Targeting postprandial hyperglycaemia with exenatide in young people with cystic fibrosis

A thesis by

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THESIS AIMS

To determine the acute effect of exenatide on postprandial glycaemia in young people with cystic fibrosis related diabetes (CFRD) or cystic fibrosis (CF) with impaired glucose tolerance (IGT) through

a) Evaluation of the effect of exenatide on postprandial glycaemic control
b) Quantification of the impact of exenatide on gastric emptying
c) Quantification of the effect of exenatide on plasma concentrations of glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), insulin and glucagon.

Hypothesis

In young people with CFRD or CF with IGT, when compared with placebo, exenatide will delay gastric emptying and improve postprandial glycaemia.

THESIS SUMMARY

This thesis is concerned with control of postprandial hyperglycaemia in paediatric populations with diabetes and specifically, those with cystic fibrosis (CF), and how postprandial hyperglycaemia can be modified in this group by use of the GLP-1 receptor agonist, exenatide. The work extends previous studies by colleagues relating to gastric emptying, the incretin effect, and postprandial glycaemia in paediatric populations with CF and type 1 diabetes (T1D), by evaluating a treatment approach that addresses the underlying pathophysiology.

Chapter 1 explores the determinants, significance, and management of postprandial glycaemia in CF. Currently, CFRD is the most common co-morbidity in adolescents and adults with CF, and can lead to a decline in nutrition and lung function. Additionally, the few management options available carry a heavy burden, leaving an ideal opening for new targeted treatments. The pathophysiology of postprandial dysglycaemia, gastric emptying and the incretin system is explored, and the opportunities for intervention are discussed.

The literature related to postprandial glycaemia as a target of treatment in the management of diabetes in children is reviewed in chapter 2. This covers all types of diabetes, and summarises the observational and interventional trials that have established the importance of targeting postprandial blood glucose, the factors that influence postprandial glycaemia, and how they can be altered using currently available therapies.

Chapter 3 details the methods to enable appropriate investigation of postprandial glycaemia, gastric emptying and the incretin axis, and compares the techniques available to evaluate each of these.

Chapter 4 details the effect of exenatide in a group of children and young adults with CF who have impaired glucose tolerance. This study compared exenatide with placebo in a randomised

crossover design. We observed that postprandial glycaemia was normalised following administration of exenatide, associated with a delay in gastric emptying.

Finally, the conclusion in chapter 5 reviews pertinent publications released subsequent to the exenatide trial, and discusses possible avenues for further investigation.

DECLARATION

Name: Myfanwy Clare Geyer Program: Master of Philosophy

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Signature: Date: 22/02/2022

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PUBLICATIONS ARISING FROM THE THESIS

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CHAPTER 1. INTRODUCTION

1.1 SUMMARY

The development of cystic fibrosis related diabetes (CFRD) is associated with increased morbidity and mortality. The improved life expectancy of people with CF (with better management of respiratory and nutritional aspects of the disease) has resulted in greater focus on the optimal management of complications, the most common of which is CFRD (Moran, Becker, et al. 2010; Moran, Dunitz, et al. 2009). The initial deficit is in the first phase insulin response, resulting in postprandial hyperglycaemia (Granados et al. 2019). The only available current treatment is insulin, which has a significant additional treatment burden in a condition that requires multiple medications and other therapies (Moran, Brunzell, et al. 2010).

Postprandial glycaemia is physiologically determined by the complex relationship between preprandial glycaemia, meal composition, the enteroendocrine system (including incretins, insulin and glucagon) and the rate of gastric emptying (Bell, Smart, et al. 2015; Nauck 2009). Postprandial glycaemic control is an ideal target in cystic fibrosis to support nutrition and optimise lung function.

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist (i.e. an incretin mimetic) with insulinotropic and glucagonostatic effects, which also slows gastric emptying (Nauck 2011). It is used widely in the management of type 2 diabetes, but any potential role in cystic fibrosis has yet to be investigated.

1.2 CYSTIC FIBROSIS AND CFRD

Cystic Fibrosis (CF) is the most common life-limiting autosomal recessive condition affecting Caucasian populations, with an incidence of 1 in 2,500 live births (Barrio 2015; Rana et al.

2011). Life expectancy has increased to 48 years with improved management of the respiratory and malabsorption components of the disease (CF Foundation 2020). Given this, there has been an increased incidence of co-morbidities, the most common of which is cystic fibrosis related diabetes (CFRD). CFRD affects approximately 40-50% of adults with CF (CF Foundation 2020; Ode et al. 2019). CFRD is associated with poorer outcomes in relation to pulmonary function and nutritional status, resulting in a higher morbidity and mortality (Bismuth et al. 2008; Lombardo et al. 2003; Milla, Warwick & Moran 2000), when compared to CF patients without diabetes.

CFRD is distinct from type 1 and type 2 diabetes in its pathophysiology and clinical presentation. Its development is attributed primarily to a decline in beta cell function and insulin deficiency, with fluctuating insulin resistance influenced by infection or glucocorticoid use (Granados et al. 2019; Hameed, Jaffe & Verge 2011; Moran, Becker, et al. 2010). Its onset is insidious and commonly asymptomatic. Postprandial, rather than fasting hyperglycaemia is the initial finding, so treatments that target postprandial glycaemia represent a logical therapeutic aim (O'Shea & O'Connell 2014; Perano et al. 2014). For up to 2-6 years prior to the diagnosis of CFRD, declines in lung function and nutritional status have been noted (Hameed, Jaffe & Verge 2011, 2015). When aggressively managed with insulin, lung function, frequency of infections and nutritional status (BMI) all improve (Hameed, Shihab et al. 2012; Mozzillo et al. 2009).

Currently, insulin is the only recognized treatment for CFRD, but carries a risk of hypoglycaemia and represents a significant treatment burden, given the need for frequent blood glucose level (BGL) monitoring and multiple daily injections (Moran et al. 2018). In context, this adds to the heavy treatment burden related to respiratory and gastrointestinal aspects of CF, and can reduce quality of life, particularly in the adolescent and young adult years. A novel

treatment without such significant risks and burdens, that specifically targets postprandial hyperglycaemia, would likely bring both physical and psychological benefit.

1.3 POSTPRANDIAL GLYCAEMIA AND GASTRIC EMPTYING

The contribution of postprandial glycaemia to overall diabetes control has been increasingly recognised, with post-meal glucose excursions accounting for up to 70% of the variation in glycated haemoglobin in patients with diabetes (Marathe et al. 2013; Monnier, Lapinski & Colette 2003; Woerle et al. 2007). Meanwhile, postprandial hyperglycaemia in cystic fibrosis (for both CF with IGT and CFRD) has been shown to have deleterious effects on lung function and nutrition (Alves, Della-Manna & Albuquerque 2020). Historically, CFRD was further differentiated as being with or without fasting hyperglycaemia, and treatment with insulin was usually commenced only when fasting hyperglycaemia developed. However, the consequences of postprandial hyperglycaemia are similarly deleterious whether or not fasting hyperglycaemia is present. As a result, the differentiation of CFRD based on the presence or absence of fasting hyperglycaemia has been removed and aggressive postprandial glycaemic management is now standard practice, and has been shown to improve nutrition and lung function (Moran, Brunzell, et al. 2010).

Postprandial glycaemia has multiple determinants including gastric emptying rate, meal content, incretin hormone secretion and preprandial glycaemia. Rapid gastric emptying is associated with greater postprandial glycaemic spikes when compared with more gradual emptying (Phillips et al. 2015), due to increased availablity of ingested carbohydrate for abosprtion in the small intestine. Inter-individual differences in gastric emptying contribute to approximately 35% of glycaemic variability in adults (Horowitz et al. 1993). In children with T1D, rapid gastric emptying has been shown to result in higher increments in postprandial

glycaemia (Perano et al. 2015; Raman & Heptulla 2009). Few studies measuring gastric emptying have been undertaken in CF, and these have yielded variable outcomes (Collins et al. 1997; Corral et al. 2016; Cucchiara et al. 1996; Kuo et al. 2011; Perano et al. 2014). The rate of gastric emptying is affected by both the blood glucose concentration and the secretion and action of the incretin hormones. The presence of hyperglycaemia and/or high concentrations of the incretin hormone GLP-1 (as well as other gut peptides including cholecystokinin and peptide YY) delays gastric emptying, resulting in a lower and delayed peak postprandial glucose response. Conversely, the presence of hypoglycaemia or diminished GLP-1 concentrations results in more rapid gastric emptying (Marathe et al. 2013; Nauck 2009).

Exocrine pancreatic insufficiency is present in 80-90% of patients with CF (Symonds et al. 2003). Pancreatic enzyme replacement therapy (PERT) dramatically improves but does not completely restore fat absorption (Wouthuyzen-Bakker, Bodewes & Verkade 2011). Pancreatic exocrine insufficiency has been associated with a deficient incretin response and accelerated gastric emptying, because digestion of triglycerides to liberate free fatty acids is required to stimulate the release of the incretin hormones (Collins et al. 1997; Marathe et al. 2013; Perano et al. 2014). While carbohydrate has the greatest direct effect of the macronutrients on postprandial glycaemia, the addition of fat to a meal has been shown to slow gastric emptying, reduce the initial glycaemic excursion and delay its peak (Bell, Smart, et al. 2015; Lodefalk, Aman & Bang 2008). The author's research group previously showed that pancreatic enzyme replacement therapy (PERT) lowered postprandial hyperglycaemia through slowing gastric emptying and augmenting incretin hormone release after a high fat/high carbohydrate meal (Kuo et al. 2011; Perano et al. 2014).

1.4 INCRETINS

The “incretin effect” refers to the substantially increased insulin release in response to an oral rather than a comparable intravenous glucose load (Baggio & Drucker 2007; Meier & Nauck 2015). This effect accounts for 50-70% of the insulin response to an oral glucose load in healthy individuals (Ma et al. 2009; Nauck 2009). The “incretin” hormones responsible for the incretin effect, GLP-1 and glucose dependent insulinotropic polypeptide (GIP), are secreted from L and K cells respectively in the small intestine in response to exposure to nutrients. All macronutrients stimulate secretion of the incretins, although fat (above carbohydrate and protein) has the most potent action. Endogenous incretins are rapidly degraded by dipeptidyl peptidase 4 (DPP4) to inactive metabolites in the circulation (Baggio & Drucker 2007; Marathe et al. 2013).

GLP-1 and GIP augment insulin secretion only when blood glucose is elevated (i.e. their insulinotropic effects are glucose-dependent), while GLP-1 has an additional glucagonostatic effect. In type 2 diabetes, while plasma concentrations of the incretin hormones are not necessarily reduced, the insulinotropic effect of GIP is markedly diminished, while that of GLP-1 is largely retained (Holst, Vilsboll & Deacon 2009; Michaliszyn et al. 2013), making GLP-1-based treatments the main focus of incretin-based therapy (Marathe et al. 2014; Nauck & Meier 2016). Despite conflicting reports as to absolute incretin levels in T1D, data show an improvement in postprandial glycaemia when GLP-1 agonists are administered in this condition (Dupre, Behme & McDonald 2004; Raman et al. 2010). Given the lack of endogenous insulin in T1D, the benefits of GLP-1 based therapy in this instance must rely on a delay in gastric emptying and/or suppression of glucagon. Similarly, in CF, there have been inconsistent reports as to absolute incretin levels, but the incretin effect is evidently reduced and gastric emptying of high fat/high carbohydrate meals is accelerated, resulting in postprandial hyperglycaemia (Frost et al. 2019; Kuo et al. 2011; Perano et al. 2014).

1.5 INCRETIN BASED THERAPIES

GLP-1 receptor agonists have been available in Australia for type 2 diabetes since exenatide was approved by the TGA in 2012. Since then, longer acting formulations have been approved with subtle differences in effect/benefit. All GLP-1 receptor agonists provide supraphysiological levels of GLP-1 and are resistant to breakdown by DPP4, in contrast to the short half-life (about 2 minutes) of endogenous GLP-1. DPP4 inhibitors block the degradation of endogenous GLP-1, increasing circulating levels of the intact hormone two or three fold, while also increasing intact GIP concentrations. Both GLP-1 receptor agonists and DPP4 inhibitors have been shown to improve glycated haemoglobin, and postprandial and fasting glycaemia, in type 2 diabetes (Blevins et al. 2011; Klein et al. 2014; Nauck et al. 2021). GLP-1 receptor agonists have also shown improvement in glycaemic control when used as an adjunct to insulin in T1D (Ilkowitz et al. 2016; Raman et al. 2010; Varanasi et al. 2011).

As with endogenous incretins, GLP-1 receptor agonists reduce postprandial glycaemia through insulinotropic and glucagonostatic effects, and by delaying gastric emptying (Cernea & Raz 2011; Perfetti & Merkel 2000). Longer acting GLP-1 agonists (once weekly/QW) have a more profound effect on fasting glycaemia, as there is some tachyphylaxis for the effects on gastric emptying with sustained exposure (Umapathysivam et al. 2014). Effects on gastric emptying are likely to be less marked for long- than short-acting formulations, although for the long-acting (QW) form of exenatide at least, some effect to slow gastric emptying persists with sustained use (Jones et al. 2020). DPP4 inhibitors also stimulate insulin and suppress glucagon, albeit less potently, but have no substantial effect on gastric emptying (Peters 2010).

GLP-1 receptor agonists are generally well tolerated. The most common adverse effects are gastrointestinal, including nausea, which usually reduces in intensity with ongoing treatment (Cernea & Raz 2011; Klein et al. 2014; Malloy et al. 2009). The risk of hypoglycaemia with

incretin based treatments is minimal given their stimulation of insulin release is glucose dependent (Meloni et al. 2013). Therefore, there is less requirement for blood glucose monitoring than with insulin analogues.

GLP-1 receptor agonists and DPP4 inhibitors have been studied in paediatric T1D and type 2 diabetes, where they have reduced both postprandial and fasting hyperglycaemia (Raman et al. 2010; Tamborlane et al. 2019; Tamborlane et al. 2018). Exenatide's pharmacokintetic properties (half-life 2 hours) make it a logical choice over the longer acting formulations for this mechanistic study, where the slowing of gastric emptying is likely to be an important property.

In summary, the development of CFRD represents a continuum of increasing postprandial hyperglycaemia, to which a diminished incretin response contributes (Frost et al. 2019). The role of incretin-based therapies in this population is, however, yet to be explored.

CHAPTER 2. TARGETING POSTPRANDIAL GLYCAEMIA IN CHILDREN WITH DIABETES: OPPORTUNITIES AND CHALLENGES

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Co-Author Contributions

By singing the Statement of Authorship, each author certifies that:

i) the candidate's stated contribution to the publication is accurate (as detailed above);

ii) permission is granted for the candidate to include the publication in the thesis; and

iii) the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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2.1 INTRODUCTION

The microvascular complications of diabetes have an irrefutable link to overall glycaemic control and achieving optimal management of glycaemia from the onset of diabetes in children is critical in minimising the risk of complications (Gubitosi-Klug et al. 2016; Lind et al. 2014; Stratton et al. 2000). Since the outcomes of the Diabetes Control and Complications Trial (DCCT) were reported, children with type 1 diabetes have achieved major improvements in glycaemic control (The DCCT Research Group 1993; Cameron et al. 2013; Gubitosi-Klug et al. 2016; Rosenbauer et al. 2012). However, few attain recommended HbA1c goals (de Beaufort et al. 2013; Phelan et al. 2017) and, until recently, much of the focus has been on fasting and preprandial glycaemic control. The importance of specifically targeting postprandial hyperglycaemia is now a central strategy in diabetes management (Cavalot et al. 2006).

The aim of this review is to explore the determinants and management of postprandial glycaemia in children and adolescents with type 1 and type 2 diabetes, mature onset diabetes of the young (MODY), and cystic fibrosis related diabetes. Following a discussion of the importance of postprandial glycaemic control, determinants, including the nutritional macronutrients, insulin and glucagon, other enteroendocrine factors, incretins and gastric emptying, will be explored in parallel with the implications for clinical management.

2.2 THE IMPORTANCE OF POSTPRANDIAL GLYCAEMIC CONTROL

Overall glycaemic control is a reflection of the contributions of both fasting (or preprandial) glycaemia and postprandial glycaemia. The advent of continuous glucose monitoring (CGM),

in particular, has revealed the substantial contribution of the latter to the overall glycaemic profile (Figure 2.1). Postprandial glycaemic excursions predominate over fasting blood glucose in contributing to overall glycaemia in adult type 2 patients when HbA1c is less than ~8.0% (64 mmol/mol) (Ceriello et al. 2004; Monnier, Lapinski & Colette 2003; Riddle et al. 2011), and have a substantial impact on glycaemic variability. The latter is associated with increased oxidative stress and adverse effects on endothelial function (Ceriello et al. 2002; Madsbad 2016), which may be why postprandial hyperglycaemia is more predictive of cardiovascular events and mortality than pre-prandial hyperglycaemia, in adults with type 2 diabetes (Ceriello et al. 2002; Madsbad 2016) (Cavalot et al. 2006; Qiao, Tuomilehto & Borch-Johnsen 2003). Notably, in maturity onset diabetes of the young secondary to the glucokinase mutation (MODY 2), which is characterised by fasting hyperglycaemia, but normal postprandial glycaemia, there is no increase in micro- or macrovascular complications unless insulin resistance develops (Rubio-Cabezas et al. 2014). Furthermore, in population-based adult cohorts without known diabetes, postprandial glucose is a better predictor of cardiovascular outcomes than HbA1c (de Vegt et al. 1999; Meigs et al. 2002). In type 1 diabetes, assessment of glycaemic variability in the DCCT, by 7 point blood glucose profile, prior to the availability of continuous glucose monitoring (CGM), suggested that neither glycaemic variability, preprandial, nor postprandial glycaemia are additional predictors of the development of complications above their effect on mean blood glucose (Lachin et al. 2017). More recent studies with CGM, giving a more complete picture of variability have, however, indicated that glycaemic variability influence both overall glycaemic control (HbA1c) and endothelial function (Battelino & Bolinder 2008; Buscemi et al. 2010). Long term studies with CGM relating to the development of complications are not yet available.

In cystic fibrosis related diabetes (CFRD), HbA1c is an unreliable means of assessing glycaemic control (Moran, Brunzell, et al. 2010), since red blood cell turnover is increased

when lung function falls below 70% of normal. Postprandial hyperglycaemia is known to precede fasting hyperglycaemia by a number of years in CFRD, typically with spikes of shorter duration than those seen in type 1 or 2 diabetes (Godbout et al. 2008; Hardin et al. 1999) and contributes to poor weight gain, an increase in lung infections, and decline in lung function (Lombardo et al. 2003; Milla, Warwick & Moran 2000). It is now recommended that postprandial hyperglycaemia be treated more aggressively in CF, before the development of fasting hyperglycaemia, in order to improve both nutritional status and lung function (Moran, Brunzell, et al. 2010; Moran, Dunitz, et al. 2009).

Gastric emptying, the incretin system, and preprandial glycaemia, are interdependent factors that affect postprandial glycaemia. An increased understanding of the impact of different macronutrients in addition to rapidly advancing technology for insulin delivery and continuous blood glucose monitoring, provides new opportunities to improve postprandial control in children with all forms of diabetes (Elleri et al. 2015; Heptulla et al. 2008; Perano, SJ et al. 2014; Perano et al. 2015; Rodriguez et al. 2009; Wu et al. 2013).

2.3 HOW DOES MEAL CONTENT INFLUENCE POSTPRANDIAL HYPERGLYCAEMIA?

All macronutrients contribute to postprandial glycaemia, but carbohydrates have the greatest effect. Current recommendations advise that the insulin dose be adjusted according to the calculated carbohydrate intake (Smart et al. 2014). However, the relationship of the postprandial glucose excursion to carbohydrate intake is not linear above a certain ingested load (Bell, King, et al. 2015). The influence of gastric emptying, which occurs at a relatively fixed caloric rate within individuals, but varies between individuals between 1-4 kcal/min even in health, results in a relatively constant delivery of nutrients to the duodenum. This means that increasing the carbohydrate load above a certain level does not lead to further elevation in peak

blood glucose, but rather a more prolonged postprandial excursion (Bell, King, et al. 2015). This may be of particular relevance to the large carbohydrate loads typically consumed during adolescence. Despite its widespread use, the impact of carbohydrate counting on overall glycaemic control has been modest at best, showing small improvements in HbA1c in individual studies, and no statistical improvement in meta-analysis in both children and adults (Bell et al. 2014).

The glycaemic index (GI) of carbohydrate impacts on both the magnitude and timing of the blood glucose excursion (Brand-Miller et al. 2009), albeit with substantial inter- and intra-individual variation for a given food (Matthan et al. 2016). Nevertheless, a lower GI diet can reduce glycaemic excursions and mean daytime blood glucose by ~2.5 mmol/L in children with type 1 diabetes (Nansel, Gellar & McGill 2008).

In adolescents with type 1 diabetes, the addition of both fat and protein to a carbohydrate meal increases the glucose area under the curve (AUC) between 4 and 12 hours postprandially, and maximally at 6 hours (Neu et al. 2015). When studied individually, the addition of fat to a meal has been shown to slow gastric emptying and reduce glucose AUC in the initial 2-3 hours, while delaying peak glucose by up to 90 minutes, and resulting in higher blood glucose values later in the postprandial period (Bell, Smart, et al. 2015; Lodefalk, Aman & Bang 2008; Wolpert et al. 2013). The addition of protein also increases glycaemia between 3-5 hours postprandially (Paterson et al. 2016).

Insulin bolus calculations that take account of the glycaemic effects of protein and fat can, therefore, reduce postprandial blood glucose excursions. Moreover, continuous subcutaneous insulin infusion (CSII) protocols that employ a dual wave bolus, when compared with standard, square wave or double boluses, result in reduction in postprandial glucose levels in children and adults with type 1 diabetes (Chase et al. 2002; O'Connell et al. 2008), as well as

HbA1c, although adherence outside of clinical trials may be compromised by their complexity, so these benefits cannot necessarily be generalised for all patients (Pankowska et al. 2009).

2.4 HOW DO INSULIN AND GLUCAGON INFLUENCE POSTPRANDIAL GLYCAEMIA?

In health, postprandial glycaemia is directly controlled by the interaction of insulin and glucagon. Impairment of the first phase insulin response is one of the earliest markers of beta cell dysfunction in type 1 (Sosenko et al. 2013) and type 2 diabetes (Gerich 2002), CFRD (Moran, Becker, et al. 2010) and MODY (Tripathy et al. 2000). As a result of the outcomes of landmark studies over the last 2 decades unequivocally linking glycaemic control to the risk of vascular complications, intensive basal-bolus regimens have become standard therapy in type 1 diabetes, and have shown to improve HbA1c in all age groups (The DCCT Research Group 1993; Gubitosi-Klug et al. 2016). The ultra-short-acting insulins (aspart and lispro) provide a more physiological profile when taken approximately 15 minutes before food. CSII and continuous glucose monitoring (CGM) provide further sophistication in insulin delivery and dose calculation. However, despite these improvements in insulin delivery and monitoring systems, the substantial majority of children still have an HbA1c level above target (Phelan et al. 2017). Subcutaneous insulin therapy is limited by variable absorption and the need for complex dosing calculations so that the rise in blood glucose is only partially prevented (Heptulla et al. 2008). The systemic, rather than intra-portal, delivery of exogenous insulin is a further limitation resulting in peripheral insulin resistance and a higher insulin requirement (Carpentier et al. 2001).

As well as insulin secretion and action, alpha cell function and the secretion of glucagon is dysregulated in type 1 and 2 diabetes. In health, the rise in blood glucose associated with nutrient ingestion suppresses glucagon secretion from the alpha cells in the presence of intra-

islet insulin and, thereby, reduces hepatic glucose release (Greenbaum et al. 1991; Hope et al. 2004). In children with type 1 diabetes, failure to suppress glucagon, thought to reflect the lack of endogenous intra-islet insulin, exacerbates hyperglycaemia (Fredheim et al. 2015; Porksen et al. 2007). Additionally, there is dysregulation of the counter-regulatory response to hypoglycaemia in type 1 diabetes, with reduced glucagon release (Sherr et al. 2013; Siafarikas et al. 2012). In adolescents with type 2 diabetes, or obesity alone, there is an excessive glucagon response to a mixed meal or OGTT, when compared to lean controls, demonstrating that glucagon suppression is impaired in these groups, as is the case in adults with obesity and type 2 diabetes (Manell et al. 2016).

Closed loop systems incorporating both CGM and CSII enable constant adjustment of insulin dose according to the subcutaneous glucose concentration and provide tight regulation of basal insulin requirements. Their efficacy in the postprandial period, however, has been limited by the lag time between sensing the rise in blood glucose and the absorption and onset of action of exogenous subcutaneous insulin (Gingras et al. 2018). Accordingly, fully automated closed loop systems have resulted in significant improvements to overnight glycaemic control, however, they have hitherto not demonstrated substantial benefit to daytime (including prandial) control (Chase et al. 2014; Elleri et al. 2015; Zisser et al. 2014). Closed loop systems with manual meal priming reduce the impact of this lag time and improve prandial control significantly while also reducing late postprandial hypoglycaemia and increasing time in target range in paediatric and adult populations (Bally et al. 2017; Thabit et al. 2015; Weinzimer et al. 2008). A small fully automated closed loop study that incorporated CGM, heart rate and activity level improved time in glycaemic target and hypoglycaemia (Turksoy et al. 2013). The incretin mimetics and pramlintide (as discussed later) primarily reduce postprandial glycaemic excursions through effects to slow gastric emptying and suppress glucagon. Adjunctive treatment with these agents may delay and prolong the postprandial glycaemic excursion,

reducing the limitations of closed loop systems. Proof of concept crossover trials with such systems delivering insulin, together with adjunctive pramlintide or liraglutide, have demonstrated reductions in both the peak and the area under the curve for the glycaemic response (Ilkowitz et al. 2016; Weinzimer et al. 2012).

The benefits of infusing glucagon, as well as insulin, in artificial pancreas systems remain unresolved; reductions in both mean daily glucose concentrations and the percentage of time below target glucose (less than 3.3 mmol/L) have been reported (Kowalski 2015; Russell et al. 2016); in other studies, single and dual hormone closed loop systems exhibit similar improvements in the percentage of time in target as measured by CGM, when compared to conventional CSII (Haidar et al. 2015; Haidar et al. 2016).

In patients with CFRD, rapid acting prandial insulin administration that targets postprandial glycaemia can increase BMI and improve lung function (Moran, Pekow, et al. 2009). Basal insulin administration may also improve these endpoints, perhaps in part because of the anabolic effect of insulin and the provision of pancreatic beta cell 'rest' (Mozzillo et al. 2009). Whether the commencement of insulin earlier, at the stage of impaired glucose tolerance, improves pulmonary function is the subject of current trials (Hameed, S., Jaffe & Verge 2015).

2.5 WHAT ENTEROENDOCRINE FACTORS INFLUENCE POSTPRANDIAL GLYCAEMIA?

As displayed in figure 2.2, hyperglycaemia in diabetes results not solely from a deficiency in insulin (absolute or relative), but also from an imbalance of the enteroendocrine axis, that impacts specifically on insulin and glucagon responses to meals, and, in some patients, on the rate of gastric emptying (Fredheim et al. 2015; Heptulla et al. 2008; Perano et al. 2015).

2.5.1 THE ROLE OF THE INCRETINS

The incretin effect is defined as the augmentation of insulin secretion in response to oral or enteral administration of glucose, when compared to an isoglycaemic intravenous glucose load. It is accounted for by the release of glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1 (GLP-1), from the K and L cells respectively in the small and large intestine, primarily in response to the presence of nutrients in the lumen of the gut. All macronutrients stimulate incretin release, although fat may be the most potent stimulus. The incretins reduce postprandial hyperglycaemia through their insulinotropic effects, which are glucose-dependent, while GLP-1 also suppresses glucagon and slows gastric emptying (Nicolaus et al. 2011). In health, GIP may account for the greater proportion of the incretin effect. However, on the spectrum of impaired glucose tolerance and diabetes, there is a markedly reduced insulin response to GIP, while the insulinotropic effect of GLP-1 remains relatively intact (Nauck, MA & Meier 2016). The incretins are rapidly metabolised by a ubiquitous enzyme, dipeptidyl peptidase 4 (DPP4), to yield "inactive" metabolites (Baggio & Drucker 2007).

Type 2 diabetes in adults is associated with a diminished incretin effect (Faerch et al. 2015; Holst, Vilsboll & Deacon 2009; Nauck, M et al. 1986), reflecting reductions in the insulinotropic response to GIP, functioning beta cell mass, and maximum insulin secretory capacity (Meier & Nauck 2010; Vilsboll et al. 2002). Despite variation in the reported concentrations of GIP and GLP-1 (both reduced and increased (Aulinger et al. 2016; Kaas et al. 2012; Manell et al. 2016; Michaliszyn et al. 2014)), meta-analyses indicate that there is no substantial alteration in GIP or GLP-1 secretion in type 2 diabetes (Calanna et al. 2013a, 2013b). A reduced incretin effect is also seen in adolescents with impaired glucose tolerance or type 2 diabetes (Aulinger et al. 2016; Michaliszyn et al. 2014). In type 1 diabetes, there is, predictability, a reduced incretin effect in terms of insulin response, and glucagon suppression is also impaired (Greenbaum, Prigeon & D'Alessio 2002).

GLP-1 receptor agonists (RAs), which are resistant to degradation by DPP4, and administered subcutaneously, have been developed primarily for use in type 2 diabetes. Two of these, exenatide bid and liraglutide, have been studied in children. Exenatide bid is a 'short-acting' GLP-1 RA with a twice daily dosing regimen. While it enhances insulin, and suppresses glucagon secretion under hyperglycaemic conditions, its main action to improve postprandial glycaemia is by slowing gastric emptying (Linnebjerg et al. 2008). Liraglutide is a 'long-acting' GLP-1 RA with daily dosing requirements. Prolonged exposure to longer acting agonists may attenuate their inhibitory effect on gastric emptying (Meier et al. 2015; Umapathysivam et al. 2014). DPP4 inhibitors, for example sitagliptin, which block the inactivation of endogenous GIP and GLP-1, are also available and are administered orally. Both GLP-1 RAs and DPP4 inhibitors are associated with minimal risk of hypoglycaemia, since the insulinotropic action of the incretins is glucose-dependent. Moreover, unlike insulin, DPP4 inhibitors are body weight-neutral, while GLP-1 RAs are associated with modest weight loss. The latter provide a supraphysiological level of GLP-1 receptor stimulation, resulting in more potent glucose-lowering than DPP4 inhibitors.

In the adult type 2 diabetes population, GLP-1 RAs improve both postprandial glycaemia and overall glycaemic control (Horowitz et al. 2012; Nauck, MA et al. 1993; Scott et al. 2013). Both liraglutide and semaglutide are associated with improved cardiovascular outcomes, while lixisenatide appears neutral in terms of cardiovascular risk (Marso, Bain, et al. 2016; Marso, Daniels, et al. 2016; Pfeffer et al. 2015), and the reasons for these inconsistencies remain to be defined. Data relating to the use of GLP-1 RAs in children with type 2 diabetes are sparse. In a study of 13 adolescents with type 2 diabetes, acute dosing with exenatide reduced postprandial glucose and glucagon concentrations, without inducing hypoglycaemia or increasing insulin concentrations (Malloy et al. 2009); this is consistent with the effects of GLP-1 RAs to inhibit glucagon secretion and slow gastric emptying. In 14 adolescents with

type 2 diabetes, treatment with liraglutide for 5 weeks was associated with a reduction of 0.86% [9mmol/mol] in HbA1c (%) compared to placebo, and was well tolerated (Klein et al. 2014). Gastrointestinal adverse effects during dose escalation were transient, and there were no episodes of hypoglycaemia. Moreover, the pharmacokinetics of liraglutide appear similar in adolescents to adults (Klein et al. 2014). In a similar population, sitagliptin, at standard adult doses, increased endogenous intact GLP-1, insulin and C-peptide while suppressing glucagon, and tended to reduce blood glucose concentrations at 2 hours after oral glucose or a mixed meal (Fraser et al. 2018).

In adults with type 1 diabetes, the addition of exenatide to insulin therapy reduces postprandial glucose and glucagon concentrations and slows gastric emptying (Creutzfeldt et al. 1996; Dupre, Behme & McDonald 2004). These effects are comparable in those with and without C-peptide production (Ghazi et al. 2014). The recent ADJUNCT ONE study showed that the addition of liraglutide in adults with established type 1 diabetes was associated with modest lowering of HbA1c, along with reductions in insulin dose requirements and weight. Liraglutide treatment was associated with an increased frequency of symptomatic hypoglycaemia, defined as BGL < 3.9mmol/L with any symptoms of hypoglycaemia without an increased frequency of severe hypoglycaemia. This effect may have been the outcome of the more rigid insulin titration protocol. The frequency of hyperglycaemia with ketosis, but not diabetic ketoacidosis, was also increased in the liraglutide population. As a result, liraglutide's potential use in type 1 diabetes was concluded as limited (Mathieu et al. 2016). In an open label study of patients with type 1 diabetes, the addition of exenatide or sitagliptin reduced insulin requirements 12 months after diagnosis by an additional 24.1 and 8.5 units per day respectively, when compared with insulin alone, without an increase in hypoglycaemia (Hari Kumar, Shaikh & Prusty 2013). Published evidence in the paediatric type 1 population is minimal. In a study of 8 adolescents with type 1 diabetes, the addition of small doses of exenatide (a quarter and an eighth of the

adult dose) to insulin monotherapy acutely reduced postprandial glucose, associated with slowing of gastric emptying, but did not suppress glucagon (Raman et al. 2010).

Incretin-based therapy may also have an effect to preserve beta cell function. The outcome of early animal studies was optimistic showing improved beta cell function when human islets, engrafted to non-obese diabetic mice were treated with sitagliptin and lansoprazole. Disappointingly, The REPAIR-T1D trial was unable to show an improvement in humans in stimulated C-peptide, postprandial glucose, or HbA1c following 12 months of treatment with sitagliptin (Griffin et al. 2014).

Initial safety concerns regarding pancreatitis with incretin-based therapy have largely been dispelled (Azoulay et al. 2016; Li et al. 2014). The incretin mimetics have, however, been implicated in gall bladder disease in patients with type 2 diabetes (Monami et al. 2017). The 'short-acting' preparations are associated with more prominent upper GI side effects (such as nausea and vomiting); but, the mechanism of these may well be central, rather than a result of delayed gastric emptying (Rayner et al. 2017). Longer acting preparations may be associated with more lower GI effects (such as diarrhoea) (Horowitz et al. 2017). The safety profile of the incretin mimetics in children and other forms of diabetes is not yet known.

A further issue relevant to CFRD is the presence of exocrine pancreatic insufficiency (PI) in about 85 percent of these patients. Impaired digestion, particularly of ingested fats to fatty acids, which are a potent stimulus of the incretin axis (Beglinger et al. 2010), results in deficient gut hormone release and accelerated gastric emptying (Carney et al. 1995; Collins et al. 1997; Marathe et al. 2013). In adolescents with cystic fibrosis (with and without diabetes), we have shown that postprandial incretin concentrations are reduced, associated with postprandial hyperglycaemia, but can be restored with timely administration of pancreatic enzyme

supplementation, resulting in improvement (but not normalisation) of postprandial glycaemia (Perano, SJ et al. 2014).

2.5.2 THE ROLE OF AMYLIN

Amylin is co-secreted with insulin by the beta cell, and may stabilise postprandial glycaemia by slowing gastric emptying, suppressing glucagon, and increasing satiation. In adults with type 1 diabetes, amylin concentrations are reduced, while in type 2 diabetes, amylin is initially elevated, but declines later in the course of the disease, in parallel with decreasing insulin secretion (Scherbaum 1998). Amylin deficiency has also been confirmed in children with type 1 diabetes (Heptulla et al. 2008), while levels are intermediate in children with type 2 diabetes (Rodriguez et al. 2009).

Pramlintide is an amylin analogue approved by the FDA for use in adults with type 1 or type 2 diabetes in conjunction with insulin therapy. In children, as in adults, pramlintide slows gastric emptying substantially (Chase et al. 2009), to delay the peak and reduce the magnitude of the postprandial glucose excursion (Chase et al. 2009; Heptulla et al. 2005; Weinzimer et al. 2012), while suppressing glucagon (Chase et al. 2009; Heptulla et al. 2005; Heptulla et al. 2009). These effects carry a risk of hypoglycaemia in the postprandial period when insulin is co-administered (Heptulla et al. 2005), which has been minimised in research settings by reducing the prandial insulin dose (Chase et al. 2009; Weinzimer et al. 2012), and/or giving supplemental postprandial glucagon (Heptulla et al. 2005).

2.5.3 GASTRIC EMPTYING

The rate of gastric emptying is an important, and often over-looked, determinant of postprandial glycaemia; it contributes to approximately 35% of the variance in the postprandial rise in blood glucose concentrations (Horowitz et al. 1993; Marathe et al. 2013). Relatively accelerated gastric emptying results in a brisker postprandial rise and, conversely, delayed

gastric emptying produces a more gradual rise and fall in blood glucose, with a lower peak and area under the curve (Marathe et al. 2017). Conversely, acute fluctuations in blood glucose influence the rate of gastric emptying, such that hyperglycaemia slows emptying, while hypoglycaemia accelerates it(Marathe et al. 2013); these potentially represent compensatory mechanisms for blood glucose homeostasis.

The 'gold standard' technique for measurement of gastric emptying is scintigraphy, although this is not favoured in children due to the risks of exposure to ionising radiation. The available non- radioactive methods include ultrasonographic measurement of gastric antral width over time, 3D ultrasound, the kinetics of oral paracetamol absorption, and stable isotope breath tests. Each technique has been validated in different settings, has its own limitations, and normal ranges are not directly comparable between different techniques (Hauser et al. 2006). As a result, the limited number of studies in which gastric emptying has been evaluated in children with diabetes have predictably yielded inconsistent outcomes (Heptulla et al. 2008; Vazeou et al. 2004). ^{13}C-octanoic acid breath tests provide the most reproducible results amongst the non-invasive tests (Rao et al. 2011). The large inter-individual variation in gastric empting, even in health, and the fact that abnormally delayed or accelerated gastric emptying correlates only weakly with gastrointestinal symptoms, contribute further to these inconsistencies (Horowitz & Dent 1991; Marathe et al. 2013). In adults with type 1 diabetes, abnormally delayed gastric emptying is associated with worse glycaemic control, though not necessarily with "gastroparesis" symptoms, or evidence of cardiac autonomic dysfunction (Cucchiara et al. 1998). We recently reported that adolescents with type 1 diabetes, as a group, have accelerated gastric emptying and that the magnitude of the postprandial rise in blood glucose is related to the rate of gastric emptying (Perano et al. 2015). The latter supports the case for further clinical trials of agents that slow gastric emptying, such as GLP-1 RAs, in this population.

In adults with type 2 diabetes, the use of macronutrient preloads can reduce postprandial glycaemia through a mechanism of 'priming' the incretin system in advance of a meal. Administration of carbohydrate, fat or protein preloads 15-30 minutes before a carbohydrate rich meal attenuates postprandial glycaemia, associated with slowing of gastric emptying and stimulation of gut hormones, including the incretins (Gentilcore et al. 2006; Ma et al. 2015). These effects have not been studied in children, or other types of diabetes.

2.6 FUTURE DIRECTIONS OF RESEARCH AND CLINICAL PRACTICE

Postprandial glycaemic control should be a priority in the management of all forms of diabetes that affect children. Indeed, MODY (other than type 2) and CFRD are primarily disorders of postprandial glycaemia. More information regarding enteroendocrine function in this age group will guide the most appropriate management. The role of macronutrient pre-loads also warrants further investigation, especially in unique clinical situations where undernutrition and hyperglycaemia are present together, as in CFRD. The substantial body of evidence supporting the use of incretin-based therapy in adults with type 2 diabetes has not been explored adequately in children with type 2 diabetes. However, these agents, particularly GLP-1 RAs, hold considerable promise in an increasingly prevalent disease in which the efficacy of both lifestyle and metformin treatment has been disappointing (Zeitler et al. 2012). With increasing use of liraglutide, in particular, in children with type 2 diabetes, we will gain more data to inform management guidelines. The realisation that the pharmacokinetics of these agents in adolescents with type 2 diabetes are similar to from those in adults should accelerate their availability in a disease that urgently requires solutions (Nadeau et al. 2016). Closed loop systems hold major promise in type 1 diabetes. Their current limitations in the timely control

of postprandial glucose excursions will be reduced by the development of faster acting insulins, use of adjunctive GLP-1 RAs or amylin analogues, and more precise predictive algorithms.

Figure 2.1. Continuous glucose monitor reveals postprandial hyperglycaemia in a 3 year old boy with excellent overall glycaemic control of his type 1 diabetes (HbA1c of 6.6% [49mmol/mol]).

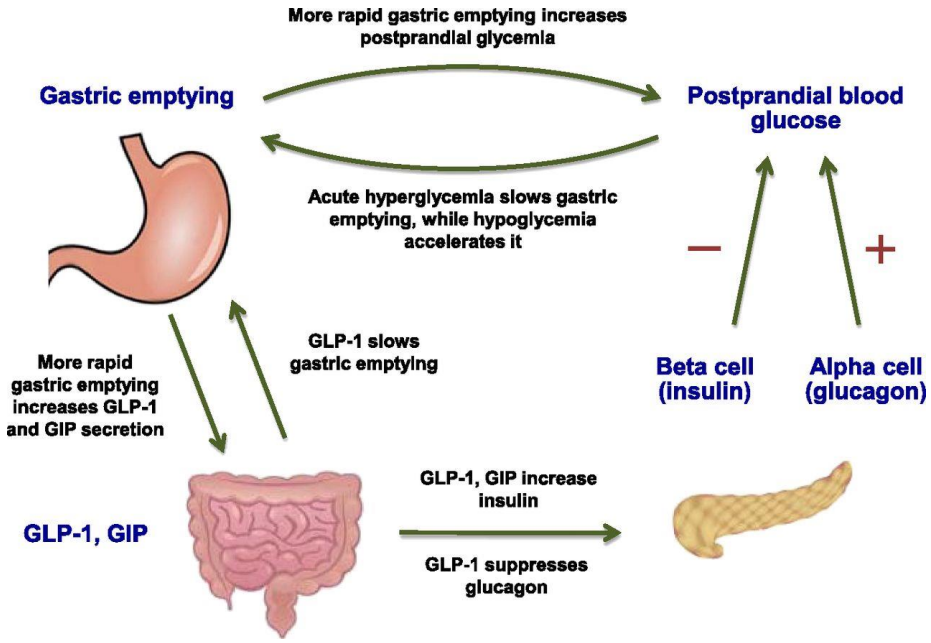

Figure 2.2. Schematic representation of the complex interplay between gastric emptying, enteroendocrine system and postprandial control. Reproduced from Marathe et al. (2013)

CHAPTER 3. METHODS

3.1 INTRODUCTION

The study reported in the following chapter used assessments of postprandial glycaemia, gastric emptying and incretin hormones, insulin and glucagon levels and acute symptomatology to ascertain the effects of exenatide when compared with placebo. This chapter reviews the recruitment, measurements and methods used to assess gastric emptying and incretins, and discusses limitations and potential adverse effects. The experimental protocol and statistical analysis are discussed in chapter 4.

3.2 SUBJECTS

Six subjects aged 10-25 years with confirmed CF, pancreatic exocrine insufficiency and impaired glucose tolerance (IGT) were recruited by the primary investigator from tertiary CF clinics (Women's and Children's and Royal Adelaide Hospitals) or during hospital admission, over a 12 month period.

Initially, the protocol included participants aged 10-18 years, but difficulty with recruitment in this age range was encountered for a number of reasons, so that application was made and approval granted by the Human Research Ethics Committee to extend the upper age limit to 25 years and involve an adult tertiary CF unit. The CONSORT diagram (figure 3.1) provides more information regarding recruitment.

The main reason for exclusion in the paediatric group was participants not wanting to miss school and only being willing to participate if they were admitted to hospital for other reasons. Additionally, the exclusion criteria of low weight and past upper GI surgery ruled out a number of otherwise eligible volunteers. In the adult population, the main reason for declining the study

was, once again, work and study commitments or being “too busy”. The most common reasons for exclusion were pancreatic sufficiency, deranged liver function tests or past history of pancreatitis.

Recruitment was conducted through initial information about the study being mailed in hard copy to eligible individuals. This was then followed up by discussions about the study at tertiary clinic visits (which generally occurred on a 3 monthly basis). Additionally, individuals who were admitted to hospital for optimisation of lung function were approached toward the end of their admission.

After the recruitment and completion of the study protocol in 6 participants, a decision was made to proceed with analysis of the available data due to substantial difficulty with any further recruitment, rather than waiting to accumulate 10 participants as originally planned.

Of the volunteers recruited, all had CF and IGT and none had CFRD. This is likely because CF with IGT is a precursor to CFRD and is therefore more prevalent.

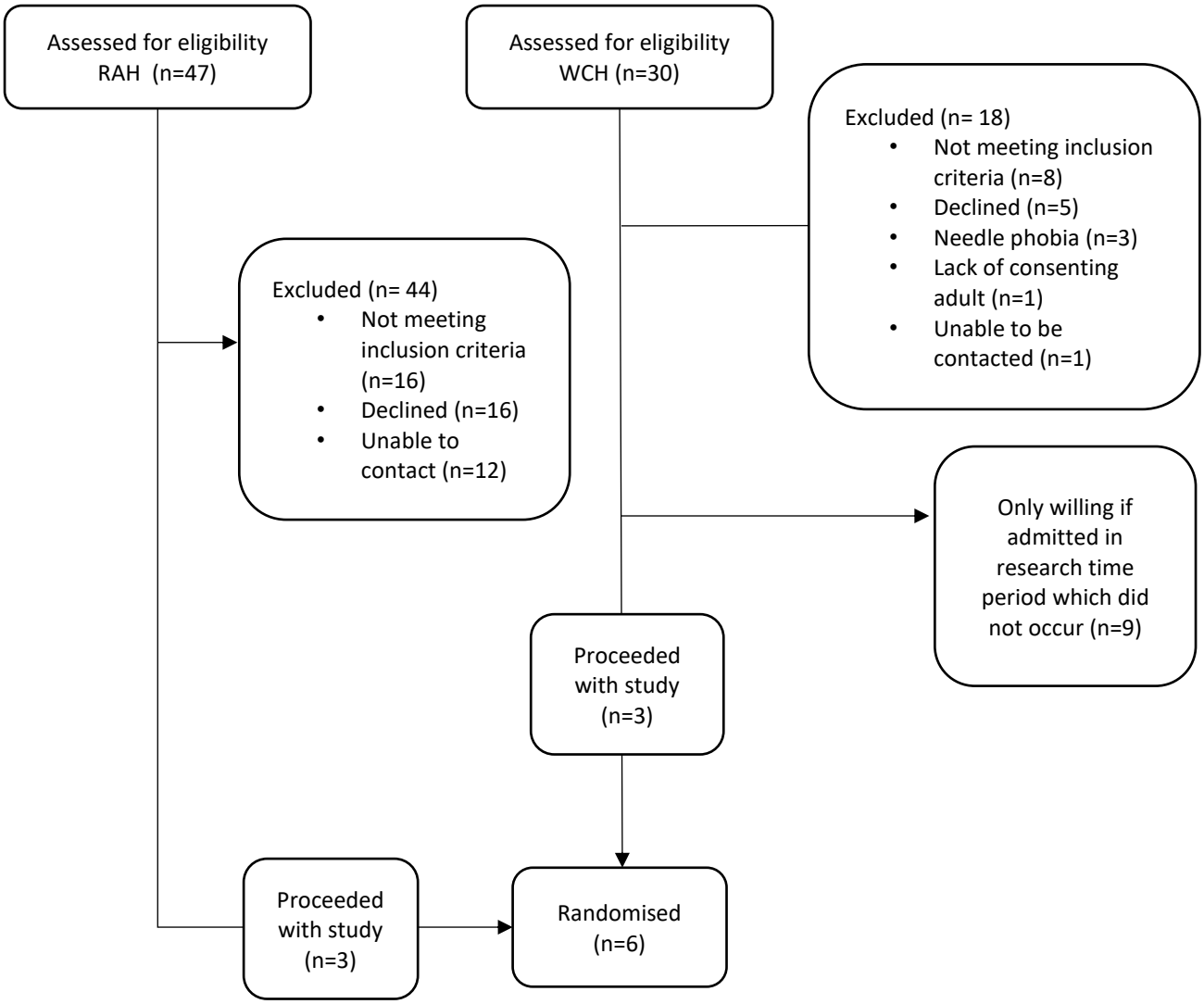

Figure 3.1. CONSORT diagram showing recruitment pathway (RAH – Royal Adelaide Hospital, WCH - Women's and Children's Hospital)

3.3 MEASUREMENTS

3.3.1 GASTRIC EMPTYING

The 'gold standard' method for measuring gastric emptying is scintigraphy, where a radiolabelled standardised meal is ingested and images of retained radioactivity in the stomach are acquired over time, revealing what fraction of the meal has emptied from the stomach. While this is a non-invasive test, the radiation exposure that it entails is not considered

acceptable in the paediatric population. Other options for assessment of gastric emptying that do not involve radiation exposure include paracetamol absorption, ultrasonography, the wireless motility capsule and stable isotope breath tests.

The paracetamol absorption test involves ingestion of a meal together with paracetamol, followed by frequent blood sampling for plasma paracetamol levels. While this method is generally well tolerated, the standardisation and consistency of results is questionable given the variety of test meals used and the tendency of paracetamol to empty with the liquid rather than solid phase of the meal, as well as the variability of absorption due to factors other than gastric emptying. This has resulted in highly variable results that are not comparable to standardised scintigraphy (Bartholome et al. 2015). Ultrasonography estimates gastric emptying mainly through cross-sectional measurements of antral area, although 3D ultrasonography (while not widely available) can image the entire gastric volume, while duplex ultrasound can measure transpyloric flow. Ultrasonography is only validated for liquid emptying measurement and is highly operator dependent (Rao et al. 2011). The wireless motility capsule measures pH, intra-liminal pressure and temperature as it transits through the gastrointestinal tract. When the capsule passes from the stomach into the duodenum, a rise in pH is detected, allowing for estimation of gastric emptying time. It requires ingestion of a large capsule and the wearing of a data receiver, and has a sensitivity of 87% and specificity of 92% in identifying delayed gastric emptying (Rao et al. 2011).

Finally, stable isotope breath tests utilise ^{13}C labelled substrates (e.g. octanoic acid or sodium octanoate added to a liquid or solid meal. The labelled substrate is rapidly absorbed in the small intestine after gastric emptying and metabolised in the liver to $^{13}CO_2$ which is exhaled from the lungs. Gastric emptying is the rate limiting step, so can be estimated from rate of $^{13}CO_2$ excretion in the breath (Hauser et al. 2006). This method has low intra-individual variation, but higher inter-individual variation, the impact of which was minimised in the current study by

the crossover design. The lack of radiation exposure, ease of assessment (the test can be performed at the bedside or in the clinic and the breath samples transported to a centralised laboratory for analysis) and reproducibility make breath tests a logical choice for the paediatric population (Gatti et al. 2000). Standardisation has been undertaken and normative values published (Hauser et al. 2016), with the provision of correction factors for infants (Omari et al. 2005).

3.3.2 BIOCHEMISTRY/HORMONE STUDIES

Blood samples were taken and placed in ice chilled tubes and immediately returned to ice. For hormone studies, plasma was separated after collection by centrifugation at 3200rpm for 15 minutes at 4°C and stored at -80ºC for subsequent analysis.

Biochemistry

Bedside blood glucose measurement was performed immediately, as part of monitoring for safety, by portable glucometer (MediSense Optium Xceed, MediSense Inc). The laboratory subsequently analysed blood glucose by the glucose oxidase method.

Free fatty acids (FFA) and triglycerides were measured by the colorimetric method (FA 115; Randox).

Hormone studies

Insulin was measured by ELISA immunoassay (10-1113, Mercodia, Uppsala, Sweden). The sensitivity of the assay was 1.0 mU/L and the coefficient of variation was 2.7% within assays and 7.3% between assays.

C-peptide was measured by ELISA immunoassay (10-1136-01, Mercodia, Uppsala, Sweden). The sensitivity of the assay was 15 pmol/L and the coefficient of variation was 7.4% between assays and 3.7% within assays.

Glucagon was measured by RIA (GL-32K, Millipore, Billerica, MA).Minimum detectable limit was 20 pg/ml, inter- and intra-assay CVs were 13.2% and 3.2% respectively.

Total GLP-1 was measured by RIA (GLPIT-36HK, Millipore, Billerica, MA). Minimum detectable limit was 3 pmol/L, intra- and inter-assay CVs were 5.5% and 8.8% respectively.

Plasma GIP was measured by radioimmunoassay using some modifications of a previously published method (Wishart JM, Morris HA, Horowitz M Radioimmunoassay of gastric inhibitory peptide in plasma. Clin Chem 1992; 38: 2156-7). The standard curve was prepared in buffer rather than extracted charcoal stripped serum and the radio-iodinated label was supplied by Perkin Elmer (Coston, MA). Minimum detectable limit was 2 pmol/L, inter-assay CV was 9.5% and intraassay CV was 4.9%.

3.3.3 SYMPTOM ASSESSMENT

Visual analogue scales were used to assess gastrointestinal symptomatology at 6 timepoints throughout the study, from before the intervention, and subsequently at 30-60 minute intervals. The questionnaire assessed symptoms of nausea, bloating, hunger, fullness, anxiety and drowsiness during the study. Each question was answered on a 100mm horizontal line with 0mm being no symptom sensation and 100mm the maximum sensation. Symptoms were quantified with a score out of 100.

3.4 LIMITATIONS

The main limitation of the study was the population size and difficulty recruiting participants as described above. Another limitation was the need for frequent venous bloods sampling, and consideration could have been given to the use of continuous glucose monitoring (CGM) as a measure of postprandial glycaemia. However, when the study commenced, CGM was limited

by lack of availability, inaccuracy and user dissatisfaction. Over the past 5 years, significant advances have been made in accuracy and ability to predict hypo- or hyperglycaemia as well as increased availability which has resulted in high uptake among the paediatric diabetes population (Johnson et al. 2022). Consequently, consideration to measurement of postprandial glycaemia with CGM could be considered in future trials.

This was a proof-of-concept trial to establish the effect of a GLP-1 agonist on postprandial glycaemia in CF. As such, there was no assessment of the long term benefits or adverse effects associated with the use of this medication, and evaluation of these aspects in future is warranted.

3.5 ADVERSE EFFECTS

The intervention in the study involved administration of the GLP-1 receptor agonist, exenatide, which is associated with adverse effects including gastrointestinal symptoms (predominantly nausea), hypoglycaemia (primarily when participants are concurrently treated with insulin or sulphonylureas) and headache. Rare adverse effects include hypersensitivity/anaphylactic reactions and pancreatitis.

Hypoglycaemia was monitored for by frequent blood sampling, and was not detected in any participant, whether receiving active drug or placebo. No severe or rare adverse effects were observed. One participant experienced a mild headache 40 minutes after exenatide administration, which resolved with sips of water. Another participant described her “tummy feeling funny” 50 minutes after receiving exenatide. This was associated with an increase in the visual analogue score for nausea (to 24/100 after exenatide when compared to 0/100 at the corresponding time point after placebo). This sensation resolved within 30 minutes without any requirement for antiemetic medication, which was offered.

3.6 CONCLUSION

The methods used in this study are well validated and were deemed to be the most appropriate for the paediatric and young adult population. The welfare of the participants was a priority throughout the planning and execution of the study, which was very well tolerated. The methods described are believed to represent the best available to address the hypothesis in this study population.

CHAPTER 4. EXENATIDE CORRECTS POSTPRANDIAL HYPERGLYCAEMIA IN YOUTH WITH CYSTIC FIBROSIS AND IMPAIRED GLUCOSE TOLERANCE: A CROSSOVER RANDOMIZED TRIAL.

STATEMENT OF AUTHORSHIP

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Principal Author

Candidate	Myfanwy Clare Geyer		
Contribution	Conception, design, recruitment of participants, consent and full conduct of the study, data analysis and drafting of manuscript		
Overall percentage	80%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	14/02/2022

Co-Author Contributions

By singing the Statement of Authorship, each author certifies that:

i) the candidate's stated contribution to the publication is accurate (as detailed above);

ii) permission is granted for the candidate to include the publication in the thesis; and

iii) the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution	Data interpretation, statistical analysis and reviewing the manuscript		
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4.1 SUMMARY

Impaired glucose tolerance (IGT) in cystic fibrosis (CF) manifests as postprandial hyperglycemia. Pancreatic enzyme supplementation reduces the latter; restoring incretin secretion and slowing gastric emptying. We aimed to determine the acute effect of exenatide on postprandial glycemia in youth with CF and IGT.

6 participants with CF and IGT were studied on 2 days, in a double-blind randomized crossover trial. After overnight fasting, they received exenatide 2.5 mcg or placebo (0.9% saline) subcutaneously 15 minutes before a pancake meal labelled with ^{13}C octanoate and pancreatic enzyme replacement.

The primary outcomes, area under the curve over 240 minutes (AUC_{240}) for blood glucose ($p<0.0001$) and peak blood glucose (7.65mM±0.34 [mean±SE]vs9.53mM±0.63, $p<0.0001$), were markedly lower after exenatide than placebo. AUC_{240} for insulin, C-peptide, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) were also lower after exenatide. Gastric emptying was markedly slower after exenatide, as assessed by time for 10% gastric emptying and peak $^{13}CO_2$ excretion.

We report for the first time that exenatide corrects postprandial hyperglycemia in youth with CF and IGT. GLP-1 agonists are a candidate treatment in CF related diabetes.

4.2 INTRODUCTION

Cystic fibrosis related diabetes (CFRD) is the most common comorbidity of cystic fibrosis (CF), and typically has an insidious onset accompanied by declines in BMI and pulmonary function from about five years prior to diagnosis (Hameed, S., Jaffe & Verge 2011; Moran, Dunitz, et al. 2009). CFRD, and its precursor, impaired glucose tolerance (IGT), manifests as

postprandial hyperglycaemia, providing a distinct therapeutic target (Perano, S et al. 2014). Improvement in postprandial hyperglycaemia is associated with gains in pulmonary function and BMI (Mozzillo et al. 2009). However, the only current treatment available for CFRD is insulin, which carries a risk of hypoglycaemia and can be a significant burden given the need for frequent injections and blood glucose monitoring.

The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), released from the gut in response to nutrients, regulate postprandial glycaemia through augmentation of insulin secretion; this "incretin effect" accounts for 50-70% of the insulin response to an oral glucose load in healthy individuals (Ma et al. 2009). Also, GLP-1 has glucagonostatic effects and slows gastric emptying. We have reported that CF patients have impaired postprandial secretion of GLP-1 and GIP, rapid gastric emptying, and marked postprandial hyperglycaemia after a high fat/high carbohydrate meal, which are improved, but not normalised, with pancreatic enzyme replacement (PERT) (Kuo et al. 2011; Perano et al. 2014).

Incretin-based therapy, including GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, is routinely used in the management of type 2 diabetes (Herman et al. 2017). Because insulin stimulation is in a glucose dependent manner, the risk of hypoglycaemia is much less than that associated with insulin therapy, and less intense dosing and monitoring are required. The major effect of 'short-acting' GLP-1 agonists (exenatide BID and lixisenatide) to diminish postprandial glycaemic excursions in type 2 diabetes appears to reflect slowing of gastric emptying (Phillips et al. 2015). There are minimal data with these therapies in adolescents and none in CF in any age group. We therefore aimed to determine the acute effect of exenatide on postprandial glycaemia in patients with CF and IGT.

4.3 METHODS

4.3.1 SUBJECTS

Six subjects aged 10-25 years with confirmed CF, pancreatic exocrine insufficiency, and impaired glucose tolerance (IGT) were recruited by MG from tertiary CF clinics. Diagnosis of IGT was made in accordance with ADA guidelines, (ie. plasma glucose level at 2 hours between 7.8 and 11.0 mmol/L during a 75g OGTT) ('Standards of Medical Care in Diabetes - 2017: American Diabetes Association' 2017) in annual screening which commences at 10 years of age. Patients with severe pulmonary disease (forced expiratory volume at 1 sec <30% predicted), intercurrent infection or acute pulmonary exacerbation, significant liver disease (Child-Pugh score >6), previous upper gastrointestinal surgery, or using medications known to affect gastrointestinal motility (eg. erythromycin) or glycaemia (eg. prednisolone) were excluded. The protocol was approved by the Human Research Ethics Committees of the Women's and Children's Health Network and the Royal Adelaide Hospital. Written informed consent was obtained from each participant and from guardians for those less than 18 years. The study was registered on the Australian and New Zealand Clinical Trial Register (ACTRN12615001029583) and carried out in accordance with the Declaration of Helsinki.

4.3.2 EXPERIMENTAL PROTOCOL

Each subject participated in two study days, receiving either subcutaneous exenatide or placebo in a randomized, double-blind, crossover design. Randomisation of the order of study days was performed using computer-generated sequence (block size 2), by the dispensing pharmacy. Exenatide (2.5mcg-Byetta 250micrograms/mL, Eli Lilly Pty Ltd, West Ryde, New South Wales, Australia) and placebo (0.9% NaCl) were drawn up into identical syringes by an un-blinded nurse for administration on each study day. The appearance of each was

indistinguishable and both the investigator conducting the study and the patient remained blinded throughout.

Each study day commenced between 0800-0900h, after an overnight fast of at least 10 hours. The two study days were separated by at least 48 hours to ensure complete clearance of exenatide (half-life 2.4 hours). The study was performed in the clinical research room next to the laboratory. Blood sampling was from an IV cannula inserted at the start of the study or from an implantable venous access port. Exenatide or placebo was administered via subcutaneous injection 15 minutes prior to commencement of the test meal. The meal, consisting of Green's^{TM} original pancake mix (70g mixed with 60mL water, 20g sugar) and 100mg ^{13}C Na-octanoate cooked in 10g butter (total 8.8g fat, 50.3g carbohydrate, 2.5g protein, 224.1 kcal), was consumed over 10 minutes, immediately after administration of a PERT (10000 units Creon [Abbott Products Pty Ltd, Pymble, New South Wales, Australia]).

Breath samples for measurement of gastric emptying and blood samples for measurement of blood glucose, plasma insulin, glucagon, GLP-1, GIP, C-peptide, free fatty acids, and triglycerides were collected at 15-30 minute intervals for 4 hours. Blood glucose was measured by the glucose oxidase method. FFA and triglycerides were measured by colorimetric method (FA 115; Randox). The remaining blood was placed in ice-chilled tubes containing EDTA. Plasma was separated and stored at -80ºC for subsequent analysis of insulin and C-peptide by ELISA (10-1113; Mercodia and 10-1136-01; Mercodia respectively) and glucagon, GLP-1 by RIA (GL-32K; Millipore and GLPIT-36HK; Millipore respectively) and GIP by RIA by previously described method (Wishart, Morris & Horowitz 1992). Breath samples were analysed for $^{13}CO_2$ using an isotope ratio mass spectrometer (Europa Scientific ABCA 20/20). A visual analogue scale was used to assess gastrointestinal symptomatology at 6 timepoints throughout the study.

4.3.3 STATISTICAL ANALYSIS

Assuming a SD of 2mmol/L for the difference in peak postprandial blood glucose levels between treatment and placebo conditions, as estimated from our similar crossover trial in CF patients (Perano, SJ et al. 2014), a sample size of 6 patients would allow for the detection of differences between treatment and placebo conditions of 3mmol/L or larger with 80% power (alpha = 0.05).

The primary outcome measure was postprandial blood glucose, measured as (i) area under the curve over 240 minutes (AUC_{240}) and (ii) peak postprandial value. Secondary outcomes were plasma insulin, glucagon, GLP-1, GIP, FFA, C-peptide and triglycerides concentrations, evaluated as AUC_{240} and peak value. The rate of gastric emptying was an additional secondary outcome, evaluated by the half-emptying time ($t_{1/2}$)(Omari et al. 2005), lag time defined as 10% emptying time (t_{lag}) and time to peak $^{13}CO_2$ excretion (t_{max}).

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All outcomes were compared across intervention and placebo conditions using linear regression models. Generalised estimating equations assuming an independence working correlation structure were used to account for dependence in the data resulting from repeated measures (due to the crossover design of the study). Absolute AUCs for primary and secondary outcomes were calculated using the trapezoidal rule. Results for the intervention and placebo conditions were summarised using means and standard errors.

4.4 RESULTS

Six subjects (3 male, 3 female) were recruited and completed both study days (Table 4.1). There were no significant differences in baseline measures of fasting glucose, insulin, C-peptide, glucagon, GLP-1 or GIP between exenatide and placebo study days.

The studies were well tolerated. One patient complained of mild abdominal discomfort 40 minutes after exenatide for less than 10 minutes. There were no significant differences between exenatide and placebo on the symptom questionnaire. There were no other adverse effects reported, including no hypoglycaemia.

4.4.1 BLOOD GLUCOSE CONCENTRATIONS

After the meal, AUC_{240} for blood glucose (1431±54 [mean±SE] vs 1814±109 mmol/L/min, p<0.0001) and peak glucose (7.65±0.34 vs 9.53±0.63 mmol/L, p<0.0001) were lower after exenatide than placebo (Fig 4.1A).

4.4.2 INSULIN, C-PEPTIDE, GLUCAGON AND INCRETIN CONCENTRATIONS

Insulin AUC_{240} (2516±293 vs 3581±422 mU/L/min, P=0.0016) and C-peptide AUC_{240} (188186±24103 vs 264763±25629ng/dL/min, P<0.0001) were lower after exenatide than placebo, while glucagon AUC_{240} did not differ. GLP-1 AUC_{240} (4459±561 vs 5983±382 pmol/L/min, P=0.0083) and GIP AUC_{240} (8264±1006 vs 10045±846 pmol/L/min, P=0.0045) were also lower after exenatide than placebo. (Fig 4.1 B,C,D,E,F)

4.4.3 GASTRIC EMPTYING

Gastric emptying was markedly slower after exenatide than placebo, as assessed by the time for 10% gastric emptying (t_{lag} 138.8±33.0 vs 54.7±5.9 minutes, p= 0.0044) and the peak $^{13}CO_2$ excretion (t_{max} 320.85±59.6 vs 143.8±15.1 minutes, p=0.0007). The gastric emptying half time showed a trend to be slower with exenatide ($t_{1/2}$ 357±62 vs 236±48 minutes, p=0.0757).

4.5 DISCUSSION

We report for the first time that exenatide, in a dose of 2.5 micrograms, markedly reduced the glycaemic response associated with slowing of gastric emptying in youth with CF and IGT,

associated with reductions in circulating insulin, C-peptide, GLP-1 and GIP concentrations. These findings extend our previous studies showing that PERT lowers postprandial glycaemia and restores the incretin response (Kuo et al. 2011; Perano, SJ et al. 2014). Importantly, exenatide achieved euglycaemia, rather than simply reducing postprandial hyperglycemia as we had previously observed with PERT in adolescents with CF, and was well tolerated.

The profound slowing of gastric emptying explains the reduction in postprandial insulin, C-peptide, GLP-1 and GIP concentrations, particularly as there was no difference in postprandial glucagon. We had anticipated that the latter would be lower with exenatide than placebo (Nauck, M 2015) – it is possible that slowing of gastric emptying occurs at a lower plasma concentration of exenatide than insulinotropic and glucagonostatic properties. However, the latter are also known to be glucose dependent, requiring a blood glucose greater than approximately 8mmol/L making it difficult to comment on as this value was not reached.

Exenatide has a lower treatment burden than insulin with less risk of hypoglycaemia and therefore less requirement for frequent blood glucose monitoring. While longer acting GLP-1 agonists and DPP-4 inhibitors have the advantage of a less frequent dosing schedule, their apparent lesser effects on gastric emptying intuitively makes them less suitable to prevent postprandial hyperglycaemia in CF (Umapathysivam et al. 2014). The CF population is classically lean or underweight, which could be considered a contraindication to the use of exenatide. However, the modern epidemic of overweight and the efficacy of CFTR modulators in patients with specific genotypes allow for improved absorption of food and reduced catabolism (Ramsey et al. 2011). Up to approximately 25% of the paediatric population with CF are overweight (Hanna & Weiner 2015). Further, in adults with type 2 diabetes and BMI <30 kg/m^2, there is no significant weight reduction with exenatide (Wolffenbuttel et al. 2016). Therefore, concern for using exenatide due to the risk of weight loss may not be justified, provided there is careful patient selection and regular monitoring. Initial concerns regarding

pancreatitis have been dispelled; however cholelithiasis may be more common in adult patients with type 2 diabetes treated with exenatide (Monami et al. 2017).

The small sample size of this study is its main limitation; however, we had adequate power given the size of the effect of exenatide, and differences between the study days were clear cut. Further studies are desirable to extend our observations including a more prolonged duration of monitoring given that blood glucose and hormone values had not returned to baseline by 240 minutes. Our observations indicate that a longer term clinical trial of exenatide is needed.

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Table 4.1 Participant characteristics

	Participants
M:F	3:3
Age (years)	17.1 (11-24 years) †
Puberty (Tanner 2 -5)	4
BMI Z score	-0.56 (-1.15-0.13)
FEV1%	82.25 (48-98.9%)

† mean (Range)

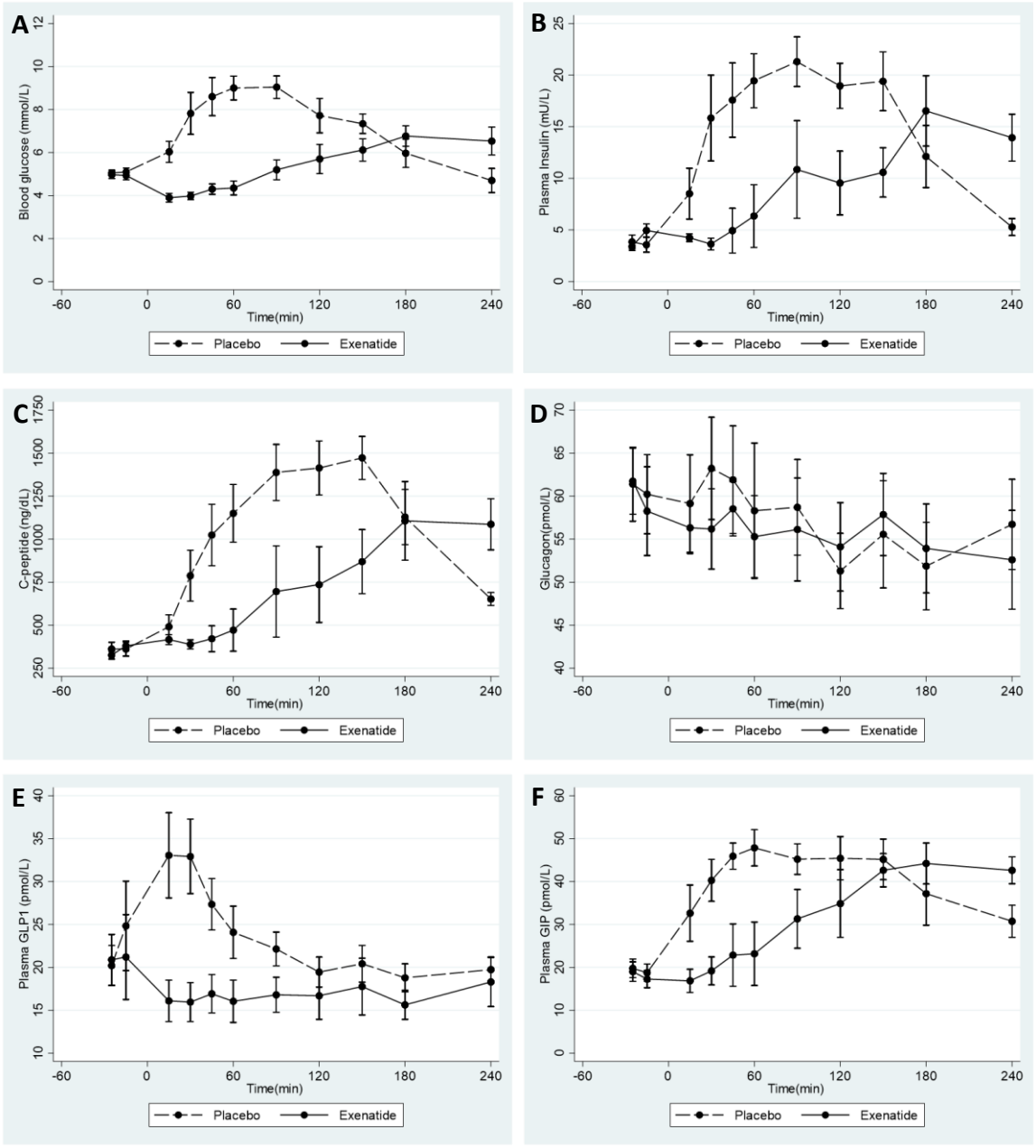

Fig 4.1 Blood glucose (A), plasma insulin (B), C-peptide (C), glucagon (D), GLP-1 (E) and GIP (F) concentrations in patients with CF IGT given exenatide or placebo before a high carbohydrate pancake meal consumed between t = -10 and 0 min. Results represent mean ± SE. A, Exenatide markedly attenuated the glycaemia response to the pancake meal. AUC blood glucose was lower and the peak blood glucose eliminated on the exenatide study day (both $p<0.0001$). B, Plasma insulin was less on the exenatide study day ($p=0.0016$). C, Plasma C-peptide was less on the exenatide study day ($p<0.0001$). D, Plasma glucagon did not differ between study days. E, Plasma GLP-1 was less on the exenatide study day ($p=0.0083$) and F, Plasma GIP was less on the exenatide study day ($p=0.0045$).

CHAPTER 5 – CONCLUSION

This thesis has reviewed postprandial glycaemia as a target for diabetes control in children, and has specifically reported the effect of the GLP-1 receptor agonist, exenatide, in young people with cystic fibrosis and impaired glucose tolerance. When compared with placebo, exenatide corrected postprandial hyperglycaemia and was well tolerated. This builds on the previous evidence from the author's research group that pancreatic enzyme replacement therapy improves (even if it does not normalise) postprandial glycaemia in cystic fibrosis, associated with greater incretin hormone release and slowing of gastric emptying.

The study involving exenatide has introduced a possible alternative treatment for CFRD/CF with IGT in place of insulin, which is an important breakthrough because the latter carries a high treatment burden including the risk of hypoglycaemia and need for frequent blood glucose monitoring. As such, it represents an important 'proof of concept' for the use of GLP-1 agonists in this context. There are many GLP-1 receptor agonist preparations now available, but the majority are untried in children and adolescents with any form of diabetes. While the need for multiple daily injections of exenatide does increase the burden of treatment, this is still less than would be associated with injections of insulin. Adolescents with CF already have a high treatment burden, and reducing this would likely have a significant impact on adherence. Oral treatments have much greater acceptance among adolescents. At present we await the outcome of the PIONEER TEENS trial of the oral formulation of the GLP-1 receptor agonist, semaglutide, in adolescents with type 2 diabetes (clinicaltrials.gov NCT04596631). Further investigations will be required with youth in all diabetes populations (CFRD, T1D and T2D). Six months treatment with the DPP4 inhibitor, sitagliptin, resulted in increased GIP and GLP-1 and improved first phase insulin response in patients with CF and abnormal glucose tolerance, but did not impact postprandial glycaemia in a standardised mixed meal tolerance test when

compared with placebo (Kelly, A et al. 2021). Searches of clinical trials databases indicate that clinical trials of the long-acting GLP-1 RA, dulaglutide, in adults with CF related glucose intolerance (Clinicaltrials.gov NCT04731272), and the C-peptide response in this population to intravenously infused GLP-1 (Clinicaltrials.gov NCT01851694), are currently in the recruitment phase.

Since the publication of this study, a relevant case report has been published relating to the use of a GLP-1 receptor agonist in CFRD (Gnanapragasam et al. 2020). A 21 year old man whose CFRD was managed with a basal-bolus insulin regimen (Glargine and TDS Humalog) initiated treatment with weekly subcutaneous semaglutide injections (titrated to 0.16mg, compared to the standard adult dose of 0.5 to 1.0 mg). Over 6 months, the meal-time insulin was ceased and his HbA1c improved from 9.1% to 6.7%, without any episodes of hypoglycaemia or other adverse effects, other than modest (2kg) weight loss. There was no change in serum lipase or amylase, which were monitored monthly.

Liraglutide and the QW formulation of exenatide (given once weekly), are both long-acting GLP-1 RAs, with a solid evidence base in adults and more recently, paediatric patients with type 2 diabetes. GLP-1 RAs were initially approved for use in T2D, given their mechanism of action (insulinotropic and glucagonostatic primarily for the long-acting preparations) and the associated benefit of modest weight loss (as opposed to weight gain with insulin). Both T1D, and, in a more insidious manner, CFRD, are associated with insulin deficiency, so a therapy relying substantially on insulinotropic effects may not prove effective. Furthermore, tachyphylaxis for the effects of long-acting GLP-1 receptor agonists on gastric emptying may render this mechanism of improving postprandial glycaemia less relevant with long-acting formulations, although this has yet to be adequately tested (Horowitz et al. 2020). There are minimal data evaluating the use of GLP-1 RAs in paediatric populations. In T1D, postprandial hyperglycaemia was reduced with adjunctive short-acting exenatide when compared to

placebo, despite an accompanying reduction in insulin doses (Raman et al. 2010). A trial of the short-acting form of exenatide showed a mean weight loss over 4kg but minimal change in overall glycaemic control as measured by HbA1c (Johansen et al. 2020). In adult populations, two longer term studies (ADJUNCT ONE and ADJUCT TWO) of liraglutide in T1D have shown only marginal reduction in HbA1c and some evidence of increased tendency to both hypoglycaemia and hyperglycaemia with ketosis, with the authors concluding that the indication for GLP-1 agonists in T1D is limited (Ahren et al. 2016; Mathieu et al. 2016). HbA1c is a challenging primary endpoint in T1D, given that insulin is the primary therapy and most likely to have the greatest impact, and more subtle effects may not be apparent. In order to evaluate glycaemic control in fasting and postprandial periods separately, continuous glucose monitoring may be more beneficial. The ADJUNCT ONE and TWO studies compared liraglutide to placebo in T1D with differing insulin regimens. ADJUNCT ONE showed improvement in HbA1c with a 'treat-to-target' insulin dosing schedule (no limit to increasing insulin doses). To limit the effect that insulin may have had in reducing HbA1c, ADJUNCT TWO had a participant-specific capped (upper limit) insulin dose and again showed improved HbA1c. The liraglutide groups in both studies had an increased incidence of hypoglycaemia and hyperglycaemia with ketosis. This resulted in recommendation that GLP-1 RAs are unlikely to be listed as adjunctive treatment in T1D. However, they may provide important benefits in targeted groups, for example those who are overweight or obese. In the specific subgroup of overweight and obese adults with T1D managed with insulin pumps, adjunctive liraglutide reduced HbA1c, and reduced total insulin dose and mean body weight, when compared with placebo over a six month period (Dejgaard et al. 2020). Therefore, in paediatric populations with T1D, there is minimal evidence as yet for an overall benefit of GLP-1 agonists, and further investigation is warranted after the benefits and the best formulations are established in children with type 2 diabetes. This is becoming an increasingly important

subgroup, with more than 30% of children with T1D in Australia being overweight/obese (Phelan et al. 2017; Van der Schueren et al. 2021).

Similarly, in cystic fibrosis, the rate of overweight and obesity is increasing, with 19 percent of adult patients having a BMI greater than or equal to 25kg/m^2 (Litvin & Yoon 2020). Historically, the CF population was viewed as malnourished and an increase in BMI was looked upon positively. Given that use of GLP-1 RAs is typically associated with weight loss, the implications in CF need further evaluation, e.g. as to whether weight loss is associated with any decline in lung function, as is the case in the lead up to a diagnosis of CFRD. As for the type 1 population, the subgroup of obese patients with CF and IGT or CFRD would be ideal candidates for a trial of a GLP-1 RA.

In our small study, a single, low dose of exenatide was well tolerated, with only mild transient gastrointestinal adverse effects being recorded. In most studies, gastrointestinal adverse effects are frequently reported but tend to diminish with ongoing GLP-1 RA use, although the true symptom burden is not always apparent because most studies have not evaluated GI symptoms using validated questionnaires (Rayner et al. 2017).

In summary, this study has introduced for the first time a therapeutic option for the management of abnormal glucose tolerance in CF that should be evaluated further. There have been significant gains in the management of adult and paediatric type 2 diabetes and obese populations with the addition of GLP-1 RAs; however in T1D, these are likely to be limited to subgroups including the overweight and obese. The increasing prevalence of overweight /obesity in both T1D and CF is noteworthy. In CF, further investigation is required to identify less burdensome treatments (e.g. once weekly or oral GLP-1RAs) which will optimise adherence and therefore therapeutic benefit. Similar to T1D, further studies should be

undertaken in patients who struggle with both CF and overweight/obesity, in whom the greatest benefit may be shown.

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