Assessing Glycaemic Control in Cystic Fibrosis

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Doctor of Medicine (MD)
in the Faculty of Medical and Human Sciences

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JENNIFER HELM

SCHOOL OF MEDICINE
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ABSTRACT

Assessing Glycaemic Control in Cystic Fibrosis

Jennifer Helm, University of Manchester, Doctor of Medicine (MD) thesis submission, June 2011

Four studies investigating the assessment of glycaemic control in cystic fibrosis are presented within this thesis.

The first was a validation study of continual glucose monitoring (CGM) in cystic fibrosis (CF). 50 stable adults with CF underwent home CGM for 3 days, during which time they attended the CF centre for OGTT. Gold standard fasting (0 hour) plasma glucose and 2 hour plasma glucose values during OGTT were compared with concurrent CGM sensor glucose values using a ‘limits of agreement’ analysis. CGM was found to be valid in adults with CF, with its accuracy being consistent with that published in non-CF populations.

The next investigation compared OGTT with CGM with several objectives: to determine whether OGTT is a relevant and adequate measure of glycaemia in CF, find out whether CGM could offer a superior alternative to OGTT and explore whether OGTT and CGM results are associated with prior change in lung function and weight in adults with CF. Data from the first study was used to show that the OGTT can only identify abnormal glycaemic control in CF at a late stage, and that CGM is a more relevant reflection of everyday glycaemia in CF. No correlation was found between prior change in lung function and nutritional status in CF and glycaemia measured by OGTT or CGM.

The subsequent study investigated whether CGM could identify early abnormal glycaemic control in CF. This involved ten non-CF healthy controls undergoing the same study protocol as the 50 stable adults with CF, to determine ‘normal’ glycaemic control parameters. Of 25 CF patients with normal glucose tolerance by OGTT, 19 (76%) had significantly higher mean and/or variability of CGM levels than healthy controls. This lead to changes in their management, including 2 subjects being commenced on insulin therapy.

The final investigation was a questionnaire study, asking the 50 CF patients to provide information on their experience of undergoing CGM. 58% of patients responded, with replies indicating that they found CGM broadly acceptable, interfering little in their lives and that their experiences were generally positive. This insight into patients’ experiences of CGM can be used to guide future clinical and research roles for this tool.

These studies have provided novel data regarding the assessment of glycaemic in CF. Information captured by CGM has greater relevance to CF patients’ daily lives than OGTT. CGM can identify early problems with glycaemic control leading to changes in management that may not be detected by conventional measures. CGM offers potential in further clinical application and research to improve the lives and outcomes for adults with CF.
DECLARATION

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THE AUTHOR

The author is currently a Specialty Trainee in adult Respiratory and General Internal Medicine. She qualified with MBChB from the University of Manchester in 2001 and worked within the North West Deanery, gaining MRCP (UK) in 2005. Following overseas experience in Respiratory Medicine she returned to the UK as a Clinical Research Fellow in Cystic Fibrosis at the Manchester Adult Cystic Fibrosis Centre, undertaking the research presented in this MD thesis submission.
LIST OF ABBREVIATIONS

ADA American Diabetes Association
AUC Area under the curve
AUC OGTT Area under the curve during the oral glucose tolerance test as measured by continual glucose monitoring
BMI Body mass index
CBG Capillary blood glucose
CF Cystic fibrosis
CFRD Cystic fibrosis related diabetes
CFTR Cystic fibrosis transmembrane conductance regulator
CGM Continual glucose monitoring
DCCT Diabetes Control and Complications Trial
DGT Diabetic glucose tolerance
DIOS Distal intestinal obstruction syndrome
DM Diabetes mellitus
FEV$_1$ Forced expiratory volume in one second
GCT Glucose challenge test
GORD Gastro-oesophageal reflux disease
HbA1c Glycosylated haemoglobin
IFG Impaired fasting glycaemia
IGT Impaired glucose tolerance
IQR Interquartile range
ISPAD International Society for Pediatric and Adolescent Diabetes
MACFC Manchester Adult Cystic Fibrosis Centre
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<td>Normal glucose tolerance</td>
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<td>Non-invasive ventilation</td>
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<td>NRES</td>
<td>National Research and Ethics Service</td>
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<td>OGTT</td>
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<td>OGTTmax</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>T1DM</td>
<td>Type 1 diabetes mellitus</td>
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<td>T2DM</td>
<td>Type 2 diabetes mellitus</td>
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<td>UHSM</td>
<td>University Hospital of South Manchester</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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CYSTIC FIBROSIS

1.1 Epidemiology and Historical Background

In the UK, over 8500 adults and children have cystic fibrosis (CF). (CFTrust, 2009) This is the commonest inherited disorder associated with a reduced life expectancy, manifested by progressive multisystem disease. It is most prevalent in Caucasians, with an incidence of one in 2500 live births in the UK population. (Dodge et al., 1993) It is rare in Afro-Caribbean races but several types of mutations exist in Asian groups. (Hamosh et al., 1998; Bowler et al., 1993) Around one in 25 people in the UK carry a CF gene mutation and inheritance is autosomal recessive.

Affected babies likely to have had CF were recognised several centuries ago in Europe. It was not until the 1930s that CF was described as distinct from coeliac disease. (Andersen, 1938) At this time, life expectancy for those affected with CF was only measured in months. (Andersen, 1938) Treatments and care for people with CF evolved and improved such that expected survival in the mid-1970s was into the mid-teens. These advances have been sustained and current statistics point to a predicted median life expectancy of over 37 years with a significant number of individuals reaching their sixth decade. (CFF, 2008; Dodge et al., 2007) (See Figure 1.1) Most recent UK registry data indicates a median survival of 38.8 years. (CFTrust, 2009)
Figure 2.1 Median predicted survival in cystic fibrosis (reproduced from Cystic Fibrosis Foundation Annual Report Data 2007 (CFF, 2008))

This figure shows a sustained increasing improvement in median predicted survival in CF over a 22 year period, calculated from North American registry figures.
1.2 The CF Gene Mutation

The specific gene which when mutated, leads to CF, was located and fully mapped over 20 years ago, on the long arm of chromosome seven. (Kerem et al., 1989; Riordan et al., 1989; Rommens et al., 1989) There is incorrect coding for the cystic fibrosis transmembrane conductance regulator (CFTR). (O'Sullivan and Freedman, 2009) This is a cyclic AMP-regulated chloride channel, which is present in many epithelial surfaces and blood cells. (O'Sullivan and Freedman, 2009) The protein regulates sodium and water movements across cell membranes. (Kerem et al., 1989) Individuals affected with CF must have mutations in both copies of the gene coding for CFTR. Mutations are classed into six different categories according to the degree of abnormal CFTR function. Class I, II and III disrupt production, processing and regulation of CFTR and confer the most severe disease manifestations. (Morral et al., 1994) Class IV to VI defects result in reduced action of CFTR and affected individuals are typically exocrine pancreatic sufficient with milder CF phenotypes. (Rowe et al., 2005) (Ratjen and Doring, 2003)

More than 1500 different gene mutations are recognised to be causative for CF. (Boyle, 2007) ‘DeltaF508’, the deletion of phenylalanine at codon 508 is the commonest, accounting for two thirds of CF mutations in the UK and Northern Europe. (Morral et al., 1994) In the UK 54% of people with CF are homozygous for DeltaF508 and a further 38% are heterozygotes. (CFTrust, 2009) There is significant variation in disease severity, even among homozygous DeltaF508 individuals. (Lester et al., 1994) Non-CFTR ‘gene modifiers’ such as mannose binding lectin and transforming growth factor beta-1 as well as environmental factors are thought to be responsible. (Drumm et al., 2005; Accurso and Sontag, 2008; Merlo and Boyle, 2003; Boyle, 2007)
1.3 Multi-system Manifestations

CFTR is expressed in most body systems, in epithelial-lined organs, particularly in the airway, sweat ducts, pancreatic ducts, intestines, biliary tree and vas deferens. (Ratjen and Doring, 2003) Defective CFTR leads to viscous secretions and it is in the lungs, where this has the most severe impact on symptoms and survival for those with CF. Airway surface liquid is depleted and dehydrated secretions become infected by bacterial pathogens, ultimately leading to inflammation, chronic infection and destruction. (Ratjen and Doring, 2003) In the pancreas, in exocrine pancreatic insufficient individuals, there is a reduced volume of pancreatic secretions, low concentrations of bicarbonate and pancreatic enzymes are not secreted effectively. In this acidic environment, retained enzymes are activated and cause progressive pancreatic destruction. (Kopelman et al., 1985) Dehydration in the digestive tract can cause intestinal obstruction.

1.3.1 Respiratory System

Viscous secretions in the lungs predispose to infection with bacterial pathogens. An associated inflammatory response ensues, involving the release of elastase and free radicals from neutrophils, damaging the lungs. Over time, a vicious cycle of infection, inflammation and obstruction causes progressive and irreversible structural change. (Armstrong et al., 1997)

Initial bacterial infection in childhood is usually with Haemophilus influenzae, followed by Staphylococcus aureus. (Armstrong et al., 1996) Most people with CF have become chronically infected with Pseudomonas aeruginosa by their teenage years. P.aeruginosa is associated with accelerated lung function decline and poorer clinical status. (Kerem et al., 1990) The first appearance of non-mucoid strains should always be treated aggressively to
attempt to prevent chronic infection. (Valerius et al., 1991; Frederiksen et al., 1997) If left untreated, \( P.\text{aeruginosa} \) adapts with development of a mucoid phenotype which forms a ‘biofilm’ layer and is virtually impossible to eradicate. (Govan and Deretic, 1996) Once chronic infection is established, treatment is directed at suppressing the total bacterial load, which results in clinical improvement. (Govan et al., 1987; Regelmann et al., 1990)

Some strains of \( P.\text{aeruginosa} \) are transmissible between patients. Recent research suggests that though these may not be associated with increased mortality, there is evidence of increased health care input and antibiotics in patients with these strains. (Jones et al., 2010) Segregation of patient groups with separate clinics, ward side rooms and lung function equipment was introduced some years ago and should prevent cross infection. (Jones et al., 2005)

The \textit{Burkholderia cepacia} complex (Bcc) are other highly important pathogens in CF, as they are associated with an increased morbidity and mortality. (Soni et al., 2002; Corey and Farewell, 1996; Isles et al., 1984) There are at least 17 different species (genomovars) within the complex, the most significant of which are certain epidemic strains of \textit{Burkholderia cenocepacia}. Lung transplants are not offered to those infected with \textit{B.cenocepacia}, due to proven poorer outcomes. (Aris et al., 2001; Chaparro et al., 2001; DeSoyza et al., 2001) ‘Cepacia syndrome’, a necrotising pneumonia and septicaemia can occur in some individuals and almost always rapidly progresses to death. (Jones et al., 2001) Eradication by aggressive antibiotic therapy should be considered following the first isolation of Bec bacteria (as per our local Manchester Adult Cystic Fibrosis Centre protocol) Failing this, patient segregation and bacterial load suppression with nebulised or intravenous antibiotics is the focus of treatment.
There are several other important emerging pathogens in CF, such as *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Ralstonia* species, *Pandoraea* species, *Methicillin Resistant Staphylococcus Aureus* (MRSA) and non-tuberculous mycobacteria.

Non-infective pulmonary manifestations of CF include pneumothoraces, which usually take longer to resolve than in non-CF lungs (Flume et al., 2005a) and haemoptysis, which may be massive. (Flume et al., 2005b)

Allergic bronchopulmonary aspergillosis (ABPA) affects approximately 10% of people with CF (Elphick and Southern, 2000) and is associated with pulmonary deterioration. Prolonged courses of medication may be required to reduce the allergic response and limit bronchiectasis. (Davies et al., 2007) Sinus disease and nasal polyposis are very common in CF, with polyps tending not to respond well to local steroids and often requiring repeated surgery. (Khalid et al., 2009)

1.3.2 Gastrointestinal System

Intestine

CFTR is expressed in large quantities in the intestinal epithelium, and those affected with CF are very susceptible to intestinal obstruction. (O'Sullivan and Freedman, 2009) Twenty five percent of neonates with classic CF disease present with meconium ileus at birth, due to inspissated material in the small and large bowels. (Wilschanski and Durie, 2007) Later in life, the equivalent pathological process is referred to as distal intestinal obstruction syndrome (DIOS), caused by viscous intestinal secretions, malabsorption and reduced gut
motility. (O'Sullivan and Freedman, 2009) This rarely requires surgery, usually resolving with hydration, osmotic laxatives and gastrografin. Constipation is a frequent occurrence.

Intussusception occurs in CF up to 20 times more commonly than in the general population, caused by dehydrated bowel contents adhering to the gut wall, though can resolve spontaneously. (Wilschanski and Durie, 2007) Gastro-oesophageal reflux disease (GORD) is more common in CF than in the general population. Respiratory factors, physiotherapy, lower oesophageal sphincter dysfunction and delayed gastric emptying are presumed to contribute to GORD. (Wilschanski and Durie, 2007) Acute appendicitis occurs less commonly than in the general population, though affected individuals have the potential for significant complications due to delayed diagnosis. (Wilschanski and Durie, 2007) There is an increased incidence of gastrointestinal malignancy in the CF population. (Neglia et al., 1995) The reasons for this are unclear, but physicians should be mindful of this when managing gastrointestinal complications of CF. (Wilschanski and Durie, 2007)

Pancreas
Those with class I, II, or III CF gene mutations (85% of people with CF) have exocrine pancreatic insufficiency. CFTR is expressed in large quantities in pancreatic duct epithelia, which regulates anion and fluid transport into the duct lumen. (Wilschanski and Durie, 2007) Dysfunctional CFTR results in reduced chloride and bicarbonate in the ducts, producing concentrated acidic secretions. (Wilschanski and Durie, 2007) This in addition to reduced enzyme secretion causes digestive enzymes to be retained and activated locally, destroying pancreatic tissue and causing fibrosis, leading to malabsorption. (Kopelman et al., 1985) Exocrine pancreatic insufficient individuals are required to take supplementary
digestive enzymes with each meal or snack and fat-soluble vitamins should also be supplemented. (O'Sullivan and Freedman, 2009)

A distinct form of diabetes mellitus, CF related diabetes (CFRD) occurs in some people with an exocrine pancreatic insufficient status. CFRD occurs with increasing frequency with age, being present in 25 percent of those over the age of 20 years with CF. (Lanng et al., 1991) Progressive pancreatic damage is implicated though the mechanism is not fully understood. The onset is insidious, without the occurrence of ketoacidosis, due to impaired glucagon secretion failing to stimulate ketone formation. Affected individuals retain some basal insulin secretion, but have delayed and reduced insulin secretion following a glucose load and relative insulin resistance. (Moran et al., 1999) Before frank diabetes occurs, individuals may exhibit ‘impaired glucose tolerance’, having higher glucose levels than those considered to be in the normal range. The degree of insulin resistance varies, being particularly increased at times of infection or with other stressors. Insulin therapy is indicated to manage hyperglycaemia and may be intermittent, during infections or alongside oral glucocorticosteroid treatment, or may be required permanently.

Exocrine pancreatic sufficient individuals do not usually develop CFRD but may experience recurrent episodes of idiopathic pancreatitis. With repeated insults over time, they may also require enzyme supplementation.

As survival in CF improves, there is an increasing awareness of a small proportion of adults who are actually overweight, and who display features consistent with a picture of type 2 diabetes mellitus.
Liver and Biliary System

CFTR is expressed in the cells of the biliary tract and individuals with class I to class III (severe) CF mutations are at increased risk of developing CF related liver disease. (Wilschanski et al., 1999) Dysfunctional CFTR causes reduced bile flow and concentrated bile secretions, causing obstructed bile ductules which can lead to focal biliary cirrhosis. (Wilschanski and Durie, 2007) For most patients this is not clinically significant and only a minority go on to develop multilobular cirrhosis with portal hypertension. (Wilschanski and Durie, 2007) Liver disease in CF also includes gallstones in up to 10% of patients and fatty infiltration causing hepatomegaly. (Nagel et al., 1989)

1.3.3 Skeletal System

Patients with CF are at higher risk of osteoporosis than the general population, owing to risk factors which include malabsorption and malnutrition, deficiencies of calcium and vitamins D and K, chronic inflammation and sepsis, oral glucocorticosteroid use, altered sex hormone production, pubertal delay and reduced physical activity. (Haworth et al., 1999; Conway et al., 2000) CF-related low bone mineral density is more prevalent as adults develop more severe lung disease and a poorer nutritional status, suggesting an aetiology related to the increased prevalence of risk factors as patients survive longer. (Aris et al., 2005) CF-related low bone mineral density has also been reported in exocrine pancreatic sufficient individuals. (Aris et al., 2005)

CF-related arthropathy may occur in up to 8.5% of patients, usually at the time of an infective exacerbation, and may be accompanied by a vasculitic reaction. (Botton et al., 2003) Arthritis and hypertrophic osteoarthropathy are also reported. (Botton et al., 2003)
1.3.4 Reproductive System

Males with CF have mal-development of the vas deferens, epididymis and seminal vesicles, so although healthy sperm are produced, they cannot leave the testes. (Oppenheimer and Esterly, 1969) Men with CF are therefore infertile, but can go on to biologically father children with advanced fertility treatments involving sperm retrieval then intracytoplasmic sperm injection (ICSI) and in vitro fertilisation. (Silber, 1997)

Females with CF may have near normal fertility, though effects of pregnancy on their health should be taken into consideration on an individual basis prior to conception. (Goss et al., 2003)

1.3.5 Urinary System

Stress urinary incontinence is common but under-reported in females with CF. It is caused by raised intra-abdominal pressures principally from persistent coughing but chronic constipation and organomegaly also contribute. (McVean et al., 2003) Although no CFTR is expressed in the kidney, patients may encounter renal problems with an increased prevalence of renal calculi and renal toxicity relating to drug treatment, in particular aminoglycosides. (Watson, 2007)

1.4 Psychosocial Issues

People with CF and their families may encounter difficulties relating to the burden of a chronic progressive disease and its treatment, education and employment, financial
matters, fertility treatment, transplant decisions and palliative care and bereavement. Anxiety and depression appear to occur more commonly in CF than in the general population (Riekert et al., 2007; Cruz et al., 2009) and may require specialist input. The presence of depressive symptoms may impact negatively on quality of life, even after correcting for disease severity. (Havermans et al., 2008)

1.5 Current Management

1.5.1 Multidisciplinary Team Care

The importance of multidisciplinary team (MDT) care in CF cannot be over-emphasised. The team includes dedicated specialist ward and outpatient nurses, physicians, physiotherapists, dieticians, social workers, psychologists, pharmacists and supporting administrative staff. The MDT fosters close links with other specialty teams within the hospital.

Patients with CF whose care is coordinated by dedicated CF centres have better outcomes than those who may be seen in general clinics with a specialist interest in CF. (Mahadeva et al., 1998) Personalised targeted care is essential because of the complexities of CF present for any one patient.

1.5.2 Survival and Outcome Measures

Survival in CF is related to nutritional status and lung function. (Kerem et al., 1992) Forced expiratory volume in one second (FEV₁) and body mass index (BMI) are the main markers of disease severity. (Kerem et al., 1992)
Recently a UK team reported that their CF patients are living longer with end stage lung disease (FEV$_1$<30% predicted), challenging the prognostic value of traditional outcome measures.

1.5.3 Physiotherapy

Specialist CF physiotherapists work with patients with CF for a tailored approach to effective airway clearance for each patient, so that they can continue with their daily regime at home. A variety of techniques may be involved, including the active cycle of breathing technique, postural drainage, flutter devices and positive expiratory mask therapy. These are vital to clear secretions, open up small airways and improve ventilation. Dedicated CF physiotherapists are involved with the assessment of functional ability and exercise testing.

Musculoskeletal therapy is frequently required due to adverse effects on the posture from CF or for joint pains or tendon problems. Specialist physiotherapy assessment and treatment may also be required for urinary incontinence in female patients with CF.

1.5.4 Medical Therapy

Respiratory treatment targets the cycle of infection and inflammation by preventing the development of chronic bacterial infection where possible and prompt treatment of acute infective exacerbations with antibiotics. Exacerbations are usually treated for 14 days with oral or intravenous (IV) agents. Some centres advocate regular three monthly IV antibiotic courses. (Elborn et al., 2000) Patients commonly have indwelling venous ‘port’ devices to ensure easy IV access.
Chronic infection is often treated with a combination of nebulised and oral antibiotics. Many patients take long term oral flucloxacillin to prevent *staphylococcal* infection. One particular agent, azithromycin, has not only antimicrobial properties but is anti-inflammatory and has a protective effect on pulmonary function. (Wolter et al., 2002) Mucolytics such as dornase alpha (Fuchs et al., 1994; Jones and Wallis, 2010) and hypertonic saline (Elkins and Bye, 2006; Elkins et al., 2006) are commonly used to aid sputum clearance.

In chronic or acute-on-chronic respiratory failure, patients may need to be established on non-invasive ventilation, usually with the help of a specialist inpatient team. This therapy was previously seen solely as a bridge to transplantation in end stage respiratory failure (Hodson et al., 1991) but is increasingly used earlier in the disease process for ongoing respiratory support. Non-invasive ventilation has been shown to improve gas exchange, reduce work of breathing (Milross et al., 2001; Gozal, 1997) and improve oxygenation during physiotherapy. (Holland et al., 2003; Fauroux et al., 1999) Recently an Australian team carried out a novel randomised placebo-controlled crossover study with a small number of patients, demonstrating that nocturnal NIV is superior to placebo in improving chest symptoms, nocturnal hypoventilation, capacity to exercise and breathlessness on exertion. (Young et al., 2008) Larger trials are needed, in particular to examine the effect of NIV on survival in CF.

1.5.5 Nutritional Support

The main aim is for normal growth in childhood and optimal nutritional status in adulthood because being underweight is associated with poorer lung function. (Matel and Milla, 2009) Dedicated dieticians regularly review patients at routine clinics to ensure that they
are maximising their energy intake from food, taking adequate pancreatic supplements and achieving sufficient fat soluble vitamin levels. They may prompt the team to consider intervening with nutritional supplements or enteral feeding when nutritional status is unsatisfactory. CF dieticians are closely involved with the ongoing assessment and treatment of impaired glucose tolerance and CFRD.

1.5.6 Segregation
Patient segregation prevents cross-infection of epidemic strains of bacteria between patients. It is vital to segregate patient groups infected with different organisms and different strains of the same organism into separate clinics and as inpatients. Patients may become infected with new pathogens at any time, and many therefore need to be re-classified into a different patient group, so ongoing microbiological surveillance is vital.

1.5.7 Lung Transplantation
Lung transplantation is the most effective way of improving quality of life for those with end stage lung disease from CF (Quattrucci et al., 2005), considered to be when a patient has a life expectancy of less than two years. Traditionally a marker for this prognosis has been FEV$_1$ < 30%, but this has recently been shown to be poorly predictive of death within 2 years. (Mayer-Hamblett et al., 2002; Ketchell et al., 2009) A positive outcome in relation to survival and quality of life depends on appropriate selection of candidates, timing of referral for transplant and development of postoperative complications such as infection and organ rejection. (Quattrucci et al., 2005) Although a successful transplant may give freedom from many of the respiratory consequences of CF, it necessitates major surgery with a lengthy recovery and rehabilitation, coupled with a lifelong complex regime of
immunosuppressive medications. There is significant morbidity and mortality associated with lung transplant. (Yankaskas et al., 2004) In the UK and US, the one year and five year survival rates following lung transplant are 80 % and 40 to 50 % respectively. (Meachery et al., 2008; Ganesh et al., 2005)

1.6 The Future

Back in 1989 with the discovery of the CF gene it had been hoped that gene therapy i.e. medication to repair the defective gene, would be in common use by this current decade. Trials of research medications have encountered fundamental problems with safety and efficacy. There are, however, ongoing studies aiming to make gene therapy a reality for a future generation of patients with CF.

Newborn screening has now been introduced throughout the UK and in many centres worldwide. This brings about further challenges, such as how to manage infants and children with CF who are asymptomatic.

Even if genetic therapies are still not established, with the continued growth of the adult CF population there are implications for provision of adequate CF specialist services. (Dodge et al., 1997) It is anticipated that babies born with CF in the year 2000 can expect, on average, a median survival to over the age of 50 years. (Dodge et al., 2007)
CYSTIC FIBROSIS RELATED DIABETES

2.1 Historical Background

Survival of patients with CF has continually improved, giving rise to a median life expectancy improvement from six months, now into the fourth decade. Recent UK figures show a median predicted survival of 38.8 years. (CFTrust, 2009) As longevity improves, more adult consequences of the disease are recognised.

In 1938, Dorothy Andersen observed hyperinsulinaemia within a series of post-mortem reports on children with CF. (Andersen, 1938) In the 1950s, a link between CF and frank diabetes mellitus was described with an article detailing cases of three children with CF who had developed diabetes. (Shwachman et al., 1955) Lowe also reported a number of cases of children with CF and glucose intolerance. (Lowe and Pessin, 1959) This finding was uncommon and it would not have been possible to realise its significance. More recently, many investigators have observed that abnormal glycaemic control (impaired glucose tolerance and diabetes) is prevalent in cystic fibrosis and of great clinical importance.

2.2 Epidemiology

Estimates of the prevalence of abnormal glycaemic control have been revised upwards through the decades as survival increases. They have also varied due to differing age and ethnicity of patients in CF centres and the exact methods used to define and detect impaired glucose tolerance (IGT) and CF related diabetes (CFRD). An individual’s blood
glucose control fluctuates over time, further complicating how to define abnormal glycaemia.

Lanng et al published a large cross-sectional study from their Danish centre in 1991, where patients underwent annual OGTT. (Lanng et al., 1991) This demonstrated that the incidence and prevalence of diabetes in CF was increasing with age. (Lanng et al., 1991) In approximately 200 prospectively examined unselected patients from age 2 years to 40 years, the prevalence of CFRD was 11%, (Lanng et al., 1991) consistent with several earlier studies estimating prevalence at 2.5% to 12%. (Rodman et al., 1986; Finkelstein et al., 1988; Reisman et al., 1990) One flaw of this research was that CFRD appeared to be defined by a diabetic glucose tolerance (DGT) result alone, without further follow up of glucose levels. It was clear though, that DGT was more prevalent in CF than in the non-CF population. (Lanng et al., 1991; Dodge and Morrison, 1992) Subsequent research places the prevalence of CFRD slightly higher at 14% to 16%, (Yung and Hodson, 1999; Wilson et al., 2000; Milla et al., 2000) though these epidemiological findings are influenced by age groups and ethnicities of each study population.

The commonest age of onset of diabetes has been estimated to lie between 15 years to 24 years. (Moran et al., 1999; Dodge and Morrison, 1992; Yung and Hodson, 1999; Wilson et al., 2000) It is more predominant in females who may have a lower median age of onset. (Lanng et al., 1994a; Moran et al., 1999; Dodge and Morrison, 1992) Females with CFRD have a higher risk of death than males with CFRD. (Milla et al., 2005) A recent report from a large North American CF centre has suggested that with an aggressive approach to diagnosis and treatment of CFRD, the mortality gap may be reduced. (Moran et al., 2009) Two centres reported large screening studies with well defined criteria, finding that
diabetes was present in only 3% to 9% of subjects by age ten years, but in 43% to 76% of those over the age of 30 years. (Lanng et al., 1994a; Moran et al., 1999)

2.3 Normal Glycaemic Control

In health, secretion of insulin (from beta cells in the pancreatic islets) occurs during the absorption of a carbohydrate meal, stimulated by a rise in blood glucose concentration. One of the most important actions of insulin is to promote the uptake of glucose into cells. There it is converted to glycogen in liver and muscle, and converted to fat in adipose cells. Glucagon secretion (from alpha cells in the pancreatic islets) is inhibited by a rise in plasma glucose. (Guyton and Hall, 2005)

Between meals, when blood glucose levels begin to fall, this stimulates glucagon release and inhibits insulin secretion. Glucagon promotes the release of glucose from the liver by glycogenolysis and gluconeogenesis. (Guyton and Hall, 2005)

2.4 Type 1 and Type 2 Diabetes Mellitus

In diabetes mellitus (DM), hyperglycaemia is caused by either deficient insulin secretion or tissue insulin resistance. Type 1 diabetes mellitus (T1DM) is a disease of autoimmunity in which the beta cells are progressively destroyed, ultimately secreting little or no insulin. Glucose is not taken up by cells and synthesis of fat in adipose cells is much reduced. Fat breakdown occurs, releasing free fatty acids which may be converted into ketone bodies in the liver. Glucagon levels are abnormally high, stimulating hepatic glycogenolysis and the conversion of fatty acids into ketone bodies. Left untreated, diabetic ketoacidosis may develop, which may ultimately lead to coma and death. T1DM tends to develop in the first
two decades of life and its symptomatic onset is rapid. Treatment is with exogenous insulin. (Turner and Wass, 2002)

Type 2 diabetes mellitus (T2DM) is primarily a disease of insulin resistance, with those affected having normal or even increased blood insulin levels, but tissue responsiveness to insulin is much decreased. This form of DM is insidious in onset and commonly associated with obesity, as this decreases tissue sensitivity to insulin. There is a familial aspect to this disease. Initial treatment is usually with dietary measures and exercise, to decrease insulin resistance. Oral hypoglycaemic drugs may be required and some individuals progress to require insulin therapy. (Turner and Wass, 2002)

Both forms of DM, if poorly controlled, lead to macrovascular complications such as stroke, ischaemic heart disease and peripheral vascular disease. Microvascular complications include retinopathy, neuropathy and nephropathy.

2.5 Classification of CF Related Diabetes

Over the last 20 years, CFRD came to be recognised as a distinct clinical entity from both T1DM and T2DM (see Table 2.1).
**Table 2.1** Comparison of characteristics of Type 1 diabetes, Type 2 diabetes and CFRD (adapted with permission(O'Riordan et al.))

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>T2DM</th>
<th>CFRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Acute</td>
<td>Insidious</td>
<td>Insidious</td>
</tr>
<tr>
<td><strong>Peak age of onset</strong></td>
<td>Children &amp; adolescents</td>
<td>Adults</td>
<td>18-24 yrs</td>
</tr>
<tr>
<td><strong>Antibody (+)</strong></td>
<td>YES</td>
<td>NO</td>
<td>Probably NO</td>
</tr>
<tr>
<td><strong>Insulin secretion</strong></td>
<td>Eventually absent</td>
<td>Decreased</td>
<td>Severely decreased but not absent</td>
</tr>
<tr>
<td><strong>Insulin sensitivity</strong></td>
<td>Somewhat decreased</td>
<td>Severely decreased</td>
<td>Somewhat decreased</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Insulin</td>
<td>Diet, oral meds, insulin</td>
<td>Insulin</td>
</tr>
<tr>
<td><strong>Microvascular complications</strong></td>
<td>YES</td>
<td>YES</td>
<td>YES but less</td>
</tr>
<tr>
<td><strong>Macrovascular complications</strong></td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td>Cardiovascular disease, nephropathy</td>
<td>Cardiovascular disease</td>
<td>Pulmonary disease</td>
</tr>
</tbody>
</table>

This table displays the characteristics of T1DM, T2DM and CFRD, showing how each is a distinct clinical entity.
Although CFRD shares some common features of T1DM, presenting at a relatively young age and requiring exogenous insulin therapy, it is non-ketotic (patients do retain some exogenous insulin secreting capacity and impaired glucagon secretion may fail to stimulate ketone formation). (Yung and Hodson, 1999) CFRD is not a disease of autoimmunity. Its onset is insidious, not unlike T2DM, and there are some similarities in pathophysiological findings but the presentation and aetiology are otherwise separate. Occasionally T1DM may occur independently of CF and should be suspected if the onset is at less than ten years of age or if presentation is with ketoacidosis.

In T1DM the requirement for exogenous insulin is absolute but in CFRD where some basal insulin secretion is retained, there may be varying degrees of insulin resistance according to disease status at the time. Individuals with CFRD therefore demonstrate a fluctuating level of glucose intolerance, and may only require insulin intermittently.

The World Health Organisation (WHO) defines DM as a level of hyperglycaemia, which, if left untreated, would lead to microvascular and macrovascular complications. (WHO, 1999) (WHO, 2006) Categories of glucose tolerance in CF are derived from the WHO criteria for the definition of diabetes and impaired glucose tolerance (WHO, 1999) based on the oral glucose tolerance test (OGTT) and are agreed on by the Cystic Fibrosis Foundation Consensus Conference. (Moran et al., 1999) This American group updated their guidelines in 2010, keeping the OGTT as the screening test of choice for CFRD. (Moran et al., 2010) The OGTT categories were originally formulated with groups at risk of T2DM in mind, rather than those with CF, as the threshold values were those above which treatment has been proven to prevent complications.
An oral glucose tolerance test (OGTT) is the ‘gold standard’ method used to determine the level of abnormal glycaemic control. Following an overnight fast, a subject has baseline blood glucose tested, then drinks a standard glucose load of 1.75g/kg to a maximum of 75g. They should rest over the next two hours, at which time a second blood glucose test is performed. (See Table 2.2 for threshold values.)
Table 2.2 OGGT threshold glucose values for the diagnosis of diabetes mellitus and other categories of hyperglycaemia (WHO, 1999) (WHO, 2006)

<table>
<thead>
<tr>
<th>Glucose tolerance category</th>
<th>OGGT plasma glucose criteria</th>
</tr>
</thead>
</table>
| Diabetes mellitus          | Fasting plasma glucose ≥ 7.0 mmol /L  
2hr post load glucose ≥ 11.1 mmol/L |
| Impaired glucose tolerance | Fasting plasma glucose < 7.0 mmol /L  
2hr post load glucose ≥ 7.8 mmol/L |
| Impaired fasting glycaemia  | Fasting plasma glucose > 6.1 mmol /L  
2hr post load glucose < 7.8 mmol/L |
| Normal glucose tolerance   | Fasting plasma glucose ≤ 6.1 mmol/L  
2hr post load glucose < 7.8 mmol/L |

This table displays the threshold glucose values for the diagnosis of diabetes mellitus and other categories of hyperglycaemia, according to World Health Organisation criteria.
The WHO updated these recommendations in 2006, adding the category of impaired fasting glucose. (WHO, 2006) This category has been shown to be poorly discriminatory in CF and has not, to date, been adopted for use in the CF population. (Mueller-Brandes et al., 2005) Current UK CF Trust guidelines recommend OGTT in combination with serial blood glucose monitoring as the most sensitive and specific tool in screening for CFRD. (CFTrust, 2004)

2.6 Aetiology and Pathophysiology

In CF the adult pancreas has undergone gradual gross histological change. Over time blocked ducts from thickened secretions lead to acinar atrophy and fatty and fibrous replacement, with eventual stranded islets of Langerhans separated by fibrous bands. (Dodge and Morrison, 1992) A relative loss in beta cell mass is well described. (Dodge and Morrison, 1992; Hodson, 1992) There may also be a subsequent, less severe, loss in alpha cells. (Dodge and Morrison, 1992)

Greater disruption is noted in exocrine pancreatic insufficient subjects, (Dodge and Morrison, 1992) about 85 to 90% of CF patients, but there are conflicting findings about whether the beta cell mass reduction is greater in those who develop CFRD. Other investigators point out a poor level of correlation between the degree of pancreatic destruction and level of abnormal glycaemia. (Yung et al., 2002) CFTR is not expressed in the islet cells of the pancreas and so far, there is no adequate unifying explanation for the loss in beta cell mass. (Wilson et al., 2000)

Some additional factors are thought to be of significance. Amyloid deposition occurs in the CF pancreas and a pathological role such as in T2DM has not been excluded. (Mackie et
al., 2003) Some authors have postulated that in order to develop CFRD, individuals must not only be pancreatic insufficient but have gene defects which could otherwise be responsible for T2DM. (Wilson et al., 2000) There is however no evidence for genetic factors other than pancreatic insufficiency in the development of CFRD. Those patients with preserved exocrine pancreatic function (having ‘mild’ class IV, V or VI mutations) do not normally develop CFRD. A further study in Lanng’s Danish centre examined 34 patients with CFRD with age, gender and chronic *Pseudomonas aeruginosa* positive status matched controls. (Lanng et al., 1993a) Individuals with CFRD were found to have no strong positive family history of diabetes, no HLA-DR association and no serological evidence for autoimmune destruction of the pancreatic islet cells. (Lanng et al., 1993a) Homozygosity for DeltaF508 may predispose to the risk of developing CFRD and N1303K, another ‘severe’ CFTR mutation, may offer protection against diabetes. (Cucinotta et al., 1999)

Insulin secretion and sensitivity are regarded to be key factors in the development of CFRD. Those with exocrine pancreatic insufficiency have an abnormal insulin response to a glucose load, even those with NGT. This is demonstrated by Yung et al (see Figure 2.1).
Figure 2.1 Insulin and glucose profiles in CF and healthy controls. (Reproduced with permission (Yung et al., 2002))

This figure demonstrates the differing plasma insulin and glucose profiles during extended OGTT in healthy controls and CF subjects with differing glycaemic status (○ healthy controls, n=8; ● CF-NGT, n=16; ▲ CF-IGT, n=6; ■ CF-DGT, n=2). The 120 minute time point for determining glucose tolerance is shown by the dashed line. The time to peak insulin levels is progressively increased through those without CF, those with CF and NGT, those with CF and IGT and those with CF and DGT. There is a corresponding increase through the same groups for glucose area under the curve during OGTT.
CF patients with NGT or IGT have low insulin levels but maintain relatively normal glucose levels because they are sensitive to insulin. (Milla et al., 2005) The abnormal insulin release is reduced further with increasing glucose intolerance. (Lanng et al., 1993b) Evidence on insulin sensitivity and resistance is conflicting, though reasonable consensus opinion is that initially insulin sensitivity increases in response to insulinopaenia, early in the spectrum of abnormal glycaemic control. (Wilson et al., 2000) Additional insulin resistance occurs in the setting of known stressors or risk factors such as acute and chronic infection, oral corticosteroid therapy and pregnancy. (Wilson et al., 2000) People with CF have varying degrees of insulin resistance depending on their current clinical status. The relative contributions of insulin secretion and insulin resistance are to date not fully established or understood. (Costa et al., 2007) A further complicating factor is that the metabolic insulin clearance rate is increased in CF and may contribute to insulinopaenia. (Ahmad et al., 1994)

Cucinotta et al performed a prospective ten year study in children and adolescents with CF, demonstrating that all those with CF have decreased amounts of insulin secretion and decreasing glucose tolerance over time. (Cucinotta et al., 1999) Subsequent work supports the theory that insulin deficiency (impaired beta cell function) is the primary defect of glucose tolerance in CF, reasoning that this leads to detrimental outcomes by decreased suppression of protein catabolism. (Rosenecker et al., 2001) An impaired glucagon response to stimuli such as oral glucose and insulin-induced hypoglycaemia is acknowledged, (Lanng et al., 1993b; Moran et al., 1991) as well as very low levels of pancreatic polypeptide secretion in pancreatic insufficiency. (Lanng et al., 1993b)
Glucose metabolism in CF is influenced by several other factors including malnutrition, malabsorption, infection, increased energy expenditure, glucagon deficiency, abnormal intestinal transit time and liver dysfunction. (Moran et al., 1999) Investigators have noted the importance of oral corticosteroid therapy, overnight supplemental feeding and CF liver disease to be risk factors for CFRD. (Wilson et al., 2000) Dodge et al put forward the theory that attempts to improve nutrition could actually contribute to worsening glucose tolerance. (Dodge and Morrison, 1992) They postulate that weight gain to improve nutritional status could reduce the amount of insulin receptors, leading to glucose intolerance and ultimately CFRD. (Dodge and Morrison, 1992)

2.7 Clinical Consequences

There is an increased mortality among individuals with CFRD compared to those with CF without diabetes. Finkelstein and colleagues noted in their large study in 1988 that although 60% of people with CF without diabetes were surviving to the age of 30 years, this was only the case for 25% of people with CFRD. (Finkelstein et al., 1988) US registry data published almost a decade later gives a three to six fold increased mortality for CFRD patients compared to those with CF and no diabetes (CFF, 1997), though as mentioned previously, this gap could now be closing. (Moran et al., 2009)

Poor clinical status is present at the time of diagnosis with CFRD but more importantly a pre-diabetic decline has also been shown to occur. Among one of the first investigators to confirm this deterioration before the clinical diagnosis of diabetes was Finkelstein’s group, who discovered that objective measures of clinical status were worse from two years
before CFRD developed. (Finkelstein et al., 1988) Lanng and co-workers found a decline in lung function up to three years before diagnosis and a lower body mass index up to four years prior to diagnosis. (Lanng et al., 1992) A follow up study after treatment with insulin for at least two years showed that insulin restores body mass index and improves lung function in CFRD patients, (Lanng et al., 1994b) suggesting a cause and effect relationship between decreased insulin and clinical deterioration. Further support for this argument is found in a large cross-sectional analysis of more than 7500 patients from the European Registry published in 2001. (Koch et al., 2001)

More recent work has shown that the rate of pulmonary decline is inversely proportional to baseline insulin secretion, (Milla et al., 2000) and that ‘area under the curve’ during OGTT and reduced early insulin secretion have a stronger association with a worse clinical condition than the conventional glucose tolerance categories. (Costa et al., 2007) Dobson et al highlighted that in view of overall glycaemia being increased in CF, even those with NGT, the appropriateness of current diagnostic thresholds (derived from a non-CF population) (WHO, 1999) is brought into question. (Dobson et al., 2004)

Mechanisms postulated for the observed pulmonary decline include the direct effect of hyperglycaemia causing structural changes in lung tissue and indirectly increasing susceptibility to infection. (Brennan et al., 2004) Chronic abnormal pulmonary function has been recognised in both T1DM and T2DM in non-CF populations. (Niranjan et al., 1997; Davis et al., 2004) A large dataset from the European Registry showed the presence of CFRD to be tightly linked to lung function and concluded that CFRD is a more important determinant of lung pathology than was previously thought. (Koch et al., 2001)
It is thought that the poor nutritional status at CFRD diagnosis reflects the relative catabolic effect of insulinopaenia and/or insulin resistance, as the primary effect of insulin is to decrease total body proteolysis. (Wilson et al., 2000) Insulin therapy also promotes protein synthesis, leading to increased muscle mass and therefore the capacity to enhance respiratory muscle function. (Mackie et al., 2003; Rosenecker et al., 2001; Brennan et al., 2004)

2.8 Diagnosis

The diagnosis of CFRD is difficult and optimal methodology remains unresolved. Currently diagnosis of CFRD or IGT requiring treatment depends on a consideration of the OGTT result, together with home monitoring results and a patient’s clinical symptoms and condition. Prompt diagnosis is essential to avoid unnecessary clinical deterioration, so regular screening is advised. Current UK guidelines recommend annual OGTT for all patients over the age of 12 years. (CFTrust, 2004) This is supported by Lanng’s earlier research, demonstrating this to be the only reliable means to screen for CFRD. (Lanng et al., 1991) However it must be noted that of those with IGT, approximately 60% can expect to have reverted to NGT at the repeat testing. (Lanng et al., 1995) The UK CF Trust recommends that a diabetic OGTT should be followed by a period of home blood glucose monitoring. (CFTrust, 2004)

UK guidelines point out that glycaemic status should also be assessed in the setting of hyper- or hypoglycaemic symptoms, unexplained clinical deterioration, during infection or oral or IV glucocorticosteroid therapy, before starting supplemental feeding and in pregnancy. (CFTrust, 2004)
Screening based on symptoms alone is flawed, as a majority of patients are asymptomatic at diagnosis. Urinalysis is not validated in CF. HbA1c has too much ‘overlap’ (a large majority of those with IGT had normal HbA1c) and is also affected by red blood cell turnover and other factors in CF. US guidelines do include an elevated HbA1c (greater than 6.5%) in their diagnostic criteria for CFRD but acknowledge that a normal HbA1c does not exclude diabetes. (Moran et al., 2010) These latest US guidelines include criteria for diagnosis of CFRD in unwell patients and patients on enteral feed. (Moran et al., 2010) (see Figure 2.2) This shows a step towards recognising the spectrum of abnormal glycaemic control, and the need for criteria for diagnosis of CFRD outside the OGTT and healthy outpatients.
Figure 2.2 US guidelines for diagnosis of CFRD from 2010 include criteria for ‘unstable’ patients (adapted from Moran et al., 2010).

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**Continuous Drip Feedings**
- Diagnosis based on mid- or immediate postfeeding glucose ≥ 11.1 mmol/L
- Should be confirmed on two separate nights
- If measured by CBG should be confirmed by laboratory measurement

**Acute Illness, Systemic Steroids**
- Diagnosis based on hyperglycaemia that persists for >48 hours
- Hyperglycaemia is defined as:
  1. Fasting plasma glucose ≥ 7.0 mmol/L
  2. 2 hour postprandial glucose ≥ 11.1 mmol/L
- If measured by CBG, should be confirmed by laboratory measurement

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**Healthy Outpatients**
- OGTT of choice
- Diagnosis based on
  1. Fasting plasma glucose ≥ 7.0 mmol/L
  2. 2 hour OGTT glucose ≥ 11.1 mmol/L
  3. HbA1c ≥ 6.5%
  4. Random glucose ≥ 11.1 mmol/L plus polyuria, polydipsia
- All but no.4 should be repeated

**Pregnancy**
- Diagnosis based on 75g fasting OGTT if any of the following plasma glucose levels are present:
  1. Fasting ≥ 5.1 mmol/L
  2. 1 hour ≥ 10.0 mmol/L
  3. 2 hour ≥ 8.5 mmol/L
It has been pointed out that fasting blood glucose cannot always be relied upon as patients may not be sufficiently fasted. (Lanng et al., 1991) Other workers, although agreeing that the OGTT is the gold standard test, have commented on its demands on patients and clinic staff (Dodge and Morrison, 1992; Yung et al., 1999) and suggested a more selective approach. The demands on patients include having to fast for at least 8 hours overnight before the test, which for many will involve a long journey to the CF centre. Patients often report that the Polycal drink is unpleasant, and that it is difficult having to wait a further 2 hours before they can eat or drink anything else. CF staff may find the process of OGTT demanding on time and resources and patients and team alike can get exasperated when venepuncture is difficult.

2.9 Management
Principles of management of abnormal glycaemic control in CF are to achieve and maintain optimal clinical status and control hyperglycaemia to reduce the likelihood of complications but avoid hypoglycaemia. (Moran et al., 1999; Yung and Hodson, 1999; Wilson et al., 2000; CFTrust, 2004)

General recommendations of a non-CF diabetic diet include reducing fat intake, increasing fibre, limiting sugar and sugary foods and reducing salt intake to 6 grams per day or less. (Bantle et al., 2008) The recommended dietary management of CFRD contradicts that of non-CF diabetes mellitus in all these areas. Conflicting dietary advice should always be resolved in favour of a typical CF diet rather than a diabetic diet. In general, hardly any foods are restricted in the CFRD diet. Energy intake is usually 120% to 150% of the daily energy requirements, with 40% of the total energy being derived from fat and 45% to 50%
from carbohydrate. A high fat diet has been advocated in CF since Corey et al in Toronto found this to be associated with significantly greater survival than a diet low in fat. (Corey et al., 1988) Dietary fibre is only advised in those with a more than adequate nutritional status. Protein and salt are not restricted. Snacking is encouraged. At present, the only suggested dietary restrictions in CFRD are high sugar drinks, unless accompanying a meal, and glucose polymer products. (Mackie et al., 2003) Current emerging opinion emphasises a tailored management plan for each individual with CFRD, as an increasing proportion of patients are actually overweight and unrestricted intake may be contraindicated. (Morton, 2008) Specialist CF dieticians have close input with each patient, working alongside specialist diabetes nurses and diabetologists.

In CFRD, insulin is the mainstay of treatment. Insulin requirements can fluctuate over a short period of time due to disease severity and other therapies, such that some people may only require insulin intermittently during infective exacerbations or with oral corticosteroid therapy. The treatment profile needs to be tailored to the specific requirements, dietary intake, eating habits and therapeutic goals for each patient and there must be flexibility in the regime. Since CFRD patients have some basal insulin, some subjects only require short acting insulin to cover meals, snacks or overnight feed. Prospective research by Rafii et al investigated protein metabolism in CF, finding that subjects with newly diagnosed CFRD had the highest protein breakdown rates. (Rafii et al., 2005) They concluded that the optimal wellbeing of patients with CFRD involves ensuring that their protein metabolism is fully corrected, which appears to require exogenous insulin. (Rafii et al., 2005)

Oral hypoglycaemics are not drugs of choice in CFRD as they tend to treat insulin resistance, or have a prohibitive side effect profile, whereas treating the insulin deficiency
with exogenous insulin results in desirable anabolic effects. Metformin is contraindicated
because of the risk of lactic acidosis in the presence of hypoxia, though in practice this is
rare. Recently a Dutch group reported their positive experience of giving metformin in
addition to insulin in two adults with CFRD. (vandenBerg, 2009) Gastrointestinal side
effects of oral hypoglycaemic agents often preclude their use in CF, where they are
difficult to tolerate due to pre-existing chronic constipation and slow gut transit. There is
some evidence that sulphonylureas may inhibit and bind to CFTR (Sheppard and Welsh,
1992) Oral hypoglycaemic therapy may have a role where insulin therapy is not practical,
for example, in individuals with needle phobia.

2.10 Complications

In the past, it was erroneously thought that microvascular complications did not occur in
CFRD, but as longevity improved their presence was unmasked. (Lanng et al., 1994a)
There is plentiful evidence documenting the incidence of nephropathy, retinopathy and
neuropathy in individuals with CFRD, (Lanng et al., 1994a; Moran et al., 1999; Yung and
Hodson, 1999) though they tend not to be recognised until the CFRD has been present for
at least 5 years. A recent prospective case matched study examined 79 individuals with
CFRD and compared diabetic complications with individuals with T1DM. (vandenBerg et
al., 2008) The rate of complications was similar, with less retinopathy and more
microalbuminuria in those with CFRD than T1DM, possibly owing to other CF related
pathology. (vandenBerg et al., 2008) One UK group recommends annual screening for
retinopathy in CFRD exceeding ten years duration. (Yung et al., 1999) The current UK
guidelines recommend annual screening for diabetic complications. (CFTrust, 2004)
There is growing interest in non-CF diabetes in the role of the degree of variation in glucose levels contributing to the development of diabetic complications. (Sharp and Rainbow, 2002) This may explain why individuals with apparently similar glycaemia by HbA1c do not develop complications at the same rate and it may be valuable to explore this in the CF population.

Macrovascular complications of CFRD have not yet been reported, but may become apparent as survival further increases. Patients with exocrine pancreatic insufficient status appear to have lower lipid levels (than those with exocrine pancreatic sufficiency) which may offer a protective effect. (Figueroa et al., 2002; Schwarzenberg et al., 2007)

2.11 CFRD in the future

There is still much to learn regarding the best methods of diagnosing and managing diabetes in CF. The concept of a spectrum of glycaemic control along which a patient moves according to their clinical status at the time, rather than fitting into fixed criteria of normal, impaired or diabetic glucose tolerance is crucial to furthering our understanding. Much work is published on evaluating glycaemic control, including continual glucose monitoring, which is discussed in detail in the next chapter.
Chapter 3

METHODS OF ASSESSING GLYCAEMIA IN CYSTIC FIBROSIS

The optimal way of diagnosing CFRD remains unclear, with various methods being employed (capillary blood glucose (CBG), fasting and random plasma glucose, OGTT, glycosylated haemoglobin), and poor uptake of the gold standard recommendations. (Mohan et al., 2008) A great body of evidence supports the existence of a pre-diabetic decline in nutritional and pulmonary status, resulting from insulin deficiency. Neither individuals with CFRD nor those in the pre-diabetic state are easily recognised with current methods of assessment.

3.1 Diabetes Diagnostic Thresholds and Control Criteria in Non-CF Populations

The American Diabetes Association (ADA) publish their own diagnostic criteria for the diagnosis of DM (ADA, 2001) and there is much agreement with WHO recommendations, though the ADA prioritises fasting plasma glucose estimation over the two hour OGTT value because of greater acceptability and lower cost.

There are non-CF population recommendations for HbA1c targets, to achieve optimal diabetic control and reduce the risk of diabetic complications, carefully balanced against the risk of hypoglycaemic events. The US Diabetes Control and Complications Trial research group recommend intensive treatment to aim to achieve ‘normoglycaemia’ (HbA1c 6.05%) wherever safely possible. (DCCT, 1996) Subsequently the ADA have recommended a more modest target of HbA1c less than 7.0%. (ADA, 2001) No such HbA1c target is currently recommended in CFRD in the US, though quarterly checks are
advised. (Moran et al., 1999) UK guidelines recommend HbA1c is checked at annual review and give an example of one adult centre’s target of < 7.0% for optimal control. (CFTrust, 2004)

3.2 CF Consensus Guidelines

In 1999 a consensus conference report for the diagnosis, screening and management of CFRD was published. (Moran et al., 1999) These guidelines have recently been updated, as previously mentioned. (Moran et al., 2010) The 1999 document highlighted that the WHO criteria were defined by populations at high risk for T2DM, with high prevalence of obesity, hypertension and dyslipidaemia. (Moran et al., 1999) People with CF having the same degree of IGT or DGT cannot be assumed to have similar co-morbidities and indeed the implications of abnormal glucose tolerance on clinical status and respiratory function in CF is likely to differ from that in non-CF DM.

Despite these issues, the US CF Diabetes Working Group largely accepts non-CF diagnostic criteria. (Moran et al., 2010) To screen for the presence of new CFRD in healthy outpatients, the group recommend the OGTT as the best available screening test. (Moran et al., 2010)

The UK CF Trust Diabetes Working Group recommend that routine annual OGTT should be carried out for all patients over 12 years old. (CFTrust, 2004) Their report reminds us that an abnormal OGTT simply reflects abnormal glucose handling at the time and should be followed by a period of home CBG monitoring. (CFTrust, 2004)
3.3 The Oral Glucose Tolerance Test in Cystic Fibrosis

Lanng’s group in Denmark performed one of the first large cross sectional studies of glucose intolerance in CF, using the OGTT in an entire clinic population of over 200 adults and children. (Lanng et al., 1991) The authors indicated that in previous research, varying diagnostic criteria for glucose intolerance and DM were used, study numbers were often small and individuals were highly selected. (Lanng et al., 1991) 210 children over the age of two years and adults underwent the OGTT, HbA1c estimation and clinical assessment. The authors concluded that the OGTT was reliable in detecting diabetes in patients with CF (whereas symptoms, testing for glycosuria, fasting plasma glucose and HbA1c were not) and proposed OGTT to be carried out on an annual basis. It should be made clear that this OGTT was a standard 2 hr test, but cut-off points for normal, impaired and diabetic glucose tolerance were higher than our current threshold levels.

They planned further work to identify the most appropriate age at which to commence this screening. (Lanng et al., 1991) At this point, the higher prevalence of DM in CF compared with the non-CF population was acknowledged, but it was not yet regarded as distinct from T1DM and T2DM. As stated earlier, one limitation of this study is that it is unclear whether any further measures were taken to confirm CFRD clinically, following a diabetic OGTT.

By 1995, this group had completed a 5 year prospective study, during which 191 children and adults with CF had 5 consecutive annual OGTT, with clinical assessment and measures of fasting glucose and glycosylated haemoglobin. (Lanng et al., 1995) Selection bias is inevitable, with this research confirming that of all these means of assessing glycaemia, only OGTT is reliable to identify DM. Since the diagnostic criteria for DM
depend on OGTT this is not surprising. It is noteworthy though, that few of those with DGT had elevated HbA1c, fasting plasma glucose or symptoms of hyperglycaemia. Only two children under the age of 10 years had DM, both of whom were diabetic at the start of the study and had HLA types DR3/4 and DR4, suggesting possible coincidental T1DM and CF. The authors therefore suggested that OGTT be performed routinely in those with CF over the age of 10 years. (Lanng et al., 1995) This longitudinal study had the potential for strong data but though the group showed glucose tolerance decreasing gradually over time, they did not provide thorough data on patients whose results improved on repeat testing. It is unclear whether unwell patients with chest exacerbations or weight loss at the time of testing were excluded, leaving the possibility of some subjects having an abnormal OGTT which may have subsequently improved. It is notable that by the end of the study, 46 patients were considered diabetic though only 34 were receiving insulin. Adequate reasons were given for only half of those not on insulin.

A further negative aspect of Lanng’s work is that some asymptomatic subjects could be considered to have DM on the basis of an OGTT result in the diabetic range, confirmed on repeat testing but with no further blood glucose monitoring carried out. This raises the possibility of ‘over-diagnosing’ CFRD. The UK CF Trust guidelines aim to eliminate this, by stressing the importance of serial home glucose monitoring following an abnormal OGTT result. (CFTrust, 2004)

Solomon et al prospectively examined 94 paediatric and adolescent patients (ages 10 years to 18 years) with CF and no prior diagnosis of CFRD. (Solomon et al., 2003) Their aim was to compare clinically recognised CFRD with prospective OGTT analysis. Although the study population was highly selected (those on oral corticosteroids, those within one
month of oral antibiotic treatment, those with pulmonary exacerbations and pregnant patients were excluded), a surprising 20% of the participants had abnormal OGTT, but none of these were found to have hyperglycaemic symptoms, raised fasting blood glucose or glycosuria. (Solomon et al., 2003) Despite some elevated HbA1c levels in these patients with abnormal glucose tolerance, the apparent conclusion, supporting Lanng’s earlier work but specifically focussing on children and adolescents with CF, was that no other form of assessment of glycaemia other than OGTT could be relied upon to indicate glucose tolerance abnormalities. (Solomon et al., 2003) The authors’ suggestions were consistent with Lanng’s; OGTT should be performed in CF patients aged over 10 years as part of routine clinical practice, stressing that testing should be done during clinical stability. (Solomon et al., 2003)

The OGTT may be described as inconvenient and time consuming for patients and CF staff. One paper goes further, suggesting that the need to perform this test may result in missed appointments. (Yung et al., 1999) This team sought an alternative approach to screening all clinic patients by prospectively evaluating various methods of assessing glycaemia in 91 clinically stable people with CF. 12 patients were newly recognised as having DGT on OGTT. 11 of these would have been identified by having one or more of: random blood glucose >11.0 mmol/L, HbA1c >6.1%, hyperglycaemic symptoms, unexplained weight loss. When these criteria were applied to the whole study population, only 28 satisfying them would have had to undergo OGTT in order to identify 11 of 12 with DGT. This at first may seem strong evidence against annual OGTT screening for all, but there are several further considerations. It is not clear that individuals at higher risk of developing CFRD due to having IGT, would be identified by this select approach. A further flaw is that individuals symptomatic of hyperglycaemia or with weight loss were
considered to be in the ‘clinically stable’ group. Furthermore, over 10 years after this study, larger scale work to validate these findings has not been done.

A Toronto team, also searching for an acceptable alternative to the gold standard OGTT, compared it with a simplified one hour Glucose Challenge Test (GCT) which has not been validated in CF. (Lee et al., 2007) They anticipated greater participation and compliance with the simpler test; it requires subjects to ingest a 50g glucose load, with plasma glucose levels taken immediately before and one hour afterwards, but individuals do not need to attend fasted. A positive GCT was determined by a 1 hour post 50g glucose load plasma glucose $\geq$ 7.8 mmol/L. 31 of 57 eligible patients with no prior history of CFRD completed both oral glucose tests. All those with hyperglycaemia on OGTT also had hyperglycaemia on GCT, while 11 out of 31 were positive only on GCT, suggesting that the gold standard OGTT underestimated glycaemia in a proportion of patients, or the GCT overestimated glycaemia (See Table 3.1). These results favour the simpler test for detecting abnormal glucose tolerance but surprisingly, the expected increase in compliance was not seen. This was not explained by the investigators.
Table 3.1 Oral glucose tolerance test and glucose challenge test characteristics with post-load glucose $\geq 7.8$ mmol/L considered to show hyperglycaemia (reproduced from Lee et al., 2007)

<table>
<thead>
<tr>
<th></th>
<th>Oral Glucose Tolerance Test</th>
<th>Oral Glucose Tolerance Test</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hyperglycaemia</td>
<td>no hyperglycaemia</td>
<td></td>
</tr>
<tr>
<td>Glucose Challenge Test</td>
<td>9</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>hyperglycaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose Challenge Test</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>No hyperglycaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>9</td>
<td>22</td>
<td>31</td>
</tr>
</tbody>
</table>

This table displays ‘gold standard’ oral glucose tolerance test results at 2 hours (hyperglycaemia if $\geq 7.8$ mmol/L) against glucose challenge test results (non-fasted 1hr post 50g glucose, hyperglycaemia if $\geq 7.8$ mmol/L) for 31 patients with CF who completed both tests.

Positive results were detected on both tests in 9/31 patients. All those with hyperglycaemia on OGTT had a positive glucose challenge, but 11 individuals had hyperglycaemia on glucose challenge testing with a negative OGTT. This suggests that the OGTT underestimates hyperglycaemia or the glucose challenge test overestimates hyperglycaemia in CF.
This group provide detail on the ‘unique glucose kinetics’ seen in CF; following a glucose challenge (50g oral glucose), peak glucose levels are reached after 55 to 83 minutes, so one hour testing could be better placed than formal OGTT to discriminate abnormal glucose excursions. (Lee et al., 2007) However, much further validation work is required to determine whether it could ultimately replace the OGTT as the current gold standard screening tool for hyperglycaemia, and whether such a test would be readily taken up by CF subjects.

There has been much interest in interim OGTT values (using the gold standard WHO test), with a new category used in US CF guidelines of ‘indeterminate glycaemia’ (any mid-OGTT glucose ≥ 11.1 mmol/L). (Moran et al., 2010) A recent paper from a North American paediatric CF centre has shown a clear association between increasing plasma glucose at 1 hour and poorer pulmonary function. (Brodsky et al., 2011) This raises further questions on the variability of such results and the most appropriate clinical steps to take next.

Several research groups have carried out studies involving OGTT with interim time point glucose levels in addition to the default baseline and 2 hour results. One such study performed OGTT with 5 time points (0 minutes, 30 minutes, 60 minutes, 90 minutes and 120 minutes) on 109 CF patients with no prior history of CFRD, and 14 matched healthy non-CF controls. (Costa et al., 2007) By conventional analysis 28% of CF subjects had IGT, 12% had CFRD and 60% of CF subjects and all non-CF controls had NGT. When the glucose area under the curve (AUC) was examined, all CF patients had an increased value compared to controls. Furthermore, increased glucose AUC was associated with a decreased pulmonary function but conventional glucose tolerance categories were not.
Results showed that over time, with increasing glucose intolerance, there is first a decrease in insulin secretion, then a decrease in sensitivity, before a progression of both. Though the authors recommend performing a 5 time point OGTT, in clinical practice this generates a high workload for CF staff and laboratory colleagues. Patients without an indwelling venous access device may be reluctant to have cannulation or repeated venous sampling. The group’s findings imply that standard OGTT may not be the most accurate means for detecting abnormal glucose tolerance in CF, particularly for the identification of early glucose intolerance, which may still exert an important negative clinical effect. (Costa et al., 2007)

This is supportive of earlier work, on a smaller scale by Dobson et al. (Dobson et al., 2002) This team identified 4 young adults with CF who had normal OGTT and HbA1c results, despite deteriorating lung function and weight loss. Although they did not satisfy clinical diagnosis of CFRD, they were given modest doses of insulin therapy and all demonstrated clinical improvement over a period of 3 months. The researchers therefore proposed that clinically significant insulin deficiency can occur before CFRD (as defined by OGTT) develops. (Dobson et al., 2002). This has recently been reported in an Australian study involving children and adolescents with CF. (Hameed et al., 2010) Larger studies are needed to confirm these small scale findings. In a separate study this group performed a 5 time point OGTT in CF patients and 21 non-CF healthy controls. Although there was no difference in fasting or 2 hour glucose between the two groups, there were significantly elevated interim glucose values in those with CF, along with an increased glucose AUC, similar findings to Yung et al, mentioned in Chapter 2, though their group measured glucose more frequently. (Yung et al., 2002; Dobson et al., 2004) The clinical status of the recruited CF patients is not reported and the study involves small numbers of subjects.
Improvements and alternatives to the OGTT continue to be sought. There is a need for further work following that of Yung *et al.* (Yung et al., 2002) evaluating frequent glucose and insulin levels during the OGTT to provide more insight into the relationship between insulin deficiency and glucose intolerance.

**3.4 Glycosylated haemoglobin in non-CF and CF populations**

As previously mentioned, glycosylated haemoglobin measurements are used to monitor glycaemic control in non-CF DM and are linked to risk of developing microvascular complications. (ADA, 2001; DCCT, 1996) Work has been done evaluating the potential of HbA1c as a screening tool for the diagnosis of non-CF DM but its usefulness is limited by considerable inter-individual variation in those with apparently similar levels of glycaemia. (Kilpatrick et al., 1998) Another factor is that changes in haemoglobin levels, caused for example by iron deficiency anaemia or iron replacement, could affect HbA1c. (Brennan et al., 2006) Glycosylated haemoglobin has also been found to be reduced in the setting of increased erythrocyte turnover. Some authors report that red blood cell survival and rate of glycation contribute significantly more to HbA1c result than ambient blood glucose levels. (Kilpatrick et al., 1998)

Numerous HbA1c assays are available commercially and only in recent years have results started to be standardised. Following a period of ‘dual reporting’, since June 2011 the UK has reported HbA1c results as International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recognised standard units (mmol/L), rather than previous Diabetes Control and Complications Trial (DCCT) derived percentage result.
Researchers in non-CF DM have explored the relationship between HbA1c and mean blood glucose value using continual glucose monitoring. (Sharp and Rainbow, 2002) They found that the mean CGM glucose value over time correlates with HbA1c at the time but no other standard measure of glucose control. This may have implications for individuals with ‘changeable’ profiles, i.e. significant high and low variation, for whom HbA1c may not be a helpful marker of glycaemic control.

All these problems with HbA1c are relevant to the CF population and, in particular, iron deficiency anaemia is common and erythrocyte turnover is believed to be increased secondary to chronic inflammation. The assay is not recommended in screening for CFRD or IGT as there is considerable ‘overlap’, with those with abnormal glucose tolerance having normal HbA1c and those with NGT having abnormal HbA1c, although new US guidelines incorporate HbA1c ≥ 6.5% as diagnostic of CFRD. (Moran et al., 2010) It is not yet established whether HbA1c targets recommended for T1DM and T2DM will result in a similar reduced risk of microvascular complications in CFRD.

3.5 Continual Glucose Monitoring in Cystic Fibrosis

Continual interstitial glucose monitoring has been developed for use in T1DM and T2DM, due to a demand for intensive blood glucose monitoring, in order to optimise therapy and achieve as near ‘normoglycaemia’ as possible. A certain level of understanding, practical ability and motivation are required to carry out adequate CBG (‘finger prick’) monitoring but even the most fastidious individuals can miss high and low glucose trends, particularly during the night. (Gross and Mastrototaro, 2000) Boland et al noted that children and adolescents with T1DM tend not to check postprandial or nocturnal glucose values,
outlining a definite role for continual glucose monitoring in these groups. (Boland et al., 2001)

CGM devices use a disposable subcutaneous sensor; a platinum electrode incorporating glucose oxidase to convert interstitial (extracellular) glucose into an electrical current. (Gross and Mastrototaro, 2000) The sensor has an external electrical contact connected to a portable monitor. A sensor reading is taken every ten seconds and an average value determined every five minutes, leading to 288 values being recorded every 24 hours. (See Figure 3.1 for an example of the resulting CGM trace).
Figure 3.1 Example of 24 hours of a continual glucose monitoring trace.

Glucose in mmol/L is shown on the y axis and time of day is on the x axis. The red line shows the continual glucose levels and the blue crosses depict the capillary blood glucose levels taken by the wearer.
Periodic CBG results are required to calibrate the device data retrospectively. (Gross and Mastrototaro, 2000) The physiological relationship between interstitial (extracellular) and blood glucose is not fully understood, but it is generally accepted that glucose diffuses from the capillaries into the interstitial space, introducing this physiological ‘lag time’. Interstitial glucose dynamics vary, dependent on the rate and direction of change of blood glucose. Other variables are features of the sensor site i.e. its vascularity, presence of adipose or scar tissue and insulin availability and sensitivity. Continual glucose monitor manufacturers attempt to address some of these issues. They advise siting sensors away from scar tissue or insulin injection sites. The interstitial glucose values recorded by the device are ‘shifted backwards’ to estimate blood glucose, applying a fixed correction for diffusion time.

Any inaccuracy in CBG values will be reflected in interstitial sensor values, since they are used for retrospective calibration of stored sensor readings. The ADA recommend that CBG results should be accurate to within 10% of laboratory blood sample reference values (ADA, 1987; ADA, 1994) though in real life circumstances only around 60% of meters achieve results in this range. (Poirier et al., 1998) The International Society for Pediatric and Adolescent Diabetes (ISPAD) have slightly different criteria for accuracy, namely 95% of CBGs reading within 20% of corresponding plasma glucose levels. (Rewers et al., 2009)

CGM values are only deemed accurate up to 22.2 mmol/L and any values above this will not be shown in downloaded data. Sensor values are not visible to the wearer, but stored in the monitor. Older devices require a cable connecting the sensor and monitor but models
developed more recently are wireless (see Figure 3.2 below). Sensors have a lifetime of at least 72 hours.
Figure 3.2 The ‘iPro’ wireless continual glucose monitoring sensor and recording device (actual width 30mm) (reproduced with permission from Medtronic, USA)

This figure depicts the wireless ‘iPro’ continual glucose monitoring device from Medtronic. The larger white part of the device houses the data storage unit and clips on to the smaller clear plastic part, which contains the distal portion of the sensor. The proximal part of the sensor (not shown on this picture) is inserted subcutaneously.
Following initial research into accuracy and reliability of the devices in healthy volunteers, several trials were conducted in non-CF DM (mainly adults with T1DM) in clinical and home settings.

The CGM was found to provide previously unattainable detail about excursions, and nocturnal hypoglycaemia and was recommended as a useful supplement to home CBG checks as part of multidisciplinary care. (Gross and Mastrototaro, 2000) It was found to be safe when used without direct supervision. Positive feedback from patients was reported. The CGM was thought to be of particular value in establishing patterns of glucose control during normal activities and helping patients understand their glycaemic control. (Gross and Mastrototaro, 2000)

There were few adverse events, comprising simply mild local skin reactions at the sensor insertion site. In subsequent studies, sensor failure (sensor not functioning at some point following insertion) has been reported in 28% (Sachedina and Pickup, 2003) and 18% (Metzger et al., 2002) of CGM readings. It should be stressed that the CGM is intended to determine glycaemic ‘trends’ rather than absolute glucose values, since its accuracy is quoted as CGM glucose value having a mean absolute deviation from CBG of approximately 14% to 19% (Bode et al., 1999; Gross et al., 2000; Sachedina and Pickup, 2003) (See Table 3.2 for a summary of reported accuracy of CGM devices). These differences may seem alarming in magnitude but may not result in a change of clinical decision for higher blood glucose values. Higher accuracy would be more desirable at lower glucose levels because of the clinical importance of hypoglycaemia.
<table>
<thead>
<tr>
<th>Study population</th>
<th>Number of subjects</th>
<th>Reported accuracy of CGM compared to reference standard</th>
<th>Reference standard used</th>
<th>Article reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1DM</td>
<td>9</td>
<td>Mean absolute difference (%) 19.1 ± 9.0</td>
<td>CBG values used in calibration</td>
<td>Bode et al., 1999</td>
</tr>
<tr>
<td>T1DM &amp; T2DM</td>
<td>62</td>
<td>Mean absolute difference (%) 0.3 ± 32.4</td>
<td>CBG values used in calibration</td>
<td>Gross and Mastrototaro, 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean absolute difference (mmol/L) 0.3 ± 2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1DM</td>
<td>135</td>
<td>Mean absolute difference (%) 18.0 ± 19.8</td>
<td>CBG values used in calibration</td>
<td>Gross et al., 2000</td>
</tr>
<tr>
<td>T1DM</td>
<td>18</td>
<td>Mean bias (%) * 14.0</td>
<td>CBG values independent of calibration</td>
<td>Sachedina and Pickup, 2003</td>
</tr>
<tr>
<td>CF Non-CF controls</td>
<td>14, 15</td>
<td>Mean absolute difference (%) 24.9 ± 21.0 28.8 ± 22.9</td>
<td>0 hour and 2 hour OGGT plasma glucose</td>
<td>Dobson et al., 2003</td>
</tr>
<tr>
<td>CF</td>
<td>102</td>
<td>Mean bias (mmol/L) * 0.81 ± 2.90</td>
<td>0 hour and 2 hour OGGT plasma glucose</td>
<td>O'Riordan et al., 2009</td>
</tr>
</tbody>
</table>

Reported accuracy is shown as mean ± standard deviation, where standard deviation is given in the literature.

* Mean bias is from limits of agreement analyses, representing the mean difference between continual glucose monitoring sensor values to paired reference standard glucose values.
It is questionable whether comparing CGM sensor glucose values with CBG levels is valid, since they are not independent – the sensor value is derived from the CBG values using company software following data download from the CGM devices.

An Israeli group re-analysed the CGM manufacturers raw data by Bland-Altman plot (Bland and Altman, 1986), (whereby the difference between pairs of measurements by different methods is plotted against the averages, and 95% limits are drawn within which most differences lie). They compared limits of agreement between sensor glucose values and capillary blood glucose values. (Metzger et al., 2002) The 95% limits of agreement were +/- 3.2 mmol/L for each CGM glucose value, compared to the concurrent CBG. (Gross and Mastrototaro, 2000)

Soon after CGM devices were available commercially, research teams proceeded to investigate their role in the T1DM and T2DM population. Boland et al investigated whether the CGM had a place in optimising the management of children with T1DM. (Boland et al., 2001) The 56 subjects recruited were mostly on treatment with insulin pumps and had satisfactory HbA1c levels and pre-meal glucose values close to the target range. Despite these parameters suggestive of good control, three day CGM studies revealed high postprandial glucose levels without symptoms in most of the patients. The authors pointed out that caution is needed when interpreting low glucose levels recorded by CGM, as they may be less accurate and further work in this area is warranted. However, the post-meal peaks were of particular importance, since evidence was emerging that such fluctuations had a role in the development of diabetic complications. (Ceriello, 2000)
The same team found that the mean of the 12 CBG values taken by each individual was very similar to their mean CGM value and that therefore ‘finger prick’ values could provide a surprisingly accurate impression of overall glycaemia. (Boland et al., 2001) They were able to note, however, that in their study population, high postprandial glucose levels were being offset by low nocturnal glucose values and that there was more to good diabetic control than lowering HbA1c and having good pre-prandial glucose checks. It must be remembered that the studied population here were non-CF and highly selected. Though the conclusions drawn are of interest, they may not be immediately applicable to children or adults with CF.

A study similar in design was carried out by Salardi et al on 28 children and young adults with T1DM. (Salardi et al., 2002) In contrast, their cohort of patients had recognised poor control, reflected by elevated HbA1c results or a history of frequent hypoglycaemic events. The CGM traces revealed a high frequency of asymptomatic nocturnal hypoglycaemia and prolonged hypoglycaemic episodes. Postprandial peaks were not seen, as with Boland’s work, but this study population did not have generally good diabetic control, so did not necessarily have a healthy baseline glucose level from which clear excursions would be appreciated. The CGM glucose area under the curve (AUC), but not postprandial glucose values, positively correlated with HbA1c. It was found that patient’s HbA1c results could be significantly improved up to six months after completing the CGM. (Salardi et al., 2002) The authors concluded that in order to improve glycaemic control, it was necessary to lower the glucose AUC, rather than just postprandial glucose levels. (Salardi et al., 2002)
Despite the acknowledged increasing importance of CFRD, the CGM device is yet to be robustly validated for adults with CF. Some early work was carried out by Dobson et al, who proposed that the reliability of CGM devices in CF may be affected by different tissue composition and dynamics. (Dobson et al., 2003) The team inserted the CGM in 21 non-diabetic CF patients and 21 age matched non-CF controls. A five time point OGTT was performed and the CGM devices left to record for a further 48 hours. Approximately two thirds of those recruited returned 24 hours of acceptable data, though it is not clear whether this was due to sensor or user error. The correlation coefficients between CGM values and CBG values (and CGM and laboratory plasma glucose values) were similar in CF subjects and non-CF subjects. One would expect correlation coefficients to be reasonably high when comparing two measurement methods for the same variable. This analysis does not measure the degree of agreement, which is required when assessing accuracy. Also, repeatability and reproducibility are not explored. The CGM device was well tolerated by those with CF. (Dobson et al., 2003)

Following on from this preliminary report, the same group published a more detailed analysis on the same study data. (Dobson et al., 2004) HbA1c had also been recorded during the investigation. For CF participants and controls with normal glucose tolerance by WHO OGTT criteria, the CF subjects had a higher mean CGM glucose value and more CGM glucose excursions above 11.1mmol/L (which mostly occurred outside of the OGTT). This was despite there being no difference in demographics, HbA1c, fasting plasma glucose or two hour plasma glucose between the two groups. Dobson et al concluded that conventional methods (HbA1c, and 0 hour and two hour time point OGTT values) underestimate glycaemia in CF. This adds weight to the argument that OGTT may not reflect ‘real life’ glucose control in CF, where the potential value of CGM lies. CGM
also has the advantage of being portable and being able to be performed at home. The authors did comment on the drawbacks of interstitial glucose monitoring, relating to high cost, practical issues and greater value in assessing glucose trends rather than individual glucose readings. (Dobson et al., 2004) Only 10 of 21 subjects were reported to have had concurrent CGM and OGTT though the full reasons for this are not given.

Jeffries et al later carried out a comparison of OGTT and CGM on a specific ‘high risk’ (declining clinical status, supplemental feeds and any previous blood glucose reading > 7.0 mmol/L) adolescent population of nineteen individuals with CF. (Jefferies et al., 2005) They reported seven new cases of CFRD and six with IGT defined by OGTT, the remainder having NGT. CGM traces were examined and interpreted as diabetic, impaired or normal by finding the highest excursion value during OGTT and grouping into conventional diagnostic ranges. By CGM, the same seven individuals with newly diagnosed CFRD were recognised. One other participant was categorised as NGT by OGTT but diabetic by CGM excursion although their OGTT was technically compromised due to vomiting. There were other disagreements in categorisation for those with normal and impaired glucose tolerance. Mean CGM glucose levels were said to correlate with HbA1c values but detail was not provided. Glucose AUC and relation to conventional glucose tolerance category by OGTT was not explored. Nonetheless the authors concluded that CGM was a useful tool for detecting hyperglycaemia in patients with CF and a potential tool to improve the detection of CFRD. (Jefferies et al., 2005) In this study the OGTT and CGM (although performed just days apart) were not concurrent. Again the accuracy, repeatability and reproducibility are not explored.
One of the most robust studies of CGM in CF, from Ireland, recently published, validates continuous glucose monitoring in children and adolescents with CF. (O'Riordan et al., 2009) Over 100 patients underwent CGM and concurrent OGTT. After at least 12 months, recruited subjects underwent repeat CGM. The authors do not state inclusion and exclusion criteria or the number of patients found to be in each glucose tolerance category. Control subjects also underwent CGM though it is not clear how many and whether they were matched to CF participants. Mean CGM glucose level (with SD) was calculated for all subgroups of glucose tolerance and was found to be statistically significantly higher than controls, even for those with NGT. They examined reliability, reproducibility and repeatability in depth, commenting on the need to look further than correlation between CGM and OGTT values. Firstly, a Bland Altman analysis of agreement between the two methods is performed showing 95% of CGM values within +/- 2.9 mmol/L of OGTT values, deemed to be ‘reasonably acceptable bias for clinical practice’. This is the first study in CF to examine coefficients of variation of CGM values, finding no significant change between the first and second CGM in CF individuals in all glucose categories. This is somewhat surprising as glycaemic control in an individual might be expected to change over a 12 month time period, particularly in adolescents, who may exhibit greater insulin resistance than other age groups.

Continual glucose monitoring has been reported, in a multicentre clinical trial, to be associated with improved glycaemic control in some adults with T1DM. (Tamborlane et al., 2008) Another group recently reported benefit from continual glucose monitoring in pregnancy in gestational diabetes (Murphy et al., 2008), though neither group directly addresses reliability or accuracy of the device. To perform similarly powered research in a CF population would require huge numbers of centres to be involved. The major area of
interest concerning the CGM in CF is in its place in screening for early abnormal glucose control and whether it has the potential to be more accurate than, and ultimately replace, the OGTT, our current gold standard.

One novel application of CGM in CF has been described by Brennan et al, who used the device in 10 CF patients and 10 healthy controls to determine the percentage of time each had a blood glucose above 8.0 mmol/L. (Brennan et al., 2007) A substantial amount of time over this threshold implied a persistently elevated airway glucose level with potential to impact on microbial growth. (Brennan et al., 2007)

The continual glucose monitoring method may help us better identify individuals with CF who are entering the state of insulin deficiency and pre-diabetic decline as they may be expected to show more variability in glucose levels than healthier individuals. Those identified could be treated early with exogenous insulin and monitored closely to avoid further deterioration and improve their clinical status. Recently Hameed et al published a prospective study in children and adolescents with CF, where continual glucose monitoring was used to identify clinically relevant abnormal glycaemia. (Hameed et al., 2010) In a platform presentation at the North American CF Conference in October 2010 S. Hameed reported that their group are now carrying out a prospective interventional trial of early insulin treatment aiming to prevent pre-diabetic decline in their patients.

It may be that continual glucose monitoring has the potential not only to improve outcome in CFRD but to delay the time at which CF patients become diabetic (if it could indicate where insulin could be introduced as an intervention for early abnormal glycaemic
control), thereby improving the survival and clinical wellbeing of the CF population as a whole.

In summary, CGM has the advantages of being a portable method of revealing ‘real life’ glucose handling, and could also be used in situations where glucose tolerance may be altered, such as during infective exacerbations. The best means of diagnosing CFRD or the prediabetic state is unclear, but the current UK gold standard of OGTT with or without home CBG testing has many disadvantages. CGM has the potential to meet the current needs of our CF population and should therefore be fully validated and studied.
Chapter 4

AIMS AND OBJECTIVES

There are a number of gaps in the evidence for how best to evaluate glycaemic control in cystic fibrosis. I undertook a number of studies to address the following research questions.

4.1 Is continual glucose monitoring (CGM) valid in adults with CF?

Current published validation studies of CGM in CF lack robust work in adults, with sufficient numbers to assess the accuracy of the devices. I aimed to recruit sufficient participants to perform a ‘limits of agreement’ analysis between CGM and the gold standard OGTT plasma glucose results for validation, which has not to date been reported in an adult CF population. When CGM has been investigated in adults with CF, the study population has often been highly selected, whereas I aimed to investigate glycaemia across the whole range of patients seen in our clinic. This study is detailed in Chapter 6: ‘Validation of continual glucose monitoring in adults with CF’.

4.2 Is the oral glucose tolerance test (OGTT) a relevant and adequate measure of glycaemia in CF, and could CGM offer a superior alternative?

The OGTT categorises individuals as having normal, impaired or diabetic glucose tolerance. World Health Organisation (WHO) threshold values for these groups are derived from studies of patient populations at high risk for type 2 diabetes mellitus and relate to their risk of developing future diabetic complications. (WHO, 2006) These threshold values may not be clinically important for people with CF. I wished to address the need for more relevant criteria with which to classify glycaemic control in individuals with CF.
Existing work comparing OGTT and CGM has not always involved the patients having these tests simultaneously, for a true comparison of measuring glycaemic control. Also previous work investigating the OGTT in CF, does not always report the clinical status of patients at the time of testing. I aimed to investigate the relationship of glycaemia during OGTT to ‘real life’ glycaemia over 72 hours in stable patients with CF. I sought to evaluate concurrently performed OGTT and CGM in CF patients. This work is reported in Chapter 7: ‘Comparison of the OGTT and CGM in assessment of glycaemic control’.

4.3 Could CGM be used to detect early abnormal glycaemic control?

In order to identify early abnormal glycaemic control, ‘normal’ glycaemia needs to be defined. Few studies have compared CGM in CF with that in healthy normal controls. I aimed to gather data from healthy subjects without CF to define normal glycaemic control. I then sought to establish criteria with which to define abnormal glycaemic control in adults with CF.

I aimed to compare glycaemic control (measured using CGM) in people with CF to healthy non-CF controls, with particular focus on those with CF who have ‘normal glucose tolerance’ by OGTT. This is addressed in Chapter 8: ‘Using continual glucose monitoring to detect early abnormal glycaemic control in adults with cystic fibrosis’.

4.4 What are patients’ experiences of continual glucose monitoring?

There are no published data on the acceptability of CGM for people with CF, which would be necessary if CGM were to be recommended as a superior means of assessing glycaemia compared to OGTT. I aimed to address this by inviting all recruited patients to complete an anonymous questionnaire after the clinical study. I based the questionnaire domains and
ratings on similar published work involving individuals with type 1 and type 2 diabetes (Newman et al., 2009). This work is reported in Chapter 9: ‘Patient experience of continual glucose monitoring’.
Chapter 5

METHODS

5.1 Study characteristics

I carried out a single centre prospective observational pilot study to investigate the assessment of glycaemic control in adults with cystic fibrosis.

5.2 Inclusion and exclusion criteria

Patients aged 18 years and over with CF attending the Manchester Adult Cystic Fibrosis Centre (MACFC) were invited to enter the study. Patient participants had a diagnosis of CF, based on either genotype and/or phenotypic presentation. No patients were excluded according to previous recorded glucose tolerance and patients with established CF related diabetes were included in the study.

Pregnant female patients and subjects who were unable to give informed consent were not eligible for participation.

Healthy non-CF controls were over 18 years and up to 40 years old, without any known diabetes, not pregnant, and not on any medication known to affect glycaemic control.
5.3 Consent

All subjects gave written informed consent to the study procedure, their records to be used for research purposes and their general practitioners being informed about their participation.

5.4 Ethical approval

The study (NRES ref: 08/H1016/43) was approved by the North West Research Ethics Committee no.10 (formerly ‘Lancashire and Cumbria B’), including later substantial amendments to include healthy volunteers and carry out the patient questionnaire. Wythenshawe Hospital Research & Development Department granted site-specific approval for the study.

5.5 Study procedure for CF patients and healthy non-CF controls

(see Figure 5.1)
Figure 5.1 Study procedure flow chart

All CF patients invited to enter study prior to annual assessment

Healthy controls invited to enter study

50 CF patients and 10 non-CF healthy controls had 72 hours of CGM including a 2 hour OGTT

50 CF patients invited to complete & return questionnaire (1 x reminder sent)

29 patient questionnaires returned

Clinical study data from 50 CF patients and 10 healthy non-CF controls
5.5.1 CF patients

50 Participants had a 72 hour CGM at home during a time of clinical stability. During this 72 hour period they attended for OGTT in the outpatient department. Clinical stability was defined by absence of an infective respiratory exacerbation, meeting the following criteria: (1) Only up to one of the following: increased shortness of breath, increased cough, thicker or increased volume of sputum, haemoptysis, fall in FEV\textsubscript{1} of greater than 10 percent. (2) No supplemental antibiotics (intravenous or oral), short term oral corticosteroids or change in long term oral corticosteroid dose in the preceding two weeks.

5.5.1.1 Continuous Glucose Monitoring

Set up of CGM took place either in the outpatient clinic or the patient’s home, depending on their preference. Informed written consent was obtained.

After identification of a suitable site on the abdomen, the skin was cleansed and a subcutaneous glucose sensor (Medtronic, USA) inserted, between 3 cm and 8 cm lateral to the umbilicus. This was allowed to ‘wet’ for at least 10 minutes, during which time the patient was familiarised with capillary blood glucose (CBG) checking technique, and how to complete the 72 hour food and events diary sheet.

After this time either a wireless recorder (‘iPro’, Medtronic, USA) or an older wired recorder (‘CGMS Gold’, Medtronic, USA) was connected to the sensor. For the wireless devices, a live software package (‘iPro Solutions’, Medtronic, USA) was used to ‘initialise’ the recorder and sensor. If the older devices were used (for the first 7 study patients), the recorder itself underwent a 60 minute initialisation process. A glucometer (Aviva Accuchek, Roche, UK) was synchronised with the iPro CGM device, and the same
glucometers were issued to patients who used the CGMS Gold devices. All patients used the glucometer over the 72 hours to record 4 CBG daily for calibration. CBG testing strips were quality controlled prior to use. Subjects were instructed that pre-prandial and bedtime CBG sampling times were preferred but not compulsory and that no more than 12 hours should elapse between consecutive CBG samples.

The CGM device was covered by a waterproof dressing, allowing showers and exercise but not immersion in water.

The patients were instructed to keep a written log of CBG results, food and drink consumed, any insulin, oral corticosteroid or antifungal medication taken, any exercise and any adverse events. Sensor data is stored in the recorder for subsequent download following removal, with no ‘real time’ visible reading available to the wearer. Participants were advised not to modify their usual diet or activity during the 72 hour recording period, apart from fasting overnight (at least 8 hours) prior to the OGTT.

The subjects had written instruction on how to remove the CGM device and return it with study paperwork and glucometer after the 72 hour monitoring period. Some subjects had their OGTT at the end of the 72 hour period and their recorder was removed in the clinic and collected in with their study paperwork and glucometer.

5.5.1.2 Glucose Tolerance

OGTT was scheduled for 1, 2 or 3 days after CGM placement. This degree of flexibility was required in order to keep to strict clinic microbiological cohort segregation protocols.
Subjects attended an outpatient clinic having fasted for at least 8 hours overnight and omitted any usual overnight nasogastric or gastrostomy feeding. Any long or intermediate acting insulin from the previous evening and any morning insulin was omitted.

Baseline fasting venous samples (including plasma glucose and glycosylated haemoglobin) and a capillary blood glucose were taken. The subject then had up to 5 minutes to ingest a standard oral liquid glucose load (comprising 1.75g/kg to a maximum of 75g). Participants then rested, seated for 2 hours, without any further oral intake. Repeat venous plasma glucose and CBG samples were taken 2 hours after complete ingestion of the glucose load. Participants were allowed home following the OGTT and instructed to carry on with usual daily diet and activities, including any overnight nasogastric or gastrostomy feeding.

5.5.1.3 Pulmonary Function and Nutritional Status

At the time of OGTT, subjects had their weight and height recorded and performed spirometry (*Vitalograph, UK*) according to our centre’s standard procedure. Percentage predicted FEV$_1$ and BMI are recorded for each participant. Casenotes were used to record demographic characteristics, most recent glucose tolerance status, usual medications, requirement for supplementary nutrition, pancreatic enzymes and disease complications.

5.5.2 Healthy control subjects

10 healthy non-CF control subjects were recruited to undergo simultaneous CGM and OGTT. Set up of CGM was exactly the same as for adults with CF. Control subjects had
height and weight recorded but did not perform spirometry. During OGTT, the only additional blood sample taken at baseline was HbA1c.

5.6 Statistical Analysis

5.6.1 Software
Excel Microsoft Office 2003 (*Microsoft, USA*) was used to collate raw data and SPSS (version 15.0, *Microsoft, USA*) was used for statistical analysis of the raw data. ‘Solutions’, the software used to download the CGM recording devices, combined the stored sensor data with CBG calibration values and performed regression calculations to produce each CGM glucose trace. This software also produces summary data for each 72 hour CGM study, showing mean and standard deviation sensor glucose and CBG for each day and over the whole 72 hour study period.

Descriptive statistics performed with SPSS were used to describe the demographics and characteristics of those recruited.

5.6.2 Validation of CGM in CF
(Chapter 6)
A Bland-Altman plot determined limits of agreement between CGM glucose levels and the reference standard paired plasma glucose values (taken during OGTT).

5.6.4 Comparison of OGTT and CGM
(Chapter 7)
Participant data was grouped according to the gold standard OGTT result (normal, impaired and diabetic glucose tolerance, as per WHO criteria).
Several measures of CGM data were examined (including mean and SD sensor glucose, area under the curve sensor glucose during OGTT, maximum glucose value during OGTT, percentage time spent above threshold levels) and compared for each OGTT result group.

The same measures of glycaemic control by CGM from the 72 hour profile and OGTT were compared with HbA1c measurement and analysed for correlation, using Pearson’s or Spearman’s correlation coefficient, according to whether data was parametric or non-parametric.

Rate of change (slope) of FEV₁, weight and BMI was derived for all patients over the preceeding 2 years at our centre (or for as long as they had been at our centre, if this was less than 2 years). These values were correlated against glycaemic control variables using SPSS (version 15.0, Microsoft, USA)

Use of CGM to define early abnormal glycaemic control

(Chapter 8)

CGM data from our 10 healthy controls was used to define normal (healthy non-CF) ranges for sensor glucose (mean sensor glucose value and variability of sensor glucose values, variability being the standard deviation of sensor glucose values). Confidence intervals of 99% were used due to the small sample size. CF patient data was examined to see if it was within these healthy ‘normal’ parameters or not.
5.6.8 Evaluating patient experiences of CGM

(Chapter 9)

A questionnaire was sent out to all patients who completed the study protocol with a letter of invitation and a stamped addressed envelope for return to our centre. Administrative staff set up a system to ensure anonymous replies. In some cases the questionnaire was posted within 2 weeks of completing the CGM and in others it was several months later. One reminder letter was sent 2 weeks following the questionnaire to those who had not returned it.

The 4 page document covered many aspects of the patients’ experience of CGM, with many questions asking for ratings of acceptability on a five point scale and also free text responses. The questionnaire drew on a previously published study, evaluating acceptability of CGM for people with type 1 and type 2 diabetes mellitus (Newman et al., 2009), with author permission. The questionnaire was designed to take approximately 15 minutes for patients to complete.

SPSS (version 15.0, Microsoft, USA) was used to collate all patient responses and perform simple summary statistics on the data.
Chapter 6

VALIDATION OF CONTINUAL GLUCOSE MONITORING IN ADULTS WITH CYSTIC FIBROSIS

6.1 Background

As explained in Chapter 3, there is a need for newer means of assessing glycaemic control in cystic fibrosis (CF). Conventional measures do not always recognise early and clinically relevant abnormalities in an individual’s everyday glucose levels.

One problem with the oral glucose tolerance test (OGTT) is that the test threshold values were derived from populations at risk of developing type 2 diabetes mellitus (T2DM), a clinically distinct group from those with CF. OGTT results may therefore be less relevant or applicable to people with CF. Indeed the baseline value of the test (fasting glucose) is rarely abnormal unless frank diabetes has developed, and basal insulin production is affected, which is late in the spectrum of abnormal glycaemic control. The 2 hour glucose value may or may not be helpful. A normal 2 hour glucose (≤ 7.7 mmol/L) does not exclude abnormal glycaemia, but UK CF Trust guidelines (2004) do not recommend any further monitoring after such ‘normal glucose tolerance’ results. (CFTrust, 2004) When checked, interim glucose values (for example at 30, 60 or 90 minutes) are often abnormal, returning to normal by 2 hours, though few CF centres carry out this additional monitoring during the test. A raised 2 hour glucose value ≥11.1 mmol/L represents ‘diabetic glucose tolerance’, a prompt to carry out serial blood glucose monitoring. (CFTrust, 2004)

Impaired glucose tolerance by OGTT (a 2 hour glucose value of ≥ 7.8 and < 11.1 mmol/L)
in practice may or may not correspond to abnormal blood glucose monitoring in everyday life. In summary the OGGT may be neither an adequate or relevant measure of glycaemia in CF.

Furthermore, when capillary blood glucose (CBG) profiles are carried out, in keeping with recommendations in UK guidelines, they may not capture clinically relevant high or low excursions in glucose level, thereby providing false reassurance of normal glycaemic control. To accurately capture these ‘highs and lows’ of glucose control in a CBG profile, very frequent finger prick testing would be required for each individual, and this is often not acceptable to patients. Even fastidious subjects who would accept such repeated inconvenience may not wish to wake to check glucose levels during the night, or during overnight feeding.

Elevated glycosylated haemoglobin (HbA1c) levels have recently been introduced to United States (US) CF guidelines for diagnostic criteria of CF related diabetes (CFRD). Whilst a raised HbA1c (≥6.5%) may indicate abnormal glycaemia, this may simply reflect that a late phase has been reached in the spectrum of abnormal glycaemic control, somewhat akin to a raised fasting glucose level. Conversely, a normal HbA1c level cannot exclude day to day abnormal glycaemia. Indeed, some CF patients may have a falsely low HBA1c due to high red blood cell turnover in chronic anaemia and iron deficiency. Additionally, the rate and mechanism of glycation of haemoglobin in people with CF, may be different to those without CF due to the specific pattern of glycaemic excursions which tend to be very high short-lived post prandial peaks, rather different to patterns seen in those with Type 1 diabetes mellitus (T1DM) or T2DM. Even if a raised HbA1c was a reliable marker for abnormal glycaemic control in CF, abnormal results still require further
monitoring to look into everyday glucose control and examine whether any intervention is warranted. Conventionally this would be with CBG profiles, with their inherent problems as previously mentioned.

Clinical symptoms of hyperglycaemia, such as polyuria, polydipsia and fatigue are not always present in those with clinically relevant abnormal glycaemia and CF. Alternatively these symptoms may be present in those with CF who have no clinically relevant hyperglycaemia. The presence or absence of such symptoms is not sensitive or specific enough to be relied upon when diagnosing abnormal glycaemic control. Similarly the presence of glycosuria is not specific or sensitive enough to accurately predict clinically relevant abnormal glycaemia.

Continual glucose monitoring (CGM), whereby an interstitial glucose sensor is placed over several days, and the subject completes a food and events diary as well as a CBG profile, offers the potential to recognise abnormal glycaemic control in any part of the spectrum, relevant to real life variations in glucose whilst being acceptable to patients. Large validation studies of CGM in healthy adults and children, and those with T1DM and T2DM are published. (Gross et al., 2000) In CF, the CGM devices have been validated in children and adolescents but evidence is scant in CF adults, and a robust formal controlled validation study is lacking. My study attempts to fill this evidence gap, involving a substantial number of individuals and appropriate statistical analysis to show that CGM is valid for use in adults with CF. This validation is necessary, before specific applications of CGM in CF can be investigated.
6.2 Aim

My aim was to compare simultaneously obtained CGM results with OGTT results in a study population of stable adults with CF. I investigated how closely glucose values by CGM agreed with plasma glucose values at 0 hours and 2 hours of the OGTT and compared data on accuracy and reliability of CGM with that already in the literature for non-CF subjects.

6.3 Methods

Full methodology is given in the previous chapter. Briefly, 50 adults with CF were recruited to my single centre prospective observational pilot study. At a time of clinical stability (no exacerbation or change in management in the preceding 2 weeks) each subject underwent a 72 hour home CGM (with a ‘CGMS Gold’ or ‘iPro device’, Medtronic, USA) study and had a 2 hour OGTT during this time. Participants were asked to check and record at least 4 CBG levels per day for calibration of interstitial glucose data, and record their food and drink intake, relevant medication intake and any exercise and significant symptoms over the 72 hours.

Subjects attended the Manchester Adult Cystic Fibrosis Centre (MACFC) for the OGTT, which was 1, 2 or 3 days after the start day of the CGM. Patients fasted for at least 8 hours prior to the OGTT, then had plasma glucose and CBG taken at baseline. These 2 measures of glucose level were repeated 2 hours after the ingestion of the standard OGTT glucose load. HbA1c was also recorded, along with weight, height and spirometry during this clinical visit.
Casenote review was carried out to document demographic and clinical characteristics data. All subjects provided formal written consent and ethical approval was granted by the North West Research Ethics Committee no. 10. Site-specific approval was given by the University Hospitals of South Manchester Research and Development Department.

### 6.4 Statistical Analysis

CGM devices were downloaded using the compatible ‘Solutions’ software (*Medtronic, USA*) and summary data reports were produced as part of this process. Microsoft office Excel 2003 (*Microsoft, USA*) was used to store sensor data given by the CGM software and other study data. SPSS (*version 15.0, Microsoft, USA*) software package was used to generate descriptive statistics on the data and perform statistical functions.

Group comparisons were performed using Spearman’s correlation coefficient to analyse correlation between paired plasma glucose values and CBG results, as well as paired plasma glucose and CGM results. Two-tailed tests with a significance level of *P* < 0.05 were used.

Bland-Altman plots were used to determine limits of agreement between paired glucose values (plasma glucose with capillary blood glucose, and plasma glucose with continual sensor glucose). Simple descriptive statistics were used to define the mean bias and 95% confidence limits of agreement.

### 6.5 Results

Patient demographic and characteristics are shown in Table 6.1
### Table 6.1 Demographics and characteristics of study population by OGTT result

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glucose Tolerance Category by OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All n=50</td>
</tr>
<tr>
<td></td>
<td>Normal n=25 (50.0%)</td>
</tr>
<tr>
<td></td>
<td>Impaired n=9 (18.0%)</td>
</tr>
<tr>
<td></td>
<td>Diabetic n=16 (32.0%)</td>
</tr>
<tr>
<td>Age (yrs) median (IQR)</td>
<td>27.1 (22.6 to 37.9)</td>
</tr>
<tr>
<td></td>
<td>24.0 (22.1 to 32.2)</td>
</tr>
<tr>
<td></td>
<td>29.8 (28.0 to 42.0)</td>
</tr>
<tr>
<td></td>
<td>28.8 (22.7 to 38.8)</td>
</tr>
<tr>
<td>Female No. (%)</td>
<td>20 (40.0)</td>
</tr>
<tr>
<td></td>
<td>11 (44.0)</td>
</tr>
<tr>
<td></td>
<td>4 (44.4)</td>
</tr>
<tr>
<td></td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>DF508 homozygous No. (%)</td>
<td>32 (64.0)</td>
</tr>
<tr>
<td></td>
<td>17 (68.0)</td>
</tr>
<tr>
<td></td>
<td>3 (33.3)</td>
</tr>
<tr>
<td></td>
<td>12 (75.0)</td>
</tr>
<tr>
<td>DF508 heterozygous No. (%)</td>
<td>17 (34.0)</td>
</tr>
<tr>
<td></td>
<td>8 (32.0)</td>
</tr>
<tr>
<td></td>
<td>5 (55.6)</td>
</tr>
<tr>
<td></td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>BMI Mean (SD)</td>
<td>21.7 (3.0)</td>
</tr>
<tr>
<td></td>
<td>21.4 (3.1)</td>
</tr>
<tr>
<td></td>
<td>21.9 (4.0)</td>
</tr>
<tr>
<td></td>
<td>22.0 (2.4)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; % predicted</td>
<td>57.5 (20.6) [1 missing]*</td>
</tr>
<tr>
<td></td>
<td>63.2 (20.6) [1 missing]*</td>
</tr>
<tr>
<td></td>
<td>53.6 (20.7)</td>
</tr>
<tr>
<td></td>
<td>50.9 (19.3)</td>
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<tr>
<td>Pancreatic sufficient No. (%)</td>
<td>4 (8.0)</td>
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<tr>
<td></td>
<td>3 (12.0)</td>
</tr>
<tr>
<td></td>
<td>1 (11.1)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
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<tr>
<td>Supplemental feed No. (%)</td>
<td>8 (16.0)</td>
</tr>
<tr>
<td></td>
<td>3 (12.0)</td>
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<tr>
<td></td>
<td>2 (22.2)</td>
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<tr>
<td></td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>On azole No. (%)</td>
<td>6 (12.0)</td>
</tr>
<tr>
<td></td>
<td>1 (4.0)</td>
</tr>
<tr>
<td></td>
<td>2 (22.2)</td>
</tr>
<tr>
<td></td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>On long term oral steroids No. (%)</td>
<td>6 (12.0)</td>
</tr>
<tr>
<td></td>
<td>2 (8.0)</td>
</tr>
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<td></td>
<td>1 (11.1)</td>
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<td>3 (18.8)</td>
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<td>CF liver disease or transplant No. (%)</td>
<td>6 (12.0)</td>
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<td>2 (8.0)</td>
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<td></td>
<td>2 (22.2)</td>
</tr>
<tr>
<td></td>
<td>2 (12.5)</td>
</tr>
</tbody>
</table>

* One patient did not have spirometry due to recurrent small pneumothoraces in preceding months, though was otherwise stable.

N.B. Mean (SD) given for datasets with parametric distribution and Median (IQR) given for datasets with non-parametric distribution.
6.5.1 Capillary Blood Glucose results during OGTT

The study protocol included capillary blood glucose (CBG) and plasma glucose to be taken at baseline (0 hours) and 2 hours during the OGTT. There were 97 valid CBG results taken during the OGTT (see Table 6.2), which were analysed for accuracy, compared to their paired plasma glucose results (see Table 6.3). Table 6.4 shows how this data compared to established standards. Spearman’s correlation coefficient of plasma and CBG glucose values is 0.935 (P<0.01) and plotted values are shown in Figure 6.1

Limits of agreement for paired plasma glucose and CBG were determined, and found to change as glucose levels increased. Splitting the data pairs into those with plasma glucose \( \leq 12.0 \) mmol/L and plasma glucose >12.0 mmol/L gave satisfactory distributions (see Figure 6.2 and Figure 6.3).

6.5.2 Continuous Glucose Monitoring

All 50 subjects completed continuous glucose monitoring (CGM). Our sensor failure rate during OGTT was 2/50 (4.0%), due to calibration errors occurring at the 2 hour time point, reported by iPro software. The validity and accuracy of CGM (‘sensor’) results with respect to paired plasma glucose values are shown in Table 6.5 and Table 6.6

The correlation coefficient of plasma and CGM glucose values is 0.875 (P<0.01) and plotted values are shown in Figure 6.4

Limits of agreement for paired plasma glucose and CGM were determined, and found to change as glucose levels increased. Splitting the data pairs into those with plasma glucose \( \leq 12.0 \) mmol/L and plasma glucose >12.0 mmol/L gave satisfactory distributions (see Figure 6.5 and Figure 6.6).
Table 6.2 Concordance of capillary blood glucose results

<table>
<thead>
<tr>
<th>CBG result</th>
<th>OGTT time point</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>Valid</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Invalid</td>
<td>1 omitted</td>
<td>1 technically incorrect</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

OGTT baseline and 2 hour glucose results were obtained for all 50 subjects. In some cases, there was no valid paired CBG result. This table summarises this data, with explanations for any invalid results.

Table 6.3 Accuracy of capillary blood glucose with respect to paired plasma glucose

<table>
<thead>
<tr>
<th>Deviation of CBG from paired plasma glucose</th>
<th>Overall</th>
<th>OGTT time point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 hours</td>
</tr>
<tr>
<td>Absolute deviation (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.7 (0.7)</td>
<td>0.4 (0.3)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.5 (0.0 to 4.2)</td>
<td>0.3 (0.0 to 1.2)</td>
</tr>
<tr>
<td>Percentage deviation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.8 (7.4)</td>
<td>7.4 (6.2)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>7.5 (0.0 to 31.8)</td>
<td>5.2 (0.0 to 31.6)</td>
</tr>
</tbody>
</table>

This table summarises the deviation of capillary blood glucose values from paired plasma glucose values, overall and for each time point of the oral glucose tolerance test, in absolute (mmol/L) and percentage terms.
Table 6.4 Accuracy of capillary blood glucose results according to standard criteria

<table>
<thead>
<tr>
<th>Definition</th>
<th>ADA*</th>
<th>ISPAD**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBG within 10% of corresponding plasma glucose</td>
<td>CBG within 20% of corresponding plasma glucose</td>
</tr>
<tr>
<td>Standard</td>
<td>≥60% ‘Good’ 55% to 59.9% ‘Satisfactory’</td>
<td>95%</td>
</tr>
<tr>
<td>Study data meeting criteria n (%)</td>
<td>58/97 (59.8)</td>
<td>88/97 (90.7)</td>
</tr>
</tbody>
</table>

* American Diabetes Association
** International Society for Pediatric & Adolescent Diabetes

This table shows criteria for accuracy of capillary blood glucose results compared to corresponding plasma glucose values according to ADA and ISPAD standards. Below these, the relevant accuracy figures from my study are given, demonstrating that I achieved ‘satisfactory’ accuracy of CBG results by ADA standard but did not meet ISPAD accuracy criteria.
**Figure 6.1** Plot of Plasma glucose (mmol/L) against capillary blood glucose (mmol/L) during the oral glucose tolerance test. A line of best fit is included. Spearman’s correlation coefficient is 0.935 (p<0.01).

**Figure 6.4** Plot of plasma glucose values against paired continual glucose monitoring values during the oral glucose tolerance test. A line of best fit is included. Spearman’s correlation coefficient is 0.875 (p<0.01).
Figure 6.2 Limits of agreement (average against absolute difference) for plasma glucose values ≤ 12.0 mmol/L and paired CBG values. Lines of mean bias and 95% confidence limits are shown by the dotted black and orange lines respectively.

Figure 6.5 Limits of agreement (average against absolute difference) for plasma glucose values ≤ 12.0 mmol/L and paired CGM values. Lines of mean bias and 95% confidence limits are shown by the dotted black and orange lines respectively.
Figure 6.3 Limits of agreement (average against absolute difference) for plasma glucose values > 12.0 mmol/L and paired CBG values. Lines of mean bias and 95% confidence limits are shown by the dotted black and orange lines respectively.

Figure 6.6 Limits of agreement (average against absolute difference) for plasma glucose values > 12.0 mmol/L and paired CGM values. Lines of mean bias and 95% confidence limits are shown by the dotted black and orange lines respectively.
Table 6.5 Concordance of continual glucose monitoring results

<table>
<thead>
<tr>
<th>CGM (‘sensor’) result</th>
<th>OGGT time point</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>Valid</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>Invalid</td>
<td>1 corresponding CBG omitted</td>
<td>2 calibration errors, 1 out of range, 1 corresponding CBG incorrect</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 6.6 Accuracy of continual glucose monitoring (‘sensor’) glucose and paired plasma glucose during OGGT

<table>
<thead>
<tr>
<th>Measure of deviation of CGM from paired plasma glucose</th>
<th>Overall</th>
<th>OGGT time point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 hours</td>
</tr>
<tr>
<td>Absolute deviation (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.0 (0.8)</td>
<td>0.7 (0.6)</td>
</tr>
<tr>
<td>Med (range)</td>
<td>0.9 (0.0 to 3.5)</td>
<td>0.6 (0.0 to 2.5)</td>
</tr>
<tr>
<td>Percentage deviation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.3 (11.6)</td>
<td>14.6 (13.0)</td>
</tr>
<tr>
<td>Med (range)</td>
<td>12.5 (0.0 to 65.8)</td>
<td>12.0 (0.0 to 65.8)</td>
</tr>
</tbody>
</table>
6.6 Discussion
This study attempts to address the ongoing requirement for robust data on the validity of CGM in adults with CF. With 50 patients recruited, considerably more data has been generated than in previous validation studies in adults with CF. In addition, I have included adults across the range of patients in our clinic, covering the whole glycaemic control spectrum, rather than highly selected patients as in some published work. This study carries out the OGTT when patients are stable, as per CF Trust guidelines, and this is not always documented in similar studies. Finally, I examined CGM and OGTT findings from tests carried out concurrently, in order to provide a true comparison of results.

Providing CGM is a valid tool to use in CF, it has great potential for recognising clinically significant problems in real life glycaemic control that may not be detected using conventional measures and guidelines.

6.6.1 Patient demographics and characteristics
I consider that my study results are broadly applicable to adult CF patients, due to the spread of ages and sexes recruited and inclusion of subjects having long term oral steroids, azoles and supplementary enteral feeding.

In our centre, CGM has been in use for some time in individuals with established CFRD, to guide management. Diabetic individuals were included in the study and represent a similar proportion of total subjects as those in our clinic population (around a third). This adds to the broad applicability of results of this pilot study to the general adult CF population.
6.6.2 Plasma glucose monitoring accuracy

When 2 hour plasma sampling was delayed, due to multiple attempts at intravenous port access or venepuncture (uncommonly, less than 5% of occasions) inaccuracies have been introduced. The plasma glucose level can be declining at a substantial rate at the 2 hour point of OGTT in subjects with CF. Therefore even 1 or 2 minutes delay in sampling could result in a falsely low plasma glucose value or even incorrect glucose tolerance result. Testing was done in an everyday clinical setting, so timing of samples is not as accurate as that achievable under controlled laboratory conditions. However accuracy of timing of sampling does reflect that achieved in usual practice in our centre, and therefore results are applicable to our clinic population.

6.6.3 Capillary blood glucose monitoring accuracy

CBG accuracy during OGTT in my study did not meet ADA ‘good’ or standard ISPAD criteria. I am aware of one case where a patient did not carry out effective handwashing prior to CBG testing and returned a spuriously high result, likely due to traces of polycal on their hands. This result was excluded from analysis, but it is possible that there are similar occurrences of which I am unaware, which could introduce a falsely high difference between CBG and paired plasma glucose value.

A further and likely more common source of error relates to the 2 hour CBG results. Unlike the baseline CBG values, these were being measured when the glucose blood level was often swiftly falling, rather than stable, so any small time delay in taking the CBG from the exact 2 hour time point could result in a relatively inaccurate result. This error has been introduced by suboptimal methodology, as usually only one operator sampled both
plasma glucose and CBG at 2 hours during the OGTT. In further work, an additional team member could sample CBG simultaneously as the 2 hour plasma glucose is drawn.

The Bland-Altman limits of agreement plot (Figure 6.2) shows that for plasma glucose readings of ≤12.0 mmol/L, CBG results tend to overestimate plasma glucose very slightly (0.1 mmol/L) and vary from this mean bias by ± 1.3 mmol/L. For plasma glucose levels >12.0 mmol/L, CBG results tend to underestimate plasma glucose by 1.4 mmol/L and vary from this by ± 3.0 mmol/L. This level of accuracy is generally felt to be acceptable in clinical practice, balancing the convenience of CBG sampling with more accurate but more invasive and expensive plasma glucose determination.

6.6.4 Continuous glucose monitoring

In this study the sensor failure rate (due to calibration error) during OGTT was low, though this factor is not often addressed in other research involving CGM. Literature from the CGM manufacturers (Medtronic, USA) states that calibration errors are more likely to occur when a calibration CBG value is significantly different from the paired CGM (‘sensor’) value, which is more likely to happen during phases of rapidly changing glucose levels. Considering that the OGTT is intended to cause glucose excursion, it is reassuring to note that in the majority of cases, this did not result in a software calibration error.

The accuracy data for CGM glucose values in this study is comparable with those published in healthy individuals, subjects with type 1 and type 2 diabetes mellitus, and other studies involving people with CF. My study suggests that in simple terms, CGM is as
valid in people with CF as those without CF. I have evaluated the accuracy of CGM in people with CF in more detail than most of the previously available literature.

6.6.5 Correlation of continual glucose monitoring and paired plasma glucose results

Though I observe a very close correlation between our pairs of glucose values measured by CGM and in plasma during the OGTT, this is only a measure of association. I would expect such a high level of association when comparing results from two methods of measuring the same variable, so still need to examine the degree of agreement to determine whether one method (CGM) could actually be used to predict the other (plasma glucose).

6.6.6 Limits of agreement between continual glucose monitoring and plasma glucose

Limits of agreement between these two methods of estimating glucose levels are most satisfactory when dealing with glucose levels up to approximately 12.0 mmol/L (Figure 6.5). This range is particularly appropriate to examine, since I am chiefly exploring the potential for CGM to recognise early abnormal glycaemic control. OGTT, HbA1c, fasting glucose and even CBG profiles may still be normal despite such early abnormal glycaemia being present.

For plasma glucose readings ≤12.0 mmol/L, CGM values tend to overestimate plasma glucose results slightly (by approximately 0.4 mmol/L). I am confident that in 95% of cases, CGM values for glucose are within approximately 1.75 mmol/L of this mean bias.

When interpreting CGM traces which include higher glucose levels >12.0 mmol/L (Figure 6.6), values are less accurate, tending to underestimate true plasma glucose levels by approximately 2.0 mmol/L. My 95% confidence limits here are approximately ± 2.0
mmol/L. This should not detract from the usefulness of CGM demonstrating glucose excursions at higher glucose levels, but implies that trends of CGM traces may be more useful for interpretation than absolute CGM values.

These error margins are similar to those for CBG compared to plasma glucose, though wider. This is unsurprising, since CGM (‘sensor’) glucose values are ultimately derived from the calibration CBG values, when iPro software performs sophisticated mathematical transformation of the raw interstitial glucose data downloaded from the iPro device. Unlike many available publications concerning the accuracy of CGM, I did not compare CGM values with CBG values. Instead I compared CGM values with paired plasma glucose, as these two results are independent as far as device accuracy is concerned.

6.6.7 Limitations of continual glucose monitoring in cystic fibrosis

As in Chapter 3, continual glucose monitoring measures interstitial (extracellular) glucose. The physiological relationship between interstitial glucose and blood glucose is not fully understood, but it is generally accepted that glucose diffuses from the capillaries into the interstitial space, introducing a physiological ‘lag’ time.

Interstitial glucose dynamics vary, dependent on the rate and direction of change of blood glucose. Other variables are features of the sensor site, for example its vascularisation, presence of adipose or scar tissue and insulin availability and sensitivity.

The iPro manufacturers attempt to address some of these aspects. They state that the sensor should be sited away from any scar tissue or insulin injection sites. The iPro device records interstitial glucose every 10 seconds, and stores an average reading for every 5 minutes,
resulting in 288 readings per 24 hours of monitoring. These values are ‘shifted backwards’ by 10 minutes to estimate blood glucose, applying a fixed correction for diffusion time.

CBG values are required for calibration, but any inaccuracy in these values (such as in my study, where only 90.7% of our CBGs performed during the OGTT were within 20% of the corresponding plasma glucose value) affects the accuracy of the ‘sensor’ glucose level.

Literature on how the interstitial glucose dynamics in CF may differ from those in non-CF is sparse. There are likely to be differences in CF, as other work has shown differences between interstitial glucose physiology in normal healthy subjects and those with T1DM or T2DM. (Palerm et al., 2006) However, my pilot study data suggests that the accuracy of CGM is comparable, not only to other similar data in CF but quoted ranges of accuracy in studies where CGM was used in non-CF study populations.

6.6.8 Application of continual glucose monitoring in cystic fibrosis

There is evidence for CGM determining early abnormal glycaemic control which is associated with prior nutritional and pulmonary deterioration, where standard OGTT results were normal. (Hameed et al., 2010) Dobson et al also reported a case series where conventional measures had failed to identify abnormal glycaemia but CGM had done so. (Dobson et al., 2002) This group went on to observe clinical improvements in all cases within 3 months of commencing insulin therapy.
6.7 Conclusion

Despite the limitations of CGM, it is a valid tool for use in adults with CF, with potential to identify clinically relevant abnormal glycaemia in CF at an earlier stage than conventional measures. Reasonable steps to optimise CGM accuracy in clinical use can be taken, and interpretation of results should allow for limitations in accuracy.
Chapter 7

COMPARISON OF THE ORAL GLUCOSE TOLERANCE TEST AND CONTINUAL GLUCOSE MONITORING IN ASSESSMENT OF GLYCAEMIC CONTROL

7.1 Background

In 2002 Dobson et al reported a case series of clinical improvement in CF with early insulin treatment, that is, before insulin would have been indicated by an abnormal OGTT. (Dobson et al., 2002) These three adults and one adolescent had deteriorating weight and lung function, but normal OGTT and HbA1c. The authors commented that insulin may be indicated early, on the basis of everyday home monitoring (all individuals had high random levels on CBG profile), rather than an abnormal OGTT result. As in the preceeding chapter, this concept remains very relevant for our CF population, as we are interested in identifying and treating early abnormal glycaemic control in CF to prevent clinical deterioration.

As reported in Chapter 3, Hameed et al published a prospective study in children and adolescents, where continual glucose monitoring was used to identify clinically relevant abnormal glycaemia. (Hameed et al., 2010) Subjects with CGM glucose above a threshold level of 7.8 mmol/L for a specific percentage of time were found to have had greater deterioration in weight and lung function in the preceeding 12 months. There was no such correlation with clinical deterioration for OGTT results. From the same study it was reported that a maximum CBG result of over 8.2 mmol/L on a five time point OGTT (CBG every 30 minutes) correlated with a significantly greater clinical decline in the prior year,
suggesting that interim values from the OGTT are more relevant in early abnormal
glycaemia than the 2 hour result. At the North American CF Conference in October 2010
S.Hameed presented on their group now carrying out a prospective interventional trial of
ey early insulin treatment aiming to prevent pre-diabetic decline in their patients.

As mentioned in previous chapters, the WHO defined OGTT threshold values are derived
from T2DM populations at risk of developing microvascular complications. (WHO, 2006)
Although microvascular complications do occur with abnormal glycaemic control in CF,
the impact on pulmonary function and nutritional status may be more relevant and may
occur at different thresholds.

7.2 Aims

Objectives of this study were:

1) To determine if the OGTT is a relevant and adequate assessment of glycaemic control in
adults with CF i.e. does the OGTT reflect ‘real life’ glycaemia (the variations and patterns
of change in glucose levels observed when the patients are going about their usual
everyday activities, rather than attending the CF outpatient department)?

2) To explore if OGTT and continual glucose monitoring results are associated with prior
change in lung function and weight in adults with CF.

3) To see whether continual glucose monitoring is superior to the OGTT in assessment of
glycaemia in adults with CF.
7.3 Methods

7.3.1 Study characteristics

This was a prospective observational study, involving 50 adults with CF who were clinically stable. It was carried out at a single centre, the Manchester Adult Cystic Fibrosis Centre (MACFC).

7.3.2 Inclusion and exclusion criteria

The patients had to be aged at least 18 years and have phenotypic and/or genotypic features of CF. Pregnant patients were excluded. Subjects who were unable to give informed consent, patients with learning difficulties were not eligible for participation.

7.3.3 Consent

All patients and control subjects gave informed written consent to being in the study, which included permission for their GP to be informed of their participation and for researchers to have access to their clinical records relating to the study.

7.3.4 Ethical approval

The study was approved by the North West Research Ethics Committee no.10 (formerly Lancashire and Cumbria B). Site-specific approval was granted by the Research and Development Department of the University Hospital of South Manchester NHS Foundation Trust.

7.3.5 Study procedure

50 Participants had a 72 hour CGM at home during a time of clinical stability and attended for an OGTT in the outpatient clinic during this 72 hour monitoring period.
Clinical stability was defined by absence of an infective respiratory exacerbation, meeting the following criteria:

(1) Only up to one of the following: increased shortness of breath, increased cough, thicker or increased volume of sputum, haemoptysis, a decrease in FEV$_1$ of greater than ten percent.

(2) No supplemental antibiotics (IV or oral), short term oral corticosteroids or change in long term oral corticosteroid dose in the preceding 2 weeks.

7.3.5.1 Continual glucose monitoring

Setting up of continual glucose monitoring took place either in the outpatient clinic or the patient’s home, depending on their preference. Informed written consent was obtained.

After identification of a suitable site on the abdomen, the skin was cleansed and a subcutaneous glucose sensor (Medtronic, USA) inserted, between 3 cm and 8 cm lateral to the umbilicus. This was allowed to ‘wet’ for at least 10 minutes, during which time the patient was familiarised with capillary blood glucose (CBG) checking technique, and how to complete the 3 day food and events diary sheet.

After this time the wireless recorder (‘iPro’, Medtronic, USA) was connected to the sensor. A live software package (‘iPro Solutions’, Medtronic, USA) was used to ‘initialise’ the recorder and sensor. The first 7 of 50 stable CF patients used the previous generation of CGM recorders, the ‘CGMS Gold’ (Medtronic, USA), which was not wireless, and undertook its own 60 minute initialisation process with no need for live computer software. All 50 patients used the identical type of disposable sensors and set-up of CGM was
identical in every other aspect. During this process, a glucometer (Aviva Accucheck, *Roche, UK*) was synchronised with the iPro CGM device, which the patients used over the 72 hours to record 4 CBG daily for calibration. CBG testing strips were quality controlled prior to use. Subjects were instructed that pre-prandial and bedtime CBG sampling times were preferred but not compulsory and that no more than 12 hours should elapse between consecutive CBG samples.

The CGM device was covered by a waterproof dressing, allowing showers and exercise but not immersion in water. In the case of the first 7 patients using the ‘CGMS Gold’ (*Medtronic, USA*) recorders, ‘showerpacks’ were issued, disposable plastic covers which were used to protect the CGM recorders during showering and exercise.

Subjects were instructed to keep a written log of CBG results, food and drink consumed, any insulin, oral corticosteroid or antifungal medication taken, any exercise and any adverse events. Sensor data is stored in the recorder for subsequent download following removal, with no visible reading available to the wearer. Participants were advised not to modify their usual diet or activity during the 72 hour recording period, apart from fasting overnight prior to the OGTT.

The subjects had written instruction on how to remove the CGM device and return with study paperwork and glucometer after the 72 hour monitoring period.
7.3.5.2 Glucose Tolerance

OGTT was scheduled for 1, 2 or 3 days after CGM placement. (This degree of flexibility was required in order to keep to strict clinic microbiological cohort segregation protocols). Subjects attended an outpatient clinic having fasted for at least 8 hours overnight and omitted any usual overnight nasogastric or gastrostomy feeding. Any long or intermediate acting insulin from the previous evening and any short acting morning insulin was omitted.

Baseline fasting venous glucose, glycosylated haemoglobin (HbA1c) and capillary blood glucose were taken. The subject then had up to 5 minutes to ingest a standard oral liquid glucose load (comprising 1.75g/kg anhydrous glucose to a maximum of 75g). Participants then rested, seated for 2 hours, without any further oral intake. Repeat venous plasma glucose and CBG samples were taken 2 hours after complete ingestion of the glucose load.

Participants were allowed home following the OGTT and instructed to carry on with usual daily diet and activities, including any overnight nasogastric or gastrostomy feeding.

7.3.5.3 Pulmonary Function and Nutritional Status

At the time of OGTT, subjects had their weight and height recorded and performed spirometry (Vitalograph, UK) according to our centre’s standard procedure. Percentage predicted FEV₁ (Knudson et al., 1983) and BMI were recorded for each participant.

Casenotes were used to record demographic characteristics, most recent glucose tolerance status, usual medications, requirement for supplementary nutrition, exocrine pancreatic enzymes and other CF and non-CF disease complications.
Patient records were reviewed to collect spirometry, weight and BMI values for each subject in the 2 years prior to the study period (or during their time at the centre for patients who had been at MACFC for less than 2 years). Spirometric and weight values from ‘unwell’ visits, for example when starting on IV or oral antibiotics for an infective exacerbation, were omitted.

7.3.6 Statistical analysis

Raw data was stored using Microsoft Excel 2004 (Microsoft, USA). ‘Solutions’ software (Medtronic, USA) was used to download raw data from the continual glucose CGMS Gold and iPro monitors. This software performs regression analysis to produce CGM glucose levels for every 5 minutes from raw sensor data and calibration CBG values, resulting in each individual’s CGM trace and summary data report. The sensor glucose values for each 5 minute time values were stored for each patient in Excel, so that I could produce tailored summary data relevant to my research, rather than using Medtronic software summary data. Simple statistical functions within excel were used to determine summary demographic and glycaemic control data.

Excel was used to store and perform calculations on the lung function and weight data for each participant, including the ‘slope’ of each parameter for up to 2 years prior to the study date.
Excel formulas were used to analyse CGM trace data for area under the curve (AUC) for glucose monitoring and ‘OGTTmax’ by CGM (maximum glucose level during the OGTT as measured by CGM).

SPSS was used to perform group comparisons. Tests of correlation between slope of lung function or weight and glycaemic control parameters were performed using SPSS, with either Pearson’s correlation coefficient or Spearman’s correlation coefficient, as appropriate depending on whether variables were Normally distributed or not.

7.4 Results

See Chapter 6 Table 6.1 for a summary of demographics and characteristics of the study population.

Slope (change over time) for FEV1, weight and BMI could be determined for 48 of the 50 study subjects. For these patients, the median number of days over which slope data was determined was 692 (IQR 663 to 714) and the mean number of values used was 13.1 (SD 3.9). The remaining 2 individuals each from the NGT group had only 4 and 6 valid (stable) readings of lung function and weight data at our centre respectively, over a 168 day and 127 day period respectively, insufficient to determine accurate slope data.

Summary glycaemic control results and slope of lung function and weight data for patients grouped by OGTT result category are shown below in Table 7.1.
Table 7.1 Measures of glycaemic control and change in weight and lung function for cystic fibrosis patients, grouped by oral glucose tolerance test result category.

<table>
<thead>
<tr>
<th></th>
<th>CF patients by conventional glucose tolerance category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=50)</td>
</tr>
<tr>
<td>Plasma glucose 0 mins OGTT (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>5.2 (3.8 to 9.0)</td>
</tr>
<tr>
<td>Plasma glucose 120 mins OGTT (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>7.8 (2.7 to 22.0)</td>
</tr>
<tr>
<td>Mean CGM 72 hrs (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>6.3 (4.8 to 11.7)</td>
</tr>
<tr>
<td>Variability CGM 72 hrs (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.8 (1.0)</td>
</tr>
<tr>
<td>Standardised AUC glucose during total 72hr CGM (mmol/L/5mins) Median (range)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.5 (18.1 to 58.4)</td>
</tr>
<tr>
<td>Standardised AUC glucose during OGTT by CGM (mmol/L/5mins) Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>45.3 (14.4)</td>
</tr>
<tr>
<td>Max glucose during OGTT by CGM (‘OGTTmax’)(mmol/L) Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.8 (4.0)</td>
</tr>
<tr>
<td>Mean amplitude of glycaemic excursion during 72hr CGM (mmol/L) Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.1 (1.6)</td>
</tr>
<tr>
<td>% time glucose ≥ 7.8mmol/L Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>22.0 (21.0)</td>
</tr>
<tr>
<td>HbA1c(%) Median (range)</td>
<td>6.0 (4.4 to 9.0)</td>
</tr>
<tr>
<td>Slope FEV1 (% predicted/yr) Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-3.0 (4.8)*</td>
</tr>
<tr>
<td>Slope weight (kg/yr) Median (range)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.4 (-4.7 to 8.1)*</td>
</tr>
<tr>
<td>Slope BMI (kg/m2/yr) Median (range)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.4 (-1.5 to 3.0)*</td>
</tr>
</tbody>
</table>

* Insufficient data to calculate slope for 2 NGT patients, n=48
** Insufficient data to calculate slope for 2 NGT patients, n=23
$ ‘Variability’ of CGM over 72 hours is the standard deviation of sensor glucose level over the full 72 hour continual monitoring trace

Data shown as Mean (SD) if parametric and Median (range) if non-parametric
All measures of glycaemia, whether derived from plasma glucose or continuous monitoring, correlate with one another. See Table 7.2 for a summary of these results.
Table 7.2 Summary of significant correlations between glycaemic variables in all cystic fibrosis patients

<table>
<thead>
<tr>
<th>1st variable</th>
<th>2nd variable</th>
<th>Correlation type</th>
<th>r value</th>
<th>Significance (two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC OGTT</td>
<td>AUC 72hrs</td>
<td>Spearman’s</td>
<td>0.492</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Mean CGM</td>
<td>0 hours plasma glucose</td>
<td>Spearman’s</td>
<td>0.523</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Variability CGM</td>
<td>O hours plasma glucose</td>
<td>Spearman’s</td>
<td>0.387</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Variability CGM</td>
<td>2 hours plasma glucose</td>
<td>Spearman’s</td>
<td>0.707</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>OGTT max</td>
<td>Mean amplitude glycaemic excursion</td>
<td>Pearson’s</td>
<td>0.760</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Mean CGM</td>
<td>Spearman’s</td>
<td>0.639</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Variability CGM</td>
<td>Spearman’s</td>
<td>0.575</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>HbA1c</td>
<td>AUC 72 hrs</td>
<td>Spearman’s</td>
<td>0.642</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>HbA1c</td>
<td>AUC OGTT</td>
<td>Spearman’s</td>
<td>0.559</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>HbA1c</td>
<td>OGTT max</td>
<td>Spearman’s</td>
<td>0.559</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>
For all individuals, the area under the curve during OGTT (measured from CGM trace) correlates with area under the curve during the entire 72 hour CGM study (Spearman’s correlation coefficient is 0.492, p<0.001). Mean CGM glucose level and variability CGM glucose level correlate with measures of glycaemic control from the OGTT derived from plasma glucose (baseline glucose level and 2 hour glucose level) and from CGM (maximum glucose level during OGTT). The maximum glucose level during OGTT by CGM (‘OGTTmax’) correlates with the mean amplitude of glycaemic excursion for the entire 72 hour CGM trace.

In addition, HbA1c correlates with mean CGM (Spearman’s correlation coefficient r=0.639, p<0.01) variability CGM, area under the curve for 72 hour CGM trace and maximum glucose during OGTT.

For all subjects, there was no significant correlation between any slope data and any glycaemic control measure, either derived from plasma glucose levels or CGM. The same was found when analysed within NGT, IGT and DGT subgroups.

### 7.5 Discussion

This study aims to compare the OGTT and CGM, in their relevance and adequacy when assessing glycaemia in adults with CF. As pointed out by Dobson et al in 2002, the OGTT may fail to identify individuals with clinically relevant abnormal glycaemic control and a superior means of assessment is desirable. (Dobson et al., 2002) In addition I explore if any measures of glycaemia relate to prior change in weight or lung function parameters in adults with CF, as reported by Hameed et al, in their recently studied population of children and adolescents with CF. (Hameed et al., 2010)
7.5.1 Study population

The patient study population here is the same as that in Chapter 6, and therefore representative of the Manchester Adult Cystic Fibrosis Centre clinic population. Furthermore, this study is inclusive of those on long term corticosteroids, those on supplementary feeding, patients taking azoles and patients who have had a liver transplant. The glycaemic status of these 50 patients is a reflection of their ‘real life’ glycaemic control and normal life events.

7.5.2 Limitations

This is a pilot observational study involving a small number of subjects. I have trusted subjects to accurately self-report the timings and amounts of dietary intake, blood glucose levels and exercise. There could be some recall bias or simple human error affecting the accuracy of results, though no more than we would expect when using CGM in the ordinary clinical setting.

We must rely on the ‘Solutions’ software for CGMS Gold and iPro recorders (Medtronic, USA) to analyse the raw sensor data and producing CGM traces in a reliable and reproducible manner.

Not all those recruited used the same type of CGM recording device. The first seven CF patients recruited used one of 2 ‘CGMS Gold’ monitors rather than any of the pool of 4 newer wireless ‘iPro’ monitors. We have assurance from Medtronic, that there is no difference between these 2 types of recording device in the technology used to sense interstitial glucose level or store data, however, as the only differences are in the size and
housing of the hardware and convenience to users. There was no formal repeatability testing of the 4 individual iPro monitors used.

As stated in chapter 6, the accuracy of CBG values and therefore CGM values, HbA1c levels and plasma glucose will be variable, reflecting the real-life clinical setting in which this research was carried out. Under laboratory conditions, accuracy could be improved, but some insight into true everyday variations in glucose control for individuals would be lost.

The diabetic glucose tolerance group in this study was a heterogenous group, including treated diabetics, individuals who had returned diabetic OGTTs previously (but were not considered to have CFRD and therefore not on treatment), as well as individuals who had not had a diabetic OGTT result before. Because some of this group were on insulin normally and had benefitted from regular diabetic review, their glycaemic control would have been optimised and this may have affected results, for example because their data may have been more like those with normal or impaired glucose tolerance.

7.5.3 Determining if the OGTT is a relevant and adequate assessment of glycaemic control in adults with CF i.e. does the OGTT reflect ‘real life’ glycaemia?

The fact that plasma glucose at 0 hours and 2 hours of the OGTT correlates with area under the glucose curve, mean glucose level and variability of glucose level by CGM, suggests that the OGTT does actually relate to real life glycaemic control. The OGTT and CGM are therefore closely related and the OGTT must then be relevant with regard to glucose levels during normal life events for adults with CF. The difference between OGTT and CGM however, is that the OGTT does not identify which adults with CF have
clinically relevant early abnormal glyaemic control. That is, we know that those returning a diabetic OGTT need further investigation of their glycaemia, but this is a late event in the spectrum of abnormal glucose control. For those who returned NGT and IGT, it is only CGM which can tell us which individuals have problematic glycaemic control and leads us in addressing this clinically.

7.5.4 Exploring whether OGTT and CGM results are associated with prior change in lung function and weight in adults with CF

Unlike Hameed et al, in my cohort no measure of CGM or OGTT was related to clinical decline up to 2 years prior to the study. (Hameed et al., 2010) There may simply not be enough numbers in either study to draw reliable conclusions. I did consider there to be a substantial amount of clinical data from which to determine the slopes for lung function, weight and BMI for all but 2 individuals, although this aspect is not commented on in the published paper. There are several other possible reasons behind my differing results.

Firstly, the diabetic tolerance group were heterogenous, with some individuals being established diabetics treated with insulin. Their slope data may not have shown decline in weight and lung function due to being optimised clinically, unlike that which would be expected for newly diagnosed diabetics.

My data was taken only from centre visits when patients were known to be stable, and it is unclear whether this was the case in the Australian group’s work. One known difference is that the children and adolescents studied did not have glucocorticoid treatment at the time of the study OGTT and CGM, whereas several of my patients included these in their maintenance medication regime. There are likely to be many similar confounding variables
in my study population, such as individuals having other complications of CF, differing microbiological profiles, different clinical management strategies in each centre etc. Not least is the fact that the Australian study concerned children and adolescents whereas mine only involved adults. The expected change in lung function and weight over a 2 year period would be different in children than adolescents, and similarly adolescents and adults.

Last of all, there may simply be no true correlation in adults with CF, between lung function or weight in the preceding 2 years and real life glycaemia as measured by either CGM or OGTT.

7.5.5 Is CGM superior to the OGTT in assessment of glycaemia in adults with CF?
CGM offers a superior means of assessing glycaemic control in CF than the OGTT. The OGTT is a historical test in CF, and is interesting in spite of whether centres wish to use it or not.

If we think of OGTT as a screening test, highlighting if patients are at risk of CFRD, then it does fulfil its role, but only late on in the spectrum of glycaemic control, when patients return a DGT result. There is still much to do clinically with such patients to determine their daily glycaemic control and whether insulin treatment is warranted. Conversely those returning normal or impaired results could have substantially abnormal glycaemia or acceptable stable glucose control, but such individuals cannot be discriminated from OGTT results alone. Continuous glucose monitoring has evolved from the OGTT and other conventional means of assessing glycaemia, and can actually represent the true day-to-day variability of glucose level during normal life events for those with CF.
Of note, HbA1c correlated with mean CGM level and variability of CGM glucose level, showing glycaemia over 72 hrs can also be associated with glycaemia over 8 to 12 weeks. OGTT alone or in combination with HbA1c or CBG profile is not as informative as CGM alone.

7.6 Conclusions

The OGTT is an adequate but not relevant measure of glycaemic control in adults with CF. It does reflect real life glycaemia, but is a ‘snapshot’ of this whereas the CGM in comparison, could be likened to a ‘film’ quality assessment.

There is no relationship in this study of 50 adults with CF, between change in lung function or weight over 2 years prior to assessment and glycaemia measured by OGTT or CGM.

CGM has a potential role in recognising early abnormal glycaemia and forms a basis for ongoing management. We still don’t know how best to utilise CGM in clinical practice, but realise it has implications for tracking the variable glycaemic control in normal life, supplementary feeding, during exacerbations and for pregnant patients with CF. In any setting, CGM allows tailoring of insulin therapy to an individual’s requirements.

I go on to explore the use of CGM to explore early abnormal glycaemic control in the next chapter and following that, determine how acceptable CGM is to adults with CF.
Chapter 8

USING CONTINUAL GLUCOSE MONITORING TO DETECT EARLY ABNORMAL GLYCAEMIC CONTROL IN ADULTS WITH CYSTIC FIBROSIS

8.1 Background

In 2002 Yung et al reported from a prospective study of glucose handling in adults with CF and healthy controls that even in those with CF and normal glucose tolerance (NGT) by OGTT, pancreatic beta cell function is already compromised compared with healthy controls. (Yung et al., 2002) This finding remains very relevant for our CF population, as we are ultimately interested in identifying abnormal glycaemic control at an early stage, and if necessary intervention with insulin treatment to prevent pre-diabetic pulmonary and nutritional clinical decline.

Since current UK CF guidelines do not recommend any changes in management for those with NGT (CFTrust, 2004), we may be missing out on opportunities to address abnormal glucose handling in these individuals. Continual glucose monitoring (CGM) offers the ability to pick up abnormal glycaemic control at this early stage where conventional methods of assessing glycaemic control such as OGTT, HbA1c and capillary blood glucose (CBG) profile may still all be unremarkable. CGM may have a role in recognising and treating early insulin deficiency.
8.2 Aims

Objectives of this study were:

1) To explore how glycaemic control differs in those with CF compared with healthy controls, using the OGTT, CBG profiles, HbA1c and CGM.

2) To see if individuals with CF and NGT had abnormal glycaemic control, compared to healthy volunteers, measured by CGM.

8.3 Methods

8.3.1 Study characteristics

This was a prospective observational study, involving 50 adults with CF who were clinically stable and 10 adult healthy control volunteers. It was carried out at a single centre, the Manchester Adult Cystic Fibrosis Centre (MACFC).

8.3.2 Inclusion and exclusion criteria

The patients had to be aged at least 18 years and have phenotypic and/or genotypic features of CF. Pregnant patients were excluded. Subjects who were unable to give informed consent, were not eligible for participation.

Healthy control volunteers had to be aged 18 years to 40 years inclusive, mostly to match the age range of patients but also to decrease the risk of recruiting individuals with undiagnosed diabetes. Control subjects were not included if pregnant, or if they had any medical conditions or took any medications known to affect glycaemic control.
8.3.3 Consent
All patients and control subjects gave informed written consent to being in the study, which included permission for their GP to be informed of their participation and for researchers to have access to their clinical records relating to the study.

8.3.4 Ethical approval
The study was approved by the North West Research Ethics Committee no.10 (formerly Lancashire and Cumbria B). Site-specific approval was granted by the Research and Development Department of the University Hospital of South Manchester NHS Foundation Trust.

8.3.5.1 Study procedure – stable patients
50 Participants had a 72 hour CGMS at home during a time of clinical stability and attended for an OGTT in the outpatient clinic during this period.
Clinical stability was defined by absence of an infective respiratory exacerbation, meeting the following criteria:
(1) Only up to one of the following: increased shortness of breath, increased cough, thicker or increased volume of sputum, haemoptysis, greater than ten percent fall in FEV$_1$.
(2) No supplemental antibiotics (IV or oral), short term oral corticosteroids or change in long term oral corticosteroid dose in the preceding two weeks.

Continual glucose monitoring
Setting up of CGM took place either in the outpatient clinic or the patient’s home, depending on their preference. Informed written consent was obtained.
After identification of a suitable site on the abdomen, the skin was cleansed and a subcutaneous glucose sensor (*Medtronic, USA*) inserted, between 3 cm and 8 cm lateral to the umbilicus. This was allowed to ‘wet’ for at least 10 minutes, during which time the patient was familiarised with capillary blood glucose (CBG) checking technique, and how to complete the 3 day food and events diary sheet.

After this time the wireless recorder (‘iPro’, *Medtronic, USA*) was connected to the sensor. A live software package (‘iPro Solutions’, *Medtronic, USA*) was used to ‘initialise’ the recorder and sensor. The first 7 of 50 stable CF patients used the previous generation of CGM recorders, the ‘CGMS Gold’ (*Medtronic, USA*), which was not wireless, and undertook its own 60 minute initialisation process with no need for live computer software. All 50 patients and 10 healthy control volunteers used the identical type of disposable sensors and set-up of CGM was identical in every other aspect. During this process, a glucometer (Aviva Accucheck, *Roche, UK*) was synchronised with the iPro CGM device, which the patients used over the 72 hours to record 4 CBG daily for calibration. CBG testing strips were quality controlled prior to use. Subjects were instructed that pre-prandial and bedtime CBG sampling times were preferred but not compulsory and that no more than 12 hours should elapse between consecutive CBG samples.

The CGM device was covered by a waterproof dressing, allowing showers and exercise but not immersion in water. In the case of the first 7 CF patients using the ‘CGMS Gold’ (*Medtronic, USA*) recorders, ‘showerpacks’ were issued, disposable plastic covers which were used to protect the CGM recorders during showering and exercise.
The patients were instructed to keep a written log of CBG results, food and drink consumed, any insulin, oral corticosteroid or antifungal medication taken, any exercise and any adverse events. Sensor data is stored in the recorder for subsequent download following removal, with no visible reading available to the wearer. Participants were advised not to modify their usual diet or activity during the 72 hour recording period, apart from fasting overnight prior to the OGTT.

The subjects had written instruction on how to remove the CGM device and return with study paperwork and glucometer after the 72 hour monitoring period.

Glucose Tolerance

OGTT was scheduled for 1, 2 or 3 days after CGM placement. (This degree of flexibility was required in order to keep to strict clinic microbiological cohort segregation protocols). Subjects attended an outpatient clinic having fasted for at least 8 hours overnight and omitted any usual overnight nasogastric or gastrostomy feeding. Any long or intermediate acting insulin from the previous evening and any morning insulin was omitted.

Baseline fasting venous samples (plasma glucose and glycosylated haemoglobin) and capillary blood glucose were taken. The subject then had up to 5 minutes to ingest a standard oral liquid glucose load (comprising 1.75g/kg anhydrous glucose to a maximum of 75g). Participants then rested, seated for 2 hours, without any further oral intake. Repeat venous plasma glucose and CBG samples were taken 2 hours after complete ingestion of the glucose load.
Participants were allowed home following the OGTT and instructed to carry on with usual daily diet and activities, including any overnight nasogastric or gastrostomy feeding.

Pulmonary Function and Nutritional Status

At the time of OGTT, subjects had their weight and height recorded and performed spirometry (*Vitalograph, UK*) according to our centre’s standard procedure. Percentage predicted FEV$_1$ (Knudson et al., 1983) and BMI were recorded for each participant. Casenotes were used to record demographic characteristics, most recent glucose tolerance status, usual medications, requirement for supplementary nutrition, exocrine pancreatic enzymes and other CF and non-CF disease complications.

8.3.5.2 Study procedure – healthy control subjects

10 healthy non-CF control subjects were recruited to undergo the simultaneous CGM and OGTT. Control subjects had height and weight recorded but did not perform spirometry. During OGTT, the only additional blood sample taken was HbA1c.

8.3.6 Statistical analysis

Raw data was stored using Excel (Microsoft Office 2004). ‘Solutions’ software (*Medtronic USA*) was used to download raw data from the continual glucose CGMS Gold and iPro monitors. This software performs regression analysis to produce CGM glucose levels for every 5 minutes from raw sensor data and calibration CBG values, resulting in each individual’s CGM trace and summary data report.
Descriptive statistics performed within SPSS (version 15.0, Microsoft, USA) were used to determine summary demographic and glycaemic control data.

SPSS was used to calculate Spearman’s or Pearson’s correlation coefficient (as appropriate, depending on whether variables were parametric or non-parametric) from the raw data for mean CBG and HbA1c, mean CGM and HbA1c and mean CBG and mean CGM for stable adults with CF.

‘Normal’ healthy (non-CF) values for mean and variability of CGM level were derived from the 10 healthy control CGM traces following statistical advice (Prof J Morris, UHSM). Confidence intervals of 99% were used, rather than 95%, due to the small sample size.

The Two-sample t-test or Mann-Whitney U test was used, dependent on whether variables were Normally distributed or not, to compare mean values of glycaemic variables between the healthy non-CF control group and those with CF and normal glucose tolerance by OGTT.

**8.4 Results**

Summary demographic data and glucose tolerance results are shown in Table 8.1 and summary glycaemic control results are shown below in Table 8.2.
Table 8.1 Demographic data and glucose tolerance test results for stable cystic fibrosis and healthy control subjects

<table>
<thead>
<tr>
<th></th>
<th>Male n (%)</th>
<th>Age (years) Median (IQR)</th>
<th>BMI (kg/m$^2$) Mean (SD)</th>
<th>Glucose tolerance n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable CF patients</td>
<td>30 (60)</td>
<td>27.1 (22.6 to 37.9)</td>
<td>21.7 (3.0)</td>
<td>NGT 25 (50) IGT 9 (18) DGT 16 (32)</td>
</tr>
<tr>
<td>(n=50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>6 (60)</td>
<td>31.6 (30.0 to 35.0)</td>
<td>23.6 (2.5)</td>
<td>NGT 10 (100)</td>
</tr>
<tr>
<td>(n=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8.2 Summary data for fasting plasma glucose, 2 hour plasma glucose, mean capillary blood glucose, HbA1c and mean and variability of continual glucose monitoring glucose level for groups of stable CF patients and healthy controls according to glucose tolerance category

<table>
<thead>
<tr>
<th>Glucose tolerance category by OGTT</th>
<th>Controls</th>
<th>Stable CF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(All NGT) n=10</td>
<td>All n=50</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td></td>
<td>NGT n=25</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.7 (4.4 to 4.9)</td>
<td>5.2 (4.5 to 5.9)</td>
</tr>
<tr>
<td>2 hour plasma glucose (mmol/L)</td>
<td></td>
<td>IGT n=9</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.3 (4.0 to 4.7)</td>
<td>7.8 (5.4 to 13.0)</td>
</tr>
<tr>
<td>Mean CBG (mmol/L)</td>
<td></td>
<td>DGT n=16</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.0 (4.8 to 5.3)</td>
<td>6.0 (5.5 to 7.1)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td>5.8 (5.3 to 6.1)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.0 (4.9 to 5.1)</td>
<td>5.6 (5.5 to 5.9)</td>
</tr>
<tr>
<td>Mean CGM (mmol/L)</td>
<td></td>
<td>6.0 (5.6 to 6.0)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.9 (4.7 to 5.3)</td>
<td>5.9 (5.6 to 6.1)</td>
</tr>
<tr>
<td>Variability* CGM (mmol/L)</td>
<td></td>
<td>7.4 (6.6 to 8.5)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.6 (0.1)</td>
<td>1.3 (0.6)</td>
</tr>
<tr>
<td>% time CGM glucose ≥ 7.8 (mmol/L)</td>
<td></td>
<td>1.7 (0.9)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.0 (N/A)</td>
<td>2.8 (1.0)</td>
</tr>
</tbody>
</table>

*Variability of continual glucose monitoring level is the standard deviation of sensor glucose level throughout all the values from the 72 hour trace
Correlations between methods of assessing glycaemia in stable adults with CF

There are positive correlations between Mean CBG and HbA1c (Spearman’s, r=0.639, p<0.01), Mean CGM and HbA1c (Spearman’s r=0.639, p<0.01) and Mean CGM and Mean CBG (Spearman’s, r=0.666, p<0.01).

Comparison of glycaemia between adults with CF and NGT and healthy non-CF controls

There is a notable difference between mean CGM glucose, variability of CGM glucose, HbA1c, and Mean CBG between healthy non-CF controls and CF subjects with normal glucose tolerance. Table 8.3 below shows ‘normal’ ranges defined from the 10 healthy CF control subjects’ data and the number of CF patients who are above these ranges (grouped by OGTT category).
**Table 8.3** Healthy glycaemia by continual glucose monitoring of controls and number of stable cystic fibrosis patients above reference range

<table>
<thead>
<tr>
<th>99% confidence interval for healthy continual glucose monitoring reference range</th>
<th>Stable CF patients above range</th>
<th>no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (mmol/L) 4.01 to 5.89</td>
<td>Normal n=25</td>
<td>Impaired n=9</td>
</tr>
<tr>
<td></td>
<td>14 (56)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Variability (mmol/L) 0.27 to 1.01</td>
<td></td>
<td>15 (60)</td>
</tr>
<tr>
<td>No. (%) of CF patients above range for mean and / or variability</td>
<td>19 (76)</td>
<td>8 (89)</td>
</tr>
</tbody>
</table>
8.5 Discussion

This study aims to explore glucose handling in stable adults with CF and healthy subjects using conventional (OGTT, HbA1c, CBG) and newer means of assessing glycaemia (CGM). In particular, glycaemic control in individuals with CF and normal glucose tolerance is explored, using a non-CF healthy group of individuals to define ‘normal’ limits of continual glucose monitoring.

8.5.1 Study population

As in Chapter 6, our 50 stable adults with CF are broadly representative of our MACFC clinic population. Table 8.1 shows that our 10 control subjects were matched for sex, but not for age. This is partly due to a wide range in age in our clinic population (we have several patients in their seventh decade) and partly as we deliberately did not recruit controls over age 40 years to avoid undiagnosed T2DM. Our CF patients tended to have a lower BMI than our volunteer healthy controls. All our control participants had NGT, as anticipated, as they were without any known factors affecting glycaemic control. The proportion of individuals with CF in each glucose tolerance category is representative of our whole clinic cohort, as discussed earlier in Chapter 6.

8.5.2 Exploring how glycaemic control differs in those with CF compared with healthy controls, using the OGTT, CBG profiles, HbA1c and CGM

Using OGTT category to group our CF patients and healthy control volunteers (Table 8.2), those with CF have a greater range of glycaemia, as one would expect, with half of the CF adults having impaired or diabetic glucose tolerance, and none of the healthy subjects having impaired or diabetic glucose tolerance.
Those with CF have a higher level of glycaemia than control subjects, with all methods of assessing glycaemic control (Table 8.2, comparing the ‘All CF’ column with the ‘Controls’ column). For example, the median 72 hour CBG value is 6.0 mmol/L in CF, compared with 5.0 mmol/L in controls, the median HbA1c value is 6.0% in CF, compared with 5.0% in controls, and the median ‘mean CGM’ and mean ‘variability CGM’ over 72 hours are 6.3 mmol/L and 1.8 mmol/L in CF, compared with 4.9 mmol/L and 0.6 mmol/L respectively in controls.

As glucose intolerance increases, those with CF have an increasing percentage of time with sensor glucose $\geq 7.8$ mmol/L as (NGT 11.4%, IGT 20.0% and DGT 38.9%), whereas healthy non-CF controls did not record any sensor glucose levels above this threshold value.

8.5.3 Determining whether those with CF & NGT have abnormal glycaemic control, compared to healthy volunteers, measured by CGM (using a ‘normal’ CGM reference range derived from control data)

Table 8.3 shows that of the 25 individuals with CF and a normal OGTT result, 14 (56%) have a higher mean CGM than controls and 15 (60%) have a higher variability of CGM than controls. In total, 19 (76%) have a higher mean or variability of CGM than control participants.
8.5.4 Clinical relevance of CGM results for those with CF and NGT

Two patients in this group were commenced on insulin as a result of their CGM traces.

Figure 8.1 below shows an example of one of these individual’s CGM traces.
**Figure 8.1** Example of 24 hours of continual glucose monitoring trace from a person with cystic fibrosis and normal glucose tolerance who was subsequently commenced on insulin
There were pre-existing clinical concerns surrounding these patients’ failure to gain weight. A third patient in this group was to be commenced on insulin as a result of their CGM trace (showing sharp post-prandial glucose excursions followed by hypoglycaemic dips), though it subsequently transpired that their dietary intake during the study had been chosen to provoke the symptoms of hypoglycaemia which they had reported was interfering with their daily work and home life. Repeat monitoring following dietary modification showed a more acceptable trace.

Three patients in this CF-NGT group were advised to make immediate dietary modifications to avoid potentially adverse clinical hyper- and hypoglycaemia. A further 5 patients were ‘earmarked’ as potentially requiring insulin during hospital admission for infective exacerbations or if weight gain was needed in future.

8.5.5 Clinical relevance of CGM results for those with CF and IGT

Four out of the nine CF patients with impaired glucose tolerance were in fact reassured that they had satisfactory everyday glycaemic control. This shows how the WHO threshold criteria for categorising glucose tolerance may not be so meaningful in people with CF. In addition to recognising early abnormal glycaemic control, CGM also has the potential to reassure those with acceptable ‘real life’ glycaemia, when the OGTT has been abnormal. See Figure 8.2 below for an example of a CGM trace from a CF patient with IGT, who was considered to have normal glycaemic control by CGM.
**Figure 8.2** Example of a continual glucose monitoring trace from a patient with cystic fibrosis and impaired glucose tolerance who was considered to have normal glycaemic control.
8.5.6 CGM as a tool to pick up early abnormal glycaemic control

Consistent with Yung’s earlier work (Yung et al., 2002), this study shows that people with CF who have normal glucose tolerance results still have abnormal glucose handling, when measured by CGM. Indeed, three quarters of our CF with NGT individuals have abnormal high mean CGM or abnormally variable CGM levels, or both. Of these 19 individuals none had impaired fasting glucose (plasma glucose 6.1 to 6.9 mmol/L (WHO, 2006)). All 19 had a normal HbA1c (<6.5%). (ADA, 2001)

It is notable that our CF patients had substantial periods of time spent with sensor glucose ≥ 7.8 mmol/L though healthy controls did not have sensor glucose readings above this level. It may be that percentage time with sensor glucose ≥ 7.8 mmol/L is one of the more useful discriminating outcomes of continual glucose monitoring.

Those sceptical about a role for CGM may argue that an average CBG level taken over 72 hours correlates just as well with HbA1c, so why bother with an expensive new CGM tool? The answer lies in its usefulness not only as a diagnostic test but for forming the basis of a management plan and being appealing and acceptable to patients (more of this in Chapter 9). CBG profiles just cannot provide the same ‘picture’ of real-life glycaemia as a CGM trace.

8.5.7 Limitations

This is a pilot observational study involving a small number of subjects. The CF patients are however reasonably representative of our CF clinic population. Only 10 healthy control subjects were recruited and these could not be age-matched to CF participants. Data from
these 10 controls has been used to define ‘normal’ glycaemic control by CGM, when it would clearly be preferable to use greater numbers of healthy subjects for this. Some attempt to account for this small number of controls has been made by using 99% rather than the standard 95% confidence intervals for the control data.

As in Chapter 7, for this work I have trusted subjects to report food intake, blood glucose and exercise with sufficient accuracy, allowing possible recall bias or human error to affect results.

Although we speculate that abnormal early glycaemic control picked up by CGM is associated with insulin deficiency and/or insulin resistance in CF, we have not confirmed this with laboratory measurements of insulin in our study. For any further work it would be relevant to examine fasting insulin levels and the ‘insulin curve’ during OGTT to estimate beta cell function and insulin resistance in subjects with CF and healthy controls, as per Yung et al. (Yung et al., 2002) For this research this would have been prohibitively expensive and beyond the scope of the objectives of the study.

As in Chapter 7 I am reliant on the accuracy of ‘Solutions’ software for CGMS Gold and iPro recorders (Medtronic, USA). Once again, the first 7 patients used the older ‘CGMS Gold’ monitors while the remainder used the ‘iPro’ devices, and no formal reproducibility or repeatability testing was carried out.

As stated in chapter 6, the accuracy of CBG values and therefore CGM values, HbA1c levels and plasma glucose will be variable, reflecting the real-life clinical setting in which this research was carried out.
8.6 Conclusions

In individuals with CF, the OGTT fails to discriminate those with NGT or IGT who are at risk of clinically relevant abnormal glycaemia from those with NGT or IGT who are truly stable.

CGM has a role in early recognition of abnormal glycaemic control in ‘real life’ in stable adults with CF, regardless of OGTT result.
Chapter 9

PATIENT EXPERIENCE OF CONTINUAL GLUCOSE MONITORING

9.1 Background

I have shown that continual glucose monitoring (CGM) is valid in adults with CF and that it has a broad potential clinical application including the early recognition and treatment of abnormal glycaemia in CF. If these clinical roles are to be fulfilled, then it is vital that we have insight on the views and experiences of CGM from people with CF. This knowledge could be used to improve CGM technique and protocol to seek optimal patient satisfaction, which should aid uptake and compliance with this method of clinical assessment.

A review of the literature failed to locate published evidence on patient experience of CGM in CF, though there is one such article available in individuals with T1DM and T2DM. (Newman et al., 2009) A questionnaire study in subjects with CF who have undergone CGM should provide new insight into this area of care.

9.2 Aim

My aim was to evaluate the CF patients’ experiences of having CGM, determining how much it interfered in their lives and how acceptable they found this, as well as whether CGM was useful to them and how it compared with having an OGTT.

I also wanted to gather views from patients using older ‘Gold’ monitors, newer wireless ‘iPro’ devices and if possible, patients with experience of both.
I wanted to determine themes within the collective patients’ experiences and feedback, which may guide future considerations for CGM.

9.3 Methods

Drawing on the questionnaire survey by Newman et al (Newman et al., 2009), and with permission from this author, I devised a questionnaire. This document was sent to all 50 CF patients who completed my original study. The questionnaire included open and closed questions in relation to the procedures used in the original study.

9.3.1 Data Collection

A letter was sent to the 50 adults with CF who took part in the original study. The letter outlined the purpose of collecting information about the acceptability of procedures they have undergone and asked them to complete an enclosed questionnaire. It was made clear that replies would be anonymous. An administrative assistant set up a system for disseminating and collating questionnaires and replies, without the identity of the patient being known to the researchers. A prepaid envelope was provided so that participants could return it without any delay. Those failing to return a questionnaire within two weeks were sent out a reminder letter. If there was no response received for two weeks after the reminder letter was sent it was assumed that the patient did not wish to participate in the questionnaire project.
9.4 Analysis

Data from the returned questionnaires was collated using statistical computer package SPSS (version 15.0, Microsoft, USA). Emphasis was on descriptive statistics. Inferential work was done, comparing responses from individuals who used different types of monitors, though results are interpreted with caution, as no formal power calculation was conducted. Free text comments were typed verbatim into a Microsoft Word 2004 document (Microsoft, USA). A thematic analysis was employed with these data.

9.5 Results

50 questionnaires were distributed, and after one reminder letter 29/50 (58%) were returned completed.

9.5.1 Whether ‘CGMS Gold’ or ‘iPro’ monitor used in the study

6/29 (21%) respondents used the older ‘CGMS Gold’ devices and 23/29 (79%) used the newer wireless ‘iPro’ devices. A greater proportion (6/7, 86%) of those using the ‘CGMS Gold’ completed the survey than those using the ‘iPro’ (23/43, 53%).

9.5.2 Interference with activities of daily living

Generally CGM interfered only a little, if at all, with activities of daily living. The numbers involved are too small for quantitative analyses. Moderate interference was only reported on a small number of occasions, and in those, more often with the older monitors than the newer wireless devices (despite only 6 respondents using Gold and 23 using iPro)
monitors). When any device was reported to have interfered, the respondents almost always found this very or completely acceptable.

9.5.3 Practical aspects of using the monitor and its impact

The majority of respondents (23/29) were happy with the number of finger pricks required and length of time for the monitor to be worn (26/29). If respondents were unhappy, it was more often related to number of finger pricks than length of time worn.

The majority of subjects (22/29) would be interested in using the CGM technique in future and would recommend to others in a similar situation to them.

9.5.4 Undesirable Effects

A large proportion (from 11 to 17 out of 29) of respondents indicated they had each of the 5 specific side effects enquired about from wearing their monitor. None indicated that these were not acceptable and increasing numbers of applicants found these ‘slightly’, ‘moderately’, ‘very’ and ‘completely’ acceptable.

9.5.5 Reasons for taking part

The majority of those completing the survey said that they wanted to help the unit by taking part in research. Two thirds of patients wanted to find out about their glucose control. Small numbers had specific reasons for undertaking CGM such as improving their diabetic control, having an abnormal OGTT result, high or low CBGs at home, and difficulty gaining or maintaining weight. One patient specified wanting to investigate the reasons behind their previous hypoglycaemic symptoms with CGM. Because patients
could give more than one reason for participating, it is not possible to know how many took part simply to help the unit with research without any other personal incentive.

9.5.6 Whether participants found continual glucose monitoring useful

Of those who reported finding CGM useful as part of the study (21/29, 72%), the reasons given tended to fall under 4 themes:

A third of patients who found CGM useful reported that the whole process was informative and interesting. A similar proportion cited finding CGM useful because of specific findings relating to their blood glucose at particular times of day, blood glucose levels relating to certain foods, drinks or supplemental feeding, or monitoring helping to improve diabetic control. Three respondents specified that CGM had helped to confirm or exclude the presence of diabetes for them, or had given them an understanding of their personal risk of developing diabetes. Three patients reported that CGM was useful as they felt it was more accurate than other types of tests.

Only one participant reported that they did not find CGM useful but qualified this by saying that they were satisfied that they were ‘helping the unit with research, which may in turn help others’. Several patients did not state whether they had found CGM useful or not.

9.5.7 Helping subjects to understand glucose control in CF

Two thirds (19/29, 66%) of respondents indicated that they felt taking part in the study had helped them to understand glucose control in CF ‘a lot’.
9.5.8 Preference for CGM or OGTT at future annual assessments

Over half (16/29) of participants said they would prefer CGM to OGTT. Reasons given included: CGM is ‘more accurate’, CGM gives ‘more useful information’ and OGTT ‘requires you to starve’. Amongst those that preferred the OGTT, reasons included: CGM ‘causes discomfort’, OGTT is ‘easier’/’simpler’/’quicker’ than CGM and ‘doesn’t interfere with routine as much’.

9.5.9 Preference for ‘CGMS Gold’ or ‘iPro’ device

All the 6 subjects who had used both CGM device types by the time of completing the questionnaire preferred the wireless iPro monitor but reasons for this were not given.

9.6 Discussion

For this questionnaire survey, subjects were able to remain anonymous to encourage honest feedback. 29/50 (58%) of invited participants completed the questionnaire, a respectable response rate for this method. This may in part be due to the enthusiasm and positive attitude of this group of patients for the original study. A significant number of those in the clinical study had established CFRD, were familiar with CGM and were already advocates of this technique, which does raise the possibility of selection bias. The worst case scenario is that all non-respondents (21/50, 42%) had negative experiences of CGM but no incentive to feed this back via the survey. There are also variable degrees of recall bias for patients, some of whom completed their CGM several months before the questionnaire was distributed.
6/7 (86%) of those who wore the Gold monitors responded to the survey, compared with 23/43 (53%) who used the iPro. The first 7 study patients used Gold monitors and these first patients were more likely to be keen on volunteering to take part and more likely to be patients with CFRD and a strong incentive to undergo further CGM monitoring. It follows that such individuals may have a stronger interest in feeding back about their experience of being in the study and undergoing CGM than others who may have volunteered to help the unit’s research but have no personal interest in CGM.

With a total of 29 completed surveys, the numbers of different responses are too small for quantitative analysis, but useful themes and trends in data have emerged.

The data implies that CGM interferes little with activities of daily living, and when it does interfere this is generally very well accepted. Minor side effects are very common but patients are very tolerant of these. Those patients who had used both the older and newer CGM devices preferred the newer form, consistent with the trend in the acceptability data for the smaller device to cause less interference and be more tolerable than its larger predecessor. The older wired CGM recorders are now obsolete and any patient having CGM would now use the small wireless versions. Technology is improving not only in terms of device size but device accuracy and newer monitors may require less CBG values for the same or greater degree of device accuracy. Patients would be likely to find such monitors more acceptable than the CGM recorders currently in use.

The substantial proportion of participants who felt that using CGM helped them to understand glucose control in CF may be attributable to the pictorial results that the CGM traces provide and the associated personal feedback from the dietician, diabetologist or
specialist nurse. With hindsight, further questioning on this aspect of patients’ understanding of glycaemic control from CGM would have been desirable.

It is useful to know some of the reasons why patients prefer CGM over OGTT and vice versa for assessing glycaemic control. It is not possible to know if the respondents who prefer CGM are mainly those with established CFRD or if a significant number have the potential to have early abnormal glycaemia. Again, this would have been valuable to build in to the questionnaire survey.

The majority of questionnaire participants reported that they found CGM useful, would be interested in using CGM in future and would recommend this tool to others in a similar position. This positive feedback from the patients’ collective experiences adds weight to the potential broader role of CGM as an acceptable and well-tolerated clinical tool to identify and treat early abnormal glycaemia.

9.7 Conclusion
This small questionnaire study gives valuable insight into the CF patients’ experiences of CGM. Carrying out CGM interferes little in their lives, such interference being acceptable, and broadly users report positive experiences. Positive and negative aspects of CGM from the patients’ perspectives can be used to guide in which circumstances it would be most beneficial for adults with CF in future.
Chapter 10

SUMMARY AND CONCLUSIONS

CF-related diabetes is increasingly common as adult survival improves in CF, yet it represents one of the greatest challenges to manage for both patients and clinicians. The historical screening test for diabetes in CF, the oral glucose tolerance test (OGTT), adapted from other populations, does not seem to meet the needs of the CF population, in terms of identifying abnormal glycaemic control at an early stage to prevent future complications. The limitations of the OGTT in CF have given rise to a search for newer methods of assessing glycaemia, and the CF community has looked to the wider non-CF diabetic community for solutions. One particular means of assessing glycaemia investigated is continual glucose monitoring (CGM) and I investigated roles for this within CF by carrying out a number of studies.

Validation of Continual Glucose Monitoring in CF

The validation study showed that the accuracy of interstitial glucose monitoring in adults with CF is comparable to that in non-CF population, including those with type 1 and type 2 diabetes mellitus. Validation of the CGM as a tool in adults with CF has been overlooked or assumed by some authors who have reported on its clinical applications. This important step in my pilot study should contribute to future work to evaluate the best clinical utilisation of CGM and how best to interpret results.

All low and high trends in glycaemic control are captured with CGM, unlike with CBG profiles, though it must be remembered single point glucose values cannot be as accurate
as that of plasma glucose or CBG. Though my reported accuracy of CGM in CF is comparable to that published in non-CF studies, a greater degree of accuracy in the clinical setting will always be desirable. Caution is recommended, to consider in combination all other glycaemic control measures available for a person with CF, when interpreting CGM traces, as the trends of the traces rather than absolute individual values, are likely to be more useful. Reasonable steps can be taken, however, in the clinical setting of performing CGM, to optimise its accuracy.

Robust reliability and reproducibility analyses were not incorporated into this validation study and future work would address this important factor.

The validation study findings lead on to comparison of CGM and OGTT in stable adults with CF, finding relationships between these tests, and exploring any added value of CGM.

**Comparison of OGTT and Continual Glucose Monitoring**

My second study showed that various measurements derived from the OGTT do relate to real-life glycaemic variations over 72 hours, as measured by CGM. I found no relationship between prior slope of lung function or weight with glycaemia during the study period in my 50 adult subjects, though this is an area warranting further study.

This study shows that OGTT is a historical categorisation, with little relevance to the daily lives of people with CF, other than identifying late abnormal glycaemic control with a diabetic tolerance test result. CGM in comparison, provides the same basic information as OGTT but also captures the unique glucose variations seen in people with CF. CGM is able to assess ‘real life’ glucose levels over 72 hours, beyond the artificial setting of a
patient having an assessment visit to a CF unit for OGTT. The information gathered by CGM has greater relevance to patients’ daily lives. Also the CGM can guide immediate changes in management, as opposed to the OGTT providing a diagnostic or screening result which then requires further investigation.

Use of Continual Glucose Monitoring to identify early abnormal glycaemic control

My validation work and comparison of OGTT and CGM resulted in a further study involving healthy control subjects alongside adults with CF. This showed that glycaemic control measured by CGM differs markedly in people with CF compared to healthy non-CF controls. Furthermore, CGM was used to identify those individuals with CF and normal glucose tolerance by conventional criteria, who had clinically relevant abnormal glycaemic control. CGM showed problems with glycaemic control leading to changes in management that may not have been detected by CBG profiles, HbA1c and OGTT.

These findings show potential for future studies using CGM to evaluate therapeutic intervention for early abnormal glycaemic control.

Patient Experience

Finally, the simple patient experience study has achieved unique insight into what patients think of undergoing CGM and OGTT. Their feedback will allow us to consider changes to CGM technique and protocol for better acceptability to patients.

I hope that these studies contribute in some way, to a better understanding of glycaemic control in CF, and how we may best take continual glucose monitoring forward, in order to optimise survival and quality of life for patients.
Chapter 11

FURTHER WORK

This original research has lead to the potential for further research and ideas. Favourable responses from abstract presentations at national and international meetings have also stimulated discussion on further directions for applications of continual glucose monitoring in clinical practice and research.

11.1 Application of findings to clinical practice

I have shown that CGM is a valid tool for assessing glycaemic control in CF. Furthermore CGM can recognise clinical significant abnormal glycaemic control, even when conventional measures of glycaemia may be unremarkable. It is a more relevant and adequate assessment of glycaemia than the OGTT and acceptable to CF patients. CGM therefore needs to be incorporated into the standard practice of CF teams.

11.1.1 Clinical situations in which to use Continual Glucose Monitoring

We need to establish clinical situations in which to apply CGM, such as:
1) In asymptomatic patients, with suspected abnormal glycaemic control.
2) During infective exacerbations.
3) Pre- and post- supplemental feeding, oral corticosteroids, anti-fungal drugs and pregnancy.

11.1.2 Standardised reporting of Continual Glucose Monitoring in CF

We need to have a standard methodology for reporting of CGM in clinical practice.
11.2 Research

11.2.1 Reliability and reproducibility of continual glucose monitoring

We need to have acceptable standards for reliability and reproducibility of CGM devices and sensors.

11.2.2 Patient satisfaction

I have shown that patients are satisfied with CGM. Further work to determine whether shorter monitoring periods would still provide enough clinical information to recognise and address problems with glycaemic control would be advantageous.

11.2.3 Insulin levels

There is a great deal of work to be done examining insulin levels as well as glucose levels in CF to evaluate the progressive loss in beta cell function. CGM may have a role in such research.

11.2.4 Airway glucose levels

Another potential area of research is use of CGM in examining the relationships between interstitial and airway glucose levels.

11.2.5 Early insulin therapy to delay the onset of CFRD

We are aware of a prodromal phase of CFRD, but have difficulty in detecting and treating this. CGM has a potential research role in recognising individuals in this pre-CFRD phase and guiding their management.
Continual glucose monitoring is in its infancy in CF. My research has provided directions which could be taken for its use in therapeutic intervention.


**European Cystic Fibrosis Conference,**


