Cystic Fibrosis Related Diabetes - An Update

Frost F[1,2], Walshaw MJ[1,2], Nazareth D[1,2]

Author Affiliations: [1]=Adult CF Centre, Liverpool Heart & Chest Hospital NHS Foundation Trust, Liverpool, UK

[2]=Institute of Infection & Global Health, University of Liverpool, Liverpool, UK

Keywords: Cystic Fibrosis Related Diabetes (CFRD); Continuous Glucose Monitoring (CGM); Diabetic Pulmonopathy;

Corresponding Author:

Dr Freddy Frost,

Adult CF Centre, Liverpool Heart & Chest Hospital NHS Foundation Trust, Thomas Drive, Liverpool, UK, L14 3PE

Freddy.Frost@lhch.nhs.uk

Funding Source: None

Conflict-of-Interest Disclosure: None relevant

Acknowledgements: None

Abstract:

Cystic fibrosis (CF) is the most common life-threatening inherited condition in the Caucasian population, where mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene result in a multifactorial syndrome, with pulmonary disease representing the largest contributor to morbidity and mortality. Life expectancy has improved and the recent development of disease-modifying CFTR modulator therapies is likely to further improve survival. However, increasing life expectancy brings new challenges related to the complications of a chronic disease including an increasing prevalence of cystic fibrosis related diabetes (CFRD), itself associated with increased morbidity and early mortality. This review provides an update as regards the underlying mechanisms, investigation and management of CFRD.

Learning points:

- Glucose intolerance is common in cystic fibrosis with approximately half of adult people with CF (pwCF) eventually diagnosed with cystic fibrosis related diabetes (CFRD).
- Single point tests to evaluate glucose handling are not suitable and continuous glucose monitoring is the most sensitive method to pick up early glucose abnormalities.
- CFRD requires treatment with insulin although other agents are undergoing clinical trial evaluation.

Cystic fibrosis (CF) is the most common life-threatening inherited condition in the Caucasian population. [1] Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene result in a multifactorial syndrome, with pulmonary disease representing the largest contributor to morbidity and mortality. Life expectancy has improved dramatically in the last 20 years and children born today are predicted to have median life expectancy of at least 47 years. [2] The recent development of disease-modifying CFTR modulator therapies is likely to further improve life expectancy in the near future. However, such increased life expectancy

brings new challenges related to the complications of a chronic disease. One of the most important extra-pulmonary complications of CF is CFRD, which differs from other conventional forms of glucose intolerance, ultimately affecting over 50% of adult pwCF. [3] CFRD is directly associated with poorer outcomes and this review gives an overview of the disease and its management

Epidemiology

CFRD was recognised as a unique entity was in 1955 and since then the association with a number of comorbidities and increased mortality has been well described. [4] Few pwCF have normal glycaemic control but the median age of onset of CFRD is 20 years, with women developing it at a younger age. CFRD is present in about 20% of adolescents and up to 50% of adults and accompanies increasing age, worse pulmonary function, poor nutrition, liver dysfunction and steroid use.[5][6] Although it shares features of both Type 1 and Type 2 diabetes (Table 1), unlike those with T1DM, individuals with CFRD retain some basal insulin secretion.

Pathophysiology

The pathophysiology of CFRD is incompletely understood but is probably multifactorial, with progressive pancreatic β-cell destruction resulting in gradual insulin deficiency an important factor. [5,7] Insulin resistance and a defective incretin hormone axis have also been implicated. [8,9] Interestingly, CFTR has been shown to play a role in insulin release, potentially explaining how early dysglycaemia can precede significant pancreatic damage. [10] CFRD is characterised by post-prandial hyperglycaemia: fasting or pre-meal hyperglycaemia are late sequelae, due to residual baseline insulin production from the pancreas. In keeping with this, the development of ketoacidosis is rare in CFRD. Dysglycaemia is also highly variable, up to 20% of oral glucose tolerance tests (OGTT) within the frank diabetic range spontaneously converting to normal glucose tolerance when repeated. [11] Such variability may in part be explained by fluctuating systemic inflammation associated with chronic pulmonary infection and resultant changes in insulin resistance. [9]

Clinical implications of CFRD

The presence of CFRD is associated with a six-fold increase in early mortality, where the cause of death is progressive respiratory failure rather than the macrovascular complications associated with conventional diabetes. [4,6] Accelerated pulmonary function decline, increased infection and complex metabolic and mechanical changes within the lung have been

linked to hyperglycaemia within the airways and interstitium and together have been termed "diabetic pulmonopathy". [12,13] However the most serious acute complication of CFRD is hypoglycaemia, which can occur secondary to insulin treatment, spontaneously in the fasting state due to malnutrition and/or increased energy needs due to inflammation and infection, and postprandially, related to delayed and discordant insulin secretion. [14] Microvascular disease in pwCF does not become clinically apparent until they have had CFRD for at least 5 years and have developed fasting hyperglycaemia.[15] Renal failure solely due to CFRD is uncommon, but microalbuminuria occurs in up to 21% in individuals. [16] Although retinopathy occurs in up to 23% of those with CFRD, neuropathy is uncommon. [15] Gastroparesis is common in CFRD and can make glycaemic control problematic. [17]

Diagnosis and monitoring

The WHO criteria for the diagnosis of diabetes are based upon thresholds for the development of microvascular complications in the non-CF population and do not take into account the damage that occurs in pwCF associated with a lesser degree of glucose intolerance: such criteria may therefore not always be relevant in people with CFRD. Thus, OGTT, fasting glucose, and HbA1c all have inherent limitations in their applicability to CFRD and hence more recent guidelines include continuous glucose monitoring (CGM) as a diagnosis modality. CGM is well validated to detect early dysglycaemia missed by standard OGTT, and insulin treatment based upon dysglycaemia seen on CGM has been associated with clinical improvement. However, diagnostic and treatment thresholds need to be validated in large clinical trials. [18,19]

Management of CFRD

The management of CFRD is complex and differs from that of type 1 and type 2 diabetes, requiring those responsible for the care of pwCF to work closely with colleagues across different specialities and disciplines, including the diabetologist, CF physician, nurses, physiotherapists, psychologists, pharmacists and dieticians. A major distinguishing feature between conventional diabetes and CFRD is the recommendation for a high calorie, high fat diet for nearly all pwCF to meet the increased metabolic demands associated with the disease in the knowledge that the cardiovascular risk is low. [5] There is no evidence to support reductions in carbohydrate load in individuals with CFRD or to avoid high glycaemic index foods as this might reduce total energy intake and thereby impair nutritional status. Specialist dietician input is vital to ensure optimisation of pancreatic enzyme replacement therapy to

improve gastric emptying, incretin hormone responses and post-prandial hyperglycaemia in people with CF.

A lack of insulin is the primary defect in CFRD and insulin is the only recommended pharmacological therapy.[5] Insulin treatment has been associated with stabilising lung function and improved nutritional outcomes in prospective clinical trials and long-term observational studies. [20,21] Insulin initiation can delay lung decline by up to 34 months. [22] The choice and regime of insulin depends on individual needs – basal monotherapy can be used early in the disease where it provides background insulin and a continuous anabolic effect; basal-bolus regimes including short acting insulin help control post-prandial hyperglycaemia and allow for variable eating patterns. [5] Individuals receiving overnight supplementary feeding to meet their nutritional requirements require more individualised regimes including nocturnal insulin. Continuous subcutaneous insulin pumps are increasingly used where there is difficulty in achieving good glycaemic control with injected insulin, but their use can contribute to the already high burden of treatment for pfCF.

CFTR Modulators

The development of CFTR modulator drugs such as ivacaftor (a CFTR channel potentiator useful in class III gating mutations), lumacaftor and tezacaftor (CFTR correctors that facilitate CFTR protein folding and maturation, useful in class II mutations such as ΔF508, used in combination with ivacaftor) have dramatically altered the care of people with CF. Recently a triple therapy (ivacaftor/tezacaftor/elexacaftor) has become licensed in the US and demonstrates remarkable improvements in CFTR function and relevant clinical outcomes for mutations that involve 90% of pwCF. [23] Although the main outcomes in CFTR modulator clinical trials have focused on an improvement in pulmonary function and reduction in pulmonary exacerbations, there is also evidence of significant extrapulmonary benefit. Initial short-term improvements in glycaemic control have been reported with ivacaftor use and these findings are supported by data from large registry studies which found lower prevalence of CFRD and 30% reduction in relative risk of developing CFRD compared with untreated controls with similar genotype profiles. [24,25] The picture is less clear for the dual combination modulators but if glycaemic outcomes mirror the pulmonary outcomes of the triple therapy combination then there is a real possibility of reversal of CFRD in some pwCF, and delaying of its onset in others.

Future directions

Whilst insulin remains the only recommended treatment at present, studies are underway examining the utility of incretin analogues. The incretin effect is lost in CFRD but supraphysiological incretin stimulation may be able potentiate insulin secretion, particularly in early disease, and could be associated with a reduced treatment burden compared to insulin regimes.

CGM has been extensively validated in the detection of dysglycaemia in people with CF, but its uptake has been limited by cost and a lack of validated outcomes. The development of flash glucose monitors, wearable sensors which relay glucose levels to a smartphone, are relatively cheap and ideally suited to pwCF given their demographics and experience in managing chronic disease. There are currently no trials supporting their use in CF but in conventional diabetes they have been associated with increased glycaemic "time in range" and reduced hypoglycaemia, both important outcomes for pwCF. Further research is needed to confirm the benefits of such an approach in CF and also to validate treatment initiation thresholds.

The era of highly effective CFTR modulators has arrived and will improve CF outcomes over the next decade. Although they may reduce CFRD prevalence, CFRD will still play a major role in the morbidity and mortality of pwCF. Macrovascular complications, currently a rarity, may become more common and the traditional dietary recommendations for people with CF may need to be modernised. Careful observation of the short and long-term outcomes for those with CFRD after modulator therapy initiation will be needed.

Summary:

CFRD is one of the most important complications associated with CF, causing significant morbidity and mortality. Glucose intolerance in CF is a dynamic process and conventional fixed-point tests to evaluate glucose handling are unsuitable. CGM appears to be the most sensitive test for detecting early glucose abnormalities but is not yet in widespread use. Treatment of CFRD requires insulin, although oral incretin analogues are under investigation. CFTR modulators are set to change the landscape of CF management in the coming years and may also have a significant long-term impact on the development of CFRD and CF-related complications. Nevertheless, CFRD will still attribute considerable morbidity for pwCF and careful, proactive diagnosis and management in an MDT approach is warranted.

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Table 1: Comparison of features of different forms of diabetes [5]

	Type 1 DM	**Type 2 DM**	**CFRD**
Prevalence	0.2%	11%	35%
Onset	Usually acute	Insidious	Insidious
Peak age of onset	Children, youth	Adults	18-24 y
Usual body habitus	Normal	Obese	Normal-underweight
Autoimmune etiology?	Yes	No	No
Insulin deficiency	Nearly complete	Partial, variable	Severe, not complete
Insulin sensitivity	Somewhat decreased	Severely decreased	Somewhat decreased [a]
Ketones	Yes	Rare	Rare
Usual treatment	Insulin	Diet, oral meds, insulin	Insulin
Microvascular complications	Yes	Yes	Yes
Macrovascular complications	Yes	Yes	No
Metabolic syndrome	No	Yes	No
Cause of death	Cardiovascular	Cardiovascular	Pulmonary

[a] insulin sensitivity becomes severely decreased during acute illness