of Fiasp, 2) 75% reduced dose of Fiasp, 3) 50% reduced dose of insulin aspart, 4) 75% reduced dose of insulin aspart (**Figure 9**). The reduced doses would be taken in identical insulin units alongside the pre- and post-exercise meals. Basal insulin degludec dose was taken as per normal in the morning.

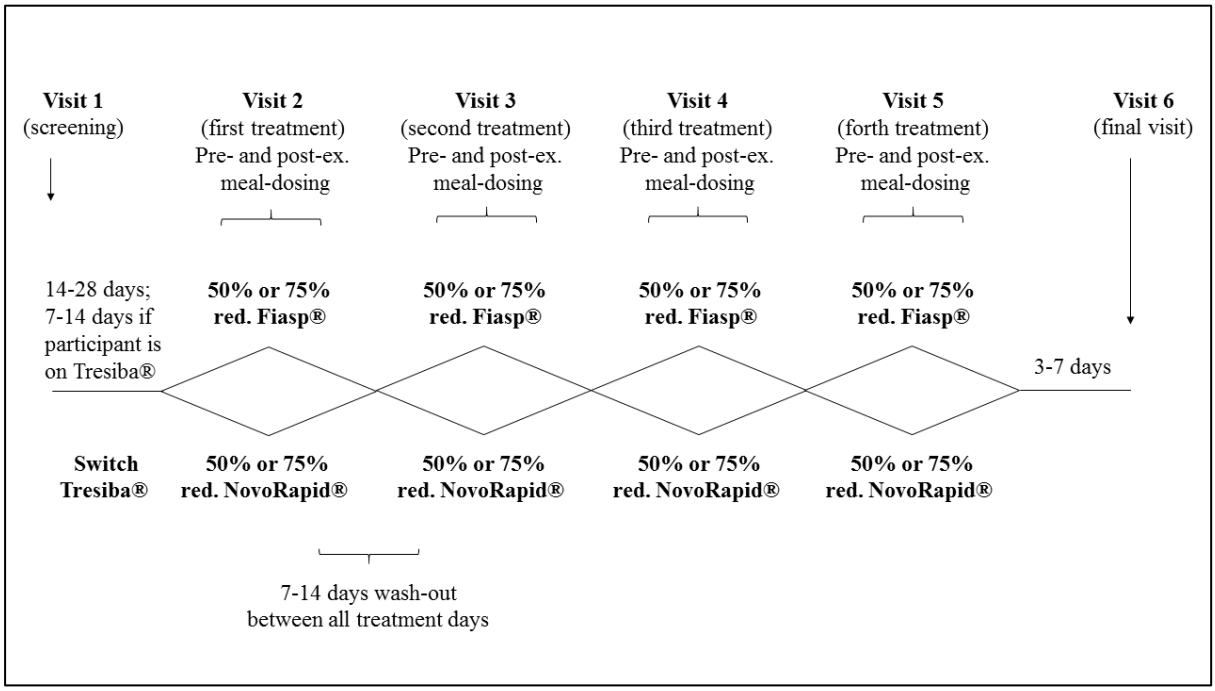


Figure 9*: Schematic overview of the trial design.*

2.13.2 Pre-trial standardisation procedures

To control for potential variables that are subject to variance between trial days, pre-trial day (-24 hours) procedures were provided in hard copy format for participants to freely review and as an electronic reminder via e-mail closer to the trial day. These comprised of requests to abstain from strenuous physical activity (-24 hours), avoid any hypoglycaemia (≤3.0 $mmol.L^{-1}$ [≤70 $mg.dL^{-1}$]; -24 hours), abstain from alcohol consumption (-24 hours), fast from the night before while avoiding caffeinated products (-8 hours), and avoid insulin injections (-5 hours).

It was emphasised that participants prioritise their own health and safety throughout the study and as such they should continue with their normal action plan for treating hypo- or hyperglycaemia (i.e., carbohydrate consumption or correction dosing). If these actions contradicted pre-trial standardisation requests, then the visit was postponed to a later date. All These procedures contributed towards trial day eligibility which were performed prior to protocol commencement on each of the trial days (**Table 11**).

Table 11*: Eligibility criteria for trial day participation. Participants must pass all inclusion, be negative for all exclusion, criteria to attend the main trial visit.*

Trial day inclusion criteria	Trial day exclusion criteria
24 hours before testing no glucose concentrations below 3.0 mmol.L^{-1} or glycaemic stability issues which is posing a safety problem as judged by the investigator	Illness on and/or before testing day
No alcohol 24 hours before trial day	Mental capacity or unwillingness to partake in trial
No structured physical activity 24 hours before trial day	Defective FGM
Informed consent taken	Any condition that the investigator feels would interfere with the trial participation or evaluation of data

2.13.3 Experiment trial day procedures

For each of the trial arms, participants attended an identical trial day at the research facility (Swansea University, UK) excluding points of, or resulting from, investigation. Participants arrived at 07.30 after an overnight fast and were invited to be seated or lie at an incline on a facility bed where they were based for the whole trial day apart from the bout of exercise and bathroom breaks (**Table 24**). At 08.00, a normal dose of insulin degludec was injected into the lateral region of the thigh. Between 08.00-08.20 a cannula was inserted into the antecubital vein of either arm, the participant filled in an IPAQ, and a 3-lead ECG was fitted. A second cannula to help maintain prompt sampling timings was identically placed on the opposite side if blood draws were difficult prior to exercise and the participant felt this was still comfortable, though this was not mandatory for the study.

To maintain double blinding, a nurse not otherwise involved in the trial prepared the types and (reduced) doses for the bolus insulin injection according to pre-coded randomisation from

study statistician. Specialised blinded pens were provided by Novo Nordisk A/S so that the type of insulin was not apparent by observing the outer casing of the pen (which would otherwise reveal the insulin type on normal pens), and an opaque seal was placed over the insulin units display by the nurse. At 08.30 (0 min) participants self-administered the pre-set insulin pen into the abdomen, using normal technique and rotating between injection areas as per their healthcare team guidance. The unblinded nurse checked that all units had been dispensed from the pen after injection. Alongside this morning dose, participants consumed a carbohydrate-rich breakfast, equating to 1 g of carbohydrate per kg of body mass. Meals were in liquid form and were standardised using the same commercially available product (Fortijuice, Nutricia, Netherlands). The meal was comprised of the following macronutrients per 100 mL: Energy 635 kJ (150 kcal), Carbohydrates 33.5 g (of which sugars 14.4 g), Fat 0 g, Protein 3.9 g. The carbohydrate content of the meal were predominantly high-glycaemic index ingredients (e.g., glucose syrup and maltodextrin). No other food was consumed during the trial unless used as treatment of hypoglycaemia (Section 2.13.6). Water was available ad libitum.

Insulin dose reductions were calculated relative to the participant's insulin:carbohydrate ratio. The blinded pens could only provide insulin doses in integer units; hence, 50% or 75% reductions that were non-integer were rounded (**Table 12**).

***Table 12**: Comparisons between calculated and provided trial day insulin doses*

Dose reduction	Calculated dose (UI)	Provided dose (UI)	Absolute dose difference (UI)
50%	4.7±5.2	4.9±5.2	0.18±0.24
75%	2.4±2.6	2.5±2.6	0.30±0.2

UI, unit of insulin

At 09.27, participants engaged in a bout of 45 minutes of moderate-intensity cycling exercise (Section 2.13.4) in a separate room to where they were based. For ease of sampling, participants stayed seated/reclined in this room until 10.30 (+120 min) when sampling frequency changed from 5- to 10-minute intervals, before being moved back to their bed.

PD/PK sampling continued up to, and throughout the second dosing period. Another identical 1g.kg^{-1} carbohydrate-rich drink-meal was consumed at 12.30 alongside the same reduced

insulin type and dosage taken with the morning meal. The trial day ended at 16.30 after the final PD/PK sample timepoint. All cannulas and ECG equipment were removed and the participant was offered a snack and a beverage before departure (recommended in instances of blood glucose < 6 mmol.L^{-1}).

2.13.4 Exercise protocol and sampling

Participants were asked to wear sports clothing for the bout exercise. On the trial day, if blood glucose measurements were <6 mmol.L^{-1} immediately prior to exercise, the visit was cancelled and re-scheduled as the pre-exercise reduced dose would be mismatched (too high) against the meal consumed. Meal-time insulin doses for that participant would be re-evaluated.

The exercise session consisted of a 3-minute passive seated period on the cycle ergometer, a 3-minute warm-up at 20-40 W, a 42-minute bout of continuous cycling exercise at the individualised intensity (Section 2.8.9), and a 3-minute seated passive cooldown. The first 3-minute seated period commenced at 09.27, so the warm-up cycling/exercise session could start at 09.30 (+60 min). During the passive seated period, 10 µL of fingertip capillary blood were drawn into a microcuvette and placed into the haemoglobin analyser to measure and report haemoglobin concentrations. Concurrently, a capillary blood sample of 80 µL from the earlobe was drawn into a glass capillary tube (Na-Heparinized Haematocrit tubes, Hawksley, UK) and occluded with clay (Cristaseal, Hawksley, UK) for centrifugation (Heraeus Megafuge 8 Centrifuge, Hawksley, UK) and determination of haematocrit proportion (Micro Haematocrit Reader, Hawksley, UK). The same samples were taken during the passive cooldown period at the end of exercise. Haemoglobin and haematocrit samples were only taken from one site (n=22), so application of plasma volume corrections were not employed (Appendix D) [201].

Capillary fingertip, capillary earlobe, interstitial glucose, and RPE measurements were taken once during the 3-minute passive seated period, once after the active warm-up, 6-minutely during exercise, and once during the passive cooldown. Pharmacodynamic and pharmacokinetic sampling continued (5-minutely) throughout the exercise session as per the sampling schedule in addition to the exercise-specific venous samples (Section 2.13.3). ECG and spirometry measurements were taken continuously during exercise, both linked to a computer to display live information. A medical professional was present during each screen and main trial visit to observe the ECG trace and was able to intervene in the exercise session in the event of a health concern.

Earlobe capillary blood samples collected throughout exercise were analysed after the session for blood lactate and glucose concentrations. For on-the-spot determination of blood glucose, the FreeStyle Libre in-built glucose monitor was used from fingertip capillary blood samples. If a hypoglycaemic episode occurred (blood glucose ≤3.9 mmol.L^{-1}), the exercise session was terminated at the point of measurement and 10-20 g of carbohydrate gel was administered as per hypoglycaemia treatment protocol. All measurements intended to be taken at the end of exercise were taken at the point of hypoglycaemia-induced exercise cessation. Pharmacodynamic/pharmacokinetic sampling continued as per the sampling schedule.

2.13.5 Experimental trial day sampling

Resting venous blood samples of 1.2 mL drawn into a monovette with anticoagulant (S-Monovette Glucose, Sarstedt, Germany) for the determination of plasma glucose (pharmacodynamics [PD]) and 1.2 mL was drawn into a monovette without coating (S-Monovette Serum, Sarstedt, Germany), for the determination of serum insulin (pharmacokinetics [PK]) were taken at 08.25 (-5min). Another PD/PK sample was taken at 08.30 (0 min) immediately prior to insulin injection. Thereafter, venous blood sampling (2 X 1.2 mL) followed a schedule that separated samples by 5-, 10-, and 15-minute intervals (**Table 24**).

Additional venous blood samples were taken in and around the exercise session for future secondary outcome analysis. At the start (60 min), middle (82 min), and end (105 min) of exercise two separate samples of 4 mL (4 mL K_2EDTA or K_3EDTA Vacutainer, Becton, Dickinson and Company, USA) and 5 mL (5 mL Aprotinin Vacutainer, Becton, Dickinson and Company, USA) of venous blood were drawn into vacuumed tubes.

2.13.6 Trial day treatment of hypoglycaemia and hyperglycaemia

Trial day hypoglycaemia was defined as blood glucose concentrations ≤3.9 mmol.L^{-1} in-line with the ADA [202]. Immediately upon reaching this threshold, participants were given 10-20g of carbohydrate gel (Glucogel, BBI Healthcare, UK). All hypoglycaemic episodes, and treatments, were reported. If blood glucose measurements did not return to >3.9 mmol.L^{-1} within 15 minutes, the procedure was repeated. In the case of severe hypoglycaemia, participants would be given glucagon injection or, failing a blood glucose response to injection,

a 10% intravenous dextrose infusion and the visit would be cancelled. In the event of a loss of consciousness, the clinical research facility first aid plan would be performed.

If blood glucose was ≥17 mmol.L^{-1} and blood ketones ≥1.5 mmol.L^{-1}, a bolus dose of insulin aspart individualised to their correction factor was subcutaneously administered and recorded. Blood glucose concentrations ≥17 mmol.L^{-1} alone were not enough to warrant treatment and were, in part, expected after a carbohydrate-rich meal. In the event of an unscheduled administration of insulin aspart, the visit was truncated as the pharmacodynamic/pharmacokinetic samples would no longer be a result of the peri-exercise administered doses.

2.13.7 Processing venous samples

All venous samples were centrifuged (EBA 200, Hettich, Germany) at 5000 revolutions per minute for 5 minutes to separate plasma or serum from haematocrit. 360 µL plasma of the pharmacodynamic venous samples were aliquoted via pipette (Elite Adjustable-volume 1000 µL, Fischer Scientific, UK) with 1000 µL standard pipette tips (Sarstedt, Germany) into 2 mL screw-cap microtubes (Sarstedt, Germany) or push-cap microtubes (Sarstedt, Germany) and labelled (Tough Tags, Merck, Germany) for each sample timepoint. All labels designated study name, participant ID, visit ID, and analyte.

The before, during, and after exercise EDTA and Aprotinin venous samples were also centrifuged and separated into plasma aliquots of 400 µL and 500 µL. Pharmacokinetic samples were left at room temperature before centrifugation for at least 30 minutes to allow for clotting action to take place. 250 µL serum of the pharmacokinetic sample were aliquoted into different coloured microtubes, each labelled for the corresponding timepoint. The plasma and serum samples were then stored at -80ºC (Green Line, Skadi, China) for preservation until later analysis. Details of PD/PK sample analysis are in **Table 13**.

***Table 13**: Methods of PD/PK sample analysis*

Analyte	Medium	Type of assay	Manufacturer	System	Range
Glucose	Plasma	Glucose hexokinase	Roche Diagnostics	Cobas® C501 anay	0.11-41.6 $mmol.L^{-1}$
Insulin	Serum	Chemiluminescent	Siemens Healthineers	ADVIA Centaur® XPT	0.5-300 mU/L

2.14 Follow-up visit

A final visit was attended to re-evaluate the participant's eligibility in the study, take repeat measurements for comparison against screen visit values, and to provide the participant with an opportunity to ask any questions about, or reflect on, the study.

Following completion of all exercise tests, the participant and their diabetes consultant could decide if the participant wanted stay on insulin degludec and/or Fiasp/aspart. This concluded their participation in the study. Participants were paid an inconvenience allowance per main trial visit (four visits) and had travel expenses reimbursed where appropriate.

2.15 Data analysis

2.15.1 Study 1 data analysis

Standardized mean difference was calculated between reduced vs full dose trial arms using Hedges' *g* effect size. Effect size thresholds were classed as ≤0.20 = very small, 0.21-0.49 = small; 0.50-0.79 = moderate; ≥0.80 = large [203]. A restricted maximum likelihood (REML) random effects model was used to conduct the meta-analysis. Cochran's *Q* test was used as an initial indicator for the presence of heterogeneity. Higgin's I^2 statistic was used to evaluate the extent of heterogeneity, where ≤25% = low; 26-50% = moderate; 51-75% = high; >75% = very high heterogeneity [204]. Funnel plot inspection and Egger's regression test were used to indicate publication bias of the included trials. Random-effects meta-regression analysis was used to determine the impact of differing pre-exercise bolus insulin dose reductions on effect sizes. All statistical analysis and graphical plots were carried out using SPSS 29.0 statistical software (SPSS, Chicago, Illinois, USA).

2.15.2 Study 2 data analysis

CGM data were analysed according to the total 24-hour period for each day and was also split into day (06:00-23:59) and night (00:00-05:59). CGM data were stratified according to percentage time spent in predefined glycaemic ranges, in accordance with international consensus guidelines [1,188] : Level 2 hypoglycaemia (L2Hypo) <3.0 mmol.L^{-1}, Level 1 hypoglycaemia ≥3.0 to ≤3.8 mmol.L^{-1}, Euglycemia ≥3.9 to ≤10.0 mmol.L^{-1}, L1 hyperglycaemia (L1Hyper) ≥10.1 to ≤13.9 mmol.L^{-1}, and L2 hyperglycaemia (L2Hyper) >13.9 mmol.L^{-1}. Dysglycaemia refers to glucose outside of the euglycaemic range (<3.9 or >10.0 mmol.L^{-1}). All statistical analyses were carried out using SPSS 26.0 statistical software (SPSS, Chicago, Illinois, USA). Data were tested for normality using Shapiro-wilk test. Between group (Fiasp *vs*. IAsp) comparisons were made using independent t-test. Relationships between variables were assessed via general linear regression. Cross tabulation analysis was used to determine odds ratios between nominal values, with Fisher's Exact test used to identify statistical significance. p≤0.05 (two-tailed) was considered statistically significant.

2.15.3 Study 3 data analysis

Outlier identification

To identify outliers in time series data, an adjusted Hampel filter [205] was employed, as used in recent analyses of blood glucose-related time series data [206,207]. Adjustment was made after assessment of its aggression or leniency towards known outliers and known acceptable, but extreme, values (i.e., the apex or nadirs of steep curves). Where an outlier was identified (Equation 2), the value was checked (e.g., via visual inspection of a box and whisker plot) before being removed from the dataset.

$$x_s - m_i > (4 \cdot Median|x_i - m_i|) + (0.15 \cdot m_i)$$

Equation 2

Where:

x_s = the sample/datum

m_i = median for window length *i* around x_s (*i*=3 data points either side of x_s for this study))

x_i = given sample in window

Area under the curve calculation

Incremental area under the curve (AUC), over non-incremental AUC, was selected to accommodate different starting analyte concentrations. AUC was calculated via trapezoidal rule (Equation 3), as described previously in diabetes research [208].

$$A \approx \sum_{i=0}^{n-1} \left(\frac{yi + yi_{+1}}{2}\right) |xi_{+1} - xi|$$

Equation 3

Where:

A = Area under the curve

yi = y-value at the *i*th data point

xi = *x*-value at the *i*th data point

Calorimetry calculations

Exercise-related carbohydrate and fat oxidation were calculated from spirometric measurements via stoichiometric equations adjusted for moderate-intensity exercise [209]. For the purposes of this study where carbohydrate oxidation was dominant during moderate-intensity exercise, it was assumed that protein oxidation was negligible (Equation(s) 4).

Carbohydrate oxidation ($g.min^{-1}$) = $4.210 \cdot VCO_2 - 2.962 \cdot VO_2 - 2.37 \cdot n$

Fat oxidation ($g.min^{-1}$) = $1.695 \cdot VCO_2 - 1.701 \cdot VO_2 - 1.77 \cdot n$

Energy expenditure from 1 g carbohydrate (20% glucose and 80% glycogen) = 4.07 kcal

Energy expenditure from 1 g fat = 9.75 kcal

Equation(s) 4

Where *n* = urinary nitrogen excretion

Data analysis

All statistical analysis was performed on SPSS 29.0 (IBM, USA). As sample n<50, normality testing was carried out using the Shapiro-Wilk test [210]. Comparisons between the four trial arms were made using repeated-measures analysis of variance (ANOVA). Sphericity testing was performed using Mauchley's test of sphericity. Where the assumption of sphericity was violated, Greenhouse-Geisser correction was implemented. In instances of ANOVA significance, (pre-specified) post-hoc analysis via Bonferroni-corrected t-tests were performed to identify significance between all possible group pairings. Comparison of screen to final visit measurements were made using paired samples t-test. The metrics relating to maximum concentration (C_{max}) and time to maximum concentration (t_{max}) were individualised by identifying each participant's C_{max} and t_{max}. Comparison of t_{max} between glucose and insulin concentrations was made using an independent samples t-test. Comparisons of the change in glucose concentrations, both in standard units and as a rate of change, during exercise from C_{max} vs from start of exercise were also made using the independent samples t-test.

2.16 Candidate roles and responsibilities

The candidate had a lead role in all study processes (comprehensively from conception through to final analysis) in Study 1. Data collection was performed prior to candidate involvement in Study 2. Data identification, organisation, and analysis were all performed by the candidate as part of a secondary analysis of the data. The funding and initial design of Study 3 was established prior to candidate involvement. Subsequent adjustments to study design (as part of discussions with research team), ethical approval, performance of trials at Swansea University,

day-to-day liaison with Medical University of Graz team, sample handling, data exchange, and data analysis were all led by the candidate.

Chapter 3

The effects of full versus reduced pre-exercise bolus insulin dosing on changes in blood glucose during continuous exercise: a systematic review and meta-analysis

3.1 Introduction

The same physiological stressors induced by physical exercise that have been shown to provide numerous health benefits (e.g., Chimen et al. [211]), are the same stressors which can pose as a potent stimulant for glycaemic change during exercise in people with T1D. During non-fasted continuous moderate-intensity exercise, blood glucose concentrations decline at approximately -4.5 $mmol.L^{-1}.h^{-1}$ [159]. This decline comes as a result of increased skeletal muscle glucose update and the potential for relative hyperinsulinaemia in the immediate hours after exogenous insulin injection, promoting whole-body glucose uptake, inhibiting lipid oxidation, and inhibiting hepatic glucose output [212]. To avoid hypoglycaemia, people with T1D therefore need to carefully prepare for, monitor, and react to blood glucose changes around this modality of exercise. With the many factors that influence blood glucose concentrations, there are a multitude of glucose management strategies for maintaining glucose within target range [128]. Principle management strategies include insulin dosing adjustments, carbohydrate consumption, and exercise characteristic changes. While they are not mutually exclusive, each strategy provides some unique advantages, which are further detailed elsewhere [213]. When exercise is anticipated, bolus insulin doses can be reduced with the preceding meal, effectively reducing the insulin:carbohydrate ratio and causing an elevated glucose response to the meal, without the need to consume a higher quantity of carbohydrates.

Current recommendations for adjusting pre-exercise bolus insulin doses in MDI regimens are mostly congruent across different guidelines. In brief, insulin reductions are recommended on a continuum of both time and intensity, whereby each threshold increase in either is likely to cause a greater decline in blood glucose concentrations and therefore demands a greater reduction in insulin dose. A summary of guideline recommended pre-exercise bolus insulin dose reductions is provided in **Table 14**.

***Table 14**: Summary of recommendations for pre-exercise bolus insulin dose adjustments based on current guidelines* [6,128,214].

Exercise intensity	**Exercise duration**	
	30 min	**60 min**
Mild aerobic exercise (~25% VO_{2max})	-25%	-50%
Moderate aerobic exercise (~50% VO_{2max})	-50%	-75%
Heavy aerobic exercise (70-75% VO_{2max})	-75%	-
Intense aerobic or anaerobic exercise (>80% VO_{2max})	No reduction recommended	-

Despite the agreement in these dose reductions, there still exists a relative paucity of information. In the ADA consensus statement by Colberg and colleagues [6], evidence supplying guidelines on pre-exercise insulin reductions was rated B ("supportive evidence from well-conducted cohort studies" [215]). Further, only the same three to four studies where MDI insulin reductions are used are referenced by guideline recommendations [167,172,176,178]. These studies present a group of well-designed randomised controlled trials, albeit using a variety of exercise protocols, in which some employ just one insulin reduction arm (i.e., a comparison of insulin dose reductions is not the primary outcome in these studies). Although this serves as a useful platform to prescribe insulin reductions based on previously reported exercise protocols, there is a lack of understanding of how different insulin reductions affect changes on blood glucose within exercise when employing the same exercise protocol.

Previous work has detailed how a reduction in pre-exercise bolus insulin dose can provide elevated blood glucose concentrations at the start of exercise [216]. This may exert a protective effect against hypoglycaemia as the exercise-related decline in blood glucose is starting from a point further away from the hypoglycaemic threshold. However, this is under the assumption that the decline in blood glucose during exercise is similar when using insulin dose reductions *vs.* without. Evaluating the effect of insulin dose reductions on the change in blood glucose during exercise based on inter-study comparisons is severely limited by the multiple variables inconsistent between study protocols that may greatly impact blood glucose (e.g., duration, intensity, pre-exercise meal characteristics, insulin type, etc.). While individual studies have investigated the effects of using dose reductions against full dose before exercise, these represent isolated analyses [171,173,178,217].

Studies are increasingly including the use of the latest generation of ultra-rapid-acting (and ultra-long-acting) insulins as part of study protocols. The divergence in pharmacokinetic profiles of these insulins compared to previous generations presents a new variable that has the potential to influence the way blood glucose changes with exercise. Hence, it is timely to assess the current evidence of how the implementation of pre-exercise insulin dose reductions influences the change in blood glucose during exercise via a multi-study comparison analysis.

The aim of this study was therefore to analyse the rate of change of blood glucose concentrations amalgamated from intra-study comparisons comparing full and reduced bolus insulin dosing in people with T1D in studies identified through a systematic review.

3.2 Methods

A systematic review was performed adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2020) [190]. The research question and primary objective was organised using the Patient, Intervention, Comparison and Outcome (PICO) format (**Table 15**).

***Table 15**: PICO framework for this systematic review*

Patient	People with type 1 diabetes using a multiple daily insulin regimen.
Intervention	Acute exercise performed with a pre-exercise bolus insulin reduction and measured effects on blood glucose.
Comparison	Comparisons primarily between normal (full) doses and reduced doses of insulin.
Outcome	Blood or interstitial glucose concentrations or other derived metrics from these measurements.

3.2.1 Key eligibility criteria

The full list of eligibility criteria is provided in Section 2.3. Key eligibility criteria based on the PICO framework include: (1) Participants must be diagnosed with T1D and using MDI regimens, with the insulin types being specified; (2) Study protocol must contain at least two trial arms that allow the comparison between the use of a full bolus insulin dose against a reduced bolus insulin dose, taken with a meal prior to an acute continuous exercise session; (3) The relative or absolute change in blood or interstitial glucose from pre- to post-exercise must be included and reported in $mmol.L^{-1}$ or $mg.dL^{-1}$. The search was limited to randomised controlled trials published in peer-reviewed journals written in the English language.

3.2.2 Search strategy

The systematic review was performed on electronic bibliographic databases relevant to the research area: Embase, MEDLINE, Web of Science, SPORTDiscus, CINAHL and CENTRAL. The search terms employed in this systematic review were split into four key themes, in-line with the PICO research question: 1) The inclusion of people with T1D, 2) the inclusion of an exercise component, 3) the inclusion of a blood or interstitial glucose related outcome, and 4) the exclusion of references to type 2 diabetes. The search was conducted using no minimum date of publication, up to 12th July 2023. All search terms were applied - and individualised/formatted according to the platform - to all databases. The full search term list is provided in Section 2.4.2. The search strategy was developed to balance including as many relevant studies as possible *versus* excluding as many irrelevant studies as possible. A list of studies that were known to be relevant to the research question was generated by the author and initial search strategies were developed against their inclusion of these studies (Appendix A). The search strategy was further peer-reviewed by an independent specialist via the Peer Review of Electronic Search Strategies (PRESS) checklist [190].

3.2.3 Selection process

Search results were exported via a referencing software (Endnote, Clarivate, USA) to a systematic review manager software (Covidence, Australia). Duplicate records were logged and removed automatically at this stage (**Figure 10**). Two reviewers (J.P. and C.N.) independently screened the title and abstract of each record. Instances of conflict of decisions were discussed and resolved between the reviewers, involving the consultation with a third reviewer (R.B.) where necessary. Records that were deemed eligible underwent full review independently by the same two reviewers.

3.2.4 Data extraction

Relevant data from these studies were then extracted by the primary author into an electronic spreadsheet (Excel 16, Microsoft Corporation, USA). In instances where any one study involved multiple trial arms that met eligibility criteria, these arms would be analysed separately. The primary outcome of blood glucose change from pre- to post-exercise was extracted from the individual trial arms alongside its respective pre-exercise bolus insulin dose. Where the rate of change of blood glucose was reported, this value was extracted in place of the non-time-relativised change of blood glucose to account for study-specific differences in exercise durations and protocols. In the absence of this metric, the rate of change of blood

glucose (BG_{ROC}) was calculated in relation to the reported exercise session duration, as given in *Equation 5*.

$$BG_{ROC} = \frac{BG_{post-exercise} - BG_{pre-exercise}}{Time_{post-exercise} - Time_{pre-exercise}}$$

Equation 5

To allow for the calculation of standardised mean differences, instances where studies reported variability metrics around the mean other than the standard deviation were converted to standard deviation. Campaigne et al.[217] only reported the primary outcome mean and standard graphically. For this paper, a conversion process was conducted via graphical digitisation software (PlotDigitizer, USA), in accordance with the Cochrane Handbook for Systematic Reviews [218]. McCarthy et al.[171] reported two trials of full doses in the same study as two trials with reduced doses. Following inspection, the two trials were similar enough in outcome variables (the difference between the two calculated as a 'small' effect size) to be averaged, providing a single comparator full dose trial arm.

Where HbA_{1c} was not provided in units of $mmol.mol^{-1}$ (The International Federation of Clinical Chemistry and Laboratory Medicine [IFCC]), *Equation 6* and *Equation 7* were used to convert from % to $mmol.mol^{-1}$ for means and standard deviations, respectively [219,220].

$$IFCC\ (mmol.mol^{-1}) = (10.93\ X\ HbA1c\ [\%]) - 23.50$$

Equation 6

$$IFCC\ (mmol.mol^{-1}) = (10.93\ X\ HbA1c\ [\%])$$

Equation 7

Where HbA_{1c} % is measured using standardisation provided by the National Glycohaemoglobin Standardisation Program (NGSP)[221].

3.2.5 Data analysis

All statistical analysis and graphical plots were carried out using SPSS 29.0 statistical software (SPSS, Chicago, Illinois, USA). Standardized mean difference was calculated between reduced vs full dose trial arms using Hedges' *g* effect size. Effect size thresholds were classed as 0.00-0.20 = very small, 0.21-0.49 = small; 0.5-0.79 = moderate; >0.80 = large [203]. A REML random effects model was used to conduct the meta-analysis. Cochran's *Q* test was used as an initial indicator for the presence of heterogeneity. Higgin's I^2 statistic was used to evaluate the extent of heterogeneity, where 0-25% = low; 26-50% = moderate; 51-75% = high; >75% = very high heterogeneity [204]. Funnel plot inspection and Egger's regression test were used to indicate publication bias of the included trials. Random-effects meta-regression analysis was used to determine the impact of differing pre-exercise bolus insulin dose reductions on effect sizes.

3.3 Results

3.3.1 Study selection

A total of four randomised controlled studies were extracted from an initial search of 5882 results to form the meta-analysis (**Figure 10**) [171,173,178,217]. Of these search items, 2880 were removed via duplication identification, from which a further 2695 were removed via dual reviewer independent screening. 303 of the remaining search items were removed via full screen review, where the three most common reasons included 'No insulin reductions employed' (e.g., studies performed without insulin in the fasted state), 'No insulin reduction comparison to MDI full dose' (e.g., only one reduced dose employed), and 'Wrong study design' (e.g., clamp studies).

The total sample size of the four studies included in the meta-analysis was n = 38. Of the four studies, three used two or more unique trial arms with different dose reductions, compared to the full dose arm(s). These were separated into individual trial comparisons to provide a total of nine trials analysed in the meta-analysis. The total sample size of these compared trial arms was n = 80. Uniquely, the study by Rabasa-Lhoret et al. (2001)[178] investigated three different conditions – with varying exercise duration and intensities – under which a reduced insulin dose was compared to a full dose.

3.3.2 Study characteristics

Characteristics of the participants within the included studies are detailed in **Table 16**. Characteristics of the pre- and within-exercise study protocols are detailed in **Table 17**. All studies were performed using adult participants with T1D with moderate to fair glucose control (relative to <6.5% [48 mmol.mol^{-1}] target threshold, set by the National Institute for Health and Care Excellence [NICE] guidelines [222]) using a MDI dosing regimen. Pre-exercise bolus insulin dose reductions included -25% (n=1), -50% (n=6), and -75% (n=2). The pre-exercise meal included a major carbohydrate component which was consumed 60-120min before exercise in all study protocols. Exercise intensities were classified as low (n=1), moderate (n=6), and vigorous (n=2) [223]. Exercise sessions were either 30 minutes (n=3), 45 minutes (n=3), or 60 minutes (n=3) in duration. Venous blood was used for determining blood glucose concentrations for all studies.

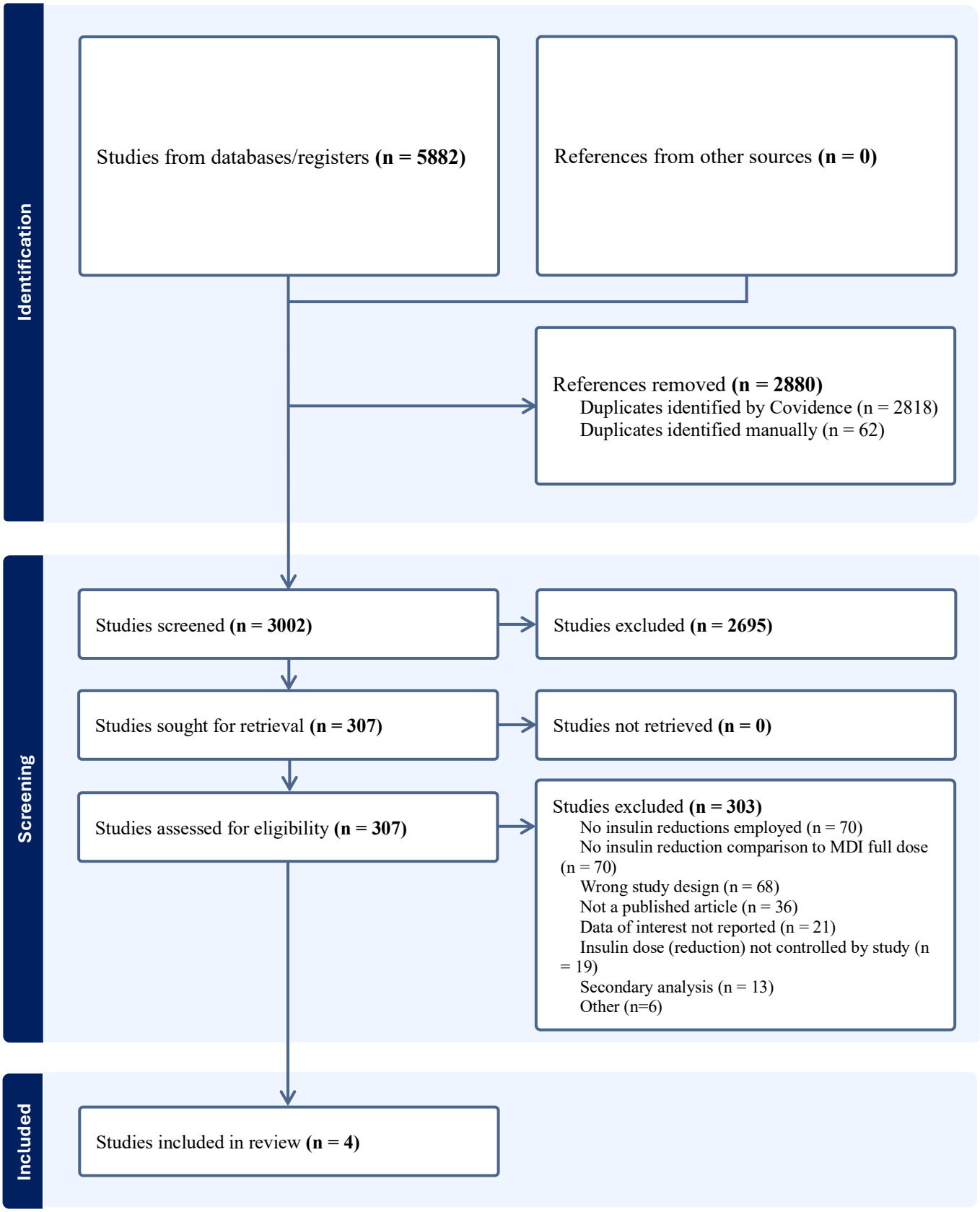


Figure 10: *PRISMA flow diagram of study selection. MDI, multiple daily injection regimen.*

***Table 16**: Inter-study participant characteristics.*

Authorship and date of publication	Sample size (M:F)	Age (years)	HbA1c (%) [mmol.mol]	Diabetes duration (years)	VO_{2peak} ($mL.kg^{-1}.min^{-1}$)	Basal insulin	Bolus insulin
Campaigne et al. (1987)[217]	9 (9M:0F)	35±2	7.4±0.3 [57.4±3.3]	17±3	ND	Intermediate-acting insulin	Soluble insulin
McCarthy et al. (2020)[171]	16 (13M:3F)	35±14	7.2±1.3 [55.2±14.2]	14±11	40.3±10.3	Degludec	Aspart
Rabasa-Lhoret et al. (2001)[178]	6 (6M:0F)	33±3	6.0±0.0 [43.9±0.0]	13±3	37.8±3.5	Ultralente	Lispro
West et al. (2010)[173]	7 (6M:1F)	34±2	8.3±0.1 [60.2±2.9]	16±1	ND	Glargine (U100)	Aspart (n=5) or lispro (n=2)

ND, No data; VO_{2peak}, peak rate of volume of oxygen uptake.

***Table 17**: Inter- and intra-study pre- and within-exercise protocols.*

Authorship and date of publication	Pre-exercise insulin adjustment (% reduction from normal dose)	Pre-exercise insulin and feeding timing (minutes before start of exercise)	Pre-exercise feeding CHO quantity	Pre-exercise CHO type/characteristics (macronutrient profile as % of total kJ)	Exercise modality	Intensity (%VO_{2peak})	Duration (mins)
Campaigne et al. (1987)[217]	0	Insulin 105 min before start of exercise. Feeding 75 min before start of exercise	ND	Mixed meal (52% CHO, 32% Fat, 16% Protein)	Cycling	60	45
	-50						
McCarthy et al. (2020)[171]	0	60	1g per kg of body mass	Brown rice-based vegetable meal (65% CHO, 20% Fat, 15% Protein)	Cycling	60	45
	-50						
	-50						
Rabasa-Lhoret et al. (2001)[178]	0	90	75 g	Bread, margarine, one egg, herbal tea (ND)	Cycling	50	30
	-50					75	30
	0					25	60
	-50					50	30
	0					50	60
	-75					50	60
West et al. (2010)[173]	0	120	60 g	Wheat-based foods and peaches (90% CHO, 7% Fat, 3% Protein)	Running	70	45
	-25						
	-50						
	-75						

CHO, carbohydrate; ND, no data.

Table 18 shows the (non-weighted) rate of change in blood glucose during exercise under the included study trial arms.

Table 18*: Rate of blood glucose change during exercise in included study trial arms (raw data). These data are listed in the same order as* ***Figure 11****.*

Authorship and date of publication	**Pre-exercise bolus insulin (% reduction from normal dose)**	**Rate of change of blood glucose during exercise ($mmol.L^{-1}.min^{-1}$)**	
		Pre-exercise bolus insulin: Reduced dose	**Pre-exercise bolus insulin: Full dose**
Campaigne et al. (1987)[217]	0		-0.100
	-50	-0.105	
McCarthy et al. (2020)[171]	0		-0.115
	-50	-0.090	
	-50	-0.080	
Rabasa-Lhoret et al. (2001)[178]	0		-0.049
	-50	-0.054	
	0		-0.112
	-50	-0.075	
	0		-0.100
	-75	-0.090	
West et al. (2010)[173]	0		-0.136
	-25	-0.096	
	-50	-0.122	
	-75	-0.071	
Mean		**-0.088**	**-0.111**

3.3.3 Meta-analysis

Blood glucose decreased in all conditions from pre- to post-exercise (**Table 18**). The pooled analysis of the 9 included trials showed that there was an overall lower rate of decline in blood glucose concentrations when using a reduced insulin dose compared to when taking a full dose, indicated by a Hedges' *g* effect size estimate of 0.59 (95% CI: 0.17 to 1.01; p=0.006). This effect size was determined to be 'moderate' in size ($0.50 < 0.59 > 0.80$) [203]. The pooled analysis is depicted in (**Figure 11**). There was only a trend towards heterogeneity between studies (Q=15.4; p=0.051), where the extent of heterogeneity between studies was moderate (I^2=44.1%) [204]. Hence, 44% of the variability in effect size across studies in this meta-analysis can be attributed to heterogeneity rather than chance.

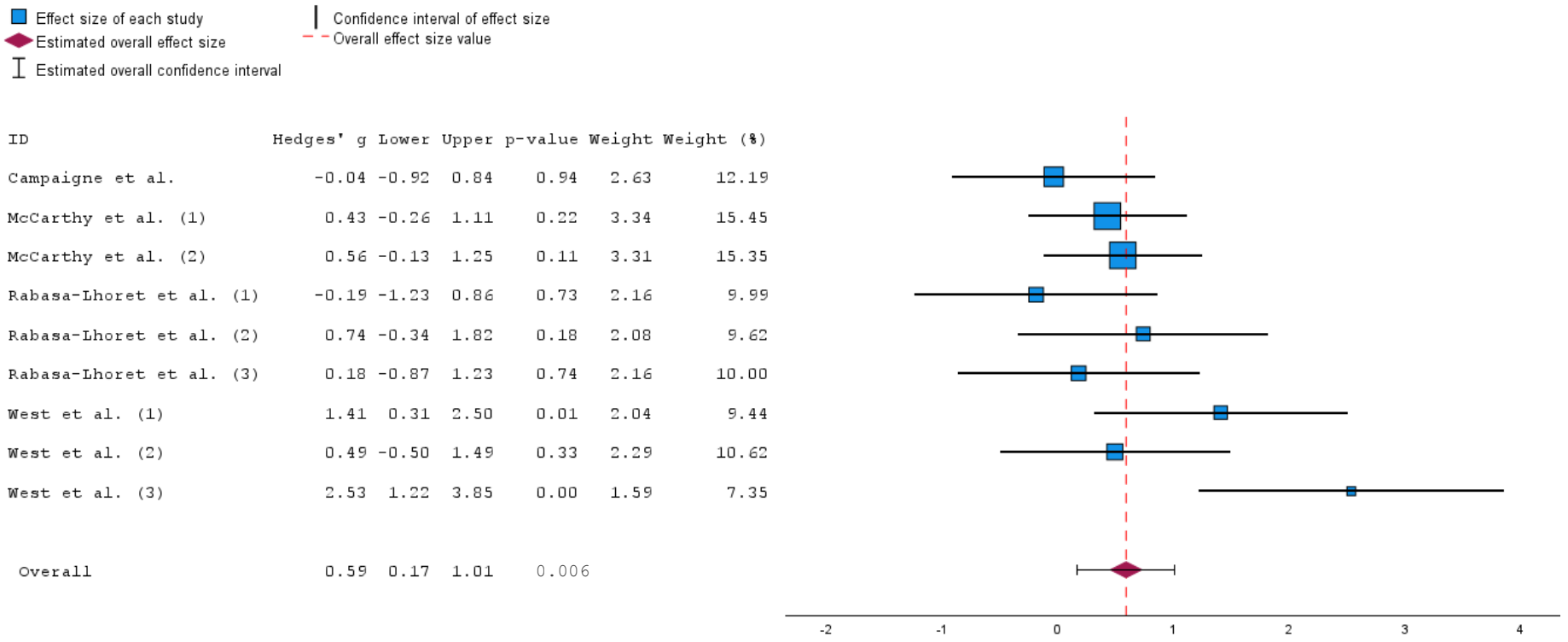


Figure 11: *Forest plot of randomised controlled trials comparing the effect of pre-exercise bolus insulin reduction on the rate of change of blood glucose concentrations during exercise in a random effects model (n=9 trials). Positive values indicate a slower rate of change. Study effect sizes, relevant to the reduced dose blood glucose changes, are listed in the same order as* ***Table 18***. *Studies with multiple comparator trial arms are distinguished via numbers in brackets after the study ID.*

To assess publication bias, a funnel plot with Egger's regression test was used (***Figure 12***). We determined no asymmetry in the funnel plot, which was confirmed via non-significant Egger's test (p=0.343).

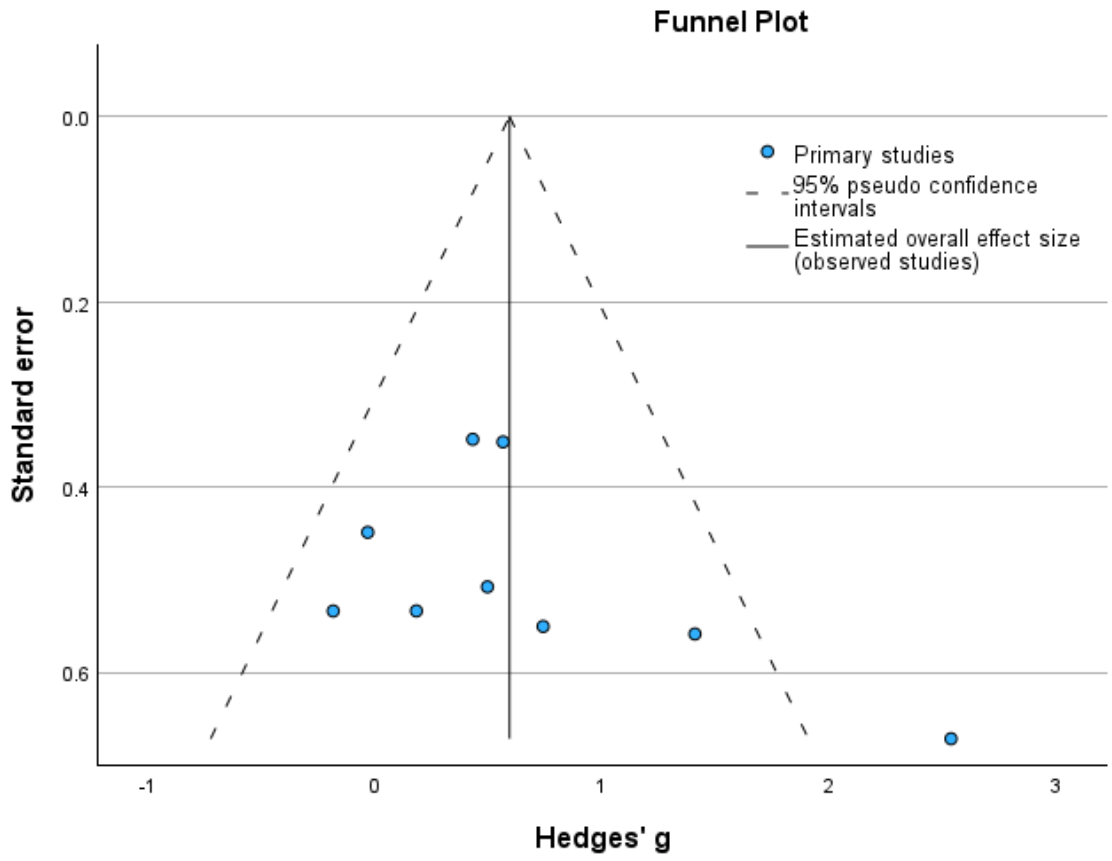


Figure 12*: Funnel plot of study trials' standard errors. Egger's test,* p*=0.343.*

To ascertain the effect of the extent of pre-exercise bolus insulin dose reduction on the rate of blood glucose change during exercise, a random-effects meta-regression was conducted. Given the limited number of trials that were included in this analysis (i.e., < 10), only insulin dose was assessed as a moderator variable as part of the primary analysis (**Figure 13**). There was no association between the insulin dose reduction and the rate of blood glucose change effect size estimate (β<-0.01, R^2<0.01, p=0.835).

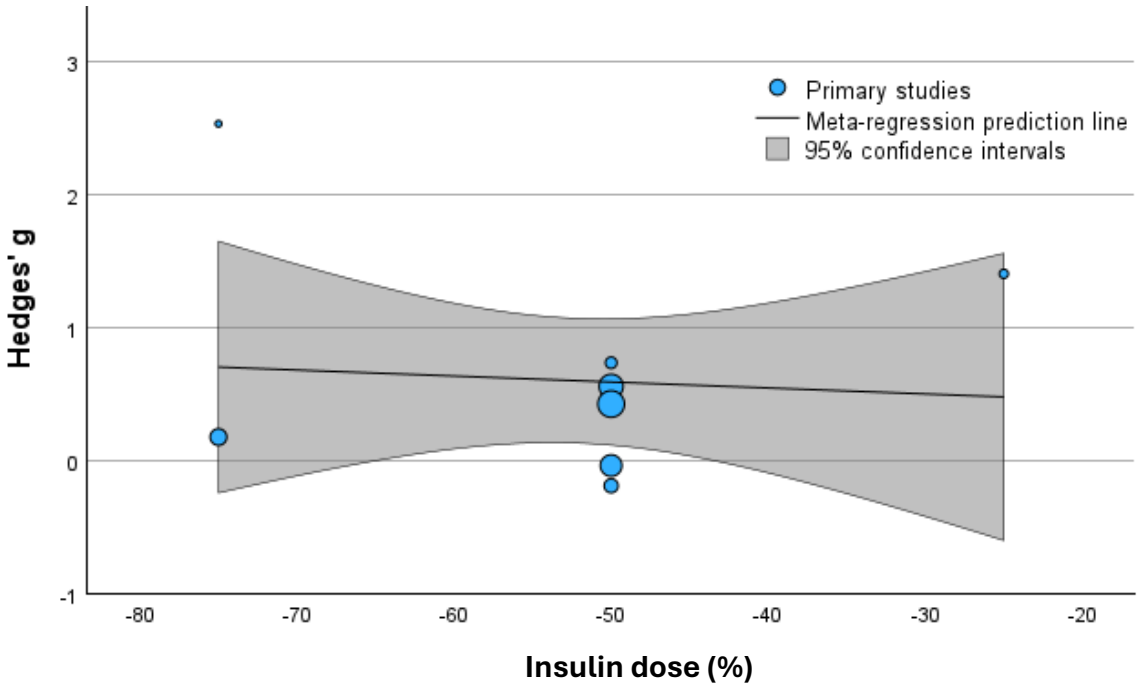


***Figure 13**: Scatter plot with meta-regression line for (reduced) insulin dose predictor of rate of change of blood glucose during exercise effect size.*

3.4 Discussion

The current systematic review identified nine trial arms from four studies from an initial non-duplicated search result of 3002 search items to compare the rate of blood glucose change during exercise when employing pre-exercise bolus insulin reductions *vs.* full dose. The difference in the rate of blood glucose decline when using reduced against full dosing was standardised and used in a meta-analysis. This is the first meta-analysis to show that the rate of blood glucose decline during exercise is lesser when using a reduced insulin dose *vs.* when using a full dose.

Blood glucose concentrations declined across all conditions, in alignment with other studies employing either moderate-vigorous exercise for moderate durations or low-intensity exercise for prolonged (≥60 minutes) durations [128]. The results of the meta-analysis are in concordance with studies that have compared the exogenous glucose requirements in the presence of low *vs.* high insulin concentrations under clamp [177,224–226] and MDI (non-clamp)[227] conditions. When performing continuous exercise at moderate intensity, all studies refer to an increase in exogenous glucose requirements to maintain glucose concentrations and avoid hypoglycaemia when insulin concentrations are higher. This has been shown to be the product of both an

increase in the rate of glucose disappearance and an inhibition of endogenous glucose production [225]. It cannot be differentiated from our meta-analysis what different dose reductions may have on either the rate of glucose appearance or the rate of disappearance, rather, the results indicate the overall balance shifted towards a net disappearance of blood glucose that is lower when employing pre-exercise insulin reductions.

Francescato et al.[227] investigated the effect of performing exercise at different time intervals from the previous regular insulin injection on the carbohydrate requirements to avoid hypoglycaemia. To this effect, insulin concentrations were lower with each interval (1.0, 2.5, 4.0, and 5.5 hours) further from the time of injection. The quantity of alimentary carbohydrates required to avoid hypoglycaemia was linearly related to the average insulin concentration during each trial (p<0.001), which consisted of 1 hour of cycling at ~50% VO_{2peak} for 1 hour. Although this finding is in agreement with the current meta-analysis, it should be noted that different dosing volumes may alter the pharmacokinetic profile of the insulin [228], potentially altering the glucose dynamics during exercise – a variable that would not have been present in the study performed by Francescato and colleagues where dosing was identical between trial days.

To explore whether the extent of dose reduction would influence the (standardised) rate of change of blood glucose, a meta-regression was performed. This analysis showed no relationship between the two variables (p=0.835). This finding counters the investigations performed by other labs which demonstrated a dose-response relationship between insulin infusion and carbohydrate administration rates during moderate-intensity exercise [177,224–226]. It is likely the meta-regression model used in the current study was biased towards the dose reduction patterns used in the study protocols. Only three different doses were included in the meta-analysis, with a heavy bias towards 50% reductions. Based on the discrepancy between these findings, a greater number of studies covering a more even spread of dose reductions may yield a more representative outcome.

This meta-analysis has shown that the rate of blood glucose decline is non-similar when participants use a full versus reduced dose of insulin during the same exercise bout, in the context of moderate heterogeneity (I^2=44.1%). This indicates that the role of altering insulin dose reductions goes beyond the goal of starting exercise with elevated blood glucose concentrations. Hence, when exercising following a full pre-exercise bolus dose, greater emphasis should be placed on monitoring glucose concentrations throughout the exercise

session as the decline is likely to be quicker. Although there was no impact of the extent of dosing reduction on this decline, it is plausible that the findings of previous studies could be applied to this context, where smaller dose reductions (e.g., -25%) – and therefore higher insulin concentrations – may also demand greater vigilance of blood glucose tracking within exercise.

The reduction of insulin requires anticipation and planning prior to an exercise session. In instances where an individual is unable to reduce insulin prior to engaging in physical activity that would otherwise warrant a reduction, awareness that blood glucose concentrations may not only start lower, but also decline quicker, would aid in the exercise-related management of glycaemia (e.g., checking interstitial glucose concentrations more often).

3.4.1 Strengths and limitations

This is the first meta-analysis to compare the effects of taking a full insulin dose versus a reduced insulin dose on the rate of change of blood glucose during continuous exercise. A strength of this study lies in the derivation of effect sizes from within-study trial comparisons, effectively reducing the influence of other variables on blood glucose, assuming conditions were kept consistent between study trials. Further, the search terms used in the systematic review were made more conservative following initial search tests on known relevant studies. The studies included in the systematic review, following the key themes, were effectively all studies in the used databases that investigated people with T1D that was related to physical activity or exercise that included blood or interstitial glucose outcomes. Nevertheless, only four studies, which yielded nine applicable trials, were identified, limiting the overall sample size and the capacity to perform multiple meta-regression analysis with further moderator variables [229]. In the study performed by Campaigne et al.,[217] post-exercise blood samples were taken 15 minutes after the end of exercise, while all other studies sampled immediately following exercise cessation. While this disparity in methods would likely have a minimal effect on the intra-study full *vs.* reduced dose comparison, it is a likely source of effect size heterogeneity in the analysis.

3.4.2 Future recommendations

This study has shown an initial disparity in the rate of blood glucose decline during exercise when using full versus reduced insulins. However, further studies that compared different pre-exercise insulin dose reductions would benefit future analyses in exploring their effect on blood

glucose. Additionally, more studies employing the latest generation of ultra-rapid-acting insulins (i.e., Fiasp and ultra-rapid-acting-lispro) would benefit the evidence based for the comparison between insulin dosing strategies, owing to the different pharmacokinetic profiles. It is likely that the use of these insulins will continue to grow; hence, further studies including their usage are warranted.

3.5 Conclusion

The rate of blood glucose concentration decline during exercise in this analysis was lesser when pre-exercise bolus insulin dose reductions were used compared to full insulin dose under the same study protocols. This finding may help guide individuals with T1D in understanding the trajectory of blood glucose concentrations during exercise depending on the glycaemic strategies used, or unused, prior to exercise start.

Chapter 4

Glycaemic impact of faster-acting insulin aspart as part of a multiple daily insulin regimen in professional cyclists with type 1 diabetes

4.1 Introduction

The need to safely incorporate insulin therapy into exercise sessions remains paramount for individuals with T1D to maintain glucose control before, during, and after exercise, while reaping the health benefits of physical exercise. There now exists a wealth of studies that have demonstrated effective glucose management strategies around exercise by manipulating insulin therapy (basal/bolus dosage and timing) [169,171,230], carbohydrate consumption (type, amount, timing) [175,231], and exercise variables (modality, duration, intensity) [232–234]. Without careful planning to conduct exercise, people with T1D are susceptible to deviations in blood glucose concentrations. Many studies have focused on exercise regimes consisting of moderate-intensity exercise lasting between 30-60 minutes where the synergistic effect of relative hyperinsulinaemia and increased uptake of glucose by working muscles cause blood glucose levels to drop, in the context of an impaired glucoregulatory system. The decline in blood glucose imposes the risk of exercise-induced hypoglycaemia – a cited barrier to regular participation in physical activity by those with T1D [7]. However, only a handful of studies have investigated longer durations of exercise, at sustained moderate intensities, in this cohort [235,236].

The introduction of novel bolus insulin analogues brings differing pharmacodynamic profiles. In the context of exercise with T1D, the individual must administer the insulin in recognition of the insulin's specific glucose-lowering ability to enter the exercise session, and recover from it, with appropriate glucose concentrations. Fiasp represents the latest generation of ultra-rapid-acting insulin that has shown a shorter onset of appearance and time until peak concentrations than its predecessor, insulin aspart [237].

Considering the dearth of literature investigating prolonged exercise in people with T1D, and the absence of information on the incorporation of Fiasp into an exercise routine, observations on the use of Fiasp around prolonged bouts of endurance exercise in comparison to the already established insulin aspart are warranted. Current understanding of Fiasp and insulin aspart comparison in real world setting has largely come from studies where insulin is delivered as part of an automated insulin delivery system (AID), and elements of controlled laboratory conditions are present [180–182]. Previous observational studies have investigated inter-day comparisons in time-in-range metrics in an elite cyclist group under training [185] and racing [186] conditions, yet comparisons have not been made between different insulins used by the professional riders with focus on the consequent glycaemic impact experienced within the long-duration (e.g. >4 hours) cycling being performed.

The aim of this study was therefore to explore the glycaemic impact of incorporating Fiasp in a multiple daily injection insulin regimen, in comparison to insulin aspart, in professional endurance cyclists with T1D.

4.2 Methods

4.2.1 Study design

This is a retrospective observational study design to detail the glycaemic time in range for thirteen professional cyclists with T1D using either Fiasp or insulin aspart as the bolus component of their insulin regime. Thirteen male cyclists with T1D from one professional cycling team volunteered to participate with the study. Informed consent was obtained from all riders after full verbal description of the study. Participants were retrospectively separated into two groups: 1) those who used faster-acting insulin aspart (n=6; Fiasp group) and 2) those who used insulin aspart (n=7; IAsp group). Data were then analysed as comparison between the two groups to determine observational differences in glycaemia during the training camp.

4.2.2 Participants' insulin regimes

All participants were using MDI regimen. Riders were all using either Fiasp (n=6) or insulin aspart (n=7) as their rapid-acting insulin. Distribution of basal insulin therapy is described in **Table 19**. Cyclists' self-reported total insulin doses ranged between 24±14 (minimum) and 28±15 (maximum) IU daily, consisting of a bolus of 11±4 (minimum) to 12±4 (maximum) IU daily, and basal of 13±10 (minimum) to 16±12 (maximum) IU daily. Daily (calculated per hour) bolus insulin doses were reduced over the course of the 5-day competitive event (p=0.03), while no adjustments were made to basal insulin dosing (p=0.64) [186].

***Table 19**: Participant insulin therapy.*

Group	**Fiasp**		**Aspart**	
Insulin parameter	**No. participants**	**% study participants**	**No. participants**	**% study participants**
Glargine U300	1	8	1	8
Glargine	3	23	4	31
Detemir	2	15	2	15

Detemir taken n=1 bi-daily, n=1 once-daily, for both groups.

4.2.3 Cycling training schedule

Participants took part in a 9-day training camp in Spain, where they performed training rides on eight of the nine days. Training rides were on average (Mean±SD [range]) 132 ± 49 (18-200) km, 4.3 ± 1.5 (0.7-6.3) hours, performed at 69.9 ± 7.0 (50.5-91.1) % heart rate maximum, at an average power of 190.5 ± 34.8 (104.0-255.0) W (no difference between Fiasp and IAsp for any variables, p>0.05). Participants performed all race stages on an individual time-trial basis with a mobile power meter (Pioneer, USA) and with a cycle computer (Wahoo, Wahoo Fitness, USA) mounted on their bike which allowed the monitoring of cycle metrics and was later uploaded via the Training Peaks computerized cloud-based package (Training Peaks, USA). Heart rate was measured during training sessions using a portable chest strap (Garmin, USA).

From this same group of riders, and one additional rider also from the cycle team, six riders also competed in a 5-day road race as part of Union Cycliste Internationale (Tour of Slovenia). All riders who competed in the Tour of Slovenia used Fiasp. Informed consent was received additionally for the use of competition data. Data has been presented for this event in addition to training data to describe the use of Fiasp during competitive cycling, without comparison against insulin aspart in the same event. The methods of collecting data were identical between the training camp and competition.

4.2.4 Continuous glucose monitoring

Riders were each provided with a CGM system (Dexcom G6, USA) and wore the sensor for the entire training week. Recorded data from the sensor was linked to Clarity online platform (Dexcom, USA) which was later exported and analysed.

4.2.5 Data analysis

CGM data were analysed according to the total 24-hour period for each day and was also split into day (06:00-23:59) and night (00:00-05:59). CGM data were stratified according to percentage time spent in predefined glycaemic ranges, in accordance with international consensus guidelines [1,188]: Level 2 hypoglycaemia (L2Hypo) <3.0 mmol.L^{-1}, Level 1 hypoglycaemia (L1Hypo) ≥3.0 to ≤3.8 mmol.L^{-1}, Euglycemia ≥3.9 to ≤10.0 mmol.L^{-1}, L1 hyperglycemia (L1Hyper) ≥10.1 to ≤13.9 mmol.L^{-1}, and L2 hyperglycemia (L2Hyper) >13.9 mmol.L^{-1}. Dysglycaemia refers to glucose outside of the euglycaemic range (<3.9 or >10.0

mmol.L^{-1}). All statistical analyses were carried out using SPSS 26.0 statistical software (SPSS, Chicago, Illinois, USA). Data were tested for normality using Shapiro-wilk test. Between group comparisons were made using independent t-test. Relationships between variables were assessed via linear regression. Cross tabulation analysis was used to determine odds ratios between nominal values, with Fisher's Exact test used to identify statistical significance. $p \leq 0.05$ (two-tailed) was considered statistically significant.

4.3 Results

4.3.1 Overall glycaemia (in- and out of-ride)

Participant characteristics are detailed in **Table 20**.

Table 20*: Anthropometric and maximal cardiopulmonary exercise test data for all 13 participants during training camp.*

Characteristic	Mean±SD		P value
	Fiasp (n=6)	Aspart (n=7)	
Age (years)	25±4	28±5	0.173
Duration of diabetes (years)	10.2±3.2	11.0±6.4	0.770
Height (m)	1.77±0.05	1.78±0.07	0.734
Body mass (kg)	69.1±5.7	67.2±7.7	0.652
BMI ($kg.m^{-2}$)	21.7±1.7	21.2±1.5	0.574
HbA_{1c} (%)	6.6±0.5	6.9±0.6	0.613
HR_{max} (bpm)	193±9	190±10	0.595
P_{max} (W)	423±40	392±48	0.267
VO_{2max} ($L.min^{-1}$)	5.07±0.29	4.88±0.55	0.498
VO_{2max} ($mL.kg^{-1}.min^{-1}$)	72.2±4.2	71.3±4.5	0.748

In the average 24-hour period for each day of training camp recorded by the CGMs, including time spent cycling, participants were able to spend the majority of time (74.0 ± 18.8 %) in a euglycaemic state. Between group comparison revealed that Fiasp (80.3 ± 12.7 %) recorded a greater percentage of time in euglycaemia compared to IAsp (68.6 ± 21.3 %; p=0.004), concurrent with a lower time spent in L2Hypo in Fiasp (0.53 ± 1.33 %) compared to IAsp (3.45 ± 7.63 %; p=0.008). **Figure 14** depicts the comparisons for TIR stratified glycaemic states between the groups. The average peak interstitial glucose concentration recorded from all days and all riders were comparable between the two groups (Fiasp 11.3 ± 2.8 *vs* IAsp 11.6 ± 3.6 $mmol.L^{-1}$; p=0.643).

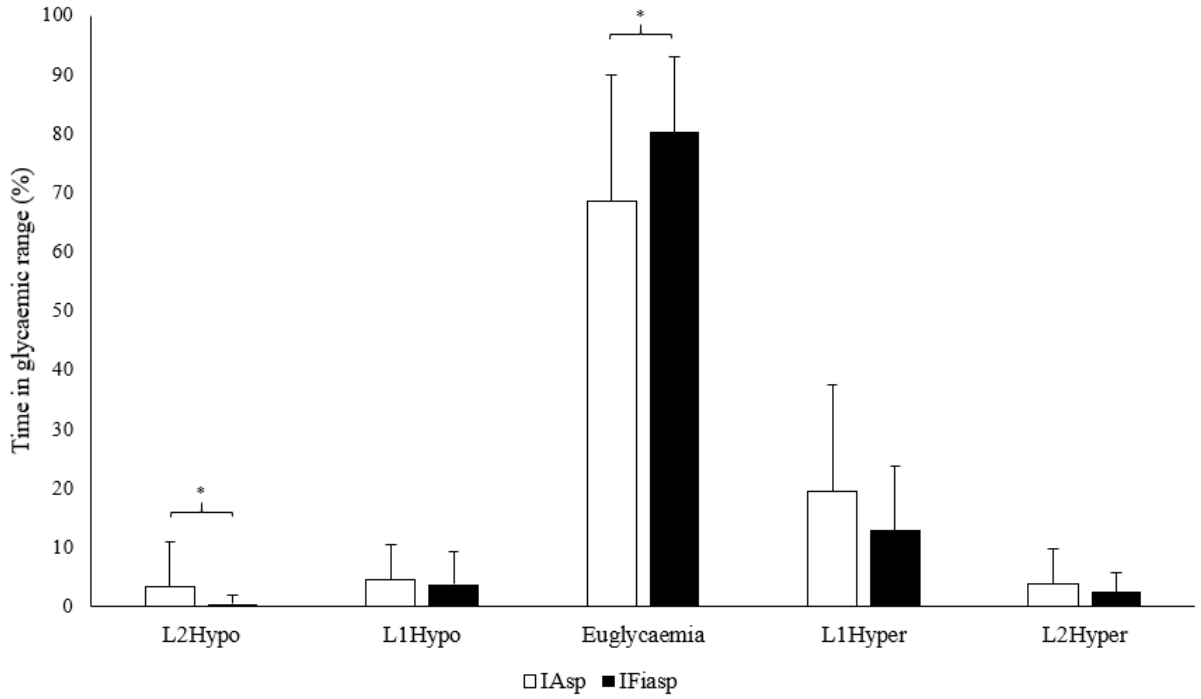


***Figure 14**: 24-h trace of time in range separated into categories of glycaemia during training camp. * Denotes p<0.05 for inter-insulin comparisons.*

When stratified into day and night periods, significant differences between the two groups extend to the same daytime L2Hypo (Fiasp 0.32 ± 1.03 *vs* IAsp 4.22 ± 13.94 %; *p*=0.002), and daytime euglycaemia TIR states (Fiasp 79.77 ± 11.98 *vs* IAsp 70.34 ± 21.12 %; *p*=0.013). Night-time L2Hyper was 5-fold higher in IAsp, which approached a statistically significant difference to Fiasp group (*p*=0.051). Full breakdown of glycaemic states during the two periods are presented in **Table 22**.

***Table 21**: Comparison of glycaemic ranges for Fiasp vs insulin aspart for day and night CGM data during training camp.*

Category of time in range	Value		P value
	Fiasp	IAsp	
Night			
L2 Hypo (%)	1.3±4.9	3.5±9.4	0.102
L1 Hypo (%)	6.1±14.0	5.1±11.2	0.950
Euglycaemia (%)	79.6±25.7	67.2±33.1	0.660
L1 Hyper (%)	11.5±19.14	17.4±26.4	0.382
L2 Hyper (%)	1.6±5.7	6.8±15.3	0.051
Day			
L2 Hypo (%)	0.3±1.0	4.2±13.9	*0.002**
L1 Hypo (%)	3.4±4.6	4.2±5.9	0.443
Euglycaemia (%)	79.8±12.0	70.3±21.1	*0.013**
L1 Hyper (%)	13.6±10.9	18.7±16.9	0.133
L2 Hyper (%)	2.9±4.4	2.5±3.8	0.704

IAsp, insulin aspart; L1Hyper, Level 1 hyperglycaemia; L2Hyper, Level 2 hyperglycaemia; L1Hypo, Level 1 hypoglycaemia; L2Hypo, Level 2 hypoglycaemia. * Denotes $p<0.05$.*

4.3.2 In-ride glycaemia

During cycle training sessions, mean interstitial glucose (Fiasp 8.0 ± 2.5 *vs* IAsp 7.7 ± 2.3 mmol.L^{-1}; p=0.463) and coefficient of variation (Fiasp 19.2 ± 10.2 *vs* IAsp 18.6 ± 8.8 %; p=0.754) were similar between the two groups. Average peak concentrations of glucose were also not different between Fiasp (10.8 ± 3.2 mmol.L^{-1}) and IAsp (10.2 ± 3.4 mmol.L^{-1}; p=0.389).

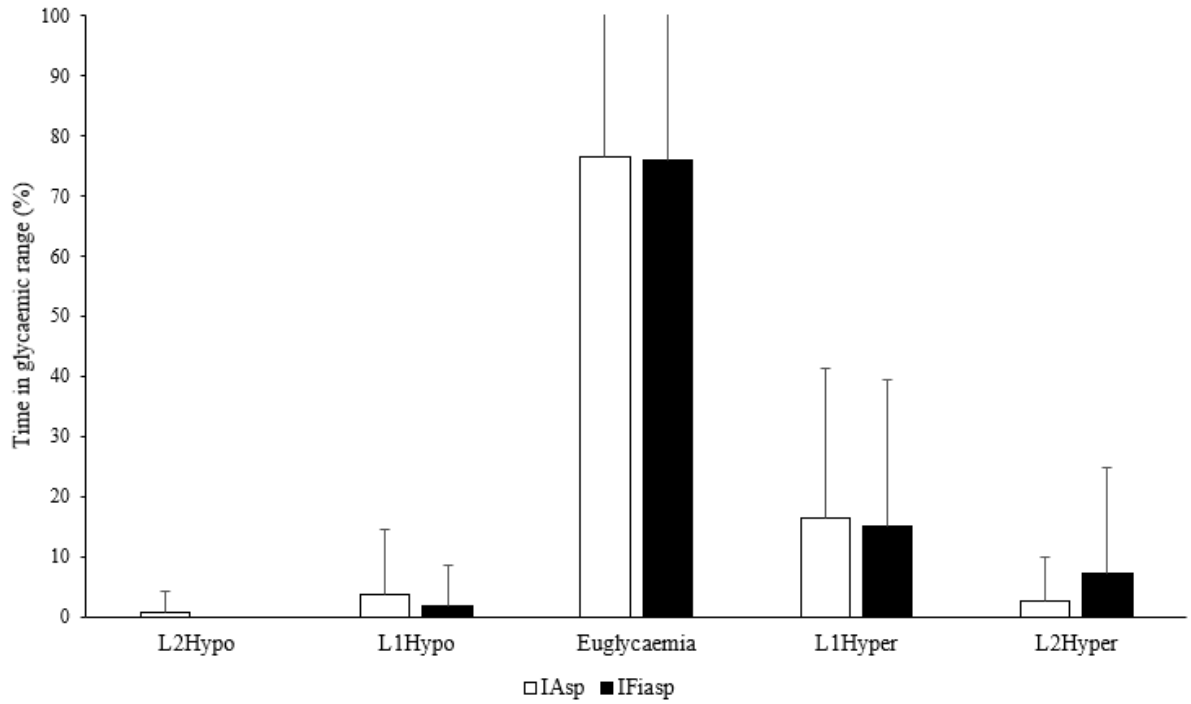


***Figure 15**: Within-exercise percentage of time in range separated into categories of glycaemia for riders using Fiasp and insulin aspart during training camp. L1Hyper, Level 1 hyperglycaemia; L2Hyper, Level 2 hyperglycaemia; L1Hypo, Level 1 hypoglycaemia.*

Figure 15 shows the percentage contributions to the glycaemic states to the time spent in the cycle training sessions. No significant differences were found when comparing in-ride glycaemic ranges (p>0.05). Riders maintained most time spent in euglycaemia while cycling when using either Fiasp (75.8 ± 32.7 %) or insulin aspart (76.6 ± 29.6 %; p=0.915). Ride duration was not associated with time in range in either Fiasp (R^2=0.01, p=0.592) or IAsp (R^2=0.01, p=0.631), nor was mean heart rate for Fiasp (R^2=0.07, p=0.239) or IAsp (R^2=0.06, p=0.146).

Table 22 presents the number of instances where participants experienced hyper- or hypoglycaemic events and the number of participants who experienced the instance of dysglycaemia. In 31 out of 104 total rides (29.8%), riders managed to maintain 100% of time in euglycaemia. Out of the thirteen riders, three riders in IAsp each experienced an instance of L2Hypo, whereas no participants from Fiasp had glucose concentrations extend below 3.0 mmol.L^{-1}. Fewer instances of L1Hypo were experienced in Fiasp compared to IAsp, while hyperglycaemic episodes were of similar frequency in both groups. There was no evidence to suggest that use of either of the insulin types was more associated with deviations from euglycaemia (odds ratio 1.31 [95% CI 0.63-2.71], p=0.577).

***Table 22**: Number of instances of dysglycaemia experienced by participants during the training camp and the number of participants in which these instances occurred. Numbers are taken from all 8 days of cycling.*

	L2Hypo (<3.0 mmol.L^{-1})		L1Hypo (≥3.0 to ≤3.8 mmol.L^{-1})		L1Hyper (≥10.1 to ≤13.9 mmol.L^{-1})		L2Hyper (>13.9 mmol.L^{-1})	
	Fiasp	IAsp	Fiasp	IAsp	Fiasp	IAsp	Fiasp	IAsp
Number of instances of dysglycaemia experienced	0	3	4	11	20	23	9	7
Number of participants to experience an instance of dysglycaemia	0	3	2	6	6	6	3	3

L1Hyper, Level 1 hyperglycaemia; L2Hyper, Level 2 hyperglycaemia; L1Hypo, Level 1 hypoglycaemia; L2Hypo, Level 2 hypoglycaemia.

4.3.3 Race event

The participant characteristics for the six riders who took part in the 5-day *Union Cycliste Internationale* road cycling race (Tour of Slovenia) are presented in **Table 23**.

***Table 23**: Anthropometric and maximal cardiopulmonary exercise test data for all 6 participants during cycling competition.*

Characteristic	**Mean±SD**
Age (years)	28 ± 4
Diabetes duration (years)	10 ± 6
Height (m)	1.8 ± 0.1
Body mass (kg)	68.3 ± 5.6
BMI (kg.m^{-2})	21.4 ± 1.6
HbA_{1c} (%)	6.4 ± 0.4
Heart $rate_{max}$ (beats.min^{-1})	187 ± 11
$Power_{max}$ (W)	409 ± 41
VO_{2max} (L.min^{-1})	5.0 ± 0.3
VO_{2max} (mL.kg^{-1}.min^{-1})	73.9 ± 4.3

BMI, body mass index; HbA_{1c}, glycated haemoglobin; VO_{2max}, maximum volume of oxygen uptake.

During the race event, the 24-h interstitial glucose concentrations recorded by CGM recorded over three-quarters of time spent in euglycaemic range (L2Hypo 0.8 ± 1.3%, L1Hypo 4.4 ± 3.5%, Euglycaemia 74.6 ± 12.0%, L1Hyper 16.6 ± 8.1%, L2Hyper 3.5 ± 3.5%). The average peak interstitial glucose concentration recorded from all days and all riders was classified as L1Hyper (13.5 ± 3.6 mmol.L^{-1}).

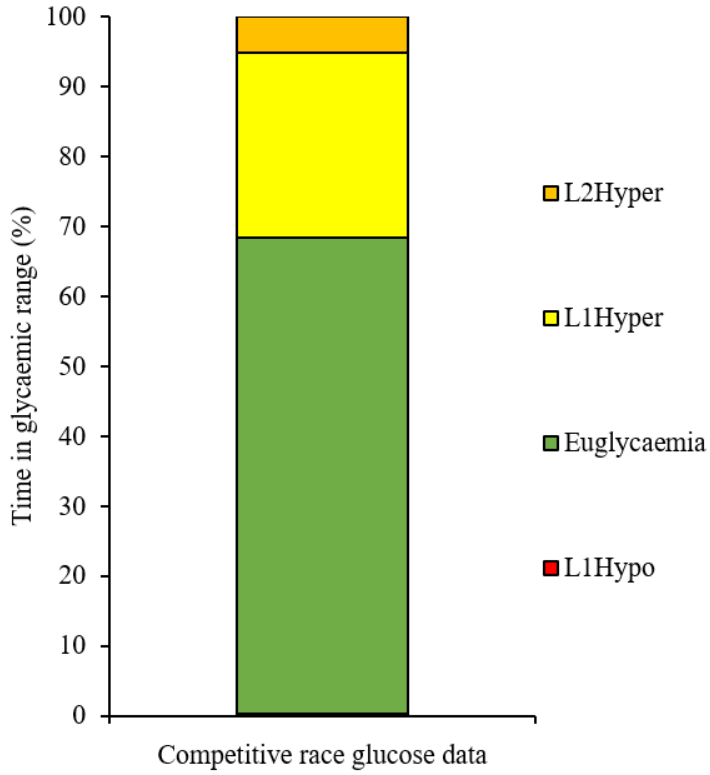


***Figure 16**: Within-exercise percentage of time in range separated into categories of glycaemia for all riders in the competitive race, all using Fiasp. Note: None of the riders spent any time in L2Hypo during the competitive race event so it has been excluded graphically. L1Hyper, Level 1 hyperglycaemia; L2Hyper, Level 2 hyperglycaemia; L1Hypo, Level 1 hypoglycaemia.*

Riders who competed in the cycle race also spent the greatest portion of time in euglycaemia (68.1 ± 9.6%), reflected in the mean interstitial glucose 9.2 ± 2.8 mmol.L^{-1}, with a mean coefficient of variation of 30.3 ± 7.3%. While hypoglycaemia was limited to just 0.4 ± 1.14% of in-ride time spent in L1Hypo, most time spent out of range was in L1Hyper (26.4 ± 7.74%) or extended to L2Hyper (5.11 ± 5.69%; **Figure 16**). Average peak concentrations of interstitial glucose, across all days of riding, reached 16.0 ± 3.0 mmol.L^{-1}.

4.4 Discussion

This study investigated the use of Fiasp in a comparative cross-sectional analysis against insulin aspart in prolonged exercise training sessions in professional cyclists with T1D. Participants were able to maintain euglycaemia for the majority of their training sessions whether using Fiasp or insulin aspart. However, there was a tendancy for those using Fiasp to experience less time during L2Hypo during exercise and during each 24-h period, contributing to more time spent per 24-h in euglycaemia in Fiasp group compared to IAsp group. In a competitive race environment, riders reduced bolus insulin dose progressively over the 5-day event, while making no changes to their basal insulin. In the context of these dose reductions, riders were still able to maintain the majority of time in euglycaemic ranges and spent no time in L2Hypo during races.

4.4.1 24-h glycaemia

Clinical consensus guidelines endorsed by international diabetes associations recommend adult intistitial glucose time in range targets to attain <1% in L2 Hypo, <4% in L1 Hypo, >70% in euglycaemia, <25% in L1 Hyper, and <5% in L2Hyper [1]. Of interest, participants taking Fiasp achieved well beyond the target percentage time in euglycaemia (~80%), while those taking insulin aspart achieved an average time in range just below the 70% target (~69%). Although both groups of riders' daily schedule and basal insulins were similar to one another, it is not possible to attribute this finding purely on the difference in mealtime insulin being used. It is likely that the inter-individual differences in racing strategy and glycaemic management, in addition to the individualised daily habits of the riders, are significant influencers on time spent in glycaemic ranges. The percentage time spent in euglycaemic range (~75%) during the race event days also exceeded the >70% recommendation.

4.4.2 In-ride glycaemia

Glycaemic data retreived from synchronised CGM worn by the participants revealed both Fiasp and IAsp groups maintained large portions of the exercise session in a euglycaemic range. The consensus guidelines that provide targets for time in range to the general population with T1D[1] were designed for 24-h periods (i.e., the time in range target for one day); however, by applying them to the within-exercise percentage time spent, it is evident that the riders were on average still managing to meet these targets, in both groups (e.g., within-ride glycaemia in IAsp [mean]: 0.8% L2Hypo, 3.8% L1Hypo, 76.6% euglycaemia, 16.3% L1Hyper, and 2.5% L2Hyper), despite the metabolic demands of long distance riding. Time spent in glycaemic ranges were statistically comparable between the two groups. Meeting time in range targets during

prolonged exercise is commendable, considering the successive hours spent maintaining moderate-high (relative) intensity in the saddle and the large number of calories consumed per day (~5000 kcal) [185]. Even in healthy individuals, blood glucose homeostasis may become threatened during prolonged exercise as the high rate of glucose (energy) demand driven by working muscles exceeds the rate of glucose supply from liver glycogen stores via systemic circulation [238]. For people with T1D, internal factors affecting the risk of exercise-related dysglycaemia extends beyond the metabolic capacity of the individual to exercise include: exercise-induced relative (exogenous) hyperinsulinaemia [92], occurrence of antecedent hypoglycaemia [185,239], pre-exercise blood glucose concentrations [240], fasted state [241], individual response to exercise intensity [128], and diabetes characteristics (e.g., hypoglycaemic unawareness[183]).

The occurrence of hypo- and hyperglycaemia is not only associated with adverse clinical symptoms, but also with serious implications on exercise performance. Hill et al. [236] showed in their study that power output was significantly lower when riders were in the hypoglycaemic range, compared to all other glycaemic ranges. From a psychological perspective, riders tended to attribute negative feelings towards spending time in hypoglycaemia. Furthermore, exercising in a hyperglycaemic state influences energy substrate usage, specifically the potential for hyperglycaemia to increase rates of carbohydrate oxidation without sparing muscle glycogen stores in people with T1D, the depletion of which is associated with local fatigue [242]. Collectively, the effort to maximise time in range remains a clinical prioirty as well as a potential ergogenic benefit for people with T1D. The current study suggests that Fiasp can be incorporated into training and racing routines in professional cyclists with T1D with low occurrence of hypoglycaemia and within-target time spent in euglycaemic ranges. By demonstrating that Fiasp can be used in professional cyclists who exercise for longer durations and at higher intensities multiple times per week, we have confirmed that the choice of bolus insulin does not, *per se*, limit an individual's ability to maintain the majority of time in euglycaemia during exercise over successive days. Further, encouragement in manipulating bolus insulin doses around prolonged exercise can be found in these data where daily bolus insulin doses were reduced while achieving commendable time in range.

4.4.3 Study strengths and limitations

This is the first study to compare the use of Fiasp against an established rapid-acting bolus insulin in highly-trained athletes with T1D. By collecting in-ride data during a training camp and an international race event, the findings are applicable to this population using these insulins a real-world setting and are not possible to be studied in laboratory conditions. As the only professional cycling team in the world with T1D, the athletes used in this study best represent the elite exercising population, performing at the professional standards of road cycling. This is particularly reflected in the riders' high VO_{2peak} values (>70 $mL.kg^{-1}.min^{-1}$).

This study is limited by the inter-individual differences that are present when comparing two cohorts using two different insulin analogues. This includes the usage of different basal insulins and individualised approaches to race performance and glycaemic management. Further research would benefit from studies investigating the use of Fiasp in an exercise context closely aligned to consensus guidelines for the overall population of people with T1D, with emphasis placed on controlling the long-lasting insulin participants are using and standardising exercise protocol without disturbing training.

4.5 Conclusion

The use of Fiasp as part of a multiple daily injection regimen has yet to be examined and compared to a rapid-acting insulin in an applied sports context. This study has shown that Fiasp can be safely incorporated into prolonged exercise bouts, in the context of professional-level cycle training camp and an international race event in athletes with T1D. Riders using Fiasp were able to better achieve the recommended time in range target during training camp and approach the same target during a 5-day race event while reducing daily bolus dosing.

Chapter 5

Comparison of the pharmacodynamic, pharmacokinetic, and metabolic effects between faster-acting insulin aspart and insulin aspart when using insulin dose reductions around moderate-intensity exercise in people with type 1 diabetes

5.1 Introduction

Physical exercise presents the potential for a wide range of health benefits to those with T1D but also poses additional challenges to glucose control. With impaired homeostasis, blood glucose concentrations are more susceptible to the exercise-induced shift in skeletal muscle energy demands which can lead to dysglycaemia during and after an acute bout of exercise. Indeed, a loss of control of blood glucose concentrations, particularly causing hypoglycaemia, and a lack of understanding of the effect of exercise on diabetes control remain leading diabetes-specific barriers to physical activity for people with T1D [133,134].

To counter the risk of hypoglycaemia, a reduction in the insulin dose taken with a meal prior to continuous aerobic exercise is recommended by international guidelines [6,128]. By effectively reducing the insulin-to-carbohydrate ratio, the rate of post-prandial whole-body glucose uptake is reduced, thus reducing the likelihood that any exercise-related decrease in glucose concentrations would result in hypoglycaemia [216]. Studies to date have sought to identify the appropriate pre-exercise insulin reduction, which can vary depending on multiple factors including the type of meal consumed beforehand [243], exercise duration[178], and exercise intensity [172].

The pharmacokinetic differences between mealtime and basal insulins give clear reason for distinct approaches in insulin reductions. Current insulin reduction recommendations apply to these insulins broadly as either a basal or bolus insulin, on the basis of little discernable difference between the insulin profiles within each type. The advent of the new generation of 'ultra'-rapid-acting insulins, namely Fiasp and ultra-rapid lispro insulin (Lyumjev), has brought faster PD/PK bolus insulin profiles. In comparison to their respective older generation insulins (insulin aspart and insulin lispro), ultra-rapid-acting insulins exhibit a left-shift in PD/PK properties, with an earlier onset of appearance and greater early insulin effect [244–246]. It has been demonstrated that Fiasp can be taken immediately before or up to 20 min after eating with noninferior glycaemic metrics compared to mealtime insulin aspart [247]. Hypothetically, therefore, the same exercise and pre-exercise mealtime protocols will produce differing glucose outcomes when switching from a rapid-acting insulin to an ultra-rapid-acting insulin, particularly when exercise is performed within the main window of insulin action (e.g., ~2 h). Given the integration of ultra-rapid-acting insulin use in clinical practice, information provided on the comparative differences between ultra-rapid-acting and rapid-acting insulins effects on

blood glucose around exercise would be timely to supplement new insulin reduction recommendations.

The aim of this study was therefore to compare the effect of an ultra-rapid-acting insulin (Fiasp) and a rapid-acting insulin (insulin aspart) for the same peri-exercise dose reductions on blood glucose concentrations, with a primary outcome investigating the effects of both dose reduction and insulin type effects on the change of blood glucose during exercise.

5.2 Materials and Methods

5.2.1 Study Design

This study was a prospective, two-site, double-blind, randomised four-arm cross-over, clinical trial (German Clinical Trials Register; DRKS00015855). The study was performed in accordance with the Declaration of Helsinki (1996) and Good Clinical Practice. Ethical approval was provided by a national ethics committee (18/WA/0421).

5.2.2 Screening visit

Participants were invited to attend a screen visit to take informed consent, gauge eligibility for the study, take baseline measurements, and to perform a CPET. Key eligibility criteria included: 18-65 years of age (inclusive), T1D >12 months, multiple daily injection regimen >12 months, HbA_{1c} <9.5% [80.3 $mmol.mol^{-1}$], and free from other relevant medical conditions. After trial inclusion, participants were switched to a basal-bolus regimen of insulin Tresiba® (degludec) and insulin Novorapid® (aspart), unless already prescribed. Insulin therapy dosing was adapted where necessary to ensure stable blood glucose control.

5.2.3 Experimental trials visits: trial protocol

This study consisted of four experimental trial days in a randomised crossover design. Participants arrived to the research facility on an experimental trial day at 07.30, with the prerequisites of being fasted, without having taken a bolus insulin dose for the previous 5 hours, and without having undergone strenuous physical activity, alcohol intake, or Level 2 hypoglycaemia (<3.0 $mmol.L^{-1}$; as checked via CGM data and confirmation from participant) for the previous 24 hours. Participants were weighed, asked to fill in a physical activity questionnaire (The International Physical Activity Questionnaire [Short Form] [195]), had a cannula inserted into a vein in the antecubital fossa, and had an Holter monitor ECG fitted (eMotion Faros 180°, Bittium Biosignals Ltd., Finland). At 08.00, basal insulin degludec was taken as per usual regimen (one participant took a split-dose of insulin degludec the evening before and on the morning of each trial day). At 08.30, participants injected a dose of mealtime insulin according to the allocated randomised trial arm: 1) 50% reduced dose of Fiasp (**F50**), 2) 75% reduced dose of Fiasp (**F75**), 3) 50% reduced dose of insulin aspart (**A50**), 4) 75% reduced dose of insulin aspart (**A75**). Both researchers and participants were blinded to insulin dose and type (Figure 9). Following this, participants consumed a drink meal (Fortijuce, Nutricia, Netherlands [Macronutrients per 100mL: carbohydrates 33.5 g, fats 0.0 g, protein 3.9 g]) equating to 1 g carbohydrate per 1 kg of body mass.

At 09.30, the exercise protocol commenced, consisting of a 3-minute warm-up (20-40 W) and 42 minutes of moderate-intensity exercise on a cycle ergometer (Lode Corival CPET, Cranlea, UK) cycling at 70-80 revolutions per minute. Experimental trial visits' (moderate) exercise intensity was calculated as the midpoint between lactate turnpoint 1 and lactate turnpoint 2 achieved during the CPET.

An identical drink meal and (reduced) insulin dose from the morning protocol were taken at 12.30. Participants remained rested throughout trial days outside the exercise session, apart from bathroom breaks, until 16.30 when the trial concluded. Water was consumed *ad libitum* and reported. Hypoglycaemia (≤3.9 $mmol.L^{-1}$) was treated with 10-20 g of high glycaemic index carbohydrates (Lift Glucose Shots, Lift, UK) once every 15 min until blood glucose ≥4.0 $mmol.L^{-1}$. If blood glucose ≥17.0 $mmol.L^{-1}$ and ketones >1.5 $mmol.L^{-1}$, or at the participant's own volition, a bolus insulin dose would be administered in relation to the individualised correction factor and recorded. Trials would be truncated if unscheduled insulin was injected (one trial for one participant post-exercise, prior to the second feeding period).

5.2.4 Experimental trials visits: methods of testing

Venous blood samples of 1.2 mL for the analysis of plasma glucose (S-Monovette Glucose, Sarstedt, Germany) and serum insulin (S-Monovette Serum, Sarstedt, Germany) concentrations were taken throughout the day to track PD/PK changes. Time intervals in between venous sample timepoints were either 5, 10, or 15 minutes (see Table 24).

***Table 24**: Trial day relativised PD/PK sampling timepoints and frequency.*

Trial day timepoints (relativised to dosing timepoints)	**Trial day timepoints (non-relativised)**	**Time of day**	**Time interval between samples (minutes)**	**Number of samples collected**
-5 min	-5min	08.25	N/A	1
First experimental insulin dose (0 min, 08.30)				
0 min to +120 min	0 min to 120 min	08.30-10.30	5	25
+130 min to +180 min	130 min to 180 min	10.40-11.30	10	6
+195 min to +240 min	195 min to 240 min	11.45-12.30	15	4
Second experimental insulin dose (+240min, 12.30)				
++5 min to ++120 min	245 min to 360 min	12.35-14.30	5	24
++130 min to ++180 min	370 min to 420 min	14.40-15.30	10	6
++195 min to ++240 min	435 min to 480 min	15.45-16.30	15	4
Total				70

0 min = start of first dosing period (08.30), ++0 min = start of second dosing period (12.30).

Additional venous blood samples of 4mL (4 mL K2EDTA or K3EDTA Vacutainer, Becton, Dickinson and Company, USA) and 5 mL (5 mL Aprotinin Vacutainer, Becton, Dickinson and Company, USA) were taken at the start (+60 min), middle (+82 min), and end (+105 min) of exercise for the analysis of adrenaline and noradrenaline.

CGM (FreeStyle Libre 2, Abbott, USA), spirometry (METAMAX 3B, Cortex, Germany), ECG, and heart rate (Polar T31, Polar, Finland) data were measured continuously throughout exercise. Finger-prick capillary blood glucose (FreeStyle Libre, Abbott, USA), earlobe capillary blood glucose and lactate (Biosen C-Line, EKF Diagnostics, Germany), and RPE (Borg Scale [198]) were taken immediately before the warm-up, immediately after the warm-up,

once every 6 minutes during exercise, and immediately after exercise. Blood ketones (FreeStyle Libre, Abbott, USA) were measured when blood glucose ≥17.0 mmol.L^{-1}.

5.2.5 Data analysis

Metrics relating to maximum concentration (C_{max}) and time to maximum concentration (t_{max}) were individualised by identifying each participant's C_{max} and t_{max}. Incremental area under the curve was calculated via trapezoidal method. For details on data processing, see Section 2.15.3. All statistical analysis was performed on SPSS 29.0 (IBM, USA). As n<50, normality testing was carried out using the Shapiro-Wilk test [210]. Comparisons between the four trial arms were made using repeated-measures ANOVA. Sphericity testing was performed using Mauchley's test of sphericity. Where the assumption of sphericity was violated, Greenhouse-Geisser correction was implemented. In instances of ANOVA significance, (pre-specified) post-hoc analysis via Bonferroni corrected t-tests were performed to identify significance between all possible group pairings. Comparison of t_{max} between glucose and insulin concentrations was made using an independent samples t-test. Comparisons of the change in glucose concentrations, both in standard units and as a rate of change, from C_{max} *vs.* from start of exercise were also made using the independent samples t-test.

5.3 Results

5.3.1 Participant characteristics

Baseline and final visit participant characteristics are detailed in **Table 25**. There were no differences between body mass or Hb_{A1c} metrics at screen *vs.* final visit (all $p>0.05$).

***Table 25**: Participant characteristics at screen and final visit.*

Characteristic	Screen visit		Final visit	
	Mean ± SD	**Range**	**Mean ± SD**	**Range**
Participant information				
Sample size	n=44			
Sex (M:F)	30:14			
Age (years)	38.8 ± 13.3	18.8-62.0	-	-
Anthropometrics				
Body mass (kg)	77.5 ± 13.8	58.5-126.9	77.6 ± 14.5	57.5 – 132.8
BMI ($kg.m^{-2}$)	24.4 ± 3.5	19.2-38.3	-	-
Diabetes information				
Diabetes duration (years)	15.2 ± 12.0	1.3 – 49.0	-	-
Hb_{A1c} (%)	6.9 ± 1.0	5.1 – 8.8	6.9 ± 1.0	4.7 – 8.8
HbA1c ($mmol.mol^{-1}$)	51.6 ± 10.5	32.2 – 72.7	51.4 ± 10.3	27.9 – 72.7
Pre-study total daily insulin dose ($IU.kg^{-1}$)	0.57 ± 0.27	0.24 – 1.51	-	-
Insulin dosage for 50% reduced conditions	4.9 ± 5.2	2-36	-	-
Insulin dosage for 75% reduced conditions	2.5 ± 2.6	1-18	-	-
Cardiopulmonary exercise test information				
VO_{2peak} ($L.min^{-1}$)	2.85 ± 0.80	1.78-5.12	-	-
VO_{2peak} ($mL.kg^{-1}.min^{-1}$)	36.7 ± 9.0	20.0-58.0	-	-
$Power_{peak}$ (W)	220 ± 59	133-380		
Blood $lactate_{peak}$ ($mmol.L^{-1}$)	9.3 ± 2.3	4.2-13.1		
Heart $rate_{peak}$ ($beats.min^{-1}$)	175 ± 14	153-202		

BMI, body mass index; HbA1c, glycated haemoglobin. VO_{2peak}, peak volume of oxygen uptake.

A total of 23,578 out of a possible 24,220 venous blood samples (97.3%) were taken in this study. A further 20 venous blood sample datapoints were excluded via filtration of outliers. Of 44 participants randomised to the study experimental visits, one dropout occurred after the participant's first experimental visit, for personal reasons (**Figure 17**).

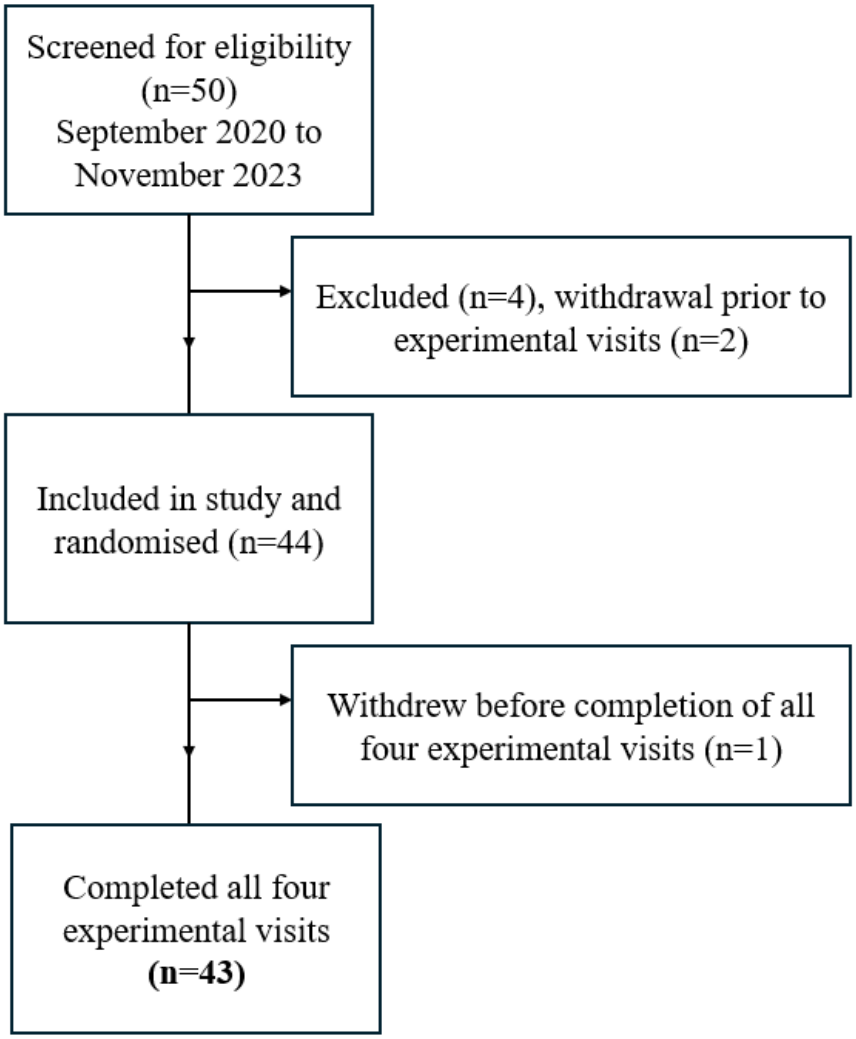


Figure 17: *Recruitment CONSORT-based flowchart* [248].

5.3.2 Blood glucose concentrations over each trial arm

Figure 18 depicts blood glucose concentrations at each sampling timepoint throughout each trial arm. Statistical determinations are detailed in subsequent sections below.

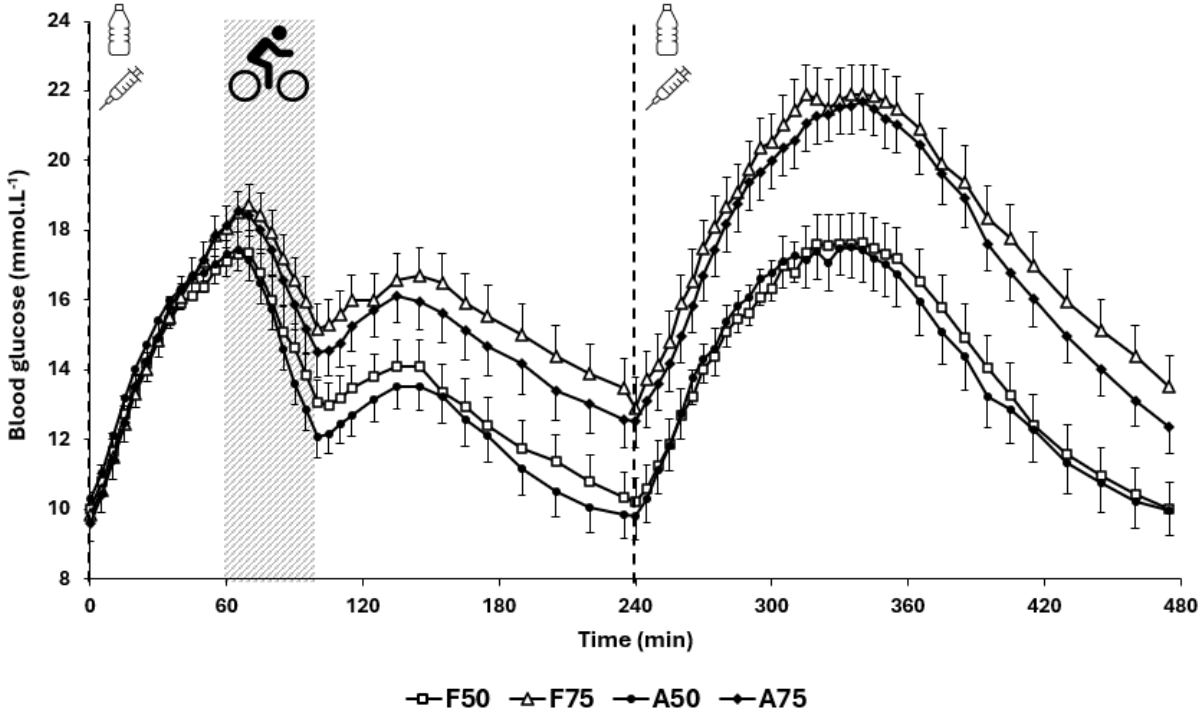


Figure 18: *Blood glucose concentrations over the trial day (0-480min), involving two carbohydrate drinks, two bolus insulin administrations, and one exercise period. Dashed vertical black lines indicate insulin administration immediately prior to consumption of a carbohydrate drink (1 g per kg body mass). Grey dashed box indicates the exercise session. All data are means with SEM error bars (n=44). Markers of statistically significant comparisons have been omitted for clarity and detailed in subsequent sections.*

5.3.3 Blood glucose during the first post-prandial period (Rest-120min)

Participants arrived fasted at the research facility with similar blood glucose concentrations across conditions (**F50** 9.8 ± 3.2, **F75** 9.5 ± 3.0, **A50** 10.0 ± 3.3, **A75** 9.4 ± 3.5 mmol.L^{-1}; p=0.544). **Figure 19** depicts the changes in blood glucose concentrations relative to rest (BG_{R0}) over the initial post-prandial and exercise period (0-105 min).

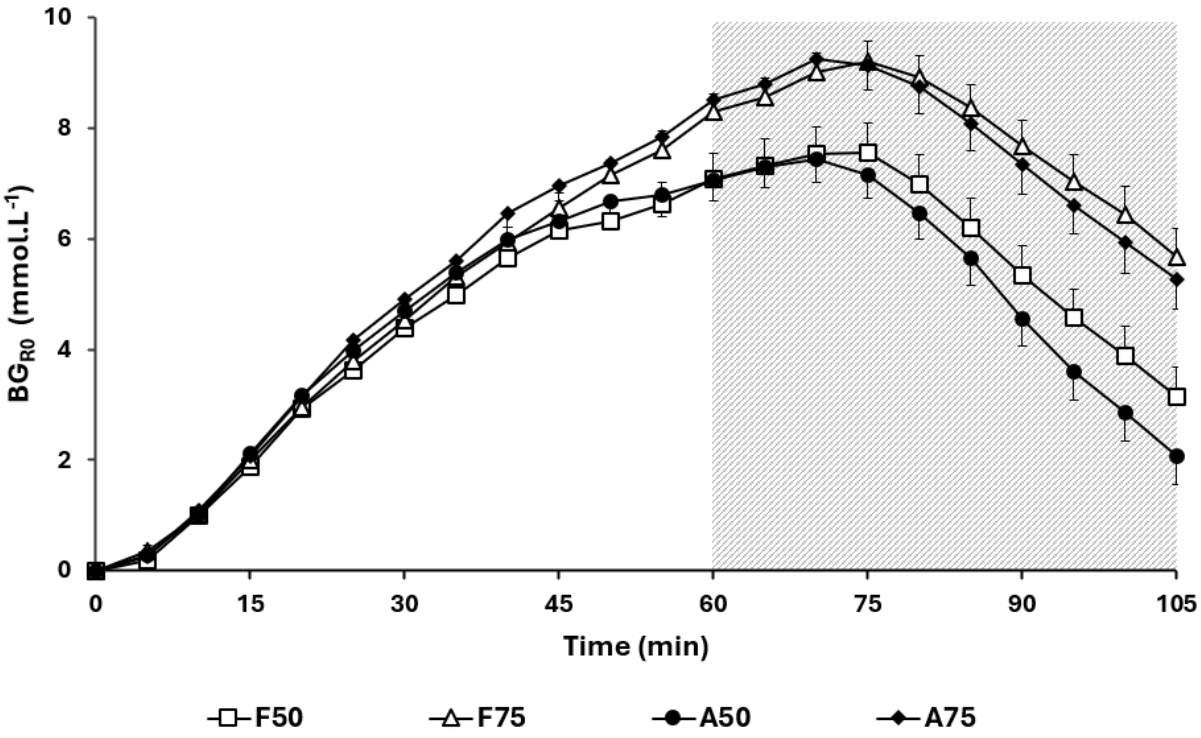


Figure 19: *Early post-prandial and physical exercise (0-105min) changes in blood glucose relativised to baseline (BG_{R0}) across all conditions. Grey dashed box indicates cycle exercise. All data are means with SEM error bars. Markers of statistically significant comparisons have been omitted for clarity and detailed in subsequent sections.*

There were significant rises from baseline to 60 minutes post-injection in all trials, with the greater rises seen in both **F75** and **A75** conditions compared to both **F50** and **A50** conditions (**Table 26**). At 60 min there were no differences between the blood glucose concentrations (**F50** 16.9 ± 4.0, **F75** 17.7 ± 4.0, **A50** 17.1 ± 4.1, **A75** 17.9 ± 4.3 mmol.L^{-1}; p=0.263). Analyses of blood glucose metrics related to the initial (0-60 min) post-prandial period are shown in **Table 26**.

Table 26: *Blood glucose metrics relative to baseline (0min) of the first post-prandial period (0-60 min).*

Parameter	Condition				P value
	F50	F75	A50	A75	
Timepoint metrics					
ΔBG at 15 min (mmol.L^{-1})	+1.9 ± 1.0	+2.0 ± 0.9	+2.1 ± 1.0	+2.1 ± 0.8	0.504
ΔBG at 30 min (mmol.L^{-1})	+4.3 ± 1.5	+4.5 ± 1.4	+4.7 ± 1.6	+4.9 ± 1.2	0.156
ΔBG at 45 min (mmol.L^{-1})	+6.1 ± 2.2	+6.5 ± 1.7	+6.3 ± 2.1	+7.0 ± 1.6	0.080
ΔBG at 60 min (mmol.L^{-1})	+7.1 ± 2.8^{a}	+8.3 ± 2.2^{b}	+7.0 ± 2.6^{bc}	+8.6 ± 1.9^{ac}	**<0.001***
AUC metrics					
BG_{R0} $AUC_{0\text{-}15min}$ (mmol.min.L^{-1})	11 ± 7	12 ± 7	12 ± 8	12 ± 6	0.727
BG_{R0} $AUC_{15\text{-}30min}$ (mmol.min.L^{-1})	48 ± 17	50 ± 16	52 ± 20	54 ± 15	0.237
BG_{R0} $AUC_{30\text{-}45min}$ (mmol.min.L^{-1})	79 ± 27	85 ± 26	85 ± 27	91 ± 19	0.090
BG_{R0} $AUC_{45\text{-}60min}$ (mmol.min.L^{-1})	98 ± 38^{a}	111 ± 27	100 ± 33^{b}	116 ± 26^{ab}	**0.003***
BG_{R0} $AUC_{0\text{-}60min}$ (mmol.min.L^{-1})	240 ± 80	262 ± 70	251 ± 82	274 ± 57	0.088

*All data relativised to resting blood glucose concentration taken at baseline (BG_{R0}). BG, blood glucose; AUC, area under the curve (incremental). * Denotes statistical significance.* ^{a,b,c} *represent statistically significant ($p \leq 0.05$) post-hoc comparison between two conditions.*

5.3.4 Blood glucose during exercise

The pre-exercise blood glucose concentrations were similar across all conditions (**F50** 16.9 ± 4.0, **F75** 17.7 ± 4.0, **A50** 17.1 ± 4.1, **A75** 17.9 ± 4.3 mmol.L^{-1}; p=0.263). During exercise, blood glucose fell in all conditions (**F50** -4.0 ± 2.8, **F75** -2.8 ± 3.3, **A50** -5.1 ± 3.0, **A75** -3.4 ± 3.3 mmol.L^{-1}; p<0.001 [**Figure 20**]) with post-hoc analysis revealing that the decline in blood glucose in **F50** was not different to all other conditions (all p>0.05). **A50** fell to a greater degree than both **F75** (p<0.001) and **A75** (p=0.001), which themselves fell similarly to each other (p=1.000). Blood glucose concentrations at the end of exercise were hyperglycaemic for all conditions (**F50** 12.9 ± 4.0, **F75** 15.2 ± 4.9, **A50** 11.9 ± 3.7, **A75** 14.4 ± 4.7 mmol.L^{-1}). After the start of exercise, there was a significant rise in glucose (Δ+1.5 mmol.L^{-1}; p<0.001) until peak ($C_{max\ 0\text{-}105min}$) 3-14 minutes later (**Table 27**).

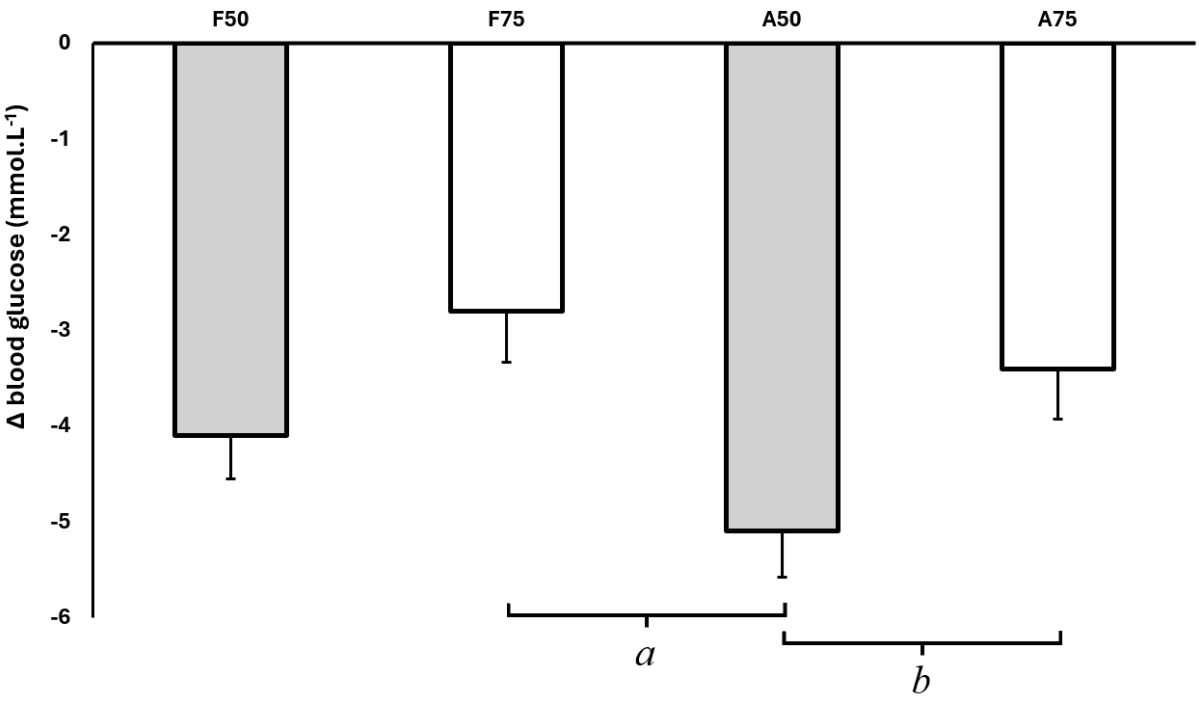


Figure 20: *Decline in blood glucose concentrations over the exercise session. a,b indicate a significant difference between trial arms. Data are reported as means with SEM,* $p \leq 0.05$.

Analysis of blood glucose metrics during exercise are shown in **Table 27**.

***Table 27**: Blood glucose metrics during exercise.*

Parameter	F50	F75	A50	A75	P value
Exercise start BG_{R0} ($mmol.L^{-1}$)	$+7.1 \pm 2.8^{a}$	$+8.3 \pm 2.2^{b}$	$+7.0 \pm 2.6^{bc}$	$+8.6 \pm 1.9^{ac}$	**<0.001***
$C_{max0\text{-}105min}$ ($mmol.L^{-1}$)	$+8.4 \pm 2.7^{ab}$	$+9.9 \pm 2.1^{ac}$	$+8.3 \pm 2.3^{cd}$	$+10.0 \pm 2.2^{bd}$	**<0.001***
$t_{max\ Cmax0\text{-}105min}$ (min)	65.8 ± 14.1^{a}	73.6 ± 11.2^{ab}	63.1 ± 11.4^{bc}	72.1 ± 11.1^{c}	**<0.001***
Difference between baseline (0 min) and end of exercise BG ($mmol.L^{-1}$)	$+3.0 \pm 3.2^{ab}$	$+5.6 \pm 3.4^{ac}$	$+2.0 \pm 3.3^{cd}$	$+5.0 \pm 3.3^{bd}$	**<0.001***
Within-exercise BG decline metrics					
Reduction in BG from start to end of exercise ($mmol.L^{-1}$)	-4.0 ± 2.8	-2.8 ± 3.3^{a}	-5.1 ± 3.0^{ab}	-3.4 ± 3.3^{b}	**<0.001***
Reduction in BG from $C_{max0\text{-}105min}$ to end of exercise ($mmol.L^{-1}$)	-5.3 ± 2.1^{a}	-4.2 ± 2.4^{b}	-6.3 ± 2.7^{abc}	-4.9 ± 2.8^{c}	**<0.001***
Reduction in BG from $C_{max0\text{-}105min}$ to end relativised for time ($mmol.L^{-1}.min^{-1}$)	-0.14 ± 0.05	-0.13 ± 0.05	-0.15 ± 0.05	-0.14 ± 0.06	0.222
Exercise BG AUC					
BG_{R0} $AUC_{60\text{-}105min}$ from start to immediate post-exercise ($mmol.min.L^{-1}$)	252 ± 139^{ab}	347 ± 94^{ac}	245 ± 129^{cd}	337 ± 112^{bd}	**<0.001***
$AUC_{60\text{-}105min}$ relative to exercise start ($pmol.min.L^{-1}$)	-44 ± 71	-16 ± 82^{a}	-68 ± 84^{a}	-42 ± 91	**0.014***
$AUC_{0\text{-}105min}$ ($mmol.min.L^{-1}$)	483 ± 194^{a}	601 ± 142	509 ± 194^{b}	604 ± 147^{ab}	**0.003***

*All data relativised to resting blood glucose concentration taken at baseline (BG_{R0}) unless otherwise indicated. $C_{max0\text{-}105min}$, individualised maximum blood glucose concentration between rest (0 min) and end of exercise (105 min); $t_{max\ Cmax0\text{-}105min}$, individualised time until maximum blood glucose concentration between rest (0 min) and end of exercise (105 min); BG, blood glucose; AUC, area under the curve (incremental). * Denotes statistical significance for main effect. ^{a,b,c,d} represent statistically significant ($p \leq 0.05$) post-hoc comparison between two conditions.*

During exercise, one participant experienced one episode of hypoglycaemia (≤3.9 mmol.L^{-1}) which was treated with quick-acting carbohydrates. The exercise session was truncated after this point. Blood glucose concentration nadir was 3.77 mmol.L^{-1}, which occurred 30 minutes after the start of exercise (+90 timepoint) in **F50** condition. One other participant was treated with quick-acting carbohydrates 35 minutes after the start of exercise in **A50** condition to prevent hypoglycaemia occurring during one exercise session; the participant completed the exercise session without stopping or experiencing hypoglycaemia.

5.3.5 Blood glucose during the post-exercise period (105-240 min)

Following exercise, there was a similar rise in blood glucose concentrations in all conditions (**F50** +1.9 ± 2.2, **F75** +2.6 ± 2.5, **A50** +2.4 ± 2.0, **A75** +2.6 ± 2.1 mmol.L^{-1}; p=0.107). After this 'peak' until the end of the first prandial period (240-minute timepoint), there were no differences in the change in blood glucose between conditions, which all fell (**F50** -4.6 ± 2.2, **F75** -4.5 ± 2.1, **A50** -4.8 ± 1.8, **A75** -4.6 ± 1.6 pmol.L^{-1}; p=0.909). When comparing against baseline concentrations (0 min), relative blood glucose was only higher at the end of the first prandial period (240 min) in **F75** and **A75** conditions (**F50** 0.4 ± 3.8, **F75** 3.6 ± 5.1, **A50** -0.3 ± 4.8, **A75** 3.2 ± 4.7 mmol.L^{-1}; p<0.001). During the first prandial period (0-240min), AUC was also lower in both 50% dose reduction arms compared to both 75% reduction arms (i.e., **F50** and **A50** vs **F75** and **A75**; all p≤0.05) and comparisons between insulins were similar (i.e., **F50** and **F75** vs **A50** and **A75**; all p>0.05).

5.3.6 Blood glucose during the second post-prandial period (240-480 min)

At 240 min (the sample taken immediately before second prandial insulin injection and carbohydrate drink) blood glucose concentrations were different between conditions (**F50** 10.2 ± 4.6, **F75** 13.1 ± 5.8, **A50** 9.6 ± 4.5, **A75** 12.3 ± 5.3 mmol.L^{-1}; p<0.001) with both 50% dose arms lower than both 75% reduced dose arms (all p≤0.05), while Fiasp and insulin aspart comparisons within each equivalent dose condition remained similar (all p>0.05). Analysis of the second prandial period are presented in **Table 28**. The carbohydrate quantity (g) used to treat hypoglycaemia was weighted more towards the 50% reduction conditions than 75% conditions as a percentage of overall treatments (**F50** 36%, **F75** 14%, **A50** 44%, **A75** 7%).

Table 28: *Blood glucose metrics for the second post-prandial period (240-480 min).*

Parameter	F50	F75	A50	A75	P value
$t_{max\ Cmax240\text{-}345min}$ (min)	89.0 ± 18.3	94.2 ± 10.6	87.9 ± 18.4	93.3 ± 14.8	0.113
$C_{max240\text{-}345min}$ ($mmol.L^{-1}$)	+8.1 ± 2.8^{ab}	+9.5 ± 2.6^{a}	+9.0 ± 2.8	+9.8 ± 2.7^{b}	**0.004***
$AUC_{240\text{-}255min}$ ($mmol.min.L^{-1}$)	2.8 ± 7.2	3.2 ± 6.7	6.0 ± 6.8	5.4 ± 7.9	0.146
$AUC_{240\text{-}270min}$ ($mmol.min.L^{-1}$)	30.5 ± 30.0	36.5 ± 24.5	45.7 ± 25.7	42.6 ± 28.9	0.056
$AUC_{240\text{-}300min}$ ($mmol.min.L^{-1}$)	162 ± 100^{a}	204 ± 68	213 ± 83	226 ± 85^{a}	**0.006***
$AUC_{240\text{-}345min}$ ($mmol.min.L^{-1}$)	438 ± 207^{ab}	567 ± 193^{a}	538 ± 185	609 ± 185^{b}	**0.006***
ΔBG from start of second prandial (240 min) to end of visit (480min) ($mmol.L^{-1}$)	-0.5 ± 2.7	+0.5 ± 2.8	+0.3 ± 2.5	+0.3 ± 3.0	0.266
BG_{R0} $AUC_{0\text{-}480min}$ ($mmol.min.L^{-1}$)	1329 ± 1474^{ab}	2847 ± 1699^{ac}	906 ± 1882^{cd}	2837 ± 1724^{bd}	**<0.001***
BG_{R0} at end of visit ([480 min] $mmol.L^{-1}$)	-0.3 ± 4.5^{ab}	3.5 ± 5.2^{ac}	-0.2 ± 5.5^{cd}	3.0 ± 5.6^{bd}	**<0.001***
Non-relativised BG at end of visit ([480 min] $mmol.L^{-1}$)	9.4 ± 4.5^{ab}	12.6 ± 5.1^{ac}	9.6 ± 4.5^{cd}	11.9 ± 5.0^{bd}	**<0.001***

*All metrics are relativised to the start of the second prandial period (240 min), unless otherwise indicated. $t_{max\ Cmax240\text{-}345min}$, individualised time until maximum blood glucose concentration between start of second prandial period (240 min) and the time equivalent to end of exercise (345 min); $C_{max240\text{-}345min}$, individualised maximum blood glucose concentration between the start of second prandial period (240 min) and the time equivalent to end of exercise (345 min); AUC, area under the curve (incremental). * Denotes statistical significance for main effect. ^{a,b,c,d} represent statistically significant ($p \leq 0.05$) post-hoc comparison between two conditions.*

5.3.7 Insulin concentrations over each trial arm

Participants arrived at the research facility with similar serum insulin concentrations across conditions (**F50** 49.2 ± 26.9, **F75** 45.5 ± 20.5, **A50** 46.7 ± 22.6, **A75** 46.5 ± 23.1 pmol.L^{-1}; p=0.267). **Figure 21** depicts serum insulin concentrations at each venous blood sampling timepoint through the trial day.

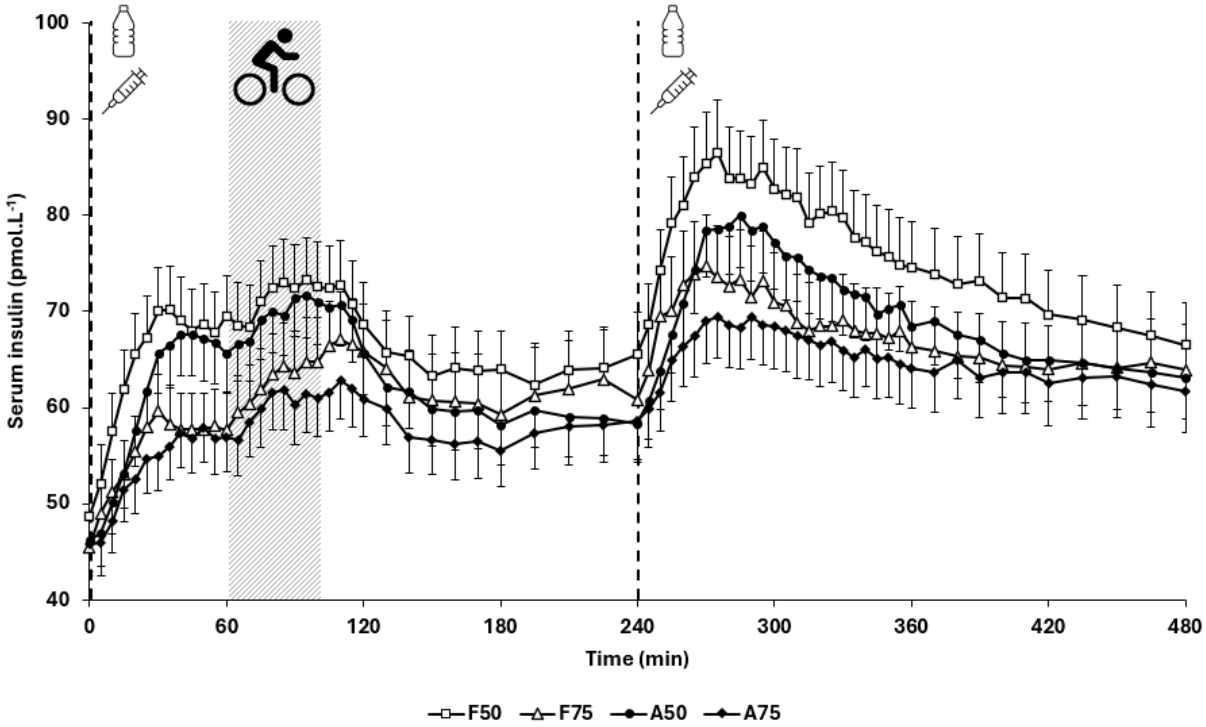


Figure 21: *Serum insulin concentrations over the trial day (0-480min) involving two carbohydrate drinks, two bolus insulin administrations, and one exercise period. Dashed vertical black lines indicate insulin administration prior to consumption of a carbohydrate drink (1 g per kg body mass). Grey dashed box indicates the exercise session. All data are means with SEM error bars (n=44). Markers of statistically significant comparisons have been omitted for clarity and detailed in subsequent sections.*

5.3.8 Insulin concentrations in the early post-prandial period (0-60 min)

Insulin concentrations relative to baseline (INS_{R0}) rose similarly in 50% reduction arms to a greater extent than 75% reduction arms (p≤0.05 for all inter-dose comparisons) to the start of exercise at 60min (**F50** 21.3 ± 13.2, **F75** 13.7 ± 11.0, **A50** 20.6 ± 12.6, **A75** 11.6 ± 7.9 pmol.L^{-1}; p<0.001). **Table 29** details the insulin concentration metrics between rest and exercise.

***Table 29**: Serum insulin metrics between rest (0 min) to start of exercise (60 min)*

Parameter	F50	F75	A50	A75	P value
Timepoint metrics					
ΔSerum insulin at 15 min (pmol.L^{-1})	+13.2 ± 8.6^{abc}	+8.1 ± 7.2^{a}	+8.4 ± 11.4^{b}	+5.8 ± 5.5^{c}	**<0.001***
ΔSerum insulin at 30 min (pmol.L^{-1})	+21.1 ± 12.3^{ab}	+14.3 ± 11.8^{ac}	+19.6 ± 15.4^{cd}	+9.3 ± 7.9^{bd}	**<0.001***
ΔSerum insulin at 45 min (pmol.L^{-1})	+20.4 ± 10.7 ^{ab}	+12.8 ± 10.5^{ac}	+21.2 ± 15.6^{cd}	+11.2 ± 8.0^{bd}	**<0.001***
ΔSerum insulin at 60 min (pmol.L^{-1})	+21.3 ± 13.2^{ab}	+13.7 ± 11.0^{ac}	+20.6 ± 12.6^{cd}	+11.6 ± 7.9^{bd}	**<0.001***
Pre-exercise C_{max} metrics					
$t_{max\ Cmax0\text{-}60min}$ (min)	42.1 ± 13.4	42.9 ± 14.7	44.2 ± 12.6	43.6 ± 11.6	0.889
$C_{max0\text{-}60min}$ (pmol.L^{-1})	+26.6 ± 12.5^{ab}	+18.2 ± 11.8^{ac}	+26.7 ± 16.0^{cd}	+14.8 ± 7.9^{bd}	**<0.001***
AUC metrics					
INS_{R0} $AUC_{0\text{-}15min}$ (pmol.min.L^{-1})	92 ± 74^{abc}	62 ± 58^{ad}	40 ± 66^{b}	24 ± 40^{cd}	**<0.001***
INS_{R0} $AUC_{15\text{-}30min}$ (pmol.min.L^{-1})	261 ± 156^{ab}	171 ± 130^{ac}	203 ± 195^{d}	118 ± 84.8^{bcd}	**<0.001***
INS_{R0} $AUC_{30\text{-}45min}$ (pmol.min.L^{-1})	311 ± 177^{ab}	197 ± 145^{ac}	309 ± 232^{cd}	162 ± 108^{bd}	**<0.001***
INS_{R0} $AUC_{45\text{-}60min}$ (pmol.min.L^{-1})	310 ± 187 ^{ab}	199 ± 158 ^{ac}	315 ± 200 ^{cd}	172 ± 114 ^{bd}	**<0.001***
INS_{R0} $AUC_{0\text{-}60min}$ (pmol.min.L^{-1})	992 ± 580^{ab}	628 ± 475^{a}	877 ± 703^{c}	471 ± 325^{bc}	**<0.001***

*All data relativised to insulin concentrations at baseline (INS_{R0}). $t_{max\ Cmax60min}$, time until maximum concentration before start of exercise (60 min); $C_{max60min}$, maximum concentration before start of exercise (60 min); AUC, area under the curve. * Denotes statistical significance for main effect. ^{a,b,c,d} represent statistically significant ($p \leq 0.05$) post-hoc comparison between two conditions.*

5.3.9 Insulin concentrations during exercise

From exercise start to end, serum insulin concentrations relativised to baseline (INS_{R0}) increased from 62.5 to 67.1 pmol.L^{-1} (p<0.001); the increase was similar across all conditions (**F50** +3.4 ± 9.1, **F75** +6.9 ± 15.1, **A50** +3.4 ± 8.8, **A75** +5.2 ± 7.7 pmol.L^{-1}; p=0.328). Within- and immediate post-exercise insulin concentration metrics are listed in (**Table 30**).

***Table 30**: Serum insulin concentration metrics during exercise*

Parameter	F50	F75	A50	A75	P value
$t_{max\ Cmax60\text{-}105min}$ (min)	86.8 ± 15.2	92.4 ± 14.7	90.2 ± 12.9	88.3 ± 14.6	0.167
$C_{max60\text{-}105min}$ (pmol.L^{-1})	+29.0 ± 14.0^{a}	+23.3 ± 21.0	+29.7 ± 12.2^{b}	+20.1 ± 9.4^{ab}	**0.002***
ΔSerum insulin at 105 min (immediate post-exercise) (pmol.L^{-1})	+23.9 ± 15.2	+20.8 ± 22.3	+24.0 ± 11.1	+17.3 ± 9.5	0.097
INS_{R0} $AUC_{60\text{-}105min}$ (pmol.min.L^{-1})	1014 ± 595^{a}	817 ± 782	1073 ± 528^{b}	673 ± 325^{ab}	**0.003***
$AUC_{60\text{-}105min}$ relative to exercise start (pmol.min.L^{-1})	85 ± 239	187 ± 396	112 ± 260	132 ± 188	0.410
INS_{R0} $AUC_{0\text{-}105min}$ (pmol.min.L^{-1})	2004 ± 1122^{a}	1448 ± 1199	1957 ± 1187^{b}	1175 ± 573^{ab}	**<0.001***

*All data relativised to insulin concentrations at baseline (INS_{R0}) unless otherwise indicated. $t_{max\ Cmax60\text{-}105min}$ = time until maximum concentration during exercise (60-105 min). $C_{max60\text{-}105min}$ = maximum concentration during exercise (60-105min). * Denotes statistical significance for main effect. ^{a,b} represent statistically significant ($p \leq 0.05$) post-hoc comparison between two conditions.*

Maximum insulin concentrations prior to exercise ($C_{max0\text{-}60min}$) were similar to the maximum concentrations during exercise ($C_{max60\text{-}105min}$) (**F50** Δ2.5 ± 9.6, **F75** Δ5.0 ± 15.2, **A50** Δ3.0 ± 10.8, **A75** Δ5.4 ± 7.4 pmol.L^{-1}; p=0.390).

Incremental area under the curve from baseline (0 min) to end of exercise (105 min) was greater in F50 and A50 compared to A75 (**F50** 2004 ± 1122, F75 1448 ± 1199, A50 1957 ± 1187, A75 1175 ± 573 pmol.min.L^{-1}), while all other inter-condition comparisons were similar (p>0.05). **Figure 22** depicts the changes in serum insulin concentrations relative to rest (INS_{R0}) over the initial post-prandial and exercise period (0-120 min).

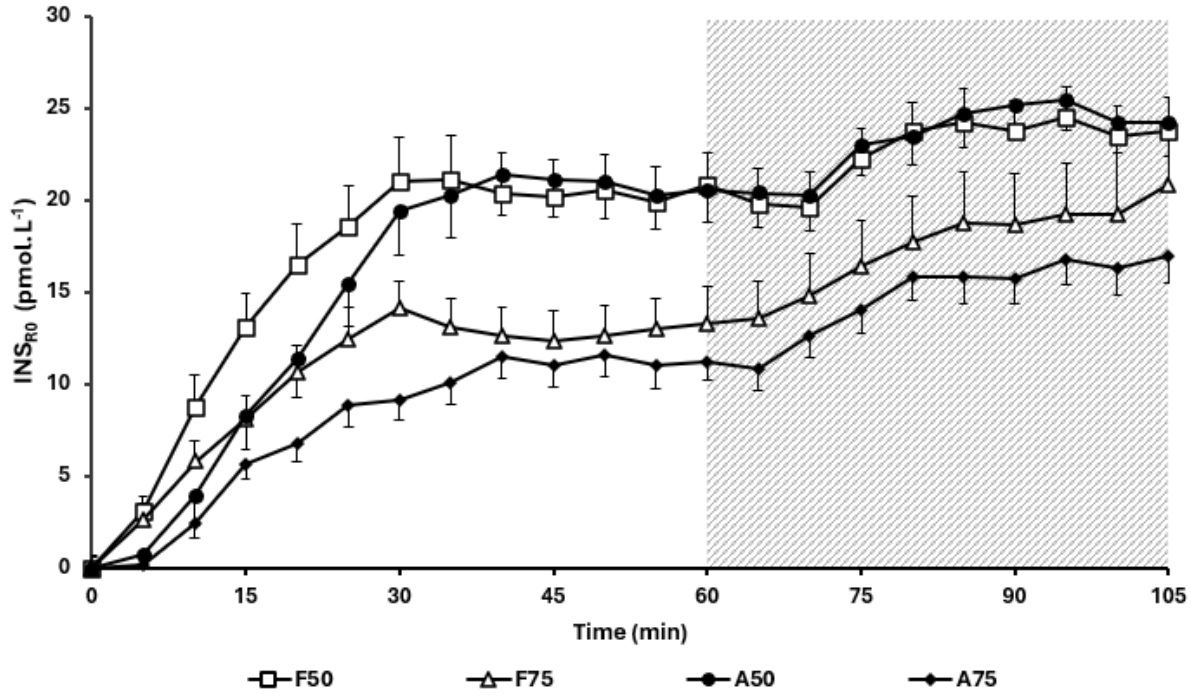


Figure 22: *Early post-prandial (0-105min) changes in serum insulin concentrations relativised to baseline (INS_{R0}) across all conditions. Grey dashed box indicates exercise session. All data are means with SEM error bars. Markers of statistically significant comparisons have been omitted for clarity and detailed in subsequent sections.*

Area under the curve during the first prandial period (0-240 min) was higher in the 50% dose reduction arms compared to the 75% reduction arms, without an insulin type effect (**F50** 519 ± 234, **F75** 679 ± 179, **A50** 534 ± 237, **A75** 671 ± 189 pmol.min.L^{-1}; p<0.001).

5.3.10 Insulin second post-prandial period

At 240 min (the sample taken immediately before second prandial injection and drink meal), serum insulin, relativised to baseline (0 min), were similar between trial arms (**F50** +16.0 ± +17.8, **F75** +16.5 ± 24.3, **A50** +12.5 ± 9.7, **A75** +14.6 ± 13.3 pmol.L^{-1}; p=0.518). Analyses of serum insulin concentrations relativised to the start of the second post-prandial period (240min [INS_{R240}]) are shown in **Table 31**.

Table 31: *Second (post-exercise) post-prandial period serum insulin concentrations.*

Parameter	F50	F75	A50	A75	P value
$t_{max240\text{-}345min}$ (min)	47.2 ± 22.6	41.4 ± 22.6	50.7 ± 18.9	52.2 ± 25.8	0.105
$C_{max240\text{-}345min}$ (pmol.L^{-1})	25.9 ± 14.2^{ab}	17.3 ± 8.8^{ac}	26.8 ± 17.6^{cd}	16.1 ± 8.2^{bd}	**<0.001***
$AUC_{240\text{-}255min}$ (pmol.min.L^{-1})	94.2 ± 82.6^{ab}	74.8 ± 66.7	52.0 ± 58.6^{a}	40.1 ± 58.9^{b}	**<0.001***
$AUC_{240\text{-}270min}$ (pmol.min.L^{-1})	368 ± 292^{ab}	240 ± 180^{a}	261 ± 229	156 ± 159^{b}	**<0.001***
$AUC_{240\text{-}300min}$ (pmol.min.L^{-1})	1010 ± 674^{ab}	578 ± 387^{ac}	975 ± 673^{cd}	473 ± 402^{bd}	**<0.001***
$AUC_{240\text{-}345min}$ (pmol.min.L^{-1})	1602 ± 955^{ab}	796 ± 550^{ac}	1722 ± 1095^{cd}	822 ± 664^{bd}	**<0.001***
$AUC_{240\text{-}480min}$ (pmol.min.L^{-1})	2470 ± 2069^{ab}	1134 ± 1744^{ac}	2888 ± 2035^{cd}	1314 ± 1593^{bd}	**<0.001***
INS_{R0} Timepoint 480min (end of visit) (pmol.L^{-1})	19.1 ± 22.3	18.9 ± 20.2	17.6 ± 14.9	17.7 ± 14.6	0.944
INS Timepoint 480min (non-relativised) (pmol.L^{-1})	67.3 ± 29.8	64.3 ± 30.1	63.3 ± 29.8	63.6 ± 27.9	0.434

*All metrics are relativised to the start of the second prandial period (INS_{R240}), unless otherwise indicated. $t_{max\ Cmax240\text{-}345min}$, individualised time until maximum serum insulin concentration between start of second prandial period (240 min) and the time equivalent to end of exercise (345 min); $C_{max240\text{-}345min}$, individualised maximum serum insulin concentration between the start of second prandial period (240 min) and the time equivalent to end of exercise (345 min); AUC, area under the curve (incremental). * Denotes statistical significance for main effect. ^{a,b,c,d} represent statistically significant ($p \leq 0.05$) post-hoc comparison between two conditions.*

5.3.11 Exercise intensity characteristics

Spirometry-derived data are presented in **Table 32**. There were no differences between conditions in any spirometry-derived exercise data (all $p>0.05$).

***Table 32**: Spirometry-derived data during exercise.*

Parameter	F50	F75	A50	A75	P value
VO_2 ($L.min^{-1}$)	1.74 ± 0.39	1.72 ± 0.36	1.73 ± 0.38	1.73 ± 0.38	0.688
VCO_2 ($L.min^{-1}$)	1.65 ± 0.37	1.62 ± 0.36	1.65 ± 0.36	1.63 ± 0.37	0.534
VO_2 ($mL.kg^{-1}.min^{-1}$)	23.3 ± 4.7	22.9 ± 4.4	23.0 ± 4.3	23.0 ± 4.4	0.570
$\%VO_{2peak}$	61.9 ± 6.1	61.2 ± 7.3	61.4 ± 6.6	61.4 ± 7.0	0.763
RER	0.94 ± 0.04	0.94 ± 0.04	0.95 ± 0.04	0.94 ± 0.04	0.364
VE ($L.min^{-1}$)	49.9 ± 9.7	49.2 ± 9.5	50.4 ± 10.2	49.4 ± 9.5	0.410
Energy expenditure ($kcals.min^{-1}$)	8.6 ± 1.9	8.6 ± 1.9	8.7 ± 1.9	8.6 ± 1.9	0.788
Energy expenditure ($kJ.min^{-1}$)	36.2 ± 8.1	35.8 ± 7.9	36.2 ± 7.9	36.0 ± 8.0	0.787
Carbohydrate oxidation ($g.min^{-1}$)	1.76 ± 0.47	1.74 ± 0.49	1.81 ± 0.47	1.76 ± 0.51	0.385
Lipid oxidation ($g.min^{-1}$)	0.16 ± 0.12	0.16 ± 0.10	0.14 ± 0.11	0.16 ± 0.12	0.441
Carbohydrate oxidation percentage energy expenditure (%)	82.9 ± 12.5	82.4 ± 11.3	85.0 ± 11.3	82.8 ± 13.6	0.348
Lipid oxidation percentage energy expenditure (%)	17.1 ± 12.5	17.6 ± 11.3	15.0 ± 11.3	17.2 ± 13.6	0.348

*Data are presented as Mean±SD. * Denotes statistical significance. VO_2, volume of oxygen uptake; VCO_2, volume of carbon dioxide output; RER, Respiratory exchange ratio; VE, minute ventilation. Data for one participant were removed after the point of carbohydrate ingestion (i.e., 35 min after the start of exercise) to avoid hypoglycaemia.*

There were no differences between conditions in metrics of exercise effort (**Table 33**). Participants' RPE averaged ratings between the guidance notes of 'Fairly light' (11) and 'Somewhat hard' (13) in the Borg scale [198]. There was no difference between in the change in lactate from rest to exercise between conditions (p=0.537).

***Table 33**: Resting and exercise metrics relating to exertion.*

Parameter	F50	F75	A50	A75	P value
Blood lactate at rest ($mmol.L^{-1}$	1.09 ± 0.25	0.99 ± 0.22	1.04 ± 0.26	0.96 ± 0.22	**0.003***
Blood lactate during exercise ($mmol.L^{-1}$)	2.9 ± 1.0	2.8 ± 1.1	2.7 ± 0.9	2.7 ± 1.0	0.331
RPE at rest	6.0 ± 0.2	6.0 ± 0.2	6.0 ± 0.0	6.0 ± 0.1	0.276
RPE during exercise	12.4 ± 1.8	12.3 ± 2.1	12.2 ± 2.1	12.1 ± 2.0	0.173
HR ($beats.min^{-1}$) during exercise	136 ± 16	134 ± 16	136 ± 17	132 ± 23	0.294
O_2pulse ($mL.beat^{-1}$)	13.0 ± 3.3	12.8 ± 2.9	12.8 ± 3.2	13.3 ± 4.1	0.446
Cycling cadence ($revolutions.min^{-1}$)	72.4 ± 4.1	72.8 ± 4.1	73.0 ± 4.0	72.6 ± 3.4	0.638
Power during exercise (W)	113 ± 34	113 ± 34	113 ± 34	113 ± 34	-

*Data are presented as Mean±SD. * Denotes statistical significance. RPE, rating of perceived exertion; HR, heart rate.*

5.4 Discussion

This study compared the glycaemic and metabolic effects of different dose reductions of Fiasp and insulin aspart during moderate-intensity continuous exercise in people with T1D. The following discussion is compartmentalised into different phases of (i) pre-exercise, (ii) exercise, (iii) post-exercise, and (iv) another rested feeding phase and discussed with an emphasis on blood glucose and serum insulin responses. Additional measures are discussed, where appropriate.

5.4.1 Pre-exercise period: serum insulin concentrations

5.4.1.1 Insulin type

Serum insulin concentrations increased from rest in all conditions following subcutaneous insulin injection. **F50** produced the largest early exposure to insulin concentration compared to other conditions, as evidenced by the greater AUC and relative point concentrations after 15 minutes. AUC from 0-15 minutes also indicated that circulating insulin was higher under **F75** compared to **A75** but was similar to **A50**. By 30 minutes, point concentrations between insulin types were similar across conditions; however, **A75** AUC was smaller than all other conditions, while **F50** and **A50** were similar to each other. At 45 and 60 minutes, insulin concentrations expressed as relative point concentrations and AUC were similar between Fiasp and aspart when administered at the same dose.

Our data align with studies in which the pharmacokinetics of Fiasp and insulin aspart were compared. Heise et al.[162] demonstrated that under rested conditions, Fiasp taken as a single 0.2 $UI.kg^{-1}$ dose had a ~4.5-fold greater AUC in the first 15 minutes compared to insulin aspart in adults with T1D in moderate glucose control. While statistical analysis was not performed for comparison means in this study, a subsequent pooled analysis performed between multiple studies suggest that AUC remains higher in Fiasp *vs.* insulin aspart from early exposure through to 60 minutes post-injection [249]. While the difference in AUC between Fiasp and insulin aspart narrowed in this pooled analysis at timepoints 30 minutes and 60 minutes post-injection, the statistically significant difference between the insulins remained. This distinguishes these data from the current study's findings in which differences between insulins were effectively indistinguishable in AUC and point concentrations for both 45 minutes and 60 minutes.

A potential reason for the discrepancy in these findings may be due to the different insulin doses employed between studies. The pooled analysis data, of which the study presented by

Heise et al.[162] was included, consisted of studies where the provided dose was 0.2 UI.kg^{-1} [249]. By contrast, the current study employed reduced insulin doses in consideration for a planned exercise bout. On average, dosing for the 50% reduced trials was 0.06 UI.kg^{-1}, while dosing for the 75% reduced trials was 0.03 UI.kg^{-1}, nearly six times less than that employed in the pooled analysis. Altered dosages can influence Fiasp pharmacokinetics. In a separate study, Heise et al. [237] compared the pharmacokinetic effects of Fiasp against insulin aspart using either 0.1, 0.2, or 0.4 UI.kg^{-1}. A similar trend of Fiasp favouring early exposure was seen in this study, where Fiasp exhibited higher AUC after 15 and 30 minutes; however, in the 0.1 UI.kg^{-1} condition, AUC was similar between conditions after 60 minutes. The similarity in AUC after 60 minutes between insulins aligns with our data, which is closest to the 0.1 UI.kg^{-1} trial arm, albeit still some magnitudes less in dosage. Smaller injection depots have greater room for (quicker) expansion in the subcutis, favouring the formation of dimers and monomer insulin units[228]; hence, the early absorption of both insulins may be increased when employing lower insulin dosages. This effective left-shift in insulin aspart time-action profile may be more prominent than the already ultra-rapid-acting time-action profile of Fiasp, which may shift the rate-limiting factor of insulin absorption outside of the hexamer:dimer:monomer equilibrium between the 30- and 60-minute timepoints when injecting low insulin doses. A further reason for inter-study discrepancies may refer to the different AUC intervals used between studies, where the current study's use of smaller incremental intervals effectively removed the early exposure effects of Fiasp absorption with each subsequent AUC interval.

5.4.1.2 Insulin dose

In our study, **F50** resulted in higher serum insulin concentrations after 15 minutes when compared to **F75**, yet **A50** and **A75** were similar. In the AUC between 15-30 minutes post-injection, both 50% dose conditions were greater than their respective 75% conditions. However, at 30 minutes after insulin injection, conditions with the same dose reduction were similar to each other, but both **F50** and **A50** were greater than **F75** and **A75**, respectively. This pattern continued up to (and beyond) 60 minutes post-injection, where a dose effect but no insulin interaction effect was observed for both point concentration and AUC data. There were no insulin type or dose effects on the time to achieve individualised maximum insulin concentrations during the pre-exercise period ($t_{max\ Cmax0\text{-}60min}$). Higher peak serum insulin concentrations were found in the pre-exercise period ($C_{max0\text{-}60min}$) for both 50% reduced conditions when compared to both 75% conditions, with no differences between insulin types

under the same dose reduction conditions. **F50** condition had a $C_{max0\text{-}60min}$ which was 46% larger than that of **F75**. Interestingly, the $C_{max0\text{-}60min}$ **A50** was 80% larger than that of **A75**.

As a whole, the pharmacokinetics of the four conditions taken at rest align with previous data comparing early effects of injecting Fiasp or insulin aspart. Our data indicate that the type of insulin is most distinguishable in the first 15 minutes after injection, yet by 30 minutes and beyond, insulin kinetics only differed between dose reductions. This implicates that the 1-h prandial glucose response prior to exercise is more heavily influenced by a difference in 50% vs 75% dose reduction than a difference in Fiasp and insulin aspart.

5.4.2 Pre-exercise period: blood glucose concentrations

5.4.2.1 Insulin type

An interesting finding from our data revealed that despite differing serum insulin concentrations during the early pre-exercise period, there were no differences in the rise in blood glucose concentrations nor glucose exposure relative to baseline between insulin type conditions throughout the pre-exercise period. At 60 minutes post-injection, blood glucose concentrations had risen by ~7-9 $mmol.L^{-1}$ across all trials. These data might be explained by a low glucose-lowering capability of reduced doses of both insulins relative to the rapid influx of a large amount of carbohydrate as glucose into the circulation from the digestive system. Furthermore, the carbohydrate-heavy meal (1 $g.kg^{-1}$ carbohydrates [~90%], ~0.1 $g.kg^{-1}$ protein [~10%], 0 $g.kg^{-1}$ fat [0%]) contained predominantly high-glycaemic index ingredients (i.e., glucose syrup and maltodextrin) which may have further contributed to the steep rise in blood glucose concentrations over a 1-hour rested period..

This rise in blood glucose is greater than that presented in previous studies comparing responses to both Fiasp and insulin aspart after a bolus meal. In a mixed meal test at rest (103 g carbohydrate [67%], 25 g protein [17%], and 10 g fat [16%]), participants with T1D using CSII experienced a rise in blood glucose between 3-5 $mmol.L^{-1}$ after 60 minutes; however, the rise was 1.6 $mmol.L^{-1}$ less under the Fiasp trial arm *vs.* insulin aspart ($p<0.05$) [250]. In another study, blood glucose in participants using a 50% reduced insulin injection via insulin pen when consuming a mixed-meal (for women, 50 g CHO [55%], 25 g proteins [27%], 16 g fats [18%]; for men, 65 g CHO [60%], 25 g protein [23 %], 18 g fats [17%]) increased by 3 $mmol.L^{-1}$ after

60 minutes, where the rise in glucose was similar when using Fiasp (2.5 mmol.L^{-1}) and insulin aspart (3.5 mmol.L^{-1}; p>0.05) [174].

The differences in findings between these three studies are possibly partly attributable to the choice of insulin dosing and meal content. The similarity between the rise in blood glucose after 60 minutes between insulins is shared only by our current study and the study by Molveau et al [174], which also employed reduced insulin dosing. However, the rise in glucose concentrations were significantly less in this study compared to our findings. The meal consumed during this study contained higher proportions of fat and protein than the current study, potentially slowing the rate of glucose absorption into the blood. Increased fat and, particularly, protein content in meals slows gastric emptying and alter the blood glucose response to foods by effectively slowing the rate of absorption from the small intestine [251,252]. Comparatively, the meal used in our study contained no fat and had a low protein to carbohydrate ratio, subsequently causing a more rapid glucose response. By further comparison, our current study used 4.9 UI in 50% reduced trial arms, Molveau et al. [174] used 4.6 UI, and CSII boluses of ~0.27 UI.kg^{-1} were used in the study conducted by Bode et al. [250]. With the assumption of similar participant body masses between studies, the bolus insulin dosing used in the MDI studies' 50% trial arms (~0.06 UI.kg^{-1}) is considerably lower than that used by Bode and colleagues [250]. This may in part be as a result of bias for participants in exercise-related studies having higher insulin sensitivity. As discussed previously (Section 5.4.1.1), the dosing amount may influence the pharmacokinetic differences between Fiasp and insulin aspart and therefore may explain some of the variance in findings between the studies.

5.4.2.2 Insulin dose

There was no effect of insulin dosage amount on the rise in blood glucose during the early pre-exercise period. However, by 60 minutes, the gap between both **F50** and **A50** *and* **F75** and **A75**, respectively, increased such that both 75% reduction conditions were greater than **A50**, while **A75** (but not **F75**) was greater than **F50**. These data reflect a pattern of similarity in the glucose-effect between Fiasp and insulin aspart when administering considerably reduced doses of insulin. At the level of 50% and 75% reduced dosing, the blood glucose data up to 60-minute post-prandial in this study suggest that dosing remains the dominant factor in dictating changes in blood glucose concentrations.

5.4.3 Exercise period

5.4.3.1 Exercise characteristics

The cycle exercise sessions were designed to be of moderate intensity, where recreationally active individuals with T1D could complete the required exercise workload. Cycle intensity was determined from key biomarkers obtained from the CPET, i.e., VO_{2peak} and two lactate turn-points. The moderate-intensity nature of the exercise sessions was verified by ventilatory data, where participants exercised at ~61 %VO_{2peak} and had an RER of ~0.94; heart rate data, ~135 beats.min^{-1}; blood lactate data, ~2.8 mmol.L^{-1}, and RPE, ~12. Exercising at 61 %VO_{2peak} falls within guidelines for exercise in people with T1D recommended by the American College of Sports Medicine (ACSM) [127]. All exercise variables were statistically similar between conditions.

Substrate oxidation data during cycling demonstrated that carbohydrate was the dominant energy substrate over lipids (~83% of total oxidative energy expenditure), a finding that was similar between all conditions. People with T1D exercising under hyperglycaemic conditions have been shown to shift towards carbohydrate oxidation [242]. This is an applicable scenario in the current study, brought on by reduced insulin dosages and a high glycaemic index, high carbohydrate load prior to exercise. The hyperglycaemia (11 mmol.L^{-1}) induced by the hyperglycaemic clamp technique in the study of Jenni et al. was lower than concentrations at the start of exercise in our study in all conditions (~17-18 mmol.L^{-1}). Thus, rapid rates of appearance of a large amount of carbohydrate into the circulation presents skeletal muscle with an available fuel that has been shown to alter endogenous fuel selection [253]. Furthermore, this lipid-suppressing effect of hyperglycaemia might also potentially explain why carbohydrate oxidation was dominant over lipid oxidation regardless of pre-exercise insulin dosage. To promote a lower carbohydrate oxidation and increased lipid oxidation rate, visualised by a shift towards a lower RER during exercise, people with T1D may consider consuming a less amount of a low glycaemic index carbohydrate source or indeed possibly performing morning fasted exercise [243,254].

5.4.4 Exercise period: serum insulin concentrations

5.4.4.1 Insulin type

Serum insulin concentrations rose similarly by approximately 7% during cycling in all conditions. The pattern of serum insulin rise when expressed as AUC over exercise was also similar between Fiasp and insulin aspart conditions. The exercise sessions in this study took place between 60 and 105 minutes after injection. In PD/PK studies taken at rest, this would typically be a period where rapid-acting insulin concentrations would peak, plateau, and subsequently begin to decline (e.g., Heise et al. [165]). Furthermore, in people without T1D performing moderate-intensity exercise, pancreatic insulin output decreases to prevent an unregulated decline in blood glucose concentrations. The above points are in contrast with the transient rise in insulinaemia demonstrated in our study and in other studies in people with T1D [188]. More than one plausible explanation for this increase exists.

The onset and continuation of physical exercise initiates changes in the fluid dynamics within the body. Increases in blood pressure in addition to elevated osmolarity, local to contracting muscles, exert a net outward shift of fluids during exercise and subsequent relative hypovolaemia [255]. This phenomenon effectively leads to a relative increase in concentrations of solutes in the blood – in this instance insulin. The increase in haemoglobin concentrations and decrease in haematocrit in response to cycle sessions suggest that these fluid dynamics were present in our observations also. In a subset of the study trials (n=22), plasma volume was calculated as Δ-2.21% between exercise start and end (Appendix D)[201,256]. When applied to the wider dataset, the correct pre-exercise insulin concentrations would only shift from 62.5 to 63.9 $pmol.L^{-1}$, less than the 67.1 $pmol.L^{-1}$ exercise concentrations we observed. Hence, there are likely other factors driving the exercise-related increase in insulin concentrations.

Physical exercise has previously been found to influence the rate of absorption of insulin from the subcutaneous tissue into circulation [257]. These observations have been made in both studies via obtained blood samples and via the (increased) rate of radiolabelled insulin disappearance from injection site, indicating a true effect of exercise. While the underlying mechanisms for this increase in insulin absorption are not yet fully elucidated, there are likely multiple factors local to the injection site that may be involved, including increased capillary recruitment, massage-like effect, increased blood flow, and temperature [257]. Hence, the finding in this study of an exercise-related increase in serum insulin concentrations are in-line with previous

observations; however, we found no statistical differences in the magnitude of rise in serum insulin when comparing Fiasp *vs.* insulin aspart.

5.4.4.2 Insulin dose

No differences between the rise in insulin concentrations from the start to the end of exercise between different dose conditions were observed. However, the highest concentration (relativised to baseline) reached during the exercise period ($C_{max\ 60\text{-}105min}$) was greater in both the **F50** and **A50** conditions compared to **A75** (but not **F75**). This finding highlights a difference in time-action profiles between the different dose conditions. While it was not statistically examined in this study, the earlier occurrence of $C_{max\ 60\text{-}105min}$ in the -50% dose conditions may have been followed by a plateau or decline in insulin concentrations prior to the end of exercise. On the other hand, the later time to $C_{max\ 60\text{-}105min}$ would reduce the time during exercise where insulin concentrations plateaued or declined; hence, overall, the increase in insulin concentrations between dosing conditions from pre- to post-exercise remained similar, despite the different timings of $C_{max\ 60\text{-}105min}$.

The influence of exercise on serum insulin concentrations has previously been investigated in different dose reductions. West and colleagues [173] studied seven participants with T1D while running at 70% VO_{2peak} after having injected a full, -25, -50, or -75% insulin aspart or lispro dose. Serum insulin concentrations were found to be similar between start and end of exercise, albeit with a trend of increased insulin concentration in the larger dose reductions of -50% and -75% when compared to each other (p=0.07). The contrast in these findings to the current study is likely in part due to the later timing of exercise after insulin injection (2 h) in West et al. At this point in insulin aspart and lispro's time-action profiles, insulin concentrations are reducing in alignment with the known PD/PK characteristics; hence, any exercise-related impact on increase insulin concentrations appear to be counterbalanced by the predicted PD/PK decline at this stage. This is supported by the findings from other studies which have shown an increase in insulin concentrations during 45 minutes of moderate-intensity exercise which is commenced 60 minutes after injection, more in alignment with our findings [167,175,176,188].

This study shows that Fiasp-driven serum insulin concentrations increased during cycling in a manner similar to insulin aspart. This increase was not dependent on pre-exercise insulin dosage between 50% and 75% reductions. Further, the assay used to determine the serum

concentrations is unable to distinguish between insulin types; hence, the contribution of insulin degludec to this data is unknown.

Data from the four conditions of this study, alongside aforementioned previous studies employing dose reductions prior to moderate-intensity exercise, demonstrate that relative hyperinsulinaemia can occur during exercise. The choice of insulin dose over type (Fiasp *vs.* insulin aspart) is the dominant factor in determining serum insulin concentrations during exercise; however, regardless of dose and type, serum insulin concentrations rise during exercise at a time of already high circulating post-prandial insulin. This phenomenon should be considered in models predicting both PD/PK characteristics around exercise in T1D.

5.4.5 Exercise period: blood glucose concentrations

5.4.5.1 Insulin type

This is the first study to compare the glycaemic effects of different reduced dosages of Fiasp and insulin aspart around exercise. With similar starting blood glucose concentrations, cycling induced a progressive reduction in glucose by the end of the exercise period. Regarding the comparison between insulins, blood glucose concentrations fell similarly between insulin types in both -50 and -75% conditions. Post-hoc testing revealed that, while blood glucose declined similarly in **F50** compared to all other conditions, **A50** fell to a greater extent than both **F75** and **A75** conditions. While there was a trend for **A50** (-5.1 ± 3.0 mmol.L^{-1}) blood glucose to decline further than **F50** (-4.0 ± 2.8 mmol.L^{-1}), this did not reach statistical significance (p=0.067). Molveau et al.[174] recently performed a comparable study, where 50% reduced Fiasp or insulin aspart was injected 60 or 120 minutes prior to 60 minutes of moderate-intensity continuous exercise on a cycle ergometer. When combining the timing effects, Fiasp was reported to have declined to a lesser extent compared to insulin aspart (-4.1 ± 2.3 *vs.* -4.4 ± 2.8 mmol.L^{-1}; p=0.037), a result that is in partial agreement with our findings. A potential explanation for this difference in statistical significance may lie in the greater variability of the decline in glucose in our study (coefficient of variation in -50% insulin conditions of 64.4%) compared to the study of Molveau and colleagues (calculated coefficient of variation of 59.9%), which may have been sufficient to blur the differences between conditions. This higher coefficient of variation in itself may be attributable to the higher starting glucose concentrations reported at the start of exercise in the current study (~17 mmol.L^{-1}) from consuming a large amount of a high glycaemic index meal *vs* Molveau and colleagues (~12 mmol.L^{-1}) in which participants consumed a mixed-meal. Further, data from Molveau et al. are taken from two trial

arms where insulin was taken at either 60 min or 120 min prior to exercise. There were significant differences between these conditions on the change of blood glucose during exercise (a larger decline in the 120 min condition across both insulins) which may also restrict direct comparison. Area under the curve insulin data from our study were similar during the exercise; hence, any diverging effects of the two insulins on blood glucose during exercise are likely to have materialised prior to exercise start. Nevertheless, the high coefficient of variation in the change in blood glucose concentrations during exercise, and indeed that of each timepoint of blood glucose and serum insulin concentrations, reflect the high inter- and intra-variability of performing exercise in T1D, even under standardised conditions.

The overall exercise-induced decline in blood glucose from this study align with findings of another investigation in which participants using either Fiasp or insulin aspart performed 45 minutes of cycling exercise at 60% VO_{2peak} under hyperglycaemic or euglycaemic conditions [184]. Under hyperglycaemic conditions – those most similar to the current study's – glucose declined from (mean ± SEM) 13.7 ± 0.7 to 10.1 ± 0.6 mmol.L^{-1} (p<0.05). Interestingly, when the same participants performed exercise with blood glucose starting in euglycaemia, no decline in blood glucose was observed ([mean ± SEM] 10.4 ± 0.4 to 7.5 ± 0.7 mmol.L^{-1}). While the average decline across all conditions between this study (~ -3.8 mmol.L^{-1}) and the current study (~ -3.8 mmol.L^{-1}) are comparable, the lack of segregation of insulins and insulin administration types (both CSII and MDI used), as well as the potential variance of participant carbohydrate and insulin administration prior to exercise, restrict further meaningful comparisons.

The decline in blood glucose during exercise observed in both Fiasp and insulin aspart in this study, as well as others, run concurrent with the decline in blood glucose well-documented in moderate-intensity continuous exercise in T1D [6,128]. In brief, exercising muscles stimulate a large increase in glucose uptake via cellular insulin-independent pathways causing an overall increased rate of glucose disappearance from the blood [258]. Without a decrease in exogenous or endogenous insulin provision, the combination of insulin-dependent pathways from relative hyperinsulinaemia and increased insulin-independent pathways from skeletal muscle glucose uptake lead to a substantial decline in blood glucose concentrations, increasing the risk of hypoglycaemia [128]. Furthermore, in addition to increasing whole-body glucose disposal, relative hyperinsulinaemia inhibits the capacity for endogenous (hepatic) glucose production, further promoting decrements in blood glucose [226]. We have found the reduction in blood

glucose during exercise to be no different between Fiasp and insulin aspart when employing either a -50% or -75% dose reduction.

5.4.5.2 Insulin dose

There was a significant dose effect on changes in blood glucose during exercise in which **A50** exhibited a greater decline compared to both -75% insulin reduction conditions. Changes in blood glucose in **F50** during exercise were similar to all other conditions.

Changes in blood glucose during cycling were further explored by measuring the change in glucose from the point of peak glucose concentrations within exercise ($C_{max0\text{-}105min}$). Despite the commencement of a warm-up and moderate-intensity workload, glucose concentrations continued to rise after the start of exercise. Hence, the reported decline in blood glucose concentrations in our study from the start of cycling was neither immediate nor linear. We found there to be a greater drop in blood glucose between $C_{max0\text{-}105min}$ and exercise end between **A50** and all other conditions, which was otherwise similar in all other conditions. However, $tmax_{0\text{-}105min}$ varied between conditions, occurring later by ~8-9 minutes in -75% conditions compared to -50%. To account for the variance in $t_{max0\text{-}105min}$, a further calculation that relativised the blood glucose drop to remaining exercise time was performed. The subsequent rate of change of blood glucose from $C_{max\ 0\text{-}105min}$ to end was similar between all conditions and suggests the earlier $t_{max\ 0\text{-}105min}$ in **A50** negated the greater rapidity in blood glucose decline.

Only two other studies have compared different pre-exercise dosing in insulin aspart. West et al. [173] investigated the effects of a -25%, -50%, and a -75% reduction against full dose prior to 45 minutes of running using insulins lispro and aspart, while McCarthy et al. [171] compared full dose *vs.* -50% dose reduction in aspart alone prior to 45 minutes of cycling. Interestingly, there is no clear pattern on the effect of insulin reduction on the rate of change of blood glucose within and between these two studies. West and colleagues reported a greater decline in blood glucose with full dose (-6.1 $mmol.L^{-1}$) compared to -25% (-4.3 $mmol.L^{-1}$) and -75% (-3.2 $mmol.L^{-1}$) trial arms but not -50% (5.5 $mmol.L^{-1}$). McCarthy et al. reported no differences between the rate of blood glucose change between trials. These studies contradict the premise that performing moderate-intensity exercise in the presence of relative hyperinsulinaemia leads to a more-rapid decline in blood glucose [225,259]. It should be noted in all three studies, however, participants had moderate control of insulin and modest insulin:carbohydrate ratios (e.g., ~1:10). Hence, the difference in injected insulin units between reduced-dose trial arms are

minimal. Indeed, some individuals in our current study had an equivalent full dose of 3-4 UI, resulting in a difference of only 1 unit of insulin injected between trial arms. In this regard, one or a number of the many factors which influence the change in blood glucose during exercise are likely to outweigh the effect on glucose dynamics over changes in insulin [260]. The high sampling frequency before and during exercise in this study facilitated our observations of a continued rise in blood glucose during exercise before a rapid decline. Hence, the pre- to post-exercise change in glucose is likely heavily influenced by the high glycaemic index, high carbohydrate load consumed as a rapidly absorbed meal prior to exercise. Nevertheless, glucose concentrations at the end of exercise were better preserved, albeit hyperglycaemic, after injecting -75% insulin doses compared to -50% doses (**Table 27**).

Overall, the decline in blood glucose concentrations observed in the current study were similar between Fiasp and insulin aspart when employing the same insulin dose reduction. Although a 50% reduction in Fiasp dosing pre-exercise produced a change in glucose during exercise similar to all other conditions, a 50% reduction in insulin aspart dosing was found to exert a greater change in blood glucose during exercise compared to both -75% reduction conditions. From these findings, reductions in Fiasp can be employed in alignment with current pre-exercise bolus insulin reduction guidelines equivalent to reductions already defined in insulin aspart [6,128]. A trend in our study data towards a lesser decline in Fiasp compared to insulin Aspart – finding which corroborates with a similar study [174] – implies a more protective effect of Fiasp over insulin aspart during exercise when using a -50% reduction. A more conservative effect of Fiasp on changes in glycaemia after mealtimes has also been observed at rest in real-world conditions, reinforcing this observation [261]. Clinicians and T1D recommending or using Fiasp may seek assurance from this data about its efficacy when used in-line with consensus guidelines pre-exercise, particularly in comparison to the well-established insulin aspart.

5.4.6 Post-exercise period

Following exercise cessation, blood glucose concentrations rose to another ‘smaller peak’, the extent to which was similar in all conditions. Subsequently, blood glucose declined by a similar amount between doses and insulin types; however, given the higher starting concentrations at exercise end and post-exercise ‘peak’, -75% conditions had elevated glucose at the end of the first prandial period, 4 h after the injection at baseline compared to -50% conditions (~3 $mmol.L^{-1}$).

The occurrence of a post-exercise rise in glucose could possibly be attributable to altered digestive processes during exercise and a shunting of blood away from the viscera. At 70% VO_{2max}, splanchnic blood flow can be reduced by up to 80%, in addition to delayed gastric emptying at higher exercise intensities and carbohydrate-heavy feeding [262,263]. The full content of the carbohydrate drink consumed at baseline may not have been fully absorbed at the start of exercise before entering into a dynamic state of lower absorption during exercise; hence, the rise in glucose concentrations could be attributed to digestive processes returning to normal rates post-exercise. Alternatively, counterregulatory hormones have been shown to remain elevated post-exercise compared to rest conditions 15-30 minutes after exercise in people with T1D, potentially protecting glucose concentrations from decline post-exercise [176]. During the post-exercise period, insulin concentrations decreased from end of exercise until the second prandial period, at which point concentrations were similar between injections.

5.4.7 Second prandial period: serum insulin concentrations

Serum insulin concentrations were greatest in **F50** condition in the early second prandial period, following a trend similar to the first prandial period after 15 minutes. AUC between baseline and 60 minutes indicated that differences were only present between insulin dose reductions arms, with any effect of differences in insulin type now negligible. Inter-individual variability in AUC metrics was again significant, emphasising the need for individual responses before, during, and after exercise to be considered when adjusting insulin dosing around exercise. Nevertheless, the pattern of elevated AUC in -50% over -75% reduction condition continued consistently throughout the second prandial period. As part of an exploratory analysis, serum insulin area under the curve from the first injection to end of exercise (105 minutes) was compared to the area under the curve from the second injection to the equivalent time to the end of exercise (345 minutes). Area under the curve was greater during the first prandial period between these timepoints than the second (+385 pmol.min.L^{-1}; p<0.001), reflecting the effect of exercise on insulin exposure when performed within the first two hours of a (ultra-)rapid-acting insulin's duration of action. It should be noted, however, that insulin concentrations had not yet returned to baseline at the start of the second prandial, potentially influencing this finding. The similarity between Fiasp and insulin aspart at the point of the second injection allows previously established duration of insulin action guidelines to be applied to the reduced doses of Fiasp as with insulin aspart, where the individual with T1D should be mindful that residual insulin activity may be present 4 h after the first bolus injection of the day – particularly in pump users – to avoid insulin stacking [264,265].

5.4.8 Second prandial period: blood glucose concentrations

There were no differences between conditions in blood glucose exposure until the first hour of the second prandial period. Here, AUC was less in **F50** vs **A75** – a difference that was not found in the first prandial period – while all other inter-condition comparisons yielded similar results. However, beyond this point, **F50** displayed lower glucose exposure up until the time equivalent of end of exercise (345 minutes) and a lower $C_{max240\text{-}345min}$ compared to both **F75** and **A75**. Interestingly, there was no difference when comparing AUC between first ($AUC_{0\text{-}105min}$) and second ($AUC_{240\text{-}345min}$) prandial periods between injection and the time equivalents of the end of exercise(p=0.448). Acute physical exercise initiates mechanisms to increase glucose uptake into skeletal myofibers for ATP regeneration. Non-insulin mediated mechanisms rise and fall approximately in-line with exercise workload, while an increase in insulin sensitivity is sustained for many hours after exercise end [258,266]. During the first prandial, insulin sensitivity is under baseline conditions until exercise start, where acute exercise-related mechanisms increase glucose rate of disappearance. Conversely, during the second prandial period, insulin sensitivity is likely elevated from the exercise session, and increases glucose disposal throughout the second prandial period, while non-insulin mediated mechanisms approach levels similar to baseline [258]. Hence, these opposing factors appear to balance one-another out when comparing the area under the curve at these timepoints. This may provide a useful indicator for people with T1D engaging the same insulin-related management strategies for the first meal with exercise and the second meal without, will result in an approximate similar glucose exposure outcome. Indeed, participants employing -50% insulin reduction trial arms end the trial arms averaged ~Δ-0.25 $mmol.L^{-1}$ at 480 minutes, compared to 0 minutes baseline. However, on the basis that glucose exposure is determined by both concentrations and time, there is still scope for point concentrations to differ between first (with exercise) and second (without exercise) prandial periods while maintaining an equivalent area under the curve.

5.4.9 Strengths and limitations

This study has several strengths. This is the first study to compare two insulin dose reductions and using an ultra-rapid-acting insulin, Fiasp, and a rapid-acting insulin, aspart. To achieve this, a double-blind, four arm, two-site, randomised crossover clinical trial, to control for multiple variables and standardise comparison metrics was performed. A high venous sampling frequency was used, up to every 5 minutes, to gain high resolution of blood glucose and serum

insulin changes throughout periods where pharmacokinetic differences between Fiasp and insulin aspart have been shown to be marginal. By using the same protocol across two-sites, a large sample size (randomised n=44) was achieved. However, the study is not without limitations. The use of a high glycaemic index drink with a high carbohydrate load at mealtimes frequently led to level 2 hyperglycaemia throughout the trial day [1]. While this provided a platform to examine the glucose lowering effects of the different insulin conditions with significant changes in blood glucose concentrations, the daily life applicability is limited and in such situations of prolonged hyperglycaemia the individual with T1D may otherwise choose to take a correction dose. Secondly, starting blood glucose concentrations were not controlled beyond the participant's own responsibility to follow pre-visit requests; hence, it is unknown how individuals with higher *vs*. lower starting blood glucose concentrations may have impacted the variance between trial days, despite having titrated to an insulin regimen comprised only of degludec and either Fiasp or insulin aspart.

We included both males and females in this study which provides improved applicability than the inclusion of any single sex alone and facilitates split sex-related outcomes in future secondary analyses. However, we did not account for female menstrual cycle, which may impact blood glucose concentrations during the day and during exercise [267]. Lastly, data collection was halted during government-enforced lockdown due to COVID-19, significantly protracting the data collection period over which the study was performed.

5.5 Conclusion

This is the first study to compare the use of Fiasp and insulin aspart when using different bolus insulin dose reductions around exercise. It has been demonstrated that altering insulin dose reductions between 50% and 75% exerts a greater influence on glycaemia around exercise than altering between ultra- or rapid-acting insulins, and that insulin dose reductions around acute aerobic exercise can be used with similar glucose-lowering effects in Fiasp and insulin aspart.

Chapter 6

Discussion

6.1 Summary of key findings

The overall aim of this thesis was to identify the glycaemic effects of pre-exercise bolus insulin dose reductions, with application in using Fiasp as part of a multiple daily injection regimen in real-world and clinical trial settings in recreationally active individuals and trained athletes with T1D.

- Therein, the aim of Chapter 3 was to compare the intra-study rate of change of blood glucose concentrations during aerobic exercise when using different pre-exercise bolus insulin doses. The results from this meta-analysis indicate that a lesser rate of blood glucose decline occurs when reducing insulin doses before exercise.
- The use of Fiasp was subsequently compared with insulin aspart in a professional cycling team performing prolonged exercise in Chapter 4. Riders using Fiasp were found to maintain recommended glucose time in range during training and race events, equally so those using insulin aspart.
- Finally, a randomised controlled trial was performed in Chapter 5 to further compare Fiasp and insulin aspart when cycling with different insulin dose reductions. This study found similar effects of Fiasp and insulin aspart on within-exercise rate of change of blood glucose. To this end, the significant effect of pre-exercise insulin reductions on blood glucose rate of decline during exercise was demonstrated; however, the use of an ultra-rapid-acting insulin compared to a rapid-acting insulin appears not to alter this effect, nor the glycaemic outcomes when performing prolonged bouts of exercise.

Acute physical exercise is a potent stimulus for changes in blood glucose concentrations. For example, a single bout of continuous moderate-intensity exercise can cause rapid declines in glucose in a person with T1D, and even modest declines in those without T1D after longer periods of exercise. The need to employ extra care when managing glucose around exercise is therefore paramount. The profound effect of exercise on blood glucose concentrations was demonstrated across this thesis. Regardless of insulin dosing, exercising in the early (<2 h) post-prandial period causes a decline in glucose from exercise start, averaging -0.088 $mmol.L^{-1}.min^{-1}$ (averaged across doses) when reducing insulin dosing, contrary to -0.111 $mmol.L^{-1}.min^{-1}$ when taking a full dose. This difference was reflected in a moderate standardized mean difference of 0.59 (95% CI: 0.17, 1.01) calculated in the meta-analysis in Chapter 3. Data from Chapter 4 indicated that, despite excellent glucose management during prolonged cycling,

professional cyclists with T1D can experience multiple hypoglycaemic events while also spending considerable time in hyperglycaemic ranges. A similar amount of time in range (TIR) was maintained in riders using Fiasp (75.8 ± 32.7%) or in riders using insulin aspart (76.6 ± 29.6%) during training. During a racing event, riders using Fiasp were still able to maintain good glycaemic control (68.1 ± 9.6% TIR) in-ride, while reducing Fiasp doses across consecutive days. Results from Chapter 5 found that, regardless of both insulin type and reduction, insulin declines during 45 minutes of continuous exercise in a controlled laboratory setting. There were no differences between the decline of blood glucose during exercise when taking a 50% reduction in Fiasp (-4.0 ± 2.8 mmol.L^{-1} [-0.091 ± 0.062 mmol.L^{-1}.min^{-1}]) prior to exercise compared to a 75% reduction in Fiasp (-2.8 ± 3.3 mmol.L^{-1} [-0.062 ± 0.073 mmol.L^{-1}.min^{-1}]) or insulin aspart (-3.4 ± 3.3 mmol.L^{-1} [-0.076 ± 0.073 mmol.L^{-1}.min^{-1}]) or a 50% reduction in insulin aspart (-5.1 ± 3.0 mmol.L^{-1} [-0.113 ± 0.067 mmol.L^{-1}.min^{-1}]). There was, however, a greater decline in blood glucose when taking the 50% reduction in insulin aspart compared to 75% in either insulin.

6.2 General discussion

6.2.1 The influence on pre-exercise insulin reductions on the rate of decline of blood glucose during recreational exercise

There is an additive effect of insulin and exercise on increasing the rate of glucose uptake during exercise [212,259]. After administering exogenous insulin with a meal, people with T1D are unable to adjust levels of insulin 'on-board'. This combined with the supra-physiological concentrations of insulin in the periphery that occur as a result of injecting via the subcutis creates a milieu for elevated glucose disappearance from circulation and a net fall in blood glucose concentrations during moderate-intensity physical exercise [268]. The strategy of reducing insulin prior to exercise to preserve glycaemia will therefore remain applicable while there is a need to administer large non-adjustable and non-responsive (i.e., not glucose-sensing [269]) insulin doses with a meal ahead of a bout of exercise.

Blood glucose concentrations increase quickly after the consumption of a meal with a major carbohydrate component in the person with T1D, even with a full dose of insulin individualised to their insulin:carbohydrate ratio. A reduction in this dosage incurs a greater increase in glucose concentrations. From the data available in studies from Chapter 3, and the four conditions in Chapter 5, the difference in immediate pre-exercise (post-prandial) blood glucose concentrations between dose conditions never exceeded 2.4 mmol.L^{-1}. This demonstrates an

initial buffer against hypoglycaemia, which is otherwise a barrier to people with T1D [133]. This is not to say that elevated blood glucose concentrations alone are a sufficient strategy for avoiding hypoglycaemia. For example, ensuring blood glucose concentrations at the start of exercise are 10 mmol.L^{-1} (180 mg.dL^{-1}) as opposed to 5 mmol.L^{-1} (90 mg.dL^{-1}) only equates to an additional 5 g of carbohydrates (glucose) stored in the circulation. This presents a limited fuel depot in the context of the ~1.8 g carbohydrate oxidation per minute calculated from the exercise sessions in Chapter 5. Conversely, elevated blood glucose concentrations in the early post-prandial period (because of reducing insulin dosing) represents a dynamic point of net accumulation of glucose from the digestive system, on top of that which would otherwise occur with a full dose. Nevertheless, an exaggerated glucose response to the meal (e.g., by an additional 2.4 mmol.L^{-1} in the referenced studies) may be sufficient to induce unwanted hyperglycaemia ahead of exercise [216]. This may itself deter people from using a pre-exercise insulin reduction strategy, despite exercise being safe to perform in this state in the absence of symptoms and blood ketones of >0.6 mmol.L^{-1} [5].

The results from Chapter 3 indicate that a reduced bolus dose of insulin pre-exercise leads to a lesser rate of decline in blood glucose compared to a full dose. This was reflected in Chapter 5 where a larger 50% reduction dose resulted in a significant (**A50**) or trending (**F50**) increase in rate of decline with a higher dose. Nevertheless, regardless of the dose, aerobic exercise performed post-prandially is shown in this thesis to be associated with meaningful declines in blood glucose. Therefore, the individual with T1D looking to further temper or completely avoid a decline in blood glucose during exercise, or avoid pre-exercise elevated glucose concentrations, must implement glycaemic management strategies complimentary or alternate to insulin reductions.

In contrast to reducing the effects of net glucose *disappearance* in circulation exerted by insulin, people with T1D can increase the relative rate of glucose *appearance* via carbohydrate consumption strategies. Current guidelines recommend consuming between 10-60 g [6,128] of carbohydrates per hour of moderate-intensity exercise to maintain glucose levels [6]. While these recommendations are provided with the primary aim of preventing within-exercise hypoglycaemia, it is interesting to note that the upper end of the guidelines effectively overlap with the lower end of guidelines for carbohydrate consumption directed at people with[188] and without[270] T1D for sports performance. Indeed, riders in Chapter 4 consumed an average of 40-50 g carbohydrates during prolonged cycle rides to effectively maintain glycaemia and train or compete professionally [271]. The consumption of carbohydrates provides an increased

appearance of exogenous glucose into the blood and subsequent increased exogenous carbohydrate oxidation during exercise [272]. However, provision of exogenous glucose to induce modest hyperglycaemia does not appear to attenuate endogenous glucose production under basal insulin conditions in people with T1D, unlike the attenuation which occurs in those without T1D [225]. Hence, a combination of insulin dose reduction, to facilitate higher endogenous glucose production and reduce insulin-dependent glucose uptake, *and* within-exercise carbohydrate consumption, to increase the rate of glucose appearance, may serve as an effective means to temper the rate of decline of blood glucose otherwise observed in the person with T1D not employing any glycaemic management strategies during aerobic exercise. The finding of a lower rate of blood glucose decline, concomitant with a greater pre-exercise glucose response to the meal, when using insulin reductions in Chapter 3 may alleviate the need for carbohydrates during exercise sessions which are shorter in duration (e.g., <30 min), particularly if blood glucose is started within recommended ranges (7-10 $mmol.L^{-1}$) [5,128].

A list of glycaemic management strategies that can be used in conjunction with insulin reductions to influence the rate of blood glucose decline are listed in **Table 34**. In the instance where the individual with T1D would rather avoid pre-exercise insulin reductions altogether, performing exercise after an overnight fast without bolus insulin dosing provides a stable blood glucose response [273]. Conversely, the results comparing the effects of insulin timing prior to exercise performed in the post-prandial period are conflicting [174,230]. It is likely that a combination of these strategies (or methods used by the research teams in this context), in addition to the insulin dosing as a strategy itself, explain the differences between the rates of change of blood glucose during exercise over Chapters 3, 4 and 5. Appropriately combining strategies around exercise may benefit acute glycaemic management [274].

Table 34: *Strategies that can be used in conjunction with bolus insulin reductions to affect the rate of blood glucose decline during aerobic exercise and/or post-prandial pre-exercise glycaemia.*

Strategy	Influence on pre-exercise glycaemia	Influence on (rate of) BG change during exercise
Carbohydrate consumption related		
Within-exercise carbohydrate supplementation	-	An increased rate of appearance of exogenous carbohydrate into the blood tempers the decline or increases BG. [6,128]
Low glycaemic index carbohydrate-containing pre-exercise meal	Carbohydrate GI is proportional to the prandial BG response.	Similar BG response. Lower carbohydrate oxidation and greater lipid oxidation with low GI meal. [243]
Exercise characteristics related		
Adjust exercise intensity	-	Exercise intensity is proportional to the rate of BG decline until ~80-85% VO_{2peak}. [6,128]
Change exercise modality	-	Different modalities may change BG differently with other variables held constant (e.g., intensity, duration, etc.). [275]
Perform bout of resistance exercise before aerobic exercise	-	A lesser rate of BG decline occurs when resistance exercise is performed prior to aerobic exercise. [276]

BG, blood glucose; GI, glycaemic index; VO_{2peak}, peak volume of oxygen uptake.

6.2.2 The application of insulin reductions on glycaemia during prolonged exercise and competitive endurance events

The riders in Chapter 4 employed a combination of insulin reduction and carbohydrate ingestion strategies around prolonged exercise sessions in both training and racing conditions [186,271]. Ahead of competitive events, a rise in glucose levels due to apprehension may occur, reducing the need to actively elevate glucose concentrations and even requiring additional strategies to counter this natural rise (e.g., engage in a prolonged aerobic warm-up or psychological strategies) [188]. This may initially suggest that a bolus insulin reduction is less important prior to a prolonged exercise session or a competitive event. However, the results from this thesis indicate that reducing the bolus insulin dose before exercise exerts glycaemic

effects that extend beyond raising pre-exercise glucose and beyond reducing the rate of decline during acute exercise.

Of the four studies included in Chapter 3, one study by West et al.[173] measured glycaemia beyond 1-h post-exercise without providing planned (i.e., not to treat hypoglycaemia) carbohydrate. The authors in this study observed that a 75% reduction in bolus insulin resulted in 3-h blood glucose concentrations (relative to baseline) significantly greater than concentrations in the full dose trial at the same time point. Other reduction trials from this study had glucose concentrations that tended to be higher than the full dose trial. These findings are in alignment with data from Chapter 5, where glucose concentrations in the 75% dose reduction conditions were higher after 2 h 15 min after exercise compared to 50% dose reduction conditions. The preserving glycaemic effects of insulin reduction in these studies continued after the end of exercise up until the last post-exercise sample (which was either 4 h or 5 h 45 min post-injection) and, therefore, the effects extended even beyond the 4-h 'duration of action' typically recognised in rapid-acting insulins. For the riders in Chapter 4 exercising for an average of ~4 h, this emphasises the concept that reducing the bolus dose pre-exercise exerts mechanisms to maintain blood glucose long after having exerted the effect of raising glucose prior to exercise. Nevertheless, the relative effects of reducing bolus insulin will decrease with exercise duration in prolonged exercise. The longest duration of training rides was 6.3 h; hence, the relative effects of other strategies employed throughout exercise (e.g., carbohydrate consumption and within-exercise insulin dosing) will appear greater in these rides compared to the pre-exercise insulin reduction [277].

Uniquely to the professional athletes with T1D, including riders in the cycling team in Chapter 4, the need for maintaining good glycaemic control must, in part, be balanced with the need to facilitate exercise performance. Insulin reductions that are too severe will increase the risk of Level 2 hyperglycaemia (>13.9 mmol.L^{-1}) with potential for concomitant symptoms [71]. These symptoms alone may distract from race tactics or technique execution, even if hyperglycaemia has not been shown to negatively influence performance physiologically in the limited available literature [278]. Furthermore, experiencing hyperglycaemia may dissuade the individual with T1D from intaking carbohydrates for ergogenic purposes, although there is a dearth of information on the effects of carbohydrate intake during (prolonged) exercise in different glycaemic states (e.g., hyper- vs euglycaemia) [278]. Indeed, data from Moser and colleagues that show four athletes from Chapter 4 injected 5 ± 2 UI of insulin during races, suggesting that an effort was made to avoid excessive hyperglycaemia. Despite these in-ride injections, data from

Chapter 4 revealed that ~22-25% of time was still spent in hyperglycaemia (Levels 1 and 2) during both training and race rides, indicating that hyperglycaemia was a preferred state rather than risking hypoglycaemia. Nevertheless, these riders consumed 40-50 g of carbohydrates per hour of training rides and competitive races while also reducing daily bolus insulin dosing by approximately 50% [186,271], effectively employing a combination of insulin reduction and carbohydrate ingestion strategies around the prolonged exercise sessions. Future research including these athletes would benefit from collecting data on the timing of within-exercise carbohydrate consumption and within-exercise insulin injections, particularly to investigate any relationship between time from study start (and therefore the pre-exercise injection) and the supplements or insulin doses.

Collectively, these data suggest that the role of pre-exercise insulin may differ in the context of prolonged and/or competitive endurance events compared to shorter non-competitive bouts of exercise performed by recreationally active individuals. Insulin reductions may serve to protect against hypoglycaemia during exercise by providing an initial buffer with raised pre-exercise glucose concentrations and by reducing the rate of blood glucose decline during exercise. While these same mechanisms also hold true for prolonged exercise and competitive endurance events, the rate of change of blood glucose in these scenarios are more influenced by factors outside of pre-exercise insulin dosing, particularly with increased duration. Even so, the prolonged glycaemic preserving effects highlighted here provide argument that reducing mealtime insulin prior to, and around, endurance events are an effective glucose management strategy.

Reducing the mealtime insulin dose in anticipation of a bout of aerobic exercise to maintain glucose control is well recognised in exercise guidelines for T1D [6,128]. This thesis has highlighted or first identified that reducing insulin in this manner exerts the following influences to preserve glucose throughout the pre-exercise, within-exercise, and post-exercise periods:

1. Glucose concentrations are elevated immediately pre-exercise.
2. There is a lesser rate of decline in blood glucose during acute exercise (<60 minutes).
3. Glucose concentrations remain elevated in the post-exercise period for >2-3 h. This implies a preservative glycaemic effect in prolonged exercise bouts (>60 min); however, further research is needed to explore this.

6.2.3 Reducing insulin doses around exercise exerts similar effects in Fiasp and insulin aspart

Fiasp represents the latest generation of mealtime insulins. As an ultra-rapid-acting insulin, Fiasp has an earlier onset of appearance, earlier exposure, and earlier time to peak than its predecessor insulin aspart. These benefits favour Fiasp in use for faster-acting corrections, glucose control, and flexibility around mealtimes. These advantages do not, however, translate to meaningful differences into long-term clinical outcomes, suggesting that this latest generation may represent the end of progressive advances in speed in mealtime insulins developed thus far with insulin analogues [279]. Findings from this thesis can progress the knowledgebase regarding the use of this insulin around exercise and might, therefore, be applicable until the administration of ultra-rapid-acting mealtime insulins around exercise are effectively replaced.

The results from Chapter 5 overall demonstrate a similarity in glycaemic effects between Fiasp and insulin aspart when taken as a 50% or 75% dose reduction around exercise. Despite an initial (15 min post-injection) greater serum insulin exposure of Fiasp under the 50% and 75% conditions compared to their respective insulin aspart conditions, no differences in glycaemia were observed pre-, during, or post-exercise. Notwithstanding, there was a trend for the rate of decline in blood glucose in the 50% Fiasp condition to be less than that of 50% reduction in insulin aspart (p=0.067). In a comparable study, Molveau et al. found a 50% dose of Fiasp to decline significantly slower during moderate-intensity exercise than the same dose in insulin aspart [174].

The findings from Chapter 5 and Molveau and colleagues in tandem suggest that Fiasp has an equivalent if not conservative effect on the rate of change of blood glucose during moderate-intensity exercise, without elevating pre-exercise glycaemia. Participants from both studies spent considerable time in hyperglycaemic range before, during, and after exercise. Glucose concentrations (relative to baseline) before exercise were, however, significantly elevated in Chapter 5 (~Δ7-8 mmol.L^{-1}) compared to the study by Molveau et al. (~Δ3.5 mmol.L^{-1}) with similar elevated comparisons continuing through the exercise and post-exercise periods [174]. This is likely due to the differences in carbohydrate load and glycaemic index in the pre-exercise meal. In Chapter 5, the meal consisted of carbohydrates high in load and glycaemic index, *vs.* a mixed meal with a lower glycaemic index and only 50-65 g carbohydrates in the study of Molveau et al. As randomised controlled trials, both studies can provide comparative measures between Fiasp and insulin aspart, having been performed under the same conditions.

Although the glycaemic state in Chapter 5 was predominantly hyperglycaemia (>10.0 mmol.L^{-1}), a comparison between Fiasp and aspart was enabled with minimal interference from glucose input from exogenous fat or protein conversion. Hence, Fiasp performance has been found to be equivalent, or more conservative, compared to insulin aspart after a predominantly carbohydrate load (Chapter 5) and after a mixed meal [174].

Fiasp may be taken at the start of or 20 minutes after the start of mealtimes and still provide a glucose-lowering effect that effectively matches glucose absorption profiles [164]. Conversely, insulin aspart is recommended to be taken 15 min prior to the start of mealtimes. Regarding the recreationally active person with T1D for whom, unlike professional athletes, a strict exercise schedule may not be practical, flexibility in managing glycaemia around exercise is advantageous. In using Fiasp at a time closer to (or after) a meal, there may be less notice required to reduce insulin ahead of a bout of exercise compared to a rapid-acting insulin, effectively allowing the person with T1D to better react to upcoming exercise or provide more freedom of choosing exercise timing. Examples of such patient-orientated conveniences are often not recorded in physiology-based studies.

Results from Chapter 5 suggest that a 50% reduction in Fiasp will result in 2-h 15-min post-exercise glucose concentrations similar to those at baseline, that is, before the pre-exercise meal (Δ +0.4 mmol.L^{-1}). At the same timepoint, blood glucose concentrations were elevated under the Fiasp 75% reduction condition (Δ +3.6 mmol.L^{-1}; p<0.001). Molveau et al. observed concentrations most similar to baseline after 90 min post-exercise when injecting a 50% reduction in Fiasp dose 60 minutes pre-exercise (Δ -2.8 mmol.L^{-1}) compared to 120 min (-4.6 mmol.L^{-1}; p=0.001). Combined, these data indicate that a person taking a 50% reduced dose of Fiasp 60 minutes prior to a bout of 45-60 minutes of moderate-intensity continuous exercise can attain glucose concentrations similar to baseline ~2 h after exercise.

The results from Chapter 4 indicate that using Fiasp is non-inferior to using insulin aspart in and around prolonged (~4 h) training rides in professional athletes with T1D. Furthermore, Fiasp can be effectively used as part of a glycaemic management strategy during a physically demanding 5-day race event to maintain recommended time in range. Although spontaneous bouts of exercise are less common during competitive season for the riders in this team, using Fiasp may benefit riders who choose to administer insulin correction doses during exercise sessions. The quicker glucose-lowering effect may allow riders to bring glucose concentrations

down more quickly and enable them to assess if glucose concentrations are returning to target range earlier than when using insulin aspart.

Collectively, the findings of these studies indicate that Fiasp exerts comparable glycaemic effects to insulin aspart when employed around exercise. There may be advantages in using Fiasp to suit both trained athletes and recreationally active individuals. Specifically, the findings of this thesis combined with data from previous studies indicate that:

1. Fiasp can be used when employing either 50% or 75% pre-exercise dose reductions at either 60 or 120 min prior to a bout of moderate-intensity continuous exercise with similar glucose-lowering effects to insulin aspart.
2. Altering insulin dose reductions between 50% and 75% exerts a greater influence on glycaemia around exercise than altering between ultra- or rapid-acting insulins.
3. Fiasp may also be used to maintain appropriate time in range during prolonged endurance exercise bouts similarly to insulin aspart. Its successful application to international race events has been demonstrated when reducing daily insulin doses.

6.3 Applications of insulin reduction and Fiasp in current and emerging diabetes technologies and therapies

6.3.1 Continuous glucose monitors

The rate of change of blood glucose during exercise is an acute predictor in direction and magnitude of glucose concentrations and upcoming glycaemic status. Randomised controlled trials are able to use invasive techniques (such as clamps) or 'standalone' high frequency venous sampling (as used in Chapter 5) to closely track accurate changes in blood glucose concentrations. These techniques are inaccessible to the person with T1D performing exercise under real-world conditions. Alternative blood glucose measures via fingerstick sampling are painful and can be cumbersome with high sampling frequencies while exercising, either recreationally or during competition. CGMs therefore provide a useful surrogate marker to track the rate of change of glucose concentrations during exercise. CGMs convert the rate of change of blood glucose to arrow trends that can be used to gain a quick informative picture on the direction of blood glucose (**Figure 8**). Perhaps easiest to calculate, a rate of change of glucose of –0.100 $mmol.L^{-1}min^{-1}$ equates to a change in glucose of -1 $mmol.L^{-1}$ every 10 minutes. In the FreeStyle Libre 2, currently provided to people with T1D living in the UK by

the National Health Service, a decline in <-0.100 mmol.L^{-1}min^{-1} is translated as an arrow pointing directly downwards. This represents the most severely declining indicator displayed by the Libre 2. Averaged data from Chapter 3 indicates that a full dose of insulin (-0.111 mmol.L^{-1}.min^{-1}) is associated with a decline in glucose <-0.100 mmol.L^{-1}min^{-1}. Conversely, the reduce dose trials (-0.088 mmol.L^{-1}min^{-1}) demonstrated a decline in glucose >-0.100 mmol.L^{-1}min^{-1}. This was also reflected in the rate of decline during Fiasp 50% (-0.091 mmol.L^{-1}min^{-1}) and 75% (-0.062 mmol.L^{-1}min^{-1}) reduction conditions in Chapter 5. Hence, performing low-moderate-intensity exercise with reduced doses may produce a live CGM arrow pointing diagonally downwards, compared with pointing fully downwards when performing with a full dose. Based on the individual's current glucose reading and trend arrow during exercise, a decision can be made on managing glycaemia within target range via current guidelines [5]. A directly downward arrow with interstitial glucose concentrations of 7.0 mmol.L^{-1} is recommended to be treated with 35 g carbohydrates, effectively increasing glucose concentrations and, at least temporarily, tempering the decline shown by the trend arrow [5]. Given the diminishing sensor with rapidly changing glucose concentrations, including during exercise, knowledge of the likely rate of change of blood glucose ahead of exercise would benefit the person with T1D in making informed decisions in their actions reactive to sensor readings [280].

6.3.2 Smart pens

Insulin pens that have been designed with the capability to store and display data such as date, time, and volume of insulin doses have been termed smart pens and have recently been made available on prescription for people with T1D in the UK [281]. To this end, smart pens can track an individual's daily insulin dosing habits. For the exercising individual, insulin dose reductions can be more easily recorded to refine glycaemic management for personal use and for communication with the clinician. This can be combined with time-matched data from CGM data (e.g., Libre 2 via LibreLink mobile application) and uploaded carbohydrate consumption data to harmonise and track glycaemic management strategies around exercise [282]. One smart pen available in the UK, NovoPen Echo®, allows half-unit injections which may cater to individuals who would otherwise need to round a dose reduction to the nearest integer unit (**Table 12**). Particularly in those taking smaller doses, this would permit closer replication of guideline dosing recommendations. Adjustments to basal insulin or lowering the total daily insulin intake from exercise training-induced insulin sensitivity can also be better tracked using

this technology. Combined with CGM, people with T1D on MDI have access to live glucose- and insulin-related digital platforms that can promote general glucose control and help tailor strategies around physical exercise.

6.3.3 Automated insulin delivery systems

Recently announced guidelines provide recommendations on the use of automated insulin delivery (AID) systems around exercise [283]. AID systems represent a closed loop system (otherwise referred to as hybrid closed-loop systems [HCLs] or artificial pancreas) consisting of a CGM sensor, an insulin pump, and an algorithm to calculate the appropriate insulin dose to automatically administer based on previous insulin doses and glucose concentrations, among other variables. Previous research has indicated that AID systems can be favourable for glucose control compared to standard care in children and adolescents; however, input is still required by the user to most effectively maintain glycaemia around exercise [284].

Current guidelines recommend multiple strategies specific to AID systems for glucose control around aerobic exercise, namely: 1) set a higher glucose target 1-2 h pre-exercise, 2) reduce pre-exercise prandial insulin by 25-33%, and 3) consume small (<20 g) carbohydrate supplements when glucose is <7.0 $mmol.L^{-1}$; 4) set higher glucose target immediately for unplanned exercise and consume 10-20 g when glucose is <7.0 $mmol.L^{-1}$. These strategies align well with recommendations made to people with T1D using MDI regimens, centred around insulin adjustments and carbohydrate consumption. Unique to pump-based systems, AID systems can be programmed to reduce basal insulin rates acutely prior to exercise to counter the exercise-related decline in blood glucose.

Studies that have investigated the use of Fiasp around exercise in AID systems have not demonstrated significant benefit in using an ultra-rapid-acting insulin [180–182]. Similar to Chapters 4 and 5, Fiasp was compared against insulin aspart in all three studies. In all exercise-related glycaemic outcomes, no significant differences were found when using Fiasp over aspart. The AID system guidelines recommend setting higher glucose targets before and during activity. Area under the curve pharmacodynamic profiles that are initially dissociated between insulins are increasingly comparable over time between Fiasp and insulin aspart, demonstrated in studies at rest[112] and around exercise in Chapter 5. It is plausible that under the state of a prolonged glucose target, Fiasp and aspart will be equally effective as the rapid onset of appearance qualities of Fiasp are not being exploited. Dovc et al. [180] tested the hypothesis that

Fiasp may be able to outperform aspart, as a consequence of being able to enact an earlier 'response', upon unannounced exercise (and meals). Interestingly, within exercise glycaemia was similar between insulins, while 1-h glucose response was contrastingly higher in the Fiasp condition. The authors suggested that the AID system used in the study was not optimized for an ultra-rapid-acting insulin, potentially stemming from a miscalculation of the insulin on board for Fiasp. No other study has since looked at Fiasp *vs.* insulin aspart in the context of announced exercise.

It is interesting to note that all riders in the professional cycling team in Chapter 4 were using MDI regimens instead of pump or AID systems. Beyond losing an element of manual glucose control at rest, AID systems may not yet be favourable for endurance events such as road cycling. An overconsumption of exogenous carbohydrates during exercise, to either temper glucose decline or increase glucose concentrations, may result in an AID-predicted hyperglycaemia – instigating insulin delivery and increasing the risk of hypoglycaemia. Hence, guideline recommendations do not exceed carbohydrate loads of 20 g during exercise. In contrast, the athletes in Chapter 4 consumed between 40-50 g of carbohydrates per hour of prolonged exercise, whereas other athletes have reported rates of intake that far exceed this [188].

The application of AID systems to exercise is still in development. Reducing the rate of insulin delivery is less likely to cause unwanted pre-exercise hyperglycaemia in these systems as target glucose is pre-defined, favouring its use over MDI. Nevertheless, issues remain around incorporating ultra-rapid-acting insulins and incorporating sufficient carbohydrate consumption for exercise performance. Considering the within-exercise similarity demonstrated in Chapters 4 and 5 between insulin types in the current thesis, together with available AID system studies, it is plausible that Fiasp can serve as a therapeutic option for mealtime insulin in AID systems but without clinically meaningful glycaemic benefits distinguishable from other rapid-acting insulin analogues during steady-state exercise.

6.3.4 The use of Fiasp with insulin icodec

Insulin icodec (brand name Awiqli®) is a once-weekly insulin with a similar albumin-binding mechanism to insulin degludec to protract its half-life to 196 h [285]. Insulin icodec has undergone phase 4 trials with the aim of receiving final marketing authorization in the EU before 2025. A once-weekly insulin has several advantages over a once-daily insulin. Reducing the frequency of taking the basal insulin negates the risk of missing a lone day's basal dose. Further, the

person with T1D will need to inject fewer times over the course of the week, reducing burden and pain of injecting [286]. Nonetheless, using a once-weekly insulin may come with some drawbacks, including a lack of flexibility and potential increased level 2 hypoglycaemia (<3.00 mmol.L^{-1}) [287].

Regarding exercise-related changes in insulin icodec's pharmacokinetics, exercise has been shown to increase the rate of absorption of insulin from the subcutaneous depot [257]. This, however, appears to be limited to mealtime or intermediate-acting insulins, as no effect was found in once-daily basal insulins. Even through multiple bouts of exercise within a week, the putative mechanisms for increased absorption do not overlap with the increased albumin binding that insulin icodec uses to protract its action. The pharmacodynamics of the insulin are stable and irreversible throughout the 196-h half-life; hence, adjustments to insulin around exercise will need to be driven solely from bolus insulins. Therefore, employing an ultra-rapid-acting insulin to better tailor the prandial glucose response, and provide equivalent performance around exercise, may be of benefit to the person with T1D.

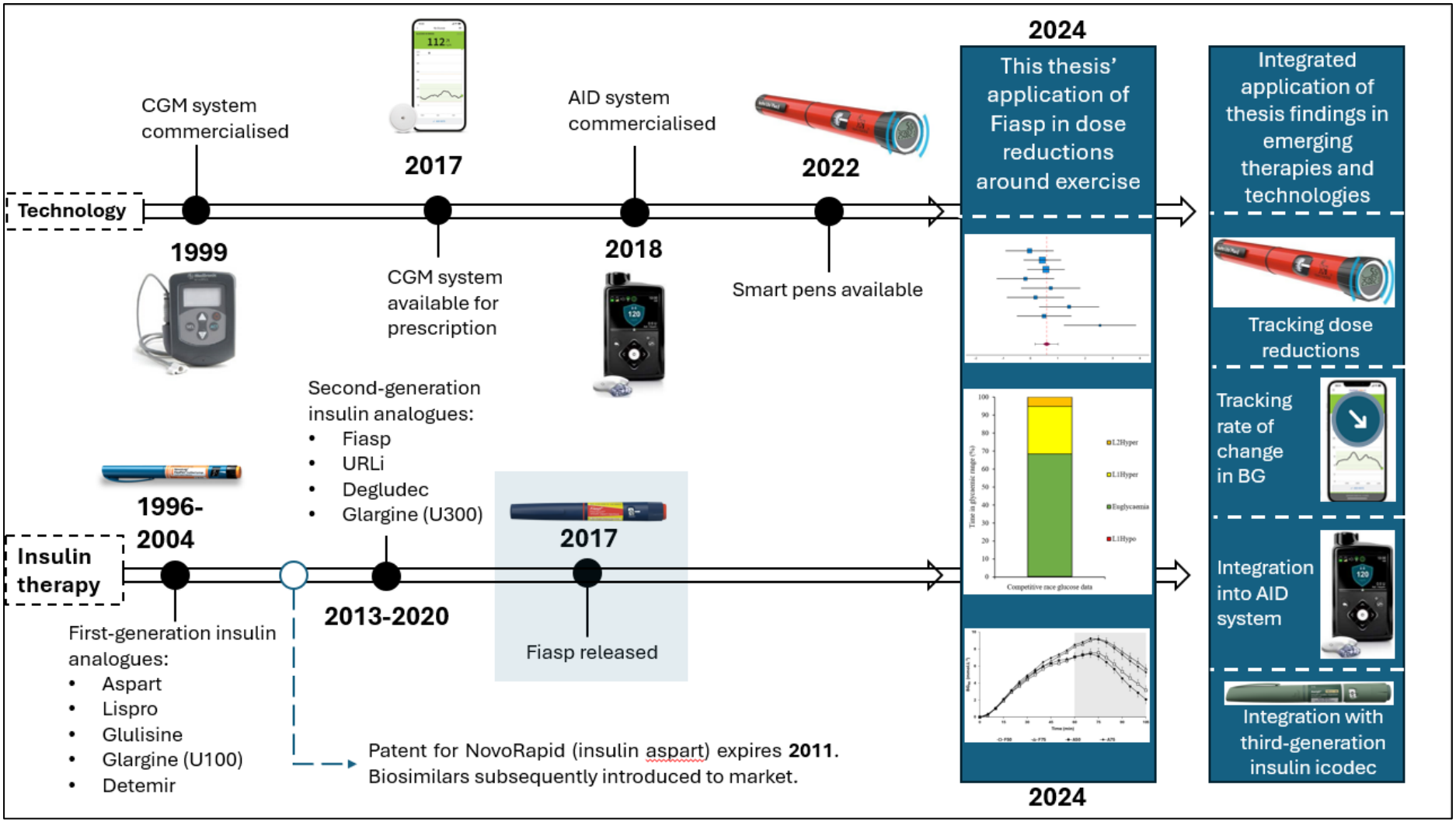


***Figure 23**: Application of thesis findings in emerging diabetes therapies and technologies. Dates are relevant to availability in the UK.*

6.4 Limitations

This thesis allowed for a diverse investigation into the application of pre-exercise bolus insulin reductions to Fiasp. Chapters 3 and 5 employed randomised controlled trials via database search and lab-based protocol, respectively, to compare the glycaemic effects of insulin doses, whereas Chapter 4 was an observational study where data was collected during real-world conditions. The methods for the latter study were required to strike a balance between measuring the desired relevant data from the training camp and race event but without interfering too much with the exercise sessions or day-to-day activities, in doing so potentially distracting riders or misaligning their schedules. Consequently, Chapter 4 was without detailed timing and dosing of participants' insulin regimen acutely around exercise, preventing further comparison against Chapters 3 and 5.

Although Chapter 5 included a dosing comparison around exercise, a full dose was not included that would otherwise enable its addition to the meta-analysis in Chapter 3. To enable the addition of Chapter 5 (and any subsequent papers that may investigate different doses under the same protocol with or without a full dose comparison arm) an updated meta-analysis may need adjustment such that regression coefficients or gradients are instead analysed. This would, however, demand several further studies to power a meta-analysis.

The pre-exercise meal in Chapter 5 was a high-carbohydrate load, high glycaemic index drink. This drink minimized the contribution of glucose flux from exogenous fats and proteins; however, participants spent prolonged periods in a hyperglycaemic state, limiting the applicability of the study protocol to real world implementation.

6.5 Future recommendations

Chapter 3 highlighted the lack of a comprehensive referenced literature base regarding insulin reductions in MDI regimen around exercise, beyond that included in the study which focused on comparing intra-study dose reductions. A systematic review which covers all clinical trials that have investigated insulin dose reductions around exercise, either as primary or secondary study aim, would provide a wider base of studies to inform consensus recommendations. Further, examples of insulin doses combined with the specific study protocols which produced favourable glycaemic outcomes may be highlighted and replicated to provide initial guidance on glycaemic management strategies for a patient's targeted exercise.

Research able to accurately track insulin dosing and timing, alongside food and beverage consumption, during prolonged exercise sessions performed by the TNN riders would provide more rounded information on the glycaemic strategies and outcomes derived from training or racing conditions. Furthermore, riders are often members of the team over multiple seasons or from adolescence in the development squad and graduate into the first team. Providing longitudinal data on both glycaemic management strategies and physiological markers (e.g., pre-season VO_{2max}) aligned with performance metrics (e.g., time trial durations and power outputs) may be of interest for characterising elite riders' development and the change or consistency in glycaemic management and performance.

This thesis has focused on the study of Fiasp as an ultra-rapid-acting insulin by comparison to insulin aspart. Since the commencement of the thesis' studies, ultra-rapid-acting insulin lispro (Lyumjev ®) has been made available to the UK market. The findings of this thesis can provide an initial insight into the likely interaction between ultra-rapid-acting insulin lispro and exercise; however, the PDPK comparison is not identical to Fiasp, as ultra-rapid-acting insulin lispro potentially performs as a slightly faster-acting mealtime insulin than Fiasp [245]. There is a current lack of studies on the use of ultra-rapid-acting insulin lispro which may provide a more holistic understanding of the use of the latest generation of mealtime insulins around exercise. In conjunction with this, a trial arm employing an insulin reduction of 25% alongside a low-glycaemic index meal may provide a platform to better convey the glycaemic management to real-world situations. Hence, a study involving 50% and 25% dose reduction using ultra-rapid-acting insulin lispro and rapid-acting insulin lispro around exercise may, in combination with the data presented in Chapter 5 and by Molveau and colleagues[174], provide a sufficient literature base to warrant inclusion in clinical guidelines, beyond the current recommendations on rapid-acting insulins.

This thesis has focused on pre-exercise reductions around aerobic exercise. Information is currently lacking in the use of ultra-rapid-acting insulin around high-intensity interval exercise, resistance exercise, and other modalities, where full insulin doses and/or post-exercise corrections may be appropriate [128].

6.6 Thesis conclusions

1. Insulin reductions provide blood glucose preservation through multiple effects along different time periods relative to the exercise bout, including: raising the immediate pre-exercise blood glucose, reducing the rate of decline of blood glucose during acute exercise, and preserving glycaemia for >2-3 h post-exercise.

2. Fiasp can be used when employing either 50% or 75% insulin dose reductions prior to a bout of moderate-intensity continuous exercise with similar glucose-lowering effects to insulin aspart.

3. Altering insulin dose reductions between 50% and 75% exerts a greater influence on glycaemia around exercise than altering between ultra- or rapid-acting insulins.

4. To return to baseline concentrations ~2 h post-exercise, a 50% reduced dose of Fiasp can be taken with the pre-exercise meal 60 min before the start of a moderate-intensity continuous exercise session.

5. Fiasp can be used to maintain appropriate time in range during prolonged endurance exercise bouts similarly to insulin aspart. Its successful application to international race events has been demonstrated when reducing daily bolus doses.

Appendices

Appendix A: List of studies used to develop systematic review (Chapter 3) search strategy.

Author and Date (and reference)	**Article name**
Aronson et al. 2019 [288]	Optimal insulin correction factor in post–high-intensity exercise hyperglycemia in adults with type 1 diabetes: The FIT study
Campbell et al. 2013 [167]	Large Pre- and Postexercise Rapid-Acting Insulin Reductions Preserve Glycemia and Prevent Early- but Not Late-Onset Hypoglycemia in Patients With Type 1 Diabetes
Campbell et al. 2014a [168]	A low-glycemic index meal and bedtime snack prevents postprandial hyperglycemia and associated rises in inflammatory markers, providing protection from early but not late nocturnal hypoglycemia following evening exercise in type 1 diabetes
Campbell et al. 2014b [176]	Metabolic Implications when Employing Heavy Pre- and Post-Exercise Rapid-Acting Insulin Reductions to Prevent Hypoglycaemia in Type 1 Diabetes Patients: A Randomised Clinical Trial
Campbell 2015a [289]	Simulated games activity vs continuous running exercise: a novel comparison of the glycemic and metabolic responses in T1DM patients
Campbell et al. 2015b [169]	Insulin therapy and dietary adjustments to normalize glycemia and prevent nocturnal hypoglycemia after evening exercise in type 1 diabetes: A randomized controlled trial
Heise et al. 2016 [170]	Similar risk of exercise-related hypoglycaemia for insulin degludec to that for insulin glargine in patients with type 1 diabetes : a randomized cross-over trial
McCarthy et al. 2020 [171]	Extent and prevalence of post-exercise and nocturnal hypoglycemia following peri-exercise bolus insulin adjustments in individuals with type 1 diabetes
McCarthy et al. 2021 [290]	Blood Glucose Responses during Cardiopulmonary Incremental Exercise Testing in Type 1 Diabetes: A Pooled Analysis
Moser et al. 2015 [172]	Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin
Moser et al. 2018 [291]	Reduction in insulin degludec dosing for multiple exercise sessions improves time spent in euglycaemia in people with type 1 diabetes: A randomized crossover trial
Rabasa-Lhoret et al.	Guidelines for Premeal Insulin Dose Reduction for Postprandial Exercise of Different Intensities and Durations in Type 1 Diabetic Subjects

2001 [178]	
Turner et al. 2015 [232]	Impact of single and multiple sets of resistance exercise in type 1 diabetes
Turner et al. 2016 [292]	Similar magnitude of post-exercise hyperglycemia despite manipulating resistance exercise intensity in type 1 diabetes individuals
West 2010 [173]	Blood glucose responses to reductions in pre-exercise rapid-acting insulin for 24 h after running in individuals with type 1 diabetes
West 2011a [230]	A combined insulin reduction and carbohydrate feeding strategy 30 min before running best preserves blood glucose concentration after exercise through improved fuel oxidation in type 1 diabetes mellitus
West et al. 2011b [243]	Isomaltulose improves postexercise glycemia by reducing CHO oxidation in T1DM

Appendix B: Ethical approval from a national research ethics committee for Chapter 5.

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Gwasanaeth Moeseg Ymchwil
Research Ethics Service

Ariennir gan **Lywodraeth Cymru**
Funded by **Welsh Government**

Wales REC 3
Health and Care Research Wales Support Centre
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Cardiff CF11 9AB

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15 January 2019

Professor Stephen C Bain
Clinicial Consultant (Diabetes), Assistant Medical Director (R&D)
Swansea Univesity and NHS (ABMU)
Diabetes Research Unit
Grove Building Singelton
Swansea
SA2 8PP

Dear Professor Bain

Study title:	**A trial investigating the effect on blood glucose after the injection of fast-acting insulin aspart (FiaspÂ®) in comparison to insulin aspart (NovoRapidÂ®) around exercise in participants with type 1 diabetes**
REC reference:	**18/WA/0421**
Protocol number:	**NN-ExFiaspÂ®**
IRAS project ID:	**254422**

Thank you for your letter of 09 January 2019, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion
The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

- Minor typo in page 3, paragraph 4 of PIS – the change made has resulted in "3mL" being duplicated – please can you correct this.
- Please can you use the formal date format of day month year not numerical format in the consent i.e. change 09012019 to 9th January 2019.

Appendix C: Standard operating procedure developed to perform exercise studies at Swansea University following COVID-19 pandemic.

Swansea University
College of Engineering

Standard Operating Procedure

SOP Number *SOP201*

SOP Title ***General Procedures for Exercise Studies: Considerations for Coronavirus Disease 2019 (Covid-19)***

	NAME	TITLE	SIGNATURE	DATE
Author	*Jason Pitt, Richard Bracken, Wendy Clark*	*PHD Researcher, Associate Professor, Senior Laboratory Technician*	*Wendy Clark*	29/07/2020
Reviewer	*Richard Bracken* *Adrian Jenkins*	*Associate Professor* *Technical Manager*	*Richard Bracken* *Adrian Jenkins*	30/07/2020 30/07/2020
Authoriser	*Wendy Clark*	*Senior Laboratory Technician*	*Wendy Clark*	30/07/2020

Effective Date:	**30/07/2020**
Review Date:	**30/07/2021**

Purpose

General procedures for the safe completion of exercise testing in the School of Sport and Exercise Sciences Laboratories at Swansea University. The aim of these procedures is to help prevent the spread of Coronavirus 2019 (Covid-19). In addition to these procedures, researchers, students and staff are to obey current local guidance, complete laboratory inductions and Risk Assessments relevant to the exercise tests.

Recommendations for these procedures were sourced from current UK Government/NHS advice and legislation and other resources listed in References section.

Appendix D: Subset (n=22) measurements of haemoglobin and haematocrit changes from pre- to post-exercise in Study 3 (Chapter 5).

Analyte	**Timepoint**	
	Pre-exercise	**Post-exercise**
Haemoglobin (g/L)	145±13	150±14
Haematocrit (%)	49±4	48±4

References

1. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation : Recommendations From the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593-1601. doi:10.2337/dci19-0028

2. Castañeda J, Arrieta A, van den Heuvel T, Battelino T, Cohen O. Time in Tight Glucose Range in Type 1 Diabetes: Predictive Factors and Achievable Targets in Real-World Users of the MiniMed 780G System. *Diabetes Care*. 2024;47(5):790-797. doi:10.2337/dc23-1581

3. The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N Engl J Med*. 1993;329(14):977-986.

4. Cryer P, Davis S, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care*. 2003;26(6):1902-1912 11p. doi:10.2337/diacare.26.6.1902

5. Moser O, Riddell MC, Eckstein ML, Adolfsson P, Rabasa-lhoret R. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society f. *Diabetologia*. 2020;63:2501-2520.

6. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. *Diabetes Care*. 2016;39(11):2065-2079. doi:10.2337/dc16-1728

7. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care*. 2008;31(11):2108-2109. doi:10.2337/dc08-0720

8. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7

9. Gregory GA, Robinson TIG, Linklater SE, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. *Lancet Diabetes Endocrinol*. 2022;10(10):741-760. doi:10.1016/S2213-8587(22)00218-2

10. Green A, Hede SM, Patterson CC, et al. Type 1 diabetes in 2017: global estimates of incident and prevalent cases in children and adults. *Diabetologia*. 2021;64:2741-2750. https://doi.org/10.1007/s00125-021-05571-8

11. Vanderniet JA, Jenkins AJ, Donaghue KC. Epidemiology of Type 1 Diabetes. *Curr Cardiol Rep*. 2022;24(10):1455-1465. doi:10.1007/s11886-022-01762-w

12. Mohr SB, Garland CF, Gorham ED, Garland FC. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions

worldwide. *Diabetologia*. 2008;51(8):1391-1398. doi:10.1007/s00125-008-1061-5

13. NHS Digital. *National Diabetes Audit, 2019-20, Type 1 Diabetes*.; 2021.

14. Giwa AM, Ahmed R, Karakus KE, Thomas D. Current understandings of the pathogenesis of type 1 diabetes: Genetics to environment. *World J Diabetes*. 2020;11(1):13-25. https://www.wjgnet.com/bpg/gerinfo/240

15. Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T. Concordance for Islet Autoimmunity among Monozygotic Twins. *N Engl J Med*. 2008;359(26):2849-2850. doi:10.1056/nejmc0805398

16. Pociot F. Type 1 diabetes genome-wide association studies: Not to be lost in translation. *Clin Transl Immunol*. 2017;6(12):e162-7. doi:10.1038/cti.2017.51

17. Steck AK, Rewers MJ. Genetics of type 1 diabetes. *Clin Chem*. 2011;57(2):176-185. doi:10.1373/clinchem.2010.148221

18. Pugliese A. The insulin gene in type 1 diabetes. *IUBMB Life*. 2005;57(7):463-468. doi:10.1080/15216540500163301

19. Chiu SW-Y, David R, Leslie G, Beyan H. *Diabetes and Viruses*. (K, W T, H H, A T, A, J Z, eds.). Springer; 2013.

20. Moltchanova E V., Schreier N, Lammi N, Karvonen M. Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide. *Diabet Med*. 2009;26(7):673-678. doi:10.1111/j.1464-5491.2009.02743.x

21. Barker JM, Barriga KJ, Yu L, et al. Prediction of autoantibody positivity and progression to type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY). *J Clin Endocrinol Metab*. 2004;89(8):3896-3902. doi:10.1210/jc.2003-031887

22. Kupila A, Muona P, Simell T, et al. Feasibility of genetic and immunological prediction of Type I diabetes in a population-based birth cohort. *Diabetologia*. 2001;44(3):290-297. doi:10.1007/s001250051616

23. Rewers M, Hyoty H, Lernmark A, et al. The Environmental Determinants of Diabetes in the Young (TEDDY) Study: 2018 Update. *Curr Diab Rep*. 2018;18(12):1-25. doi:10.1007/s11892-018-1113-2.The

24. Krogvold L, Edwin B, Buanes T, et al. Detection of a low-grade enteroviral infection in the islets of langerhans of living patients newly diagnosed with type 1 diabetes. *Diabetes*. 2015;64(5):1682-1687. doi:10.2337/db14-1370

25. Quinn LM, Wong FS, Narendran P. Environmental Determinants of Type 1 Diabetes: From Association to Proving Causality. *Front Immunol*. 2021;12(October):1-15. doi:10.3389/fimmu.2021.737964

26. Rewers M, Davis B, Ludvigsson J. Environmental risk factors for type 1 diabetes Marian HHS Public Access. *Lancet*. 2016;387(10035):2340–2348. doi:10.1016/S0140-6736(16)30507-4.Environmental

27. Wilkin TJ. The convergence of type 1 and type 2 diabetes in childhood: The accelerator hypothesis Wilkin Convergence of type 1 and type 2 diabetes. *Pediatr Diabetes*. 2012;13(4):334-339. doi:10.1111/j.1399-5448.2011.00831.x

28. Sioofy-Khojine AB, Oikarinen S, Honkanen H, et al. Molecular epidemiology of

enteroviruses in young children at increased risk of type 1 diabetes. *PLoS One*. 2018;13(9):1-18. doi:10.1371/journal.pone.0201959

29. Richardson SJ, Willcox A, Bone AJ, Foulis AK, Morgan NG. The prevalence of enteroviral capsid protein vp1 immunostaining in pancreatic islets in human type 1 diabetes. *Diabetologia*. 2009;52(6):1143-1151. doi:10.1007/s00125-009-1276-0

30. Isaacs SR, Foskett DB, Maxwell AJ, et al. Viruses and type 1 diabetes: From enteroviruses to the virome. *Microorganisms*. 2021;9(7):1-26. doi:10.3390/microorganisms9071519

31. Wasserfall C, Nead K, Mathews C, Atkinson MA. The threshold hypothesis: Solving the equation of nurture vs nature in type 1 diabetes. *Diabetologia*. 2011;54(9):2232-2236. doi:10.1007/s00125-011-2244-z

32. Mahadevan V. Anatomy of the pancreas and spleen. *Surg (United Kingdom)*. 2019;37(6):297-301. doi:10.1016/j.mpsur.2019.04.008

33. Ellis H. Anatomy of the pancreas. *Surgery*. 2006;25(2):72-73. doi:10.1159/000100381

34. Tomita T. New markers for pancreatic islets and islet cell tumors. *Pathol Int*. 2002;52(7):425-432. doi:10.1046/j.1440-1827.2002.01368.x

35. Ionescu-Tirgoviste C, Gagniuc PA, Gubceac E, et al. A 3D map of the islet routes throughout the healthy human pancreas. *Sci Rep*. 2015;5:1-14. doi:10.1038/srep14634

36. Bosco D, Armanet M, Morel P, et al. Unique arrangement of α- and β-cells in human islets of Langerhans. *Diabetes*. 2010;59(5):1202-1210. doi:10.2337/db09-1177

37. Ng XW, Chung YH, Piston DW. Intercellular Communication in the Islet of Langerhans in Health and Disease. *Compr Physiol*. 2021;11(3):2191-2225. doi:10.1002/cphy.c200026

38. Kawasaki E. Anti-Islet Autoantibodies in Type 1 Diabetes. *Int J Mol Sci*. 2023;24(12):1-20. doi:10.3390/ijms241210012

39. Ziegler A, Bonifacio E. Age-related islet autoantibody incidence in offspring of patients with type 1 diabetes. *Diabetologia*. 2012;2:1937-1943. doi:10.1007/s00125-012-2472-x

40. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *Jama*. 2013;309(23):2473-2479. doi:10.1001/jama.2013.6285

41. Fousteri G, Ippolito E, Ahmed R, Hamad ARA. Beta-cell specific autoantibodies: Are they just an indicator of type 1 diabetes? *Curr Diabetes Rev*. 2017;13(3):322-329. doi:10.2174/1573399812666160427104157.Beta-cell

42. Insel RA, Dunne JL, Atkinson MA, et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society ,and the American Diabetes Association. *Diabetes Care*. 2015;38(10):1964-1974. doi:10.2337/dc15-1419

43. Burrack AL, Martinov T, Fife BT, Fife BT. T Cell-Mediated Beta Cell Destruction : Autoimmunity and Alloimmunity in the Context of Type 1 Diabetes. *Front Endocrinol (Lausanne)*. 2017;8:343-358. doi:10.3389/fendo.2017.00343

44. Roep BO, Thomaidou S, van Tienhoven R, Zaldumbide A. Type 1 diabetes mellitus as

a disease of the β - cell (do not blame the immune system?). *Nat Rev Endocrinol*. 2021;17(3):150-161. doi:10.1038/s41574-020-00443-4

45. Pugliese A. Autoreactive T cells in type 1 diabetes. *J Clin Invest*. 2017;127(8):2881-2891.

46. Visperas A, Vignali DAA. Are Tregs defective in Type 1 Diabetes and can we fix them? *J Immunol*. 2017;197(10):3762-3770. doi:10.4049/jimmunol.1601118.Are

47. Willcox A, Richardson SJ. Analysis of islet inflammation in human type 1 diabetes. *J Transl Immunol*. 2008;155:173-181. doi:10.1111/j.1365-2249.2008.03860.x

48. Richardson SJ, Rodriguez-calvo T, Gerling IC, et al. Islet cell hyperexpression of HLA class I antigens : a defining feature in type 1 diabetes. *Diabetologia*. 2016;59:2448-2458. doi:10.1007/s00125-016-4067-4

49. Saberzadeh-ardestani B, Sc M, Karamzadeh R, Ph D, Basiri M, Ph D. Type 1 Diabetes Mellitus : Cellular and Molecular Pathophysiology at A Glance. *Cell J*. 2018;20(3):294-301. doi:10.22074/cellj.2018.5513.Introduction

50. Clark M, Kroger CJ, Ke Q, Tisch RM, Thomas H. The Role of T Cell Receptor Signaling in the Development of Type 1 Diabetes. *Front Immunol*. 2021;11(2):1-18. doi:10.3389/fimmu.2020.615371

51. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet*. 2014;383(1):69-82. doi:10.1016/S0140-6736(13)60591-7

52. Jansen TJP, Brom M, Boss M, et al. Importance of beta cell mass for glycaemic control in people with type 1 diabetes. *Diabetologia*. 2023;66:367-375.

53. Gibb FW, McKnight JA, Clarke C, Strachan MWJ. Preserved C-peptide secretion is associated with fewer low-glucose events and lower glucose variability on flash glucose monitoring in adults with type 1 diabetes. *Diabetologia*. 2020;63:906-914.

54. ADA. 2 . Classification and Diagnosis of Diabetes : Standards of Medical Care in Diabetes — 2022. *Diabetes Care*. 2022;45(January):S17-S38.

55. Cherubini V, Grimsmann JM, Åkesson K, Birkebæk NH, Cinek O. Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016 : results from 13 countries in three continents. *Diabetologia*. 2020;63:1530-1541.

56. Shields BM, Peters JL, Cooper C, et al. Can clinical features be used to differentiate type 1 from type 2 diabetes ? A systematic review of the literature. *BMJ Open*. 2015;5:1-9. doi:10.1136/bmjopen-2015-009088

57. Holt RIG, Devries JH, Hess-fischl A, et al. The Management of Type 1 Diabetes in Adults . A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2021;44(11):2589-2625.

58. Petersen MC, Shulman GI, Mc P, Gi S, Action I, Physiol IR. Mechanisms of insulin action and insulin resistance. *Physiol Rev*. 2018;98:2133-2223. doi:10.1152/physrev.00063.2017

59. Natali A, Del Prato S, Mari A. Normal beta-cell function. In: *International Textbook of Diabetes Mellitus: Fourth Edition*. ; 2015:108-124.

60. Pasquier A. Lysosomal degradation of insulin granules promotes β -cell failure in type 2 diabetes. *Endocrinol Metab*. Published online 2019.

61. Campbell JE, Newgard CB. Mechanisms controlling pancreatic islet cell function in insulin secretion. *Nat Rev Mol Cell Biol*. 2021;22(2):142-158. doi:10.1038/s41580-020-00317-7

62. Wiedemann SJ, Rachid L, Illigens B, Böni-Schnetzler M, Donath MY. Evidence for cephalic phase insulin release in humans: A systematic review and meta-analysis. *Appetite*. 2020;155. doi:10.1016/j.appet.2020.104792

63. Prashant, Nadkarni, Chepurny, Oleg G., Holz, George G. Regulation of Glucose Homeostasis by GLP-1. *Prog Mol Biol Transl Sci*. 2014;121:23-65. doi:10.1016/B978-0-12-800101-1.00002-8.Regulation

64. Prentki M, Matschinsky FM, Madiraju SRM. Metabolic signaling in fuel-induced insulin secretion. *Cell Metab*. 2013;18(2):162-185. doi:10.1016/j.cmet.2013.05.018

65. Fu Z, R. Gilbert E, Liu D. Regulation of Insulin Synthesis and Secretion and Pancreatic Beta-Cell Dysfunction in Diabetes. *Curr Diabetes Rev*. 2012;9(1):25-53. doi:10.2174/15733998130104

66. Najjar SM, Perdomo G. Hepatic Insulin Clearance: Mechanism and Physiology. *Physiology*. 2019;34(3):198-215. doi:10.1152/physiol.00048.2018

67. Meier JJ, Veldhuis JD, Butler PC. Pulsatile Insulin Secretion Dictates Systemic Insulin Delivery by Regulating Hepatic Insulin Extraction In Humans. *Diabetes*. 2005;54(6):1649-1656.

68. McClatchey PM, Williams IM, Xu Z, et al. Perfusion controls muscle glucose uptake by altering the rate of glucose dispersion in vivo. *Am J Physiol - Endocrinol Metab*. 2019;317(6):1022-1036. doi:10.1152/ajpendo.00260.2019

69. Lee WL, Klip A. Endothelial transcytosis of insulin: Does it contribute to insulin resistance? *Physiology*. 2016;31(5):336-345. doi:10.1152/physiol.00010.2016

70. Sylow L, Tokarz VL, Richter EA, Klip A. The many actions of insulin in skeletal muscle, the paramount tissue determining glycemia. *Cell Metab*. 2021;33(4):758-780. doi:10.1016/j.cmet.2021.03.020

71. Warren RE, Deary IJ, Frier BM. The symptoms of hyperglycaemia in people with insulin-treated diabetes: Classification using principal components analysis. *Diabetes Metab Res Rev*. 2003;19(5):408-414. doi:10.1002/dmrr.396

72. Nakhla M, Rahme E, Simard M, Larocque I, Legault L, Li P. Risk of ketoacidosis in children at the time of diabetes mellitus diagnosis by primary caregiver status: A population-based retrospective cohort study. *Cmaj*. 2018;190(14):E416-E421. doi:10.1503/cmaj.170676

73. Dabelea D, Rewers A, Stafford JM, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: The search for diabetes in youth study. *Pediatrics*. 2014;133(4). doi:10.1542/peds.2013-2795

74. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853. doi:10.1016/S0140-

6736(98)07019-6

75. Seres-Noriega T, Gimenez M, Perea V, et al. Use of the Steno T1 Risk Engine Identifies Preclinical Atherosclerosis Better Than Use of ESC/EASD-2019 in Adult Subjects With Type 1 Diabetes at High Risk. *Diabetes Care*. 2022;45(3):2412-2421. doi:doi.org/10.2337/dc22-0118

76. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. *Clin Diabetes*. 2011;29(3):116-122. doi:10.2337/diaclin.29.3.116

77. Brownlee M. Biology of Diabetic Complications. *Nature*. 2001;414(December):813-820.

78. Nishikawa T, Edelstein D, Brownlee M. The missing link: A single unifying mechanism for diabetic complications. *Kidney Int*. 2000;58:26-30. doi:10.1046/j.1523-1755.2000.07705.x

79. Russell NDF, Cooper ME. 50 Years Forward: Mechanisms of Hyperglycaemia-Driven Diabetic Complications. *Diabetologia*. 2015;58(8):1708-1714. doi:10.1007/s00125-015-3600-1

80. Funk SD, Jr AY, Orr AW. Hyperglycemia and Endothelial Dysfunction in Atherosclerosis : Lessons from Type 1 Diabetes. *Int J Vasc Med*. 2012;12:378-390. doi:10.1155/2012/569654

81. Mameli C, Mazzantini S, Nasr M, Fiorina P, Scaramuzza AE, Zuccotti G. Explaining the increased mortality in type 1 diabetes. *World J Diabetes*. 2015;6(7):889. doi:10.4239/wjd.v6.i7.889

82. Cryer PE. Hypoglycemia in type 1 diabetes mellitus. *Endocrinol Metab Clin North Am*. 2010;39(3):641-654. doi:10.1016/j.ecl.2010.05.003

83. Cryer PE. The Barrier of Hypoglycemia in Diabetes. *Diabetes*. 2008;57(10):3169-3176. doi:10.2337/db08-1084

84. Senthilkumaran M, Zhou XF, Bobrovskaya L. Challenges in Modelling Hypoglycaemia-Associated Autonomic Failure: A Review of Human and Animal Studies. *Int J Endocrinol*. 2016;2016:1-13. doi:10.1155/2016/9801640

85. Mitrakou A, Ryan C, Veneman T, et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol - Endocrinol Metab*. 1991;260:67-74. doi:10.1152/ajpendo.1991.260.1.e67

86. Verhulst CEM, Fabricius TW, Teerenstra S, et al. Glycaemic thresholds for counterregulatory hormone and symptom responses to hypoglycaemia in people with and without type 1 diabetes: a systematic review. *Diabetologia*. 2022;65(10):1601-1612. doi:10.1007/s00125-022-05749-8

87. Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycaemia in adults with type 1 diabetes. *Diabet Med*. 2008;25(4):501-504. doi:10.1111/j.1464-5491.2008.02413.x

88. Wong CY, Martinez J, Dass CR. Oral delivery of insulin for treatment of diabetes: status quo, challenges and opportunities. *J Pharm Pharmacol*. 2016;68:1093-1108. doi:10.1111/jphp.12607

89. Chan J, Cheng-Lai A. Inhaled Insulin: A Clinical and Historical Review. *Cardiol Rev*. 2017;25(3):140-146. doi:10.1097/CRD.0000000000000143

90. Leuenberger Jockel JP, Roebrock P, Shergold OA. Insulin depot formation in subcutaneous tissue. *J Diabetes Sci Technol*. 2013;7(1):227-237. doi:10.1177/193229681300700128

91. Gradel AKJ, Porsgaard T, Lykkesfeldt J, et al. Factors Affecting the Absorption of Subcutaneously Administered Insulin: Effect on Variability. *J Diabetes Res*. 2018;2018. doi:10.1155/2018/1205121

92. Pitt JP, McCarthy OM, Hoeg-Jensen T, Wellman BM, Bracken RM. Factors Influencing Insulin Absorption Around Exercise in Type 1 Diabetes. *Front Endocrinol (Lausanne)*. 2020;11(October):793-802. doi:10.3389/fendo.2020.573275

93. Wilcox G, Willetts KE, Ekangaki A, et al. Insulin and insulin resistance. *Clin Biochem Rev*. 2005;26(2):19-39. doi:10.1016/S0025-7125(03)00128-7

94. Hassiepen U, Federwisch M, Mülders T, Wollmer A. The lifetime of insulin hexamers. *Biophys J*. 1999;77(3):1638-1654. doi:10.1016/S0006-3495(99)77012-8

95. Jensen SS, Jensen H, Cornett C, Møller EH, Østergaard J. Insulin diffusion and self-association characterized by real-time UV imaging and Taylor dispersion analysis. *J Pharm Biomed Anal*. 2014;92:203-210. doi:10.1016/j.jpba.2014.01.022

96. Cengiz E, Bode B, Van Name M, Tamborlane W V. Moving toward the ideal insulin for insulin pumps. *Expert Rev Med Devices*. 2015;13(1):57-69. doi:10.1586/17434440.2016.1109442

97. Bolli GB, Di Marchi RD, Park GD, Pramming S, Koivisto VA. Insulin analogues and their potential in the management of diabetes mellitus. *Diabetologia*. 1999;42(10):1151-1167. doi:10.1007/s001250051286

98. Dimitriadis GD, Gerich JE. Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. *Diabetes Care*. 1983;6(4):374-377. doi:10.2337/diacare.6.4.374

99. Sheldon B, Russell-Jones D, Wright J. Insulin analogues: An example of applied medical science. *Diabetes, Obes Metab*. 2009;11(1):5-19. doi:10.1111/j.1463-1326.2008.01015.x

100. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin: A rapidly absorbed analogue of human insulin. *Diabetes*. 1994;43(3):396-402. doi:10.2337/diab.43.3.396

101. Heinemann L, Heise T, Wahl LC, et al. Prandial glycaemia after a carbohydrate-rich meal in type I diabetic patients: Using the rapid acting insulin analogue [Lys(B28), Pro(B29)] human insulin. *Diabet Med*. 1996;13(7):625-629. doi:10.1002/(SICI)1096-9136(199607)13:7<625::AID-DIA134>3.0.CO;2-2

102. Simpson D, McCormack P, Gillian K, Lyseng-Williamson K. Insulin Lispro: A Review of its Use in the Management of Diabetes Mellitus. *Drugs*. 2007;67(3):407-434. doi:10.1016/S0304-5412(12)70418-3

103. Plank J, Wutte A, Brunner G, et al. A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care*. 2002;25(11):2053-2057.

doi:10.2337/diacare.25.11.2053

104. Danne T, Becker RHA, Heise T, Bittner C, Frick AD, Rave K. Pharmacokinetics, prandial glucose control, and safety of insulin glulisine in children and adolescents with type 1 diabetes. *Diabetes Care*. 2005;28(9):2100-2105. doi:10.2337/diacare.28.9.2100

105. Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. *Diabetes, Obes Metab*. 2012;14(9):780-788. doi:10.1111/j.1463-1326.2012.01580.x

106. Hamidli N, Pajaziti B, Andrási M, Nagy C, Gáspár A. Determination of human insulin and its six therapeutic analogues by capillary electrophoresis – mass spectrometry. *J Chromatogr A*. 2022;1678(July):463351. doi:10.1016/j.chroma.2022.463351

107. Sherr J, Cengiz E, Tamborlane W V. From pumps to prevention : recent advances in the treatment of type 1 diabetes. 2009;14(10):973-981. doi:10.1016/j.drudis.2009.06.011

108. NHS Digital. *National Diabetes Insulin Pump Audit 2017-18*.; 2019. http://www.digital.nhs.uk/pubs/ndapump1718

109. Pettus J, Cavaiola T, Tamborlane W, Edelman S. The past, present, and future of basal insulins. *Diabetes Metab Res Rev*. 2015;32(11):478-496. doi:10.1002/dmrr

110. Candido R, Wyne K, Romoli E. A Review of Basal-Bolus Therapy Using Insulin Glargine and Insulin Lispro in the Management of Diabetes Mellitus. *Diabetes Ther*. 2018;9(3):927-949. doi:10.1007/s13300-018-0422-4

111. Goldman J, Kapitza C, Pettus J, Heise T. Understanding how pharmacokinetic and pharmacodynamic differences of basal analog insulins influence clinical practice. *Curr Med Res Opin*. 2017;33(10):1821-1831. doi:10.1080/03007995.2017.1335192

112. Heise T, Pieber TR, Danne T, Erichsen L, Haahr H. A Pooled Analysis of Clinical Pharmacology Trials Investigating the Pharmacokinetic and Pharmacodynamic Characteristics of Fast-Acting Insulin Aspart in Adults with Type 1 Diabetes. *Clin Pharmacokinet*. 2017;56(5):551-559. doi:10.1007/s40262-017-0514-8

113. Leohr J, Dellva MA, Coutant DE, et al. Pharmacokinetics and Glucodynamics of Ultra Rapid Lispro (URLi) versus Humalog® (Lispro) in Patients with Type 2 Diabetes Mellitus: A Phase I Randomised, Crossover Study. *Clin Pharmacokinet*. Published online 2020. doi:10.1007/s40262-020-00901-2

114. Lindholm A, Jacobsen L. Clinical Pharmacokinetics and Pharmacodynamics of Insulin Aspart. *Clin Pharmacokinet*. 2001;40(9):641-659. doi:10.2165/00003088-199937020-00002

115. Becker R, Frick A. Clinical Pharmacokinetics and Pharmacodynamics of Insulin Glulisine. *Clin Pharmacokinet*. 2008;47(1):7-20. doi:10.1007/s40262-016-0464-6

116. Haahr H, Heise T. A Review of the Pharmacological Properties of Insulin Degludec and Their Clinical Relevance. *Clin Pharmacokinet*. 2014;53(9):787-800. doi:10.1007/s40262-014-0165-y

117. Clements JN, Threatt T, Ward E, Shealy KM. Clinical Pharmacokinetics and Pharmacodynamics of Insulin Glargine 300 U/mL. *Clin Pharmacokinet*.

2017;56(5):449-458. doi:10.1007/s40262-016-0464-6

118. Jones MC, Patel M. Insulin detemir: A long-acting insulin product. *Am J Heal Pharm*. 2006;63(24):2466-2472. doi:10.2146/ajhp060102

119. Koehler G, Treiber G, Wutte A, et al. Pharmacodynamics of the long-acting insulin analogues detemir and glargine following single-doses and understeady-state conditions in patients with type 1 diabetes. *Diabetes, Obes Metab*. 2014;16(4):57-62. doi:10.1136/bmjopen-2017-020290

120. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. *Biomark Insights*. 2016;11:95-104. doi:10.4137/Bmi.s38440

121. Parrinello CM, Selvin E. Beyond HbA1c and Glucose: the Role of Nontraditional Glycemic Markers in Diabetes Diagnosis, Prognosis, and Management. *Curr Diab Rep*. 2014;14(11). doi:10.1007/s11892-014-0548-3

122. Sherwood J, Russell S, Putman M. New and Emerging Technologies in Type 1 Diabetes. *Endocrinol Metab Clin N Am*. 2020;49:667-678.

123. Edward R, Priefer R. A comparison of continuous glucose monitors (CGMs) in diabetes management: A systematic literature review. *Prim Care Diabetes*. 2023;17(6):529-534. doi:10.1016/j.pcd.2023.10.009

124. Olczuk D, Priefer R. A history of continuous glucose monitors (CGMs) in self-monitoring of diabetes mellitus. *Diabetes Metab Syndr Clin Res Rev*. 2018;12(2):181-187. doi:10.1016/j.dsx.2017.09.005

125. de Bock M, Codner E, Craig ME, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes. *Pediatr Diabetes*. 2022;23(8):1270-1276. doi:10.1111/pedi.13455

126. Diabetes UK. Getting active and staying active. Accessed December 3, 2018. https://www.diabetes.org.uk/Guide-to-diabetes/Managing-your-diabetes/Exercise

127. ACSM. *American College of Sports Medicine Guidelines Diabetes Mellitus (Type 1) (ACSM's Guidelines for Exercise Testing and Prescription)*.; 2008. Accessed December 3, 2020. http://www.chtc.org/dl/handouts/20080108/Handout 6.pdf

128. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol*. 2017;5(5):377-390. doi:10.1016/S2213-8587(17)30014-1

129. Sigal RJ, Armstrong MJ, Bacon SL, et al. Physical Activity and Diabetes: 2018 Clinical Practice Guidelines. *Can J Diabetes*. 2018;42(1):54-63. doi:10.1016/j.jcjd.2017.10.008

130. Canada D. Exercise and activity. Accessed December 1, 2020. https://www.diabetes.ca/nutrition---fitness/exercise---activity#:~:text=Your goal should be to,building up to your goal.

131. Diabetes U. Diabetes and Exercise.

132. Wadén J, Forsblom C, Thorn L, et al. Physical Activity and Diabetic Complications in

Patients With Type 1 Diabetes. *Diabetes Care*. 2008;31(2):230-232. doi:10.2337/dc07-1238.Additional

133. Brazeau A-S, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to Physical Activity Among Patients With Type 1 Diabetes. *Diabetes Care*. 2008;31(11):2108-2109. doi:10.2337/dc08-0720.

134. Lascar N, Kennedy A, Hancock B, et al. Attitudes and barriers to exercise in adults with type 1 diabetes (T1DM) and how best to address them: A qualitative study. *PLoS One*. 2014;9(9):1-8. doi:10.1371/journal.pone.0108019

135. Bohn B, Herbst A, Pfeifer M, et al. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: A cross-sectional multicenter study of 18,028 patients. *Diabetes Care*. 2015;38(8):1536-1543. doi:10.2337/dc15-0030

136. World Health Organisation. *Global Health Risks*.; 2009.

137. Kennedy A, Nirantharakumar K, Chimen M, et al. Does Exercise Improve Glycaemic Control in Type 1 Diabetes ? A Systematic Review and Meta-Analysis. *PLoS One*. 2013;8(3):e58861. doi:10.1371/journal.pone.0058861

138. Ishii. TY, Yamakita. T, Sato. T, Tanaka. S, Fujii. S. Resistance training improves insulin sensitivity in NIDDM subjects without altering maximal oxygen uptake. *Diabetes Care*. 1998;21(8):1353-1355. doi:10.2337/diacare.21.8.1353

139. Short KR, Vittone JL, Bigelow ML, et al. Impact of Aerobic Exercise Training on Age-Related Capacity. *Diabetes*. 2003;52(9):1888-1896. doi:10.2337/diabetes.52.8.1888

140. Tikkanen-Dolenc H, Waden J, Forsblom C, et al. Physical activity and premature mortality in patients with type 1 diabetes. *Diabetes Care*. 2017;40(12):1727-1732. doi:http://dx.doi.org/10.1007/s00125-017-4350-z

141. Powers S, Howley E. Exercise metabolism. In: *Exercise Physiology: Theory and Application to Fitness and Performance*. 11th ed. McGraw-Hill; 2020:52-72.

142. Fox E, Bowers R, Foss M. *The Physiological Basis for Exercise and Sport*. 6th ed. Brown & Benchmark; 1997.

143. Purdom T, Kravitz L, Dokladny K, Mermier C. Understanding the factors that effect maximal fat oxidation. *J Int Soc Sports Nutr*. 2018;15(1):1-10. doi:10.1186/s12970-018-0207-1

144. Hargreaves M, Spriet LL. Skeletal muscle energy metabolism during exercise. *Nat Metab*. 2020;2(9):817-828. doi:10.1038/s42255-020-0251-4

145. Teixeira AL, Vianna LC. The exercise pressor reflex: An update. *Clin Auton Res*. 2022;32(4):271-290. doi:10.1007/s10286-022-00872-3

146. Joyner MJ, Casey DP. Regulation of increased blood flow (Hyperemia) to muscles during exercise: A hierarchy of competing physiological needs. *Physiol Rev*. 2015;95(2):549-601. doi:10.1152/physrev.00035.2013

147. Richter EA. Is GLUT4 translocation the answer to exercise-stimulated muscle glucose uptake? *Am J Physiol - Endocrinol Metab*. 2021;320(2):240-243.

doi:10.1152/AJPENDO.00503.2020

148. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiol Rev*. 2013;93(3):993-1017. doi:10.1152/physrev.00038.2012

149. Cochran B, Marbach EP, Poucher R, Steinberg T, Gwinup G. Effect of acute muscular exercise on serum immunoreactive insulin concentration. *Diabetes*. 1966;15(11):838-841. doi:10.2337/diab.15.11.838

150. Petersen KF, Price TB, Bergeron R. Regulation of net hepatic glycogenolysis and gluconeogenesis during exercise: Impact of type 1 diabetes. *J Clin Endocrinol Metab*. 2004;89(9):4656-4664. doi:10.1210/jc.2004-0408

151. Ertl AC, Davis SN. Evidence for a vicious cycle of exercise and hypoglycemia in type 1 diabetes mellitus. *Diabetes Metab Res Rev*. 2004;20(2):124-130. doi:10.1002/dmrr.450

152. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: Effects on acute and late glycaemia in athletes with Type1 diabetes mellitus. *Diabet Med*. 2011;28(7):824-832. doi:10.1111/j.1464-5491.2011.03274.x

153. García-García F, Kumareswaran K, Hovorka R, Hernando ME. Quantifying the Acute Changes in Glucose with Exercise in Type 1 Diabetes: A Systematic Review and Meta-Analysis. *Sport Med*. 2015;45(4):587-599. doi:10.1007/s40279-015-0302-2

154. Sjøberg KA, Rattigan S, Hiscock N, Richter EA, Kiens B. A new method to study changes in microvascular blood volume in muscle and adipose tissue: Real-time imaging in humans and rat. *Am J Physiol - Hear Circ Physiol*. 2011;301(2):450-458. doi:10.1152/ajpheart.01174.2010

155. Mcmahon SK, Ferreira LD, Ratnam N, et al. Glucose Requirements to Maintain Euglycemia after Moderate-Intensity Afternoon Exercise in Adolescents with Type 1 Diabetes Are Increased in a. *J Clin Endocrinol Metab*. 2007;92(3):963-968. doi:10.1210/jc.2006-2263

156. Marliss EB, Simantirakis E, Miles D, Vranic M. Glucoregulatory and hormonal responses to repeated bouts of intense exercise in normal male subjects. *J Appl Physiol*. 1991;3:713-724.

157. Yardley JE, Kenny GP, Perkins BA, et al. Resistance versus aerobic exercise. *Diabetes Care*. 2013;36(3):537-542. doi:10.2337/dc12-0963

158. Marliss EB, Vranic M. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: Implications for diabetes. *Diabetes*. 2002;51:271-283. doi:10.2337/diabetes.51.2007.S271

159. García-García F, Kumareswaran K, Hovorka R, Hernando ME. Quantifying the Acute Changes in Glucose with Exercise in Type 1 Diabetes: A Systematic Review and Meta-Analysis. *Sport Med*. 2015;45(4):587-599. doi:10.1007/s40279-015-0302-2

160. Luijf Y, Bon A, Hoekstra J, DeVries J. Premeal Injection of Rapid-Acting Insulin Reduces Postprandial Glycemic Excursions. *Diabetes Care*. 2010;33(10):2152-2155. doi:10.2337/dc10-0692.

161. Overmann H, Heinemann L. Injection-meal interval : recommendations of

diabetologists and how patients handle it. *Diabetes Res Clin Pract*. 1999;43(12):137-142.

162. Heise T, Hövelmann U, Brøndsted L, Adrian CL, Nosek L, Haahr H. Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart. *Diabetes, Obes Metab*. 2015;17(7):682-688. doi:10.1111/dom.12468

163. Kildegaard J, Buckley ST, Nielsen RH, et al. Elucidating the Mechanism of Absorption of Fast-Acting Insulin Aspart: The Role of Niacinamide. *Pharm Res*. 2019;36(3):1-14. doi:10.1007/s11095-019-2578-7

164. Novomedlink. Fiasp: insulin aspart injection 100units/mL. Accessed October 30, 2021. https://www.novomedlink.com/diabetes/products/treatments/fiasp.html

165. Heise T, Pieber TR, Danne T, Erichsen L, Haahr H. A Pooled Analysis of Clinical Pharmacology Trials Investigating the Pharmacokinetic and Pharmacodynamic Characteristics of Fast-Acting Insulin Aspart in Adults with Type 1 Diabetes. *Clin Pharmacokinet*. 2017;56(5):551-559. doi:10.1007/s40262-017-0514-8

166. Mathieu C, Gillard P, Benhalima K. Insulin analogues in type 1 diabetes mellitus: Getting better all the time. *Nat Rev Endocrinol*. 2017;13(7):385-399. doi:10.1038/nrendo.2017.39

167. Campbell MD, Walker M, Trenell MI, et al. Large Pre- and Postexercise Rapid-Acting Insulin Reductions Preserve Glycemia and Prevent Early- but Not Late-Onset Hypoglycemia in Patients With Type 1 Diabetes. *Diabetes Care*. 2013;36(8):2217-2224. doi:10.2337/dc12-2467.

168. Campbell MD, Walker M, Trenell MI, et al. A low-glycemic index meal and bedtime snack prevents postprandial hyperglycemia and associated rises in inflammatory markers, providing protection from early but not late nocturnal hypoglycemia following evening exercise in type 1 diabetes. *Diabetes Care*. 2014;37(7):1845-1853. doi:10.2337/dc14-0186

169. Campbell MD, Walker M, Bracken RM, et al. Insulin therapy and dietary adjustments to normalize glycemia and prevent nocturnal hypoglycemia after evening exercise in type 1 diabetes: A randomized controlled trial. *BMJ Open Diabetes Res Care*. 2015;3(1):1-10. doi:10.1136/bmjdrc-2015-000085

170. Heise T, Bain SC, Bracken RM, et al. Similar risk of exercise-related hypoglycaemia for insulin degludec to that for insulin glargine in patients with type 1 diabetes : a randomized cross-over trial. *Diabetes, Obes Metab*. 2016;18:196-199. doi:10.1111/dom.12588

171. McCarthy O, Deere R, Churm R, et al. Extent and prevalence of post-exercise and nocturnal hypoglycemia following peri-exercise bolus insulin adjustments in individuals with type 1 diabetes. *Nutr Metab Cardiovasc Dis*. 2020;31(1):227-236. doi:10.1016/j.numecd.2020.07.043

172. Moser O, Tschakert G, Mueller A, et al. Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin. *PLoS One*. 2015;10(8):1-17. doi:10.1371/journal.pone.0136489

173. West DJ, Morton RD, Bain SC, Stephens JW, Bracken RM. Blood glucose responses to reductions in pre-exercise rapid-acting insulin for 24 h after running in individuals with type 1 diabetes. *J Sports Sci*. 2010;28(7):781-788. doi:10.1080/02640411003734093

174. Molveau J, Myette-Côté É, Tagougui S, et al. Assessing the influence of insulin type (ultra-rapid vs rapid insulin) and exercise timing on postprandial exercise-induced hypoglycaemia risk in individuals with type 1 diabetes: a randomised controlled trial. *Diabetologia*. Published online 2024. doi:10.1007/s00125-024-06234-0

175. Campbell MD, Walker M, Trenell MI, et al. A low-glycemic index meal and bedtime snack prevents postprandial hyperglycemia and associated rises in inflammatory markers, providing protection from early but not late nocturnal hypoglycemia following evening exercise in type 1 diabetes. *Diabetes Care*. 2014;37(7):1845-1853. doi:10.2337/dc14-0186

176. Campbell MD, Walker M, Trenell MI, et al. Metabolic Implications when Employing Heavy Pre- and Post-Exercise Rapid-Acting Insulin Reductions to Prevent Hypoglycaemia in Type 1 Diabetes Patients : A Randomised Clinical Trial. *PLoS One*. 2014;9(5):1-10. doi:10.1371/journal.pone.0097143

177. Shetty VB, Fournier PA, Davey RJ, et al. Effect of exercise intensity on glucose requirements to maintain euglycemia during exercise in type 1 diabetes. *J Clin Endocrinol Metab*. 2016;101(3):972-980. doi:10.1210/jc.2015-4026

178. Rabasa-Lhoret R, Bourque J, Ducros F, Chiasson J-L. Guidelines for Premeal Insulin Dose Reduction for Postprandial Exercise of Different Intensities and Durations in Type 1 Diabetic Subjects. *Diabetes Care*. 2001;24(4):625-630. doi:10.2337/diacare.24.4.625

179. Boughton CK. Fully closed-loop insulin delivery—are we nearly there yet? *Lancet Digit Heal*. 2021;3(11):e689-e690. doi:10.1016/S2589-7500(21)00218-1

180. Dovc K, Piona C, Mutlu GM, et al. Insulin Aspart During Day-and- Night Fully Closed-Loop Insulin Therapy in Type 1 Diabetes : A Double-Blind Randomized Crossover Trial. *Diabetes Care*. 2020;43:29-36. doi:10.2337/dc19-0895

181. Tsoukas MA, Majdpour D, Yale J, et al. Articles A fully artificial pancreas versus a hybrid artificial pancreas for type 1 diabetes : a single-centre , open-label , randomised controlled , crossover , non-inferiority trial. *Lancet Digit Heal*. 2021;3:723-732. doi:10.1016/S2589-7500(21)00139-4

182. Morrison D, Zaharieva DP, Lee MH, et al. Comparable Glucose Control with Fast-Acting Insulin Aspart Using a Second-Generation Hybrid Closed-Loop System During Exercise. *Diabetes Technol Ther*. 2022;24(2):1-9. doi:10.1089/dia.2021.0221

183. Moser O, Riddell MC, Eckstein ML, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society f. *Pediatr Diabetes*. 2020;63(12):2501-2520. doi:10.1111/pedi.13105

184. Momeni Z, Boulé NG, Prado CM, Hinz HA, Yardley JE. The Effect of Starting Blood Glucose Levels on Serum Electrolyte Concentrations during and after Exercise in Type 1 Diabetes. *Int J Environ Res Public Health*. 2023;20(3):1-15.

doi:10.3390/ijerph20032109

185. McCarthy O, Eckstein ML, Scott SN, et al. Glycemic responses to strenuous training in male professional cyclists with type 1 diabetes: A prospective observational study. *BMJ Open Diabetes Res Care*. 2020;8(1):1-9. doi:10.1136/bmjdrc-2020-001245

186. Moser O, Dietrich M, McCarthy O, Bracken RM, Eckstein ML. Bolus insulin dose depends on previous-day race intensity during 5 days of professional road-cycle racing in athletes with type 1 diabetes: A prospective observational study. *Diabetes, Obes Metab*. 2020;22(10):1714-1721. doi:10.1111/dom.14083

187. Jeukendrup A. A step towards personalized sports nutrition: Carbohydrate intake during exercise. *Sport Med*. 2014;44(SUPPL.1):S25-S33. doi:10.1007/s40279-014-0148-z

188. Riddell MC, Scott SN, Fournier PA, et al. The competitive athlete with type 1 diabetes. *Diabetologia*. 2020;63:1475-1490.

189. Scott SN, Christiansen MP, Fontana FY, et al. Evaluation of factors related to glycemic management in professional cyclists with type 1 diabetes over a 7-day stage race. *Diabetes Care*. 2020;43(5):1142-1145. doi:10.2337/dc19-2302

190. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372:1-9. doi:10.1136/bmj.n71

191. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: A prospective exploratory study. *Syst Rev*. 2017;6(1):1-12. doi:10.1186/s13643-017-0644-y

192. Glanville J, Lefebvre C. Identifying Randomised Controlled Trials. In: *Systematic Reviews in Health Research*. ; 2022:36-54.

193. Pitt JP, Bracken RM, Scott SN, Fontana FY, McCarthy OM. Different fueling strategies during racing and training in professional cyclists with type 1 diabetes. In: *57th EASD Annual Meeting of the European Association for the Study of Diabetes*. ; 2021:S185.

194. Walter-Kroker A, Kroker A, Mattiucci-Guehlke M, Glaab T. A practical guide to bioelectrical impedance analysis using the example of chronic obstructive pulmonary disease. *Nutr J*. 2011;10(35):1-8. doi:10.1186/1475-2891-10-35

195. IPAQ Group. The International Physical Activity Questionnaire (Short Form). Published 2005. Accessed October 24, 2018. http://www.ipaq.ki.se/

196. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-Country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-1395. doi:10.1249/01.MSS.0000078924.61453.FB

197. IPAQ Group. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ). Published 2005. Accessed October 18, 2018. www.ipaq.ki.se

198. Borg GAV. Psychophysical bases of perceived exertion. *Plast Reconstr Surg*. 1982;14(5):377-381.

199. Hofmann P, Tschakert G. Special Needs to Prescribe Exercise Intensity for Scientific

Studies. *Cardiol Res Pract*. 2011;2011:1-10. doi:10.4061/2011/209302

200. Faude O, Kindermann W, Meyer T. Lactate threshold concepts: How valid are they? *Sport Med*. 2009;39(6):469-490. doi:10.2165/00007256-200939060-00003

201. Dill DB, Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J Appl Physiol*. 1974;37(2):247-248. doi:10.1152/jappl.1974.37.2.247

202. ADA. Defining and Reporting Hypoglycemia in Diabetes. *Dibaetes Care*. 2005;28(5):1245-1249.

203. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Routledge Academic; 1988.

204. Huedo-Medina T, Sanchez-Meca J, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods*. 2006;11(2):193-206. doi:10.1037/1082-989X.11.2.193.

205. Hampel FR. The influence curve and its role in robust estimation. *J Am Stat Assoc*. 1974;69(346):383-393. doi:10.1080/01621459.1974.10482962

206. Nurhaliza RA, Octava MQH, Hilmy FM, Farooq U, Alfian G. Application of the outlier detection method for web-based blood glucose level monitoring system. *Bull Electr Eng Informatics*. 2024;13(4):2809-2816. doi:10.11591/eei.v13i4.7717

207. Jadhav MM, Sarwade AN, Sardar VM, Jadhav HM. Development of a Non-Invasive Blood Glucose Monitoring Device Using Machine Learning Technology. *Passer J Basic Appl Sci*. 2024;6(1):58-73. doi:10.24271/PSR.2023.388351.1272

208. Allison D, Paultre F, Maggio C, Mezzitis N, Pi-Sunyer F. The Use of Areas Under Curves in Diabetes Research. *Diabetes Care*. 1995;18(2):245-250.

209. Jeukendrup AE, Wallis GA. Measurement of substrate oxidation during exercise by means of gas exchange measurements. *Int J Sport Med Suppl*. 2005;26(1). doi:10.1055/s-2004-830512

210. Yazici B, Yolacan S. A comparison of various tests of normality. *J Stat Comput Simul*. 2007;77(2):175-183. doi:10.1080/10629360600678310

211. Chimen M, Kennedy A, Nirantharakumar K. What are the health benefits of physical activity in type 1 diabetes mellitus ? A literature review. *Diabetologia*. 2012;55(11):542-551. doi:10.1007/s00125-011-2403-2

212. Richter EA, Sylow L. Interactions between insulin and exercise. Published online 2021:3827-3846.

213. Molveau J, Rabasa-lhoret R, Taleb N. Minimizing the Risk of Exercise-Induced Glucose Fluctuations in People Living With Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion : An Overview of Strategies. *Can J Diabetes*. 2021;45(7):666-676. doi:10.1016/j.jcjd.2021.01.003

214. Adolfsson P, Riddell MC, Taplin CE, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes. *Pediatr Diabetes*. 2018;19:205-226. doi:10.1111/pedi.12755

215. ADA. Standards of Medical Care in Diabetes - 2014. *Diabetes Care*. 2014;37:14-80.

doi:10.2337/dc14-S014

216. Helleputte S, Yardley JE, Scott SN, et al. Effects of postprandial exercise on blood glucose levels in adults with type 1 diabetes: a review. *Diabetologia*. Published online 2023. doi:10.1007/s00125-023-05910-x

217. Campaigne BN, Wallberg-henriksson H, Gunnarsson R. Glucose and Insulin Responses in Relation to Insulin Dose and Caloric Intake 12 h After Acute Physical Exercise in Men With IDDM. *Diabetes Care*. 1987;10(6):3-8. doi:doi: 10.2337/diacare.10.6.716

218. Li T, Higgins J, Deeks J. Chapter 5: Collecting data. In: *Cochrane Handbook for Systematic Reviews of Interventions*. ; 2019. www.training.cochrane.org/handbook

219. ADA, EASD, IFCC, IDF. Consensus statement on the worldwide standardisation of the HbA1c measurement. *Diabetologia*. 2007;50:2042-2043. doi:10.1007/s00125-007-0789-7

220. John G, English E, Hospital RD. IFCC standardised HbA1c: should the world be as one? 2012;50(7):1243-1248. doi:10.1515/cclm-2011-0853

221. NGSP. Harmonizing hemoglobin A1c testing. Published 2010. Accessed August 29, 2023. https://ngsp.org/

222. NICE. Type 1 diabetes in adults: diagnosis and management. Published 2022. Accessed September 1, 2024. https://www.nice.org.uk/guidance/ng17/chapter/Recommendations

223. Cisternas NS. *ACSM Guidelines for Exercise Testing and Prescription.* Tenth Edit. (Deborah R, Jonathan KE, Liguori G, Magal M, eds.). Wolters Kluwer Health; 2018.

224. Shetty VB, Fournier PA, Paramalingam N, et al. Effect of Exercise Intensity on Exogenous Glucose Requirements to Maintain Stable Glycemia At High Insulin Levels in Type 1 Diabetes. *J Clin Endocrinol Metab*. 2021;106(1):83-93. doi:10.1210/clinem/dgaa768

225. Romeres D, Olson K, Carter R, Cobelli C, Man CD, Basu A. Hyperglycemia But Not Hyperinsulinemia Is Favorable for Exercise in Type 1 Diabetes : A Pilot Study. 2020;43(September):2176-2182. doi:10.2337/dc20-0611

226. Chokkalingam K, Tsintzas K, Norton L, Jewell K. Exercise under hyperinsulinaemic conditions increases whole-body glucose disposal without affecting muscle glycogen utilisation in type 1 diabetes. *Diabetologia*. 2007;50:414-421. doi:10.1007/s00125-006-0520-0

227. Francescato MP, Geat M, Fusi S, Stupar G, Noacco C, Cattin L. Carbohydrate requirement and insulin concentration during moderate exercise in type 1 diabetic patients. *Metabolism*. 2004;53(9):1126-1130. doi:10.1016/j.metabol.2004.03.015

228. Søeborg T, Rasmussen CH, Mosekilde E, Colding-Jørgensen M. Absorption kinetics of insulin after subcutaneous administration. *Eur J Pharm Sci*. 2009;36(1):78-90. doi:10.1016/j.ejps.2008.10.018

229. Deeks J., Higgins JP., Altman D. Chapter 10: Analysing data and undertaking meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions*. ; 2023.

230. West DJ, Stephens JW, Bain SC, et al. A combined insulin reduction and carbohydrate feeding strategy 30 min before running best preserves blood glucose concentration after exercise through improved fuel oxidation in type 1 diabetes mellitus. *J Sports Sci*. 2010;29(3):279-289. doi:10.1080/02640414.2010.531753

231. Scott S, Kempf P, Bally L, Stettler C. Carbohydrate Intake in the Context of Exercise in People with Type 1 Diabetes. *Nutrients*. 2019;11:1-21.

232. Turner D, Luzio S, Gray BJ, et al. Impact of single and multiple sets of resistance exercise in type 1 diabetes. *Scand J Med Sci Sports*. 2015;25(1):404-412. doi:10.1111/sms.12202

233. Zaharieva DP, Riddell MC. Insulin Management Strategies for Exercise in Diabetes. *Can J Diabetes*. 2017;41(5):507-516. doi:10.1016/J.JCJD.2017.07.004

234. Bussau VA, Ferreira LD, Jones TW, Fournier PA. A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes. *Diabetologia*. 2007;50(9):1815-1818. doi:10.1007/s00125-007-0727-8

235. Francescato MP, Stel G, Stenner E, Geat M. Prolonged exercise in type 1 diabetes: Performance of a customizable algorithm to estimate the carbohydrate supplements to minimize glycemic imbalances. *PLoS One*. 2015;10(4):1-14. doi:10.1371/journal.pone.0125220

236. Hill NE, Campbell C, Buchanan P, Knight M, Godsland IF, Oliver NS. Biochemical, Physiological and Psychological Changes during Endurance Exercise in People with Type 1 Diabetes. *J Diabetes Sci Technol*. 2017;11(3):529-536. doi:10.1177/1932296816671956

237. Heise T, Stender-Petersen K, Hövelmann U, et al. Pharmacokinetic and Pharmacodynamic Properties of Faster-Acting Insulin Aspart versus Insulin Aspart Across a Clinically Relevant Dose Range in Subjects with Type 1 Diabetes Mellitus. *Clin Pharmacokinet*. 2017;56(6):649-660. doi:10.1007/s40262-016-0473-5

238. Ørtenblad N, Westerblad H, Nielsen J. Muscle glycogen stores and fatigue. *J Physiol*. 2013;591(18):4405-4413. doi:10.1113/jphysiol.2013.251629

239. Galassetti P, Tate D, Neill RA, Richardson A, Leu S-Y, Davis SN. Effect of differing antecedent hypoglycemia on counterregulatory responses to exercise in type 1 diabetes. *Am J Physiol Metab*. 2006;290(6):E1109-E1117. doi:10.1152/ajpendo.00244.2005

240. Riddell MC, Zaharieva DP, Tansey M, et al. Individual glucose responses to prolonged moderate intensity aerobic exercise in adolescents with type 1 diabetes: The higher they start, the harder they fall. *Pediatr Diabetes*. 2019;20(1):99-106. doi:10.1111/pedi.12799

241. Yardley JE. Fasting May Alter Blood Glucose Responses to High-Intensity Interval Exercise in Adults With Type 1 Diabetes: A Randomized, Acute Crossover Study. *Can J Diabetes*. 2020;44(8):727-733. doi:10.1016/j.jcjd.2020.09.007

242. Jenni S, Oetliker C, Allemann S, et al. Fuel metabolism during exercise in euglycaemia and hyperglycaemia in patients with type 1 diabetes mellitus - A prospective single-blinded randomised crossover trial. *Diabetologia*. 2008;51(8):1457-

1465. doi:10.1007/s00125-008-1045-5

243. West DJ, Morton RD, Stephens JW, et al. Isomaltulose improves postexercise glycemia by reducing CHO oxidation in T1DM. *Med Sci Sports Exerc*. 2011;43(2):204-210. doi:10.1249/MSS.0b013e3181eb6147

244. Haahr H, Heise T. Fast-Acting Insulin Aspart: A Review of its Pharmacokinetic and Pharmacodynamic Properties and the Clinical Consequences. *Clin Pharmacokinet*. 2020;59(2):155-172. doi:10.1007/s40262-019-00834-5

245. Heise T, Linnebjerg H, Coutant D, et al. Ultra rapid lispro lowers postprandial glucose and more closely matches normal physiological glucose response compared to other rapid insulin analogues: A phase 1 randomized, crossover study. *Diabetes, Obes Metab*. 2020;22(10):1789-1798. doi:10.1111/dom.14094

246. Heise T, Hövelmann U, Zijlstra E, Stender-Petersen K, Jacobsen JB, Haahr H. A Comparison of Pharmacokinetic and Pharmacodynamic Properties Between Faster-Acting Insulin Aspart and Insulin Aspart in Elderly Subjects with Type 1 Diabetes Mellitus. *Drugs and Aging*. 2017;34(1):29-38. doi:10.1007/s40266-016-0418-6

247. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: Results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). *Diabetes Care*. 2017;40(7):943-950. doi:10.2337/dc16-1771

248. Chushieri S. The CONSORT statement. *Saudi J Anaesth*. 2019;13:27-30. doi:10.4103/sja.SJA

249. Heise T, Pieber TR, Danne T, Erichsen L, Haahr H. A Pooled Analysis of Clinical Pharmacology Trials Investigating the Pharmacokinetic and Pharmacodynamic Characteristics of Fast-Acting Insulin Aspart in Adults with Type 1 Diabetes. *Clin Pharmacokinet*. 2017;56(5):551-559. doi:10.1007/s40262-017-0514-8

250. Bode BW, Johnson JA, Hyveled L, Tamer SC, Demissie M. Improved Postprandial Glycemic Control with Faster-Acting Insulin Aspart in Patients with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion. *Diabetes Technol Ther*. 2017;19(1):25-33. doi:10.1089/dia.2016.0350

251. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1diabetes: Implications for intensive diabetes management in the continuous glucose monitoring era. *Diabetes Care*. 2015;38(6):1008-1015. doi:10.2337/dc15-0100

252. Giezenaar C, Lange K, Hausken T, et al. Acute effects of substitution, and addition, of carbohydrates and fat to protein on gastric emptying, blood glucose, gut hormones, appetite, and energy intake. *Nutrients*. 2018;10(10):1-15. doi:10.3390/nu10101451

253. Spriet LL, Watt MJ. Regulatory mechanisms in the interaction between carbohydrate and lipid oxidation during exercise. *Acta Physiol Scand*. 2003;178(4):443-452. doi:10.1046/j.1365-201X.2003.01152.x

254. Vieira AF, Costa RR, Cauduro R, et al. Effects of aerobic exercise performed in fasted v . fed state on fat and carbohydrate metabolism in adults : a systematic review and meta-analysis. *Br J Nutr*. 2016;116:1153-1164. doi:10.1017/S0007114516003160

255. Lindinger MI. A century of exercise physiology: key concepts in muscle cell volume

regulation. *Eur J Appl Physiol*. 2022;122(3):541-559. doi:10.1007/s00421-021-04863-6

256. Matomäki P, Kainulainen H, Kyröläinen H. Corrected whole blood biomarkers – the equation of Dill and Costill revisited. *Physiol Rep*. 2018;6(12):1-3. doi:10.14814/phy2.13749

257. Pitt JP, McCarthy OM, Hoeg-Jensen T, Wellman BM, Bracken RM. Factors Influencing Insulin Absorption Around Exercise in Type 1 Diabetes. *Front Endocrinol (Lausanne)*. 2020;11(October):1-9. doi:10.3389/fendo.2020.573275

258. Nguyen TP, Jacobs PG, Castle JR, et al. Separating insulin-mediated and non-insulin-mediated glucose uptake during and after aerobic exercise in type 1 diabetes. *Endocrinol Metab*. 2021;320:425-437. doi:10.1152/ajpendo.00534.2020

259. DeFronzo RA, Ferrannini E, Sato Y, Felig P, Wahren J. Synergistic interaction between exercise and insulin on peripheral glucose uptake. *J Clin Invest*. 1981;68(6):1468-1474. doi:10.1172/JCI110399

260. Colberg SR, Laan R, Dassau E, Kerr D. Physical activity and type 1 diabetes: Time for a rewire? *J Diabetes Sci Technol*. 2015;9(3):609-618. doi:10.1177/1932296814566231

261. Request placed 03/09/2024.

262. Institute of Medicine. Fluid replacement and heat stress. In: ; 1994:1-6. doi:https://doi.org/10.17226/9071

263. Qamar MI, Read AE. Effects of exercise on mesentric blood flow in man. *Gut*. 1987;28:583-587.

264. Walsh J, Roberts R, Heinemann L. Confusion Regarding Duration of Insulin Action : A Potential Source for Major Insulin Dose Errors by Bolus Calculators. *J Diabetes Sci Technol*. 2014;8(1):170-178. doi:10.1177/1932296813514319

265. Walsh J, Roberts R, Bailey TS. Insulin Titration Guidelines for Patients With Type 1 Diabetes : It Is About Time ! *J Diabetes Sci Technol*. 2023;17(4):1066-1076. doi:10.1177/19322968221087261

266. Bird SR, Hawley JA. Update on the effects of physical activity on insulin sensitivity in humans. *BMJ Open Sport Exerc Med*. 2017;2(1):1-26. doi:10.1136/bmjsem-2016-000143

267. Toor S, Yardley JE. Type 1 Diabetes and the Menstrual Cycle : Where / How Does Exercise Fit in ? *Int J Environ Res Public Health*. 2023;20:2772-2784.

268. Younk LM, Mikeladze M, Tate D, Davis SN. Exercise-related hypoglycemia in diabetes mellitus. *Expert Rev Endocrinol Metab*. 2011;6(1):93-108. doi:10.1586/eem.10.78

269. Hoeg-Jensen T. Review: Glucose-sensitive insulin. *Mol Metab*. 2021;46(xxxx):101107. doi:10.1016/j.molmet.2020.101107

270. Burke LM, Hawley JA, Wong SHS, Jeukendrup AE. Carbohydrates for training and competition. *J Sports Sci*. 2011;29(SUPPL. 1). doi:10.1080/02640414.2011.585473

271. Pitt JP, Bracken RM, Scott SN, Fontana FY, McCarthy OM. Nutritional intake when cycling under racing and training conditions in professional male cyclists with type 1

diabetes. In: *The Welsh Endocrine and Diabetes Society Autumn Meeting 2021*. ; 2021.

272. Jeukendrup AE. Carbohydrate intake during exercise and performance. *Nutrition*. 2004;20(7-8):669-677. doi:10.1016/j.nut.2004.04.017

273. Scott SN, Cocks M, Andrews RC, et al. Fasted high-intensity interval and moderate-intensity exercise do not lead to detrimental 24-hour blood glucose profiles. *J Clin Endocrinol Metab*. 2019;104(1):111-117. doi:10.1210/jc.2018-01308

274. Grimm JJ, Ybarra J, Berné C, Muchnick S, Golay A. A new table for prevention of hypoglycaemia during physical activity in type 1 diabetic patients. *Diabetes Metab*. 2004;30(5):465-470. doi:10.1016/S1262-3636(07)70144-1

275. Eckstein ML, Aziz F, Aberer F, et al. Blood glucose response to running or cycling in individuals with type 1 diabetes: A systematic review and meta-analysis. *Diabet Med*. 2023;40(2):1-14. doi:10.1111/dme.14981

276. Yardley JE, Sigal RJ. Exercise Strategies for Hypoglycemia Prevention in Individuals With Type 1 Diabetes. *Diabetes Spectr*. 2015;28(1):32-38. doi:10.2337/diaspect.28.1.32

277. Mattsson S, Jendle J, Adolfsson P. Carbohydrate Loading Followed by High Carbohydrate Intake During Prolonged Physical Exercise and Its Impact on Glucose Control in Individuals With Diabetes Type 1—An Exploratory Study. *Front Endocrinol (Lausanne)*. 2019;10(August):1-8. doi:10.3389/fendo.2019.00571

278. McGuire B, Dadah H, Oliver D. The effects of acute hyperglycaemia on sports and exercise performance in type 1 diabetes: A systematic review and meta-analysis. *J Sci Med Sport*. 2024;27(2):78-85. doi:10.1016/j.jsams.2023.11.007

279. Wong EY, Kroon L. Ultra-rapid-acting insulins: How fast is really needed? *Clin Diabetes*. 2021;39(4):415-423. doi:10.2337/cd20-0119

280. Moser O, Eckstein ML, McCarthy O, et al. Performance of the Freestyle Libre flash glucose monitoring (flash GM) system in individuals with type 1 diabetes: A secondary outcome analysis of a randomized crossover trial. *Diabetes, Obes Metab*. 2019;21(11):2505-2512. doi:10.1111/dom.13835

281. Diabetes UK. Smart insulin pens: How they work, and experiences of using them. Published 2023. Accessed September 20, 2024. https://www.diabetes.org.uk/about-us/news-and-views/smart-insulin-pens-how-they-work-and-your-experiences-using-them

282. Sy SL, Munshi MM, Toschi E. Can Smart Pens Help Improve Diabetes Management? *J Diabetes Sci Technol*. 2022;16(3):628-634. doi:10.1177/1932296820965600

283. Moser O, Zaharieva DP, Adolfsson P, et al. The Use of Automated Insulin Delivery Around Physical Activity and Exercise in Type 1 Diabetes: A Position Statement of the European Association for the Study of Diabetes (EASD) and the International Society for Pediatric and Adolescent Diabetes (ISPAD). In: ; 2024.

284. Eckstein ML, Weilguni B, Tauschmann M, et al. Time in range for closed-loop systems versus standard of care during physical exercise in people with type 1 diabetes: A systematic review and meta-analysis. *J Clin Med*. 2021;10(11):1-12. doi:10.3390/jcm10112445

285. Nishimura E, Pridal L, Glendorf T, et al. Molecular and pharmacological characterization of insulin icodec: A new basal insulin analog designed for once-weekly dosing. *BMJ Open Diabetes Res Care*. 2021;9(1):1-10. doi:10.1136/bmjdrc-2021-002301

286. Ekberg NR, Hartvig NV, Kaas A, Møller JB, Adolfsson P. Smart Pen Exposes Missed Basal Insulin Injections and Reveals the Impact on Glycemic Control in Adults With Type 1 Diabetes. *J Diabetes Sci Technol*. 2024;18(1):66-73. doi:10.1177/19322968221104142

287. Russell-Jones D, Babazono T, Cailleteau R, et al. Once-weekly insulin icodec versus once-daily insulin degludec as part of a basal-bolus regimen in individuals with type 1 diabetes (ONWARDS 6): a phase 3a, randomised, open-label, treat-to-target trial. *Lancet*. 2023;402(10413):1636-1647. doi:10.1016/S0140-6736(23)02179-7

288. Aronson R, Brown RE, Li A, Riddell MC. Optimal insulin correction factor in post–high-intensity exercise hyperglycemia in adults with type 1 diabetes: The FIT study. *Diabetes Care*. 2019;42(1):10-16. doi:10.2337/dc18-1475

289. Campbell MD, West DJ, Bain SC, et al. Simulated games activity vs continuous running exercise: a novel comparison of the glycemic and metabolic responses in T1DM patients. *Scand J Med Sci Sports*. 2015;25(2):216-222. doi:10.1111/sms.12192

290. McCarthy O, Pitt J, Wellman BEN, et al. Blood Glucose Responses during Cardiopulmonary Incremental Exercise Testing in Type 1 Diabetes: A Pooled Analysis. *Med Sci Sports Exerc*. 2021;53(6):1142-1150. doi:10.1249/MSS.0000000000002584

291. Moser O, Eckstein ML, Mueller A, et al. Reduction in insulin degludec dosing for multiple exercise sessions improves time spent in euglycaemia in people with type 1 diabetes: A randomized crossover trial. *Diabetes, Obes Metab*. 2018;21(2):349-356. doi:10.1111/dom.13534

292. Turner D, Gray BJ, Luzio S, et al. Similar magnitude of post-exercise hyperglycemia despite manipulating resistance exercise intensity in type 1 diabetes individuals. *Scand J Med Sci Sport*. 2016;26(4):404-412. doi:10.1111/sms.12472