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Cystic fibrosis related diabetes: Optimising care with a multidisciplinary approach

Freddy Frost[1], Paula Dyce[2], Alicja Ochota[3], Sejal Pandya[3], Thomas Clarke[4], Martin J Walshaw[1], Dilip S Nazareth[1]

Corresponding author:

Dr Freddy Frost BMedSci BMBS MRCP
Adult CF Centre
Liverpool Heart and Chest Hospital
Liverpool, UK
L17 0AF
Freddy.Frost@lhch.nhs.uk

[1]Respiratory Medicine, Adult CF Centre, Liverpool Heart & Chest Hospital, Liverpool, UK

[2]Cystic Fibrosis Related Diabetes Service, Adult CF Centre, Liverpool Heart & Chest Hospital, Liverpool, UK

[3]CF Specialist Dietician, Adult CF Centre, Liverpool Heart & Chest Hospital, Liverpool, UK

[4]Cystic Fibrosis Psychologist, Adult CF Centre, Liverpool Heart & Chest Hospital, Liverpool, UK

Co-authors:

Paula Dyce,
Adult CF Centre
Liverpool Heart and Chest Hospital
Liverpool, UK
L17 0AF
+441516001199

Alicja Ochota
Adult CF Centre
Liverpool Heart and Chest Hospital
Liverpool, UK
L17 0AF
+441512826473

Sejal Pandya
Adult CF Centre
Liverpool Heart and Chest Hospital
Liverpool, UK
L17 0AF
+441512826473

Thomas Clarke
Adult CF Centre
Liverpool Heart and Chest Hospital
Liverpool, UK
L17 0AF
+441516001340

Martin J Walshaw
Adult CF Centre
Liverpool Heart and Chest Hospital
Liverpool, UK
L17 0AF
+441516001616

Dilip Nazareth
Adult CF Centre
Liverpool Heart and Chest Hospital
Liverpool, UK
L17 0AF
+441516001213

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Abstract

Cystic fibrosis related diabetes (CFRD) is a common complication of cystic fibrosis (CF) and can be present in over 50% of adults with the disease. CFRD is associated with poorer clinical outcomes including accelerated pulmonary function decline and excess morbidity. The management of CFRD is complex and differs from that of type 1 and type 2 diabetes mellitus such that clinicians responsible for the care of people with CFRD must work closely with colleagues across a number of different specialities and disciplines. This review aims to discuss why a multi-disciplinary approach is important and how it can be harnessed to optimise the care of people with CFRD.

1 Introduction

Cystic fibrosis related diabetes (CFRD) is a common complication of cystic fibrosis (CF), first recognised in 1955 when Shwachman described glucose handling abnormalities in a young child with CF. [1] Despite not being associated with some of the classic macrovascular complications of Type 1 (T1DM) and Type 2 (T2DM) diabetes, CFRD causes excess morbidity and mortality in people with CF and hence presents unique challenges for clinicians, patients and families alike.[2-4] Given the complexities of CFRD, a multi-disciplinary team approach is paramount to optimise outcomes. This review highlights the unique nature of the disease and the need for an MDT approach to optimise care and outcomes in people with CF.

2 Epidemiology

Life expectancy in people with CF has improved by over 40 years since the first report of CFRD. [1]With improving survival comes an array of co-morbidities as a result of the prolonged disease process. CFRD is one such complication that already affects over one-third of all adults with CF in the UK and since prevalence increases with age, half of those over 40 years of age have the diagnosis. [5 6] Guidelines now recommend screening from 10 years of age and as such diagnosis in the 10-16 age-groups has increased by 25%. [6-9] In addition to age, risk factors for CFRD include female sex, pancreatic insufficiency and Class I-II mutations [10,11], with female sex and poor lung function identified as predictors of poorer outcomes in CFRD. [3,12]

3 Pathophysiology and Clinical implications

People with CFRD die from progressive respiratory failure rather than the macrovascular complications seen in T1DM and T2DM. In the 1980s, Finkelstein *et al* reported significantly reduced survival in CFRD and also observed deterioration in clinical status for up to 24 months prior to the diagnosis of CFRD being made. [13] It is now well recognised that CFRD is associated with accelerated pulmonary function decline and subsequent excess morbidity and mortality. [3,4,14-18]

Accelerated pulmonary function decline is thought to be related to a combination of metabolic and mechanical changes leading to the introduction of the term ‘diabetic pulmonopathy’. [19,20] The precise

mechanisms underlying diabetic pulmonopathy remain incompletely understood but are likely multi-factorial. Firstly, diabetes is known to be associated with increased infection and non-CF subjects with impaired glucose handling at diabetic thresholds have been shown to have higher morbidity and mortality from pulmonary infection than those with normal blood glucose levels. [21-23]. In normal health, glucose in the airway surface liquid (ASL) is tightly regulated at extremely low levels [24] but in disease airway glucose rises: increased ASL levels occur in both diabetes and chronic lung disease, [24,25] and this is also true in CF where those with CFRD have higher ASL glucose than their non-diabetic comparators. [26] Increased ASL glucose may provide an additional substrate for bacteria and increase bacterial growth and/or infection [27-30] Most workers have used exhaled breath condensate to estimate ASL but the only study to date measuring sputum glucose directly in people with CF found the highest levels in subjects with normal glucose tolerance and the lowest in CFRD. [17] This may be explained by increased glucose consumption by florid bacteria in the lungs of people with CFRD or by differences in glucose kinetics in their mucus filled lungs however regardless it confirms that the dynamics of airway glucose control in CF are more complex than previously thought. [31]

Hyperglycaemia causes reduced lung interstitium elasticity such that the lungs become stiffer and harder to inflate resulting in a decrease in FEV_1 and FVC: furthermore thickening of the alveolar epithelium and the pulmonary capillary basal lamina results in diminished diffusion across the alveolar/capillary membrane. These changes culminate in a greater rate of age-related decline in lung function [32,33] in those with diabetes. Additionally, changes similar to those in the diabetic kidney, although less marked. [34] also occur in the arterioles and capillaries of the lung. It seems likely that these changes, taken together, all contribute to diabetic pulmonopathy in CF.

4 Screening and diagnosis

The diagnosis of CFRD can be difficult to detect biochemically and clinically. The classical symptoms of ‘polyuria, polydipsia and poor weight gain’ seen in conventional diabetes occur in only one third of patients with CFRD [35] and subsequently, relying on symptoms to make the diagnosis would fail to recognize the vast majority of CFRD. Routine annual screening is therefore advocated from the age of 10 years by both the American Diabetic Association (ADA) and National Institute of

Clinical Excellence (NICE) in the UK. [8,36]. A lack of identifiable endocrine support has previously been identified as a barrier to optimising screening programmes, [37] and a combined collaborative approach to screening involving respiratory and endocrine teams has previously been found to improve screening rates. [38] Hence close co-operation and communication between respiratory and diabetic teams is required to facilitate effective screening programmes so that CFRD can be diagnosed at the earliest opportunity.

In addition to annual screening, unexplained lung function decline, weight loss or increased exacerbation rate may all trigger CF MDTs to look for CFRD in more detail. Screening is also particularly important in people with CF who have received solid organ transplantation as post-transplant diabetes mellitus is common and can be independently associated with increased infections and mortality. [39]

Several screening tests have been proposed for CFRD: 50g glucose challenge test, 75g OGTT, OGTT 60-minute glucose level, continuous glucose monitoring (CGM), fasting plasma glucose, HbA1c, serial capillary blood glucose monitoring or any combination of the above. [40]However, in the UK the recent NICE guidelines suggest OGTT or CGM as the preferred screening methods, where if OGTT is used the diagnosis is confirmed with CGM. [8]

5 Management

Principles of an MDT approach

Effective CFRD management relies on co-ordination of many specialist CF healthcare professionals including the doctor, diabetologist, nurses, physiotherapists, psychologists, pharmacists and dieticians. Prevention of cross-infection, a cornerstone of CF care, makes the management of CFRD by the conventional approach unfeasible. For example, unsegregated communal clinics and group educational sessions are not appropriate in CFRD due to the risk of cross-infection. Services must therefore be tailored in a more individualised bespoke manner. As a consequence many CF centres have now developed dedicated joint-care clinics for diabetes, or even in-house CFRD specialist nurses. The CF annual review; a comprehensive, individualised assessment of each patient's health

and treatment regimens, includes either a screen for CFRD or, in those already diagnosed, a thorough assessment of glycaemic control, treatment adherence and complications.

The principles of management of CFRD also differ from that of T1DM and T2DM. Treatment of T1 and T2DM is tailored towards the prevention of vascular complications and although microvascular complications are reported in CFRD, they occur late and are less frequent than in other forms of diabetes. [41] Instead, the management of CFRD aims to stabilise and improve lung function and nutritional status.

Pharmacological treatment of CFRD

Insulin deficiency is the primary defect of CFRD and insulin treatment is associated not only with improved nutritional status and lung function [42-45] but also reduced pulmonary exacerbations, a key determinant of morbidity and mortality in people with CF. [46] Hence all guidelines agree that insulin replacement is the only recommended therapy. [7,8,40]

Although the benefits of insulin are well established, there remains uncertainty as to when treatment should be initiated. Conventional diabetic thresholds on OGTT and HbA1c are validated for the long-term outcomes of people with T1 and T2DM. In CF, the deleterious clinical effects associated with CFRD often manifest themselves before dysglycaemia reaches conventional thresholds for diabetes and hence earlier intervention has been advocated by some guidelines, particularly where early dysglycaemia is seen concurrently with nutritional and/or pulmonary decline. [47] A handful of small studies have explored this strategy and although positive results were reported by some, a systematic review found the overall evidence base remains poor. [48] Large prospective studies are under way and will provide more evidence in the coming years ("CF-IDEA Trial" clinicaltrials.gov: CT01100892 and "The Impact of Insulin Therapy on Protein Turnover in Pre-Diabetic Cystic Fibrosis Patients" clinicaltrials.gov: NCT02496780).

Commonly used insulin regimes include a long-acting insulin monotherapy regime or a bolus-only regime using rapid acting insulin at mealtimes. Basal-bolus regimes can be reserved for those with fasting hyperglycaemia, a relatively late sequel. [49] There is little evidence to support one regime over

another, and treatment should instead be tailored to the individual's needs, taking their dysglycaemia into account but also considering treatment burden, lifestyle and psychological factors. Given the anabolic effects of insulin, insulin doses should be uptitrated to the maximum dose safely tolerated by each patient.

The role of the CF Diabetes Specialist Nurse

Education and training of the person with CFRD is important for successful management and is best provided by the specialist CF nurse who has an understanding of all aspects of the CF disease state, including that related to diabetes. The nurse specialist plays a pivotal role in any disciplinary team, acting not only as a first point of access, but also by coordinating the input provided by other members of the CFRD MDT. Liaison with multidisciplinary teams both external and internal is important and part of the nurse's role is to ensure that all stakeholders are aware of the differences and requirements of a patient with CFRD. Such advocacy includes providing support outside the hospital setting, for example visits within the community when required.

More recently, advanced nurse practitioner roles in CFRD have been developed and include non-medical prescribing, instigation and titration of insulin, and nurse led CFRD clinics and ward rounds. As part of this, ongoing monitoring of those with CFRD through the use of CGM has been developed, and a tri-partite approach in conjunction with the CF dietician and person with CF to devise a plan of care based on CGM feedback seems likely to become gold standard. Although there is little evidence for or against different care models for people with CFRD, lessons from other forms of diabetes suggest involving the person with CFRD in the MDT approach helps develop a more realistic and achievable CFRD care plan. [50] [51]

The advent of flash glucose monitoring (FGM) may help people with CFRD better manage their diabetes. Whilst no trials of FGM in CFRD have been performed, the demographics of people with CF and experience managing chronic conditions mean many are likely suitable candidates for FGM. FGM can be used as a short term "troubleshooting" strategy or as a longer-term tool for

improved overall glycaemic control. [52] While FGM enables self-management, liaison with the diabetic nurse over the practicalities of access and initiation of the technology is needed and, similarly to other forms of diabetes, revised education for patients/caregivers is often needed. [53] The ability for sharing of measurements for remote review gives the potentials for healthcare professionals to reassure, advise or intervene in a more timely and patient centred manner.

Nutritional recommendations – the CF Specialist Dietician

Individually tailored dietetic advice based on an understanding of CFRD and also its interaction with other CF-related complications is essential to help meet the nutritional needs of the person with CF whilst optimising blood glucose control. However, there are no randomised controlled trials dictating best practice for the dietary management of people with CFRD, including the use of a low glycaemic index diet which is currently under review.[54,55] As such, recommendations for CFRD are based predominantly on observational data and clinical consensus guidelines. [7,8,40,56]

Exocrine pancreatic insufficiency is present in nearly all people with CFRD and pancreatic enzyme replacement therapy (PERT) is a cornerstone of treatment. Specialist CF dietetic advice to adjust and optimise PERT is essential along with co-operation between nutrition and diabetic teams particularly in the formulation of enteral feeding, where unique insulin regimes are sometimes required.

Since insulin deficiency in CFRD potentiates the catabolic state, dietary recommendations differ significantly from those of T1 and T2DM (Table 1), and increased calorific intake is necessary to meet the metabolic demands associated with CF. Type of carbohydrate intake is also important in CFRD [57] demanding detailed education around the main foods groups. Complete restriction of simple sugars is often not appropriate due to the calorific requirements needed for people with CF to remain nutritionally replete. Dietary advice is therefore carefully structured to ensure calorific needs are met, alongside guidance for macronutrients.

Ongoing management of CFRD and nutritional status requires regular follow-up and assessment. Serial glucose monitoring, by conventional methods or modern “flash” monitoring can be used in

conjunction with food and activity diaries to identify how specific foods or circumstances such as stress, illness, medications and time of day, affect individuals glycaemic control. This approach can empower individuals with CFRD to tailor their treatment according to lifestyle such that outcomes are optimised whilst disruption to life is minimised.

Table 1: Comparison of dietary recommendation between CFRD and other types of diabetes. Adapted from ISPAD Clinical Practice Consensus Guidelines 2018 [40]

	Type 1 & Type 2 Diabetes	CFRD
Calories	≤100% of normal calorific intake for age and gender. Often have to watch or restrict calories to prevent overweight	Require >120% of normal calorific intake for age and gender to prevent underweight
Fat	<35% of total energy	40% of total energy
Total Carbohydrate	40-60% total energy	45-50% total energy
Fibre	Encouraged	Encouraged in nutritionally replete individuals, but in poorly nourished patients it may compromise energy intake
Protein	10-20% of total energy; not >1g per kg body weight	200% of reference nutrient intake
Salt	Low intake, <6g/day	Increased requirement

Role of the CF pharmacist

CF is a multisystem disease with a large treatment burden and adherence can be problematic, further complicated in those with CFRD. The specialist CF pharmacist plays a pivotal role in the MDT in regard to medicines management and supporting adherence. [58,59] Minimising treatment burden is key to improving adherence and pharmacists are well placed to identify barriers to improving adherence in

diabetes. [60,61] The pharmacist also plays a role in vigilance and monitoring of drug-drug interactions. Whilst insulin is a relatively inert medication, other medications commonly used in CF can impact glycaemic control, eg corticosteroids and fluoroquinolones. [62]

Role of CF Physiotherapist

CFRD is associated with increased bacterial colonisation as well as increased pulmonary exacerbation rate and optimisation of chest clearance is therefore vital. [63,64] Physiotherapists and exercise physiologists also play a role in collaborating with patients to provide individualised exercise programmes. The International Society for Paediatric and Adolescent Diabetes (ISPAD) advise that people with CFRD should do at least 150 minutes of moderate aerobic exercise a week. [49]

Screening for complications

Whilst macrovascular complications of CFRD are rare, microvascular complications are more common: neuropathy has been reported in up to 50% of people with CFRD, retinopathy in approximately 40% of those diagnosed with CFRD for > 10 years, and CFRD is associated with a 4-fold increase in chronic kidney disease. [41,65] Annual screening for microvascular complications is therefore recommended although attendance rates for screening schemes e.g. annual retinopathy screening remain poor [66]. Complications of CFRD are likely to increase in parallel with overall increased survival and robust screening programmes must therefore be integrated within the CF MDT.

Psychological

CFRD carries a considerable treatment burden, and requires patients to adapt their lifestyles to accommodate new and potentially daunting treatment regimes. It is of note that CFRD diagnoses typically occur between 18-21 years of age, [67] thereby occurring in parallel to a number of other life transitional and developmental stages, all of which pose their own challenges and the potential to exacerbate any CFRD specific psychosocial stressors as they navigate these new life experiences.

It is logical that a diagnosis of CFRD could have repercussions for patients' mental health; indeed meta-analyses of the prevalence of psychological distress in type 1 and 2 diabetes suggest that rates of

comorbid depression and anxiety are notably higher. [68,69] In CF, psychological distress (anxiety and depression) is already elevated across child, adolescent and adult populations [70]. A number of psychosocial stressors are shared between type 1 and 2 diabetes with CFRD e.g. adjustment to disease, dietary management, body image, and needle anxiety etc. It seems reasonable, therefore, to expect psychological distress is higher for those with a diagnosis of CFRD.

Psychological interventions such as cognitive behavioural, psychodynamic and systemic therapies have been suggested to be effective across the wider diabetic literature in terms of improving glycaemic control whilst simultaneously reducing distress. [71,72] However they have yet to be specifically explored within the CFRD population and any intervention must take into consideration the multifactorial nature of managing such a complex chronic life limiting disease.

Future perspectives

The CF horizon is dominated by CFTR modulators, but how these treatments will impact on CFRD is unclear. There is some evidence from small studies that insulin secretion improves with the use of ivacaftor, a CFTR corrector, yet similar effects have not been observed for the ivacaftor/lumacaftor combination licensed for people with the more common F508D mutation. [73] [74,75] Excitingly, an observational post-marketing follow up study of ivacaftor use in the UK and US found an approximately 30% reduced relative risk for CFRD in those using ivacaftor compared to matched controls, although it is not known whether this was a result of reduced incidence of new CFRD diagnoses or improvement in glucose handling in those with a previously diagnosed. [76]

As life expectancy increases in CF, macrovascular complication may become more prevalent. To date macrovascular complications related to atherosclerotic disease are exceedingly rare in CF, with only one case, to our knowledge, in the literature. [77] In a future setting where CFTR modulators may improve survival, nutrition and pulmonary status, CF MDTs may need to reconfigure dietary advice to mitigate cardiovascular complications.

Although insulin is the mainstay of treatment for CFRD currently, a recent clinical trial of oral repaglinide reported similar efficacy and safety as subcutaneous insulin [78] and the use of non-insulin

therapies warrants further exploration in the coming years. Incretin axis targeted therapies are now routinely used in the treatment of T2DM and interest in their use is growing in CF. Concerns that some agents may be associated with weight loss and/or pancreatitis have led to initial caution, however some of these fears have been assuaged. [79] Incretin axis abnormalities have been reported in people with CF and investigation of incretin targeted therapies are therefore warranted. [80-82]

Summary

Cystic fibrosis is a complex multi-system disease, and CFRD remains one of its most important co-morbidities with deleterious nutritional and pulmonary outcomes if left untreated. Optimal management of CFRD relies on timely diagnosis, insulin initiation and vigilance for diabetic complications. Achieving best care relies on a co-ordinated, proactive approach from many different healthcare professionals across a number of specialities. Importantly, the MDT must include the patient themselves and treatment must be tailored to the individual in order to minimise treatment burden, maximise adherence and improve long-term outcomes.

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