An Adaptive Real-time Intelligent System to Enhance Self-care of Chronic disease (ARISES)

by

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Abstract

Diabetes mellitus is an increasingly prevalent chronic metabolic condition characterised by impaired glucose homeostasis and raised blood glucose levels (hyperglycaemia). Broadly categorised as either type 1 (T1DM) or type 2 diabetes (T2DM), people with diabetes are largely responsible for self-managing their blood glucose levels. Despite the development of diabetes technologies such as real time continuous glucose monitoring (RT-CGM), many individuals are frequently exposed to iatrogenic low blood glucose levels (hypoglycaemia). Severe hypoglycaemia is associated with an increased risk of recurrent hypoglycaemia, impaired symptomatic awareness of hypoglycaemia, and potentially death if left untreated.

This thesis affirmed the existing clinical impact of severe hypoglycaemia and its recurrent risk in a six-month analysis of severe hypoglycaemia attended by the London Ambulance Service NHS Trust (LAS). Fewer incidents of severe hypoglycaemia observed in a date matched repeat analysis during the 2020 COVID-19 lockdown suggested improved self-management possibly motivated by a proximal fear of hospitalisation and improved structure at home. Finally, a 12-week randomised control trial demonstrating a significant difference in time spent in hypoglycaemia <3mmol/L, is the first study to prove the immediate provision of RT-CGM significantly reduces the risk of recurrent hypoglycaemia. Moreover, it highlighted the impact of socioeconomic disparity as a barrier to effective hypoglycaemia risk modification. This guided the design of an adaptive real time intelligent system to enhance self-care of chronic disease (ARISES) aimed to deliver therapeutic and lifestyle decision support for people with T1DM.

The ARISES graphic user interface (GUI) design was a collaborative process conceived in a series of focus group meetings including people with T1DM. Finally, a 12-week observational study using RT-CGM, a physiological sensor wristband, and a mobile diary app, allowed for a sub-analysis identifying

measurable physiological parameters associated with current and impending hypoglycaemia in people with T1DM.

Declaration of Originality

I hereby declare that all content of this thesis is the result of my own work. Therefore, all, participant recruitment and study visits, data collection and analysis have been performed by the author, if not stated otherwise in the text. A list of publications that arose from this work can be found in the Appendix. Additional information used from third parties has been referenced accordingly. Any collaborations and assistance are outlined below.

Chapter 2 & 3

The presented clinical study was performed in collaboration with The London Ambulance Service NHS Trust (LAS), led by Rachael Fothergill. Valentina Pendolino collected the 6-month database of severe hypoglycaemia attended by the LAS in 2019, and the database during the COVID-19 lockdown in 2020. The work in Chapter 2 has been published in a journal paper with the writer of this thesis appearing as the first author. As the author of the published article and submission of this thesis being for graduation requirements, I am permitted to reuse the full published text as part of this thesis without permission from the publisher.

Chapter 4

The presented clinical study was performed in collaboration with The London Ambulance Service NHS Trust (LAS), led by Rachael Fothergill. I presented this work as a poster at the 'Advanced Technologies and Treatments for Diabetes' in 2021.

Chapter 5

The presented study was performed in collaboration with the Faculty of Engineering, Department of Electrical and Electronic Engineering, Imperial College London, led by Prof. Pantelis Georgiou. The

concepts incorporated in the graphical user interface were concertedly conceived during multidisciplinary meetings attended by Prof. Robert Spence, Dr Kezhi Li, Taiyu Zhu, John Daniels, and recruited participants with T1DM. Dr Kehzi Li and Taiyu Zhu developed the GUI software and worked on the application programming interface (API). This work has been published in a journal paper with the writer of this thesis appearing as co-author. I also presented this work as a poster at the 'Advanced Technologies and Treatments for Diabetes' conference in 2019 and 2020. Further clinical support and assistance during the studies was provided by Narvada Jugnee.

Chapter 6

The presented clinical study was performed in collaboration with the Faculty of Engineering, Department of Electrical and Electronic Engineering, Imperial College London, led by Prof. Pantelis Georgiou. John Daniels distilled the data collected from the Empatica E4. I presented this work at the 'Advanced Technologies and Treatments for Diabetes' conference in 2021 as an oral presentation. Further clinical support and assistance during the studies was provided by Narvada Jugnee.

Copyright Declaration

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An important part of this thesis is the collaborative work performed by The London Ambulance NHS Service NHS Trust (Rachel Fothergil and Valentina Pendolino) and the engineering research team at Imperial College (Prof Pantelis Georgiou, Dr Pau Herrero, Prof Robert Spence, Dr Kehzi Li, Taiyu Zhu, and John Daniels). It was an absolute pleasure working with all of you.

Finally, I would like to dedicate this thesis to my parents and siblings who have always supported my ambitions.

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Abbreviations

AUC	Area under the curve
BMI	Body Mass Index
CSII	Continuous subcutaneous insulin infusion
CV	Coefficient of variation
DAFNE	Dose Adjustment for Normal Eating
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DPP-4	Dipeptidyl peptidase 4
DTSQ	Diabetes treatment satisfaction questionnaire
EDA	Electrodermal activity
EMS	Emergency Medical Services
GCS	Glasgow Coma Scale
GLP-1	Glucagon-like-peptide-1
GMI	Glucose management indicator
HAAF	Hypoglyaceamia associated autonomic failure
HbA1c	Glycated Haemoglobin
HFS-II	Hypoglycaemia Fear Survey II
HHS	Hyperosmolar Hyperglycaemic State
HRmax	Maximum heart rate
ICR	Insulin to carbohydrate ratio
IDDM	Insulin dependent diabetes
IHSG	The International Hypoglycaemia Study Group
IOB	Insulin on board

IQR	Interquartile range
ISF	Insulin sensitivity factor
LADA	Latent autoimmune diabetes in adults
LAS	The London Ambulance Service NHS Trust
LBGI	Low blood glucose index
MAG	Mean absolute glucose
MDI	Multiple daily injections
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDM	Non-insulin dependent diabetes
PAID	Problem Areas in Diabetes questionnaire
RCT	Randomised control trial
RT-CGM	Real-time Continuous Glucose Monitoring
SCL	Skin conductance level
SCR	Skin conductance response
SD	Standard deviation
SMBG	Self monitored blood glucose
T1DM	Type 1 Diabetes
T2DM	Type 2 Diabetes
TAR	Time above range
TBR	Time below range
TIR	Time in range
VO_2 max	Percentage of maximal oxygen uptake
WHO	The World Health Organisation

1. Chapter 1: Introduction

1.1. Chronic Disease and Diabetes Mellitus

1.1.1. Chronic Disease

Defining chronic disease invokes a variety of responses with differing opinions on the duration and rate of illness progression. The UK National Health Service (NHS) business definition is a health problem requiring ongoing management over a period of years or decades and cannot currently be cured but can be controlled using medications and therapies (1). The US National Centre for Chronic Disease Prevention and Health Promotion describes it as a condition that lasts one year or more and requires ongoing medical attention or limits activities of daily living or both (2). Differences aside, it can be agreed that individuals living with chronic disease experience persistent illness over time and require ongoing medical input. Medical advances have seen diagnostic and therapeutic improvements in the management of chronic disease. Alongside a steady increase in life expectancy, the non-curable nature of chronic disease has seen a growing population of individuals living with diagnosed chronic illness. In England this accounts for an estimated 15 million people living with a long-term chronic illness (3) and requiring significant resources from the NHS. On a global scale, The World Health Organisation (WHO) report noncommunicable or chronic diseases to be responsible for 71% of all deaths (4).

The impact of chronic disease reaches beyond the physical and psychosocial effects on the afflicted individual and extends to their social support network and the resource burden placed on a variety

of public health services. Health care needs are geared towards managing active disease, preventing complications associated with disease progression, and dealing with the psychology of living with chronic illness. Accepting lifestyle and work limitations can manifest as feelings of fear, grief, and shame when coming to terms and living with a chronic disease (5). Furthermore, encouraging treatment compliance can prove to be challenging when clinical improvement is not guaranteed, and more so when disease progression is inevitable. Addressing these factors is often a lifelong process requiring a multi-disciplinary approach and dependency on resources from a range of primary and secondary healthcare professionals. Education and self-management are important in the individual journey towards understanding and coping with the burden of living with chronic disease. Arming individuals with the knowledge to safely identify symptoms, institute appropriate therapy, and in severe cases know when to seek medical advice, is a practiced strategy to mitigate delayed treatment and promote efficient access to healthcare professionals.

1.1.2. Diabetes Mellitus

Diabetes mellitus is an increasingly prevalent chronic condition affecting an estimated 4 million UK inhabitants (6). It is characterised by elevated blood glucose levels due to the inability to mobilise glucose intracellularly. Insulin and other counter-regulatory hormones are responsive to changes plasma glucose and work in conjunction with the nervous system to maintain normal glucose homeostasis. The hormone insulin is secreted by pancreatic beta cells and is required for facilitating blood glucose uptake into cells via glucose transporter type 4 (GLUT-4). Diabetes can be categorised as either Type 1 (T1DM) or Type 2 (T2DM). T1DM is defined as autoantibody destruction of pancreatic beta cells resulting in elevated blood glucose levels (hyperglycaemia) when insulin production is not sufficient. Conversely, in T2DM cells are unresponsive or insensitive to insulin (insulin resistance). In response, pancreatic beta cells secrete significantly more insulin until they are

unable to compensate, and hyperglycaemia ensues. Prolonged compensatory exertion by beta cells in T2DM eventually results in beta cell exhaustion and diminished insulin secretion (7–9).

Glucose is an osmotically active molecule and individuals with persistent hyperglycaemia typically present with osmotic symptoms of increased urination (polyuria), increased drinking (polydipsia), and blurred vision. Blood glucose excursions after meals are physiological and considered normal if levels measure below 7.8 mmol/L (140 mg/dl) 2 hours post-prandially. However, the inability to mobilise glucose into cells due to insulin insufficiency or resistance results in persistently elevated post-prandial glucose levels and is one of the methods used in making a diagnosis of diabetes. The WHO diagnostic criteria for diabetes is the presence of osmotic symptoms and a random blood glucose or 2-hour post prandial glucose (75g carbohydrate) ≥11.1mmol/L, or fasting glucose ≥7mmol/L (10). In the absence of symptoms, a second confirmatory plasma glucose is required on a separate day. Glycated haemoglobin (HbA1c) reflects average blood glucose levels over the life span if a red blood cell (2-3 months) and is an almost universally adopted measure of glucose control. In the UK, a HbA1c above or greater than 48mmol/mol (6.5%) is considered diagnostic for diabetes. However, two separate measurements are necessary in the absence of symptoms.

T1DM represents 10% of the national diabetes population and is characterised by insulin deficiency (6). Temporal beta cell loss in T1DM and the inability to mobilise glucose into cells eventually leads to a decompensated state where normal glucose levels (normoglycemia) can no longer be achieved. If the insulin deficient state remains untreated and glycogen stores are depleted the body turns to protein and fat breakdown as a source of glucose (gluconeogenesis). This manifests clinically as catabolic weight loss and acidic ketone bodies produced as a by-product of fatty acid oxidation result in vomiting, drowsiness, coma, and potentially death (diabetic ketoacidosis). In addition to the contrasting clinical presentation, the autoimmune nature of T1DM will result in the presence of

autoantibodies which are not seen in T2DM. Antibodies against islet cell antigens, most frequently glutamic acid decarboxylase (GAD65), insulin autoantibodies, insulinoma associated protein 2 (IA-2A), and zinc transporter-T8 (ZnT8) are reliable serological markers to detect clinical and impending autoimmune diabetes (11–13). In a clinical setting, autoantibody measurement is useful in classification of diabetes which can have implications on management and available treatment options (14).

The primary objective in managing diabetes is to safely maintain blood glucose levels within the bounds of normal physiology. Insulin replacement therapy is the mainstay of treatment in T1DM and can be delivered exogenously or endogenously following pancreas or islet cell transplantation. Exogenously replaced insulin is delivered with an objective to replicate physiological insulin pharmacology. It is most accessible in the form of multiple daily subcutaneous injections (MDI) or continuous subcutaneous insulin infusion (CSII) / insulin pump therapy. Oral treatments are available to achieve euglycaemia by improving insulin sensitivity, reducing hepatic glucose output, prohibiting the breakdown of starch to sugar, facilitating urinary glucose clearance, or potentiating insulin secretory capacity in T2DM with residual beta cell function. Devices for self-monitoring blood glucose levels are necessary for individuals on insulin therapy or oral agents capable of dangerously lowering blood glucose (hypoglycaemia). Hypoglycaemia often manifests initially with autonomic symptoms such as sweating, palpitations, and hunger. These symptoms are subsequently followed by neuroglycopenic symptoms such as confusion, weakness, and impaired concentration. As glucose is the primary energy substrate for the brain, sustained hypoglycaemia carries the significant risk of seizures, loss of consciousness, and death if left untreated. The physiology and pathophysiology of hypoglycaemia and its impact in diabetes is discussed further in chapter 1.4.2.

1.2. Neuroendocrine glucose homeostasis and counterregulatory responses

1.2.1. The pancreas and autonomic nervous system

As the primary energy source for cellular activity, glucose is obtained from the breakdown of dietary carbohydrates into mono- and disaccharides, and from glycogen stores in the liver (glycogenolysis). When these sources are exhausted, glucose is generated from the breakdown of protein and lipids into glucogenic amino acids and fatty acids, respectively (15). The pancreas has an important role in metabolic homeostasis through the secretion of digestive enzymes into the intestinal tract (exocrine function). It is also crucial in regulating glucose homeostasis by secreting hormones directly into the blood stream responsible for facilitating cellular use of glucose as a substrate and mobilising glucose from the liver (endocrine function). The endocrine pancreas represents 1-2% of pancreatic tissue and consists of cell clusters within the exocrine tissue 'islets of Langerhans'. The endocrine islets of Langerhans secrete a variety of different hormones from the following specific cells, insulin secreting beta cells, glucagon secreting alpha cells, somatostatin secreting delta cells, gamma cells responsible for pancreatic polypeptide (PP) secretion, and ghrelin secretory epsilon cells (16,17). As discussed earlier, insulin primarily lowers plasma glucose by stimulating cellular glucose uptake and supressing gluconeogenesis, while glucagon increases plasma glucose by breaking down glycogen (glycogenolysis) and generating glucose from non-carbohydrate substrates (gluconeogenesis). Insulin is often described as an anabolic hormone as it drives glycogenesis, lipogenesis, and increases amino-acid branches, while glucagon has opposing effects. Somatostatin has an inhibitory role on insulin and glucagon secretion (18), and PP exerts regulatory control over both endocrine and exocrine pancreatic functions (19,20). Glucagon and somatostatin both exert a paracrine effect in the endocrine pancreas and inhibit insulin secretion (21).

The autonomic nervous system is considered as part of the peripheral nervous system and is responsible for subconsciously (autonomously) regulating many body functions including, pulse rate,

blood pressure, digestion, and respiration. It is comprised of three divisions: the sympathetic, parasympathetic, and enteric nervous system. The sympathetic and parasympathetic nervous systems often function in opposition to each other with the former associated with an increase in heart rate, stalled peristalsis, arousal, and 'fight or flight' responses. Conversely, the parasympathetic division is associated with 'rest and digest' functions, lowering the heart rate, and resuming intestinal peristalsis. Autonomic control of the endocrine pancreas is orchestrated by a neuronal network of glucose sensing cells in the mouth, gastrointestinal tract, liver, brainstem, and hypothalamus (22). Ultimately, glucose sensitive changes in sympathetic and parasympathetic activity maintain glucose homeostasis by modulating pancreatic insulin and counterregulatory glucagon secretion, beta cell morphology, and insulin sensitivity.

Detection of glucose in the oral cavity and hepato-portal system increases vagal parasympathetic stimulation to brainstem and hypothalamic nuclei, parasympathetic tone in the pancreatic beta cell, and ultimately promotes insulin secretion (23–25). The significance of the autonomic nervous system is emphasised by the suppression of this reaction following vagotomy (26). Direct vagal nerve stimulation and increasing parasympathetic tone in the pancreas have also been shown to increase insulin secretion and pancreatic beta cell mass respectively, further highlighting the role of parasympathetic innervation (27–29). Increased plasma insulin levels and neuronal c-fos expression in the arcuate and paraventricular nuclei following intracarotid glucose administration suggests direct hypothalamic glucose sensing could also stimulate insulin secretion (30). Vagotomy has also been shown to supress insulin secretion following intracerebroventricular infusion of the arcuate nucleus expressed transmitter neuropeptide Y (NPY), again emphasising its role in hypothalamic glucose sensing (31,32). Using retrograde trans-synaptic labelling with pseudorabies viruses, parasympathetic innervation of the pancreas has been explored further with links identified between the vagal nerve, paraventricular nucleus, and perifornical area (22,33). Detection of

hypoglycaemia at glucose sensing sites induces a sympathetic response to increase plasma glucose levels. Direct stimulation of sympathetic nerves and activation of α-adrenoreceptors on pancreatic beta cells have been shown to inhibit basal and glucose stimulated insulin secretion (34).

1.2.2. Counterregululatory responses to hypoglycaemia

The brain consumes an estimated 20% of glucose-derived energy and is reliant on glucose as its primary energy source. For this reason, physiological and behavioural counterregulatory mechanisms have been evolved to maintain normal glucose homeostasis and importantly avoid hypoglycaemia. The body flux of glucose have been studied before and after insulin induced hypoglycaemia using isotope dilution methodology and radiolabelled alanine in healthy human subjects (35,36). This work confirmed insulin induced hypoglycaemia is a consequence of reduced gluconeogenesis and increased glucose uptake. As plasma glucose levels decline, glucose influx reduces to baseline levels followed by an increase in glycaemia as the rate of glucose production exceeds utilisation. Increased counterregulatory glucose production during hypoglycaemia was initially stimulated by a rapid increase in glycogenolysis. As the contributions of glycogenolysis declined over time, gluconeogenesis produced a lower yet more persistent glucose output.

In normal physiology, progressively declining plasma glucose concentrations triggers a sequence of counterregulatory responses. The hierarchy in which these counterregulatory factors are activated and their defined glycaemic thresholds have been well investigated, each working alongside decrements in insulin to maintain glucose homeostasis. Stepped up hypoglycaemic clamp studies measuring arterialised venous glycaemic thresholds in healthy adults have shown cessation of insulin secretion as the first line of defence in response to the physiological range glycaemia of 4.7 − 4.4 mmol/L (85 − 80 mg/dL), thereby increasing gluconeogenesis, and ultimately reducing glucose uptake by non-vital organs (37–40). The importance of insulin dissipation was highlighted by Heller

and Cryer through observing an inverse relationship between insulin concentration and successful recovery from hypoglycaemia (41). However, insulin dissipation is not the sole mechanism responsible for physiological recovery from hypoglycaemia as proven by the stimulation of additional counterregulatory hormones, glucokinetic changes increasing blood glucose, and failure to induce severe neuroglycopenic symptoms during hyperinsulinaemic states (35,41,42).

Further decline in glycaemia below 3.8 – 3.6 mmol/L (68 – 65 mg/dL) stimulates the secretion of the following counterregulatory hormones in hierarchical order; glucagon, adrenaline, growth hormone, and cortisol (35,37,38). Selective glucagon deficiency has been shown to reduce plasma glucose without inducing hypoglycaemia following a prolonged 3-day fast (43) and in the post prandial state (44), suggesting a role for additional counterregulatory hormones in such instances. Albeit a vital counterregulatory factor, the selective absence of glucagon will significantly diminish but not completely prevent glucose recovery following hypoglycaemia. In the seminal 1981 review 'Glucose Counterregulation in Man' (45), Philip Cryer summarised a series of studies examining the effect of selective deficiencies (secretion or action) of glucose counterregulatory hormones, in isolation and in combination, on plasma glucose recovery following hypoglycaemia (42,46,47). Data from these studies demonstrate that glucose recovery is impaired by approximately 40% when glucagon secretion is inhibited. De Feo et al, demonstrated selective blockade of glucagon secretion produced an estimated 60% persistent decrease in hepatic glucose output and a significantly greater decline in plasma glucose levels compared to controls (2.1 +/- 0.1 mmol/L vs 3.4 +/- 0.1 mmol/L) following a two-fold increase in circulating insulin levels (comparable to intensive insulin treatment) (48). The observation of these findings despite other compensatory responses remaining intact highlights the importance of glucagon in hyperinsulinaemic states such as insulin dependent diabetes.

Through direct β-2 adrenoreceptor stimulation of glucagon from pancreatic alpha cells and indirectly via adrenaline stimulation from the adrenal medulla, the sympathetic nervous system plays a pivotal role in the counterregulatory response to correct hypoglycaemia (49). Unlike glucagon, suppression of adrenaline action has been shown to have no impact on plasma glucose levels in both the post prandial state (44) and following a prolonged 3-day fast (43). Similarly, isolated adrenal blockade or adrenaline deficiency has minimal impact on glucose recovery following hypoglycaemia (35,42,46,47). Interestingly, when combined with glucagon deficiency, glucose recovery is profoundly impaired beyond observations seen in isolated glucagon deficiency (35,42,46,47). This highlights the importance of both glucagon and adrenaline as counterregulatory hormones, and the critical role of adrenaline when glucagon secretion is compromised. Adrenaline and nor-adrenaline have also been shown to be the only hormones observed to increase before or in time with glucose production following insulin induced hypoglycaemia, further highlighting their importance in normal glucose recovery (35).

A cohort study investigating the impact of an absent cortisol response following an insulin infusion, revealed a 22% reduction in hepatic glucose output, 15% increase in glucose utilization, and lower plasma glucose levels at 9.5 hours post infusion (p<0.01) compared to controls (50). In contrast, rapid correction of hypoglycaemia on withdrawal of insulin infusion in both cortisol and growth hormone deficient adults has been suggested to imply both hormones wield a non-critical counterregulatory role (51). This is further supported by studies observing no significant change in plasma glucose levels and rates of glucose appearance / disappearance in cortisol and growth hormone deficient cases (52,53).

The glycaemic threshold for autonomic symptoms have been measured at 3.2 +/- 0.1 mmol/L, with neuroglycopenic and cognitive impairment ensuing at 2.8 +/- 0.1mmo/L and 2.7 +/- 0.1mmol/L

respectively (38,54). These symptoms serve to trigger a behavioural response to overcome hypoglycaemia, in this case hunger and subsequent consumption of carbohydrate. The activation of counterregulatory responses before hypoglycaemia ensues aims to prevent hypoglycaemia by correcting physiological reductions in glycaemia. Studies have observed small rises in adrenaline, nor adrenaline, glucagon, and growth hormone following glucose reductions from 11.1 to 5.5mmol/L (200 to 100mg/dL) (35,55,56). This suggests an inverse relationship between the size of the counterregulatory response and the plasma glucose concentration, with larger hormonal responses to hypoglycaemic decrements.

1.2.3. Central metabolic regulation

Located in the hypothalamus, the arcuate nucleus impacts glucose homeostasis through its effect and food intake and energy metabolism. The orexigenic neuropeptide Y (NPY) and Agouti-related protein (AgRP) neurons co-expressed in the arcuate nucleus stimulate food intake and anabolic processes (57–59), with functional loss associated with significant weight loss in mice (60,61). Diminished hepatic insulin sensitivity and increased hepatic glucose output following intracerebral NPY infusion (62,63), further highlights the role of NPY neurons in metabolic regulation. Misalignment of sleep/wake and feeding rhythms or functional loss of the hypothalamic suprachiasmatic nucleus (SCN), responsible for maintaining the light sensitive 24-hour circadian rhythm, results in insulin hyposecretion, increased post prandial hyperglycaemia, and increased hepatic glucose output (64,65). Physiological rhythms linked to food availability remain intact in the absence of the SCN (66), and studies have suggested the existence of a light independent food oscillator that controls behaviour in response to anticipated food within AgRP neurons (67).

In contrast, anorexigenic pro-opiomelanocortin (POMC) and cocaine-amphetamine related transcript (CART) neurons exert opposing catabolic effects. The α-Melanocortin-Stimulating hormone (α-MSH) is cleaved from POMC and acts as a non-selective agonist on most melanocortin receptors. Activation of melanocortin receptors 3 and 4 have been shown to stimulate glucose production, with melanocortin receptor 4 mutations developing an insulin resistant phenotype (68). The presence of insulin and the anorexigenic hormone leptin receptors within the arcuate nucleus further highlight its role as a central metabolic regulator (57,59,69,70).

Other hypothalamic regions involved in glucose metabolism and energy homeostasis include the ventromedial (VMH) and lateral hypothalamic nucleus (LHN). Studies have identified the VMH to play an integral role in identifying and triggering a recovery counterregulatory response to hypoglycaemia, with direct stimulation increasing both glucagon and glucose levels (71,72). In addition, stimulation of the VMH has been shown to increase peripheral glucose uptake, independent of insulin, predominantly in brown adipose tissue, myocardial and skeletal muscle (73). Reduced glucose uptake following local sympathetic denervation opens the possibility of a sympathetic mediated glucose transport mechanism (71). The LHN has been shown to a have a contrasting effect on the liver with stimulation increasing hepatic glycogenesis (62), consistent with outcomes seen when increasing parasympathetic vagal tone in the liver (71).

1.3.   Challenging factors in glucose control

Glucose homeostasis is directly and indirectly influenced by a range of hormonal, physiological and environmental factors. In normal physiology, counter-regulatory responses ensure blood glucose levels remain stable when exposed to variables that influence glucose control. At present, the most detailed management advice for insulin dosing and speculating blood glucose levels is largely based

on ingested carbohydrates, with lesser levels of support to address exercise. Despite clinical and anecdotal evidence confirming glucose variability following exposure to various physiological and environmental conditions, factors such as non-carbohydrate macronutrients, time of day, and menstrual hormonal changes are rarely considered in diabetes management.

1.3.1. Dietary carbohydrate

Post prandial glucose excursions are the outcome of dietary macronutrients, predominantly carbohydrates, being broken down to monosaccharides during digestion. To utilise glucose and maintain normoglycaemia insulin is secreted from the pancreatic beta cells in a biphasic profile. The initial phase commences within 2 minutes of eating and lasts for an estimated 10 minutes, followed by a sustained second phase to assist glucose utilisation. The challenge when administering bolus insulin is determining how much insulin is required for a given amount of carbohydrate and avoiding hyper- or hypoglycaemia due to a mismatch. Validated structured education programmes are advocated to assist individuals in calculating dietary carbohydrates and dose insulin based on an insulin to carbohydrate ratio (ICR). However, correct insulin dosing is further compounded by the varying rates at which carbohydrate containing foods are digested and absorbed. Fixed bolus insulin administration is delivered on the assumption that different meals have similar macronutrient composition, glycaemic loads, absorption patterns and post prandial glucose profiles. In T1DM, high glycaemic load (HG) meals have significantly been shown to have a 50% higher peak glucose appearance and faster time to reach 25%, 50% and 75% of cumulative glucose appearance compared to a carbohydrate matched low glycaemic load meal (LG). However, LG meals resulted in a more sustained rise in plasma glucose beyond 8 hours (74). The glycaemic index (GI) is a scale from 0 to 100 used to classify foods based on how quickly they effect blood glucose levels after ingestion. Foods with a high GI rapidly increase blood glucose levels with pure glucose having a reference score of 100. Whereas low GI foods tend to slowly absorb and release glucose. The disparity at which

dietary carbohydrates influence blood glucose levels and the variety of carbohydrate sources in each meal are an additional obstacle in attaining accurate insulin dosing. Uncertainty and fear of glucose fluctuations due to insulin carbohydrate mismatch can resort to compromising behaviours such as avoidance of foods and insulin dose omission. Low carbohydrate diets have long been adopted for the purposes of achieving weight loss and are becoming increasingly popular among people with diabetes to manage glucose control (75). A low carbohydrate diet is thought to promote weight loss by avoiding hyperinsulinemia, and in turn reducing lipogenesis and curtailing hunger by increasing glucose availability (76). Although effective, studies have shown low carbohydrate diets to increase LDL cholesterol (77), and low-fat diets to be equally efficacious at achieving weight loss (78). In T2DM populations, studies have shown both low carbohydrate and low fat diets to successfully achieve sustained weight loss and HbA1c reduction, with low carbohydrate diets achieving better glucose variability (79–81). Beyond the metabolic benefits associated with weight loss, the concept is largely based on reducing post prandial excursions but also reducing required insulin doses and in turn minimising the error associated with insulin carbohydrate mismatch. The evidence base exploring the use of low carbohydrate diet in managing T1DM is varied in their outcomes and definitions of what constitutes a low carbohydrate diet. A restricted diet of 75g daily carbohydrate for a duration of 12-weeks yielded a significant reduction in HbA1c and daily insulin requirement, with no effect on glucose variation compared to an unrestricted diet of 203 +/-92g daily carbohydrate (82). A more aggressive restriction of daily carbohydrate below 55g, demonstrated a reduction in glucose variability, however at the expense of dyslipidaemia and increased hypoglycaemia (83). In children, the application of low carbohydrate diet has been linked to growth deficits, fatigue, and increased metabolic risk (84). One of the biggest concerns surrounding low carbohydrate diet is the potential of physiological ketosis precipitating DKA, particularly among people with T1DM, ketosis prone T2DM, and sodium-glucose co-transporter-2 inhibitors (85,86). The

associated risk is enhanced by the fact there is no consensus threshold for restricting carbohydrate or acceptable level of physiological ketosis.

1.3.2. Non-carbohydrate macronutrients

The literature largely agrees that dietary fat causes a delayed and slower rise in post prandial glycaemia with a curtailed peak. A head to head study comparing a carbohydrate/protein matched high fat (60g) meal against a low-fat (10g) meal in people with T1DM demonstrated significantly higher post prandial hyperglycaemia lasting beyond 5 hours despite additional insulin requirements in the high fat meal group (87). However, the comparatively greater caloric content in the high fat meal needs to be considered when drawing conclusions from this data. The blunted increment in post prandial glycaemia associated with dietary fat has been attributed to suspected delayed gastric emptying (88–90). Using the paracetamol absorption method, significantly lower areas under the curve have been reported for plasma glucose and paracetamol in the first 2-hours following a high-fat meal (38g of fat) compared to a low-fat meal (2g) (88). Delayed gastric emptying and slower postprandial glucose increments appear to be dependent on lipolysis of triglycerides to free fatty acids and is more pronounced when fats are ingested in isolation 30 minutes before a carbohydrate load (89). This interval would allow time for fatty acid production and stimulation of small intestinal feedback mechanisms. The role of free fatty acids has been investigated in euglycaemic hyperinsulinaemic clamp conditions where high plasma levels were shown to significantly reduce glucose uptake after 3.5 hours, with a 46% reduction compared to the controls at 6 hours (91). Like dietary fat, protein appears to have a delayed effect on raising post prandial glycaemia in T1DM. In comparison to a low protein/low fat breakfast, greater glucose excursions were measured 180 minutes following a high protein/low fat breakfast, 210 minutes following a high fat/low protein breakfast, and between 180-300 mins following a combined high fat/high protein breakfast (92).

1.3.3. Physical activity

Diabetes and obesity are established metabolic risk factors associated with cardiovascular disease and insulin resistance. Exercise has been proven to improve insulin sensitivity, blood pressure, lipid biochemistry, mental, and cardiovascular health (93–95). To modify these risk factors, healthcare professionals and specialist guidelines strongly encourage physical activity as a form of lifestyle modification to all people with diabetes (14,96). The UK National Institute for Health and Care Excellence (NICE) advocate 30 minutes of moderate physical activity on 5 or more days a week (14). However, a survey of one hundred adults with T1DM identified fear of hypoglycaemia as the biggest barrier to undertaking exercise (97). Consuming unwanted calories for the purposes of treating hypoglycaemia can leave individuals with a sense of futility in their endeavours to achieve weight loss through exercise.

Muscle glycogen is the predominant energy source during the initial phase of exercise, whereas blood glucose taken up by skeletal muscle contributes up to 40% of oxidative metabolism. In normal physiology, intact counterregulatory responses prevent hypoglycaemia during states of increased glucose activity such as exercise. Nonetheless, moderately intense and prolonged exercise can result in depletion of hepatic glycogen stores and account for cases of hypoglycaemia following 90 minutes of exercise in healthy subjects (98). Iatrogenic insulin excess and impaired counterregulatory responses make individuals with T1DM more susceptible to hypoglycaemia during and up to several hours after exercise (99)(100).

Blunted sympathoadrenal responses to hypoglycaemia <3mmol/L (55mg/dL) in the period immediately after moderately intense exercise have been described in subjects with and without diabetes (98,99,101). However, studies have also demonstrated diminished glucagon and adrenaline counterregulatory responses one day after exercise in healthy subjects that developed

hypoglycaemia during intense exercise compared to those administered 20% dextrose to maintain euglycaemia (102). This suggests a long-lasting association between hypoglycaemia and impaired counterregulatory responses that is independent of duration and exercise intensity.

The intensity of physical activity has been shown to elicit distinctly different physiological responses. The percentage of maximal oxygen uptake (VO_2 max) or maximum heart rate (HRmax), are traditional methods used to describe relative exercise intensity (103). The anaerobic threshold is the level of exercise intensity (VO_2 max) at which lactate begins to accumulate in the circulation. VO_2 max can range between 60% in an untrained individual up to 90% in a high-performance athlete. Low to moderate intensity exercise is predominantly aerobic and can result in hypoglycaemia when glucose utilisation exceeds production. However, glycaemic regulation in high intensity activity is significantly influenced by an increase in sympathoadrenal activity. This surge in plasma catecholamines can result in hyperglycaemia due to an 8-fold increase in glucose production outstripping the rate of muscle glucose utilization (104,105). Hyperglycaemia during intense exercise is also potentiated by suppressed glucose stimulation of insulin via alpha adrenergic receptors (106). Once exhausted and intense exercise stops, plasma catecholamines quickly decline permitting insulin levels to rise and replenish depleted muscle glycogen (105,107). These gluco-productive catecholamine responses have been shown to be dominant and persist despite insulin infusion during alpha blockade or pre-exercise hyperinsulinaemia from a meal or glucose infusion (108). As a form of exercise, resistance training has been shown to exert a greater sympathoadrenal response independent of VO_2 max. Yardley et al, showed hypoglycaemia induced by anaerobic weight training to be less profound initially but mores sustained compared to aerobic running at 60% VO_2max (109).

In addition to considering how intensity and type of exercise may impact glucose control, individuals taking insulin therapy must appropriately time their treatment and meals to prevent hypoglycaemia.

Providing safe risk prevention advice for people with T1DM is equally challenging given the range of implicating factors and variability of glucose responses between and within individuals (110). Individuals with T1DM are advised to have a carbohydrate snack at hand and check blood glucose levels prior to exercise. Fasted resistance-training in the absence of bolus insulin can result in a smaller decline in blood glucose or a possible counter-regulatory increase (111). The duration of aerobic exercise following a meal and bolus insulin administration has been shown to correlate with blood glucose reductions (112–114). As a result, individuals on bolus insulin regimes are often advised to reduce or omit bolus doses if anticipating exercising soon after meals. This has not only been shown to reduce hypoglycaemia during and for 24-hours following exercise (115), but may reduce or eliminate the need for consuming unwanted snacks.

Exercise related hypoglycaemia can present many hours after physical activity with reported events up to 48 hours later. Delayed onset hypoglycaemia carries the risk of overnight hypoglycaemia, a complication so worrying for people with diabetes they often compromise their glucose control as a preventative measure. In such instances, reductions in basal insulin have been shown to mitigate risk (115,116).

1.3.4. Temperature

Seasonal temperature variations and travel to heterogenous climates are obstacles endured by a mobile diabetes population. The skin is the largest human organ and autonomic control of cutaneous blood flow is critical in redistributing blood flow and maintaining normal thermoregulation. Exposure to heat is associated with cutaneous vasodilation, increased peripheral blood flow, and increased heat loss. Whereas vasoconstriction and redistribution of blood towards the core help conserve heat during cold exposure. Hyperglycaemia has been shown to directly impact thermoregulation by blunting the capacity to dissipate heart, particularly during thermogenic

states such as exercise (117,118). The ability to respond to temperature change and effectively redistribute blood flow could be further limited by a compromised cardiovascular system as seen in many individuals with diabetes. This can result in reduced sweat output and 54% less heat loss during exercise in people with diabetes compared to size matched controls (119–121). The implications of heat stress have seen case reports of increased hospital admissions and death among individuals with diabetes (122).

Impaired thermoregulation in diabetes has implications on glucose control with hot ambient temperatures increasing insulin absorption alongside synergistic effects with physical activity to bring about significantly lower blood glucose levels (123). The effect on insulin pharmacology is demonstrated by lower post prandial glucose excursions following insulin administration to locally warmed sites (124). Studies in large diabetes populations have observed seasonal variation in glucose control (HbA1c) with peak glucose measurements seen during the colder winter months and troughs levels observed in the summer (125–128). A crossover study of nine individuals with T1DM identified significantly lower post prandial glycaemia and up to five times greater insulin absorption rates in higher ambient temperatures 30°C vs 10°C (123). Similarly, a Greek seasonal study observed lower mean fasting glucose measurements during the warm summer months (128). These uncontrollable changes in glycaemic control can make self-management and predicting the effect of insulin dosing difficult for individuals. Nordfeldt et al, identified seasonal variation in glycaemia resulted in more insulin dose adjustments and in turn increased hypoglycaemia risk (129). Potential confounders influencing the seasonal association include winter illnesses, holiday behavioural patterns, and seasonal dietary habits. Interestingly, a study investigating equatorial regions with minimal temperature variation identified little change in glycaemic control (130), further emphasising the direct influence of ambient temperature.

I investigated the seasonal association with glycaemic control by retrospectively analysing six-hundred capillary glucose measurements selected at random from the first week of every month between November 2013 and October 2017 (n=28800). All capillary measurements were undertaken by trained users across inpatient areas in a single Imperial College Healthcare NHS Trust site using the Abbott Precision Xceed pro point-of-care device.

Significant variation in median capillary glucose measurements across the 12 calendar months was observed using Kruskall-Wallis non-parametric hypothesis testing, p<0.01. However, measured trough glucose levels (7.6mmol/L) in all four seasons suggests a finding of clinical insignificance. Data from the UK national weather service confirmed the hottest and coldest seasons during the study period were summer (June to August) and Winter (December to February) respectively. Comparing glucose measurements during these two seasons revealed a small, however significant difference, with a median glucose mmol/L (IQR) of 7.8 (5.8-10.8) during summer and 8.1 (5.9-11.4) in winter, p<0.01 (Table 1.1). Difference in median glucose was also observed comparing the hottest (July) and coldest (January) calendar months, 7.6 (5.7-10.6) vs 8.3 (6.1-11.5), p<0.01. However, seasonal change appeared to have the greatest impact on frequency of severe dysglycaemia in hospital (hypoglycaemia <3.0mmol/L and severe hyperglycaemia >27mmol/L). The winter saw a significantly higher incidence of severe dysglycaemia (1.4%) compared with summer (0.8%) and the rest of the year (0.8%), p<0.01. Additionally, more than a third of all severe dysglycaemia was measured during the winter (n=99) (Table 1.1 and Figure 1.1). This observational study suggests the seasonal effect on glycaemic control has reaching effects within controlled hospital environments, with higher blood glucose measurements and a higher frequency of severe dysglycaemia during the winter months. This may reflect resource pressures during the winter and is worth considering when supporting inpatients with diabetes.

	January (n=2400)	July (n=2400)	P	Winter (n=7200)	Summer (n=7200)	p	Rest of year (n=21600)	p
Median Glucose (IQR)	8.3 (6.1-11.5)	7.6 (5.7-10.6)	<0.01	8.1 (5.9-11.4)	7.8 (5.8-10.8)	<0.01	7.7 (5.8-10.7)	<0.01
Hypoglycaemia <3.9mmol/L (n)	2.6% (62)	3.1% (74)	0.30	2.3% (164)	2.3% (163)	0.97	2.3 % (493)	0.85
Hypoglycaemia <3.0mmol/L (n)	1.1% (26)	0.4% (10)	0.01	0.8% (58)	0.5% (35)	0.02	0.5% (108)	<0.01
Hyperglycaemia >27mmol/L (n)	0.5 (12)	0.4% (9)	0.51	0.6% (41)	0.3% (23)	0.02	0.3% (71)	<0.01
<3.0 & >27 (n)	1.6% (38)	0.8% (19)	0.01	1.4% (99)	0.8% (61)	<0.01	0.8% (179)	<0.01

Table 1.1. Median (IQR) glucose, frequency of hypoglycaemia <3.9mmol/L, <3.0mmol/L and severe hyperglycaemia >27mmol/L. Results are expressed as median (IQR) and % (n). Statistically significant (p<0.05) differences between January and July, Winter and Summer, lastly Winter and the rest of the year measured by Kruskall-Wallis hypothesis test.
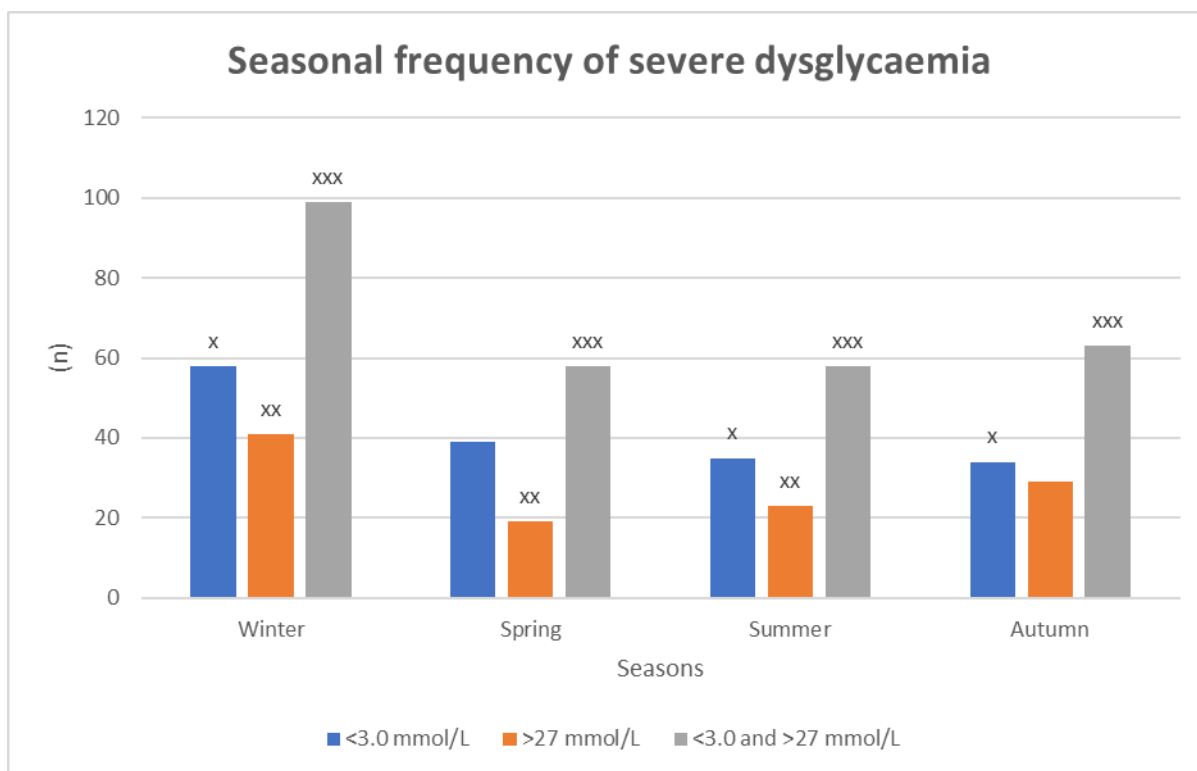
Figure 1.1. Illustrating the seasonal frequency of severe dysglycaemia. Statistically significant difference (p<0.05) in hypoglycamia <3.0mmol/L, severe hyperglycaemia >27mmo/L, and both are represented by x, xx, and xxx respectively.

1.3.5. Time (Circadian rhythm)

Hormone secretion, energy balance, and other metabolic processes all display a temporal pattern of activity and have an impact on glucose homeostasis. The circadian rhythm is responsible for synchronizing 24-hour behaviour and physiology with environmental light cycles. It is controlled centrally by the hypothalamic suprachiasmatic nuclei (SCN) and by circadian oscillators in peripheral tissues such as the pancreas (131). Animal studies comparing targeted bilateral SCN ablated mice with placebo operated counterparts revealed no statistical difference in hyperinsulinaemic glucose disposal. SCN lesioned mice however fail to suppress hepatic glucose production by a factor of 77% in comparison to the placebo controls, suggesting the circadian pacemaker has a role in hepatic

insulin sensitivity (64). Animal knock out models for the CLOCK and BMAL1 genes responsible for establishing a synchronized 24-hour circadian rhythm result in hyperglycaemia, hypoinsulinaemia, and impaired glucose stimulated insulin secretion (132). Similar findings were identified in pancreas specific BMAL1 mutation mice (133). In a randomised cross over study, Morris et al, compared the effects of the endogenous circadian system against circadian misalignment on post prandial glucose and insulin release in healthy participants after identical mixed meals (65). In a normal circadian cycle, post prandial glucose levels were significantly higher by 6.5% at 8pm compared to 8am (p<0.05), with an 18% reduction in early and late phase insulin responses (p<0.01) (65). However, circadian misalignment significantly increased post prandial glucose levels by 5.6% despite a 10% increase in late-phase postprandial insulin (p<0.05). This suggests an evening decline in pancreatic beta cell function and insulin resistance during endogenous circadian rhythm misalignment (65).

The dawn phenomenon is a well-established cause of temporal glucose variation resulting in early morning hyperglycaemia experienced in a large subset of the population without diabetes (134–137). It is understood to be the result of increased hepatic glucose output mediated by overnight circadian release of insulin counter regulatory hormones including, cortisol, glucagon, growth hormone and adrenaline. Healthy individuals without diabetes are protected from the dawn phenomenon by a morning insulin rise restraining hepatic glucose production and hyperglycaemia (135,138). The effect in early studies appears to be exaggerated by overnight decline in plasma insulin levels associated with use of shorter profile NPH insulin and overnight heat induced insulin aggregation with CSII.

1.3.6. Menstrual cycle

Blood glucose variability during the menstrual cycle is well documented. In a cohort of insulin-treated women (n=406), 67% reported peri-menstrual changes in plasma glucose or glycosuria (139).

Similarly, 61% percent from a survey of 124 women with T1DM demonstrated peri-menstrual blood glucose variability and frequent hyperglycaemia around the time of menses, with one-third requiring reactive insulin dose adjustments (140). The mechanisms behind glucose variability remain uncertain, however increased glycaemia in the luteal phase is the most commonly reported pattern with studies linking this to a cyclical rise in insulin resistance (141–144).

Utilising real-time continuous glucose monitoring (RT-CGM) in women with T1DM, lower rates of hypoglycaemia and increased hyperglycaemia have been observed in the luteal compared to follicular phase (142). Similarly, blood glucose measurements following a two-hour oral glucose tolerance test were found to be significantly higher during the luteal phase in healthy, normal body mass index (BMI) women without diabetes, suggesting metabolic changes during the menstrual cycle exist in normal physiology (145). Another CGM study monitoring blood glucose across three menstrual cycles found luteal phase hyperglycaemia in 50%, with reproducible glycaemic profiles between ovulatory menstrual cycles in all participants (n=4) (146). The phrase 'catamenial DKA' or 'catamenial hyperglycaemia' has been used to describe an increase in the incidence of DKA during the late luteal phase and menstruation itself; while 'the menstrual cycle phenomenon' highlights fluctuations in blood glucose during the menstrual cycle (147,148). Similar to the 'dawn phenomenon', both are well recognized in people with T1DM, but not universally reported (149). In an 18-year retrospective review of acidosis admissions among women with diabetes, excluding intercurrent infection and non-treatment of diabetes, 47% were menstruating at the onset of acidosis (150). These findings suggest a population of women with T1DM experience cyclical challenges with glucose management, especially during the late luteal phase. However, interpretation is limited by small participant numbers and short study durations.

1.3.7. Pregnancy

Normal pregnancy induces a metabolic state prioritising provision of energy to the growing fetus characterised by impaired insulin sensitivity and compensatory increased beta cell mass and insulin secretion (151,152). Decreased insulin sensitivity preserves carbohydrates and free fatty acids by reducing insulin mediated cellular glucose uptake, lipolysis, and fat oxidation(151,153). However, hyperglycaemia and gestational diabetes (GDM) ensue when compensatory insulin secretion is insufficient. GDM is a diagnosis of diabetes made during pregnancy in women without pre-existing diabetes and is largely driven by the physiological adaptations described above(154). Pregnant women with pre-existing diabetes experience similar physiological change, however adaptive beta cell recruitment is limited and almost non-existent in women with T2DM and T1DM respectively. Unlike women with pre-existing diabetes, GDM often resolves after delivery (154).

Diabetes during pregnancy and fetal exposure to hyperglycaemia is associated with significant complications including, pre-eclampsia, caesarean section, preterm delivery, large for gestational age, congenital anomaly, and stillbirth (155–157). Evidence indicates early detection and intervention in GDM and optimising glycaemic control before and after pregnancy in existing diabetes reduces both pregnancy and serious perinatal complications (158,159). Accordingly, NICE recommends tight glycaemic control targets during pregnancy for both GDM and pre-existing diabetes. Pre-conception counselling and optimal glucose control is advised for women with pre-existing diabetes with both RT-CGM and flash glucose monitoring provision during pregnancy for women with T1DM (14).

1.3.8. Conclusion

Most people with diabetes rely on interval capillary glucose monitoring to navigate meals and common activities of daily living. However, the combination of individual and external factors influencing glucose homeostasis make glucose control a daily challenge for this population. A greater understanding of elements affecting glycaemia is necessary to improve education and management strategies (particularly insulin dosing) available to individuals with diabetes. Such application could see improvements in maintaining time in spent in euglycaemia, but furthermore help mitigate incidents of hypoglycaemia. The multivariable complexities of glycaemic control highlight the difficulty experienced by vulnerable individuals and the importance of providing easy and accessible means of glucose monitoring.

1.4.   Diabetes complications

Diabetes related complications can present acutely due to extremes in glycaemia (hypo- and hyperglycaemia), acidosis related to insulin deficiency, or develop chronically because of prolonged exposure to hyperglycaemia.

1.4.1. Diabetic Ketoacidosis (DKA)

The inability to utilise glucose and subsequent depletion of glycogen stores in the insulin deficient state is responsible for fatty acid breakdown and acidic ketone body formation. The resultant diabetic ketoacidosis (DKA) can progress to vomiting, organ failure, seizures, coma, and death. Diabetic ketoacidosis is a medical emergency with individuals requiring hospital admission, aggressive intravenous fluid resuscitation, and intravenous insulin administration until blood ketones are successfully cleared and food can be maintained orally. It is often a presenting feature in

undiagnosed or individuals with T1DM administering insufficient insulin, with an estimated prevalence of 50 to 100 cases per 1000 patient years in adults (160).

1.4.2. Hyperosmolar Hyperglycaemic State (HHS)

In T2DM, severe hyperglycaemia can exist in the presence of sufficient endogenous insulin to prevent ketogenesis. The presence of significantly large amounts of osmotically active glucose is termed a hyperosmolar hyperglycaemic state (HHS), which left untreated over days can cause severe dehydration, weakness, altered consciousness, and thrombosis. Emergency treatment involves intravenous fluid resuscitation and judicious hyperglycaemia correction to avoid rapid changes in osmotic pressure and intracranial fluid shifts. HHS is more commonly seen in older people with diabetes and mortality rates have been reported to be as high as 5-20% (161).

1.4.3. Hypoglycaemia

A mismatch in bioactive insulin and blood glucose levels is oversimplified and tells an incomplete story of the mechanisms governing hypoglycaemia in people with insulin and insulin-secretagogue treated diabetes. As discussed in chapter 1.2.1, there is a hierarchy of counter regulatory responses and symptoms that are triggered as plasma glucose declines below defined thresholds in normal physiology. Inhibition of beta cell insulin secretion, which in turn stimulates counterregulatory alpha cell glucagon secretion and hepatic glucose output, is the first counterregulatory defence against hypoglycaemia. Using the secretagogue tolbutamide and insulin clamp techniques, Banarer et al, demonstrated intraislet hyperinsulinaemia significantly inhibited the counterregulatory glucagon response to hypoglycaemia despite alpha cell hypoglycaemia and an intact autonomic response (162). Similarly, suppressing the decrement of intraislet insulin following hypoglycaemia using diazoxide clamps produced a reciprocal reduction in glucagon secretion, further demonstrating the dominant role of insulin on glucagon regulation (163). The ability to appropriately suppress bioactive

insulin and stimulate glucagon in response to hypoglycaemia is impaired in people with beta cell failure dependent on insulin (T1DM or long-standing T2DM) or individuals on insulin secretagogues (163,164). Fukuda et al, showed a significant correlation between loss of endogenous insulin secretory capacity and a non-responsive glucagon response to hypoglycaemia (165). Cooperberg et al, further highlighted the importance of insulin mediated alpha cell regulation by demonstrating a decline and rise in exogenous insulin during hypoglycaemia reciprocally stimulated and suppressed glucagon levels respectively in individuals with T1DM (21). Intrinsic pancreatic alpha cell dysfunction and failure to mount an appropriate glucagon response to hypoglycaemia is well documented in T1DM (166,167) and long standing T2DM (168). Gerich et al, observed no glucagon rise in six individuals with T1DM following severe insulin induced hypoglycaemia despite normal responses following arginine infusion, suggesting impaired alpha cell glucose sensing in insulin dependent diabetes. Similarly, exposure to equivalent levels of hypoglycaemia has been shown to produce an 85% lower glucagon response in people with T1DM compared to non-diabetic controls (167). The same study diminished the possibility of impaired alpha cell catecholamine sensitivity as a contributing factor and showed enhanced sensitivity in T1DM by observing a three-fold higher glucagon response following an adrenaline infusion compared to controls. The inability to decrement insulin and appropriately increment glucagon renders this group vulnerable to repeated episodes of hypoglycaemia and highlights the interplay of pathological factors beyond solely exogenous insulin or secretagogue overestimation.

Glycaemic thresholds triggering couterregulatory responses are not fixed in people diabetes and shift to higher glucose concentrations in people exposed to sustained hyperglycaemia (poorly controlled diabetes) (54,169) and to lower glucose concentrations in people exposed to recurrent hypoglycaemia (intensely treated diabetes) (164,170,171). Lowering of the glycaemic threshold required to generate hormonal counterregulatory responses to hypoglycaemia creates a vicious

cycle where perception of autonomic symptoms may become diminished and in turn increase exposure to recurrent hypoglycaemia. The awareness of hypoglycaemia symptoms serves as a physiological warning to intervene by sourcing available carbohydrates. However, repeated exposure to hypoglycaemia blunts the sympathetic and the neuroendocrine counterregulatory response to hypoglycaemia (164,171). This is often termed as 'hypoglycaemia associated autonomic failure in diabetes' HAAF and is associated with a 25 times higher risk of iatrogenic hypoglycaemia during intensification of therapy and ultimately impairs awareness of hypoglycaemia (IAH) which is discussed further in chapter 1.4.4 (172,173). This supports outcomes established in the Diabetes Control and Complications Trial (DCCT) showing increased hypoglycaemia risk when endeavours are made to mitigate vascular risk through intensified insulin therapy (174).

Notwithstanding advances in diabetes management, hypoglycaemia remains a common complication associated with insulin and groups of oral diabetes treatments. A Scottish population based prospective study estimated the overall incidence of hypoglycaemia in insulin treated T2DM to be a third of the incidence in T1DM (1.15 events per person year in T1DM vs 0.35 events per person year in T2DM) (175), however this did not include the large T2DM population on insulin secretagogues. A large multi-national study reported a weekly average of 1.8 self-managed hypoglycaemia events, and 0.2-3.2 yearly accounts of severe hypoglycaemia in people with T1DM and insulin-treated T2DM (176,177). Long-term follow up studies investigating all-cause mortality in childhood onset T1DM have attributed between 4% and 10% of deaths to hypoglycaemia (178,179). Implications of hypoglycaemia have been suggested to extend beyond all-cause mortality and increase both cardiovascular and non-cardiovascular mortality in T2DM (180). Severe hypoglycaemia has been linked with an increased 5-year mortality when adjusted for age, sex, duration of diabetes, and comorbidity (181). A large adult study observed a 3.4 fold mortality increase among individuals who self-reported severe hypoglycaemia compared to those with mild or no hypoglycaemia (182).

Severe hypoglycaemia is a medical emergency where individuals are dependent on treatment from a third party and presents a significant burden for the national health service with the annual financial cost exceeding £13 million (183). On average each hospital admission due to hypoglycaemia costs over £1000 (184,185), with hypoglycaemia experienced as an inpatient significantly increasing the duration of stay, cost per admission, and mortality risk (183). These data may underestimate the health economic impact of hypoglycaemia when considering the additional comorbidities associated with hypoglycaemia such as coma, cardiovascular events, and fall related fractures (186–188).

In the hierarchy of responses to hypoglycaemia, cognitive impairment ensues when glucose concentrations fall below 2.9 to 2.7 mmol/L (37,38,189). Restoration of biochemical euglycaemia is achieved once glycaemic is restored above 4mmol/L. However, the cognitive impact of acute hypoglycaemia can persist beyond biochemical correction, particularly in individuals exposed to recurrent hypoglycaemia. Strachan et al, demonstrated general complete recovery from acute severe hypoglycaemia can take up to 1.5 days, with chronically elevated levels of depression, anxiety, and poor cognitive test outcomes (190). Long-term results from the DCCT did not report an association between frequency of severe hypoglycaemia or intensely treated individuals with cognitive decline (191). However, DCCT followed an unrepresentative population of young adults (mean age 27 years) with few episodes of hypoglycaemia for a short duration. A 22-year longitudinal cohort study of 16667 individuals with T2DM (mean age 65 years) and no history of cognitive impairment or dementia, observed an adjusted dementia risk of 2.39% per year (95% CI, 1.72%, 3.01%) between individuals with and without a history of severe hypoglycaemia (192). Dementia risk significantly rose with frequency of severe hypoglycaemia and number of hypoglycaemia related emergency admissions. Similar findings were observed in the Study of Longevity in Diabetes (SOLID) where recent severe hypoglycaemia in older adults with T1DM was associated with impaired global cognition (OR 3.22, [95% CI 1.30, 7.94]) and impaired language domain cognition (OR 3.15, [95% CI

1.19, 8.29]) (193). An earlier study in adults with T1DM observed an association between the frequency of severe hypoglycaemia and the magnitude of decline in IQ, particularly performance IQ, inspection time, and reaction time (194).

Long-term exposure to hyperglycaemia is a well-established risk factor for micro- and macrovascular complications, with the large UKPDS randomised control trial showing intensive glucose control reduced microvascular complications in newly diagnosed T2DM with, see chapter 1.4.5. The three randomised control trials investigating intense glycaemic control in people with established T2DM and increased cardiovascular risk failed to demonstrate significant reductions in cardiovascular events or mortality. Moreover, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial observed increased mortality (195), and although partly due to confounding, all three studies showed a significant association between severe hypoglycaemia and mortality, either during or distal to the hypoglycaemia episode (195–197). In the setting of pre-existing cardiovascular disease, the catecholamine counterregulatory response creates an unfavourable milieu of tachycardia, increased myocardial contractility, hypotension, and hypokalaemia. Repeated exposure to such cardiovascular stress may provoke an acute coronary syndrome or pathological arrythmia (198–200).

Both severe hypoglycaemia and IAH are often underreported by individuals due to potential negative implications on their ability to drive and gain/maintain employment within desired fields. In the UK, all individuals on insulin planned to continue beyond 3 months or experience disabling hypoglycaemia are advised to report their condition to the Driver and Vehicle Licensing Agency (DVLA) (201). The visceral fear of hypoglycaemia can encourage avoidance behaviour and a conscious decision to compromise treatment in favour of hyperglycaemia. Unfortunately, fear of the physical and socially distressing experience of hypoglycaemia are commonly reported limiting factors in achieving optimal glucose control in both T1DM and T2DM (202).

In a joint position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), the International Hypoglycaemia Study Group (IHSG) defined glucose concentrations below 3.0mmol/L as clinically significant and recommended its use in clinical trials (203). Glucose levels below 3.0 mmol/L represent the threshold for normal autonomic hypoglycaemia symptoms (38,54) and contribute to defective counterregulatory responses and IAH (204). The group went on to categorise hypoglycaemia in three levels and proposed its adoption by the wider diabetes community. Level 1 is defined as a glucose concentration between 3.0-3.9 mmol/L. Level 2 (clinically significant) denotes glucose concentrations below 3.0 mmol/L, while level 3 represents hypoglycaemia requiring third party assistance or associated with seizure/coma (203).

1.4.4. Impaired awareness of hypoglycaemia (IAH)

The autonomic symptoms triggered by the neuroendocrine response to hypoglycaemia prompting a behavioural response to (ingestion of carbohydrates) overcome hypoglycaemia (205,206). Impaired awareness of hypoglycaemia describes a failure to recognize these warning symptoms largely due to defective sympathetic glucose counter regulation. As discussed in chapter 1.4.3, beta cell failure is primarily responsible for the impaired counter regulatory response observed in T1DM and long-standing T2DM. However, impaired hypoglycaemia counterregulation, HAAF, and IAH develop earlier in T1DM due to the faster rate of beta cell decline in comparison with T2DM. Awareness of hypoglycaemia can be diminished to the extent where individuals are at risk of neuroglycopenia, unheralded seizures, coma, and death due to precariously low blood glucose levels. A large 2-year prospective analysis of adults with T1DM estimated the prevalence of IAH to be 20%, with a greater propensity in older individuals with a longer history of diabetes (207). Participants with IAH

experienced severe hypoglycaemia 6-times more frequently in the second year (207), while an estimated 17-fold risk of severe hypoglycaemia has been reported in T2DM with IAH (208).

Heller et al, highlighted the influence of the sympathetic nervous system on hypoglycaemic warning symptoms by identifying diminished adrenaline responses and reduced symptoms in 11 out of 15 people with diabetes exposed to blood glucose levels of 2.5mmol/L (209). A more recent cohort study comparing neuroendocrine responses in adults with T1DM exposed to hyperinsulinaemic clamp induced hypoglycaemia, observed a significantly lower adrenaline rise in the IAH group compared to controls with intact awareness, (1.2 ± 0.9 vs. 0.4 ± 0.4 nmol/L, P = 0.003) (210). Both groups were matched for age, duration of diabetes, BMI, and HbA1c. Participants with IAH also reported lower autonomic and neuroglycopenic visual analogue scores (210). The concept of dynamic counterregulatory glycaemic thresholds determined by previous glucose exposure supports observations of a lower glycaemic threshold in IAH, and the perception of delayed onset symptoms handicapped by the development of neuroglycopenia and altered cerebral function (211). Grimaldi et al, observed an adrenaline response at a lower glycaemic threshold of 3.1 to 1.6 mmol/L in diabetes with IAH compared to diabetes with intact awareness 4.6 to 3.2 mmol/L (212). Studies have also associated a lower HbA1c as a measure of better glycaemic control with a lower adrenaline response threshold and IAH (209,213,214). This subscribes to earlier described DCCT findings linking intensification of therapy with increased hypoglycaemia and highlights the inherent challenge faced when aspiring to optimise glycaemic control (174).

Early beliefs classifying IAH within the syndrome of diabetic autonomic neuropathy have been challenged by the observation of normal responses among individuals with established autonomic neuropathy and defective symptomatic responses in people without neuropathy (215). Ryder et al, subsequently reaffirmed no causal association between subjective IAH and autonomic neuropathy,

albeit without plasma adrenaline measurements (216). Similar findings were observed in a qualitative questionnaire based study where individuals with a history of IAH reported a higher incidence of severe hypoglycaemia and failed to demonstrate clinical evidence of cardiac autonomic dysfunction (217). Thus, followed the notion that hypoglycaemia begets hypoglycaemia and individuals with IAH can get caught in a spiral of further hypoglycaemia, and in turn worsening awareness (164,171,218–220). Heller et al, demonstrated the impact a single episode of daytime hypoglycaemia had on diminishing hormonal, autonomic, and neuroglycopenic symptoms when exposed to subsequent hypoglycaemia the following morning in healthy participants (221). Dagogo-Jack et al, repeated a similar study in subjects with insulin dependent diabetes without autonomic neuropathy (164). In this instance, exposure to afternoon hypoglycaemia not only lowered the glycaemic threshold triggering autonomic responses, but also reduced the adrenaline response to hypoglycaemia the following morning.

Adaptive cerebral responses to repeated sustained hypoglycaemia have been observed in humans with and without diabetes, with evidence of diminished autonomic symptoms but improved cognitive function (222,223). This suggests that unlike the glucose counterregulatory responses, low plasma glucose levels do not impact the glycaemic threshold for cognitive impairment and highlights the heterogenous effect hypoglycaemia has on the brain. Utilising functional MRI, Nwokolo et al identified reduced regional cerebral blood flow responses within the thalamus, right lateral orbitofrontal cortex, right dorsolateral prefrontal cortex, and the left hippocampus following insulin induced hypoglycaemia in subjects with IAH (210). Reduced perfusion to established faculties associated with arousal, decision-making, and reward processes poses the question whether individuals with IAH are limited at reasoning and responding to awareness restoration methods (210).

Sustained efforts to avoid hypoglycaemia have been proven to restore awareness (189,224,225). After four months of hypoglycaemia avoidance, Cranston et al observed a significant increase in hormonal and symptom responses to hypoglycaemia above the threshold responsible for a decline in cognitive function in individuals with long-standing insulin dependent diabetes (224). Dagogo-Jack et al, also demonstrated restoration of autonomic symptoms after 3 months of scrupulous hypoglycaemia avoidance with no associated increase in neuroendocrine counterregulatory hormone responses in subjects with insulin dependent diabetes (225), thereby dissociating restoration of autonomic symptoms with the counterregulatory neuroendocrine response. Successfully implementing avoidance of hypoglycaemia is extremely difficult to practice, especially when understanding the mechanisms underpinning IAH. Furthermore, success is likely to favour individuals with the mental and physical capacity to self-manage their diabetes, and not vulnerable individuals at greater risk of hypoglycaemia. Having confirmed regional cerebral blood flow impairment associated with IAH, Nwokolo et al observed improved perfusion when awareness is restored. However, changes in the thalamic and orbitofrontal cortical areas associated with arousal and emotional processing were refractory, and could account for individuals that fail to regain awareness despite optimal intervention (226).

In the UK, people with diabetes frequently undergo hypoglycaemia unawareness risk assessment which helps healthcare providers set individual glucose targets and can influence what treatment options are available (14). The Clark and Gold questionnaires are validated scoring systems proposed by the UK NICE guidelines to assess IAH and stratify individuals according to risk (14,220,227). The Clark method consists of 8 questions outlining the individual's exposure to moderate and severe hypoglycaemia while determining the glycaemic threshold for autonomic symptoms (227). The Gold method challenges the individual to score their hypoglycaemia awareness from a scale of 1 to 7, with 1 representing "always being aware" and 7 representing "never being aware" (220). The

Pedersen-Bjergaard method asks individuals categorise their awareness of hypoglycaemia from a choice of always, usually, sometimes, or never. Any response other than always is considered IAH in this method (228). In 80 randomly selected adults with T1DM, Geddes et al compared the concordance between all three methods in determining the prevalence of IAH and their sensitivity in identifying afflicted people (229). Both the Clark and Gold methods produced a similar prevalence of IAH, 26% and 24% respectively, and was consistent with population study outcomes estimating a degree of impaired awareness in 25% of unselected adults with T1DM (207). IAH identified using the Clark and Gold methods was also associated with significantly lower autonomic symptom scores compared to individuals with normal awareness. The Pedersen-Bjergaard method overestimated the prevalence of IAH (62.5%) and provided a less sensitive outcome in discerning individuals with IAH. Similar results were identified in a Singaporean population study investigating 374 adults with T2DM on insulin therapy for more than 6 months. Again, the Pedersen-Bjergaard methodology overestimated IAH with a prevalence of 33.2% compared to 9.6% and 13.4% identified using the Clark and Gold methods respectively (230). The Gold and Pederson-Bjergaard methods benefit from being relatively easy to implement, although the latter overestimates IAH. Although more protracted, the Clark method offers a composite scoring system allowing more objective stratification for varying degrees of IAH.

Over 30-years have passed since the mechanisms governing glucose counterregulation and impaired awareness were described, and we have yet to devise a specific treatment to address this dilemma. Advances in analogue insulin, granular insulin delivery via insulin pump therapy, continuous glucose monitoring, and structured education programmes have all been devised as successful hypoglycaemia avoidance interventions (see chapter 1.5 and 1.7). However, they are not definitive treatments and do not eliminate hypoglycaemia risk.

1.4.5. Vascular disease

Maintaining glucose levels within a physiological target reduces the risk of macro- and microvascular complications associated with long term exposure to hyperglycaemia. Macrovascular diseases such as, ischaemic heart disease, cerebrovascular disease, and peripheral vascular disease are leading causes of mortality in the UK. People with diabetes are routinely monitored for early signs of microvascular disease affecting the retina, kidneys, and peripheral nervous system. Optimising glycaemic control by means of aggressive therapy, glucose monitoring, and modifying lifestyle risk factors such as exercise and diet form the cornerstone of vascular disease risk prevention.

Prolonged exposure to hyperglycaemia being linked to an increased risk of diabetes associated micro and macrovascular disease is well documented (196,231–233). Significant outcomes include a quarter of diabetes deaths being attributed to the four-fold increased risk of coronary heart disease and cardiovascular disease (234,235). The DCCT and the United Kingdom Prospective Diabetes Study (UKPDS) identified intensive glycaemic control to significantly reduce the risk of microvascular complications in both T1DM and T2DM (231,232). A legacy effect of intensive therapy was observed with reduced rates of microvascular disease persisting long beyond the duration of the trial despite HbA1c rebounding to levels measured in the control arm (236–239). Unfortunately, striving for tight glycaemic control is seldom without the compromise of increased hypoglycaemia risk. A curvilinear relationship exists between HbA1c and vascular risk, with the greatest risk reduction achieved when glycaemic control is successfully improved from hyper- to normoglycemia, with limited benefit to be gained from further glucose reduction (233,240). Many trials including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Veterans Affairs Diabetes Trial (VADT) have failed to identify significant cardiovascular risk reduction with intensive glucose control in T2DM and

advocate a pragmatic approach to glucose reduction given the increased risk of hypoglycaemia (196)(195).

1.5. Blood glucose monitoring

The primary objective in managing diabetes is to safely maintain blood glucose levels within the bounds of normal physiology. Devices for self-monitoring blood glucose levels are necessary for individuals on insulin therapy or oral agents capable of causing hypoglycaemia.

1.5.1. Self-Monitoring of Blood Glucose (SMBG)

Self – monitoring of blood glucose (SMBG) describes the use of enzyme electrode glucose meters to estimate blood glucose levels from a drop of capillary blood on a dry reagent strip. Frequent glucose monitoring has been shown to improve glycaemic control and becomes increasingly evident when non-testing individuals self-monitor glucose at least 3-4 times a day (241–244). NICE and the American Diabetes Association (ADA) encourage individuals on multiple daily insulin injections (MDI) to monitor blood glucose levels at least four times a day to achieve target glycaemic control (14,245). Unfortunately, compliance using conventional glucose meters is hampered by the inconvenience and pain associated with multiple daily finger prick tests (246). In T1DM, compliance rates as low as 40% have been reported, with up to one-third of individuals being unaware of the recommended SMBG guidelines (243,247). Time restrictions and forgetfulness have been cited as reasons for low SMBG compliance, particularly in younger, recently diagnosed, and individuals in full time employment (247). These findings highlight psychosocial barriers hindering SMBG compliance and remind us of the importance of structured education and appropriate psychological support to harness the full potential of glucose monitoring technology. Nonetheless, SMBG remains the most prevalent mode of glucose monitoring among individuals with diabetes.

1.5.2. Continuous Glucose Monitoring (CGM)

Continuous glucose monitoring devices (CGM) measure changes in interstitial fluid glucose using a subcutaneously sited sensor. An electrode producing currents directly proportionate to glucose levels is linked to an enzyme used to make blood glucose estimations, with a peak blood glucose to interstitial glucose sensor lag of up to 15 minutes (248). RT-CGM conveniently provides instant access to real-time glucose levels, the trajectory of glucose levels, the rate of change of glycaemia, and a visual indication of time spent in a target glycaemic range. Many CGM systems use Bluetooth technology to transmit glucose measurements to a familiar and universally adopted device such as the smartphone. This not only allows for immediate access to glucose data but helps in overcoming potential operational barriers and stigma attached to using capillary glucose testing kits. Automated CGM measurements uploaded directly to the user's smartphone or proprietary receiver makes glucose monitoring intuitive and aids individuals that find SMBG difficult to remember. Current sensors have a lifespan beyond one week and do not require calibration with capillary glucose measurements, further reducing the burden of finger prick testing. Most CGM systems can inform users if glucose levels are rising, falling, or steady and in turn assist insulin dose decisions particularly when planning meals or physical activity. The mean absolute relative difference (MARD) is the most often used metric to measure the accuracy of a CGM device and is calculated using paired glucose measurements from a CGM device and a reference glucose measurement (usually a capillary blood glucose measurement) of participants in a clinical trial. The MARD is the average of the absolute difference between these values. Reported as a percentage, a value of 10% is considered as the accuracy threshold based on in silico studies (249).

As an investigative tool, CGM offers unprecedented insight into diurnal glucose patterns and allows the ability to examine circumstances surrounding glucose excursions and hypoglycaemia. The

glycaemic load estimates how much an ingested meal will increase blood glucose levels and is often significantly variable within and between individuals. Using CGM to individually characterise the glycaemic load of specific foods assists with accurate calculation of insulin carb ratios and appropriate timing of insulin dosing. Nocturnal blood glucose variation is a common occurrence best illustrated by the 'dawn phenomenon' (chapter 1.3.7) and occurs at a time when performing frequent SMBG is limited by sleep. Applying CGM overnight usefully illustrates this glycaemic pattern in individuals struggling with fasting hyperglycaemia and assists in compensatory basal insulin dose adjustments. Extended use of CGM ultimately facilitates the fine tuning of glycaemic control by informing lifestyle and therapeutic changes in response to real time and retrospectively identified behavioural trends. A feature that traditionally set CGM apart from other modes of glucose monitoring is the ability to alert users when glycaemia veers outside set parameters. This function has recently become available in the Abbot FreeStyle Libre 2 Flash glucose monitor and encourages timely intervention to avoid labile variation in blood glucose, and severe hypo- and hyperglycaemia. Alarm functions are of significant benefit to the vulnerable group of individuals with impaired hypoglycaemia awareness. Similarly, CGM can alert users of impending hypoglycaemia during exercise and aid appropriate insulin dosing before and after exercise.

Clinical application of CGM and evidence

At present CGM can be applied as a permanent adjunctive tool to facilitate daily glucose monitoring or as a short-term investigative tool to establish trends and optimise treatment. In the UK, long-term CGM provision is reserved for individuals with T1DM willing to adhere to device application for at least 70% of the time, commit to calibration when necessary, and struggle with any of the following; severe hypoglycaemia, complete hypoglycaemia unawareness, frequent asymptomatic hypoglycaemia, extreme fear of hypoglycaemia, and a HbA1c above 75mmol/mol (9%) despite 10 times daily finger prick testing (14).

The continuous application of RT-CGM has been shown to have the greatest impact in reducing HbA1c when compared against twice weekly CGM and five times daily SMBG (250). In addition to a significant reduction in HbA1c, the SWITCH study group observed a greater tendency for CGM users to deliver more frequent insulin boluses and a rebound rise in HbA1c once CGM was blinded (251). The Juvenile Diabetes Research Foundation (JDRF) multicentre trial compared multiple CGM devices against SMBG but also analysed the impact of age and CGM compliance on HbA1c outcomes (252). A significant HbA1c reduction and increased time spent in target range (4-10mmol/L) without associated increased hypoglycaemia risk (≤3.9mmol/L) was observed among participants older than 25 years. This group were also significantly more compliant than their younger counterparts, with 83% using CGM at least 6 times a week. Although the 8-14-year-old group did not see any significant HbA1c reduction associated with CGM, secondary indices of glucose control were improved, including a ≥10% relative reduction in HbA1c and more participants had a HbA1c <53mmol/mol (<7%). More recent randomised control trials have seen dedicated efforts to investigate CGM in participants with T1DM aged ≥60 years and in young adults and adolescents between 14-24 years. Comparing both trials the older population saw a greater a compliance rate with 83% using CGM ≥6 times a week compared to 68% in the adolescent and young adult group. Comparing adjusted differences between CGM and standard glucose testing controls after 6 months in both studies, similar significant differences were seen for HbA1c. However, the older adults saw greater adjusted differences in time within range (3.8-10mmo/L), time in hypoglyaemia (<3.9mmol/L and <3.0mmol/L), and frequency of hypoglycaemia, all suggesting improved CGM efficacy among the older population (253,254). These observations highlight the importance of an evidence-based selection policy to ensure clinical benefit from CGM. The DIAMOND and GOLD trials verified the beneficial effect of real time CGM in adult MDI users highlighting its impact independent of insulin pump therapy (255,256). The DIAMOND study demonstrated a 1% and 1.1% reduction in HbA1c

after 12- and 24-weeks use, respectively, with over 90% of participants using CGM at least 6 days a week. Both the JDRF and DIAMOND study demonstrated improved metrics of glucose variability with more time spent in target range, and less time in hypoglycaemia (252,256). Frequency of hypoglycaemia as an index of glucose control and diabetes risk has become increasingly relevant as a greater impetus towards lowering HbA1c has seen more individuals receive intensive insulin therapy. Individuals with a history of severe hypoglycaemia and hypoglycaemia unawareness are among a vulnerable subset and are likely to benefit most from the features offered by RT-CGM. IN CONTROL and HypoDE, both multicentre randomised control trials, successfully demonstrated a reduction in hypoglycaemia, severe hypoglycaemia, and impaired awareness when introducing real time CGM in such vulnerable participants (257,258).

Blood glucose levels above target before and during pregnancy are associated with an increased risk of complications including macrosomia and congenital malformation. A large multicentre randomised control trial showed the adjunctive use of real time CGM during pregnancy increased the time spent in target range, reduced glycaemic variability, and yielded a small HbA1c reduction at 34 weeks gestation compared to the use of SMBG alone (259). Furthermore, neonatal outcomes including large for gestational age, neonatal hypoglycaemia, neonatal intensive care admissions were all significantly reduced (259). Give the compelling benefits to both the mother and foetus, the use of RT-CGM in women with T1DM during pregnancy has been included in the UK national guidelines (14).

The benefits of CGM have been shown to extend beyond the metrics of glucose control. The long-term commitment to treatment and lifestyle modification in chronic disease can have a significant impact on an individual's quality of life. Applying thematic analysis to semi structured interviews has shown RT-CGM to enhance a sense of safety and control, while reducing stress among a majority of

individuals with T1DM at high risk of hypoglycaemia (260). However, some participants found CGM to be intrusive and frustrating, highlighting the subjectivity regarding what is considered a good quality of life (260).

Limitations of CGM

Although CGM use is becoming increasingly prevalent, there are existing factors that limit its uptake. Adopting new practices can be a daunting experience, and healthcare professionals have a responsibility in judiciously selecting and supporting a successful transition for individuals that would reap a clinical benefit from CGM. Forgetfulness is often cited as a reason for frequent SMBG non-compliance. However, sensor changes, pairing transmitters, performing steady state calibration, and analysing large glucose datasets may reinforce avoidant behaviour in CGM users. Furthermore, impaired manual dexterity, visual impairment, and overcoming the technological learning curve may hinder individuals with the best intentions of using CGM.

There remains a large disparity among healthcare professionals experienced in analysing CGM datasets, and there is no standard guidance or reference to assist in making treatment decisions based on CGM measurements. Studies have demonstrated significantly different proposed interventions from physicians presented with the same CGM datasets, highlighting the subjective approach to CGM interpretation (261). Clinical application of CGM is based on interstitial glucose being correlative with capillary blood glucose measurements. Although diffusion establishes glucose concentrations across capillary and interstitial spaces, calibration of CGM against corresponding steady state capillary glucose is advised to ensure accuracy. Unfortunately, MARD the commonly used measure of CGM accuracy is variable depending on glucose concentrations and rate of change, resulting in significant discrepancies when comparing data between trials. Sensor lag describes the delay in glucose diffusion across the capillary bed, into the interstitial space, and finally being

registered by the CGM sensor. Although current systems report a lag of only a few minutes, the cumulative effect of this delay can result in measurements drifting further apart from capillary glucose values. Alarms to notify when glucose levels veer outside of set targets are a fundamental component of CGM therapy and beyond certain measurements cannot be disabled. Higher thresholds for low glucose alarms help improve detection sensitivity, however also result in reduced specificity, more false positive alarms, and ultimately alarm fatigue (262).

1.5.3. Flash Glucose Monitoring

Flash glucose monitoring is a subset of CGM where interstitial fluid glucose levels are reported only after the user passes a proprietary reader or smartphone with pre-installed software over the subcutaneous sensor. Scanning the sensor displays the current glucose measurement, the last 8-hours of glucose data, and an arrow to represent the forecasted glucose trajectory. Flash sensors have a lifespan of 14 days and are factory calibrated overcoming the need to perform twice daily steady state capillary glucose calibration. Although this feature minimises finger prick testing it can potentially result in 'sensor drift' disparity towards the end of the sensor life cycle. Unlike CGM where glucose levels are continuously saved at 5-minute intervals, flash sensors store readings every 15-minutes and retrospective analysis is limited to the last 8-hours. Alarm notification of hypo- and hyperglycaemia is a significant CGM feature not present in flash glucose monitoring systems until recently. Prior to recent developments, users were required to scan the sensor when hypoglycaemia was suspected and potentially missed events, especially in cases of diminished hypoglycaemia awareness.

The IMPACT study showed flash glucose monitoring to significantly reduce the incidence, magnitude, and duration of time spent in hypoglycaemia (<70mg/dl, <3.9mmol/L) in well controlled adults with T1DM. Benefits of flash monitoring extended to improved metrics of glucose variability and higher

treatment satisfaction scores (263). In T2DM, flash glucose monitoring has been shown to significantly reduce hypoglycaemia (<70mg/dl, <3.9mmol/L) risk by 55% while lowering SMBG frequency (264). Selective application of flash monitoring based on these outcomes would place individuals at high risk of hypoglycaemia as the most likely to benefit. The I HART CGM study compared the efficacy of flash glucose monitoring and CGM at reducing hypoglycaemia in a prospective parallel group study among T1DM adults at high risk (265). Following a 2-week run-in with blinded CGM, participants were randomised to either real-time CGM or flash monitoring for 8-weeks with an option for all participants to continue RT-CGM for an additional 8-weeks. The group switching from flash monitoring to RT-CGM showed a significant reduction in time spent in hypoglycaemia (<54mg/dl, <3.0mmol/L) and increased time in target range (<70-180mg/dl, 3.9-10mmol/L). In contrast, no significant changes were observed in the participants that remained on RT-CGM suggesting superiority when addressing risk in T1DM adults vulnerable to hypoglycaemia.

1.6.   Glycaemic control metrics

1.6.1. Glycated haemoglobin (HbA1c)

Haemoglobin is an oxygen carrying compound found in red blood cells (erythrocytes) that binds with glucose proportionally to total blood glucose levels. Given the estimated lifespan of an erythrocyte is 90 days, measuring HbA1c reflects the average blood glucose level over this time frame. HbA1c is the most referenced metric for assessing long term glycaemic control and complication risk association. HbA1c levels above 42-53mmol/mol (6-7%) have been shown to significantly increase microvascular and cardiovascular risk in diabetes populations. As such, UK national guidance suggests a target HbA1c below 48 mmol/mol (6.5%) for people with diabetes, however individualised targets are advocated for those less likely to benefit from long term risk reduction.

As an average measure of blood glucose control, HbA1c is limited in its inability to outline diurnal glucose patterns and excursions. Diurnal glucose profiles are necessary for safe timing of insulin dosing and appropriate dose adjustments. Unfortunately, a satisfactory HbA1c measurement can convey an impression of satisfactory glycaemic control despite co-existing labile patterns of glucose excursions and hypoglycaemia.

1.6.2. Time in range, CGM metrics, and glucose variability

Daily glucose variability, labile longitudinal fasting plasma glucose, and HbA1c are metrics associated with hyperglycaemia and severe hypoglycaemia (266,267). Glycaemic variability has been linked with oxidative stress and endothelial dysfunction (268,269), and its validity as a modifiable vascular risk factor has been an ongoing subject of investigation. Early DCCT data suggested post prandial glucose excursions contributed to microvascular outcomes (174), however subsequent analysis of the dataset revealed neither prandial excursions or within and between-day glucose variability had any impact on developing microvascular complications (270). Signs of early neurodegenerative retinal change have been linked to glycaemic excursions in the setting of minimal vascular diabetic retinopathy, highlighting a neuropathic role in early diabetic retinopathy and the deleterious effects of glucose lability (271). Similarly, a longitudinal study identified fasting plasma glucose variability as an independent predictor of end stage retinal disease in T2DM (272). The long term effect of glucose variability was investigated in people with well-controlled HbA1c, where standard deviation of blood glucose (SDBG) and mean amplitudes of glycaemic excursion (MAGE) significantly correlated with 10 year cardiovascular risk in T2DM (273). As a result, consensus guidelines advocate time in range as a glycaemic control metric alongside HbA1c (274). Applying RT-CGM, the recommended measurements include time per day within target glucose range (3.9 – 10.0 mmol/L), time below range (<3.9mmol/L and 3.0 mmol/L), and time above range (>10.0 mmol/L). Using seven-point capillary glucose testing (SMBG) from the DCCT dataset, Beck et al, validated time in range as an

outcome measure for diabetes clinical trials with suggested associations with the risk of retinopathy and microalbuminuria (275). Although strongly supporting a role for time in range as a complication risk stratification tool, the data obtained from DCCT was based on SMBG measurements undertaken in the 1990's and not CGM. An analysis of the REPLACE-BG dataset comparing time in range reported by SMBG and CGM confirmed significant differences, raising the question whether inferences can be drawn across the two modalities (276).

1.7.   Therapeutics and education

1.7.1. Insulin pharmacology

Subcutaneous insulin administration is associated with delayed absorption and loss of the positive portal to peripheral insulin gradient seen when insulin is endogenously secreted. Over time insulin preparations have been adapted to achieve a close to physiological kinetic profile. Fast acting analogue insulins such as aspart, lispro, and glulisine, have quicker bioavailability, faster peak activity, and shorter half-lives. Prescribed as a bolus insulin, these preparations achieve better control of post-prandial excursions, greater reductions in HbA1c, and reduced risk of hypoglycaemia when compared to older human insulin variants (277–279). However, these preparations remain slower than endogenously secreted insulin and users are encouraged to administer doses 15-20 minutes before meals to achieve optimal outcomes. Modified insulin formulation and administration techniques have been promising in accelerating pharmacokinetics and overcoming delayed bioavailability. In comparison to standard insulin aspart, the modified faster insulin aspart (Fiasp) contains the additional excipients L-arginine and niacinamide and has been shown to produce greater HbA1c reduction in T1DM, and greater glucose lowering effects at 20-minutes post administration (280–283). Although hypoglycaemia outcomes were varied results across the trials, Fiasp serves as an attractive bolus insulin choice for individuals with faster meal absorption rates and

people who administer during or within 20-minutes of a meal. Studies show efficacy outcomes to carry over with greater glucose lowering effects when Fiasp is adopted in CSII (284–286). Lyumjev (modified lispro) joins Fiasp as another ultra-fast acting insulin with approval for use in CSII (287). The PRONTO T1DM and T2DM RCTs demonstrated superior 1 and 2 hour post prandial glucose excursions with HbA1c non-inferiority after 26 weeks of mealtime Lyumjev vs Humalog (lispro).

1.7.2. Multiple daily injection (MDI)

Multiple daily injections are commonly self-administered as a basal bolus, biphasic, or once daily regimens. Basal bolus regimens are traditionally reserved for T1DM and consist of a long-acting (basal) insulin dose delivered once a day or split to be given at 12-hour intervals. The (bolus) component comprises of short acting insulin administered at mealtimes to address post-prandial glucose excursions. A biphasic regimen applies the use of insulin with two phases of activity (short and intermediate) and is usually administered twice daily. Once daily insulin involves taking a daily dose of long or intermediate acting (basal) insulin to provide baseline insulin action. Both biphasic and once daily insulin regimens are often but not exclusively prescribed in T2DM to individuals with diminished insulin secretory capacity. Given endogenous insulin secretory capacity is not completely exhausted in T2DM, failure to provide 24-hour insulin bioavailability does not carry the same risk of ketoacidosis as seen in T1DM. Rotating injection sites is encouraged as good practice to prevent the development of local fat cell growth (lipohypertrophy) and delayed insulin absorption.

1.7.3. Continuous subcutaneous insulin infusion therapy (CSII)

CSII insulin therapy administers a continuous infusion of fast acting insulin subcutaneously via a wearable pump device. This approach circumvents the need for basal insulin between meals and the ability to programme varying rates of insulin delivery allows greater granularity to deal with blood glucose variability encountered throughout the day. Although a range of basal insulin rates can be

programmed for automated administration, bolus insulin doses still require interaction with the pump whenever required. CSII come as either a tethered insulin pump or patch pump. Tethered pump systems have a flexible length of tubing between the pump and cannula (short tube within the subcutaneous space). The pump itself houses the insulin within a refillable reservoir and an interactive interface for programming the rate of insulin delivery. Patch pumps do away with the tubing and the pump is attached directly to the skin surface. Eliminating tubing can be considered more aesthetically appealing and reduce the risk of tubes catching onto objects and disconnecting the cannula. However, patch pumps are considerably smaller to allow direct connection to the skin surface and are operated via remote control. In the UK pump therapy is approved in adults with T1DM struggling to achieve target HbA1c without disabling hypoglycaemia or a refractory HbA1c >8.5% despite high level care (14).

The degree to which pump therapy directly improves metrics of glycaemic control (HbA1c and severe hypoglycaemia) has been questioned with studies such as REPOSE showing no differences when comparing a randomised cohort of adult T1DM pump and MDI participants subjected to the same structured education(288). However, REPOSE excluded individuals motivated to adopt pump therapy, individuals that met the national guidance criteria for a pump, and those with complications or advocated as needing a pump(289). Therefore, we can affirm that provision of pump therapy across the board to all individuals with T1DM is not indicated and a targeted selection policy is necessary to glean the benefits of pump therapy. Nonetheless, a focused analysis of participants compliant with the protocol and pump use for the 2-year study duration revealed between group improvements in HbA1c and treatment satisfaction at the end of the trial, further endorsing the wider use of pump therapy (288).

1.7.4. Warming devices

As mentioned earlier, increased ambient and local skin temperatures are associated increased capillary blood flow and faster subcutaneous insulin absorption (290). The InsuPatch and InsuPad warming devices both increase skin temperature at the time of subcutaneous insulin administration to enhance absorption (291). The InsuPatch successfully increased the time of onset, peak insulin activity, and ultimately lowered post prandial glucose excursions when used alongside CSII. Greater and faster maximal insulin increments were associated with the InsuPatch warmed to 40 degrees Celsius for 15 minutes prior and up to 90 minutes post injection. In addition to improved glucose lowering effects, a 63-minute faster insulin clearance rate suggests potential to reduce late post prandial hypoglycaemia risk (292).

1.7.5. High velocity jet

High velocity jet injectors use needle free high pressure air systems to enhance absorption by delivering insulin into a greater surface area (293). Conceived to overcome the psychological phobia of self-injecting insulin. High velocity injectors can be applied as an insulin delivery technique for MDI or CSII users to speed up pharmacokinetics. However, widespread adoption is restricted by limited accessibility and difficulties sterilising injectors.

1.7.6. Continuous intraperitoneal insulin infusion (CIPII)

Intraperitoneal insulin can be delivered via an insulin pump implanted within the deep fascia with tubing passing into the peritoneal cavity. Wireless control of the insulin pump is operated using an external handset device. Alternatively, an external pump can deliver insulin through an implanted percutaneous port and intraperitoneal catheter. Delivering continuous insulin infusion into the peritoneal space addresses many pharmacological drawbacks of subcutaneous insulin. Intraperitoneal insulin delivery is absorbed directly into the peritoneal microvasculature and

establishes a more physiological portal to peripheral insulin gradient compared to subcutaneous preparations. Endogenous insulin is secreted into the portal circulation where concentrations measure up to four times higher than the peripheral circulation and immediate effects are exerted on the liver (294). Termination of hepatic gluconeogenesis helps reduce post prandial glucose excursions and is an important role seen following the first phase of insulin secretion. With a peak activity time of 15 minutes, administered intraperitoneal insulin is up to 30-45 minutes faster than subcutaneous preparations (295,296). Despite these improvements, beneficial outcomes associated with meal bolus intraperitoneal insulin administration remain dependent on the user administering doses manually and promptly. CIPII has been suggested to reduce the risk of severe hypoglycaemia by showing a greater rise in hypoglycaemia induced glucagon secretion (297). A T1DM randomised crossover trial showed continuous intraperitoneal insulin infusion to reduce the incidence of severe hypoglycaemia by more than 50% in sub optimally controlled individuals prone to frequent hypoglycaemia (298). The Accu-Chek® DiaPort is an example of a percutaneous intraperitoneal pump system shown to improve quality of life metrics, and reduce hypoglycaemia and associated weight gain in comparison to CSII using Lispro (299).

Complications arising from CIPII have become less common over the years, with implanted pump related complications reported by 20% of users after 15 years in a longitudinal observational study (300). Another longitudinal T1DM study found catheter occlusions (32.9%), pain (15.7%), and infection (10%) to be among the top complications during 283 patient years of CIPII use (301). Another barrier curbing CIPII use are the significantly greater financial and staffing costs required to insert and maintain CIPII compared with conventional subcutaneous therapy.

1.7.7. Inhaled insulin

Ultrafast inhaled technosphere insulin (Afrezza®) has a faster peak concentration (15 minutes) and is metabolised at a quicker rate than both analogue and endogenously secreted insulin (302–304). In closed loop automated insulin delivery systems, inhaled insulin has been investigated as an alternative to delivering a subcutaneous insulin bolus following post-prandial glucose excursions due to unannounced meals. Compared to subcutaneous insulin, Afrezza® saw a 21% increase in post-prandial time in range (3.9-18.0 mmol/L), 12.3% increase in daily time in range, and reduced glucose variability, all without increasing hypoglycaemia(305). However, inhaled insulin can cause bronchospasm and is not indicated for individuals with obstructive airway disease, smokers or ex-smokers who have stopped in the last 6-months (306).

1.7.8. Solid organ and islet cell transplant

Pancreas and islet cell transplantation is often reserved where optimal therapy fails to achieve glycaemic control and in cases where patients are already receiving immunosuppression or incipiently require renal replacement therapy. Solid organ pancreas transplantation can be performed alone (PTA) or after a kidney transplant (PAK) with the sole aim to improve diabetes. Alternatively, simultaneous solid pancreas and kidney transplantation can be performed (SPK) with improved survival outcomes (307). The united network of organ sharing (UNOS) and the organ procurement and transplant network (OPTN) review highlighted similar 5-year PAK and SPK survival rates, and despite greater 10-year SPK survival advocated for more PAK transplants in opposition to remaining on SPK waiting lists (308). Nonetheless, solid organ transplantation is a major surgical procedure with significant risk particularly in people with a long duration of diabetes with associated complications. Successful transplant surgery requires a lifelong commitment to immunosuppression therapy even in the event of graft failure.

Allogenic pancreatic Islet cell transplantation is the transfer of purified and processed islet cells form a deceased donor pancreas into the liver of a recipient via a portal vein catheter. The process is typically reserved for individuals with T1DM suffering from hypoglycaemia unawareness with life threatening consequences. Although the median (IQR) duration of insulin independence following islet cell transplantation is 15 months (6.2–25.5) months, 80% maintain C-peptide secretion and better glycaemic control despite losing insulin dependence. Furthermore, recipients reverting to insulin have been shown to require half their pre-transplant total daily dose (309). Successful pancreas and islet cell transplantation significantly improves quality of life, normalises hepatic glucose output, improves lipid profiles and HbA1c, and restores glucagon secretion and counterregulatory responses to hypoglycaemia (310–312).

1.7.9. Structured Education

Structured education programmes assist individuals with chronic illness to better understand and manage their condition. Its impact as a cost-effective management tool in diabetes is well established in motivating and empowering individuals to take control and make therapeutic decisions. Diabetes education is an essential and often a mandatory prerequisite to ensure benefit from many interventions including insulin pump therapy. NICE recommends people with diabetes undertake a formal, quality assured, evidence and curriculum based structured education programme at time of diagnosis and as required thereafter. The Dose Adjustment for Normal Eating (DAFNE) programme has been shown to produce sustained improvements in glucose control with HbA1c reductions of 1% at six months, 0.5% at one year, and 0.3% at seven years (313)(314). Long term observational DAFNE studies have shown up to 50% reduction in severe hypoglycaemia rates and are comparable to data from the earlier German DTTP course (Diabetes Teaching and Treatment Programme) (6,7). Studies have also shown improved IAH in up to 43% and reduced psychological

distress 1 year after DAFNE (6). Other benefits include risk reductions in DKA and improved quality of life (314–317).

A systematic review of group-based education in T2DM identified significant improvements in knowledge, self-management skillset, patient satisfaction, and body weight (318). The Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) course is a UK validated programme shown to aid lifestyle modification (weight loss and smoking cessation), and improve diabetes health beliefs and depression at 12 months (319). Similarly, the X-PERT diabetes programme improves self-management, while lowering HbA1c by 0.5% at one year (320).

Structured education programmes such as blood glucose awareness training (BGAT) apply psychological intervention to help mitigate hypoglycaemia. Over 8-weeks BGAT teaches individuals to record and analyse self-monitored glucose levels using diaries, understand the impact of external factors such as physical activity, and identify symptoms of hypoglycaemia. The training imparts the ability to anticipate, detect, treat, and ultimately prevent future hypoglycaemia. The first BGAT trials (BGAT-1) showed sustained improvement in accuracy of blood glucose estimation, hypoglycaemia detection, HbA1c, and frequency of severe hypoglycaemia (321–324). Studies also found BGAT-1 to improve preservation of counterregulatory adrenaline responses compared to educational control groups (325). BGAT-II and BGAT-III included elements on relapse prevention and expanded on how food, exercise, and insulin dynamically influence blood glucose (325–327). In addition to the positive outcomes observed with BGAT-1, long-term multicentre BGAT-III and BGAT-III trials also improved judgement on when to intervene based on blood glucose levels, when not to drive, and improved quality of life and worry metrics (325,327). Hypoglycaemia anticipation, awareness, and treatment training (HAATT) focuses specifically on reducing hypoglycaemia in people suffering from recurrent severe episodes. HAATT identified eight components responsible for severe hypoglycaemia and

developed an eight-session psychological training programme to address each component. Two large multicentre studies show HAATT to significantly improve detection and treatment of hypoglycaemia, reduced frequency of severe hypoglycaemia, reduced hypoglycaemia related sleep disturbances, and fewer motor vehicle incidents (323,328). In a 24-week randomised control trial, the HypoCOMPaSS study compared the efficacy of insulin delivery (MDI vs CSII), and modality of glucose monitoring (RT-CGM vs SMBG) in 96 adults with T1DM and IAH (329). All participants underwent up to 2 hours of hypoglycaemic focused psychoeducation, insulin dose titration, and intense weekly clinical support for the duration of the study. In the overall study population, using 7-days of blinded CGM at 4-week intervals showed time spent in hypoglycaemia ≤3.0mmo/L was reduced by more than half (53 ± 63 to 24 ± 56 min/24 h; P = 0.004) without compromising HbA1c. Improvements were achieved rapidly within the first 4-weeks and were sustained with an associated 8-unit reduction in total daily insulin requirement. Furthermore, hypoglycaemia awareness improved, episodes of severe hypoglycaemia and fear of hypoglycaemia decreased, and overall treatment satisfaction was improved. Importantly, no differences in the above outcomes were observed between insulin delivery and glucose monitoring groups, except for improved treatment satisfaction in CSII participants. A 2-year follow up showed sustained improvement in hypoglycaemia awareness and a 20-fold reduction in the annual rate/person year of severe hypoglycaemia without HbA1c compromise (330). This study highlights the sustained efficacy of educational intervention and frequent clinical support in improving IAH and reducing severe hypoglycaemia, independent of modality of insulin delivery and glucose monitoring technology. Hypoglycaemia awareness restoration programme for people with T1DM and problematic hypoglycaemia persisting despite optimised self-care (HARPdoc), is a currently active randomised control trial assessing a novel cognitive behavioural intervention focussed on addressing barriers to hypoglycaemia avoidance, as well as reinforcing hypoglycaemia detection and prevention (331). With BGAT serving as the control

arm, HARPdoc has potential to highlight the importance behaviour and belief systems as a risk factor for severe hypoglycaemia.

1.8.   Integrated technology, wearable devices, and decision support systems

1.8.1. Insulin Bolus Calculators

A successful insulin bolus is intended to prevent excessive post prandial glucose excursion or correct an elevated blood glucose level without causing hypoglycaemia. Bolus calculators apply a simple formula to calculate the amount of insulin required to address these requirements and have been integrated into many insulin pumps, glucose meters, and diabetes applications. Factors considered in a bolus dose calculation include the total amount of carbohydrate in a meal (grams), the insulin to carbohydrate ratio (ICR), current and pre-defined blood glucose levels, the insulin sensitivity factor (ISF), and the insulin on board (IOB). The ICR estimates how much carbohydrates (grams) are covered by one unit of fast acting insulin. The ISF denotes how much blood glucose levels are reduced by one unit of insulin and is often used to correct glucose levels above the target range. The estimated amount of bolus insulin on board (IOB) is determined by how long the previous insulin dose remains pharmacologically active.

The benefits of bolus calculators have been demonstrated in several studies. Gross et al, showed bolus calculators to facilitate achieving a target glucose range by a reduced frequency of correction insulin doses and rescue carbohydrates (332). Successful integration of diabetes technologies has proven to further improve glycaemic control outcomes. Factoring on board insulin when incorporating bolus calculators to insulin pump software significantly reduces mean blood glucose

and overnight glucose variability without incurring an increased risk of hypoglycaemia (333). A prospective RCT in a predominantly T1DM cohort successfully demonstrated a >0.5% reduction in HbA1c and improved treatment satisfaction when using a glucose meter with an integrated insulin bolus advisor compared to a standard meter alone (334). Having already demonstrated improved metabolic control and hypoglycaemia reduction after 4 months of bolus calculator use, Mora et al, failed to show further metabolic improvement when extending its use for a further 4 months or when introduced to an already intensified control group (335,336). Extended use however resulted in improved treatment satisfaction and significantly reduced fear of hypoglycaemia.

1.8.2. Sensor Augmented Pumps, Hybrid and Closed loop Artificial Pancreas systems

The sensor augmented pump (SAP) combines CGM and a CSII pump to deliver real time glucose readings to the pump interface. This provides convenience and continuous blood glucose feedback to support insulin dose adjustment. The STAR-3 multicentre randomised control trial demonstrated a weight neutral reduction in HbA1c after one year in SAP users compared to MDI controls (7.5% vs 8.1%, p<0.001) (337). The ability to automatically suspend insulin pump delivery once glucose levels reach a pre-configured threshold 'low glucose or threshold-suspend' is a feature adopted by SAP systems to help mitigate hypoglycaemia risk and bypass user error when responding to CGM alarm notifications. The ASPIRE trial successfully combined SAP and threshold suspend to reduce nocturnal hypoglycaemia frequency by 32% and lower the mean area under curve (AUC) by 38% over 3 months compared to SAP alone in people with T1DM and established nocturnal hypoglycaemia, p<0.001 (338). In addition to reducing exposure to hypoglycaemia, constant application of the threshold suspend feature has also been shown to reduce hyperglycaemia (339).

Closed loop artificial pancreas systems integrate CGM and pump therapy to provide a complete level of automation using an in-built control algorithm to independently titrate all insulin administration

based on CGM data. Hybrid closed loop systems are an intermediary approach delivering automated basal insulin and leaving the responsibility of bolus insulin delivery in the hands of the user. The absence of a continuous glucose data stream precludes the application of flash glucose monitoring in sensor augmented pump and artificial pancreas systems. A systematic review and meta-analysis of 40 clinical trials comparing artificial pancreas systems against insulin-based therapy (without real-time CGM or low glucose suspend SAP) showed significant increased percentage time spent in target range (3.9-10.0 mmol/L). Although a significant change in total daily insulin requirement was not reported, the positive effects extended to decreased time above >10 mmol/L and below 3.9 mmol/L(340). Identifying populations and scenarios where treatments are efficacious and can be of greatest impact is important in sustainable health economics. In a 12-week multinational RCT comparing twenty four-hour closed loop control with SAP, closed loop therapy was shown to significantly increase percentage time in range (3.9-10mmol/L), mean difference 10.8 (95% CI 8.2, 13.5, p<0.0001), reduce time <3.9mmol/L -0.83 (95% CI -1.40, -0.16, p=0.001), and time >10mmo/L -10.3 (95% CI -13.2, -7.5, p<0.0001) (341). Investigating the significance of evening and overnight closed loop control, Breton et al, conducted a randomised cross over study showing significant reductions in percentage time <3.9mmo/L and reductions in HbA1c compared to SAP, while achieving most of the benefits of 24-hour closed loop control (342). The safety and efficacy of closed loop systems has been demonstrated in high-risk individuals with T2DM on dialysis renal replacement therapy. A 20-day randomised cross over study comparing a fully closed loop system using faster acting insulin aspart with standard care, showed improvements in percentage time in range (5.6-10mmo/L), mean difference 15.1% (95% CI 8.0, -22.2, p<0.001), and median percentage time <3.9mmo/L (0.1 IQR [0.0-0.3] vs 0.2 [0.0-0.9], p=0.04) (343).

There are currently three commercially available hybrid closed loop systems in the UK. The Medtronic 780G (Minimed Medtronic, Northridge, California) and the Tandem Control lQ (Tandem

Inc., San Diego, California) are both insulin pump systems with algorithms within the pump software. Whereas the CamAPS FX (CamDiab Ltd, Cambridge) utilises a smartphone app-based algorithm to modulate the Dana Diabecare RS insulin pump via Bluetooth technology. Compared to the Medtronic 780G, the systems from Tandem and CamDiab do not require calibration. A six-month randomised control trial comparing the Tandem t:slim X2 insulin pump with Tandem Control IQ RCTs with SAP successfully demonstrated an 11% increase in time in range (3.9-10mmol/L) and a 0.9% reduction in time <3.9mmol/L without severe hypoglycaemia (344). These results were retained when assessed in a 12-month retrospective real-world analysis of Control-IQ users.

1.8.3. Bi-hormonal systems

Conventional insulin only closed loop systems depend on programmed safety measures to reduce or suspend insulin delivery and alert the user when hypoglycaemia ensues. Dual hormonal systems aim to reproduce a more physiological response by administering glucagon as counter-regulatory hormone during hypoglycaemia. Both single and glucagon dual hormone closed loop systems successfully improve measures of glycaemic control compared to standard pump treatment. However, widespread adoption of dual hormone systems is hindered by a lack of long-term safety data, the absence of a licensed stable glucagon analogue, and technical difficulties effectively deploying two independent pumps. Other hormones have been used adjunctively to address postprandial excursions and raised post-prandial glucagon levels due to insulin deficiency. The incretin hormone glucagon-like peptide-1 (GLP-1) is released post-prandially to potentiate endogenous insulin secretion and suppress glucagon levels. GLP-1 analogues and DPP-4 inhibitors have been shown to successfully lower post prandial glycaemia as adjuncts to insulin therapy in T1DM (345,346). A RCT investigating mealtime doses of sitagliptin (DPP-4 inhibitor) as an oral addition to an insulin only closed loop system significantly lowered the glucose area under the curve and insulin delivery (346).

1.8.4. Wearable technology and health apps

The global penetration rate of smartphone technology has risen exponentially over the last decade to become one of the fastest adopted technologies by consumers. The 2019 Deloitte global mobile consumer survey revealed 88% of UK adults had adopted smartphone technology, with 95% using their smartphones on a daily basis making it the most used consumer device (347).

A successful diabetes decision support app that integrates wearable technology will rely on its software 'user experience' to retain subscribers. A study from the leading mobile engagement platform identified a quarter of users abandon apps after one use (348). Inaccurate recommendations, poor usability and reluctance from healthcare providers are among a few barriers currently holding back mobile health apps. Prescriptive use of health apps advocated by healthcare professionals has been shown to increase patient retention rates suggesting a correlation between user engagement and healthcare provider support (349,350). The Vitality institute published guidelines to assist development of personalised health technology (351). Recommendations included; ensuring usability across population groups, applying evidence based principles towards improving health behaviour, and demonstrating validity and reliability (351). An editorial by Peiris et al, highlighted the limited evidence base in mobile health apps and proposed solutions to common obstacles encountered by mobile health app developers (352). The misguided concept of a 'killer app' with myopic and disease specific focused objectives often results in limited adoption figures due to failure in addressing the varied needs of stakeholders and users (353). A design approach that engages users and other non-health specialists throughout the development process encourages a multidisciplinary model that aims to understand and address the holistic views of the user (354,355). A stepwise developer's approach permits early user software interaction, in turn allowing

incorporation of feedback early in development and avoids late and expensive detection of bugs (352).

1.8.5. Diabetes health apps

Diabetes apps are often platforms aimed at presenting manual and automatically entered data to assist patients and healthcare professionals in making treatment decisions. A systematic review and meta-analysis of 14 randomised trials demonstrated a 0.49% HbA1c reduction associated with mobile app use in T2DM (356). As expected, these outcomes were enhanced in younger individuals and when combined with healthcare professional feedback. Similar glucose lowering outcomes are reported in T1DM trials with a 1.2% reduction in HbA1c after 6-months using a self-management mobile app, with effects extending into a 3 month follow up period(357). Nightscout is a cloud-based diabetes mobile platform allowing users to access uploaded CGM data via different smart devices with reported improvements in quality of life and glucose control outcomes (358). The impact of diabetes mobile applications extends beyond primary glucose control outcomes with studies demonstrating increased daily self-blood glucose monitoring and improved health behaviour (359). A cross-sectional study investigating the system identified increased use when removed from the resting home environment (e.g. work, travel and exercise), suggesting users require support when exposed to environmental variability (358).

Arsand et al, used various end-user-based assessments to evaluate the functionality of ten diabetes mobile health app features and outlined key components for future app development (360). Important features included: use of automatic data transfer; motivational and visual interface design; greater health benefit-to-effort ratio; dynamic usage; and applying context to app output. Herrero et al, analysed how various human and environmental factors such as exercise, stress and alcohol consumption, influence blood glucose levels and how these parameters can be incorporated in intelligent decision support systems (361).

A review of commercially available diabetes health apps established that having a structured display was a feature that significantly improved blood glucose control (362). This association is likely a result of positive health behaviour changes in response to well-presented health outcomes (e.g., blood glucose data). A randomized cross-over study investigating glucose prediction as part of a diabetes decision support system revealed further decision modification in 20% of cases during the intervention arm (363). The presentation of structured glucose prediction data generated from an AI with self-learning capabilities together with the ability to take account of real-time physical activity, provides an opportunity to engage the user and further improve clinical outcomes. The presence of educational and lifestyle modification features are also low risk additions that increase self-awareness and improve glucose control (362).

1.8.6. Physiological data acquisition sensors

Over the last decade, physiological data acquisition sensors, more commonly known as fitness trackers, have become increasingly popular. A 2019 Gallup survey found 19% of Americans monitor their health statistics using a fitness tracker (364) and the company Fitbit have sold over 105 million devices since 2010 (365). These devices fall into the category of health and fitness technology and allow users to digitally track their vital signs 'physiological measurements' in real-time. Often designed in the form of a wristband, with many lifestyle wristwatch manufacturers joining the trend and incorporating sensor functionality into luxury watches such as the apple iWatch.

Studies have explored how physiological vital signs correlate with blood glucose levels to better understand glucose homeostasis and identify early warning signs for hyper and hypoglycaemia. Existing research falls in line with the established neuroendocrine response to hypoglycaemia where a stimulated sympathoadrenal response increases heart rate to maintain glucose supply to the brain

and other vital organs (366). This altered sympathetic and parasympathetic balance is reflected by changes in heart rate variability (HRV) (367). Using CGM and the commercially available HealthPatch single lead electrocardiogram monitoring sensor, typical and atypical changes in mean HRV was observed when comparing parameters before and during confirmed hypoglycaemia ≤3.9mmo/L (70mg/dL) in people with T1DM (368). A typical HRV pattern consisted of an increase low frequency to high frequency ratio and or decrease in successive R-R intervals and was observed in 55% of hypoglycaemia incidents, 27% showed the opposite findings, 15% were unclear, and 3% revealed no changes. Typical changes were more prominent among individuals with a shorter duration of diabetes, with physical activity and rate of declining glucose also affecting change. Interestingly, hypoglycaemia awareness and the glucose nadir did not impact observed HRV changes.

The skin is the only organ purely innervated by the sympathetic nervous system. Sensors measuring electrodermal activity (EDA) or galvanic skin response apply constant low voltage to the skin and detect electrical changes in sweat as a marker of sympathetic innervation to the sweat glands. This has been corroborated in studies simultaneously recording high bursts of sympathetic peripheral nerve action potentials in correlation with the amplitude of rapid transient EDA events (369). Skin conductance responses (SCR) and skin conductance level (SCL) are both metrics of EDA provided by fitness trackers. The SCR is proportionally related to the number of sweat grands activated in response to a sympathetic stimulation and represents the rapid response to a stimulus. Whereas skin conductance level (SCL) measures responses to a tonic or slowly changing stimulus (370). Galvanic skin responses in diabetes have been studied for over 30 years, with changes in skin temperature, perspiration, and electrodermal activity investigated as possible triggers for hypoglycaemia alarms. The Diabalert and Sleep Sentry systems in the 1980's were curbed by low accuracy and false alarms (371,372). The SenseWear Pro Armband combines skin temperature, ECG, and acceletometer date to galvanic skin responses to estimate blood glucose levels. In a head-to-

head comparison with CGM, the device reported a MARD of 26% vs 18% following a mixed meal challenge, and 16% vs 12% during a treadmill test (373).

The spectrum of data provided by fitness trackers attracts a wide demographic field with varied user requirements. From professional athletes to curious technology consumers, the fitness tracker has become a staple in modern society. The market leader Fitbit recently launched a commercial model capable of analysing electrodermal activity (EDA) responses, heart rate metrics, sleep, and physical activity data to provide a stress management score alongside recommendations to help manage stress (374). The manufacturer has also used acquired physiological data from over 100,000 users to detect close to 50% of COVID-19 cases a day before symptoms development with 70% specificity, highlighting the potential for wearable devices in disease detection (374). The application of fitness trackers in clinical diagnostics is a promising step that will inevitably make its way into diabetes and glucose control management.

1.9.   Proposed research and Thesis organisation

1.9.1. Proposed research

Advancement in education, medical treatment, and more recently health technology has yielded significant improvements in treatment outcomes and quality of life. Nonetheless, the impact of diabetes and its related complications is a growing problem for health care providers and individuals living with the condition.

Data from the multinational global HAT study reported an 83% and 46.5% incidence of at least one episode of hypoglycaemia over a 4-week prospective period in people with T1DM and insulin treated T2DM (375). The clinical and economic impact of hypoglycaemia is well documented with an

estimated 10% of deaths in T1DM potentially attributable to hypoglycaemia (178,376) and a UK reported £20.9 million annual cost for emergency related admissions in 2018/2019 (377). Most instances of hypoglycaemia requiring third party assistance do not require support from emergency medical services (EMS), and when attended, 60% are managed at the scene without hospital transfer (378). Diabetes subtype, and modality of treatment influence outcomes following EMS attended hypoglycaemia, with greater hospital conveyance in non-insulin treated T2DM despite a higher incidence and greater severity of hypoglycaemia among insulin-treated individuals (378,379). We also know increasing age and co-morbidities are positively associated with hospital admission following EMS attended hypoglycaemia (380). However, no studies have investigated independent factors associated with receiving oral or parenteral rescue therapy in EMS attended hypoglycaemia.

The 2020 COVID-19 pandemic saw a government-imposed lockdown and reduced accessibility to healthcare providers. CGM and flash-glucose monitoring studies suggest improved percentage time in range (TIR) and variability (381–383), and a non-conclusive effect on percentage time below range (TBR) (383–385). At the time of writing this thesis, it remained unknown how the COVID-19 lockdown affected hypoglycaemia requiring EMS assistance. Moreover, it is unclear how this vulnerable group exposed to the cyclical nature of repeated hypoglycaemic, mostly without CGM technology, fared during a period of limited access to healthcare professionals.

Real-time CGM has been proven to reduce hypoglycaemia and improve overall glucose control in all age groups (185,255,386). It is also a cost-effective intervention (387) shown to improve quality of life metrics (388) and reduce fear of hypoglycaemia (389). (207,376). At the time of this study, NICE supported NHS funded RT-CGM provided by a centre with expertise in managing CGM in adults fulfilling a defined criteria (see chapter 1.5.2) (390). Assessment for CGM consideration is often undertaken in a stable outpatient clinical setting. Unfortunately, months can elapse between a

severe hypoglycaemia and commencing RT-CGM, during which time the significant risk of recurrent episodes persists. Nonetheless, studies have shown the sustained efficacy of rigorous structured education and intense clinical support in improving IAH and reducing severe hypoglycaemia, independent of mode of insulin delivery or use of RT-CGM (329,330). Currently, no studies have assessed the impact of early provision of RT-CGM following EMS attended hypogylcaemia in T1DM.

As discussed in chapter 1.3, glucose homeostasis is impacted by range of environmental and physiological factors with variation within and between individuals. The rise in accessibility to smartphone technology and improving accuracy of wearable physiological data acquisition sensors has seen greater efforts to successfully integrate wearable technology into a useable diabetes healthcare application. The aim of this research is to design an accessible adaptive real-time decision support system to enhance the self-management of T1DM and ameliorate the burden of severe hypoglycaemia. The system will run on a mobile smartphone device with an embedded machine-learning algorithm developed in collaboration with the Faculty of Engineering, Department of Electrical and Electronic Engineering at Imperial College London. Integrating real-time physiological data from clinically validated wearable sensors, the system aims to deliver accurate novel real-time forecasted blood glucose levels, adaptive insulin bolus advice, and notify individuals of trends/behaviours associated with hypoglycaemia to encourage adaptive measures to prevent recurrence.

To achieve this objective, I will analyse the immediate outcomes of severe hypoglycaemia in people with diabetes requiring assistance from emergency services (EMS) to reaffirm the clinical impact and risk associated with hypoglycaemia. The data from this study will identify risk factors associated with parenteral rescue treatment and hospital transfer, with the intention of identifying vulnerable groups. This will be followed by a randomised control trial investigating how the immediate

provision of RT-CGM in this high-risk group effects outcomes of hypoglycaemia and quality of life compared to standard care. The information learned from this work will inform the design of the system GUI and features included in the decision support system.

Designing the GUI will be a collaborative process harnessing ideas from a multidisciplinary team, including recruited participants with T1DM, aiming to create a system accessible to the most vulnerable individuals. Before testing the feasibility of the ARISES system, a longitudinal observational study using RT-CGM and a clinically validated physiological sensor wristband will identify associations between measurable physiological parameters and glycaemic control, with the intention to serve as a training set for the proposed machine-learning algorithm.

Unfortunately, unforeseen restrictions imposed by the global COVID-19 pandemic precluded a feasibility study of the ARISES system. However, a clinical sub-analysis of observational data will investigate measurable physiological parameters associated with current and impending hypoglycaemia in people with T1DM.

1.9.2. Thesis organisation

Based on the proposed research objectives, the thesis will be organised in the following sections:

Chapter 1: Introduction

This first chapter will detail the epidemiology, pathophysiology, and complications associated with diabetes mellitus. Moreover, it will emphasise the difficult task of self-managing diabetes and highlight both the benefits and shortcomings of current therapies and technologies. Lastly, how the proposed research aims to address these shortcomings and advance hypoglycaemia prevention will be discussed.

Chapter 2: Cross-sectional analysis of emergency hypoglycaemia

The second chapter details the methodology, results, and analytical discussion of a 6-month retrospective observational study of severe hypoglycaemia attended by LAS.

Chapter 3: Cross-sectional analysis of emergency hypoglycaemia during COVID-19 lockdown

Chapter 3 describes a repeat observational study of severe hypoglycaemia attended by LAS during the first government imposed COVID-19 lockdown. Comparative conclusions against date matched outcomes derived from the database analysed in Chapter 2 are discussed.

Chapter 4: Assessment of Impact of Real-time Continuous Glucose Monitoring on people presenting with severe Hypoglycaemia (AIR-CGM) study

This chapter details the concept, methodology, results, and analytical discussion of the first randomised control trial investigating the impact of immediate provision of RT-CGM following severe hypoglycaemia attended by EMS.

Chapter 5: An Adaptive Real Time Intelligent System to Enhance Self Care of Chronic Disease (ARISES) – Graphical User Interface (GUI) design

Chapter 5 describes the rationale for adopting a multidisciplinary focus-group approach, including recruited participants with T1DM, in designing a novel GUI for the ARISES decision support system. The semi-structured format of the focus-groups and agreed implemented outcomes are described.

Chapter 6: An Adaptive Real Time Intelligent System to Enhance Self Care of Chronic Disease (ARISES) – Physiological data collection and clinical sub-analysis

This chapter describes the methods and clinical sub-analysis of a six-week observational study of recruited participants with T1DM wearing RT-CGM, a physiological sensor wristband, and using a mobile diabetes app to log a series of daily activities. The clinical sub-analysis presents identified positive associations between measured physiological parameters and hypoglycaemia.

Chapter 7: Proposed research and future studies

Chapter 7 outlines proposed research plans and offers an outlook on potential future research.

Chapter 8: Outlook and Conclusion

The final chapter summarises the presented work and its clinical relevance.

2. Chapter 2: Cross-sectional analysis of emergency hypoglycaemia

2.1.   Introduction

As discussed in chapter 1, safely achieving target glycaemic control is complicated by various lifestyle and environmental factors. Insulin and other glucose lowering agents such as sulfonylureas are primary contributors to hypoglycaemia risk. The unpleasant experience and fear associated with hypoglycaemia often compromises efforts to intensify treatment (202) with many individuals choosing hyperglycaemia as a lesser of two evils. The impact of hypoglycaemia extends beyond

symptoms and metrics of glycaemic control, with an estimated 10% of deaths in T1DM potentially attributable to hypoglycaemia (178,376). Increased mortality is also observed in T2DM among individuals with cardiovascular risk factors and severe or biochemically significant hypoglycaemia (391). Mitigating the risk of severe hypoglycaemia by recognising symptoms, regular self-monitoring of blood glucose, and carrying oral carbohydrate supplies are an important feature of most diabetes structured education programmes (315).

Diabetes currently accounts for an estimated 10% of the NHS budget and is predicted to rise to 17% by 2035 (392). Severe hypoglycaemia remains a significant burden for the national health service with an annual financial cost exceeding £13 million (183). A 10-year observational study using the Hospital Episode Statistics (HES) database, observed a 39% absolute increase in hypoglycaemia-related hospital admissions in England between 2004-2015 (393). Unsurprisingly, individuals over 70 years old account for 60% of hypoglycaemia-related admissions, with half of all hypoglycaemia admissions requiring readmission for any cause within a year (394). NHS National Cost Collection data in 2018/2019 reported a cost of £20.9 million for non-elective hospital admissions for diabetes with hypoglycaemic disorders (377), with each admission costing from £563 to £3884 for people with low and high co-morbidity burdens respectively in the 2020/2021 tariff (395). Moreover, hypoglycaemia experienced as an inpatient significantly increases the duration of hospital stay, cost per admission, and mortality risk (184). These data may underestimate the health economic impact of hypoglycaemia when considering the comorbidities associated with hypoglycaemia such as cardiovascular events, and fall-related fractures (186,187).

Most instances of hypoglycaemia are self-managed in the community and do not require emergency services (EMS) intervention or hospitalisation. In the UK, the London Ambulance Service NHS Trust (LAS) serve the capitals estimated 8.17 million residents and attend to all emergencies within 620

square miles, (396).   Approximately, 20,000 diabetes related emergencies are attended by LAS annually (397). A greater understanding of population risk factors associated with out of hospital hypoglycaemia alongside predictors for successful treatment outcomes and hospital avoidance can appropriately guide management strategy and resource allocation. A literature review of Emergency Medical Services (EMS) treated hypoglycaemia identified that 60% of cases did not require hospital transfer with less than 10% re-contacting EMS within 72 hours (378). Diabetes subgroups and modality of treatment appeared to have a bearing with greater hospital conveyance observed in non-insulin treated T2DM despite a higher incidence and greater severity of hypoglycaemia among insulin-treated individuals (378,379). These findings most likely represent pathways to convey older people with multi-morbid non-insulin treated T2DM, especially those who are sulfonylurea-treated (378,379,398). This is supported in a one-year pre-hospital hypoglycaemia observational study showing 50% hospital conveyance and 21% admission rates, with age (OR 1.28 [95% CI 1.02, 1.60] per 10 years, p = 0.03) and increasing co-morbidities (OR 1.27 [95% CI 1.08, 1.48] per morbidity, p = 0.003) identified as positive predictors for admission (380).

To investigate the factors that influence the presentation and clinical outcome of emergency hypoglycaemia I analysed an urban emergency response hypoglycaemia dataset and the factors associated with parenteral treatment and conveyance to hospital. As detailed in the declaration of originality, this study was performed in collaboration with The London Ambulance Service NHS Trust (LAS) and has been published in a journal article with myself as first author (399).

2.2.   Methods

2.2.1. Data collection

This is a retrospective analysis of all incidents of adult and paediatric hypoglycaemia attended by the LAS from 1st January to 30th June 2018. London is made up of 32 geographical clinical commissioning groups (CCGs) responsible for delivering healthcare to an estimated 8.17 million people living in the capital (396). All incidents of hypoglycaemia in this analysis arose within the boundaries of the 32 London CCGs. This series defines hypoglycaemia as documented biochemical hypoglycaemia (<4 mmol/L) identified by either the patient, carer, or attending ambulance crew. The data were recorded at the scene by attending EMS clinicians and retrospectively accessed via the LAS clinical database. The dataset includes; age, gender, sub-type of diabetes, whether or not the emergency was coded as hypoglycaemia at the time of the call, ambulance response times from time of the call to arrival on-scene, vital signs on arrival (pulse rate, blood pressure, respiratory rate), seizures, alcohol consumption, capillary blood glucose and level of consciousness (Glasgow coma scale) on arrival and before departing the scene, delivered hypoglycaemia treatment, and decision to convey to hospital or not. Glasgow coma scale is a validated measure of consciousness based on ocular, verbal and motor responses to stimuli and ranges from 3 to a normal score of 15. Postal code data for geographical social deprivation analysis was not collected as it reflected the location of LAS attendance and not where individuals resided. EMS clinician's on-scene recorded nine diabetes diagnostic sub-categories: type 1 diabetes, type 2 diabetes, insulin dependent diabetes (IDDM), non-insulin dependent diabetes (NIDDM), unspecified, latent autoimmune diabetes in adults (LADA), borderline, unknown, and non-diabetic (Figure 2.1). Rescue treatment was in accordance with UK Ambulance Services Clinical Practical Guidelines (2016) and involved administering orally (15-20 grams of fast-acting carbohydrate or 40% dextrose gel) or parenterally (intravenous 10% glucose or intramuscular 1mg glucagon) (398). Parenteral dosing in children was scaled according to age as per Clinical Practice Guidelines.

All glucose meters used by patients were issued within the 32 London CCGs and meet ISO 15197:2013 standards. The Nipro TRUEresult™ is the standard glucose meter used by the LAS to measure all capillary blood glucose levels on-scene. All 'LO' meter readings represented blood glucose levels <1.1mmol/L and were recorded as a measurement of 1.1mmol/L as per the Nipro TRUEresult™ user manual (400).

2.2.2. Ethics

NHS Research Ethics Committee review was not required as this research was limited to the secondary use of information previously collected during normal care (without an intention to use it for research at the time of collection), and all the patients or service users were not identifiable to the research team in carrying out the research. The dataset used was fully anonymised to the authors

2.2.3. Statistics and Data Analysis

The analysis included the subset of incidents with a diabetes diagnosis, with stratification into two diagnostic subtypes: type 1 diabetes and type 2 diabetes. Incidents without a clear diabetes diagnosis and those that could not be placed in a diagnostic subtype 'other' were excluded from the analysis. Hierarchical stratification was performed based on the paramedic labelled diagnostic category, prescribed treatment regimens within categories, and a previously confirmed diagnosis in the case of individuals with multiple incidents (Figure 2.1). NICE guidelines advocate CSII for use only in T1DM, while sulfonylureas, and dipeptidyl peptidase 4 (DPP4) inhibitors are licenced for prescription only in T2DM. Therefore, all incidents receiving CSII were stratified as T1DM and those receiving a sulfonylurea or DPP4 inhibitor as T2DM. Unless a diagnosis of T2DM was confirmed on repeated attendances, the remaining IDDM cases receiving MDI with or without adjunctive

metformin or GLP-1 agonist were stratified as T1DM. Similarly, unless repeated incidents confirmed T1DM or T2DM, the non-allocated incidents with unspecified diabetes receiving basal bolus insulin without adjunctive oral therapy were stratified as T1DM. Metformin and or GLP-1 therapy alone were stratified as T2DM, and the remaining unspecified cases receiving non-basal bolus insulin with or without metformin or GLP-1 were categorised as 'other' considering this regimen could be prescribed in either T1DM or T2DM. All the non-insulin dependent diabetes incidents were receiving oral agents only and stratified as T2DM, and the only LADA case as T1DM. One unknown and two non-diabetic incidents were stratified as T1DM based on previous attendances, and the two borderline cases with no documented medication history as other.

Recorded variables included in our analysis were age, gender, call coded as 'hypoglycaemia', EMS response time (from emergency call answered to first vehicle arrival on scene), seizure, respiratory rate, pulse rate, systolic blood pressure, diastolic blood pressure, oral glucose therapy, parenteral glucose or glucagon therapy, capillary glucose, and intact consciousness both on arrival and before leaving the scene. Oral glucose therapy combined incidents receiving one or both modes of oral rescue treatment. Parenteral therapy combined incidents receiving one or both modes of parenteral rescue treatment. Intact consciousness is defined as incidents scoring 15 on the Glasgow Coma Scale (GCS).

Wilcoxon rank sum and Chi square statistical hypothesis tests were used to compare baseline demographics, vital signs, and treatment outcomes between T1DM and T2DM groups, and between recurrent and non-recurrent incidents. Independent predictors of receiving parenteral glucose and hospital conveyance were identified in the stratified dataset by mixed effects logistic regression modelling. The characteristics listed above plus diabetes status were considered as fixed effects and individual identity as random effect. As a sensitivity analysis, the mixed effects regression analysis

was repeated specifically in the paramedic labelled type 1 diabetes (n=948) and type 2 diabetes (n=1015) sub-groups from the complete dataset (Table 2.3). In this observational study, missing data was minimal, and a threshold of statistical significance of p<0.05 was adopted as an aid to interpretation and hypothesis generation. Statistical analyses were performed using Stata version 13 (StataCorp, College Station, TX).

2.3.   Results

2.3.1. Baseline demographics

The LAS attended 3560 hypoglycaemia incidents, of which 2862 were stratified as T1DM or T2DM for data analysis. The remaining 698 incidents consisted of non-diabetic, unknown, and diabetes cases that could not be stratified. Males represented 54.6% (n=1945) of the sample, the median (IQR) age was 64 (46-78) years, and the median (IQR) EMS response time was 10.8 (6.9-17.8) minutes (Table 2.5). Following hierarchical stratification, 52.5% (n=1503) were assigned as T1DM and 47.5% (n=1359) as T2DM (Table 2.1). The T1DM diabetes cohort were younger, median (IQR) age, 55 (36-69) years, and experienced shorter EMS response times 10.9 (7.1-17.8) minutes, compared to incidents with T2DM, 75 (66-82) years and 12.1 (7.8-21.0) minutes, respectively (Table 2.1). 958 records were recurrent incidents with individuals represented more than once within the dataset, which equates to 2% of individuals representing 10% of all incidents observed (Table 2.4). Baseline characteristics, vital signs and management outcomes of all incidents are summarised in Table 2.1. Descriptive tables of the original (pre-stratified) database and incidents observed from individuals attended to by EMS on more than one occasion (recurrent incidents) are summarised in Table 2.5 and 2.6, respectively.

2.3.2. Vital signs and symptoms

The median (IQR) arrival blood glucose level for all incidents among the stratified groups was 2.4 mmol/L (1.8-3.1), with a statistical but not clinically significant lower value in the T1DM group 2.3 mmol/L (1.7-2.9) compared to the type 2 diabetes incidents 2.5 mmol/L (2.1-3.2) (Table 2.1). Similarly, median (IQR) GCS on arrival was also lower among incidents stratified as T1DM 13 (9-15). All mean pulse rates were within the normal physiological range, and seizure rates were significantly higher in T1DM 1.1% (n=17) compared to T2DM 0.3% (n=4).

2.3.3. Interventions and Outcomes

43.2% of calls were labelled as hypoglycaemia by the EMS call handler and 50.9% of those stratified cases were conveyed to hospital (Table 2.1). The rate of incidents labelled as hypoglycaemia was significantly higher by 19% among those with T1DM compared to their T2DM counterparts, and the rate of hospital conveyance was significantly lower in the T1DM group by 28%. Incidents with T1DM had a significantly greater propensity for receiving parenteral therapy (53.6%) compared with T2DM (46.2%). Incidents from individuals attended by EMS on more than one occasion (recurrent incidents) had a significantly greater rate of parenteral treatment administration (61.7%) and a lower conveyance rate (40.7%) compared to cases from individuals requiring assistance once, 44.3% and 56% respectively (Table 2.6). Most of the individuals responsible for recurrent incidents were categorised as T1DM (56.4%) following hierarchical stratification (Table 2.4).

2.3.4. Independent influences on parenteral rescue therapy and hospital conveyance

Pre-arrival variables and diagnostic criteria

T1DM significantly reduced the odds of conveyance (OR 0.37 [95% CI 0.21, 0.66] p<0.01). Reduced odds for receiving parenteral treatment were also observed among the stratified T1DM group but

without statistical significance (Table 2.2). A longer EMS response interval and being female were both significant negative predictors for receiving parenteral rescue therapy, (OR 0.98 [95% CI 0.96, 0.99] p=0.03) and (OR 0.50 [95% CI 0.32, 0.77] p<0.01) in the stratified dataset, however statistical significance for females was not correlated in the sensitivity analysis that included only paramedic labelled incidents with type 1 and type 2 diabetes (Table 2.3).

Vital signs and symptoms

Higher capillary blood glucose measurements and a normal consciousness level (GCS 15) on arrival were both negative predictors for receiving parenteral therapy (OR 0.22 [95% CI 0.16, 0.31] p<0.01) and (OR 0.13 [95% CI 0.07, 0.24] p<0.01) respectively (Table 2.2). Whereas a higher glucose measurement and normal GCS on departing the scene negatively predicted conveyance to hospital, (OR 0.92 [95% CI 0.85, 0.99] p=0.04) and (OR 0.08 [95% CI 0.03, 0.21] p<0.01). A higher respiratory rate, and pulse rate were associated with small but significant positive associations with conveyance (p<0.05). However, only the association with pulse rate remained significant following sensitivity analysis (Table 2.3).

Interventions

Receiving oral glucose treatment significantly reduced the odds of being administered parenteral rescue therapy and hospital conveyance, (OR 0.02 [95% CI 0.01, 0.07] p<0.01) and (OR 0.25 [95% CI 0.14, 0.45] p<0.01) respectively (Table 2.2). Whereas parenteral treatment positively predicted hospital conveyance (OR 2.52 [95% CI 1.46, 4.33] p<0.01). All these findings remained significant following sensitivity analysis (Table 2.3).

2.4.   Discussion

I analysed 2862 incidents of hypoglycaemia attended by the LAS within a six-month period with 50.1% requiring parenteral treatment and a 50.9% hospital conveyance rate. EMS response times, clinical findings, and choice of intervention therapy all independently influenced decisions to administer parenteral treatment and convey individuals to hospital.

Parenteral treatment can be lifesaving and is often reserved for severe cases of hypoglycaemia, particularly when the ability to ingest oral glucose is compromised. The presented data suggests early non-invasive interventions such as oral glucose may reduce the need for invasive parenteral rescue treatment. This is further reflected by the finding that oral glucose treatment, higher blood glucose levels and intact consciousness at the completion of on-scene treatment are negative predictors for hospital conveyance. This work identifies additional predictors and validates the only existing study assessing independent risk factors for hospital conveyance following EMS attended hypoglycaemia in confirming both a higher respiratory rate and lower post-treatment glucose levels as positive predictors for conveyance (379). It also identifies longer EMS response times and female gender as negative predictors for receiving parenteral treatment. EMS response times may reflect the level of clinical severity when triaged over the phone, with lower risk clinical triage associated with longer response times. A longer response time could allow opportunity for self-administration of rescue treatment and time for hypoglycaemia correction, mitigating the need for parenteral treatment on arrival. Female gender as a negative predictor is less readily explicable and was not observed in the sensitivity analysis (Table 2.3). As expected, a fully intact final GCS at the time of leaving the scene suggests an ability to self-manage and was negatively associated with conveyance to hospital.

T1DM was not an independent risk factor for receiving parenteral treatment despite a greater proportion of incidents with T1DM receiving parenteral therapy. In fact, when corrected for age, having T1DM significantly reduced the odds of hospital transfer by 63%. Emergency complications such as diabetic ketoacidosis and hypoglycaemia are directly associated with insulin deficiency and reliance on insulin therapy, both characteristic features of T1DM. This inherent risk often results in greater accessibility to hypoglycaemia risk reduction measures in T1DM. In the UK, structured education programmes are commissioned for patients with both T1DM and T2DM, however glucose sensor device technologies are advocated primarily for individuals with T1DM despite their impact in significantly reducing severe hypoglycaemia (14,257,258,401). Individuals with type 1 diabetes, who have completed structured education and empowered with interstitial monitoring, may have a greater understanding of hypoglycaemia symptoms, self-management strategies, and access to rescue therapies such as intramuscular glucagon. As described in a retrospective analysis of severe hypoglycaemia incidents managed by EMS, these factors could improve their clinical status on arrival and instil confidence in paramedic crews to allow individuals to self-manage at home (402). Transferring these principles to people with T2DM could help reduce conveyance among this group. A small randomised control trial successfully reported a 50% reduction in symptomatic hypoglycaemia and significantly higher adherence to hypoglycaemia management in adults with T2DM following additional hypoglycaemia focussed education (403).

The incidents with T1DM were likely to have a longer duration of diabetes and a greater proportion would have been dependent on insulin therapy, both established risk factors for developing impaired awareness to hypoglycaemia and increased glucose variability. Longitudinal semi-structured interviews among individuals experiencing out of hospital severe hypoglycaemia identified up to 60% prevalence of impaired awareness in those requiring ambulance attendance (404). These figures represent more than twice the general diabetes population, with participants

reporting lack of early hypoglycaemia symptoms and reduced time to self-manage hypoglycaemia as reasons for repeated ambulance service attendances. We identified a third of all incidents were for individuals with recurrent callouts (n=958), with repeat callouts from 2% (n=50) of individuals accounting for 10% (286) of all attended incidents (Table 2.4). Further analysis showed most individuals requiring recurrent ambulance attendance were from the stratified T1DM group (56.4%), with 5 individuals with T1DM responsible for 65 callouts. These figures may have significantly changed with CGM becoming increasingly accessible to people with T1DM considered at high risk of hypoglycaemia after the time period studied (390). Nonetheless, these results reinforce that while access to risk prevention strategies is targeted at individuals with type 1 diabetes, the incidence of recurrent severe hypoglycaemia remains highest in this group with associated cost, morbidity, and mortality.

Over 55% of confirmed diabetes incidents were not labelled as hypoglycaemia by the triaging call handler and were identified by the attending EMS clinician. This may reflect symptoms developing after EMS was contacted or the caller being unfamiliar with identifying the symptoms of hypoglycaemia. Non-coded hypoglycaemia incidents were seen 20% more frequently in our stratified T2DM group. The disparity highlights a possible lack of awareness in recognizing hypoglycaemia among people with T2DM, and their friends, family, and carers, with potential safety implications around driving and some occupations. Nonetheless, the reduced odds of receiving parenteral treatment despite waiting longer for an ambulance to arrive may suggest that individuals eventually take the initiative to correct their hypoglycaemia and avert the need for invasive treatment, further highlighting the importance of early self-managed intervention.

Roughly 90% of all incidents received rescue treatment by EMS in line with UK Ambulance Services Clinical Practical Guidelines (2016) (398). These guidelines also recommend individuals taking

glibenclamide should to be transferred to further care (398). A generally adopted low threshold for hospitalizing sulfonylurea-related hypoglycaemia is well documented and is supported by evidence of prolonged admissions and recurrent hypoglycaemia in such incidents (379,380). Studies have also shown insulin treated individuals with T2DM are more likely to be hospitalised following severe hypoglycaemia than people with T1DM (175). Our results fall in line with this practice, as having T2DM increased the likelihood of being conveyed to hospital by over two and a half fold.

Although our dataset is based on retrospectively accessed patient reports and clinical information documented by an attending EMS clinician, the large volume of real-world data and the fidelity of LAS data collection processes enhance the validity of our results. A longitudinal prospective analysis with linkage to other healthcare data would help eliminate any uncertainty associated with recorded treatment regimens and diabetes classification. This would also allow an opportunity to investigate the impact of additional factors such as social deprivation and living circumstances on outcome decisions. The heterogeneity of the population saw the inclusion of incidents where hypoglycaemia was an incidental finding in a co-existing clinical emergency which could independently skew decisions for hospital conveyance.

This study emphasises the importance of early intervention in preventing negative outcomes following severe hypoglycaemia. Moreover, it highlights a need to bridge the gap in education and available risk prevention strategies between T1DM and at-risk individuals with T2DM to reduce the burden of parenteral treatment and hospital transfer associated with hypoglycaemia. More research is required to investigate the role of structured education in reducing severe hypoglycaemia risk in type 2 diabetes. Collection of severe negative outcomes including deaths, acute coronary syndrome, cerebrovascular accidents, and coma were not included in the LAS database. Analysing the overall incidence of these outcomes would underscore the clinical importance of addressing severe

hypoglycaemia. Greater allocation of resources and increased access to hypoglycaemia prevention tools in both diabetes categories, with more emphasis on identifying and self-treating hypoglycaemia are needed to curtail the economic burden of emergency hypoglycaemia.

	All	T1DM	T2DM	P

N	2862	1503 (52.5%)	1359 (47.5%)	
Age Median (IQR) **	66 (51-79)	55 (39-69)	75 (66-82)	<0.05
Adult (≥16)	98.4% (2817)	97.1% (1460)	99.9% (1357)	
Males (n) ***	55.1% (1576)	57% (856)	53% (720)	<0.05
Response Time (mins): Median (IQR) **	10.9 (7.1-17.8)	10.0 (6.6-16.1)	12.1 (7.8-21.0)	<0.05
Alcohol (n) ***	4.9% (139)	7.0% (105)	2.5% (34)	<0.05
Labelled hypoglycaemia by EMS call handler (n) ***	43.2% (1235)	52.2% (784)	33.2% (451)	<0.05
Recurrent (n) ***	33.5% (958)	38.7% (582)	27.6% (376)	<0.05
First Glucose: Median (IQR) **	2.4 (1.8-3.1)	2.3 (1.7-2.9)	2.5 (2.1-3.2)	<0.05
Pulse: Median (IQR) **	80 (70-92)	82 (71-93)	79 (68-90)	<0.05
Systolic BP: Median (IQR) **	140 (125-156)	139 (124-154)	142 (127-160)	<0.05
Diastolic BP: Median (IQR) **	77 (67-87)	79 (68-88)	75 (65-85)	<0.05
First GCS: Median (IQR) **	14 (9-15)	13 (9-15)	14 (10-15)	<0.05
First GCS Normal (n) ***	35% (1002)	30.5% (459)	40% (543)	<0.05
Seizure (n) ***	0.7% (21)	1.1% (17)	0.3% (4)	<0.05
Respiratory rate: Median (IQR) **	18 (16-20)	18 (16-20)	18 (16-20)	<0.05
Final Glucose: Median (IQR) **	5.7 (4.6-7.6)	5.9 (4.8-7.9)	5.6 (4.3-7.2)	<0.05
Final GCS: Median (IQR) **	15 (15-15)	15 (15-15)	15 (15-15)	<0.05
Final GCS Normal (n) ***	90.5% (2589)	92.7% (1394)	87.9% (1195)	<0.05
Oral glucose (n) ***	77.3% (2213)	77.9% (1171)	76.7% (1042)	0.43
Parenteral glucose/glucagon (n) ***	50.1% (1434)	53.6% (806)	46.2% (628)	<0.05
Conveyed (n) ***	50.9% (1456)	37.7% (567)	65.4% (889)	<0.05

Table 2.1. Baseline demographics, vital signs and symptoms measured on arrival (first) and before departure (final), treatment, hospital conveyance for the stratified diabetes subset. Results are expressed as median (IQR) and % (n). Statistically significant (p<0.05) differences between T1DM and T2DM measured by Mann-Whitney test** and chi squared test ***.

	Parenteral treatment		Conveyed to hospital	

	Odds ratio (95%CI)	*p*	Odds ratio (95%CI)	*p*
Age	1.00 (0.99-1.02)	0.80	1.01 (0.99-1.03)	0.08
Female	**0.50 (0.32-0.77)**	**<0.01**	1.40 (0.86-2.26)	0.17
Labelled hypoglycaemia by EMS call handler	1.32 (0.86-2.02)	0.20	0.68 (0.45-1.04)	0.07
Response time	**0.98 (0.96-0.99)**	**0.03**	1.0 (0.99-1.01)	0.74
Seizure*	-		2.83 (0.31-25.8)	0.36
Respiratory rate	**1.05 (1.00-1.10)**	**0.04**	**1.05 (1.00-1.10)**	**0.03**
Pulse rate	0.99 (0.97-1.00)	0.06	**1.02 (1.00-1.03)**	**0.01**
Systolic BP	1.01 (0.99-1.02)	0.36	1.00 (0.99-1.01)	0.57
Diastolic BP	0.99 (0.98-1.01)	0.53	1.02 (0.99-1.03)	0.07
Arrival glucose	**0.22 (0.16-0.31)**	**<0.01**	0.94 (0.76-1.16)	0.56
Arrival GCS 15	**0.13 (0.07-0.24)**	**<0.01**	1.48 (0.84-2.62)	0.18
Final glucose	N/A	N/A	**0.92 (0.85-0.99)**	**0.04**
Final GCS 15	N/A	N/A	**0.08 (0.03-0.21)**	**<0.01**
Oral glucose	**0.02 (0.01-0.07)**	**<0.01**	**0.25 (0.14-0.45)**	**<0.01**
Parenteral glucose/glucagon	N/A	N/A	**2.52 (1.46-4.33)**	**<0.01**
Alcohol	1.46 (0.59-3.65)	0.42	1.39 (0.56-3.44)	0.47
T1DM†	0.66 (0.39-1.13)	0.13	**0.37 (0.21-0.66)**	**<0.01**
T2DM†	1.51 (0.89-2.56)	0.13	**2.67 (1.52-4.71)**	**<0.01**

Table 2.2. Mixed effects regression analysis of factors predicting parenteral rescue treatment and conveyance to hospital in the stratified confirmed diabetes subset. Results are expressed as odds ratios (95% confidence intervals). P values of <0.05 are significant and highlighted in bold. * Insufficient seizure incidents received parenteral treatment, † results are from two separate models, one showing odds for T1DM relative to T2DM, and vice versa.

	Parenteral therapy		Conveyed to hospital	

	Odds ratio (95%CI)	*p*	Odds ratio (95%CI)	*p*
Age	1.0 (0.98-1.02)	0.80	1.01 (0.99-1.04)	0.17
Female	0.67 (0.36-1.23)	0.20	1.17 (0.63-2.16)	0.62
Labelled hypoglycaemia by EMS call handler	1.32 (0.74-2.36)	0.35	0.63 (0.36-1.11)	0.11
Response time	**0.97 (0.94-0.99)**	**0.02**	1.0 (0.99-1.01)	0.71
Seizure*	-		1.42 (0.09-22.1)	0.80
Respiratory rate	1.07 (0.99-1.14)	0.05	1.04 (0.99-1.09)	0.15
Pulse rate	**0.97 (0.96-0.99)**	**0.01**	**1.02 (1.00-1.04)**	**0.01**
Systolic BP	1.0 (0.99-1.02)	0.65	1.01 (0.99-1.02)	0.15
Diastolic BP	0.99 (0.97-1.01)	0.52	1.00 (0.98-1.02)	0.85
Arrival glucose	**0.21 (0.13-0.34)**	**<0.01**	0.97 (0.74-1.26)	0.79
Arrival GCS 15	**0.13 (0.06-0.30)**	**<0.01**	1.45 (0.68-3.09)	0.34
Final glucose	N/A	N/A	0.93 (0.82-1.04)	0.20
Final GCS 15	N/A	N/A	**0.04 (0.01-0.17)**	**<0.01**
Oral glucose	**0.03 (0.01-0.10)**	**<0.01**	**0.24 (0.11-0.54)**	**<0.01**
Parenteral glucose/glucagon	N/A	N/A	**3.13 (1.51-6.48)**	**<0.01**
Alcohol	1.38 (0.37-5.08)	0.63	1.16 (0.36-3.77)	0.80
Type 1 Diabetes	0.79 (0.39-1.61)	0.52	**0.39 (0.19-0.78)**	**<0.01**

Table 2.3. Comparative sensitivity mixed effects regression analysis of factors predicting parenteral rescue treatment and conveyance to hospital in the LAS labelled type 1 diabetes (n=948) and type 2 diabetes (n=1015) population from the complete dataset. Results are expressed as odds ratios (95% confidence intervals). P values of <0.05 are significant and highlighted in bold. * Insufficient seizure incidents received parenteral treatment.

Frequency of emergency attendance	Individuals Stratified diabetes subset (n)	EMS attended incidents	T1DM Individuals	T2DM Individuals
2	252	504	53.2% (134)	46.8% (118)
3	56	168	57.1% (32)	42.9% (24)
4	22	88	63.6% (14)	33.3% (8)
5	10	50	80% (8)	20% (2)
6	10	60	90% (9)	10% (1)
7	1	7	0% (0)	100% (1)
8	2	16	0% (0)	100% (2)
9	1	9	100% (1)	0% (0)
10	2	20	100% (2)	0% (0)
12	1	12	100% (1)	0% (0)
24	1	24	100% (1)	0% (0)
Total	358	958	56.4% (202)	43.6% (156)

Table 2.4. Individuals and frequency of recurrent incidents (attended by ambulance more than once) from the confirmed diabetes stratified dataset. Results are expressed as % (n).

	All	Type 1 Diabetes	Type 2 Diabetes	Others	Recurrent
N	3560	948 (26.6%)	1015 (28.5%)	1597 (44.9%)	990 (27.8%)
Age: Median (IQR)	64 (46-78)	53 (36-65)	75 (65-82)	61 (40-79)	62.5 (50-78)
Adult (≥16)	95.3% (3392)	96.3% (913)	99.8% (1013)	91.8% (1466)	98.9% (979)
Males (n)	54.6% (1945)	57.8% (548)	52.8% (536)	53.9% (861)	53.9% (534)
Response Time (mins): Median (IQR)	10.8 (6.9-17.8)	9.8 (6.4-15.7)	12.2 (7.9-21.3)	10.7 (6.7-17.9)	9.8 (6.5-15.9)
Alcohol (n)	7.2% (256)	7.0% (66)	2.9% (29)	10.1% (161)	5.4% (53)
Labelled hypoglycaemia by EMS call handler (n)	37.8% (1344)	51.6% (489)	34.3% (348)	31.7% (507)	51.8% (513)
First Glucose: Median (IQR)	2.5 (1.9-3.2)	2.2 (1.7-2.9)	2.6 (2.1-3.1)	2.6 (1.9-3.3)	2.2 (1.6-2.7)
Pulse: Median (IQR)	81 (70-93)	81 (72-93)	80 (69-90)	82 (70-96)	81 (70-92)
Systolic BP: Median (IQR)	139 (123-155)	139 (124-153)	142 (127-160)	137 (121-153)	142 (126-157)
Diastolic BP: Median (IQR)	77 (67-87)	79 (69-88)	75 (65-85)	77 (67-87)	78 (68-87)
First GCS: Median (IQR)	14 (10-15)	13 (9-15)	14 (10-15)	14 (10-15)	12 (9-14)
First GCS Normal (n)	37.5% (1334)	30.3% (287)	41.7% (423)	39.1% (624)	24% (238)
Seizure (n)	0.9% (32)	1.1% (10)	0.3% (3)	1.2% (19)	0.9% (9)
Respiratory rate: Median (IQR)	18 (16-20)	18 (16-20)	18 (16-20)	18 (16-20)	18 (16-20)
Final Glucose: Median (IQR)	5.6 (4.4-7.4)	5.9 (4.9-7.9)	5.6 (4.3-7.3)	5.4 (4.3-7.2)	5.8 (4.6-7.5)
Final GCS: Median (IQR)	15 (15-15)	15 (15-15)	15 (15-15)	15 (15-15)	15 (15-15)
Final GCS Normal (n)	87.1% (3100)	92.7% (879)	89% (903)	82.5% (1318)	90.8% (899)
Oral glucose (n)	74.2% (2643)	78.7% (746)	76.6% (777)	70.1% (1120)	78.2% (774)
Parenteral glucose/glucagon (n)	45.3% (1614)	54% (512)	45.5% (462)	40.1% (640)	60.7% (601)
Conveyed (n)	54.6% (1943)	37.9% (359)	66.5% (675)	56.9% (909)	41.5% (411)

Table 2.5. Baseline demographics, vital signs and symptoms measured on arrival (first) and before departure (final) by attending paramedics, administered treatment and decision to convey to hospital for the complete dataset. Results are expressed as median (IQR) and % (n).

	All	Non-Recurrent	Recurrent	p
N	2862	1904 (66.5%)	958 (33.5%)	
Age: Median (IQR)**	66 (51-79)	68 (51-79)	63 (51-78)	<0.05
Adult (≥16)	98.4% (2817)	97.8% (1863)	99.6% (954)	N/A
Males (n)***	55.1% (1576)	55.6% (1059)	54% (517)	0.6
Response Time (mins): Median (IQR)**	10.9 (7.1-17.8)	9.8 (6.6-15.9)	11.5 (7.5-19.1)	<0.05
Alcohol (n)***	4.9% (139)	4.6% (87)	5.4% (52)	0.30
Labelled hypoglycaemia by EMS call handler (n)***	43.2% (1235)	39.0% (742)	51.5% (493)	<0.05
First Glucose: Median (IQR)**	2.4 (1.8-3.1)	2.5 (2.0-3.2)	2.2 (1.6-2.7)	<0.05
Pulse: Median (IQR)**	80 (70-92)	80 (70-92)	81 (70-92)	0.58
Systolic BP: Median (IQR)**	140 (125-156)	140 (125-156)	143 (126-157)	<0.05
Diastolic BP: Median (IQR)**	77 (67-87)	77 (66-86)	78 (69-88)	<0.05
First GCS: Median (IQR)**	14 (9-15)	14 (10-15)	12 (9-14)	<0.05
Respiratory rate: Median (IQR)**	18 (16-20)	18 (16-20)	18 (16-20)	0.9
Seizure (n)***	0.7% (21)	0.6% (12)	0.9% (9)	0.36
Final Glucose: Median (IQR)**	5.7 (4.6-7.6)	5.7 (4.5-7.6)	5.8 (4.6-7.6)	0.22
Final GCS: Median (IQR)**	15 (15-15)	15 (15-15)	15 (15-15)	0.69
Oral glucose (n)***	77.3% (2213)	76.6% (1459)	78.7% (754)	0.21
Parenteral glucose/glucagon (n)***	50.1% (1434)	44.3% (843)	61.7% (591)	<0.05
Conveyed (n)***	50.9% (1456)	56% (1066)	40.7% (390)	<0.05

Table 2.6. Baseline demographics, vital signs and symptoms measured on arrival (first) and before departure (final) by attending paramedics, administered treatment and decision to convey to hospital for the stratified diabetes subset. Results are expressed as mean (SD), median (IQR), and % (n). Statistically significant (p<0.05) differences between Non-recurrent and Recurrent groups measured by Mann-Whitney test** and chi squared test ***.

Figure 2.1. Diagnostic hierarchical stratification of confirmed diabetes incidents. Flow chart to illustrate the pre-labelled paramedic diagnostic categories and hierarchical stratification used to allocate incidents with confirmed diabetes into three diagnostic groups, Type 1 diabetes (Type 1), Type 2 diabetes (Type 2), and other).
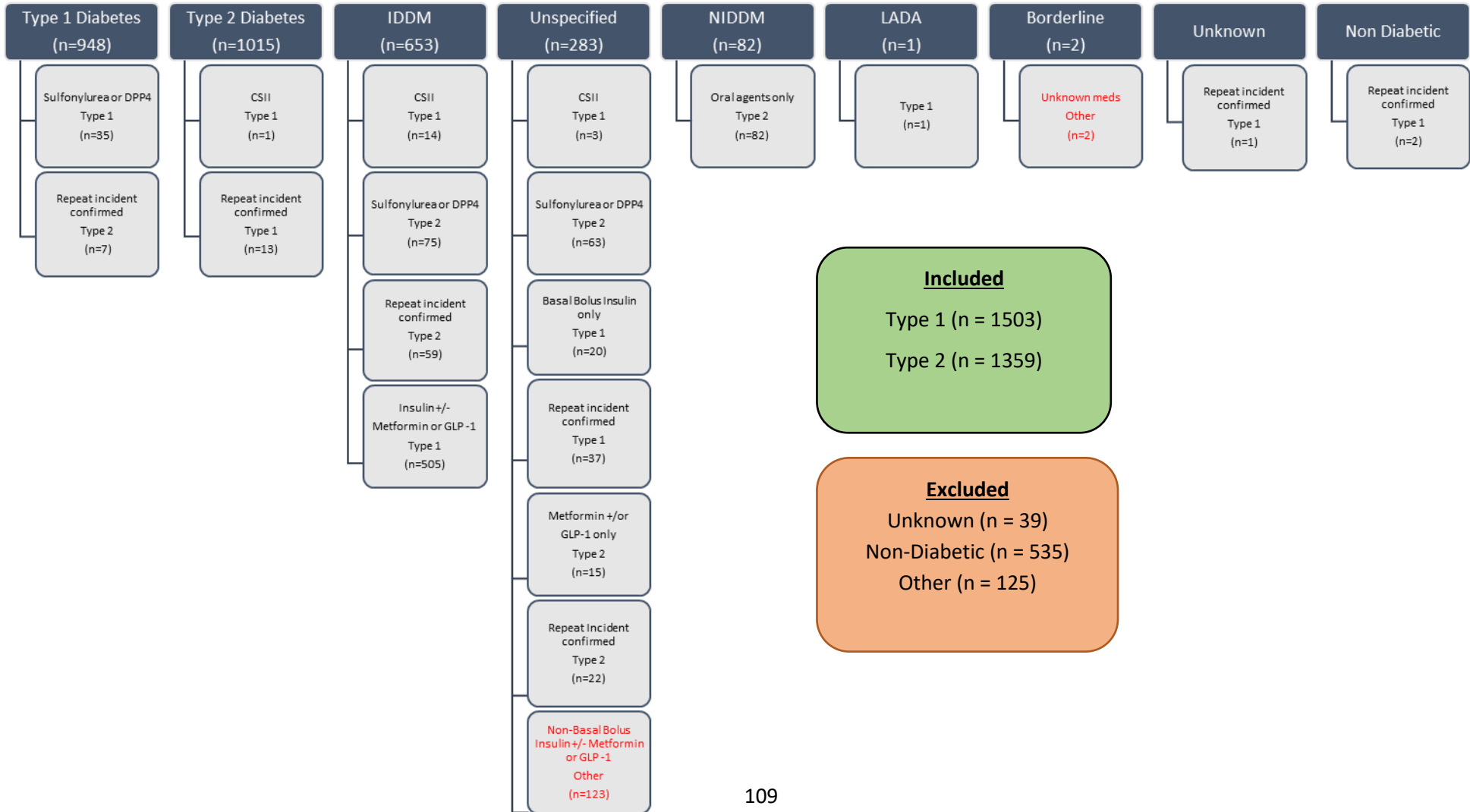
3. Chapter 3: Cross-sectional analysis of emergency hypoglycaemia during the COVID-19 lockdown

3.1.   Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) responsible for the Coronavirus (COVID-19) pandemic saw the UK government impose a twenty eight day state of lockdown commencing on the 23rd March 2020 to slow disease transmission (405).

Diabetes mellitus has an estimated prevalence of 5% in the UK and is associated with increased mortality among inpatients with COVID-19. Hyperglycaemia and obesity have been shown to be independently linked with increased mortality in people with diabetes afflicted with COVID-19 (406,407). People with diabetes are considered 'clinically vulnerable' to COVID-19, with high-risk individuals advised to practice 'shielding' during this period. Altered access to outpatient clinics, podiatry, retinal screening, and pharmacies changed delivery of care for people with diabetes during lockdown. However, continuous and flash glucose monitoring studies have shown that lockdown did not worsen metrics of glucose control (384), and may in fact improve time in range (TIR) and coefficient of variation (CV%) (381–383). This suggests glycaemic control benefits observed in people with access to interstitial glucose monitoring devices may be linked to changes in routine and more time to invest in diabetes self-management. A positive effect on hypoglycaemia has also been described with significant reductions in time below range (TBR) <4mmol/L observed during lockdown among individuals at increased risk of hypoglycaemia at beforehand >4% TBR (384).

However, studies have also reported improvements in TIR during the COVID-19 imposed lockdown without any significant change in TBR (383) and in some instances an increase in TBR (385).

During lockdown, hospitals saw a peak in COVID-19 related admissions (408), and in April 2020 witnessed a 56.6% decline in all emergency department visits and a 39% fall in emergency admissions compared with April 2019 (409). A fear of disease transmission in hospital and government advice to avoid non-essential use of emergency services are suspected factors linked to the decline in non-COVID-19 related emergency department encounters. This behavioural change in accessing emergency services has resulted in reduced admissions for reversible emergency conditions such as acute coronary syndrome (ACS) (410,411) and an 81% increase in out of hospital cardiac arrest during the first wave of the COVID-19 pandemic in London (412).

3.2.   Aims

By comparing a lockdown and date matched control dataset of LAS attended hypoglycaemia, this study aims to investigate how the COVID-19 lockdown impacted the incidence and clinical outcome of severe hypoglycaemia. I hypothesise fewer incidents of LAS attended hypoglycaemia and a lower rate of hospital conveyance during the COVID-19 lockdown compared to the control period.

3.3.   Methods

3.3.1. Data collection

This is a retrospective analysis of all hypoglycaemia incidents attended by the LAS during the twenty-eight-day lockdown (24/3/2020 – 20/04/2020) and the same period in the database analysed in chapter 2 from (24/3/2018 – 20/04/2018) (399). All hypoglycaemia incidents are defined as documented biochemical capillary glucose <4mmol/L identified by the patient, carer, or attending paramedics, and arising within the boundaries of the 32 London geographical clinical commissioning groups (CCGs). Data for both periods were recorded by the attending ambulance clinician and retrospectively accessed from the LAS clinical database. The dataset includes age, gender, sub-type of diabetes, ambulance response times from time of the call to arrival on-scene, alcohol consumption, capillary blood glucose on arrival and before departing the scene, delivered hypoglycaemia treatment (oral or parenteral), and conveyance to hospital. Oral glucose therapy combined incidents receiving one or both modes of oral rescue treatment. Parenteral therapy combined incidents receiving one or both modes of parenteral rescue treatment. All glucose meters used were issued within the 32 London CCGs and meet ISO 15197:2013 standards. The Nipro TRUEresult™ is the standard glucose meter for the LAS and measured all capillary blood glucose levels on-scene. All 'LO' meter readings represented blood glucose levels <1.1mmol/L and were recorded as a measurement of 1.1mmol/L as per the Nipro TRUEresult™user manual (400). Rescue treatment was in accordance with UK Ambulance Services Clinical Practical Guidelines (2016) (398) and involved administering oral (15-20 grams of fast-acting carbohydrate or oral 40% dextrose gel) or parenteral (intravenous 10% glucose or intramuscular 1mg glucagon) treatment. Parenteral dosing in children was scaled according to age as per Clinical Practice Guidelines. Again, postal code data for geographical social deprivation analysis was not collected as it reflected the location of LAS attendance and not where individuals resided.

3.3.2. Ethics

NHS Research Ethics Committee review was not required as this research was limited to the secondary use of anonymised information previously collected during normal care (without an intention to use it for research at the time of collection). All patients or service users were not identifiable to the research team. The dataset used was fully anonymised to the authors.

3.3.3. Statistics and Data Analysis

My analysis included the subset of incidents with a diabetes diagnosis from the lockdown and control databases, with hierarchical stratification into two diagnostic subtypes: T1DM, and T2DM (Figure 3.1 and 3.2). Incidents without a clear diabetes diagnosis and those that could not be placed in a diagnostic subtype 'other' were excluded from the analysis. Hierarchical stratification was consistent with methods applied in Chapter 2.2.1 and was based on the paramedic labelled diagnostic category, prescribed treatment regimens within categories, and a previously confirmed diagnosis in the case of individuals with multiple incidents. Wilcoxon rank sum or Fisher's exact test statistical hypothesis tests were used to compare baseline demographics, blood glucose values, interventions, and outcomes between the stratified T1DM and T2DM groups. Independent predictors of receiving parenteral glucose and of transport to hospital were identified in the stratified diabetes dataset by logistic regression with the characteristics listed above. In this observational study, a threshold of statistical significance of $p<0.05$ was adopted as an aid to interpretation and hypothesis generation. Differences between data collection periods were tested for significance using Wilcoxon rank sum test for numerical variables and Fisher's exact test for categorical variables. Statistical analyses were performed using Stata version 13 (StataCorp, College Station, TX).

3.4.   Results

Following hierarchical stratification and exclusion of non-diabetes cases, the LAS identified fewer incidents of hypoglycaemia (n=345) during lockdown compared to the 2018 date matched control period (n=448), with no significant change in the number of hypoglycaemia callouts received by EMS call handlers (Table 3.1). Incidents attended during lockdown were significantly older, median (IQR) age 72 (61-82) years compared to the control period 67 (51-78) years (p<0.01), with more alcohol related cases 4.2% vs 0.9% (p<0.01) (Table 3.1). Hierarchical stratification saw 34.5% of the lockdown group assigned as T1DM (n=119) and 61.2% as T2DM (n=211). In contrast, the control period saw a greater proportion stratified as T1DM 53.6% (n=240) in comparison to T2DM 39.1% (n=175). The difference in diabetes stratification between the two periods in both subsets was statistically significant, p<0.001 (Table 3.1). Excluding alcohol related incidents, all significant differences in baseline characteristics and measurements were also observed in the sensitivity analysis (Table 3.3)

The median (IQR) arrival blood glucose for all incidents during lockdown was 2.4 mmol/L (1.9-2.8). Following stratification, a significantly lower arrival glucose was observed among the T2DM incidents 2.4 mmol/L (2.0-2.8) during lockdown compared to the control period 2.6 mmol/L (2.2-3.2) (p<0.01). Lockdown saw a significantly greater proportion of incidents requiring parenteral therapy 58% (n=200) vs 49.1% (n=220) (p=0.01). The same trend was identified among the T2DM incidents, with 62.2% (n=132) requiring parenteral treatment during lockdown vs 41.7% (n=73) during the control period (p<0.01). The rate of hospital conveyance was lower during lockdown 44.3% (n=153) vs 46.7% (209). However, statistical significance was observed only among incidents with T2DM where lower

conveyance rates were observed during lockdown 55.2% (n=117) compared to the control period 69.1% (n=121) (p<0.01).

Binomial logistic regression identified age as a significant positive predictor for receiving parenteral treatment during lockdown (OR 1.04 [95% CI 1.02, 1.06] p<0.01) (Table 3.2). A higher arrival glucose and receiving oral glucose therapy both reduced the odds of receiving parenteral rescue therapy during lockdown and the control period (p<0.01) (Table 3.2). Hierarchical stratification as T1DM or T2DM had no significant impact on administration of parenteral treatment.

A higher final glucose measurement before departure and receiving oral glucose therapy both reduced the odds of conveyance during lockdown, (OR 0.84 [95% CI 0.75, 0.94] p<0.01) and (OR 0.36 [95% CI 0.19-0.68] p>0.01), respectively. Whereas receiving parenteral rescue therapy was a significant positive predictor for conveyance during lockdown, (OR 3.75 [95% CI 1.94, 7.26] p<0.01). Lastly, T2DM reduced the odds of hospital conveyance compared to T1DM both during lockdown (OR 2.79 [95% CI 1.47, 5.31] p<0.01) and the control period (OR 5.81 [95% CI 3.41, 9.90] p<0.01). Individual decisions to refuse conveyance against EMS advice did not change between both periods in T1DM and T2DM.

3.5.   Discussion

Fewer incidents of EMS attended hypoglycaemia and a lower rate of hospital conveyance during lockdown are both consistent with a perceived anxiety towards engaging with health services in fear of contracting COVID-19 and efforts to ease the burden on health services during the height of the COVID-19 pandemic in London.

A higher blood glucose on EMS arrival and receiving oral glucose therapy both reduced the odds of receiving parenteral treatment during both periods. This likely reflects individuals with higher initial blood glucose measurements being less incapacitated, more likely to safely tolerate oral glucose therapy, and in turn less likely to require parenteral rescue therapy. Age was also identified as a significant positive predictor for receiving parenteral treatment during lockdown only. Increased COVID-19 related morbidity and mortality among the elderly is well established (413,414), and in the UK individuals over 70 years are considered as clinically vulnerable. The presented findings highlight a possible increased requirement for invasive treatment among an elderly population apprehensive about contacting EMS and presenting in a worse clinical state in fear of contracting COVID-19. Receiving parenteral rescue therapy significantly increased the odds of hospital conveyance during lockdown by 3.5 times (p<0.01). Hypoglycaemia management guidelines reserve parenteral treatment for instances when oral treatment is insufficient or when hypoglycaemia severely impairs cognitive function (398). I suspect a fear of contracting COVID-19 could have sprung hesitancy to contact EMS resulting in delayed presentations, more unwell recipients of parenteral therapy, and ultimately increased hospital conveyance despite aggressive treatment efforts. Similarly, delayed access to EMS would result in a greater proportion of callouts from compromised individuals with incidental hypoglycaemia. Many of such cases will invariably require parenteral treatment and possible hospital conveyance.

During lockdown, receiving oral glucose treatment and a higher glucose measurement before EMS departure had a negative predictive influence of on hospital conveyance. This implies successfully treated hypoglycaemia and non-invasive therapeutic measures positively influenced outcomes to avoid hospital transfer and safely 'see and treat' patients during lockdown. NHS England outline this

behaviour with a reported 37% increase in incidents with a 'see and treat' or 'hear and treat' outcome by ambulance services in April 2020 compared to April 2019 (415,416).

During both periods, T1DM was a negative predictor for hospital conveyance while T2DM increased the odds of conveyance. Insulin dependence is a hallmark of T1DM and a significant risk factor for hypoglycaemia. As mentioned in chapter 2, this inherent risk often sees greater access to hypoglycaemia risk prevention strategies for the T1DM population. At the time of this study, sensor device technology was recommended solely for individuals with T1DM despite being proven to significantly reduce severe hypoglycaemia (14,257,258). In addition, people with T1DM are likely to have a longer duration of diabetes and more experience in understanding hypoglycaemia symptoms. Access to a combination of these factors could see earlier identification and management of hypoglycaemia in T1DM, both of which improve clinical status and decision to manage at home.

Similar limitations outline in chapter 2 apply to this study given the replicated methods applied. In addition, the fewer clinical variables on LAS arrival and departure were included in the lockdown regression analysis. Importantly, the absence of cognitive impairment (GCS) data and respiratory rate, both variables with significant outcomes in the 2018 study.

The emergency hypoglycaemia incidents during lockdown were largely comprised of individuals with T2DM, a significant shift from the predominantly T1DM incidents attended during the control period. A rise in DKA presentations among the T2DM population during COVID-19 is reported within the literature (417), with such cases likely to be commenced on insulin therapy thereafter. Initiating insulin treatment is fraught with many challenges including the ability to identify and self-manage hypoglycaemia. The impact is potentially worsened by lockdown-imposed restrictions limiting access to support and education from respective diabetes care providers. As previously stated, invasive

therapy is usually reserved for compromised cases. However, lockdown saw significantly lower hospital conveyance rates in T2DM despite proportionally more incidents receiving parenteral treatment, and no significant change in individuals declining conveyance, further emphasising an assertive endeavour to 'see and treat'.

Figure 3.1. Flow chart to illustrate the pre-labelled paramedic diagnostic categories and hierarchical stratification used to allocate incidents with confirmed diabetes into three diagnostic groups (T1DM, T2DM, and other between (24/3/2018 – 20/04/2018).
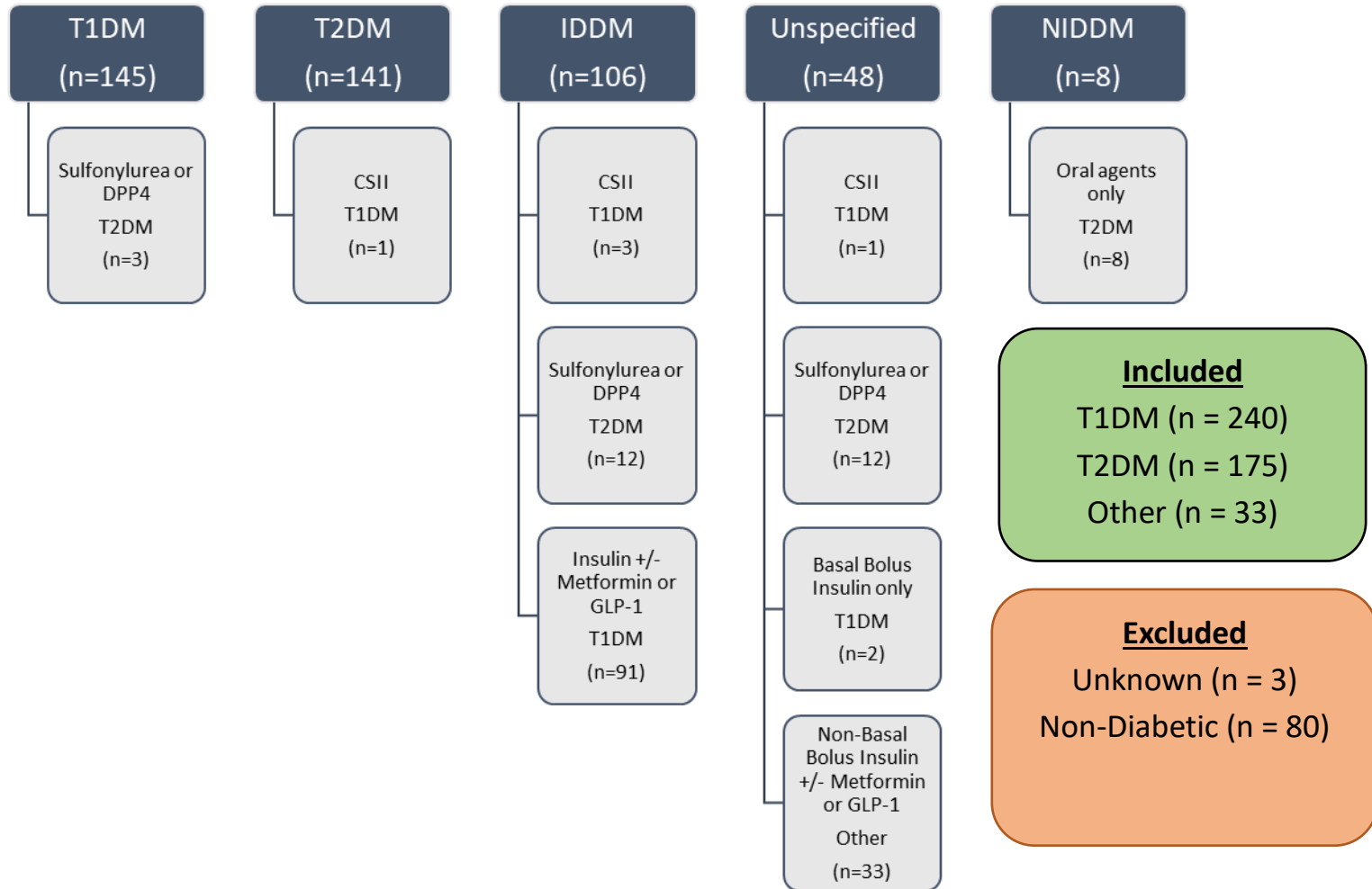
Figure 3.2. Flow chart to illustrate the pre-labelled paramedic diagnostic categories and hierarchical stratification used to allocate incidents with confirmed diabetes into three diagnostic groups (T1DM, T2DM, and other between (24/3/2020 – 20/04/2020).

120
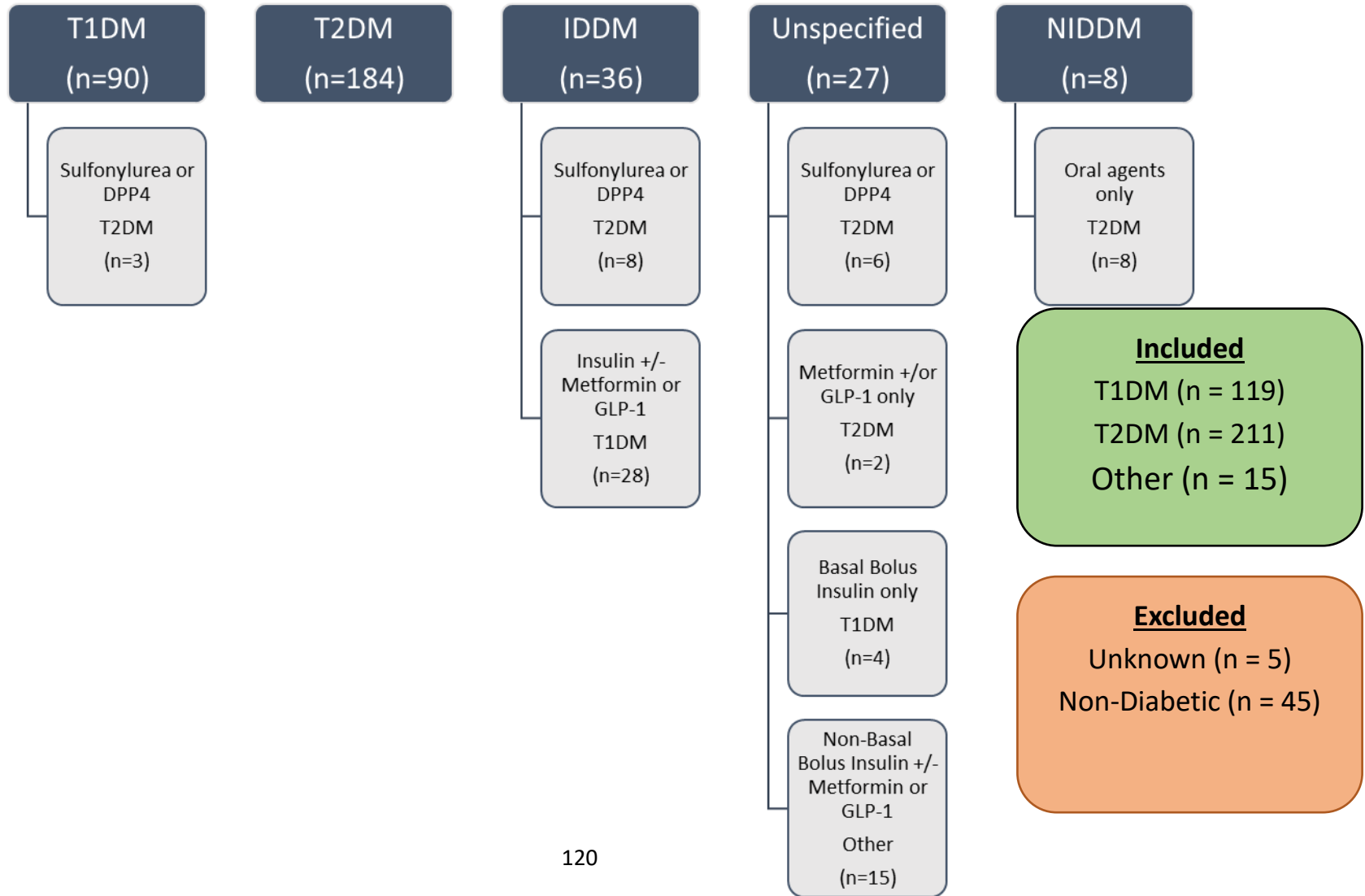
Confirmed Diabetes Database											
	All			Stratified T1DM			Stratified T2DM			Others	
	2018	2020	p	2018	2020	p	2018	2020	P	2018	2020
N**	448	345		240 (53.6%)	119 (34.5%)	<0.01	175 (39.1%)	211 (61.2%)	<0.01	33 (7.4%)	15 (4.3%)
Median Age (IQR)*	67 (51-78)	72 (61-82)	<0.01	56 (40-72)	60 (48.3-73)	0.08	74 (66-81)	77 (68-84)	0.03	70 (55-82)	69 (61-81)
Males (n)**	52.5% (235)	52.5% (181)	0.99	58.3% (140)	58.5% (69)	0.98	47.4% (83)	50.5% (107)	0.55	36.4% (12)	33.3% (5)
Response Time (mins): Median (IQR)*	11.1 (7.0-17.1)	11.4 (6.8-23)	0.07	10.3 (6.7-15.4)	9.5 (6.1-18.4)	0.84	12.5 (8.6-18.9)	12.9 (7.2-28.9)	0.59	9.1 (6.9-11.8)	11.2 (10.1-20.9)
Labelled hypoglycaemia by EMS call handler (n) ***	44.2% (198)	39.7% (137)	0.21	55.5% (133)	51.3% (61)	0.51	30.1% (53)	32.7% (69)	0.63	36.4% (12)	46.7% (7)
Alcohol (n)**	4.2% (19)	0.87% (3)	<0.01	5.8% (14)	1.69% (2)	0.07	1.1% (2)	0.47% (1)	0.11	3% (1)	0
First Glucose: Median (IQR)*	2.4 (1.9-3.1)	2.4 (1.9-2.8)	0.18	2.3 (1.8-2.9)	2.3 (1.6-2.9)	0.44	2.6 (2.15-3.2)	2.4 (2-2.8)	<0.01	2.3 (1.7-2.6)	2.4 (2.2-3.5)
Final Glucose: Median (IQR)*	5.6 (4.4-7.5)	5.7 (4.4-7.4)	0.82	5.8 (4.7-7.8)	6.2 (4.8-8.1)	0.30	5.2 (4.2-6.8)	5.5 (4.3-7.2)	0.39	5.3 (4.2-7.5)	4.4 (4-6.2)
Oral glucose (n)**	78.1% (350)	74.8% (258)	0.50	77.1% (185)	78.8% (93)	0.34	78.9% (138)	72.6% (154)	0.20	81.8% (27)	73.3% (11)
Parenteral glucose/glucagon (n)**	49.1% (220)	58% (200)	0.01	53.3% (128)	54.2% (64)	0.87	41.7% (73)	62.2% (132)	<0.01	51.5% (19)	26.7% (4)
Conveyed to hospital (n)**	46.7% (209)	44.3% (153)	0.52	29.6% (71)	25.4% (30)	0.41	69.1% (121)	55.2% (117)	<0.01	51.5% (17)	40% (6)
Patient declined (n) ***	10.4% (25)	8.9 (17)	0.56	11.8% (20)	13.5% (12)	0.68	7.4% (4)	4.3% (4)	0.40	(1)	(1)

Table 3.1. Baseline demographics, blood glucose levels measured on arrival and before departure, administered treatment and decision to convey to hospital for the pre-lockdown (2018) and during lockdown (2020) stratified diabetes subset. Results are expressed as mean (SD), median (IQR), and % (n). Statistically significant (p<0.05) differences between the 2018 and 2020 groups measured by Mann-Whitney test* and Pearson's chi-squared test**.

	Parenteral therapy (Control 2018)		Parenteral therapy (Lockdown 2020)		Conveyed to hospital (Control 2018)		Conveyed to hospital (Lockdown 2020)	
	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p
Age	1.0 (0.99-1.02)	0.85	**1.04 (1.02-1.06)**	**<0.01**	1.0 (0.99-1.02)	0.71	1.01 (0.99-1.03)	0.55
Female	0.98 (0.58-1.67)	0.95	1.28 (0.73-2.26)	0.39	1.27 (0.81-2.00)	0.30	0.83 (0.49-1.40)	0.49
Response time	0.99 (0.99-1.00)	0.38	0.99 (0.99-1.00)	0.23	0.99 (0.99-1.01)	0.88	0.99 (0.99-1.01)	0.99
Arrival glucose	**0.09 (0.05-0.15)**	**<0.01**	**0.17 (0.11-0.28)**	**<0.01**	0.81 (0.64-1.01)	0.06	**1.55 (1.01-2.39)**	**0.04**
Final glucose	N/A	N/A	N/A	N/A	0.95 (0.87-1.05)	0.31	**0.84 (0.75-0.94)**	**<0.01**
Parenteral Therapy	N/A	N/A	N/A	N/A	1.35 (0.78-2.36)	0.28	**3.75 (1.94-7.26)**	**<0.01**
Oral glucose	**0.08 (0.03-0.22)**	**<0.01**	**0.11 (0.04-0.30)**	**<0.01**	0.56 (0.30-1.05)	0.07	**0.36 (0.19-0.68)**	**<0.01**
†T2DM	0.98 (0.54-1.76)	0.94	1.03 (0.52-2.01)	0.94	**5.81 (3.41-9.90)**	**<0.01**	**2.79 (1.47-5.31)**	**<0.01**

Table 3.2. Binomial logistic regression analysis of predictors of being administered parenteral rescue treatment and conveyance to hospital in the pre lockdown (2018) and lockdown (2020) stratified confirmed diabetes subset. Odds ratios (95% confidence intervals) and p values are shown with significances p<0.05 in bold.

	Complete Dataset											
	All			T1DM			T2DM			Others		
	2018	2020	p	2018	2020	p	2018	2020	p	2018	2020	p
N*	531	395		145 (27.3%)	90 (22.8%)	0.12	**141 (26.6%)**	**184 (46.6%)**	**<0.01**	245 (46.1%)	121 (30.6%)	
Median Age (IQR)*	**64 (46-77.5)**	**71 (58-82)**	**<0.01**	52 (38-67)	57 (44.5-68.8)	**0.04**	73 (66-80)	77 (68-84)	**<0.01**	61 (38-79)	67 (50-81)	0.06
Males (n)**	51% (271)	52.7% (208)	0.63	65.5% (95)	53.3% (48)	0.06	47.5% (67)	52.2% (96)	0.41	44.4% (109)	52.9% (64)	0.13
Response Time (mins): Median (IQR)*	11.1 (7.0-17.3)	11.4 (6.8-25.1)	0.05	9.7 (6.0-14.7)	9.5 (6.0-18.3)	0.34	13.0 (8.8-18.4)	12.9 (7.1-23.2)	0.99	10.6 (7.0-17.2)	11.2 (7.3-32.8)	0.14
Alcohol (n)**	5.1% (27)	3% (12)	0.12	6.2% (9)	2.2% (2)	0.15	2.1% (3)	1.08% (2)	0.19	6.1% (15)	7.4% (9)	0.61
First Glucose: Median (IQR)*	2.5 (1.9-3.1)	2.4 (1.9-2.9)	0.08	2.3 (1.7-2.7)	2.2 (1.6-2.8)	0.99	**2.6 (2.2-3.3)**	**2.4 (2-2.8)**	**<0.01**	2.6 (1.9-3.2)	2.5 (2-3.3)	0.81
Final Glucose: Median (IQR)*	5.4 (4.3-7.3)	5.6 (4.4-7.4)	0.45	5.8 (4.8-7.8)	6.4 (5.2-8)	0.31	5.3 (4.2-7.4)	5.4 (4.1-7.1)	0.79	5.1 (4.1-6.7)	5.1 (4.3-7.4)	0.38
Oral glucose (n)**	76.8% (408)	73.4% (290)	0.49	80.7% (117)	78.9% (71)	0.86	76.6% (108)	74.5% (137)	0.78	74.7% (183)	67.8% (82)	0.38
Parenteral glucose/glucagon (n)**	**44.4% (236)**	**54.2% (214)**	**0.02**	59.3% (86)	53.3% (48)	0.37	**41.8% (59)**	**62% (114)**	**<0.01**	37.1% (91)	43% (52)	0.19
Conveyed to hospital (n)**	51.8% (275)	49.9% (179)	0.06	30.3% (44)	21.1% (19)	0.12	**70.9% (100)**	**58.2% (107)**	**0.02**	53.4% (131)	43.8% (53)	0.13

Table 3.3. Baseline demographics, blood glucose levels measured on arrival and before departure by attending paramedics, administered treatment and decision to convey to hospital for the control period (2018) and during lockdown (2020) complete dataset. Results are expressed as mean (SD), median (IQR), and % (n). Statistically significant (p<0.05) differences between the 2018 and 2020 groups measured by Mann-Whitney test* and Pearson's chi-squared test**.

4. Chapter: Assessment of Impact of Real-time Continuous Glucose Monitoring on people presenting with severe Hypoglycaemia (AIR-CGM) study

4.1.   Introduction

The clinical and health economic impact of hypoglycaemia is well established and has been detailed in earlier chapters. Predominantly an iatrogenic complication of insulin therapy, most incidents of hypoglycaemia are non-severe and self-managed in the community. A large multi-national study reported a weekly average of 1.8 self-managed hypoglycaemia events, and 0.2-3.2 yearly accounts of severe hypoglycaemia in people with T1DM and insulin-treated T2DM (176,177). However, an episode of severe hypoglycaemia is known to strongly predict future hypoglycaemia, independent of treatment intensity (418). This was supported in my 6-month analysis of emergency hypoglycaemia, where 2862 incidents of severe hypoglycaemia were attended by LAS and individuals requiring assistance on more than one occasion were responsible for a third of all attended incidents (399).

Educating people on how to successfully identify and treat hypoglycaemia is proven to reduce the frequency of hypoglycaemia and is a significant component of many T1DM structured education programmes (321–324,331). Such interventions entrust individuals to self-manage their chronic disease by instilling a level of understanding that encourages positive health behaviour. Nonetheless, many people with diabetes continue to experience severe hypoglycaemia despite full engagement with structured education. Included in this group are individuals with complete IAH whose only realisation of hypoglycaemia would occur after they are incapacitated. There is also an

understanding of refractory changes to intracranial arousal and reward regions associated with IAH that could limit reception to educational and psychological interventions among these individuals (210).

Strategies that prioritise early detection of hypoglycaemia are essential to protect this vulnerable subset from the vicious cycle of recurrent hypoglycaemia. Wearable interstitial glucose monitoring devices facilitate convenient and frequent glucose monitoring, with RT-CGM and the newly licensed Freestyle Libre 2 providing impending hypoglycaemia alarm functionality proven to improve hypoglycaemia outcomes (207,376). At the time of this study, NICE supported NHS funded RT-CGM use in T1DM adults with any of the following; more than one episode of hypoglycaemia requiring third-party assistance, complete IAH, more than 2 episodes of asymptomatic hypoglycaemia affecting daily life per week, an extreme fear of hypoglycaemia, and a HbA1c greater than 75mmol/mol despite >10 daily capillary glucose tests (390). Provision should only be by a centre with expertise in manage CGM in individuals willing to use the technology at least 70% of the time. In a real-world setting, initiating RT-CGM is largely dependent on how quickly high-risk (eligible) individuals can be identified and scheduled for initiation. Identifying eligible individuals usually occurs during annual/biannual clinic appointments and scheduling an initiation date can take additional weeks depending on time and staff availability. These are among a few challenges that delay access to RT-CGM in eligible individuals at increased risk of hypoglycaemia. No clinical trials to date have evaluated the impact of introducing RT-CGM soon after severe hypoglycaemia when individuals are at increased risk of developing further episodes.

4.2.   Aims

The aim of this study "Assessment of the Impact of Real-time Continuous Glucose Monitoring on People Presenting with Severe Hypoglycaemia (AIR-CGM)" is to assess the impact of early RT-CGM

supported remotely by a specialist healthcare team on the frequency, duration, awareness, and severity of hypoglycaemia in people with T1DM soon after an episode of severe hypoglycaemia.

The primary outcome is percentage time in clinically significant hypoglycaemia (<3.0mmol/L). The International Hypoglycaemia Study Group (IHSG) recommend reporting hypoglycaemia in studies as < 3.0 mmol/l (55mg/dL), and was therefore used as the basis for the primary study outcome (203).

Secondary outcomes included the number of severe and persistent hypoglycaemia episodes (sensor glucose <3.0mmol/L (55mg/dL) for >20 minutes), percentage time below range <3.9mmol/L (70mg/dL), time in euglycaemia 3.9-7.8mmol/L, time in target range 3.9-10mmol/L (70-180mg/dL), and time in hyperglycaemia >10mmol/L. HbA1c and other CGM derived metrics including, mean glucose, low blood glucose index (LBGI), mean absolute glucose (MAG), glucose management indicator (GMI), coefficient of variation (CV), and standard deviation (SD) were also analysed. Diabetes specific quality of life outcomes were also assessed using, Diabetes Treatment Satisfaction Questionnaire (DTSQ), Problem Areas in Diabetes questionnaire (PAID), Hypoglycaemia Fear Survey (HFS-II), Gold score, and CGM usability survey.

This is the first study to assess the impact of RT-CGM compared to standard self-monitoring of blood glucose (capillary glucose testing) soon after an episode of severe hypoglycaemia requiring ambulance assistance or admission to the Emergency Department.

4.3.   Methods

4.3.1. Recruitment

Recruitment was undertaken in collaboration with the LAS and local emergency departments serving the diverse London population, recruitment flow chart illustrated in Figure 4.1. To be included in the trial participants were required to be 18 years and older, suffered an episode of severe hypoglycaemia requiring ambulance assistance within 2-weeks, and have an established diagnosis of T1DM based on clinical features for more than 3-years. Participants were excluded if they had used real-time CGM or flash glucose monitoring within the last 6 months, were using a pre-mixed (biphasic) insulin preparation, were pregnant or planning a pregnancy, breastfeeding, were enrolled in another clinical trial, and had no access to a computer or smartphone. Reduced manual dexterity, severe visual impairment, and active or investigated malignancy were also grounds for exclusion. The study aimed to target adults with T1DM at high risk of suffering from recurrent severe hypoglycaemia who could benefit from RT-CGM. The recruitment policy is in line with other trials investigating adults at increased risk of hypoglycaemia (265,329), and included individuals with a long duration of diabetes, people with hypoglycaemia related autonomic dysfunction, and first presentations of severe hypoglycaemia secondary to temporary risk factors. Inclusion of participants with persistent risk factors such as drug or alcohol use were assessed on a case basis.

All individuals attended by LAS with an episode of severe hypoglycaemia and deemed well enough to be discharged at site (not conveyed to hospital) underwent an on-site pre-screening eligibility check by the LAS referral team. Details of individuals that met the eligibility criteria were handed over to a clinician in the Emergency Operations Centre who contacted the individual by telephone within 2 hours to check on their welfare. If the individual had capacity and was considered well enough, details of the trial were introduced, and verbal consent agreed to pass their name and contact details onto the investigating team. These individuals were contacted by the investigating team to

schedule a date for screening. Recruitment from emergency departments was carried out retrospectively by searching the diagnosis code "hypoglycaemia" on the admissions database daily.

Participants were withdrawn if their ability to give informed consent became impaired. Participants were also withdrawn at the chief investigator's discretion or if glucose control was negatively impacted using either intervention.

4.3.2. Study Protocol

This study was conducted as a twelve-week randomised control trial analysing the impact of RT-CGM following severe hypoglycaemia compared to usual care in adults with T1DM (see Figure 4.2). Once participants were referred onto the investigating (research) team, I was responsible for arranging and conducting screening, follow-up (remote and face to face), and exit visits with support from a research nurse.

Screening visit

 Once consented, participants underwent full a clinical assessment including medical history and examination, 12-lead ECG, non-fasting venous blood tests (HbA1c, plasma glucose, renal function, serum C-peptide, thyroid function test, 9 am cortisol, and coeliac serology). Women of childbearing age took a urine pregnancy test to ensure eligibility. Participants were subsequently randomised to receive RT- CGM (intervention) or continue self-monitoring blood glucose (SMBG) as per standard care (control) (Figure 5.2). I used sealedenvelope.com to randomise and stratify participants by insulin delivery modality (MDI or CSII).

I applied the Dexcom G6 CGM to participants in the RT- CGM group according to the manufacturer's instructions and provided additional sensors to last the 12-week duration of the trial. Low glucose

alert settings were standardised at <4.4 mmol/L for all participants at the start of the study and depending on participant preference were reduced to <4 mmol/L following the 2-week telephone visit. Participants were permitted to modify high glucose alerts. Participants in the control group (SMBG) were instructed to wear blinded CGM at weeks 1 and 2, weeks 4 to 6, and weeks 9 to 12 using the Dexcom G6 system (Figure 5.2). The absence of hypoglycaemia alarms and no visibility of real-time glucose data using blinded CGM allowed for comparative glucose metrics to be collected without impacting measurements. Like the RT-CGM group, controls were shown how to insert the Dexcom G6 during the screening visit and provided with sensors to last the duration of the trial. Participants were instructed to change the Dexcom G6 sensor every ten days according to the manufacturer's instructions (or sooner in the event of sensor failure). Capillary blood glucose testing was advised for all participants in the event of symptomatic hypo- or hyperglycaemia, sensor failure, or if the CGM sensor was out of the desired range. The RT-CGM group had their sensors paired to their personal smartphone or a non-blinded Dexcom receiver. CGM data for smartphone users was uploaded automatically to an anonymous study account on the secure Dexcom Clarity server. Participants using non-blinded receivers were shown how to manually upload data on the Dexcom clarity web app. I instructed the SMBG group to perform capillary blood glucose measurements a minimum of 4-times a day and send glucose meter downloads ahead of scheduled telephone follow up visits.

All participants received a structured education refresher before commencing the trial from myself or a research nurse. Education was from a predefined curriculum and supported by independent written materials focused on hypoglycaemia avoidance, recognition, and treatment. Participants also completed a semi-structured interview and diabetes specific quality of life questionnaires (DTSQ, PAID, HFS-II, CGM usability, and Gold).

Telephone visits follow-up

All participants were provided telephone support from a clinical diabetes specialist (myself) who had access to RT-CGM measurements from the RT-CGM group (intervention) and capillary glucose meter measurements from the SMBG group (control). Telephone follow-up addressed any technical issues and suggested insulin dose adjustments to optimise glucose control and reduce hypoglycaemia. Telephone support was provided twice in the first week, weekly for the next 3 weeks, and every 2 weeks thereafter for all participants. Dates and times for follow up telephone visits were made at the end of each appointment.

End of study visit

At the end of 12 weeks, I repeated blood tests to assess HbA1c and uploaded blinded Dexcom receivers returned by the SMBG group. Participants also completed a semi-structured interview and repeated diabetes specific quality of life questionnaires (DTSQ, PAID, HFS-II, CGM usability, and Gold).

4.3.3. Pandemic adaptations

Due to restrictions imposed by the COVID-19 lockdown, adaptations were made to minimise data loss and participant withdrawal. HbA1c sample kits and questionnaires with pre-paid return packaging were delivered to participants help overcome restrictions on social interaction.

4.3.4. Ethics

Ethical approval was obtained from the London Hampstead Research Ethics Committee (18/LO/1525) and the HRA. The study was conducted in accordance with the recommendations for

physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

4.3.5. Statistics and Data analysis

Based on findings from the I HART CGM trial (265), percentage time spent in hypoglycaemia (<3.0mmol/L) was expected to be 64% lower in the CGM group compared to the self-monitoring group, [mean (SD): CGM group 2.1% (2.3%); self-monitoring group 5.8% (5.9%)]. To significantly achieve this (p<0.05) with 80% power, 25 participants were needed in each group. To account for a potential 10% drop-out 55 participants were proposed for recruitment.

Due to non-compliance wearing blinded CGM data among the SMBG group, baseline data were derived from a minimum of 14 continuous days of CGM within the first six-weeks. Endpoint data represented CGM use during the last 30 days of each treatment period. Intention to treat analysis: The primary and secondary outcomes were assessed by the non-parametric Kruskall-Wallis and Fisher's exact hypothesis tests. Due to non-uniform CGM usage during the baseline and endpoint, clinically significant hypoglycaemia <3.0mmol/L lasting for >20minutes was measured as a percentage of the total number CGM measurements obtained during the respective periods. Overnight analysis of CGM included data recorded between 00:00 to 07:00 hrs. Results were considered statistically significant if p<0.05, with statistical analyses performed using Stata version 13 (StataCorp, College Station, Texas 77845 USA).
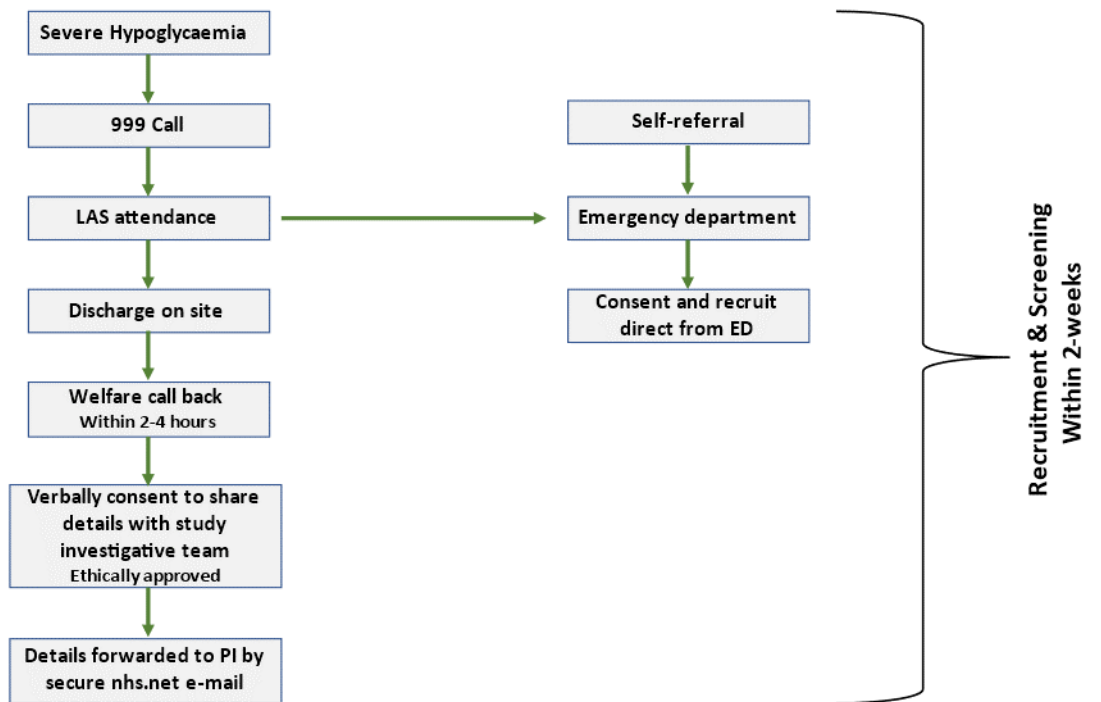
Figure 4.1. Recruitment Flow Chart. LAS = London Ambulance Service
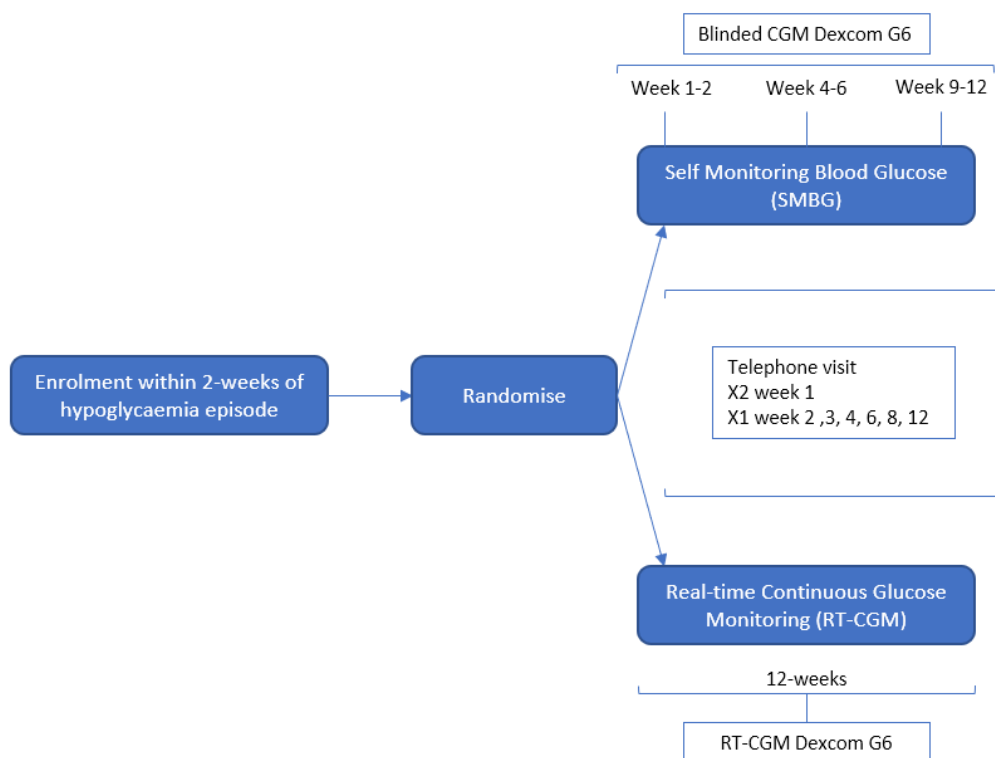
Figure 4.2. Assessment of Impact of Real-time Continuous Glucose Monitoring on people presenting with severe hypoglycaemia (AIR-CGM) study design

4.4.   Results

Thirty-five adults with T1DM (all participants had a measured c-peptide of <49pmol/L) were recruited and randomised to receive RT-CGM or continue standard care (SMBG) within 2-weeks of severe hypoglycaemia. All participants were receiving MDI insulin therapy. Of the 35 included participants, 30 completed the trial to endpoint (16 RT-CGM and 14 SMBG). The cohort distribution was further skewed to include n=15 CGM and n=8 SMBG due to a disproportionate number of SMBG participants withdrawing and not wearing blinded CGM as instructed in the protocol. The RT-CGM group saw one withdrawal due to an incidental diagnosis of adrenal insufficiency following screening blood tests. In the control group, two participants chose to withdraw immediately after being randomised to the SMBG arm, one participant was withdrawn on account of being admitted to

hospital during the trial, and another withdrew after commencing NHS funded RT-CGM. An overview of recruitment is illustrated in Figure 4.3.

The median (IQR) age, duration of diabetes, and BMI of the thirty participants completing the study was 41 years (34.3-54.5), 29 years (19-37), and 24.9 kg/m^2 (21.9-29.0) respectively. All baseline characteristics are illustrated in Table 4.1. The median % of scheduled telephone consultations attended by participants was 50% (33-75), with no significant difference between groups. Insufficient CGM use (real-time and blinded) resulting in withdrawal from head-to-head glycaemic metric analysis was observed in 23% of participants, with a significantly higher rate among the SMBG participants using blinded RT-CGM (43% vs 6%, p=0.02). As a result, 15 RT-CGM and 8 SMBG participants were included in the CGM derived glucose outcome analysis (Figure 4.3).

The four episodes of severe hypoglycaemia requiring third party assistance were reported by participants in the SMBG group. All episodes were reported by different participants, with one sustaining a fracture after a hypoglycaemia related fall (Table 4.1).

Contrasting outcomes were observed when comparing hypoglycaemia metrics between the two groups from baseline to endpoint. There was a reduction in percentage time spent in hypoglycaemia <3.0mmol/L and <2.8mmol/L in the RT-CGM group and an increase among the SMBG controls. A significant difference in change between groups was observed for both percentage time <3.0mmo/L (RT-CGM -0.06 [-1.4 to 0.2] vs SMBG 1.6 [-0.9 to 5.2], p=0.03) and time <2.8mmo/L (-0.05 [-1.1 to 0.2] vs 1.4 [-0.3 to 4.8], p=0.02). A significant difference in percentage of overnight hypoglycaemia events <3.0mmol/L lasting more than 20 minutes was also seen, with a reduction in the RT-CGM group (-0.03 [-0.1 to 0.01]) and an increase among SMBG controls (0.05 [-0.03 to 0.4]), p=0.02. A similar trend was observed for median low blood glucose index (LGBI), with a significant difference in change measured between groups (RT-CGM -0.04 [-0.5 to 0.1] vs SMBG 0.85 [-0.2 to 2.0], p=0.03).

No significant difference was observed for time spent <3.9mmol/L and other predefined thresholds of time in range and hyperglycaemia. The SMBG controls saw significantly greater reductions in mean glucose (-0.03 [-0.28 to 0.31] vs -0.78 [-1.5 to 0.1], p=0.03), GMI (-0.12 [-1.3 to 1.5] vs -3.66 [-7.0 to 0.3], p=0.03), and MAG (0.04 [-0.3 to 0.3] vs -2.0 [-10.7 to 0.3], p<0.01). Glycaemic outcome results are summarised in Table 4.2.

After excluding haemolysed samples, baseline HbA1c was measured in 14 RT-CGM participants and 12 in the SMBG group respectively. However, despite measures to overcome restrictions posed by the COVID-19 pandemic, this figure reduced to 10 RT-CGM and 3 SMBG due to participant withdrawal and failure to return postal HbA1c samples. There was no significant change in HbA1c within or between groups. The median Gold score increased from 4 (3-5) at baseline to 5 (3-6) for all participants, with no significant change within or between groups. Participants randomised to receive RT-CGM saw significantly improved median diabetes treatment satisfaction questionnaire (DTSQ) scores after 12-weeks, 29.5 (28-33.3) vs 38 (37-39), p<0.01. No significant change was seen between or within groups when comparing the remaining participant-reported questionnaires including measures of hypoglycaemia awareness (Gold score) and diabetes-specific quality of life (DTSQ, PAID, and HFS-II scores), see Table 4.3.
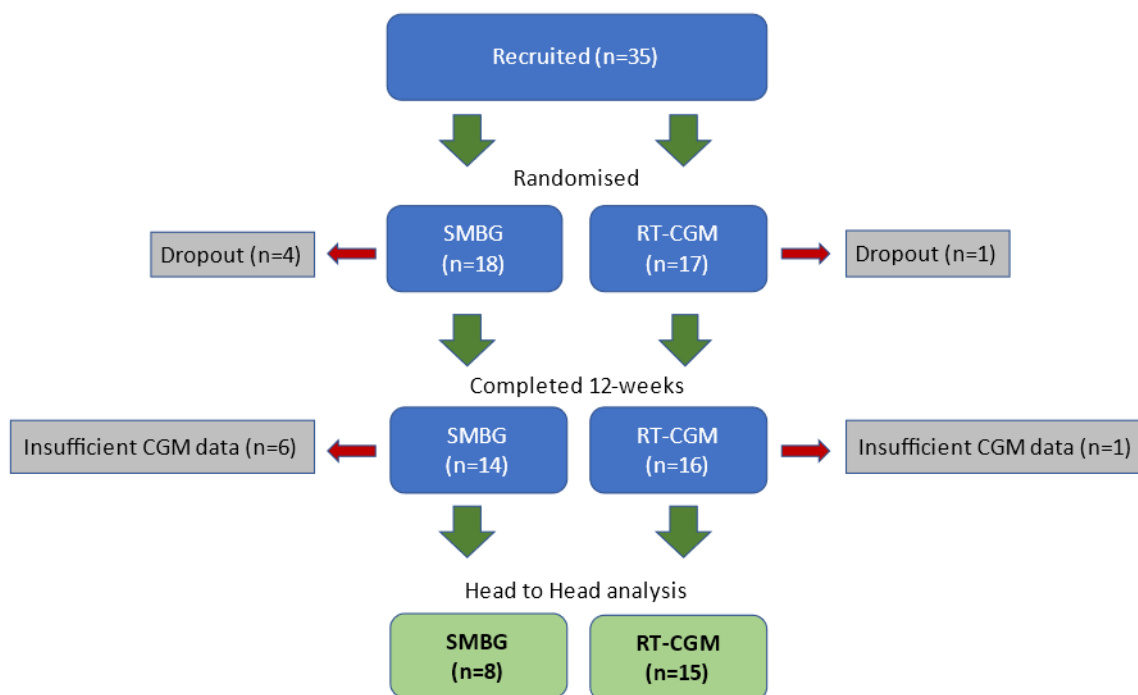
Figure 4.3. Flow chart illustrating randomisation, withdrawal, and sufficient CGM use

	ALL (n=30)	RT-CGM (n=16)	SMBG (n=14)	P
Age (years)	41 (34.3-54.5)	38.5 (31.3-52.3)	45.5 (35.3-57.8)	
Gender (male)	17 (56.7%)	8 (50%)	9 (64.3%)	
Duration of diabetes (years)	26 (19-37)	24 (22-36)	27 (13-36)	
BMI (kg/m^2)	24.9 (21.8-29.0)	25.2 (23.0-28.0)	23.4 (21.3-29.0)	
Telephone visit adherence	50 (33-75)	61 (28-89)	44 (33-56)	0.09
Insufficient CGM application (n)	23% (7)	6% (1)	43% (6)	**0.02**
Severe Hypoglycaemia (n)	4 (13.3%)	0	4 (28.6%)	**0.04**

Table 4.1. Baseline demographics and protocol adherence (telephone consultations and CGM use). Results are expressed as median (IQR) and % (n). P values of <0.05 are significant and highlighted in bold.

Metric	Control Baseline (median, IQR) N=8	Control Endpoint (median, IQR) N=8	CGM Baseline (median, IQR) N=15	CGM Endpoint (median, IQR) N=15	Control change from baseline to endpoint (median, 95%CI)	CGM change from baseline to endpoint (median, 95%CI)	p
% time in range							
3.9-10mmol/l (70 -180mg/dL)	51.5 (46.2-57.5)	62.1 (50.2-68.8)	57.3 (50.5-63.4)	58.9 (46.3-67.5)	6.9 (-4.1 to 14.5)	0.12 (-2.4 to 3.9)	0.33
% time in hypoglycaemia							
<3.9mmol/l (<70mg/dL)	8.1 (5.0-10.6)	9.9 (6.8-12.0)	7.1 (3.3-9.0)	6.4 (2.5-10.7)	2.7 (-1.7 to 6.0)	0.06 (-1.6 to 0.9)	0.12
<3.0mmol/l (<54mg/dL)	2.2 (0.9-4.1)	3.3 (1.9-5.7)	2.7 (0.9-3.5)	1.8 (0.3-3.4)	**1.6 (-0.9 to 5.2)**	**-0.06 (-1.4 to 0.2)**	**0.03**
<2.8mmol/l (<50mg/dL)	1.2 (0.5-2.6)	2.6 (0.9-4.8)	1.6 (0.5-2.6)	1.1 (0.2-2.3)	**1.4 (-0.3 to 4.8)**	**-0.05 (-1.1 to 0.2)**	**0.02**
% time in hyperglycaemia							
>10mmol/l (>180mg/dL)	37.1 (32.3-42.6)	28.1 (23.2-35.6)	33.6 (30.2-43.7)	35.3 (25.0-46.7)	-9.5 (-14.6 to -0.7)	-0.01 (-3.6 to 3.0)	0.05
Glycaemic variability measures							
Mean	9.0 (8.8-9.5)	8.2 (7.8-8.9)	8.9 (8.3-9.9)	9.1 (7.9-10.2)	**-0.78 (-1.5 to 0.1)**	**-0.03 (-0.28 to 0.31)**	**0.03**
GMI (%)	55.1 (54.0-57.5)	51.4 (49.4-54.4)	54.6 (51.8-59.2)	55.4 (49.9-60.8)	**-3.66 (-7.0 to 0.3)**	**-0.12 (-1.3 to 1.5)**	**0.03**
Standard deviation	4.2 (3.7-4.7)	3.6 (2.9-4.3)	3.7 (3.0-4.3)	3.7 (2.9-4.3)	-0.58 (-1.2 to 0.7)	0.11 (-0.3 to 0.2)	0.14
CV (%)	0.4 (0.4-0.5)	0.4 (0.4-0.5)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	-0.02 (-0.1 to 0.1)	-0.03 (-0.03 to 0.01)	0.74
LBGI	1.8 (1.0-2.5)	2.4 (1.7-3.0)	1.6 (0.9-2.2)	1.4 (0.7-2.4)	**0.85 (-0.2 to 2.0)**	**-0.04 (-0.5 to 0.1)**	**0.03**
MAG	5.3 (4.1-8.7)	2.8 (2.7-3.4)	3.5 (2.9-3.7)	3.1 (2.8-3.5)	**-2.0 (-10.7 to 0.3)**	**0.04 (-0.3 to 0.3)**	**<0.01**
% <3.0mmo/L events >20mins							
24 hours	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.2 (0.1-0.2)	0.1 (0.02-0.2)	0.01 (-0.07 to 0.13)	-0.02 (-0.1 to 0.02)	0.18
Overnight (00:00 to 07:00)	0 (0-0.2)	0.3 (0.1-0.4)	0.2 (0.1-0.3)	0.1 (0.04-0.2)	**0.05 (-0.03 to 0.4)**	**-0.03 (-0.1 to 0.01)**	**0.02**

Table 4.2. Change in glycaemic outcomes from ≥14 continuous days of CGM within the first six-weeks (baseline) and last 14 days (endpoint). Results are expressed as median (IQR) or (95% CI). P values of <0.05 are significant and highlighted in bold. *GMI = Glucose Management Indicator, CV = Coefficient of variation, LBGI = Low blood glucose index, MAG = Mean absolute glucose*

Questionnaire	All Baseline (median, IQR)	All Endpoint (median, IQR)	Control (SMBG) Baseline (median, IQR)	Control (SMBG) Endpoint (median, IQR)	p	Sensor (CGM) Baseline (median, IQR)	Sensor (CGM) Endpoint (median, IQR)	p	Change from baseline (SMBG) (median, 95%CI)	Change from baseline (CGM) (median, 95%CI)	p
Gold score Median (IQR)	(n=30) 4 (3-5)	(n=24) 5 (3.0-6.0)	(n=14) 3.3 (3-4.8)	(n=9) 3 (3-5.5)	0.90	(n=16) 4 (3-5.3)	(n=15) 5 (4-6)	0.33	(n=9) 0 (-0.6 to 1.7)	(n=15) 0 (-0.3 to 1.2)	0.67
HbA1c mmol/mol Median (IQR)	(n=26) 61 (54-71.8)	(n=13) 60 (54-67)	(n=12) 66.5 (56.8-77.3)	(n=3) 56 (47.5-64)	0.31	(n=14) 55 (51.8-63.8)	(n=10) 60 (54.5-66)	0.64	(n=3) 0 (-5.6 to 7.6)	(n=9) -3 (-9.2 to 3.7)	0.35
HFS II behaviour Median (IQR)	(n=30) 18 (12.3-29)	(n=25) 20 (17-23)	(n=14) 18 (12.3-19.5)	(n=10) 20.5 (18.3-25.5)	0.24	(n=16) 22 (14-29.6)	(n=15) 19 (16-22.5)	0.61	(n=10) 2.5 (-0.1 to 10.5)	(n=15) -1 (-6.6 to 4.3)	0.08
HFS II worry Median (IQR)	(n=30) 34.5 (23.3-44.5)	(n=25) 32 (21-47)	(n=14) 32.5 (23.5-44.0)	(n=10) 32 (25.3-35.0)	0.88	(n=16) 36.5 (22.3-44)	(n=15) 32 (20.5-50)	0.84	(n=10) 2 (-1.5 to 8.9)	(n=15) 0 (-4.7 to 5.4)	0.37
HFS II total Median (IQR)	(n=30) 53 (36.5-66.8)	(n=25) 49 (43-71)	(n=14) 49 (39.3-58.5)	(n=10) 50 (44.5-57.5)	0.66	(n=16) 60 (35.5-69.5)	(n=15) 49 (37-73)	0.83	(n=10) 4.5 (1.2 to 16.6)	(n=15) -1 (-9.5 to 7.9)	0.05
PAID Median (IQR)	(n=30) 27 (16.3-42.0)	(n=24) 29.5 (15.5-41.3)	(n=14) 26.5 (13.5-41.5)	(n=10) 36.5 (20.5-44)	0.73	(n=16) 27 (17.8-42.8)	(n=14) 28 (14.5-32.3)	0.68	(n=10) 11.5 (-1.8 to 22.4)	(n=14) -1.5(-11.0 to 5.9)	0.12
DTSQ Median (IQR)	(n=30) 28.5 (24.0-33.0)	(n=24) 37 (33-38.3)	(n=14) 26 (22-32.5)	(n=9) 30 (24-35)	0.26	**(n=16)** **29.5 (28-33.3)**	**(n=15)** **38 (37-39)**	**<0.01**	(n=9) 4 (-4.5 to 14.2)	(n=15) 7 (5.1 to 9.6)	0.32

Table 4.3. Change in questionnaire outcomes from screening (baseline) to conclusion at week-12 (endpoint). Results are expressed as median (IQR) or (95% CI). P values of <0.05 are significant and highlighted in bold. *HFS = Hypoglycaemia fear score, PAID = Problem Areas in Diabetes, DTSQ = Diabetes Treatment Satisfaction Questionnaire.*

4.5.   Discussion

As previously discussed, hypoglycaemia is common and, in most instances, managed independently. Hypoglycaemia requiring third party assistance from emergency services reflects an error in one of many aspects of self-management resulting in insulin carbohydrate mismatch and risk of repeated hypoglycaemia. The data presented is the first to demonstrate that rapid provision of RT-CGM following severe hypoglycaemia significantly improves hypoglycaemia outcomes compared to standard care. This is most evident in the disparity of recurrent severe hypoglycaemia between the two groups, with all four episodes reported by control group participants. Identifying recurrent severe hypoglycaemia in 28.6% of control participants suggests worsening hypoglycaemia following an emergency presentation and demonstrates the impact of RT-CGM in eliminating this risk. This is further supported by a significant difference in change between groups in the time spent in hypoglycaemia <3.0mmol/L. The pre-existing risk of hypoglycaemia in the study group was further emphasised by the baseline Gold score of 4 (3-5), confirming diminished hypoglycaemia awareness and reaffirming evidence associating IAH with severe hypoglycaemia. This study supports data from large RCT's showing a reduction in percentage time in hypoglycaemia <3.0mmol/L and other hypoglycaemia outcomes in people with IAH after applying RT-CGM (257,258,265).

At a glance, the comparatively greater reductions in average glucose control metrics (Mean, GMI, and MAG) in the control (SMBG) group implies the addition of frequent specialist clinical support to standard care can have a measurable impact in improving glycaemic control. However, the increased percentage time in hypoglycaemia seen in the control group suggests that without RT-CGM this is likely to increase exposure to hypoglycaemia, further highlighting the difficulty in reducing hypoglycaemia risk. This is supported in a large head-to-head analysis identifying the capacity for RT-CGM to successfully reduce HbA1c without added hypoglycaemia exposure in adults with T1DM (419).

Structured education as a clinical support tool is advocated as standard care in the national T1DM guidelines with many addressing hypoglycaemia prevention and management as part of their curriculum (14). Clinically significant hypoglycaemia <3.0mmo/L persisting beyond 20 minutes indicates a failure to timely identify or treat hypoglycaemia. The clinical implications of recurrent hypoglycaemia include physiological adaptations predisposing to impaired awareness and altered behavioural responses to hypoglycaemia, see Chapter 1.4.4. Despite participants undertaking formal structured education and a refresher immediately before commencing the trial, I observed an increase in the percentage of persistent hypoglycaemia (<3.0) overnight in the control group, with a significant change between groups (p=0.02). The provision of RT-CGM had a contrasting effect, highlighting the efficacy of CGM alarms while asleep in the context of diminished hypoglycaemia awareness.

Severe hypoglycaemia can have occupational and driving related implications with a non-represented population choosing to endure in silence in fear of driving or work restrictions. This was highlighted in a Danish study demonstrating a significant reduction in the rate of self-reported severe hypoglycaemia following the implementation of stricter European Union driving licence legislation in 2012 (420). Nonetheless, fear of hypoglycaemia remains one of the biggest barriers to achieving target glucose control, with individuals often choosing hyperglycaemia as a risk prevention strategy. The I-HART CGM pilot study and ALERTT1 trial successfully demonstrated improvement in worry related hypoglycaemia fear when transitioning from flash glucose monitoring to RT-CGM (265,421). Similarly, the DIAMOND study showed RT-CGM to improve diabetes-specific quality of life measures related to hypoglycaemia confidence, and reduce diabetes distress after 24-weeks (388). In keeping with these studies, the participants randomised to receive RT-CGM saw significant improvements in DTSQ scores after 12-weeks. However, neither RT-CGM or regular specialist consultations significantly impacted any of the remaining diabetes-specific quality of life scores. In a

relatively young study population, severe hypoglycaemia requiring third party emergency service assistance strongly indicates deficiency in delivered treatment, uptake of treatment, or both. The provision of frequent remote specialist advice was an attempt at optimising delivered treatment within the limits of what is available under the NHS. The process of organising and undertaking regular telephone consultations provided insight into the turbulent lives of this vulnerable group perpetuated and worsened by hypoglycaemia itself. Maintaining target glycaemic control and avoiding hypoglycaemia is a difficult task for even the most dedicated individuals, and often requires a habitually structured behaviour. The lifestyle of most of our participants reflected the realities of living in a modern city, with the majority either working busy jobs with little flexibility for meals, working anti-social hours, or dealing with personal stresses. This is evident in the telephone consultation attendance rate of 50%, after including successful consultations made after multiple attempts to contact participants and delayed consultations of up to 1-week. Feedback from participants emphasised difficulties in managing an already chaotic lifestyle when repeatedly exposed to hypoglycaemia, this in turn created a sense of resignation and acceptance of persistent hyperglycaemia among the control group. Despite frequent remote consultations aiming to safely mitigate hypoglycaemia, the control group saw an increase in time spent in hypoglycaemia.

Limitations to the study include the small numbers and challenges for the study team in maintaining participants in the control group as greater access to continuous glucose monitoring technologies became more widespread during the study period and participants found blinded monitoring periods challenging. The inclusion of individuals soon after emergency hypoglycaemia allowed a unique opportunity to investigate the immediate clinical and social impact of such a significant event. However, the disproportionate dropout and insufficient use of blinded CGM in the control group suggest the prospect of immediate RT-CGM access as a motivation for participation in this study. Despite encouragement and proposed plans for a one-way cross-over extension study

providing RT-CGM in the control group participants, many struggled to fully engage with the study protocol. This was likely exacerbated by the demotivating impact of recurrent severe hypoglycaemia identified when conducting regular telephone follow-up visits. The use of blinded and RT-CGM was standardised throughout the study. However, telephone support for control group participants was dependent on capillary glucose data downloaded and sent from a variety of participant owned glucometers. This made accessing SMBG data challenging due to the difficulty in supporting participants with varying levels of proficiency to download and share data from a range of different glucometers. Lastly, the unforeseen onset of the COVID-19 pandemic during the study prohibited many face to face visits and reduced uptake of blood tests (particularly endpoint HbA1c).

Despite its limitations, this study is the first to demonstrate the efficacy of RT-CGM immediately following severe hypoglycaemia and supports NICE endorsement of RT-CGM in T1DM adults at high risk of hypoglycaemia. Moreover, it highlights the limitations of current standard treatment, with even proactive follow-up having an insignificant effect on improving hypoglycaemia outcomes. The data reinforces the national incentive to increase CGM accessibility and makes a case for rapid CGM initiation following severe hypoglycaemia attended by emergency services. More importantly, it exposes the real-world obstacles faced by individuals with diabetes and supports RT-CGM provision for a vulnerable population living a non-modifiable lifestyle conducive to repeated hypoglycaemia. Repeating this study in the T2DM population exposed to severe hypoglycaemia would assess if the identified outcomes are reproducible in a population with an almost equal prevalence of emergency hypoglycaemia but not currently eligible for RT-CGM (399).

5. Chapter 5: An Adaptive Real Time Intelligent System to Enhance Self Care of Chronic Disease (ARISES) - Graphical User Interface (GUI) design

5.1.   Introduction

The physical and psychological burden of self-managing diabetes and its complications, in particular hypoglycaemia, have been highlighted and discussed in earlier chapters. I have also detailed the positive effect of RT-CGM and CSII across a variety of glycaemic control and quality of life measures, thus validating the impact of wearable technology in self-managing diabetes. This study aims to design an Adaptive Real-time Intelligent System to Enhance the Self-care of chronic diseases (ARISES). ARISES is a novel smartphone application integrating multiple data streams from wearable sensors to support people with T1DM in making lifestyle and therapeutic decisions (Figure 5.1). The system will provide dynamic glucose forecasts, meal insulin bolus recommendation (therapeutic advice), exercise and physical stress support, hypoglycaemia prevention through timely alarms and notifications, and behavioural change through identifying trends (lifestyle advice). Using an embedded machine learning algorithm, ARISES will recall previous outcomes and adapt future recommendations to deliver increasingly personalised decision support.

This chapter details the first phase in development describing the end-user focus groups, graphic user interface (GUI) design, and sub-analysis of observational clinical data collected to train the ARISES machine learning algorithm. An important requirement for the ARISES GUI was to support efficient interaction with the device while ensuring the user never lost focus of critical data. Each prototype version throughout the design process was presented at a series of semi-structured focus groups that included people with T1DM. The focus-groups served as a forum to identify requirements, obtain feedback, and validate design ideas from end-users. This study was funded by the engineering and physical sciences research council (EPSRC).
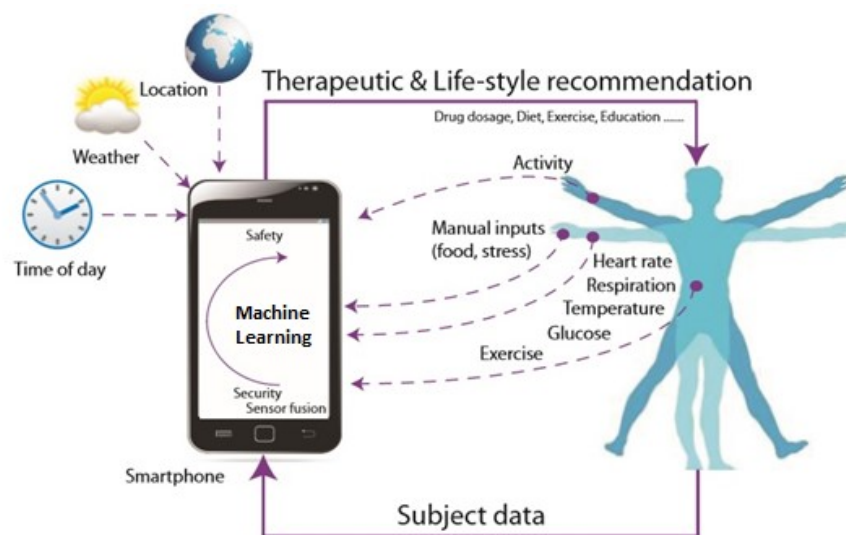
Figure 1: ARISES concept

Figure 5.1. Illustration of ARISES concept

5.2.   Aims

- Establish important usability requirements to incorporate into the ARISES GUI

- Collaboratively design a user-friendly GUI validated by end users with T1DM.

- Deliver efficient access to access decision support whilst maintaining sight of real time glucose outcomes.

5.3.   Methods

5.3.1. Recruitment

The first step in the design process was assembling a multidisciplinary team with a range of skills capable of delivering the proposed objectives. With the assistance of a research nurse, I oversaw clinical and patient safety measures, and interactions with participants. A specialist engineer in human computer interaction provided theoretic concepts and direction in drafting design ideas. Two engineers with a specialist interest in biotechnology were responsible for developing the application code and ensured design ideas remained feasible throughout the process. Lastly, end-users (people with T1DM) were recruited to provide feedback and ideas on the system design. I was responsible for recruiting participants with T1DM from the Imperial College Healthcare NHS trust T1DM outpatient clinics, registered research databases, and from interested participants who contact us.

5.3.2. Ethics

Ethical approval was obtained from the London - Fulham Research Ethics Committee (18/LO/1096) and the HRA. The study was conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

5.3.3. Multidisciplinary focus groups

The team convened on four occasions throughout the design process in a series of focus group meetings to gather feedback and discuss ideas on data presentation. In between focus groups,

additional meetings between the investigative team (excluding people with diabetes) were conducted. The specific objectives for each meeting were based around prototype designs and issues encountered from previous focus group outcomes. Focus group discussions were chaired by me and followed an interactive semi-structured format outlined below:

- Questionnaire with discussion agenda sent to participants in advance.

- 15-minute presentation of current design ideas and concepts.

- 40-minutes focused discussion and feedback on presentation objectives.

- 40-minutes focussed discussion on questionnaire.

- 25-minutes open floor discussion and conclusion

Meeting minutes were documented by an attending member of the investigative team. Outcomes from each focus group meeting, including collected participant questionnaire data, were anonymously shared among all attendees for validation. Validated outcomes were subsequently discussed among the investigative team (excluding individuals with T1DM) and where appropriate considered for integration in the GUI design.

5.4.   Results

5.4.1. Agreed outcomes

After four multidisciplinary focus group meetings it was unanimously agreed that a usable diabetes health app should maintain the ability to efficiently deliver the following five features

1. Input manual data parameters for carbohydrate, exercise, and stress.
2. Present past, current, and forecasted blood glucose outcomes.
3. Present recommended therapeutic advice (bolus insulin dosing).

4. Identify and present advice to situational and temporal blood glucose trends.

5. Explore the interrelations between entered data (macronutrients and exercise) and the forecasted outcomes (insulin dose recommendation and blood glucose) in real time.

To effectively meet these criteria, we identified five domains to input and present data to the user. These domains have been categorised into data inputs and outputs, as listed below.

INPUT

1. **FOOD** – Domain to input and visualise macronutrients (carbohydrate, protein, and fat) and alcohol parameters.

2. **EXERCISE** – Domain to enter duration and intensity of planned physical activity (current and planned).

3. **HEALTH** – Domain where users can access the glycaemic impact of recorded parameters significant to the management of diabetes. These include filter-adjusted blood glucose measurements, logged exercise, stress, and illness.

4. **ADVICE** – Domain where users can be presented with treatment and lifestyle suggestions based on trends associated with negative impact on blood glucose levels.

OUTPUT

5. **BIFOCAL DISPLAY** – Graphical presentation of real-time, historical, and forecasted blood glucose data with timestamped meal and exercise data to provide context.

Dividing the interface into data input and output domains provides a clean separation of functions and allows entered inputs to be contextualised by presenting outcomes in real-time (Figure 5.2). Avoiding hierarchy by ensuring these five domains remain visible and accessible on the home screen

are the cornerstone to ensuring the interface is easy to use. End users found this layout improved contextual engagement with glycaemic control without distraction from temporarily irrelevant features. Each input domain expands during interaction without obstructing the graphical blood glucose outputs and leaves enough space to display key information in non-active input domains (Figure 5.2).

Figure 5.2. The ARISES app GUI illustrating the input and expanded output domains in operation.

5.4.2. Output domain (bifocal display)

The bifocal display graphically illustrates RT-CGM data over the last 24-hours with a 30-minute glucose forecast. Presenting the graph on a 'bifocal display' allows the percentage time in target range and mean glucose readings from the previous three days to be represented to the left. Data from these days can easily be swiped into view as though scanning a reel of film. Colour coded

representations of time within, above, and below target blood glucose range allows for an easy grasp of glycaemic control. Forecasted glucose is illustrated as a dotted red line and a large visible arrow next to the current blood glucose informs and reassures the user of their blood glucose trajectory. Interaction with the current date on the bifocal display allows the user to select a historical date for interrogation. Clear labelling of the date ensures current glucose profiles are not confused with historical data. Details of the bifocal display are illustrated in Figure 5.3.

5.4.3. Input domains (food, exercise, health, and advice)

Food

The food domain allows users to announce meals and alcohol consumption by entering meal macronutrients in grams (carbohydrate, protein, and fat) and alcohol in units respectively (Figure 5.2). Meal entries are followed by a transition to the novel **adaptive bolus calculator** (Figure 5.6). The adaptive bolus calculator allows entered carbohydrate values to be adjusted with real-time changes in recommended bolus insulin dose and graphical forecasted glucose. Recommended insulin doses can be either accepted or modified independently with dynamic glucose forecasting before being confirmed. Entered meal carbohydrates are timestamped on the bifocal display (Figure 5.3). The included ability to save meal entries by selecting the star icon improves the efficiency of future interactions (Figure 5.4). When selecting a saved meal, the user will be informed of previous bolus recommendations, previous glucose outcomes, and will be able to contextualise data by transposing outcomes onto the bifocal display. By utilising the integrated smartphone camera function, users are able personalise labels with taken photographs. This feature is accessible by interacting with the camera icon within the food domain (Figure 5.2 and 5.4).

Exercise

The exercise domain allows planned exercise to be timestamped and saved for future reference. Exercise input includes a start time, duration, and subjective exercise intensity on a scale of light, moderate, and intense (1 − 3). Users will receive notifications of unanticipated forms of exercise identified by the physiological wristband (e.g., walking) which can be subsequently logged into the domain to strengthen the machine learning algorithm (Figure 5.2).

Health

The health domain offers the ability to filter events relevant to the management of diabetes (hypoglycaemia, exercise, illness, and stress) over the last 7, 30, or 60-days. Filtered events can be projected onto the bifocal display for detailed interrogation and review by the user's healthcare professional (Figure 5.5). The addition of stress and illness switches within the health domain allow users to announce these events to the machine learning algorithm. In time the system will learn variations in glucose homeostasis under the influence of these variables and adapt the system accordingly.

Advice

The advice domain harnesses the capabilities of the integrated machine learning by presenting solutions for impending dysglycaemia and notifying the user of learned temporal or activity related glycaemic trends (Figure 5.2). An example could be a time during the week associated with increased hypoglycaemia frequency and suggestions to adjust insulin dosing. The added ability to review events on the bifocal display helps contextualise the problem among other occurrences during the day. Learned trends and advice are delivered as notifications and not alarms to avoid alarm related fatigue.

5.4.4. Added features and accessibility

Dynamic exploration 'Brushing'

The term 'brushing' describes the ability to interactively select data from a visual representation (422). This concept allows the effect of entered data (meals and exercise) on forecasted outcomes (insulin dose recommendation and 30-minute glucose forecast) to be dynamically explored in real time. The insulin bolus recommender best illustrates the application of brushing with adjusted carbohydrate having a visually dynamic effect on recommended insulin dose in units. While both the carbohydrate and the insulin slider dynamically effect the forecasted glucose curve (Figure 5.6). Timestamped meals, insulin doses, and exercise on the bifocal display are interactive and reveal more information when touched. This optical degree of context provides an additional level of reassurance to individuals that find outcome uncertainty a barrier to making self-management decisions.

Accessibility

Throughout the design process I endeavoured to address functional requirements imposed by the sequalae associated with diabetes while optimising the interaction between human and computer. The effectiveness of user interaction with a hand-held device is crucially dependent on human visual acuity and peripheral tactile sensation. As detailed in Chapter 1, retinopathy and peripheral sensory neuropathy are microvascular complications associated with prolonged exposure to hyperglycaemia that compromise visual acuity and tactile sensation, respectively. Colour vision deficiency is another visual complication which can also occur in individuals with and without established diabetic retinopathy(423,424). Most common cases of impaired colour vision affect the red-green axis but cases of blue-yellow impairment (tritanopia) have been identified in diabetes populations(424). The ability to scale text, use customizable pictures and icons, and avoidance of high contrast colours (red, green, blue, and yellow) were applied to support accessibility to users with retinopathy. To aid

individuals with sensory neuropathy the GUI will utilises the haptic vibration feature within smart-phone hardware to reinforce tactile feedback.

5.4.5. Safety measures

Hypo and Hyperglycaemia alarms

The ARISES platform uses audio alarms to alert users of impending hypo- and hyperglycaemia. Alarms are triggered when blood glucose levels fall below or above configurable thresholds and are predictive to alert users of rapid changes in blood glucose. Alarms below 3.1mmol/L (urgent low) are non-configurable and will be initiated by the integrated Dexcom CGM system. This will enable participants to bring glucose levels back to target range in a timely fashion and limit periods spent out of range.

Fault detection system

The ARISES system will identify and send an audio alarm to alert users of any hardware or disconnection faults.

Hypoglycaemia management education

Before using the platform, users will be required to receive formal diabetes structured education and assessment on hypoglycaemia management to ensure the system is being optimally utilised. The

ARISES mobile platform will supplement education by informing users of scenarios associated with previous hypoglycaemia.

Insulin dose recommendation limits

ARISES will house a safety system to ensure a limit is placed on AI insulin dose recommendations and manually entered insulin dosing. Dose constraints will factor the measured error in active insulin on-board and other input parameters used to calculate insulin dose recommendations. This system will mitigate potential risk of hypoglycaemia and extreme erroneous recommendations compromising the adaptive learning system.

5.5.   Discussion

The ARISES design process allowed an opportunity to implement innovative features requested by end-users while addressing many limitations in existing diabetes health apps. There are many commercially available diabetes apps with the ability to present self-entered and CGM uploaded data or provide insulin bolus advice based on pre-set insulin to carbohydrate ratios. Others serve as a digital diary to log daily activity or facilitate lifestyle endeavours such as carbohydrate counting and exercise tracking. However, the ability to graphically present forecasted glucose levels responsive to real-time automated physiological data and manually entered inputs is novel to the ARISES system. The concepts applied in ARISES evolve the integration of wearable technology beyond multiple hardware data presentation and introduce the ability for users to interact and visualise the real-time impact of modifying data from different sources. Dynamic exploration and the adaptive bolus calculator are perfect examples of giving users the opportunity to see the potential effect a planned activity (e.g., a meal) could have on more than one variable (insulin recommendation and forecasted glucose). Hypoglycaemia and impending hypoglycaemia alarms are an effective hypoglycaemia prevention tool used in many CGM systems. However, with evidence suggesting a tendency for

individuals to respond to fewer alarms, especially if exposed to a high rate of false positives(262), the introduction of additional trend notifications had to be carefully implemented to avoid increasing the alarm burden. The ARISES platform sends a non-intrusive notification to the user when a behavioural or physiological trend/pattern associated with hypoglycaemia is identified by the algorithm. The intention of these notifications is to make users aware of circumstances potentially precipitating hypoglycaemia in the hope they modify behaviours or take precautions to prevent both hypoglycaemia and impending hypoglycaemia alarms. This idea of early prevention does not indicate impeding or active hypoglycaemia, and therefore can be conveyed to the user without an auditory or tactile alarm. An example would be a notification identifying increased risk of hypoglycaemia 6 hours after exercise. As described in Chapter 1, delayed exercise related hypoglycaemia is a challenge faced in people with diabetes and a notification identifying such a trend could have implications on diet and insulin dosing beyond the period of physical activity. The influence of individuals with T1DM of varying ages and social backgrounds throughout the design process was engineered to promote inclusivity. Additionally, active consideration of debilitating diabetes related complications in the design process attempts to ensure accessibility among vulnerable individuals most likely to benefit most from ARISES.

Ultimately, these features make ARISES a novel decision support system by and for the diabetes community. The qualitative data gathered from the multidisciplinary focus groups could have benefited from a thematic analysis to identify meaningful patterns and generate new hypotheses from the dataset. The process of organising (coding) the data obtained from the focus groups at a granular level facilitates the identification of recurrent patterns or themes relevant to specific research objectives (425).
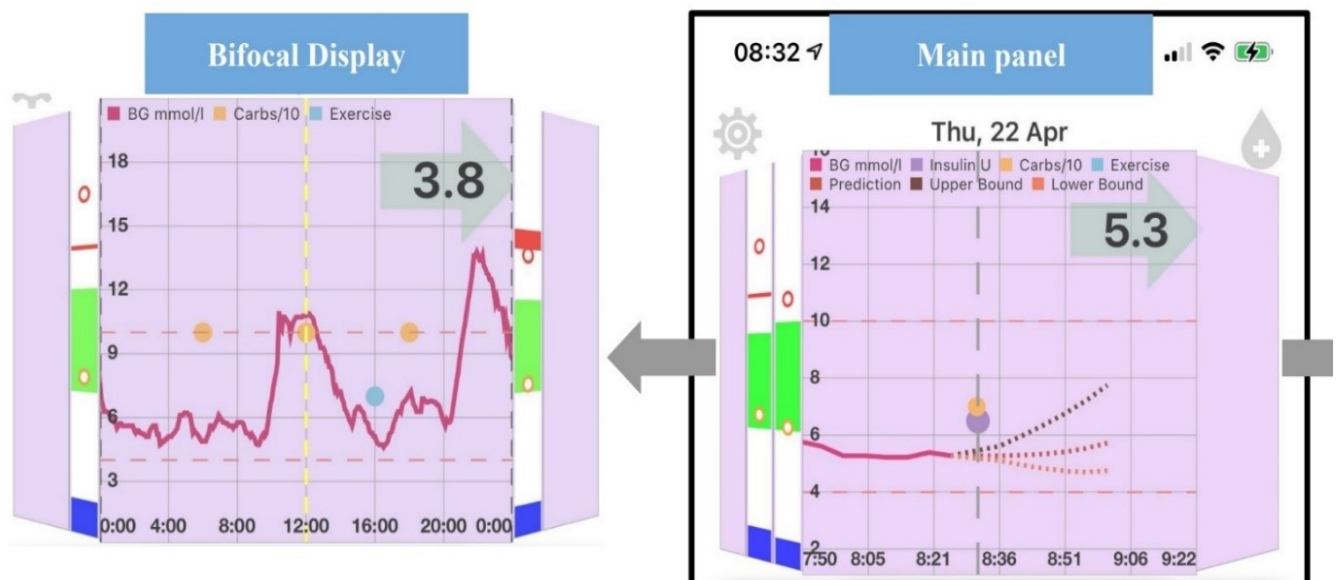
Figure 5.3. Main panel bifocal display (right) illustrating real time CGM output with dotted 30-minute glucose

forecast between upper and lower 95% confidence intervals. Proportion of time above (red), within (green),

and below (blue) target range over the last 2 days is illustrated to the left of RT-CGM graph for easy view. Data

from previous day illustrated on left by swiping across bifocal display. Manually entered carbohydrate, insulin, and exercise inputs are timestamped in orange, purple and blue circles respectively. Dotted horizontal lines clearly mark out user determined time in range and current blood glucose level with trajectory arrow is visible in the top right corner.
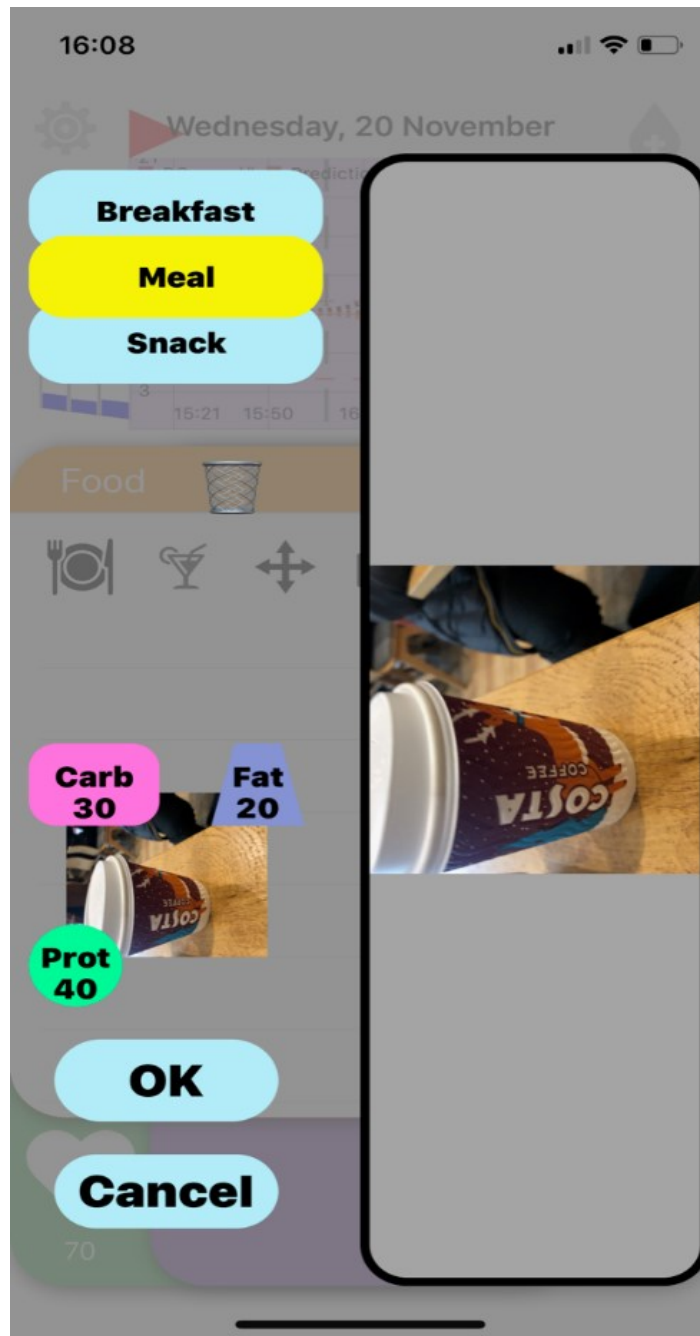
Figure 5.4. Using the smartphone camera feature, meals and respective macronutrient contents can be saved

for future reference
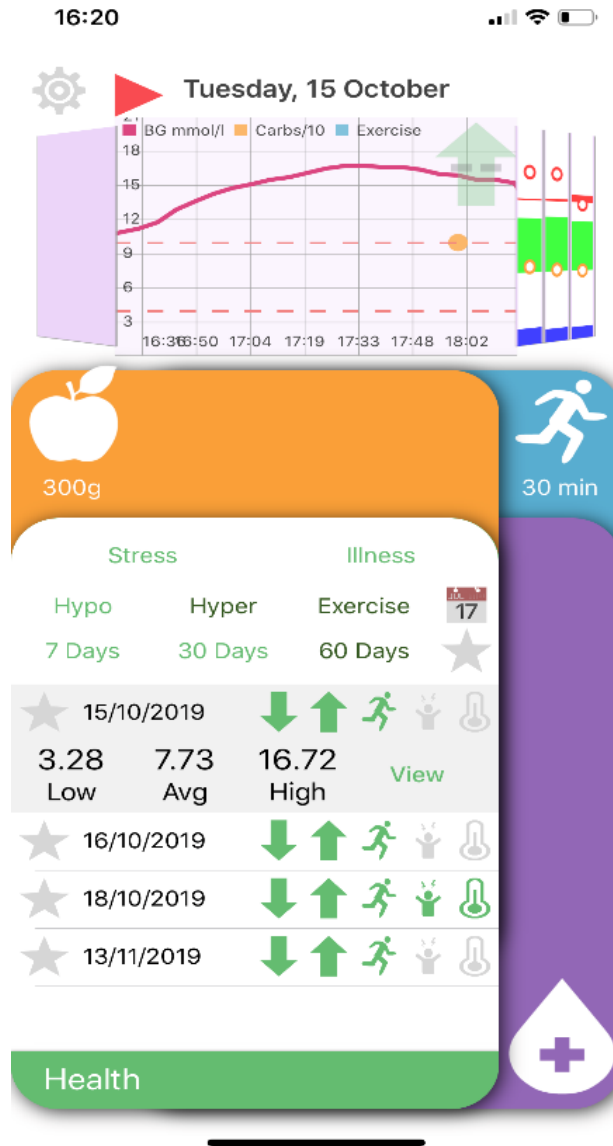
Figure 5.5. The health domain filtering out episodes of hyperglycaemia during exercise over the last 60 days (hyper and exercise text highlighted). The glucose profile during the selected episode (Tuesday 15th October) is contextually illustrated on the bifocal display. Stress and illness have been replaced with toggle switches in latest update (see Figure 5.2).
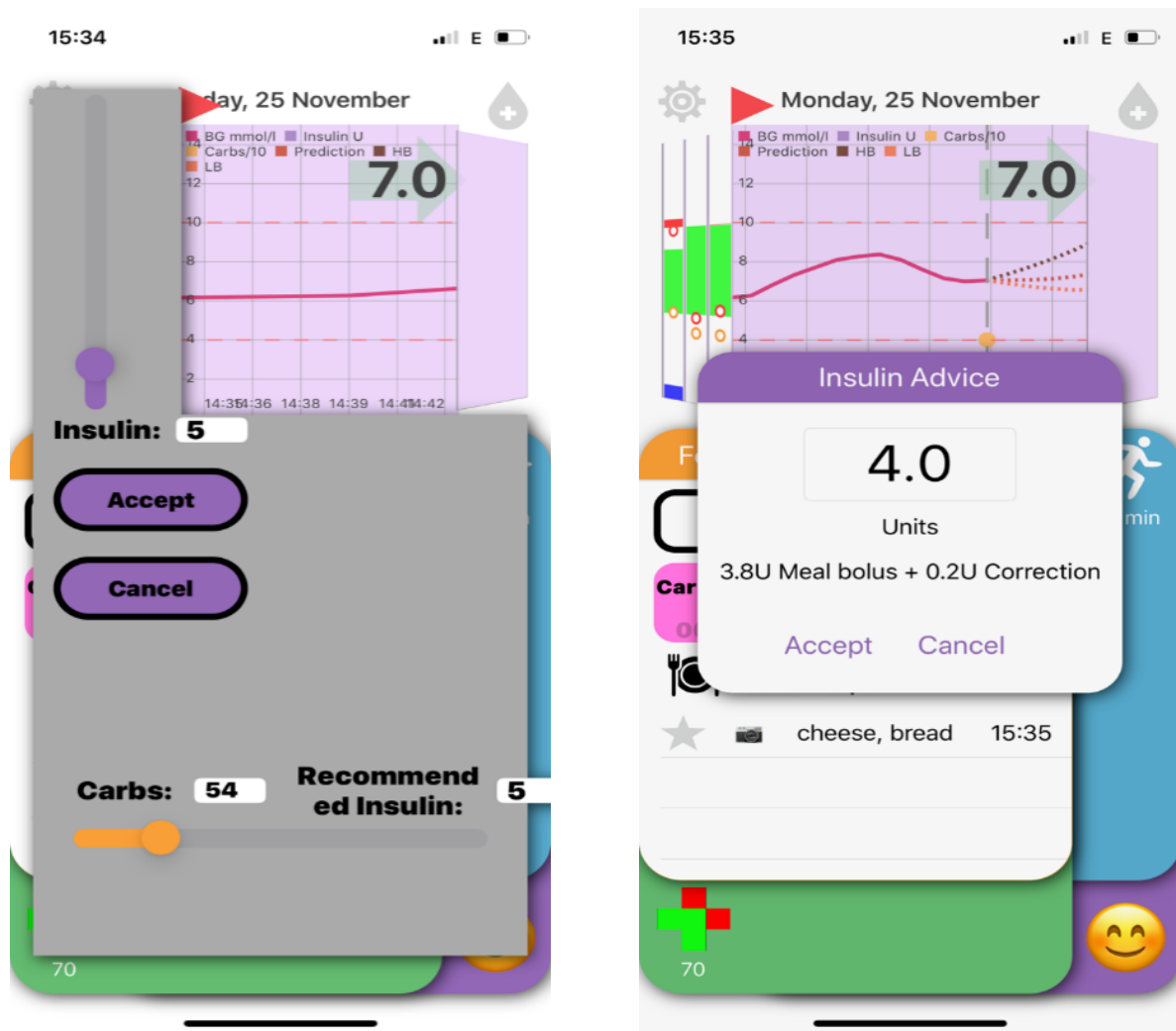
Figure 5.6. Illustrating dynamic exploration (left) with adjustments to carbohydrate slider generating variable real-time recommended insulin doses with visual effect on forecasted glucose. Users are presented with a final confirmation box with insulin bolus breakdown once accepted (right).

6. Chapter 6: An Adaptive Real Time Intelligent System to Enhance Self Care of Chronic Disease (ARISES) - Physiological data collection and clinical sub-analysis

6.1.   Introduction

Wearable physiological sensors (exercise wristbands) have become widely accessible. Although commercially available CGM devices are capable of forecasting glucose trajectories, these projections are largely derived from earlier recorded blood glucose measurements. The adjunctive application of wearable physiological sensors alongside RT-CGM allows for better understanding of how the autonomic nervous system impacts glycaemic control. Moreover, they provide a non-invasive means of continuously measuring physiological parameters with potential to improve the accuracy of identifying glycaemic trajectory and detecting hypoglycaemia.

Traditionally, people with diabetes kept handwritten diaries to log capillary blood glucose levels, administered insulin doses, meals, and other daily activities. The global adoption of smartphone technology has seen many people move their entries to mobile diary applications, with many companies offering diabetes apps with these features in mind. Analogous with wearable physiological sensors, the acquisition of digital diary data is convenient and of greater fidelity allowing for easier integration with other sensor devices. Analysing timestamped diary data with RT-CGM provides an opportunity to investigate these inputs impact glycaemic control and vice versa.

An observational study measuring real-time blood glucose correlations against physiological and digital diary data in recruited individuals with T1DM was performed primarily to serve as a training set for the ARISES machine learning algorithm. This chapter will describe the recruitment, data collection, and a clinical sub-analysis of the observational study dataset. This study was funded by the engineering and physical sciences research council (EPSRC).

6.2.   Aims

This clinical sub-analysis aimed to use clinically validated wearable sensors and a smartphone mobile diary application to

- Identify independent physiological associations with hypoglycaemia and impending hypoglycaemia

- Assess the effect of RT-CGM on dietary habits

- Assess the effect of wearing multiple sensors and daily digital diary entry on user engagement and glycaemic control metrics

- Gather real-world qualitative feedback on diabetes technology and using multiple devices

6.3.   Methods

6.3.1. Recruitment

I recruited all participants from the Imperial College Healthcare NHS trust T1DM outpatient clinics, registered research databases, and interested participants who contact us. Participants were equally stratified (six each) by gender and mode of insulin delivery (MDI or CSII).

The inclusion criteria required participants to be 18 years and older with an established diagnosis of T1DM for over one year. Participants were also required to have completed a structured education course with carbohydrate counting as part of the curriculum and have access to a personal computer to upload data to the investigative team.

Excluded from the trial were individuals that had experienced DKA, or severe hypoglycaemia requiring 3rd party assistance in the previous 6 months or suffered an acute macrovascular complication (acute coronary syndrome, transient ischaemic attack, and cerebrovascular event) within 12 months of enrolment. IAH (Gold score ≥4), pregnancy, breastfeeding, active or investigation for malignancy, other endocrinopathies, autonomic neuropathy, inpatient psychiatric treatment, impaired renal function (eGFR <40mL/min), liver cirrhosis, alcohol or recreational drug abuse, oral steroid or beta-blocker use, and enrolment in other clinical trials were also excluded from the study. Lastly, individuals with reduced manual dexterity limiting the ability to interact with smartphones and wearable devices were excluded.

Loss of capacity to give informed consent, a serious study related adverse event, recurrent severe hypoglycaemia (requiring 3rd party assistance), DKA, pregnancy, and terminal illness were considered grounds to withdraw participants from the study. Participants were free to withdraw at any stage during the study of their own volition.

All participant visits were conducted within the clinical research unit at the NIHR/Wellcome Trust Imperial Clinical Research Facility.

6.3.2. Data collection and components

Dexcom G6 CGM

The Dexcom G6 glucose sensor (CE marked and a licensed medical device in the UK, manufactured by Dexcom) was used throughout the study. All Dexcom CGM data were transmitted wirelessly via Bluetooth to a mobile smart phone device and automatically uploaded to a secure Dexcom cloud-based server (Dexcom Clarity). Participants were non-blinded to CGM data and had access to real-time glucose measurements throughout the study. (Table 6.1 & Figure 6.1)

Empatica E4 multi-sensor wristband

Real time physiological data were recorded continuously using the clinically validated Empatica E4 wireless multi-sensor wristband (CE marked and manufactured by Empatica). The Empatica E4 wristband houses a photoplethysmography (PPG) sensor capable of monitoring heart rate and heart rate variability; two electrodes measuring electrodermal activity (EDA) used to calculate sympathetic activity in response to rapid and slow changing stimuli; an infrared thermophile for measuring peripheral skin temperature; and a 3-axis accelerometer and gyroscope used to detect motion-based activity. Double tapping the Empatica E4 during and after stressful encounters allowed timestamps to be created and cross-referenced against automated physiological measurements and manually entered logs in the mySugr app. All the above data parameters were uploaded to an Empatica manufactured secure proprietary cloud-based platform (E4 Connect) via a wired connection to a personal computer. (Table 6.1 & Figure 6.1)

Apple iPhone and mySugr app

Participants that did not own an Apple iPhone were provided an iPhone 5 for the duration of the study. All administered insulin doses, meal macronutrient composition in grams, stress, illness, and

exercise were manually entered into the mySugr mobile application (version 3.83.36) manufactured by Roche (Table 6.1 & Figure 6.1).

6.3.3. Design and Study Protocol

This was a six-week longitudinal observational study using RT-CGM, a physiological data acquisition sensor, and a smartphone diary application to identify variables associated with hypoglycaemia in adults with T1DM. I was responsible for participant recruitment, arranging and conducting screening, follow-up, and exit visits with support from a research nurse.

Screening visit

Once consented, participants underwent full a clinical assessment including medical history and examination, blood pressure, weight, 12-lead ECG, and non-fasting venous blood tests (HbA1c, full blood count, thyroid function tests, lipid profile, liver function tests, and renal function tests) before commencing the trial. Women of childbearing age took a urine pregnancy test to ensure eligibility. I subsequently applied the Dexcom G6 CGM and Empatica E4 wristband to participants according to the manufacturer's instructions. Participants were encouraged to keep CGM alarm thresholds at <4mmol/L and >11mmol/L. Finally, I installed the mySugr application on participant owned or issued iPhones devices. Participants were advised to log all insulin doses in units, meals and snack details, meal macronutrient composition in grams, alcohol intake in units, stressful events, illness, and exercise in the mySugr app. Data entries for exercise required a duration (mins) and intensity on an increasing scale of 1 to 3. Participants were instructed to send timestamped spreadsheets generated by the mySugr app to the investigating team on a weekly basis. All participants were issued anonymous study e-mail accounts for Dexcom, Empatica, and mySugr registration, and all shared data was sent to a secure NHS e-mail account. The study design is illustrated in (Figure 6.2). Before

leaving participants completed a non-validated entry questionnaire written by me to qualitatively assess pre-existing experience and expectations surrounding diabetes technology (Table 6.7)

Telephone follow-up

I contacted participants after one week to review adherence with data entry as per protocol and address any technical issues.

End of study visit

At the end of 6-weeks, participants returned the Empatica E4 wristbands and completed a non-validated exit questionnaire written by me to qualitatively assess their experience and expectations surrounding diabetes technology after 6-weeks of using multiple devices (Table 6.8).

6.3.4. Ethics

Ethical approval was obtained from the London - Fulham Research Ethics Committee and the HRA. The study was conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

6.3.5. Statistics and Data analysis

Data obtained from RT-CGM were used to measure changes in the following glycaemic metrics, percentage time in range (3.9 to 10mmol/L), percentage time in hypoglycaemia (<3.9 mmol/L and <3.0 mmol/L), percentage time in hyperglycaemia (>10 mmol/L). Mean glucose, low blood glucose index (LBGI), mean absolute glucose (MAG), glucose management indicator (GMI), coefficient of variation (CV), and standard deviation (SD) were also calculated from RT-CGM data.

Mixed effects binary logistic regression modelling was applied to RT-CGM and Empatica E4 data to calculate independent physiological predictors during and 1-hour before hypoglycaemia. The following variables were considered as fixed effects, mean heart rate, standard deviation of heart rate, mean skin temperature, minimum and maximum differential skin temperature, mean electrodermal activity, range of electrodermal activity, standard deviation of electrodermal activity, aggregate phasic skin conductance responses, maximum phasic skin conductance responses, mean tonic skin conductance, standard deviation of tonic skin conductance, range of tonic skin conductance, mean activity, standard deviation of activity, steps, and time between steps. To mitigate potential bias introduced from multiple incidents from single individuals, participants were considered as a random effect. Minimal and maximal differentials are measures of data spread and represent the smallest and largest difference between two adjacent values. Skin conductance responses (SCR) represent rapid sympathetic response to a stimulus, whereas tonic skin conductance levels (SCL) represent the sympathetic response to a tonic or slow changing stimulus. Regression analysis during hypoglycaemia was performed using physiological data recorded during blood glucose levels <4mmol/L and during clinically significant hypoglycaemia <3mmol/L. Physiological measurements recorded within 1-hour of hypoglycaemia <4mmol/L were included in the impending hypoglycaemia analysis. The non-hypoglycaemia comparative dataset comprised of measurements during blood glucose levels ≥4mmol/L and more than 1-hour before hypoglycaemia <4mmol/L.

The Kruskall Wallis hypothesis test was used to analyse differences in mySugr app entries and glucose control metrics during the first 14 (baseline) and last 14 days (endpoint) for all participants and between MDI and pump participants. In this observational study, missing data was minimal, and results were considered statistically significant if $p < 0.05$. Statistical analysis was performed using Stata version 13 (StataCorp, College Station, Texas 77845 USA).

Figure 6.1. Study components. From left to right, Dexcom G6, Empatica E4, and mySugr app on Apple iPhone

Automated inputs (Dexcom G6 & Empatica E4)	Manually inputs (mySugr App)
Blood glucose (Dexcom G6)	Meals – time and macronutrient composition (carbohydrate, protein, and fat)
Heart rate (Empatica E4)	Alcohol – time and units
Blood volume pulse (Empatica E4)	Exercise – time, duration, and (intensity 1 to 3)
Peripheral skin temperature (Empatica E4)	Stress
Motion activity (Empatica E4)	Illness
Electrodermal activity (Empatica E4)	

Table 6.1. Summary of automated and manual data inputs measured using the Dexcom G6 CGM, Empatica E4 wristband, and mySugr app.
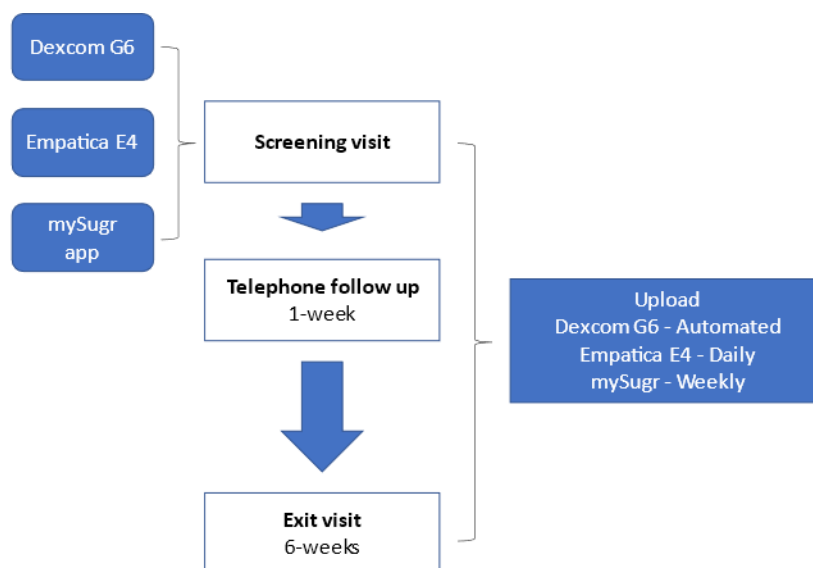
Figure 6.2. ARISES observational study design

6.4.   Results

Twelve participants were recruited and completed the study to endpoint with a median age (IQR) of 40 years (30-39) and baseline HbA1c of 54 mmol/mol (45-58). Eleven out of the twelve enrolled participants entered data for the full duration of the trial and were used for baseline and endpoint head-to-head analysis.

6.4.1. Independent predictors for hypoglycaemia and impending hypoglycaemia

Heart rate standard deviation (SD) significantly reduced the odds of hypoglycaemia <4mmol/L (OR 0.96 [95% CI 0.93, 0.99] p<0.01) and <3mmol/L (OR 0.97 [95% CI 0.96, 0.98] p<0.01). A smaller positive association with mean heart rate was observed for both levels of hypoglycaemia, <4mmol/L (OR 1.01 [95% CI 1.01, 1.01] p<0.01) and <3mmol/L (OR 1.01 [95% CI 1.00, 1.02] p<0.01). No association between heart rate metrics and impending hypoglycaemia (1-hour prior to hypoglycaemia) were identified.

A positive association was observed between mean skin temperature and impending hypoglycaemia (OR 1.02 [95% CI 1.00, 1.04] p=0.02). However, an inverse association was identified once hypoglycaemia ensued, (OR 0.96 [95% CI 0.94, 0.98] p<0.01) <4mmol/L and (OR 0.94 [95% CI 0.88, 0.99] p=0.03) <3mmol/L. Minimal skin temperature differential significantly reduced the odds of hypoglycaemia <4mmol/L (OR 0.47 [95% CI 0.29, 0.79] p<0.01). Whereas skin temperature (SD) was positively associated with hypoglycaemia <4mmol/L, (OR 1.38 [95% CI 1.12, 1.69) p<0.01). Neither of the latter two metrics were significant below 3mmol/L or during impending hypoglycaemia. (Table 6.2)

Maximum phasic skin conductance responses (rapid sympathetic responses to stimuli) were positively associated with hypoglycaemia <4mmol/L (OR 1.06 [95% CI 1.02, 1.11] p<0.01), with increasingly positive odds when glucose levels dropped <3mmol/L, (OR 1.16 [95% CI 1.06, 1.26] p<0.01). Contrastingly, an increasingly negative association between electrodermal activity (SD) and hypoglycaemia was observed, <4mmol/L (OR 0.79 [95% CI 0.63, 0.97] and <3mmol/L (OR 0.68 [95% CI 0.47, 0.97] p=0.03), respectively.

Impending hypoglycaemia was positively associated with a higher (SD) of recorded physical activity (OR 1.05 [95% CI 1.04, 1.07] p<0.01) and negligibly associated with time between steps (OR 1.00 [95% CI 1.00, 1.01] p=0.03). Mean physical activity was negatively associated with hypoglycaemia <4mmol/L (OR 0.95 [95% CI 0.92, 0.98] p<0.01). All physiological measured associations with hypoglycaemia and impending hypoglycaemia are detailed in Table 6.2.

6.4.2. Carbohydrate consumption, insulin bolus administration, and exercise

Over the duration of the study, participants ingested a median (IQR) of 160 (102-220) grams of carbohydrate daily. Access to RT-CGM throughout the study saw no significant change in daily carbohydrate intake, baseline 165 (114-220) vs endpoint 145 (101-220) p=0.77, or daily intake standard deviation 43.0 (23.1-60.3) vs 33.7 (23.7-52.6) p=0.57 (Table 6.3). Similarly, no significance was observed when comparing carbohydrate intake for labelled meals (breakfast, lunch, and dinner) (Table 2.2). Albeit non statistically significant, carbohydrate variability for all meals appeared to reduce during the trial. This was most evidently seen at breakfast where the median standard deviation (IQR) of carbohydrate fell from 14.5 (8.0-18.4) grams at baseline to 6.7 (3.5-11.9) grams at endpoint, p=0.08. The median daily amount of administered bolus insulin over the duration of the study was 20 (14.8-28.0) units, and a median of 19.5 (11.8-30.3) exercise events were recorded. Again, no significant change was observed over 6 weeks for administered bolus insulin and exercise.

6.4.3. Metrics of glucose control derived from RT-CGM

During the entire 6-weeks, the median (IQR) percentage time in range (3.9-10mmol/L), time in clinically significant hypoglycaemia <3.0mmo/L, and time in hyperglycaemia >10mmol/L were 62.5 (53.4-76.6), 0.4 (0.1-0.7), and 35.2 (16.5-42.1) respectively. Other metrics of glycaemic control and variability derived from RT-CGM included, median GMI (%) 55.5 (47.6-58.9), SD 3.1 (2.5-3.8), CV 0.4 (0.4-0.3), LBGI 0.7 (0.4-1.1), and MAG 2.6 (2.1-2.8). MDI and pump users showed no significant difference across all glycaemic control metrics measured during the entire duration of the study. All glucose control metrics during the full 6-week trial are summarised in (Table 6.4).

Statistical significance was not observed when comparing glucose control metrics between baseline and endpoint in all participants (Table 6.5). Stratifying participants based on modality of insulin treatment and comparing the median difference from baseline to endpoint identified a significant

difference in MAG between MDI users -0.2 (95% CI -0.5, 0.2) and pump users 0.2 (95% CI 0.03, 0.5), p=0.04. There was no significant change in percentage time in range, time in hypoglycaemia, and all other measured glycaemic control metrics. Within-group changes and significance levels for between group differences for all CGM outcomes are reported in Table 6.5.

6.4.4. Application engagement and behavioural analysis

A total of 5767 manual entries into the mySugr app were made during the 6-week observational trial (Table 6.6). Food was the most frequently entered parameter with counted carbohydrates responsible for 39.6% of entries, closely followed by insulin bolus dosing 20.6%. All food entries were accompanied with a carbohydrate measurement entry. However, despite encouragement to refer to food labels and health applications, protein and fat measurements were logged for 42.7% and 41.7% of food entries and accounted for only 16.9% and 16.5% of the total entries. The median (IQR) number of diary entries made by participants throughout the duration of the trial was 396 entries (237-732.3), with no significant change between baseline 152 entries (121-255.3) and endpoint 124 entries (89-229.8), p=0.42. Likewise, no significant change was observed for the median number of daily entries 7 (4-9) vs 6 (4-8), p=0.08 (Table 6.3).

6.4.5. Qualitative feedback

Responses to the non-validated questionnaires completed at screening and during the exit visit are summarised in (Table 6.7 and 6.8). Pairing with a glucose monitoring device was the most frequent reason for using a diabetes health app reported in 9 out of 10 participants, followed by accessing a carbohydrate counting tool, 3 out of 10. Seven participants had previously used a physiological activity sensor, with over half confirming it influenced diabetes care decisions, particularly before and during planned exercise. Reported barriers to using diabetes health apps included, poor usability and interface design, connectivity limitations, and financial expense. On completion of the trial, two

thirds of participants encountered challenges using the Empatica E4 physiological wristband, citing discomfort, unappealing aesthetics, and poor usability as negative factors hindering real world use. However, a smaller commercial device with a functional face and integration into other diabetes apps was considered a more appealing alternative. Nonetheless, participants prioritised optimising glycaemic control with 11 out of 12 willing to wear a physiological wristband to achieve this. Most participants (n=5) agreed a maximum of 3 wearable devices to be the most they would consider acceptable as part of a diabetes care system. However, 3 participants would not place a limit on the number of devices if the system effectively improved glucose control. Lastly, participants almost unanimously agreed that RT-CGM improved their glycaemic control (11 out of 12) and would choose to wear it all the time.

	1-hr before Hypo	<4mmol/L	<3mmol/L

	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p
Mean Heart Rate	1.00 (0.99-1.01)	0.17	**1.01 (1.00-1.01)**	**<0.01**	**1.01 (1.00-1.02)**	**0.01**
SD Heart Rate	0.99 (0.99-1.00)	0.25	**0.97 (0.96-0.98)**	**<0.01**	**0.96 (0.93-0.99)**	**<0.01**
Mean Skin Temp	**1.02 (1.00-1.04)**	**0.02**	0.96 (0.94-0.98)	<0.01	**0.94 (0.88-0.99)**	**0.03**
SD Skin Temp	1.17 (0.97-1.39)	0.09	**1.38 (1.12-1.69)**	**<0.01**	0.97 (0.48-1.92)	0.92
Min differential Skin Temp	0.69 (0.45-1.05)	0.08	**0.47 (0.29-0.79)**	**<0.01**	0.20 (0.02-1.80)	0.15
Max differential Skin Temp	1.21 (0.88-1.66)	0.25	1.16 (0.29-0.79)	0.41	0.70 (0.20-2.50)	0.58
Mean EDA	0.64 (0.16-2.56)	0.52	0.47 (0.09-2.50)	0.37	0.06 (0.00-5.01)	0.22
Range EDA	1.03 (0.96-1.11)	0.36	1.02 (0.96-1.08)	0.52	1.03 (0.93-1.14)	0.61
SD EDA	0.83 (0.64-1.06)	0.14	**0.79 (0.63-0.97)**	**0.03**	**0.68 (0.47-0.97)**	**0.03**
Aggregate phasic skin conductance responses	1.00 (0.99-1.00)	0.59	1.00 (0.99-1.00)	0.34	1.00 (0.99-1.01)	0.22
Max phasic skin conductance responses	1.02 (0.98-1.06)	0.33	**1.06 (1.02-1.11)**	**<0.01**	**1.16 (1.06-1.26)**	**<0.01**
Mean tonic skin conductance	1.56 (0.39-6.29)	0.53	2.14 (0.40-11.4)	0.37	16.0 (0.20-1285)	0.22
SD tonic skin conductance level	1.29 (0.97-1.70)	0.07	1.19 (0.93-1.53)	0.16	1.36 (0.87-2.14)	0.18
Range of tonic skin conductance level	0.98 (0.92-1.05)	0.52	0.99 (0.94-1.53)	0.92	0.99 (0.89-1.11)	0.89
Mean Activity	0.99 (0.97-1.01)	0.29	**0.95 (0.92-0.98)**	**<0.01**	0.94 (0.86-1.03)	0.18
SD Activity	**1.05 (1.04-1.07)**	**<0.01**	1.01 (0.99-1.03)	0.40	0.98 (0.93-1.03)	0.36
Steps	1.00 (1.00-1.01)	0.07	0.99 (0.99-1.00)	0.05	1.00 (0.99-1.00)	0.74

Table 6.2. Mixed effects regression analysis of physiological measurements associated with impending hypoglycaemia, and hypoglycaemia below 4mmol/L and 3mmol/L. Results are expressed as odds ratios (95% Confidence intervals). P values <0.05 are significant and highlighted in bold. *SD = Standard deviation, EDA = Electrodermal activity, Temp = Temperature*

	All	Baseline (First 14 days)	Endpoint (Last 14 days)	p
Total daily carbohydrate (grams)				
Median (IQR)	160 (114-212)	165 (117-220)	145 (101-220)	0.77
Standard deviation (IQR)	44.4 (26.9-59.7)	43.0 (23.1-60.3)	33.7 (23.7-52.6)	0.57
Daily Breakfast carbohydrate (grams)				
Median grams (IQR)	41 (25-60)	40 (26-60)	42 (29.3-58.8)	0.68
Median standard deviation (IQR)	12.2 (9.2-16.4)	14.5 (8.0-18.4)	6.7 (3.5-11.9)	0.08
Daily Lunch carbohydrate (grams)				
Median (IQR)	45 (30-60)	50 (33.8-62.8)	40 (30-65)	0.14
Standard deviation (IQR)	16.4 (12.3-21.3)	16.5 (10.8-18.6)	15.4 (12.5-22.2)	0.92
Daily Dinner carbohydrate (grams)				
Median (IQR)	50 (40-70)	50 (40-70)	50 (40-75)	0.50
Standard deviation (IQR)	19 (10.8-23.3)	15.5 (9.8-25.7)	14.7 (11.6-25.4)	0.92
Daily Bolus insulin (units)				
Median (IQR)	20 (14.8-28)	20.2 (15.9-28.6)	20 (14-27.5)	0.29
Standard deviation (IQR)	6.7 (4.1-8.6)	4.6 (2.4-9.9)	6.4 (4.6-6.9)	0.93
Total Exercise frequency (n)				
Median (IQR)	19.5 (11.8-30.3)	8.5 (7.8-12.3)	7 (2.3-8)	0.10
Daily mySugr interactions				
Median (IQR)	7 (4-9)	7 (4.8-9)	6 (4-8)	0.08
Total mySugr interactions				
Median (IQR)	396 (237-732.3)	152 (121-255.3)	127 (89-229.8)	0.42

Table 6.3. Change in daily carbohydrate intake, bolus insulin administration, exercise frequency, and interactions with the mySugr app from baseline (first 14 days) to endpoint (last 14 days) using 6 weeks of RT-CGM and daily manual data entry. Results are expressed as median (IQR). P values of <0.05 are significant and highlighted in bold. *IQR = Interquartile range*

Metric	All 6 weeks (Median, IQR)	MDI 6 weeks (Median, IQR)	Pump 6 weeks (Median, IQR)	p
% time in range				
3.9-10mmol/l (70 -180mg/dL)	62.5 (53.4-76.6)	60.3 (56-63.3)	65.0 (51.7-80.8)	0.75
% time in hypoglycaemia				
<3.9mmol/l (<70mg/dL)	2.9 (1.5-4.2)	2.9 (1.8-3.7)	3.3 (1.3-5.3)	0.63
<3.0mmol/l (<54mg/dL)	0.4 (0.1-0.7)	0.4 (0.2-0.6)	0.4 (0.1-0.8)	0.87
<2.8mmol/l (<50mg/dL)	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.2 (0.04-0.4)	0.75
% time in hyperglycaemia				
>10mmol/l (>180mg/dL)	35.2 (16.5-42.1)	36.5 (32.6-39.1)	26.4 (13.2-45.6)	0.75
Glycaemic variability measures				
Mean	9.1 (7.4-9.8)	9.2 (8.9-9.6)	8.7 (7.2-10.0)	0.52
GMI (%)	55.5 (47.6-58.9)	56.3 (54.5-57.9)	51.5 (46.6-59.8)	0.52
Standard deviation	3.1 (2.5-3.8)	3.3 (2.7-4.0)	3.0 (2.5-3.5)	0.63
CV (%)	0.4 (0.3-0.4)	0.4 (0.3-0.4)	0.3 (0.3-0.4)	0.63
LBGI	0.7 (0.4-1.1)	0.7 (0.6-0.9)	0.9 (0.4-1.5)	0.63
MAG	2.6 (2.1-2.8)	2.8 (2.1-3.2)	2.5 (2.2-2.7)	0.63

Table 6.4. Glycaemia outcomes across duration of trial. Results are expressed as median (IQR). P values of <0.05 are significant and highlighted in bold. *IQR = Interquartile range, GMI = Glucose management indicator, CV = Coefficient of variation, LBGI = Low blood glucose index, MAG = Mean absolute glucose*

Metric	First 2 weeks All (median, IQR)	Last 2 weeks All (median, IQR)	p	First 2 weeks MDI (median, IQR)	Last 2 weeks MDI (median, IQR)	First 2 weeks Pump (median, IQR)	Last 2 weeks Pump (median, IQR)	MDI change from baseline to endpoint (median, 95%CI)	Pump change from baseline to endpoint (median, 95%CI)	p
% time in range										
3.9-10mmol/l (70 -180mg/dL)	68.8 (53.5-80.5)	56.9 (52.6-74.8)	0.48	64.5 (56.1-77.8)	54.6 (52.5-57.2)	72.2 (50.9-82.0)	66.5 (54.4-77.7)	-5.7 (-19.6 to 0.5)	-3.3 (-7.6 to 4.3)	0.26
% time in hypoglycaemia										
<3.9mmol/l (<70mg/dL)	2.8 (1.0-3.8)	2.6 (0.8-5.3)	0.73	2.8 (2.4-3.5)	2.3 (0.8-4.3)	2.4 (0.9-4.8)	3.3 (1.3-5.9)	-0.1 (-2.1 to 2.1)	0.5 (-0.6 to 2.3)	0.52
<3.0mmol/l (<54mg/dL)	0.2 (0.1-0.5)	0.4 (0.2-0.9)	0.35	0.4 (0.2-0.5)	0.5 (0.2-0.8)	0.1 (0.1-0.4)	0.4 (0.3-1.1)	0.04 (-0.2 to 0.5)	0.1 (-0.3 to 0.9)	0.08
<2.8mmol/l (<50mg/dL)	0.08 (0.0-0.4)	0.2 (0.1-0.4)	0.48	0.2 (0.03-0.4)	0.3 (0.1-0.4)	0.05 (0.03-0.4)	0.2 (0.1-0.5)	-0.01 (-0.2 to 0.3)	0.01 (-0.2 to -0.4)	0.75
% time in hyperglycaemia										
>10mmol/l (>180mg/dL)	29.3 (14.1-42.8)	38.2 (16.6-45.2)	0.49	33.1 (18.3-39.9)	39.8 (37.0-44.4)	23.5 (12.8-46.8)	27.7 (14.9-43.3)	7.7 (-1.4 to 19.9)	1.4 (-4.6 to 6.6)	0.11
Glycaemic variability measures										
Mean	8.8 (7.4-9.8)	9.4 (7.6-10.0)	0.49	9.1 (8.0-9.5)	9.5 (9.2-9.9)	8.1 (7.3-10.1)	8.4 (7.2-9.9)	0.8 (0.3 to 1.5)	-0.2 (-0.5 to 0.6)	0.05
GMI (%)	54.4 (47.6-58.7)	57.2 (48.3-59.4)	0.49	55.5 (50.2-57.3)	57.6 (56.2-59.3)	51.1 (47.2-60.1)	52.3 (46.7-59.5)	3.8 (0.1 to 6.9)	-1.1 (-2.6 to 3.0)	0.05
GMI (mmol/L)										
Standard deviation	2.7 (2.4-3.6)	3.3 (2.6-3.9)	0.45	2.9 (2.4-3.9)	3.5 (2.7-4.1)	2.7 (2.5-3.3)	3.0 (2.7-3.6)	0.2 (-0.4 to 0.9)	0.3 (-0.02 to 0.4)	0.87
CV (%)	0.3 (0.3-0.4)	0.4 (0.3-0.4)	0.27	0.3 (0.3-0.4)	0.4 (0.3-0.4)	0.3 (0.3-0.4)	0.4 (0.3-0.4)	0.02 (-0.1 to 0.1)	0.02 (0.01 to 0.04)	0.52
LBGI	0.9 (0.3-1.1)	0.7 (0.3-1.3)	1.0	0.9 (0.7-1.0)	0.7 (0.3-1.0)	0.7 (0.3-1.3)	0.9 (0.4-1.5)	-0.1 (-0.6 to 0.3)	0.1 (-0.2 to 0.5)	0.26
MAG	2.9 (2.4-3.2)	3.2 (2.5-3.4)	0.49	3.0 (2.5-3.5)	3.2 (2.4-3.3)	2.8 (2.5-3.0)	3.2 (2.6-3.4)	**-0.2 (-0.5 to 0.2)**	**0.2 (0.03 to 0.5)**	**0.04**

Table 6.5. Glycaemic outcomes from the first 14 days (baseline) and last 14 days (endpoint). Results are expressed as median (IQR). P values od <0.05 are significant and highlighted in bold. *IQR = Interquartile range, GMI = Glucose management indicator, CV = Coefficient variation, LBGI = Low blood glucose index, MAG = Mean absolute glucose*

mySugr Entries	All (n=5767)		MDI (n=2988)		Pump (n=2779)	
	% (n)	Median (IQR)	% (n)	Median (IQR)	% (n)	Median (IQR)
Carbohydrates	39.6% (2285)	207 (122-249.5)	41.2% (1233)	172 (127.5-285.5)	37.9% (1052)	213 (107.5-242)
Protein	16.9% (976)	132 (33-163)	17.5% (522)	42 (4-146)	16.3% (454)	158 (138-168)
Fat	16.5% (952)	135 (31-163)	16.5% (492)	40 (4-146)	16.5% (460)	158 (140.5-168.5)
Insulin Bolus	20.6% (1189)	111 (57-142.5)	18.9% (565)	101 (50-131)	22.5% (624)	123 (77.5-144.5)
Exercise	4.5% (262)	19.5 (13-29.5)	4.9% (148)	19.5 (13.8-28.3)	4.1% (114)	18.5 (13.5-27.3)
Alcohol	1.2% (72)	6 (4-9)	0.5% (14)	2.5 (0.75-5.25)	2.1% (58)	8 (6-17)
Stress	0.3% (18)	2.5 (2-3)	0.1% (4)	2 (2-2)	0.5% (14)	3 (2.5-4)
Illness	0.3% (18)	3 (3-4.8)	0.3% (10)	10 (10-10)	0.3% (8)	3 (2.5-3)

Table 6.6. mySugr application entries over the duration of the study. Results are expressed as % (n) and median (IQR). *IQR = Interquartile range*

ARISES OBSERVATIONAL STUDY ENTRY QUESTIONNAIRE				
1	Have you previously used diabetes/health apps?	App and why	Why	Pros and cons
	Yes = 83.3% (10) No = 16.7% (2)	Freestyle Libre (n=5) CGM (n=3) Smart meter (1) Carbs and cals (3) Myfitness pal (1) mySugr (1)	Glucose monitoring Glucose monitoring Glucose monitoring Carb counting, assist insulin dosing Track fitness Track carbs and exercise	Helpful monitoring glucose, detect hypoglycaemia, but expensive. Manage finger prick data Useful visual aid but not comprehensive enough Not integrated Useful visual aid but time consuming
2	Have you used a physical activity monitor before?	Did it influence diabetes decisions?	How were decisions influenced?	
	Yes = 58.3% (7) No = 41.7% (5)	57.1% (4)	Awareness of exercise intensity Exercise with more confidence Adjusting insulin dosing according to previous outcomes Adjusting carbs before and during exercise based on previous outcomes	
3	Have you used CGM before?	How long did you use CGM?	Would you use CGM all the time?	
	Yes = 83.3% (10) No = 16.7% (2)	1-4 months (4) 1-3 years (3) Libre for years (2) Sporadically	Yes = 100% (10)	
3	Have you experienced barriers using apps and devices?		What where the barriers?	
	Yes = 41.7% (5) No = 58.3% (7)		Poor app design and usability Connectivity limitations pairing with smartphone Expensive Battery life	
4	What is the maximum number of wearable devices considered acceptable in a treatment system?			
	3 (n=5), 2 (n=2), 4 (n=1), 5 (n=1) Depends (3), no limit if effective but preferably fewer.			

Table 6.7. Entry questionnaire and outcome data

	ARISES OBSERVATIONAL STUDY EXIT QUESTIONNAIRE		
1	**Did you encounter problems wearing the Dexcom G6?**	**Explain**	
	Yes = 50% (6)	Sensor adhesive coming off (3) Sensor failure Bleeding Inconvenient deployment site Intrusive alarms	
2	**Did using RT-CGM improve your glucose control**	**Would you use CGM all the time?**	
	Yes = 91.7% (11) No = 8.3% (1)	Yes = 91.7% (11) No = 8.3% (1)	
3	**Did you encounter problems using the Empatica E4 wristband?**	**Explain**	**Would you wear a such a device if it improved glucose control?**
	Yes = 66.7% (8) No = 33.3% (4)	Rash when too tight Uncomfortable (3) Poor aesthetically Daily uploads Unclear if on or off App interface usability	Yes = 91.7% (11)
4	**What would you improve in a physiological sensor wristband?**		
	Smaller and less bulky (n=7) Integration with other devices (n=4) Functional face on wrist band (n=3) Understanding of captured data and influence on blood glucose (n=2) Less frequent uploads (n=2) Battery life		
5	**What is the maximum number of wearable devices considered acceptable in a treatment system?**		
	3 (n=4) Depends (n=3), No limit if effective Fewer the better		

Table 6.8. Exit questionnaire and outcomes

6.5.   Discussion

This observational study analyses six-weeks of real-world data derived from clinically validated wearable sensor devices and daily mobile app diary entries in 12 adults with T1DM. Applying a mixed effects model to the dataset, significant and clinically relevant physiological changes were identified during and 1-hour before biochemical hypoglycaemia. Mean heart rate had a small positive association with active hypoglycaemia, while heart rate SD had an opposing effect in lowering the odds of hypoglycaemia (Table 2.2). These associations, albeit small, align with the understood rubric where hypoglycaemia stimulates a sympatho-adrenal response and an increase in heart rate to maintain glucose supply to the brain (366,426,427). Interestingly, mean physical activity had a small effect in lowering the odds of hypoglycaemia <4mmo/L while physical activity variability (SD) was positively associated with impending hypoglycaemia. Completing recent formal structured diabetes education was an inclusion requirement in the study with most participants being well versed in hypoglycaemia self-management. The contradictory negative association between hypoglycaemia and physical could be explained by informed awareness to stop or refrain from physical activity when alerted to biochemical hypoglycaemia. As detailed in chapter 1.3.3, hypoglycaemia is a common sequalae associated with physical activity, with individuals increasingly using glucose sensors and wearable devices to mitigate the risk as the exit questionnaire ratifies (Table 6.8). Therefore, it is not surprising that increased heart rate variability (SD) was associated with impending and early hypoglycaemia <4mmol/L but not <3mmol/L. Like the associations observed with heart rate metrics, the odds ratios measured are small and their clinical significance is uncertain.

Current evidence strongly associates raised ambient temperature with increased insulin absorption and risk of hypoglycaemia (123). This correlates with the identified, however small positive association between a higher mean temperature and impending hypoglycaemia (OR 1.02 [95% CI

1.00, 1.04] p=0.02). Of greater clinical significance is the positive relationship between measures of skin temperature variability and active hypoglycaemia <4mmol/L. This highlights that although current evidence associates hypoglycaemia risk with heat exposure, lower temperatures do not eliminate this risk and hypoglycaemia risk persists across a range of thermal states. This is supported by higher minimal differential skin temperature (greater spread between two adjacent values) significantly reducing the odds of active hypoglycaemia <4mmol/L (OR 0.47 [95% CI 0.29, 0.79) p<0.01).

Electrodermal activity (EDA) serves as a metric of sympathetic activity by measuring changes in conductance at the skin surface due to sympathetic modulated sweat production (369). As detailed in Chapter 1.2, there is substantial evidence supporting a sympathetic counterregulatory response to hypoglycaemia mediated by directly stimulating glucagon release from pancreatic alpha cells and indirectly via adrenaline released from sympathetic stimulation of the adrenal glands. In the five T1DM individuals with sweating precipitated by insulin infusion induced hypoglycaemia, Pickup successfully showed a portable device capable of measuring skin conductance and alerting users at pre-set conductance levels (Diabalert) triggered alarms at glucose concentrations between 1.6 and 3.7mmol/L (371). However, the delayed onset of alarms saw three of the five participants unable to self-manage and correct hypoglycaemia due to cognitively impairment. Another cutaneous conductance sensor (The Teledyne Sleep Sentry) successfully detected two-thirds of overnight biochemical hypoglycaemia ≤3mmol/L in adults with T1DM, however was hindered by a two-thirds false alarm rate (372). Interestingly, no significant correlations were identified between mean EDA and active or impending hypoglycaemia. However, a negative correlation between EDA SD and hypoglycaemia <4mmol/L (OR 0.79 [95% CI 0.63, 0.97] p=0.03), and <3mmol/L (OR 0.68 [95% CI 0.47, 0.97] p=0.03) suggests hypoglycaemia states are occurring within a confined spread of EDA. When separating measured sympathetic responses to rapid and tonic stimuli, 'phasic' skin conductance

responses (SCR) and 'tonic' skin conductance levels (SCL) respectively, I observed an increasingly positive association between maximum phasic SCR and worsening hypoglycaemia, (OR 1.06 [95% CI 1.02, 1.11] p<0.01) when <4mmol/L and (OR 1.16 [95% CI 1.06, 1.26] p<0.01) <3mmo/L. Phasic SCR are abrupt peaks in skin conductance and reflect a response to an acute discrete stimulus, in this case hypoglycaemia. These findings are supported by a mini-review summarising glycaemic thresholds for direct autonomic islet cell and sympathoadrenal activation during hypoglycaemia, where pancreatic nor-adrenaline spill over was measured at glucose levels <2mmol/L and an adrenaline response detected between 3.6 and 4.2mmol/L.

Confirming measurable physiological associations with hypoglycaemia in a real-world setting using high fidelity clinically validated devices expands the established evidence base for hypoglycaemia risk factors. In addition, I draw attention to the ubiquitous nature of hypoglycaemia and its occurrence beyond the conventional established high-risk physiological circumstances. The application of this data alongside existing RT-CGM could serve as an adjunctive support and a safety layer to identify and prevent current and impending hypoglycaemia in high-risk groups. The clinical significance of advancing technology-based hypoglycaemia risk prevention is linked to the increasing commercial access to sensor devices. Moreover, the diabetes population are increasingly entrusting technology to mitigate hypoglycaemia risk and ultimately improve quality of life.

This dataset was originally collected as a training set for the ARISES machine learning algorithm. The primary objective of this subsidiary trial was to identify physiological correlations associated with current and impending hypoglycaemia. However, the provision of RT-CGM with integrated impending hypoglycaemia alarm features was a limitation in this study as it negatively curbed the number of physiological data points available before and during hypoglycaemia. Repeating this trial with a larger population wearing blinded CGM and a consumer available physiological sensor could

potentially reveal additional associations, strengthen the significant but small correlations identified, and validate my findings against a more accessible sensor. More importantly, repeating this study in a subset of individuals with IAH would identify whether the presented findings persist in the context of a diminished counterregulatory response and if the results are transferrable in a high-risk hypoglycaemia population.

The qualitative data from participants sheds light on the beliefs and behavioural patterns of individuals using multiple health apps and wearable devices. Whelan et al, showed reduced time spent on a Fitbit (physiological data acquisition sensor) and Freestyle Libre (Flash glucose monitor) apps over six-weeks when provided to individuals at moderate to high risk of developing T2DM (428). Furthermore, 20% and 53% of participants required prompting to charge or sync Fitbit devices respectively. I asked participants to wear two sensor devices (Dexcom G6 and Empatica E4) and engage with one smartphone applications (mySugr) daily throughout the 6-week duration of the trial. Despite requirements to manually input multiple data entries into mySugr, I observed no decline in app engagement or change in glycaemic control over the 6-weeks. Adherence with wearing RT-CGM and the Empatica E4 wristband was also largely maintained throughout the trial. Although clinical trial volunteers often come from an informed and motivated patient demographic, the consistent level of device and app engagement highlights a willingness for individuals to engage with multiple devices, and challenges concerns of poor engagement when using multiple devices. Most participants considered three to be the maximum number of wearable devices considered acceptable in a treatment system when asked before and after the trial (Table 6.7 and 6.8). The universal success of RT-CGM is evident in the 100% positive response from participants when asked if they would use CGM all the time. An estimated 60% of participants had previous experience using a physiological sensor (or physical activity monitor), of this only 57% applied it to influence diabetes care decisions. This reaffirms the increasing popularity of wearable sensor devices, however,

highlights a deficit or lack of knowledge in applying physiological data to diabetes care. The final ARISES platform aims to circumvent this by integrating these data sources within the system to provide accurate and clear decision support outcomes (glucose forecast, hypoglycaemia alerts, and insulin bolus calculation). Similarly, dietary carbohydrate entries (n=2285) exceeded those for protein (976) and fat (952) combined. This disparity highlights the current position of structured education programmes focusing primarily on carbohydrate counting and suggests participants were less confident to measure protein and fats, especially from non-labelled foods. The current evidence for non-carbohydrate macronutrient estimation is limited with no consensus on how to implement it practically. These evidence gaps will require addressing before successful clinical application. In the theme of developing a user inspired diabetes application, the questionnaire could have been co-designed and approved by participants with diabetes during the design focus groups.

7. Proposed research and future studies

7.1. Proposed research – ARISES proof of concept trial

A version of the ARISES application with integrated machine learning has received ethical approval to undergo clinical testing to assess the safety and feasibility of the system. Plans to perform further clinical trials have been placed on hold pending MHRA approval and COVID-19 related restrictions. The proposed protocol outlines a twenty-week interventional cross-over study comparing the ARISES system (ARISES mobile app, Empatica E4, and Dexcom G6) against RT-CGM (Dexcom G6) alone in adults with T1DM. Twelve participants would complete a 2-week run-in period using RT-CGM before being randomised into the intervention (ARISES) or control (RT-CGM only) arm for 8-weeks. A 2-week washout period would follow before being crossed over. Participants would have been recruited from the Imperial College Healthcare NHS trust T1DM outpatient clinics, from registered research databases and from interested participants who contact us. Groups would be equally stratified (six each) by gender and mode of insulin delivery (MDI or CSII).

The ARISES adaptive machine learning system will directly receive physiological and environmental data input automatically measured using the clinically validated Dexcom G6 and Empatica E4. As discussed in chapter 6.3.2 and illustrated in Figure 7.1, the ARISES adaptive machine learning algorithm will receive automated physiological and environmental data inputs from the Dexcom G6 and Empatica E4, and inputs entered manually (meals and exercise) from the ARISES app. ARISES would provide personalised novel decision support by illustrating the impact of common scenarios (food and exercise) on current and 30-minute forecasted glucose levels. The platform would also

provide adaptive insulin bolus dosing advice with a forecasted glucose profile, based on the individual's previous glucose responses to entered macronutrients and glucose correlations with physiological and environmental variables. Furthermore, non-intrusive notifications informing participants of temporal and activity related associations with hypoglycaemia will encourage behavioural modification and ultimately hypoglycaemia prevention. Thematic based semi-structured interviews, questionnaire assessments, and task-based simulations using the ARISES interface would be conducted over the course of the trial to validate the usability of the ARISES GUI. Task scenarios would be evaluated using quantitative metrics outlined in Table 7.1, and qualitatively using a 'Think aloud protocol' and a subjective assessment by the investigator (see Table 7.2). The Think-aloud process encourages participants to share their thoughts when interacting with a product or performing product-based tasks to assess usability (429,430). The proposed ARISES system and study design are illustrated in Figure 7.1 and 7.2.
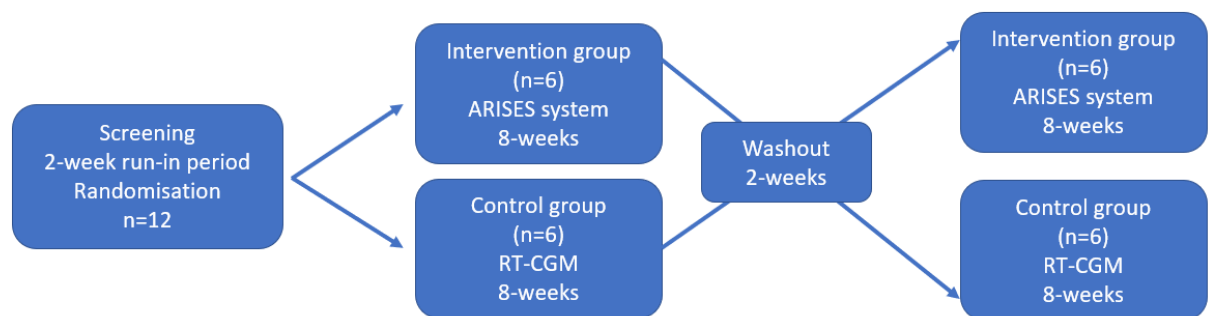
Figure 7.1. Adaptive Real Rime Intelligent System to Enhance Self-Care of Chronic Disease (ARISES) study design

The objective of the study is to demonstrate safety, technical proof of concept, and feasibility of the completed ARISES system (with adaptive machine learning enabled) in the participant's own

environment. The primary outcome was to show improved % time in target range (3.9 – 10 mmol/L) without insulin dose increase. The secondary outcomes included improved percentage time below range (<3.9mmol/L and <3.0mmol/L), and time in hyperglycaemia (>10mmol/L), HbA1c, glycaemic risk (low and high blood glucose index), and coefficient of variation. Diabetes specific quality of life outcomes would also be assessed using, Diabetes Treatment Satisfaction Questionnaire (DTSQ), Problem Areas in Diabetes questionnaire (PAID), Hypoglycaemia Fear Survey (HFS-II), and Gold score.

The proposed ARISES feasibility study remains the only adaptive machine learning study integrating real-time CGM, electrodermal activity, plethysmography, and 3-way gyroscope data inputs to graphically forecast glucose levels, offer insulin bolus calculation with dynamic glucose forecasting, and intuitively identify temporal and behavioural trends associated with hypoglycaemia in a user designed mobile application.
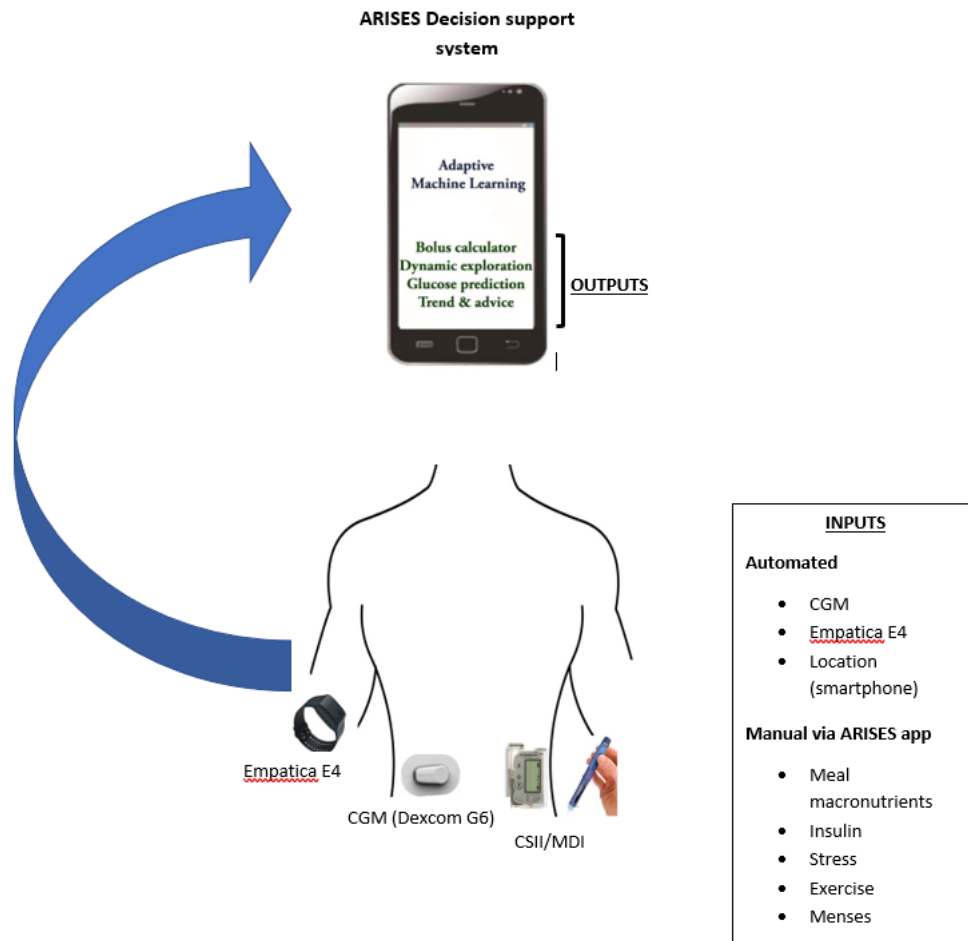
Figure 7.2. Illustration of input components and novel outcomes in the Adaptive Real-time Intelligent System to Enhance the Self-care of Chronic disease (ARISES) system.

Measurement	Attribute
Percentage of tasks completed	Effectiveness
Percentage of users able to complete a given task	Effectiveness
Number of attempts required to complete a given task	Effectiveness
Number of clicks/touches to complete task	Efficiency
Time taken to complete tasks	Efficiency
Number of errors per task	Simplicity
Severity of error (e.g. percentage error for numeric input)	Simplicity
Type of error (e.g. precision error - missed target, response	Simplicity

error – user clicks multiple times, affordance error – wrong icon or incorrect gesture, mode error etc.)	

Table 7.1. Quantitative assessment and measured attributes for task-based scenarios

Assessment	Definition
0	User completed task with zero difficulty. (Zero Frustration)
1	User completed task with only minor problem(s). (Little Frustration)
2	User completed task, but it required more effort/time/dead-ends than the user expected. (Medium/High Frustration)
3	User did not complete task. (Point of Failure)

Table 7.2. Qualitative usability assessment where the investigator will give an opinion about the participant's performance of each task using the assessment scheme above, together with an optional comment.

7.2. Future studies

The AIR-CGM study demonstrated early provision of RT-CGM following EMS attended hypoglycaemia eliminated subsequent clinically severe hypoglycaemia, reduced percentage time spent in hypoglycaemia <3.0mmol/L and reduced the frequency of enduring overnight hypoglycaemia after 12-weeks. A one way cross-over extension providing RT-CGM to control participants would be impactful by investigating if a switch to RT-CGM improves hypoglycaemia outcomes with sustained clinical support. It would also identify if continued use of RT-CGM maintains hypoglycaemia risk benefit following EMS attended hypoglycaemia.

The AIR-CGM study was challenged by difficulty providing the protocoled clinical support with a 50% participant attendance rate despite multiple attempts to reschedule telephone visits (see chapter 4). Moreover, participants did not undergo validated structured education at screening. A review of structured education programmes aimed at mitigating hypoglycaemia risk confirm up to 50% reduced incidence of severe hypoglycaemia and improved awareness of hypoglycaemia (401), with HypoCOMPaSS showing improved outcomes irrelevant of insulin modality or use of RT-CGM (329,330). This begs the question if validated hypoglycaemia prevention structured education alongside a greater initiative to provide clinical support could achieve comparable or better outcomes than RT-CGM following EMS attended hypoglycaemia. A 2x2 factorial RCT could compare structured education and weekly clinical intervention against standard care provided by their usual healthcare provider and RT-CGM against SMBG. Non-inferiority of early structured education and intense clinical input would support the fact that hypoglycaemia rates have not declined despite technological advances in diabetes care and would advocate for greater emphasis on education and clinical outreach for individuals following EMS attended hypoglycaemia. Financial modelling of the DAFNE structured education programme indicates improved quality adjusted life years, reduced incidence of diabetes related complications in adults with T1DM and is considered cost-effective by UK NICE criteria (431). With increasing accessibility to diabetes technology and rising diabetes care costs, this proposed study would reaffirm the efficacy of education as a cost-effective diabetes intervention.

Health inequalities in diabetes are associated with poorer glycaemic control (432), increased complications (433)l, and reduced life expectancy (434,435) in socio-economically deprived populations. Although contributory risk factors such as smoking and poor diet are more prevalent in deprived populations (436), evident disparity in access and engagement with diabetes care cannot be overlooked (437–439). A retrospective centre-based observational analysis identified structured

education and diabetes technology adoption rates to be the lowest among the most socio-economically deprived (439). Interestingly, disparity in technology uptake was observed despite NHS funding of diabetes technology for eligible individuals irrespective of socio-economic status. This may reflect the financial burden of self-funding required paraphernalia to achieve optimal utility (smartphones and internet connectivity) (436) and the established association between social-deprivation and missed appointments due to travel costs (440)e. Socio-economic inequalities in literacy and numeracy could also hinder effective use of diabetes technology and participation in structured education programmes. Future diabetes health inequality research would include a retrospective study exploring an association between social-deprivation and indices of hypoglycaemia and IAH. Furthermore, raising awareness among healthcare professionals and the development of more structured education courses tailored for different ethnic groups and lower levels of health literacy could help bridge the health inequality gap

8. Chapter 8: Outlook and Conclusion

8.1. Discussion

Diabetes care has seen significant advancement over the last 20 years, especially within the realm of technology and wearable devices. However, hypoglycaemia remains prevalent among people with diabetes who are expected to identify and treat hypoglycaemia independently.

Retrospectively analysing six-months of severe hypoglycaemia requiring LAS assistance, I have demonstrated the clinical impact of hypoglycaemia and further exposed the scale at which people with diabetes struggle with self-management. Successfully identifying factors linked to receiving parenteral rescue treatment and hospital transfer provides useful insight in recognising groups at increased risk of negative outcomes. I also highlight the ubiquitous risk of severe hypoglycaemia among diabetes subtypes, with significant representation in both T1DM and T2DM, the latter being positively associated with hospital conveyance. Such findings challenge presumed beliefs attributing increased hypoglycaemia risk to the inherently insulin dependent T1DM population and uncovers disparity in hypoglycaemia support provided to both subtypes. Unlike in T1DM, insulin and hypoglycaemia inducing agents are not first line T2DM treatments, hence T2DM educational programmes do not routinely provide support to independently manage hypoglycaemia. Although I detailed the efficacy of early intervention in avoiding negative outcomes, the alarming incidence of individuals repeatedly presenting with emergency hypoglycaemia (one-third) highlights a persistent risk and dependency on emergency health services.

Motivation is an important factor in achieving and maintaining goals. Self-managing diabetes is a daily endeavour requiring significant lifestyle modification and lack of motive has been cited as a major barrier in attaining target glycaemic control (441). Diabetes is commonly referred as 'the silent killer' due to many of its morbid complications linked to years of asymptomatic disease burden. Healthcare professionals often promote general health and leverage prevention of distal complications as a motivational goal to encourage lifestyle modification. However, evidence suggests such generalised and distal goals are too far removed and greater motivation can be gleaned from more immediate objectives (442,443). The COVID-19 lockdown in spring 2020 saw unprecedented fear of disease transmission among vulnerable people with diabetes and influenced how emergency health services were accessed. During this unique period, we caught a glimpse at

how previously LAS dependent individuals with severe hypoglycaemia managed at a time when health services were judiciously accessed. The fewer incidents of LAS-attended hypoglycaemia observed during lockdown may reflect a greater desire to engage in self-management motivated by an immediate fear of contracting COVID-19 if hospitalised. Studies demonstrating improved time in range during lockdown, albeit in CGM and flash glucose monitoring users, suggest lockdown afforded people the time, structure and motivation to self-manage with improved glycaemic control (381–383). Identifying such positive outcomes during lockdown highlights the impact of a committed motivational goal and calls for more time and resources to be invested in identifying tangible motives as part of individualised diabetes care. Nonetheless, the incidents of severe hypoglycaemia still requiring LAS assistance during lockdown draws attention to a subset of extremely vulnerable and dependent individuals. This was further demonstrated by the greater rates of parenteral treatment administered by LAS during lockdown.

By providing RT-CGM to people with T1DM within 2-weeks of LAS attended severe hypoglycaemia (AIR-CGM), I assessed if RT-CGM technology with low glucose alarm features reduced hypoglycaemia outcomes and improved diabetes-specific quality of life scores. A significant change in percentage time spent in hypoglycaemia <3.0mmol/L, reduced frequency of enduring overnight hypoglycaemia, and no accounts of severe hypoglycaemia after 12-weeks support RT-CGM as an efficacious adjunct in addressing severe hypoglycaemia compared to standard care. Real-time glycaemic feedback and low glucose alarms provide users a sense of control and safety unmatched by the most diligent application of standard care (SMBG). This in turn helps overcome distressing hypoglycaemia symptoms and alleviate a sense of helplessness expressed by many individuals randomised to continue standard care. Positive sentiments were shared directly by RT-CGM participants in their improved DTSQ scores and indirectly through a greater willingness to adhere to the study protocol when applying RT-CGM compared to blind CGM in the control group. Identifying IAH in the recruited

participants reinforces the known cyclical relationship with hypoglycaemia and suggests a larger number of people with diabetes lie below the iceberg of individuals with known IAH. This of clinical significance in the UK where current national guidelines advocate RT-CGM for a portion of this unidentified population likely to have complete loss of awareness.

Affirming the efficacy of adjunctive RT-CGM in reducing severe hypoglycaemia in individual's dependent on EMS does not eliminate the risk in this group. Realising the full potential of any adjunctive intervention requires optimal application of co-prescribed management strategies. Information gleaned from the participants during the trial highlighted non-modifiable socio-economic lifestyle factors as the most pertinent barriers limiting effective self-management. It was often adults with the least degree of financial freedom or dependent on working labour intense anti-social patterns that struggled the most and were least inclined to adopt change. As healthcare providers we aim to deliver equitable care across the spectrum of society, however, population data confirms socioeconomic disparity across many of the nine key processes recommended by NICE (14,444–446). In Scotland, T1DM individuals from the most deprived areas average a 8mmol/mol (95% CI 7.4, 8.9) higher HbA1c than their more privileged counterparts (447). Lower socio-economic status and increased area-level deprivation have also been linked to increased risk of DKA in T1DM (445). The NHS long term plan has committed significant financial resources to address healthcare inequality as one of the key ambitions for the service over the next 10 years (448). ARISES is a decision support mobile app created primarily to assist the self-management of T1DM with design and concept ideas derived from a range of people with T1DM. By placing ARISES directly in the hands of the most vulnerable and socially deprived, the system takes a positive step to promote accessibility to a broad diabetes population by addressing both researched and usability requirements raised in end-user focus groups. The application of haptic features and colour schemes receptive to people with microvascular complications are details aimed to ensure the demographic

at greatest need are not marginalised. Exploring the ideas and expectations of people with diabetes highlighted a need to be mindful of burdening people with technology, with most participants agreeing on 3 wearable devices as an acceptable maximum for a decision support system. However, the prospect of achieving better glucose control was the most cited reason to wear more devices and identifies a group of individuals motivated to fully embrace diabetes technology. The sustained daily engagement of participants wearing two devices and interacting with a smartphone app throughout the ARISES phase 1 observational study further suggests a willingness to commit to multiple technologies.

The clinical impact of RT-CGM in reducing severe hypoglycaemia is heavily dependent on alarms triggered by current and anticipated hypoglycaemia. Most RT-CGM systems anticipate hypoglycaemia from the trajectory of earlier glucose measurements, however, the ARISES observational study identified measurable physiological metrics associated with clinically significant hypoglycaemia <3.0 mmol/L and impending hypo (1-hour before hypoglycaemia <4.0mmo/L). Integrating data accrued from physiological wristbands adjunctively with RT-CGM has the potential to improve the accuracy of both detection and prevention of hypoglycaemia. The ARISES machine learning algorithm incorporates these concepts and introduces behaviour modification through non-intrusive notifications as an additional hypoglycaemia preventative strategy aimed to reduce alarm fatigue. Informing users of recurring patterns of behaviour resulting in hypoglycaemia applies a prevention over cure approach and allows the opportunity to address previously unidentified risk behavioural, limit hypoglycaemia, and prevent associated intrusive alarms. The proposed safety and proof of concept study (phase 2) aimed to formally evaluate these features in an accessible user designed smartphone app integrating two wearable sensor devices. A unique machine learning algorithm and novel contextual GUI features stands the planned ARISES system apart from any commercially available decision support platform.

8.2. Conclusion

In summary, this research highlights the prevalence and clinical relevance of hypoglycaemia across all subtypes of diabetes and, at the same time, suggests disparity in risk prevention between T1DM and T2DM. Greater efforts are needed to bridge the gap between both groups but also in identifying individually relatable motivators known to inspire sustained engagement. Reaffirming the effectiveness of RT-CGM in reducing severe hypoglycaemia burden is promising as sensor devices are becoming increasingly accessible. However, many people with diabetes continue to suffer from the negative effects of severe hypoglycaemia despite evidence suggesting standard care provides no benefit in reducing risk in a group comprised of the most socially vulnerable individuals. ARISES is designed to apply wearable physiological sensor data and CGM to improve the accuracy of hypoglycaemia detection and modify behaviour to reduce hypoglycaemia and alarm fatigue. A GUI and novel features inspired by people with diabetes promotes accessibility across the entire T1DM population without marginalising people with microvascular complications. Although designed primarily for people with T1DM, the features in ARISES would significantly benefit a selected insulin treated T2DM population. However, the overriding ambition is to successfully support vulnerable people with diabetes and provide safe effective technologies equitably.

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9. Appendix - Outputs arising from this work

Publications arising from this work

Journal Papers and Book Chapters

Cross-sectional analysis of emergency hypoglycaemia and outcome predictors among people with diabetes in an urban population – C Uduku, V Pendolino, I Godsland, N Oliver, M Reddy, R Fothergill – Journal Article: Diabetic Medicine, ISSN: 0742-3071

Conference Abstracts and Poster Presentations

Independent predictors of hypoglycaemia and Impending hypoglycaemia using a wearable physiological data acquisition sensor – C Uduku, K Li, T Zhu, J Daniels, P Herrero, P Georgiou, M Reddy, N Oliver – Conference: Advanced Technologies and Treatments for Diabetes 2021 (Virtual)

The Assessment of Impact of Real-time Continuous Glucose Monitoring on people presenting with severe Hypoglycaemia (AIR-CGM) study – C Uduku, N Jugnee, V Pendolino, N Oliver, R Fothergill, M Reddy – Conference: Advanced Technologies and Treatments for Diabetes 2021 (Virtual)

A novel hand-held interface supporting the self-management of type 1 diabetes – R Spence, K Li, C Uduku, T Zhu, L Redmond, P Herrero, N Oliver, P Georgiou – Conference: Advanced Technologies and Treatments for Diabetes 2020 (Madrid)

Personalized meal insulin bolus for type 1 diabetes using deep reinforcement learning – T Zhu, K Li, C Uduku, P Herrero, N Oliver, P Georgiou – Conference: Advanced Technologies and Treatments for Diabetes 2020 (Madrid)

ARISES: an advanced clinical decision support platform for the management of type 1 diabetes – J Daniels, T Zhu, K Li, C Uduku, P Herrero, N Oliver, P Georgiou – Conference: Advanced Technologies and Treatments for Diabetes 2020 (Madrid)

A deep neural network platform for predicting blood glucose levels – K Li, J Chen, P Herrero, C Uduku, P Georgiou – Conference: Advanced Technologies and Treatments for Diabetes 2019 (Berlin)

Other Journal Publications

Glucose Monitoring Devices, measuring blood glucose to manage and control diabetes – C Uduku, M Reddy, N Oliver – Book Chapter: Clinical impact of CGM use, Academic Press, 2020, Pages 135-158, ISBN 9780128167144.

Differences for Percentage Times in Glycaemic Range Between Continuous Glucose Monitoring and Capillary Blood Glucose Monitoring in Adults with Type 1 Diabetes: Analysis of the REPLACE-BG Dataset – P Avari, C Uduku, D George, P Herrero, M Reddy, N Oliver – Journal Article: Diabetes Technology & Therapeutics, Vol 22, No. 3. Feb 2020

"The bio-inspired artificial pancreas for type 1 diabetes control in the home: System architecture and preliminary results," – P Herrero, M El-Sharkawy, J Daniels, N Jugnee, C Uduku, M Reddy, N Oliver, P Georgiou – Journal Article: Journal of diabetes science and technology, vol. 13, no. 6, pp. 1017–1025, 201

Higher levels of social deprivation associated with increased percentage time in range in people with T1DM during COVID-19 lockdown – P Avari, R Unsworth, S Rilstone, C Uduku, K Logan, N Hill, I Godsland, M Reddy, N Oliver – Conference: Advanced Technologies and Treatments for Diabetes 2021 (Virtual)